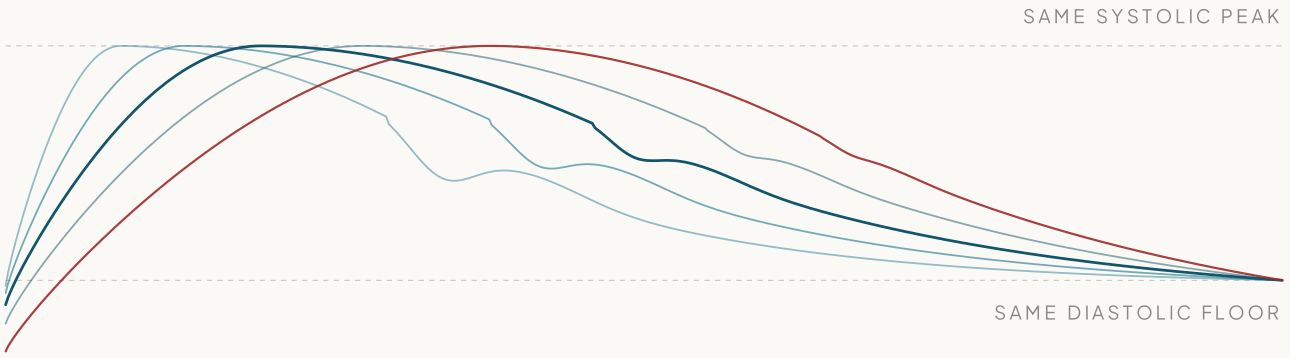
Hypertension

A Phenotype-Based Approach



VOLUME ONE

Why Is This Patient Hypertensive?

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MBBS · AFIH · OCCUPATIONAL HEALTH PHYSICIAN

Hypertension

A Phenotype-Based Approach

VOLUME ONE

Why Is This Patient Hypertensive?

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FIRST EDITION

THIS EDITION

Hypertension: A Phenotype-Based Approach
Volume 1 · Why Is This Patient Hypertensive? · Part I, Foundations of Blood Pressure
First edition · September 2026
Written and edited by Dr Ravikiran Jadhav, MBBS, AFIH

SCOPE AND LIMITS

For use by qualified medical practitioners only. This work is written for clinicians and is not a substitute for clinical judgement, current product information, or the guidelines in force where the reader practises. Clinical responsibility for any individual patient rests with the treating physician.

Every patient described in this book is an illustrative composite. Presentations, figures and courses are assembled from typical clinical patterns to demonstrate reasoning; none is a report of an identifiable individual.

Drug doses, thresholds and regulatory standards are stated as they applied at the date above and change over time. Verify every dose against current product information before prescribing.

The phenotype framework in this book is a proposed way of thinking, not a validated classification. Nothing in it has been tested as a diagnostic system. Where the guideline and the phenotype conflict, the guideline wins.

CORRECTIONS

Errors and disagreements are welcome, and are actively wanted. Send them to RavikiranBJadhav@gmail.com. Each will be recorded and addressed in the next revision, and the version number above will tell you which edition you are holding.

Set in Literata and Plus Jakarta Sans.

CONTENTS · ALL THREE VOLUMES

Hypertension: A Phenotype-Based Approach

Reproduced in the front matter of each volume, so a reader holding any single volume can locate content in the other two.

Dr Ravikiran Jadhav MBBS · AFIH · Occupational Health Physician

HOW TO NAVIGATE THIS SERIES

Every chapter reference carries a volume prefix followed by the chapter number; appendix codes follow the same convention. Where content in one volume supports another, the cross-reference appears in the chapter itself.

REFERENCE FORMAT

`V1·Ch3`	Volume 1, Chapter 3 — The renin–angiotensin–aldosterone system
`V2·Ch1`	Volume 2, Chapter 1 — ACE inhibitors
`V3·App C`	Volume 3, Appendix C — intravenous emergency drug protocols

ONE MECHANISM, ONE DRUG CLASS, ONE CLINIC DECISION

The RAAS physiology of **V1·Ch3** is the pharmacological basis for **V2·Ch1** (ACE inhibitors) and **V2·Ch2** (ARBs); its clinical application appears in **V3·Ch20** (diabetes and chronic kidney disease). Read in that order, the series is one continuous argument.

VOLUME ONE

Understanding Hypertension

Foundations · aetiology · special populations · contributing factors · drug-induced hypertension

6 PARTS · 37 CHAPTERS · ASSESSMENT CHAPTER · 2 SUPPLEMENTARY CHAPTERS · 5 APPENDICES · APPROXIMATELY 360 PAGES

PART VI — SECONDARY HYPERTENSION

SUPPLEMENTARY CHAPTERS — VOLUME 1

APPENDICES — VOLUME 1

VOLUME TWO

Choosing and Combining the Drugs

Eleven classes · which class, which molecule, which combination · how to grade a trial and when to deviate from a guideline

3 OPENING CHAPTERS · 5 PARTS · 15 CHAPTERS · 6 APPENDICES · APPROXIMATELY 195 PAGES

PART V — CHOOSING BETWEEN THEM

APPENDICES — VOLUME 2

VOLUME THREE

Clinical Practice in Hypertension

Examination · investigations · treatment · OPD practice · special situations · cases

7 PARTS · 36 CHAPTERS · 30 LONGITUDINAL CASES · 6 APPENDICES · APPROXIMATELY 345 PAGES

PART ONE — THE CONSULTATION 7 chapters

PART SEVEN — THIRTY PATIENTS, FOLLOWED FORWARD

6 blocks of 5 · the spine of the volume

Block A

Making the diagnosis

Five patients where the question is whether to treat at all, and what this is.

A1	19 M	146/62	Athlete, wide pulse pressure, energy drinks and creatine — is this hypertension at all?
A2	34 F	152/96	On a combined oral contraceptive with headaches — stop the pill or start a drug?
A3	58 F	168/78	Isolated systolic hypertension — the pulse-pressure decision
A4	28 M	178/104	Found at a health camp, entirely asymptomatic — how fast, and what to exclude
A5	31 F	148/94	Twelve weeks pregnant, previously "borderline" — chronic or gestational

Block B

The pressure that will not come down

Five escalations, each failing for a different reason.

B1	42 M	155/87	**Telmisartan, then two, then three — ending in a potassium of 3.1**
B2	55 M	on four drugs	"Resistant" — until the cuff and the tablet count are checked
B3	47 F	was controlled	Escaped after two good years — the anti-inflammatory she did not mention
B4	63 M	on three drugs	Snores, BMI 34 — sleep apnoea before the fourth drug
B5	39 M	on three drugs	Normal potassium, young, uncontrolled — the renal artery

Block C

A finding appears

Five patients where one result reopened everything.

C1	52 M	ACR 340	Proteinuria arrives — which drug, which target, and how hard
C2	60 F	creatinine 0.9 → 1.4	Two weeks after starting a blocker — accept the rise or stop the drug?
C3	49 M	grade 4 fundus	Found at a routine visit — this is malignant hypertension
C4	44 M	E/e' 15	Hypertrophy, then breathlessness on stairs — heart failure emerging
C5	57 M	small kidneys	Nephrosclerosis on ultrasound — what it forecloses and what it does not

Block D

The comorbidity that changes everything

Five patients where pressure is no longer the main problem.

D1	61 M	diabetes 9 yr	ACR 220, eGFR 48 — assembling the four-drug regimen
D2	66 M	post-infarct	152/88 at four months, heart rate 78 — what is obligatory
D3	71 F	atrial fibrillation	168/92 with a stroke score of 4 — pressure before anticoagulation
D4	68 M	post-stroke	Three weeks after infarction of the brain — when to start, how low
D5	59 F	ejection fraction 32%	98/62 — treating hypertension when the pressure is the constraint

Block E

Inherited and referred

Five patients who arrive already belonging to another doctor.

E1	54 M	a bag of tablets	No records, previous doctor retired — the structured takeover
E2	46 F	referred "for BP control"	The referral question is the wrong one, and she has a cause
E3	62 M	five drugs	From a tertiary centre to a district clinic — can it be simplified, and afforded?
E4	37 M	second opinion	Angry at being told he needs tablets for life — the consultation, not the pharmacology
E5	70 F	sent back	"For ongoing management" — what the specialist delegated, and what they did not say

Block F

Advanced, neglected and acute

Five patients at the far end.

F1	48 M	210/124	Ten years untreated, creatinine 2.8 — and why you must not normalise it today
F2	82 F	168/86	Frail, two falls — time to benefit against time remaining
F3	45 M	230/130	Headache and papilloedema — the emergency, hour by hour
F4	36 F	200/120	Decongestant and eye drops — sympathomimetic crisis
F5	58 M	"uncontrolled BP"	Tearing pain called hypertension — the one where you go fast

APPENDICES 6

V3·App

Six reference appendices

The tables a physician looks up rather than reads.

- **A** Targets by condition, across guidelines, in one table
- **B** Drug selection by compelling indication
- **C** Intravenous emergency protocols: dose, rate, monitoring
- **D** Key trials: name, number, result, what it changed
- **E** Occupational fitness criteria for safety-critical work in India
- **F** Patient handouts: pressure, tablets, salt, home monitoring

ABOUT THIS VOLUME

Part I establishes the physiology on which every later clinical decision in this series rests. It is not preamble. Each chapter ends by converting its mechanism into something the clinician can use at the bedside — which investigation to order next, how fast to lower a pressure, what to explain to the patient about their own disease, and where a mechanism bears on a choice the guideline leaves open.

The ten chapters are ordered as a single argument. Chapter 1 gives the equation that governs every reading. Chapters 2 to 6 take each mechanism that can move a term in that equation — neural, humoral, renal, sympathetic, endothelial. Chapter 7 puts the whole system on a 24-hour clock. Chapters 8 and 9 fix the definitions and the epidemiological scale. Chapter 10 assembles all of it into Page's mosaic, and derives from it the single most useful pharmacological rule in the field: why monotherapy has a ceiling.

CONVENTIONS USED THROUGHOUT

Units	SI first, conventional units in parentheses where clinically dominant. Ranges take an en dash. Doses carry route and frequency.
Drug names	Generic, lower case, always. Brand names appear in italic parentheses only where recognition matters.
Abbreviations	Expanded once at the defining occurrence, then used alone.
Cross-references	V1·Ch3 means Volume 1, Chapter 3. V3·App C means Volume 3, Appendix C.
Margin notes	The scholar margin carries definitions, magnitudes and pointers to other chapters. Nothing essential appears only in a margin note.
Cases	Every patient in this book is an illustrative composite. Presentations, figures and courses are assembled from typical clinical patterns to demonstrate reasoning; none is a report of an identifiable individual.
Sources	Where a figure is a result attributed to a named trial, cohort or meta-analysis, the source is listed at the end of that chapter, and every source listed there was opened and the figure read out of it. **No citation in this book was generated without reading the source it names.** A superscript number in the text marks a statement traceable to one specific work; the remaining entries in a chapter's list are the sources the chapter rests on more generally and carry no superscript. Figures with no source listed are standard physiological or clinical values, not study results; treat them as textbook-level and check them before quoting them anywhere it matters.
Evidence status	Three kinds of statement appear in this book and they do not carry equal weight. ESTABLISHED — supported by guideline, randomised trial or meta-analysis, and named as such. INTERPRETATION — a reasonable clinical reading of established evidence, but a reading. PROPOSED FRAMEWORK — the author's synthesis, offered as a way of organising the problem. It is not a validated classification, it has not been tested against outcomes, and it carries no authority over a guideline. Where a table carries one of these three labels, that is the status of the table as a whole.
Key points	Every chapter closes with seven numbered points. They are a revision aid, not a substitute for the chapter.

Scope and corrections

See *About this edition*, overleaf, for scope, accuracy and corrections.

ABOUT THIS EDITION

Scope, accuracy and corrections

THIS EDITION	**First edition · September 2026. This edition is final; corrections received will be held for the next edition.** Prepared and edited by Dr Ravikiran Jadhav. Digital drafting and typesetting assistance were used in its production; the author is responsible for all clinical content.
SCOPE	A practical clinical-reasoning guide for outpatient hypertension management, written to sit alongside the current hypertension guidelines rather than to compete with or restate them. **It is not a clinical practice guideline.** Where any statement, threshold, dose, target or pathway here differs from a current applicable guideline, from a drug's product information, or from specialist advice, **the current authoritative source takes precedence over this book**. The phenotype framework proposed here is not a validated diagnostic classification and must not be used in place of cardiovascular risk assessment, target-organ assessment, evaluation for secondary hypertension, or guideline-directed treatment.
ACCURACY	Every effort has been made to ensure accuracy, but no warranty is given. **Verify all doses, thresholds and protocols against current product information before prescribing** — particularly in renal impairment, hepatic impairment and pregnancy. Guideline thresholds change; the physiology does not.
CORRECTIONS	Errors and disagreements are welcome, and are actively wanted. Send them to RavikiranBJadhav@gmail.com. Each will be recorded and addressed in the next revision, and the version number above will tell you which edition you are holding.

A note on how to read a book like this. Nothing here asks to be taken on authority. Every mechanism is named, every trial is cited by name and result, and every drug recommendation states the mechanism it addresses — so that a reader who disagrees can see exactly where the disagreement lies. That is the only kind of confidence a clinical text is entitled to ask for.

Set in Literata, with Plus Jakarta Sans for tables, captions and running heads.

IF YOU READ NOTHING ELSE

This page is the floor. Everything else in this book sits on top of it, and nothing in this book overrides it. If the rest of the volume is never read, these six things still hold.

1 **Treat by the guideline. Start today.**

Confirm the diagnosis, stage it, assess cardiovascular risk, and start guideline-directed treatment in the patient who needs it. Nothing in this book is a reason to delay that. A phenotype identified next month in an untreated patient is worth less than a guideline-directed drug started this morning.

2 **Do the five things that cost nothing.**

Blood pressure in both arms, once. Standing pressure in the elderly and the diabetic. The resting heart rate. The waist circumference. Radio-femoral delay in every hypertensive under forty. Together they take about four minutes, and they find what a prescription never will.

3 **Order the three tests that identify most of what is missable.**

Urinalysis, urine albumin–creatinine ratio, and serum creatinine with electrolytes — with a four-limb pressure in the young. They are cheap and widely available, and between them they find the majority of the secondary hypertension there is to find. In the young, renal disease is about four-fifths of it.

4 **Take the drug history as a list, not as a question.**

"Are you taking anything else?" finds nothing. Ask separately about painkillers, hormonal preparations, steroids, decongestants, herbal and ayurvedic remedies, and anything bought without a prescription. Patients do not consider most of these to be medicines.

5 **Ask what changed.**

A pressure that was normal and is now not normal has a reason, and the reason is far more often in the last six months of the patient's life than in their genes. It is one question and it costs nothing.

6 **The phenotype changes the conversation more often than it changes the prescription.**

It tells you what to investigate, what to treat alongside the drug, and what to explain to the patient. It does not select the drug where a guideline has already spoken, and it is never a reason to wait. Where mechanism and guideline appear to disagree, the guideline wins.

If your clinic gives you six minutes and sixty patients

Do 1 and 2. They are the floor of the floor, they fit inside the consultation you actually have, and they are still more than most hypertensive patients in this country receive.

FROM THE AUTHOR

Why I wrote this book

Dr Ravikiran Jadhav MBBS · AFIH · Occupational Health Physician

This book was born from a clinical observation that troubled me for years: the gap between what we know about hypertension and how we actually manage it in the outpatient department.

The mechanisms are understood. The guidelines are clear. The drug classes are well studied. And yet, across thousands of outpatient consultations every day in India, a patient arrives with elevated blood pressure, a drug is prescribed, the number comes down, and the encounter is considered complete. The question that was never asked — *why does this person have high blood pressure* — remains unanswered. The mechanism driving the elevation continues unchallenged. The cardiovascular risk that extends far beyond the blood pressure number is never addressed.

Consider a 38-year-old bank branch manager. Obese. Six months of reduced exercise following a knee injury — walking dropped from 5 km to 1.5 km daily, below the therapeutic threshold every single day. Snoring. Daytime sleepiness. Morning-dominant blood pressure of 160/100 mmHg. Random glucose rising. Resting heart rate 88 bpm. STOP-BANG score 5 out of 8. A branch under review and two loan instalments.

In most outpatient departments this patient would leave with telmisartan 40 mg and advice to reduce salt. The blood pressure would come down. The doctor and the patient would both be satisfied. And the obstructive sleep apnoea driving nocturnal sympathetic surges, the insulin resistance building toward diabetes, the subthreshold exercise erosion that triggered the entire cascade — none of it would be identified, addressed or treated.

Who this book is for

This book is written for the physician who carries the whole decision alone. The medical officer at a rural health centre in Vidarbha, seeing sixty patients a day. The single-handed general practitioner in the Scottish Highlands, or on New Zealand's East Cape, whose nearest cardiologist is a ferry and a drive away. The district clinician in rural Limpopo or western Kenya. The family physician in a small town in Montana. The occupational health physician certifying workers at a factory. And the clinician in a large city who is not in a tertiary centre — a suburban practice, a workplace clinic, a polyclinic — for whom an echocardiogram still means a waiting list and a polysomnogram means referring the patient elsewhere.

It is not written *against* the specialist, and not only for those without resources. A consultant with every investigation available asks the same first question as a physician with none, and asks it before ordering anything. What changes with the resources is how much of the answer has to come from the history and the examination — which is what this book is about. Where the machines are two hours away that burden is heaviest; it is never the only place the question matters.

Because here is what the clinical science in these three volumes ultimately reduces to: the most important tool in managing a hypertensive patient is not an ABPM machine, not a plasma renin assay, not a polysomnography unit. It is a physician who asks the right question.

"Why does *this* person have high blood pressure?"

That question costs nothing. It requires only a trained mind and fifteen minutes of unhurried clinical attention. And it changes everything that follows.

What this book will change

Your first question	You will stop asking "what drug do I give for this BP level" and start asking "why does this person have high blood pressure." That shift changes every clinical decision that follows.
Your examination	You will measure BP in both arms. You will check the resting heart rate. You will measure the waist and neck circumference. You will listen for a renal bruit. You will check radio-femoral delay in every young hypertensive. None of this costs anything. All of it is diagnostic.
Your investigation strategy	You will understand that a fasting glucose, a urine albumin-creatinine ratio and an ECG together tell you more about cardiovascular risk than any more elaborate test. You will order investigations because a specific clinical question demands an answer.
Your drug selection	The guideline sets the pathway and you will follow it. What changes is your reasoning *within* it: when the guideline offers more than one appropriate next agent, you will know which one fits this patient and why. Phenotype never removes a drug the guideline indicates.
Your counselling	You will stop saying "reduce salt, lose weight, exercise" to every patient identically. You will tell *this* patient which of those matters most for *his* blood pressure, and why — the single change most likely to make a patient act.
Your definition of success	You will stop measuring success by the number on the cuff. You will measure it by whether the LDL is at target, the glucose controlled, the weight falling, the organ damage regressing — whether the patient is genuinely at lower risk of the event you are trying to prevent.
Your handover assessment	When a patient arrives from another physician with seven years of prescription slips, you will know exactly what to ask about what was and was not done — and you will complete the evaluation without diminishing your colleague.

This book and the guidelines

This book is written to sit alongside the current hypertension guidelines, not to compete with them. Where a recommendation is made, the guideline, trial or other evidence behind it is identified so you can go and check it. Guidelines are revised — the major ones have been revised while this book was being written — so **where anything here differs from the guideline you practise under, or from the current product information for a drug, the guideline and the product information take precedence, not this book.** Where this book differs from routine practice is not in *what* it recommends — but in *why*.

The gap is this. Every major guideline says "individualise drug selection based on patient characteristics and comorbidities." No guideline teaches the physician *how* to identify those characteristics in a practical clinical encounter. They assume the physician already knows how to phenotype a patient. Most do not — because no practical framework for doing so has existed at the bedside.

This book is one attempt to fill that gap. The phenotype approach is not an alternative to guideline-based medicine, and it is not a second system of hypertension care running beside the first. It is a way of thinking about the patient *underneath* guideline-directed treatment — a proposed framework, not a validated classification, and not a licence to depart from what the evidence establishes.

HOW TO USE THIS BOOK — TWO QUESTIONS, NOT ONE

Question 1 — how much does this patient's hypertension matter? Cardiovascular and renal risk, target-organ damage, comorbidities, the severity and duration of the pressure. This question decides urgency, treatment intensity and prognosis. It is answered the way the guidelines say it is answered, and nothing in this book modifies it.

Question 2 — why might this patient's blood pressure be high, or hard to control? History, examination and targeted investigation, assembled into a working phenotype. This question decides what you investigate, what you counsel, and what you address beyond the prescription.

The second question does not replace the first and never outranks it. A patient at high cardiovascular risk is treated as a patient at high cardiovascular risk, whatever his phenotype turns out to be. Phenotyping runs alongside treatment; it must never delay it — least of all in severe hypertension, established cardiovascular or kidney disease, diabetes, pregnancy, or a hypertensive emergency.

The honest commitment of this book

This book will not ask you to order investigations your patient cannot afford. It will not build a clinical framework that works only in a tertiary centre with a fully equipped hypertension clinic. Every framework in these three volumes is presented in three tiers: what *must* be done for every patient at every resource level, what *should* be done when a specific clinical question demands it, and what *can* be done when resources allow. The minimum tier is designed to generate a useful working phenotype in most patients without requiring advanced investigations. The expensive tier confirms what good clinical reasoning has already suggested.

The phenotype approach does not require more money. It requires more thinking. And thinking, as it happens, is available everywhere.

Dr Ravikiran Jadhav
MBBS · AFIH · Occupational Health Physician

OPENING CHAPTER

The question before the prescription

Two physicians. Two patients. The same chief complaint. Two different clinical trajectories — illustrating what may be missed when treatment addresses only the number.

In every outpatient department across India this scene plays out thousands of times each day. A patient arrives. The blood pressure is measured. The number is high. A drug is prescribed. The patient leaves.

This book begins with a question most clinical encounters never ask: **why is this person's blood pressure high?** Not what is the BP. Why is it elevated — in this person, on this day, given this history, this body, this occupation, this sleep, this life.

The two composite encounters below involve the same chief complaint, the same age, the same degree of obesity. One asks the question. One does not. Follow both from the first minute in the consultation room to the outcome five years later.

Encounter A — the protocol approach

Male. 38 years old. Obese. Walks into the OPD.

Chief complaint	Mild headache. BP checked by a colleague: 158/98 mmHg.
Time in consultation	`6 minutes`
Examination performed	BP confirmed 156/96 mmHg, right arm sitting. Weight: obese, noted.
Prescription written	Telmisartan 40 mg once daily. Reduce salt. Walk daily. Follow up in four weeks.
Four weeks later	BP 132/84 mmHg. Patient: "feeling better, doctor." Doctor: "very good, BP is controlled, continue the same medicine."
Six months on	BP remains 130–136/84–88 mmHg — above target on every current guideline, American or European. Doctor and patient are both satisfied. The prescription is renewed.

WHAT WAS NEVER ASKED

- ✗ Why did a 38-year-old with previously normal BP suddenly develop stage 2 hypertension?
- ✗ Are you sleeping well? Are you snoring? Has anyone seen you stop breathing at night?
- ✗ What changed in your life in the last six months?
- ✗ Is your morning BP consistently higher than your evening BP?
- ✗ Is your glucose rising?
- ✗ What is the resting heart rate? Not measured. Not recorded.

WHAT WAS NEVER EXAMINED

- ✗ Neck circumference — 41 cm, exceeding the 40 cm OSA threshold
- ✗ Waist circumference — 104 cm, central obesity confirmed
- ✗ BP in both arms — only one arm measured
- ✗ BP standing — no orthostatic assessment
- ✗ Resting heart rate — 88 bpm, a sympathetic marker, never documented
- ✗ Fundoscopy — grade 1 KWB changes already present
- ✗ Radio-femoral delay — coarctation never excluded

WHAT WAS NEVER INVESTIGATED

- ✗ HbA1c — a random glucose of 164 mg/dL at 1.5 hours after a meal is not a diagnostic test, but it is abnormal enough to demand one: fasting plasma glucose, HbA1c, or a 75 g oral glucose tolerance test
- ✗ Fasting lipid profile — metabolic syndrome, dyslipidaemia probable
- ✗ Urine albumin-creatinine ratio — early target organ damage never checked
- ✗ ECG — LVH? baseline documentation? never done
- ✗ Sleep assessment — a STOP-BANG score would have been 5 out of 8
- ✗ 24-hour ABPM — the non-dipping pattern from OSA never identified

WHAT TELMISARTAN DID

- ✓ Blocked angiotensin II at the AT_1 receptor
- ✓ Reduced systolic BP by 10–14 mmHg
- ✓ Addressed the RAAS component of the elevation
- ✓ Produced acceptable clinic readings

WHAT TELMISARTAN DID NOT DO

- ✗ Did not reduce the resting heart rate — 88 bpm, unchanged
- ✗ Did not treat obstructive sleep apnoea
- ✗ Did not address insulin resistance
- ✗ Did not reduce nocturnal sympathetic surges
- ✗ Did not restore the nocturnal dipping pattern
- ✗ Did not lower glucose or address metabolic syndrome
- ✗ Did not reduce cardiovascular risk beyond its BP effect

The same patient — five years later

ILLUSTRATIVE COMPOSITE — NOT AN OUTCOME STUDY. This trajectory is assembled from typical clinical patterns to show what a purely numerical approach can leave undetected. It is not a report of a followed-up patient, and no comparison of outcomes between approaches is claimed.

BP	Controlled. 130–136/84–86 mmHg on telmisartan. Always renewed.
HbA1c	7.8% — diabetes. Never detected. Never treated.
BMI	36. Weight gain continued unchecked.
OSA	Moderate to severe, AHI 28. Never diagnosed. Never treated.
LVMI on echo	Elevated — LVH present. Never assessed.
Urine ACR	68 mg/g — moderately increased albuminuria, KDIGO category A2. Never checked.
Standing at five years	**Diabetes, moderate-to-severe sleep apnoea, left ventricular hypertrophy and category A2 albuminuria — all present, none looked for.** Four of the five cardiovascular risk pillars remain unaddressed, and the total risk has never been quantified.

"His blood pressure was always controlled," his wife said. "He took his medicine every day without fail." Nobody had told them what else was accumulating.

The blood pressure was controlled. The disease was not.

Encounter B — the phenotype approach

Male. 38 years old. Bank branch manager. Height 176 cm. Weight 101 kg. BMI 32.6.

Chief complaint: mild headache. BP checked, 160/100 mmHg. "*It was always normal before.*"

That single phrase stops the physician. Essential hypertension does not behave this way. It rises over years, imperceptibly, incrementally. It does not jump from consistently normal to 160/100 mmHg in six weeks. A sudden escalation means something specific changed recently — and something specific that changed is identifiable.

The physician asks one question: "What changed in the last six months?"

History — twelve minutes of structured enquiry

FINDING	WHAT IT MEANS
Right knee pain, six months	Gave up the morning walk and now rides the last stretch to the branch; discomfort reduced but not resolved. Walking dropped from 5 km daily to 1.5 km — and has stayed there for six months. The patient considers himself still exercising. He is not wrong — but he is doing about a third of what he was doing, and it is the reduction, not the remainder, that is the finding.
1.5 km daily — what the reduction actually costs	1.5 km takes 15–18 minutes — about 110 minutes a week, against a WHO minimum of 150.[11] Do not overstate what that costs him. The dose–response curve for physical activity is steeply front-loaded, and there is no threshold below which activity stops counting: fifteen minutes a day already carries a 14% lower all-cause mortality (HR 0.86, 0.81–0.91), and activity below the guideline minimum retains most of the benefit of meeting it (HR 0.80 against sedentary, compared with 0.69 at one to two times the minimum). **What has fallen away is not the mortality benefit. It is the energy expenditure and the blood-pressure-specific effect, and both of those are dose-related.** Three and a half kilometres a day of walking stopped being spent; the weight has drifted up since; and at roughly 1 mmHg systolic per kilogram the drift alone will move a borderline pressure. Nobody documented the change. Nobody connected it to the rising BP.[2,8,10]
Snoring — mentioned by his wife in recent weeks	New or worsening snoring is the cardinal symptom of obstructive sleep apnoea. In an obese male who has gained weight over six months of reduced activity this is not incidental: even 2–3 kg of additional pharyngeal fat raises the apnoea-hypopnoea index by 30–40%. OSA that was subclinical at AHI 8–12 may now be moderate to severe at 20–28.
Daytime sleepiness at the desk — never before	An Epworth Sleepiness Scale is needed.[5] Daytime sleepiness in a man who previously worked twelve-hour days without difficulty suggests significant sleep disruption. The symptom appeared in the last two to three weeks, consistent with OSA crossing into moderate-severe territory.
Sleeps at 10 pm, wakes at 4–4:30 am, cannot return to sleep	Early morning awakening fits the OSA arousal pattern disrupting the final REM cycles. It is also consistent with a morning cortisol surge amplified by fragmented sleep — which explains the morning-dominant BP pattern.
Branch under review for eleven months; two colleagues redeployed. A home loan and a vehicle loan running	Job insecurity is the stressor; the fixed monthly obligations are what make it frightening, and what stop him leaving it at the branch. Sustained occupational stress of this kind raises central sympathetic outflow and keeps it raised (V1·Ch14, Ch25). **This is the silent background susceptibility that was present long before the knee injury.** It set the sympathetic set point higher than it should have been; adequate exercise was the compensatory mechanism holding it in check.
BP always below 130/90 — until the last one to two months	This is the critical timeline. Not six months of hypertension: six months of subclinical accumulation crossing the threshold in the final four to eight weeks. The grade 1 fundoscopy changes confirm the vascular process was running long before the BP crossed 140/90. Earlier readings were capturing a partially compensated state — not a truly normal one.
Random glucose 164 mg/dL at 1.5 hours post-lunch	Not diabetic yet. But not normal. Six months of subthreshold activity has measurably worsened insulin resistance — skeletal muscle glucose uptake begins declining within 72 hours of inactivity, and over six months the deficit accumulates. Fasting glucose, OGTT and HbA1c are urgent.

Examination — eight minutes

FINDING	VALUE	INTERPRETATION
Resting heart rate	88 bpm	Elevated. In a 38-year-old with sudden hypertension, sustained occupational stress and fragmented sleep, this points toward a sympathetic contribution — but a haemoglobin and a TSH come first, because anaemia and thyrotoxicosis produce the same finding. **Where the guideline permits a choice, a beta-blocker becomes worth weighing. It does not move ahead of the guideline's first-line options.**
BP right arm, sitting	158/98	Confirmed elevated.
BP left arm, sitting	154/96	Difference under 10 mmHg — normal. Right arm designated for all future measurements.
BP standing, 1 minute	152/102	No orthostatic hypotension; BP slightly higher on standing — the sympathetic response is preserved. This will matter when selecting the drug.
Neck circumference	41 cm	Exceeds the 40 cm threshold. STOP-BANG criterion positive. OSA probability now very high.
Waist circumference	104 cm	Significantly above the 90 cm South Asian threshold. Central obesity confirmed; metabolic syndrome criteria being met.[1]
STOP-BANG score	5 / 8	Snoring yes · tired or sleepy yes · observed apnoea unknown · BP elevated yes · BMI above 35 no · age above 50 no · neck above 40 cm yes · male yes. A score of 5 means **high probability of OSA — a sleep study is now mandatory.**[3,6]
Fundoscopy	Grade 1 KWB	Early arteriolar light reflex change.[7] This tells us the BP has not been as normal as clinic readings suggested: a subclinical process was already running before the acute escalation.
S4 gallop at apex	Present	Reduced LV compliance — early diastolic dysfunction. The heart has already been responding to pressure load. Echocardiography is now indicated.
Radio-femoral delay	Absent	Coarctation of the aorta excluded clinically.
Renal bruit	Not heard	Renovascular hypertension less likely. Not excluded, but deprioritised.

DOMINANT PHENOTYPE IDENTIFIED

Primary mechanism	OSA-driven acute sympathetic escalation, on a background of metabolic syndrome — obesity, insulin resistance, sedentary lifestyle and chronic circadian disruption from years of shift work.
Acute precipitant	Knee injury → exercise falls below threshold → OSA worsens → insulin resistance acutely worsens → the last protective buffer is removed.
Secondary mechanism	Insulin-ENaC mediated sodium retention supplies the volume component — which is why BP will not fully normalise on sympathetic treatment alone.
Damage already present	S4 gallop plus grade 1 fundoscopy. The subclinical process was running before the acute escalation. This patient was never as normal as his previous readings suggested.

The subclinical background susceptibility principle

PERIOD	WHAT WAS HAPPENING
Years 1–10 SILENT ACCUMULATION	Years of sustained work stress → persistent central sympathetic drive → the RVLM set point slowly rises. Weight gain to BMI 32.6 → adipose RAAS building, insulin resistance developing, perirenal fat increasing. OSA developing subclinically at AHI 8–12, below the symptomatic threshold. BP reading 125–130/82–86 mmHg — *looks* normal; is not normal for this physiology. Grade 1 fundoscopy changes already beginning.
Months 1–3 BELOW THRESHOLD	Knee pain → walking drops from 5 km to 1.5 km, below the WHO minimum from day one. Insulin resistance worsens within weeks. Weight begins increasing. OSA: AHI climbs from 10 to 18–20 as pharyngeal fat increases. BP 132–136/84–88 — still "acceptable", still documented as normal.
Months 3–5 ACCUMULATING	Weight gain of 3–4 kg probable. AHI now 22–28, moderate to severe. Nocturnal sympathetic surges rising in frequency and amplitude. The morning cortisol surge is amplified by disrupted sleep architecture. Daytime MSNA begins carrying over from the nocturnal surges. BP 136–140/86–90 — borderline, still not flagged. Random glucose beginning to edge above normal.
Month 6 THRESHOLD CROSSED	The cumulative threshold is crossed. Morning BP 155–160/98–100 mmHg; evening BP 140–145/88–92. Snoring now audible to his spouse. Daytime sleepiness affecting work. Random glucose 164 mg/dL. **What appears to be sudden-onset hypertension is the threshold-crossing of a process that took years to build.**

When a patient presents with apparent sudden-onset hypertension, the question is never "what caused this?" It is "what subclinical process was being compensated — and what removed the compensation?"

The hypertension did not develop in six months. It was revealed in six months.

Investigation strategy: three tiers

The investigation plan follows the phenotype — it does not precede it. By the time history and examination are complete the dominant mechanism is already identified. Investigations confirm what clinical reasoning has established. Each tier is triggered by a specific clinical question — never by what the patient can pay.

TIER	WHEN	CONTENT
Tier 1	Every patient. Every setting. Every resource level.	Fasting glucose and HbA1c · fasting lipid profile · serum creatinine and eGFR · urine ACR · serum K^+ · ECG · urine routine · TSH Tier 1 alone is usually enough to form a working phenotype. OSA probability is established by history and STOP-BANG; metabolic syndrome identified; baseline renal function and organ-damage markers documented. **Drug choice is already guided.**
Tier 2	When a Tier 1 finding raises a specific management question.	STOP-BANG ≥ 3 → 24-hour ABPM to confirm non-dipping and morning surge · S4 gallop or ECG LVH → echocardiography to confirm LVH and diastolic dysfunction · HbA1c 5.7–6.4% → OGTT to confirm impaired glucose tolerance · K^+ below 3.5 without a diuretic → ARR screen
Tier 3	Specialist referral, when Tier 2 requires confirmation before a major decision.	ABPM confirms non-dipping with STOP-BANG 5 → sleep physician for polysomnography · ARR positive → endocrinology for salt loading and adrenal vein sampling · significant LVH on echo → cardiology

Treatment: the guideline decides, the phenotype informs

The guideline decides what is prescribed and in what order. That does not change here, and nothing in this book asks you to withhold or substitute a drug the guideline indicates. What the phenotype changes is everything around the prescription: which reversible contributors are worth attacking first, what you tell the patient about *his* blood pressure, and — when the guideline offers more than one acceptable next agent — which of those permitted options fits this patient.

PRIORITY	INTERVENTION	MECHANISM ADDRESSED	EXPECTED BENEFIT
1	**Drug therapy: as the guideline directs** STARTS NOW — PHENOTYPE INFORMS THE CHOICE, NEVER THE OMISSION OR THE TIMING	Start and escalate on the guideline pathway. The phenotype — sympathetic and neurogenic features, resting HR 88, OSA-driven drive — is a reason to *consider* a beta-blocker among the guideline-permitted options at the point the guideline calls for an added agent	It is not a reason to withhold or replace a first-line agent, and not a reason to delay treatment. If the added agent does not deliver the response, the phenotype does not get to be right: reassess and continue down the evidence-based pathway
2	**CPAP trial for OSA** AT THE SAME VISIT AS THE PRESCRIPTION, NOT BEFORE IT	OSA-driven nocturnal sympathetic surges	3–8 mmHg systolic reduction · restoration of the dipping pattern · MSNA reduction[9]
3	**Restore exercise** UPPER BODY OR SEATED CYCLING, AVOIDING KNEE LOADING	Insulin resistance · sympathetic upregulation · weight trajectory	4–8 mmHg systolic · glucose improvement · about 1 mmHg systolic per kg lost[4]
4	**Resolve the glucose story** OGTT, HBA1C	Insulin resistance and ENaC-mediated Na^+ retention	If impaired glucose tolerance: metformin. If diabetes: an SGLT2 inhibitor — glucose, BP, weight and renal benefit together
5	**Full cardiovascular risk reduction** NOT JUST BP	LDL, glucose, weight, OSA, smoking, organ damage	All five pillars addressed: BP, lipids, glucose, weight and organ damage

WHAT THE PHENOTYPE ACTUALLY BUYS YOU HERE

Not a different prescription. A different conversation. The dominant mechanism appears to be sympathetic overactivation driven by untreated OSA, with an obesity and volume component; the telmisartan is doing real work on one contributor while the largest one goes unaddressed. That is not an argument for stopping it. It is an argument for the CPAP referral, for the glucose workup, and for telling this patient that his sleep and his weight — not his tablet — are where his blood pressure is actually being generated. **The resting heart rate of 88 is a risk marker worth acting on; whether that action is a beta-blocker is a question for the guideline and the patient's other indications, not for the phenotype alone.**

READ THIS BEFORE APPLYING ANYTHING ABOVE — A PHENOTYPE IS NOT A PRESCRIPTION

A working phenotype is a clinical hypothesis about mechanism. It is not a diagnosis, not a validated classification, and not a treatment indication. Nothing in this book has been tested as a diagnostic system: the framework proposed here has never been validated against outcomes, and no part of it should be used as one.

Where the guideline and the phenotype conflict, the guideline wins.

Do not start, stop, substitute or withhold an antihypertensive because a patient appears to fit a phenotype. Drug decisions follow the current guideline, the patient's established indications and contraindications, cardiovascular and renal risk, target-organ damage, comorbidity, pregnancy status and the product information — all of that before any phenotype is consulted.

Where the guideline leaves a legitimate choice between agents, the phenotype may reasonably inform which one is considered. Where the guideline does not leave a choice, the phenotype has no vote.

And if the treatment chosen does not produce the response expected, the phenotype has not been proved right by conviction. Reassess, and continue down the evidence-based pathway.

The difference

	ENCOUNTER A — PROTOCOL	ENCOUNTER B — PHENOTYPE-INFORMED
Time	`6 minutes`	`20 minutes — 12 history, 8 examination`
BP measured	One arm, sitting only	Both arms, three positions
Resting HR	Not recorded	88 bpm — documented, interpreted, acted upon
Drug therapy	Telmisartan, chosen off a list without a reason being formed	The same guideline pathway, chosen for stated reasons — with the contributors that were driving the pressure identified and addressed alongside it
Investigations	None ordered	Tier 1 ordered in full
OSA	Never identified	Identified by history and STOP-BANG 5; ABPM ordered, sleep study referred
Glucose	Never evaluated	Glucose story resolved — OGTT and HbA1c urgent
CV risk pillars addressed	`1 of 5 — BP only`	`5 of 5 — BP, lipids, glucose, weight, OSA`
Standing at five years	Four risk factors never looked for. Total risk never quantified	OSA treated, glucose managed, weight falling. Total risk quantified and reassessed

THE CENTRAL PRINCIPLE OF THIS BOOK

The clinical phenotype is identified through thinking — not through investigations.

Investigations confirm what good clinical reasoning already suspects. A physician who asks the right questions and performs a complete examination will identify the dominant mechanism with the Tier 1 panel and twenty minutes. A physician who orders fifteen investigations without asking why the blood pressure went up suddenly will still prescribe telmisartan empirically. **The phenotype is in the history. The investigations only confirm it.**

The five questions every physician must answer

These five questions form the spine of this book. They are not chapter headings — they are a clinical philosophy. Every case in these three volumes is filtered through them. They govern what you look for, what you investigate and what you explain. They do not govern what you may prescribe — that comes from the current guideline and this patient's own indications.

01 Why does this person have high blood pressure?

Not what is the BP number. Why is it elevated — in this person, on this day, given this history, this body, this occupation, this sleep, this life. The mechanism — neurogenic, volume-driven, RAAS-driven, endothelial, secondary or mixed — shapes what you investigate, what you explain to the patient and what you address alongside the prescription. It does not decide the prescription.

Without it: the mechanism runs unchallenged. The drug may control the number while the disease progresses silently.

02 What does this patient need — beyond a prescription?

Which examination findings are still pending? Which investigations are indicated by the clinical findings? Which specialist opinion will change management? What lifestyle intervention addresses the dominant mechanism directly? What does this patient need to understand about their own disease?

Without it: the patient receives a drug and advice to reduce salt. The OSA goes undiagnosed, the dyslipidaemia is never found, the early albuminuria is never detected.

03 Have I missed anything?

The examination finding I did not look for. The investigation I did not order because the phenotype had not yet directed me to it. The drug interaction I did not identify. The specialist who should have been consulted. This question is asked at *every* visit — not just the first.

Without it: a renal bruit goes unheard. A coarctation is never excluded. An ARR is never checked in a resistant hypertensive. A phaeochromocytoma is called a panic attack twice.

04 Should I start treatment — and if so, which one?

Start immediately, or a lifestyle trial first? The decision is risk-stratified, not uniform. The threshold, the target and the first-line class come from the current guideline and from this patient's compelling indications and contraindications. Where the guideline leaves a legitimate choice between agents, the comorbidities and the dominant mechanism can inform which of the permitted options fits. Where it leaves no choice, they do not.

Without it: every patient with grade 1 hypertension receives amlodipine and nothing further is asked — the OSA is never looked for, the primary aldosteronism that carries its own guideline-directed treatment is never diagnosed, and the patient whose pressure would have fallen on CPAP is medicated instead of investigated.

05 Am I reducing cardiovascular risk — or just controlling blood pressure?

Blood pressure is one of five pillars: BP, LDL cholesterol, glucose control, body weight and smoking. A patient with a BP of 128/78 mmHg, an LDL of 160 mg/dL, an HbA1c of 8.2%, a BMI of 34 and active smoking has excellent BP control and catastrophic cardiovascular risk management. The number on the cuff is not the outcome. The cardiovascular event is the outcome.

Without it: the blood pressure is controlled, the disease is not, and the patient has a myocardial infarction at fifty-two. The family shows seven years of prescription slips. This is the sentence that ends too many clinical stories.

Meet the six patients

Throughout these three volumes six patients will accompany you. They are introduced here as clinical encounters — the questions posed but not yet answered. The mechanisms are explained across Volume 1, the drug choices justified in Volume 2, and the complete management plans, with outcomes, presented in Volume 3.

Each is a composite built to represent a dominant phenotype, and none is a clean textbook case: each carries comorbidities, complications and decision points spanning multiple chapters. That is intentional. Real patients do not have single mechanisms.

CASE 1 NEUROGENIC · SNS-DRIVEN

Mr Arjun S.

27-year-old software engineer, Bengaluru · lean, BMI 22 · resting HR 96 bpm · stage 2 hypertension

The clue nobody noticed: BP 158/98 in a lean young non-smoker with no risk factors. Morning BP significantly higher than evening. Resting HR 96 bpm. ABPM shows very high variability. Low-sodium diet, exercises regularly, no secondary cause on standard workup. The phenotype is in the resting heart rate — and in what drives it.

CASE 2 OBESITY + OSA + SNS OVERACTIVITY

A 38-year-old bank branch manager

Male · BMI 32.6 · six months of subthreshold exercise · STOP-BANG 5

The clue nobody noticed: knee pain for six months reduced walking from 5 km to 1.5 km daily — below the therapeutic threshold every single day, for six months. Not cessation. Erosion. Snoring. Daytime sleepiness. Morning-dominant BP. Resting HR 88. Random glucose rising. The phenotype is in the question nobody asked: "what changed six months ago?"

CASE 3 ISOLATED SYSTOLIC · AORTIC STIFFNESS

Mrs Kavita K.

68-year-old retired teacher, Pune · ISH · BP 172/88 · wide pulse pressure · low renin

The clue nobody noticed: isolated systolic hypertension with a pulse pressure of 84 mmHg. Low renin. Non-dipper on ABPM. Three drugs tried — diastolic pressure drops dangerously whenever systolic is controlled. The J-curve is real in this patient. The phenotype is in the aorta, not the arterioles.

CASE 4 SODIUM RETENTION · VOLUME-DEPENDENT

Mr Suresh P.

55-year-old businessman, Ahmedabad · high dietary Na^+ · 24-hour urine Na 318 mEq · non-dipper

The clue nobody noticed: BP 164/96 on two drugs, never controlled. Papad, pickles and restaurant food daily. 24-hour urine sodium 318 mEq — double the recommended intake. Low plasma renin, normal aldosterone, non-dipper on ABPM. The phenotype is in the urine sodium report that was never ordered.

CASE 5 RAAS ACTIVATION · PRIMARY ALDOSTERONISM

Mr Dilip D.

52-year-old teacher, Mumbai · resistant hypertension · K^+ 3.6 · nocturia · low PRA

The clue nobody noticed: resistant hypertension on three drugs for six years. Serum K^+ 3.6 mEq/L — reported as "normal" every time. Nocturia twice nightly. Fatigue. ARR never checked. The phenotype is in the potassium that is "normal" but should not be, in a patient on three antihypertensives.

CASE 6 ENDOTHELIAL DYSFUNCTION

Dr Priya M.

44-year-old physician, Delhi · no identifiable mechanism · hsCRP 4.2 · ACR 42

The clue nobody noticed: non-smoker, non-diabetic, BMI 24, vegetarian, low-sodium diet, walks 45 minutes daily. BP 148/94 on ABPM. Normal PRA, normal aldosterone, normal 24-hour urine sodium. No OSA. No secondary cause. Standard workup unremarkable. hsCRP 4.2 mg/L, urine ACR 42 mg/g, carotid IMT 0.9 mm. The phenotype is in what the routine tests cannot find.

By the time you finish Volume 3 you will know exactly what is driving each of these patients' blood pressure, why each needed a different drug, and what happened to each over five years of phenotype-directed management. More importantly, you will bring that same thinking to every hypertensive patient who walks into your consultation room. **That is what this book is for.**

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ASSESSMENT VOLUME ONE · BEFORE PART I

Assessing the patient: reading the phenotype

This book claims the phenotype is in the history. This chapter is the history — and the examination, and the handful of tests, read not as a risk score but as evidence about mechanism.

BEFORE YOU READ THIS CHAPTER

The phenotype framework set out here is a proposed way of thinking, not a validated classification. Nothing in this book has been tested as a diagnostic system. **Where the guideline and the phenotype conflict, the guideline wins.**

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Measuring the pressure** before interpreting it — because most of what looks like hypertension is technique.
2. **The history that reveals mechanism**, organised by what each answer would mean.
3. **The examination** — the findings that carry weight, and the three that cost minutes and are almost never done.
4. **Target-organ damage as evidence, not only as prognosis** — the thresholds, and how poor some of the tests actually are.
5. **What a finding does and does not tell you about mechanism**, including where this book's own claim does not hold.
6. **Risk scores** — what they are for, and why a European score misleads in an Indian clinic.

A.1 Why this chapter comes before the mechanisms

The opening of this book states that the clinical phenotype is identified through thinking rather than through investigations — that the phenotype is in the history, and the investigations only confirm it. That is a strong claim, and until this chapter existed the book did not honour it: it asserted that the answer was in the history without ever setting out the history.

So this chapter comes before Part I. Everything that follows explains a mechanism; this explains how you find out which mechanism you are looking at. It is deliberately not a chapter about how to run a clinic — that belongs to Volume 3. It asks a different question of the same findings: not *how do I examine this patient*, but *what does this finding mean*.

A.2 Measure it properly, or interpret nothing

Every number in this book assumes a correctly measured pressure, and most clinic readings are not. The errors are systematic and they are large enough to move a patient across a treatment threshold: a cuff that is too small over-reads, an unsupported arm or an arm held below heart level over-reads, an

unsupported back and dangling feet over-read, a full bladder over-reads, and talking during the measurement over-reads.[26] This book does not give millimetre figures for each of these, because the sources that would fix them precisely could not be reached — but the direction of every one of them is the same, and they add.

Two consequences follow. First, a reading taken badly is not a smaller version of the truth; it is biased in one direction, and the bias compounds. Second, the targets in this book — and the target in Chapter 31 in particular — were derived from trials using standardised or unattended automated measurement, and applying them to a hurried manual reading over-treats. Chapter 8 sets out the size of that gap.

Two measurements are almost never taken and both change management. **Both arms**, at the first visit: a persistent difference points at subclavian disease, coarctation or Takayasu arteritis, and the higher arm is the one to use thereafter.[22] And **standing pressure**, at one and three minutes, in every patient over 65 and every patient with diabetes: orthostatic hypotension changes the target, changes the drug, and predicts falls.[4]

The distinction this chapter rests on

Target-organ damage is usually taught as prognosis — how much damage has been done, and therefore how urgently to treat. It is also evidence. Albuminuria, the pattern of ventricular hypertrophy, the pulse pressure and the nocturnal profile each say something about *which* mechanism is dominant. That is why this material sits in Volume 1 and not with the treatment decisions.

A.3 The history, organised by what the answer would mean

TABLE A.1 — WHAT TO ASK, AND WHAT A YES WOULD TELL YOU

ASK ABOUT	A POSITIVE ANSWER POINTS AT	READ ON
Age at which the pressure was first high	Before 30 or after 55 raises the probability of a secondary cause sharply — around a third of confirmed hypertensives aged 18 to 40 in referred series, about 2% in unselected populations (Ch 8, Ch 16). Young onset lowers the threshold to look; it does not by itself make a secondary cause likely in a first-contact clinic	Ch 8, 16, 26, 37
How it began — gradual or abrupt	Abrupt onset, or a stable hypertensive who accelerates, suggests renovascular disease or phaeochromocytoma	Ch 32, 34
Salt in the diet, and who cooks	A volume-dependent, salt-sensitive phenotype — and the single intervention most likely to work	Ch 12, 22
Snoring, witnessed apnoea, daytime sleepiness	Obstructive sleep apnoea, which is present in a large share of resistant hypertension and of non-dippers[13]	Ch 24
Sleep pattern, shift work, night duty	A disturbed circadian profile, and a reason for the pressure not to dip	Ch 7, 25
Every drug, supplement and remedy — asked as a list, not as a question	Drug-induced hypertension, the commonest reversible cause in a general clinic. Patients do not classify NSAIDs, decongestants, oral contraceptives, steroids or herbal preparations as medicines	Ch 27–30
Paroxysms — headache with palpitations and sweating together	Phaeochromocytoma. The combination carries a positive likelihood ratio of 6.3; any one alone carries almost nothing	Ch 34
Muscle weakness, cramps, polyuria	Hypokalaemia, and therefore aldosterone excess	Ch 33
Childhood urinary infections; family history of kidney disease or dialysis	Reflux nephropathy or polycystic disease — both of which present as hypertension decades later	Ch 31
Pregnancies, and whether any was complicated by hypertension or proteinuria	A history of pre-eclampsia carries a relative risk of 3.70 for later chronic hypertension	Ch 18
Occupation, job strain, noise, lead or cadmium exposure	An occupational contribution, which nobody else in the patient's care will ask about	Ch 25

ASK ABOUT	A POSITIVE ANSWER POINTS AT	READ ON
Alcohol, quantified honestly; tobacco including smokeless	Both raise pressure; smokeless tobacco matters particularly in South Asia	Ch 23

A.4 The examination

The examination in hypertension has a poor reputation, largely deserved, because most of what is taught has never had its diagnostic performance measured. This book will not quote sensitivities that do not exist — the abdominal bruit is the clearest example, discussed in Chapter 32. What follows is what is worth doing and why, with the honest note that the evidence base for most physical signs here is weak.

TABLE A.2 — THE EXAMINATION, AND WHAT EACH PART IS FOR

LOOK FOR	BECAUSE
Both arms, and all four limbs	The only way to find a coarctation or a Takayasu arteritis. Radio-femoral delay is felt only if the two pulses are palpated *together*. An upper-to-lower gradient above 20 mmHg is the threshold that matters
Standing pressure at one and three minutes	Orthostatic hypotension — and, in an untreated patient with hypertension and orthostatic symptoms, a pointer to phaeochromocytoma
Body habitus and waist	Obesity-related hypertension, and the Asian cut-offs that differ from the European ones
Cushingoid features — bruising, proximal weakness, violaceous striae, facial plethora	These discriminate. Central obesity, hypertension and diabetes do not
Thyroid	Both directions raise the pressure, and they raise different numbers
Abdomen — bruits, palpable kidneys	Renovascular disease and polycystic kidneys
Fundi	Grades 3 and 4 change the tempo of management entirely. Grades 1 and 2 do not, and cannot be reliably distinguished even by experienced observers
Apex beat, heart sounds	Ventricular hypertrophy and the aortic valve, which is bicuspid in a large share of coarctation

A.5 Target-organ damage: the thresholds, and how good the tests are

European guidance now speaks of hypertension-mediated organ damage rather than target-organ damage, and the change of word is a change of meaning: it names the damage as caused by the pressure rather than merely coexisting with it.[3] What follows are the measurements, with their thresholds and — where it is known — how well they perform. Several perform badly, and a book that quotes the threshold without the performance misleads.

TABLE A.3 — ORGAN DAMAGE: THRESHOLD, PERFORMANCE, AND PROGNOSTIC WEIGHT

MEASURE	THRESHOLD	HOW GOOD IS THE TEST, AND WHAT IT IS WORTH
ECG left ventricular hypertrophy	Sokolow–Lyon SV1+RV5/6 ≥ 35 mm; Cornell voltage RaVL+SV3 > 28 mm in men, > 20 mm in women; Cornell product > 2440 mm·ms[17]	**Insensitive, and the published figures disagree.** Sokolow–Lyon: 22% sensitivity at near-100% specificity in one series, 27% and 78% in another. Cornell voltage: 42% and 96% against 32% and 52%. Cornell product reaches 36–51% sensitivity at matched 95% specificity.[18] A normal ECG does not exclude hypertrophy; an abnormal one is worth acting on
Echocardiographic LV mass index	> 95 g/m² in women, > 115 g/m² in men[5]	The reference standard.[7] In Framingham, each 50 g/m increment of height-indexed mass carried a relative risk of cardiovascular death of 1.73 in men and 2.12 in women, and of all-cause mortality 1.49 and 2.01[27]
Urine albumin–creatinine ratio	A1 below 30, A2 30–300, A3 above 300 mg/g[16]	Cheap, reproducible, and prognostic for cardiovascular outcomes as well as renal ones. The most informative single test in this table
Carotid–femoral pulse wave velocity	Above 10 m/s[19]	Per 1 m/s increment, hazard ratio 1.17 for all-cause and 1.32 for cardiovascular mortality. Available in few clinics; where it is available it is the direct measure of the stiffness of Chapter 1
Ankle–brachial index	Normal 0.9 to 1.4; below 0.9 abnormal	Below 0.9 carries a hazard ratio of 1.7 for stroke recurrence and 2.22 for vascular events or death.[25] Requires a Doppler and ten minutes
Retinopathy	Keith–Wagener–Barker grades, or the simplified Wong–Mitchell scheme[11]	Grades 1 and 2 are not reliably distinguishable between observers and should not drive decisions. Grades 3 and 4 are a different matter: in the historical series, three-year survival was 70% with grade 1 and 6% with grade 4[10]

A.6 Reading a finding as a mechanism — and the limits of doing so

This is the chapter's distinctive claim and it must be stated carefully, because the evidence supports it in places and contradicts it in others.

TABLE A.4 — WHAT A FINDING SUGGESTS ABOUT THE DOMINANT MECHANISM

FINDING	SUGGESTS	HOW STRONG IS THIS?
Albuminuria, non-dipping, salt-sensitive history	A volume-dependent, renal phenotype	**Supported.** The association of salt sensitivity with a non-dipping profile and with renal sodium handling is well described[20]
Concentric LV hypertrophy	Chronic pressure loading[6]	**Supported.** Concentric remodelling reflects pressure overload; eccentric reflects volume overload[6]
Wide pulse pressure, raised PWV, isolated systolic hypertension	Arterial stiffness — the Windkessel failure of Chapter 1[21]	**Supported**, and PWV measures it directly
Non-dipping or reverse dipping	Renal or volume phenotype — or obstructive sleep apnoea, which is present in 48 to 84% of non-dippers in the series examined	**Supported but not specific.** It narrows the field to two; it does not choose between them
Resting tachycardia, high pressure variability	A sympathetic phenotype	**Weak.** An ESH review states that the relationship between resting heart rate and sympathetic drive is *absent* in essential hypertension.[8] Heart rate is a poor surrogate for what it is commonly used to indicate. Read it as a risk marker and as a prompt to look for a driver — not as a measurement of one, and not before anaemia and thyroid disease are excluded[23]

A.7 Risk scores, and why the European ones mislead here

A risk score answers a different question from this chapter. It estimates the probability of an event in order to decide *whether and how hard to treat*. Organ damage assessment asks *what is happening and why*. Both matter; they are not substitutes, and the treatment decision belongs to Volume 3.

Where the scores go wrong for this book's readership is calibration. SCORE2 was derived and calibrated on European cohorts — 45 cohorts across 13 countries — and it underestimates risk even within a Dutch validation, with an observed-to-expected ratio of 1.63.[9,24] Applied to South Asian populations the problem is larger: older Framingham-based work substantially underestimated risk in Indian cohorts, and UK guidance historically applied a multiplier of 1.4 for South Asian men to compensate.[1] A recalibrated Asia-Pacific version of SCORE2 exists, which is itself the acknowledgement that the original needed recalibrating.[2]

The honest limit

No single finding identifies a mechanism. One review states directly that assessing organ damage by blood pressure or pulse wave velocity alone is not comprehensive.[12] The phenotype emerges from a pattern — history, examination and two or three measurements agreeing — and where they disagree, the correct conclusion is that the phenotype is mixed, which most are.

What India's own guidance says

The ICMR standard treatment workflow recommends **no specific risk score at all** — not SCORE2, not the WHO charts, not Framingham, and no India-specific tool. That is worth knowing before importing a European number into an Indian consultation and treating it as data.[14,15]

A.8 The sequence, before any prescription

A blood pressure of 168/102 is a reading, not a decision. Ten questions stand between it and a prescription, and they have an order. The order matters: what is urgent comes before what is interesting, and risk is established before mechanism, so that the phenotype informs the conversation rather than displacing the guideline.

TABLE A.5 — TEN QUESTIONS, IN ORDER, BEFORE PRESCRIBING

	QUESTION	WHERE
1	Is the measurement valid — cuff, posture, both arms, repeated?	A.2, Ch 8
2	Is this acute or chronic — and how fast is it moving?	Ch 8
3	Is there target-organ damage?	A.5
4	Is this an emergency or an urgency?	Ch 1, Ch 8
5	What is the total cardiovascular and renal risk?	A.7, Vol 3
6	What phenotype do the findings suggest?	A.6
7	Is a secondary cause plausible?	Ch 26, Part VI
8	Which investigations would actually change management?	A.3–A.5
9	What treatment should start now — by guideline, by indication, and only then informed by phenotype?	Vol 2, Vol 3
10	When do I review, and what will I measure then?	Vol 3

Questions 5 and 6 are in that order deliberately. The phenotype shapes what you investigate, what you address alongside the drug, and what you explain to the patient. It does not decide the prescription, and it never precedes the assessment of risk.

KEY POINTS

1. **Most clinic readings are biased in one direction** — cuff, posture, support, bladder, talking — and the errors add. A badly taken reading is not a rougher truth.
2. **Both arms once, and standing pressure in the elderly and the diabetic.** Neither is usually done; both change management.
3. **The drug history must be taken as a list, not as a question.** Patients do not classify NSAIDs, decongestants, contraceptives or herbal remedies as medicines.
4. **ECG criteria for hypertrophy are insensitive and the published figures disagree** — Sokolow–Lyon sensitivity 22 to 27%. A normal ECG excludes nothing; echocardiographic LV mass index is the standard.
5. **The albumin–creatinine ratio is the most informative single test in the panel**, prognostic for cardiovascular as well as renal outcomes.
6. **Retinopathy grades 1 and 2 cannot be reliably distinguished** and should not drive decisions; grades 3 and 4 change everything.
7. **No single finding identifies a mechanism** — and resting heart rate in particular is a poor surrogate for sympathetic drive. The phenotype is a pattern, and most patients are mixed.
8. **SCORE2 is calibrated for Europe and underestimates risk in South Asians**; India's own ICMR workflow recommends no risk score at all.

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VOLUME ONE · PART I

Foundations of blood pressure

The ten mechanisms that generate every blood pressure reading — and the clinical reasoning each one licenses.

Hypertension: A Phenotype-Based Approach

Volume 1 · Why Is This Patient Hypertensive?

Dr Ravikiran Jadhav
MBBS · AFIH · Occupational Health Physician

10 chapters
Part I of five

CHAPTER 1 PART I · MECHANISM

Blood pressure physics and haemodynamics

The fundamental equation, wall tension, flow dynamics, and the clinical meaning of every BP number.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **MAP = CO × SVR** — the single equation governing every BP reading and every antihypertensive drug.
2. **Poiseuille's Law** and the fourth-power rule — why arterioles dominate vascular resistance.
3. **Systolic, diastolic, pulse pressure and MAP** — what each component tells you clinically.
4. **Laplace's Law** — wall tension, arteriolar rupture, and the haemodynamics of hypertensive emergencies.
5. **Compliance, pulse wave velocity and wave reflection** — the mechanism of isolated systolic hypertension.
6. **Autoregulation** — the rightward shift in chronic hypertension, and why rapid BP reduction causes ischaemia.
7. **Haemodynamic heterogeneity** — why the same cuff reading can reflect completely different physiology.

1.1 The fundamental haemodynamic equation

Every blood pressure reading reflects a single haemodynamic relationship, formalised by analogy with Ohm's Law of electrical circuits. In an electrical system, voltage equals current multiplied by resistance. In the cardiovascular system, pressure equals flow multiplied by resistance.[13]

Ohm's Law

Voltage = current × resistance. The cardiovascular system is the same circuit, with pressure, flow and vascular tone.

EQUATION 1.1 THE CORE HAEMODYNAMIC EQUATION

$$\mathbf{MAP = CO \times SVR} \qquad CO = SV \times HR$$

$$MAP = DBP + \frac{PP}{3} = \frac{SBP + 2 \cdot DBP}{3}$$

MAP mean arterial pressure · **CO** cardiac output · **SVR** systemic vascular resistance · **SV** stroke volume · **HR** heart rate · **PP** pulse pressure

Blood pressure can be elevated only because cardiac output is high, systemic vascular resistance is high, or both. There is no third mechanism.

NORMAL RESTING VALUES

Mean arterial pressure	70–99	mmHg
Cardiac output	4–6	L/min
Systemic vascular resistance	900–1,200	dyn·s·cm^{-5}

Every antihypertensive drug in every pharmacological class acts by reducing CO, SVR, or both. Beta-blockers reduce heart rate and renin secretion, lowering CO. Diuretics reduce circulating volume, reducing stroke volume and therefore CO. Calcium channel blockers relax arteriolar smooth muscle, reducing SVR. ACE inhibitors and ARBs block angiotensin II, the primary humoral vasoconstrictor, reducing SVR and aldosterone-mediated volume retention. No antihypertensive drug operates outside this framework.

Selecting the appropriate class therefore requires identifying which variable is primarily responsible for the elevated pressure in the individual patient. A patient whose BP is driven by high cardiac output — neurogenic sympathetic overactivation, high resting heart rate — is one in whom a drug acting on that term can be expected to work well; a patient whose BP is driven by high SVR from structural arteriolar remodelling and RAAS activation, one in whom an agent addressing those mechanisms will. But the class is chosen by the guideline and by the patient's compelling indications first, and mechanism decides only among the options those leave open. Where the guideline and the phenotype conflict, the guideline wins.

The entire clinical methodology of this book is constructed around identifying the dominant mechanism from the history, examination and investigations, then directing pharmacotherapy accordingly — inside the guideline, never over it.

Every drug, one framework

No antihypertensive acts outside CO and SVR. If you cannot say which one your drug is lowering, you have not chosen it — you have inherited it.

The method

History, examination and investigation identify the dominant mechanism. Pharmacotherapy follows from it, within what the guideline permits. That sequence is the whole book.

1.2 Mean arterial pressure

Mean arterial pressure is the time-averaged pressure throughout the complete cardiac cycle. It is not the arithmetic mean of SBP and DBP, because at resting heart rates of 60–75 bpm the heart spends approximately two-thirds of each cycle in diastole. The standard approximation MAP = DBP + PP/3 is accurate across the normal resting range and becomes less reliable above 100 bpm, as the diastolic fraction shortens.

MAP is the most physiologically meaningful single pressure value because it represents the true driving pressure for organ perfusion. In intensive care it is the primary haemodynamic target: a MAP below 65 mmHg indicates critical hypoperfusion regardless of the individual systolic and diastolic values. In hypertensive emergencies the therapeutic goal is defined as a percentage reduction in MAP rather than a fixed systolic target, because MAP reflects the true reduction in perfusion-pressure stress on the end-organ circulation.

2/3

of each cardiac cycle is spent in diastole at rest, which is why MAP is not the arithmetic mean of SBP and DBP.

MAP < 65 mmHg

Critical hypoperfusion, whatever the systolic and diastolic values are doing.

TABLE 1.1 — THE FOUR PRESSURE COMPONENTS

COMPONENT	DEFINITION	PRIMARY DETERMINANT	CLINICAL SIGNIFICANCE
Systolic BP	Peak pressure during ventricular ejection	Stroke volume, aortic stiffness, wave reflection	Strongest predictor of stroke and LVH. Elevated disproportionately in the elderly from aortic stiffening. Primary treatment target in all guidelines.
Diastolic BP	Minimum pressure during ventricular filling	SVR and arterial compliance (elastic recoil)	Strongest coronary risk predictor under age 55. Falls in the elderly as the aorta stiffens. Below 60–65 mmHg: J-curve for coronary ischaemia.
Pulse pressure	SBP minus DBP; amplitude of the BP waveform	Stroke volume divided by arterial compliance	PP > 60 mmHg is an independent CV risk marker. Rising PP with stable or falling DBP signals progressive aortic stiffness.[8]
Mean arterial pressure	Time-averaged pressure; organ perfusion driving force	CO × SVR	Target for emergency BP reduction. Best index of cardiovascular load. Used to calculate organ-specific perfusion pressures.

1.3 Cardiac output and its determinants

Cardiac output is the volume ejected by the left ventricle per minute: typically 4–6 L/min at rest, rising to 20–25 L/min during maximal exercise in trained athletes. In hypertension, elevated CO is the dominant mechanism in specific contexts — young adults with neurogenic sympathetic overactivation, hypervolaemia from renal sodium retention, thyrotoxicosis, phaeochromocytoma and anaemia.

High-CO states

Neurogenic overactivation · hypervolaemia · thyrotoxicosis · phaeochromocytoma · anaemia

Identifying a high-CO state changes the drug choice fundamentally, because pure vasodilators are partially counteracted by the baroreceptor-mediated reflex tachycardia they provoke, and because the appropriate target is the mechanism generating the excess output rather than the resistance downstream of it. Stroke volume is determined by three classical variables:

1. **Preload** — the end-diastolic ventricular volume.
   RAISED BY volume expansion: renal sodium retention · hyperaldosteronism · excessive dietary sodium · renal failure.
2. **Afterload** — the resistance the left ventricle overcomes during ejection, principally systemic vascular resistance.
   RAISED BY arteriolar vasoconstriction · structural remodelling.
3. **Contractility** — the intrinsic myocardial force-generating capacity, independent of loading conditions.
   RAISED BY catecholamine excess: phaeochromocytoma · cocaine use · severe psychosocial stress.

The haemodynamic profile of early essential hypertension in young adults is characteristically high-CO with initially normal or low SVR. Sympathetic overactivation drives elevated heart rate and contractility, raising CO and MAP despite compensatory peripheral vasodilation. Over years, the sustained high-pressure environment induces structural arteriolar remodelling: walls thicken, lumens narrow, and SVR rises permanently. Cardiac output may then normalise as the left ventricle works against a higher afterload, while the elevated SVR maintains the pressure independently of neurogenic input.

→ Ch. 10 and 15

The high-CO to high-SVR transition, and what it means for drug choice at each stage.

1.4 Systemic vascular resistance: Poiseuille's Law

Systemic vascular resistance is generated predominantly by arterioles — vessels of 50–150 μm internal diameter whose walls contain abundant smooth muscle and dense sympathetic innervation. Despite comprising a small fraction of total vascular surface, arterioles account for 50–60% of total vascular resistance. Their calibre is regulated continuously by the sympathetic nervous system, angiotensin II, endothelin-1, nitric oxide, prostacyclin and local metabolic factors.

50–60%
of total vascular resistance sits in arterioles of 50–150 μm internal diameter.

The physics of resistance in these vessels is described by Poiseuille's Law, derived empirically by Jean-Louis Marie Poiseuille in 1840 from experiments on flow through glass capillaries. It applies to laminar, Newtonian flow through rigid cylindrical tubes, and provides an accurate functional approximation for arteriolar resistance.[19]

EQUATION 1.2 POISEUILLE'S LAW OF VASCULAR RESISTANCE

$$R = \frac{8\eta L}{\pi r^4}$$

η blood viscosity · **L** vessel length · **r** internal radius

Resistance varies inversely with the fourth power of vessel radius.

Radius	-50%	Resistance	× 16
Radius	-10%	Resistance	+ 52%
Radius	+10%	Resistance	- 34%
Radius	+20%	Resistance	- 52%

The fourth-power relationship has three major clinical consequences.

1. **Vasodilating drugs produce disproportionately large BP reductions from modest receptor occupancy.** A calcium channel blocker that increases arteriolar radius by 10–15% produces a 32–43% reduction in arteriolar resistance, and a corresponding fall in SVR and MAP. This pharmacodynamic amplification applies to all arteriolar vasodilators — ACE inhibitors, ARBs, alpha-blockers and direct vasodilators all benefit from the same physics.

2. **Structural arteriolar remodelling permanently raises the SVR floor.** The inward eutrophic remodelling of essential hypertension reduces arteriolar internal diameter by only 10–15%, yet by Equation 1.2 this raises resistance by 52–92%. Once established, this structural component cannot be reversed by neurogenic or humoral intervention alone. Months to years of drug therapy are required for partial regression — ACE inhibitors and ARBs are the most effective agents for the purpose — and some component remains permanently irreversible.

3 **Blood viscosity must be considered in specific contexts.** Polycythaemia vera, severe dehydration, hypergammaglobulinaemia and erythropoietin therapy all raise haematocrit and viscosity, increasing SVR and BP through the Poiseuille numerator.

Evidence

CHOIR, targeting a normal haemoglobin with epoetin alfa, found the composite of death, myocardial infarction, hospitalisation for heart failure and stroke more frequent in the high-haemoglobin arm — 17.5% against 13.5%.[18] CREATE, targeting 13–15 g/dL, found no benefit and a non-significant excess of first cardiovascular events, 19.3% against 15.6%, with more hypertensive episodes and headache.[5] Neither trial supports normalising haemoglobin in chronic kidney disease, and a conservative target of 10–11.5 g/dL remains the safer one.

Optimal haemoglobin targeting in CKD is therefore both a safety recommendation and an antihypertensive one.

Turbulent flow and the Reynolds number

Poiseuille's Law describes laminar flow, in which blood moves in smooth concentric layers with peak velocity at the vessel centre. At high velocities, or in geometrically irregular vessels, flow becomes turbulent: chaotic eddies dramatically increase energy expenditure and effective resistance. The threshold is predicted by the Reynolds number.

Why you hear it

Korotkoff sounds are turbulence under the cuff. A bruit is turbulence at a stenosis. Both are Poiseuille's Law failing.

EQUATION 1.3 REYNOLDS NUMBER

$$Re = \frac{\rho v d}{\eta}$$

ρ blood density · **v** flow velocity · **d** vessel diameter · **η** viscosity

Turbulence above Re ≈ 2,000; transitional above ≈ 1,200.

Four clinical consequences follow directly:

— Korotkoff sounds are turbulence in the partially occluded brachial artery beneath the cuff.

— Vascular bruits are turbulence at carotid, renal or femoral stenoses.

— In anaemia, low viscosity lowers the Reynolds threshold, producing flow murmurs at normal velocities.

— An aortic flow murmur reflects turbulent ejection in severe hypertension or a hyperdynamic state.

The energy dissipated in turbulent flow during systolic ejection contributes to left ventricular workload beyond that predicted by Equation 1.1 alone, partially accounting for the LVH that develops in patients whose mean pressure appears only modestly elevated. In severe hypertension, turbulent aortic flow accelerates medial fatigue and predisposes to dissection.

1.5 Laplace's Law: wall tension and the pattern of damage

Poiseuille's Law explains the haemodynamics of resistance. Laplace's Law explains why hypertensive end-organ damage has a characteristic anatomical distribution — targeting small vessels in the brain, kidneys and retina rather than producing uniform damage throughout the vascular tree.

EQUATION 1.4 LAPLACE'S LAW FOR A CYLINDRICAL PRESSURE VESSEL

$$T = P \cdot r \quad \text{1.4a}$$

$$\sigma = \frac{P \cdot r}{h} \quad \text{1.4b}$$

T wall tension · **σ** wall stress · **P** transmural pressure · **r** radius · **h** wall thickness

At the same intraluminal pressure, the aorta carries high absolute tension but manageable stress across a thick wall; the arteriole carries low absolute tension but extreme stress across an extremely thin one.

The aorta, exposed to the highest absolute pressures, does not typically rupture from hypertension alone, because its thick elastic wall provides sufficient tensile strength. Aortic dissection arises through a different mechanism: fatigue failure of medial elastic fibres from repeated cyclical pulsatile stress. Each cardiac cycle imposes a mechanical pulse on the aortic wall; over millions of cycles in sustained hypertension the medial elastic lamellae undergo cystic degeneration, creating a structural weakness through which the systolic pressure pulse dissects a path between layers.

The target organs in hypertensive end-organ damage are therefore those supplied by small, thin-walled arterioles: the brain — penetrating lenticulostriate arteries and their branches, the source of hypertensive intracerebral haemorrhage and lacunar infarction; the kidneys — afferent arterioles, the source of hypertensive nephrosclerosis and the fibrinoid necrosis of malignant hypertension; and the retina — arterioles of 50–100 µm diameter, the source of Keith–Wagener–Barker grade changes on fundoscopy.

Where damage lands

Brain · lenticulostriate arteries
Kidney · afferent arterioles
Retina · 50–100 µm arterioles

Clinical rule

Acute aortic dissection — beta-block first, vasodilate second

The critical target is not absolute pressure but the rate of pressure rise, dP/dt — the mechanical driving force for propagation of the dissection plane.

Intravenous esmolol or labetalol reduces heart rate, smoothing the pressure waveform, and reduces the velocity of ventricular contraction, lowering dP/dt directly. Only after adequate beta-blockade should a vasodilator be added for residual pressure elevation.

Starting with a vasodilator alone provokes reflex tachycardia that raises dP/dt and propagates the dissection, despite lowering mean pressure.[9]

1.6 Compliance, pulse wave velocity and isolated systolic hypertension

The cardiovascular system is pulsatile, not a steady-flow circuit. The left ventricle ejects blood in discrete strokes, creating a high-pressure wave during systole that must be absorbed, buffered and converted into smooth continuous diastolic flow. The elastic arteries perform this buffering through arterial compliance: the volume increase produced by a unit increase in intraluminal pressure, $\Delta V/\Delta P$. The fractional version of the same quantity — the volume change as a proportion of the starting volume — is distensibility, a related but distinct measure.

Windkessel

Named by Otto Frank after the air chamber that smoothed flow in fire-engine pumps.

The Windkessel model describes how the proximal aorta and large elastic arteries function as compliance reservoirs. During systolic ejection the aortic wall distends to accommodate the stroke volume, storing kinetic energy as elastic potential energy. During diastole, elastic recoil maintains a positive diastolic pressure that drives blood forward continuously while the ventricle fills. In a young person with compliant arteries the result is a smooth, well-buffered waveform with a diastolic pressure that remains comfortably above the coronary perfusion threshold.[23]

With ageing and sustained hypertension, compliance declines progressively through four interconnected mechanisms: fatigue and fracture of medial elastin fibres from repeated pulsatile stress; replacement of elastin by stiffer collagen; medial calcium deposition; and, in diabetics, advanced glycation end-product cross-linking of collagen molecules. The Windkessel function is progressively lost, and the haemodynamic consequences define isolated systolic hypertension.

TABLE 1.2 — HOW ARTERIAL STIFFENING PRODUCES ISOLATED SYSTOLIC HYPERTENSION

CONSEQUENCE	MECHANISM	CLINICAL MANIFESTATION
Rising systolic BP	The stiff aorta cannot absorb the stroke volume; all ejected volume is transmitted as a high-pressure wave rather than stored elastically	Isolated systolic hypertension: SBP ≥140 with DBP <90. Affects more than 65% of hypertensives over age 60.[6]
Falling diastolic BP	Reduced elastic recoil during diastole; the Windkessel reservoir is depleted and runoff pressure is lower	Progressive pulse pressure widening. DBP may fall below 60–65 mmHg in advanced stiffness, reducing coronary perfusion pressure.
Widening pulse pressure	Rising SBP combined with falling DBP	PP >60 mmHg is an independent CV risk marker. Each 10 mmHg increase carries a 20% increase in CV mortality (Framingham).[7]
Increased LV afterload	Higher systolic pressure imposes greater wall stress on the ejecting ventricle, which must generate higher pressures against stiffer arteries	Concentric LVH, increased myocardial oxygen demand, diastolic dysfunction, eventual HFpEF.
Impaired coronary perfusion	Coronary arteries fill in diastole; reduced diastolic pressure from loss of Windkessel function reduces both coronary filling time and pressure	Relative subendocardial ischaemia even without obstructive CAD. The J-curve for diastolic BP is clinically real in elderly ISH.

Pulse wave velocity

Pulse wave velocity is the speed at which the pressure pulse generated by ventricular ejection travels along the arterial tree. Derived from the Bramwell–Hill equation, it is the gold-standard non-invasive measure of arterial stiffness.[2,14]

Bramwell–Hill

A stiffer wall transmits the mechanical perturbation faster. PWV is stiffness made measurable.

CAROTID-FEMORAL PWV — ESH 2023 REFERENCE VALUES[16]

Normal	< 10.0	m/s
Elevated — moderate stiffness	10.0–12.0	m/s
High risk — independent CV risk	> 12.0	m/s

Evidence

Higher pulse wave velocity carries higher cardiovascular risk independently of brachial pressure. In a meta-analysis of 17 longitudinal studies and 15,877 subjects, each 1 m/s increment carried 14% more cardiovascular events and 15% higher cardiovascular and all-cause mortality, adjusted for age, sex and risk factors.[22] PWV is included in the ESH 2023 total cardiovascular risk stratification algorithm.

Wave reflection and central aortic pressure

Timing is everything

Compliant arteries: reflection arrives in diastole and helps. Stiff arteries: it arrives in late systole and harms.

As the systolic pressure pulse travels through the arterial tree it meets impedance mismatch at bifurcations and arteriolar resistance sites, generating a reflected wave that travels back toward the heart. In young compliant arteries with low PWV, the reflected wave returns slowly and arrives during diastole, augmenting diastolic pressure and supporting coronary perfusion. In stiff arteries with high PWV, it travels faster and arrives during late systole, augmenting systolic pressure and worsening LV afterload while reducing diastolic augmentation and impairing coronary perfusion. This is the worst available combination for the hypertensive heart.

The augmentation index quantifies wave reflection: the difference between the second systolic shoulder, produced by the reflected wave, and the first systolic peak, expressed as a percentage of pulse pressure. A high augmentation index independently predicts cardiovascular events after adjustment for conventional risk factors — in men, all-cause mortality HR 1.68 (1.02–2.76) for the highest against the lowest tertile, with no significant association in women. The tertile is age-adjusted; there is no single validated threshold to quote.[10]

Evidence

Why brachial BP is not the whole story

The CAFE sub-study of ASCOT compared amlodipine-based with atenolol-based strategies that produced nearly identical reductions in brachial SBP and DBP over four years. Despite equivalent peripheral BP control, the amlodipine strategy produced significantly lower central aortic SBP (mean difference 4.3 mmHg) and lower AIx (mean difference 3.0%). This central advantage was associated with the **23% reduction in fatal and non-fatal stroke (ASCOT-BPLA; CAFE itself measured pressure, not events)** in the amlodipine arm of the parent trial.[25]

Mechanism. Atenolol reduces heart rate and prolongs systole, so the reflected wave arrives earlier within a longer ejection period, augmenting central systolic pressure despite equivalent brachial reduction. Amlodipine dilates peripheral arterioles, reducing the amplitude of the reflection without adversely affecting its timing.

This is one of the principal mechanistic reasons why atenolol is no longer recommended as a first-line antihypertensive, or as a valid comparator in cardiovascular outcome trials.

1.7 Autoregulation and the physiology of safe BP reduction

Autoregulation is the intrinsic capacity of an organ's vascular bed to maintain constant blood flow across a range of perfusion pressures, independent of systemic BP. It is mediated by the myogenic response of arteriolar smooth muscle — stretch causes constriction, reduced tension causes dilation — by local metabolic regulators produced by tissue metabolism, and in the kidney by tubuloglomerular feedback involving macula densa sodium delivery and afferent arteriolar resistance.

Three mechanisms

Myogenic response · local metabolites (CO_2, adenosine, K^+, H^+, lactate) · tubuloglomerular feedback in the kidney

TABLE 1.3 — AUTOREGULATORY RANGE BY ORGAN, AND WHAT HAPPENS WHEN IT IS BREACHED

ORGAN	NORMAL RANGE	LOWER LIMIT	CONSEQUENCE IF BREACHED
Cerebral	MAP 60–150 mmHg THE CLASSICAL LASSEN RANGE — SEE THE CAUTION BELOW	MAP ≈ 60 mmHg INDIVIDUAL, NOT FIXED	Below: watershed infarction. Above 150 mmHg: blood-brain barrier disruption, cerebral oedema, hypertensive encephalopathy.
Renal	MAP 75–160 mmHg	MAP 75–80 mmHg	Below: acute tubular necrosis, oliguria, ischaemic nephropathy. Above: glomerular hypertension, proteinuria, accelerated nephrosclerosis.
Coronary	DBP 60–130 mmHg	DBP ≈ 70 mmHg AN ASSOCIATION, NOT A FLOOR	The observational association: in ONTARGET/TRANSCEND the lowest risk for all outcomes sat at an achieved diastolic of 70 to under 80 mmHg, and below 70 myocardial infarction rose (HR 1.54), heart failure hospitalisation (HR 1.81) and all-cause mortality (HR 1.19) — the diastolic J-curve.[1] Read it as an association rather than a floor: in SPRINT it does not survive adjustment for the illnesses that lower diastolic pressure,[29] and V3 Ch13 sets out the wider evidence. The physiology — subendocardial ischaemia when coronary perfusion pressure falls — is real; the number at which it bites in a given patient is not fixed. Symptoms, not the number, are the signal to ease off.
Retinal	OPP > 30 mmHg	MAP – IOP > 30 mmHg	Below: ischaemic optic neuropathy, visual loss. Relevant when treating malignant hypertension in a patient with pre-existing optic nerve ischaemia.

Two cautions about the numbers in the table above, because they are quoted far more confidently than the evidence supports. The 60–150 mmHg cerebral range is **Lassen's 1959 curve**, and a modern reappraisal in *Physiological Reviews*

keeps the concept "albeit with some important caveats and modifications" while rejecting the word *plateau* altogether — flow slopes across the range rather than sitting flat, so "gradient" is the better term. The autoregulatory range is also **individual and relative to the patient's own resting pressure**, and far narrower than the table implies: within-person studies put it at roughly 5–10 mmHg either side of resting pressure, and it buffers a rise better than a fall. A separate reanalysis, excluding the data points obtained with vasodilator drugs, gives a plateau far narrower than the 90 mmHg span usually taught.[11] Treat the table as a teaching frame, not as a set of thresholds to titrate against.[3]

The rightward shift in chronic hypertension

The most clinically critical feature of autoregulation is that the entire curve shifts rightward in patients with longstanding elevated BP. Structural remodelling of resistance arterioles — thickened media, narrowed lumen, increased collagen — means a higher basal pressure is required to maintain adequate flow through geometrically restricted vessels. Over years of poorly controlled hypertension, the lower limit of cerebral autoregulation shifts from a MAP of about 60 mmHg in normotensives to 85–95 mmHg or higher.[4]

85–95
mmHg — the lower limit of cerebral autoregulation in a longstanding hypertensive, against ≈60 in a normotensive.

The practical consequence is that blood pressure values which are haemodynamically safe in a normotensive person can produce end-organ ischaemia in a chronic hypertensive whose autoregulatory range has adapted upward. Reducing MAP from 150 to 120 mmHg — a 20% reduction, well within guideline targets for hypertensive emergencies — may still cross the lower autoregulatory limit in a patient whose vessels have remodelled around chronically high pressures.

With sustained BP control over weeks, the curve gradually shifts leftward toward normal as the structural remodelling partially reverses and the myogenic setpoint readjusts. This is why the same degree of BP reduction that was dangerous in the acute setting becomes well tolerated in the adequately treated chronic patient.

TABLE 1.4 — FOUR RULES GOVERNING SAFE BP REDUCTION

CLINICAL SITUATION	RULE	PHYSIOLOGICAL BASIS
Hypertensive emergency ACUTE ORGAN DAMAGE	Reduce MAP by **20–25% in the first hour** — not to normal. Further staged reduction over 24–48 hours.[20,21,24]	The rightward-shifted curve means a 'normal' MAP may sit below the ischaemic threshold of adapted organs.
Hypertensive urgency NO ACUTE DAMAGE	No reduction target inside the first hours. Restart or intensify oral therapy and bring the pressure down over 24 to 48 hours, with review within a week.[24,30] **No sublingual nifedipine IR.** No acute normalisation. The staged sequence in the row above belongs to emergency, not here.	Same rightward-shifted curve — the reason not to hurry, not a reason to stage a rapid reduction. Rapid lowering offers no benefit without organ damage and risks hypoperfusion; sublingual nifedipine IR crosses the autoregulatory threshold with uncontrolled rapidity.
Neglected hypertensive NEVER TREATED, BP 180–200	Start a low-dose two-drug combination, as the guideline directs, and titrate over weeks rather than days.[27] The caution here is about the pace of reduction and about symptoms, not about the number of drugs: two agents at low dose lower the pressure more predictably and more gently than one pushed to full dose. **Do not chase a normal pressure in the first days.**	Weeks of controlled reduction are needed for the autoregulatory curve to shift leftward toward normal.
Elderly ISH WIDE PULSE PRESSURE	Aim for a systolic of 120–129 mmHg where it is tolerated, as in any treated adult; relax the target for symptomatic orthostatic hypotension, age 85 or over, or moderate-to-severe frailty.[28] Record the DBP throughout titration, but titrate against symptoms, not against the diastolic — V3 Ch13.	Benefit persists in the old (HYVET, STEP). The diastolic J-curve[17] is an observational association, largely non-causal — see Table 1.3.

1.8 Haemodynamic heterogeneity: the same number, different physiology

The clinical synthesis of the physics in this chapter is the concept of haemodynamic heterogeneity: identical blood pressure values at the brachial cuff can be generated by fundamentally different haemodynamic states, each with a different dominant mechanism, a different pattern of organ damage, and a different pattern of response to the drug classes the guideline permits.

Evidence

Essential hypertension is not one disease

The haemodynamic studies of Julius and Lund-Johansen in the 1960s and 1970s, using direct intra-arterial pressure measurement and indicator-dilution cardiac output determination, established that essential hypertension is haemodynamically heterogeneous:[12,15]

HYPERKINETIC	MIXED	STRUCTURAL
≈30%	≈55%	≈15%
↑ CO · SVR normal/low	↑ CO · ↑ SVR	↑ SVR · CO normal/low
Neurogenic sympathetic overactivation; young patients.	Both variables mildly elevated — the largest group.	Low-renin, remodelled arterioles; older patients.

These proportions shift with age: the hyperkinetic phenotype predominates in young patients, the high-SVR structural phenotype in older patients after years of vascular remodelling.

One rule governs the table that follows, and it is the rule of the whole series: **where the guideline and the phenotype conflict, the guideline wins.** The right-hand column names the classes whose mechanism fits — it does not license any class the guideline does not already permit for that patient, and a compelling indication always takes precedence over a phenotype.

TABLE 1.5 — THE PROPOSED CLINICAL PHENOTYPE FRAMEWORK PROPOSED FRAMEWORK

PHENOTYPE	TYPICAL PATIENT	BEDSIDE CLUES	CLASSES WHOSE MECHANISM FITS — WHERE THE GUIDELINE PERMITS A CHOICE
High CO, low–normal SVR NEUROGENIC	Young (<40), lean, anxious, high-stress occupation; shift worker; recent stressor	Resting HR >80 bpm; palpitations; high BP variability on ABPM; morning-dominant pattern; elevated plasma renin activity	The guideline first-line classes, as for any uncomplicated hypertensive — ACE inhibitor or ARB, calcium channel blocker or thiazide-type diuretic; an ACEi/ARB is the natural first pick where renin is high. A beta-blocker only where a compelling indication exists — angina, prior infarction, heart failure, rate control.[27] Its mechanism (lower heart rate, lower renin) fits this phenotype, but a high resting heart rate is a risk marker and a prompt to exclude anaemia and thyroid disease, not an indication on its own.
Normal CO, high SVR RAAS-DRIVEN	Middle-aged, moderate risk factors, microalbuminuria; diastolic pattern; normal or elevated renin	Normal HR; DBP disproportionately elevated; responds to an ACEi/ARB trial; microalbuminuria on urine ACR	ACEi or ARB as primary agent — addresses the dominant vasoconstrictor and renal endothelial damage.
Low–normal CO, high SVR VOLUME, LOW-RENIN	Elderly, Afro-Caribbean, South Asian, obese, high dietary sodium; low plasma renin. CKD and diabetes share the physiology but carry their own RAAS-blocker indication — see the last column	Normal or slow HR; isolated systolic hypertension; non-dipping on ABPM; high 24-hour urinary sodium; low PRA	Thiazide-type diuretic (chlorthalidone or indapamide) or CCB will usually be the more effective pressure-lowering agent in a low-renin, salt-loaded patient. That says nothing about whether a RAAS blocker is indicated: with albuminuria, diabetic kidney disease, heart failure or prior infarction a RAAS blocker is required on outcome grounds whatever the renin, and is added, not substituted.
High CO and high SVR MIXED, METABOLIC	Obese, metabolic syndrome, OSA, insulin-resistant diabetes, resistant hypertension phenotype	Elevated HR with volume signs; non-dipping with morning surge; STOP-BANG positive; rising glucose; waist >90 cm	Combination from day one: ACEi/ARB with CCB or diuretic. Treat the OSA. SGLT2 inhibitor if diabetic.

WHAT THIS FRAMEWORK IS, AND IS NOT

These phenotypes are **working clinical constructs, not directly measured haemodynamic states**. That hypertension is haemodynamically heterogeneous is established, and the invasive haemodynamic work cited above demonstrates it. That the heterogeneity can be read at the bedside from these particular clues, and that drug choice should follow, is the **framework this series proposes** — examined against pharmacology in Volume 2 and against evidence and outcomes in Volume 3. Bedside clues such as heart rate, blood-pressure pattern, obesity, sleep apnoea and renin may *suggest* a dominant mechanism; they do not *establish* cardiac output or systemic vascular resistance. The framework is intended to complement — not replace — guideline-based treatment and appropriate investigation.

Clinical rule

Read the pulse before you read the cuff

The resting heart rate is the most accessible bedside clue to the dominant haemodynamic mechanism — and the most easily over-read. It is a prompt to look for sympathetic activation, not a measurement of it, and it means nothing until anaemia and thyroid disease have been excluded.

Above 80 bpm in an untreated hypertensive points toward a high-CO neurogenic mechanism — and is simultaneously an independent predictor of cardiovascular mortality. Each 10 bpm increase in resting heart rate is associated with about 9% higher all-cause mortality — a pooled estimate from a meta-analysis of 46 studies and over 1.2 million participants, not a Framingham figure, though Framingham established the qualitative point that resting heart rate predicts mortality independently of blood pressure.[26]

Below 65 bpm in an untreated hypertensive points toward a structural, volume-mediated or low-renin mechanism.

This haemodynamic framework is the foundation of the clinical methodology developed throughout the three volumes of this series. Equation 1.1 is the beginning of every clinical reasoning chain. Chapters 2 to 10 of this volume describe the specific mechanisms that elevate CO or SVR in different patient contexts. The physics in this chapter is not preamble. It is the clinical tool.

→ Volumes 2 and 3

Volume 2 analyses each drug class by the variable it addresses. Volume 3 applies the framework from clinic to emergency.

KEY POINTS

1. **MAP = CO × SVR** governs every BP reading. Pressure is elevated only because CO is high, SVR is high, or both, and every antihypertensive reduces one or the other.
2. **Poiseuille's Law:** resistance varies inversely with the fourth power of vessel radius. A 10% reduction in arteriolar radius raises resistance by 52%; structural remodelling permanently raises the SVR floor.
3. **Laplace's Law:** wall stress = pressure × radius ÷ wall thickness. Thin-walled arterioles carry the greatest stress per unit pressure. In dissection the target is dP/dt — beta-block first, vasodilate second.
4. **Arterial stiffness produces ISH:** SBP rises, DBP falls, pulse pressure widens. PWV >10 m/s is an independent risk marker — each 1 m/s carries 14% more CV events.[22]
5. **CAFE:** amlodipine and atenolol produced equal brachial BP reduction, but amlodipine lowered central aortic pressure, augmentation index — and cardiovascular events.
6. **Autoregulation shifts rightward** in chronic hypertension. Reduce MAP by no more than 25% in the first hour of an emergency, not to normal. The curve shifts back over weeks of control.
7. **Haemodynamic heterogeneity:** the same cuff reading arises from different physiology — roughly 30% hyperkinetic, 55% mixed, 15% structural. The resting heart rate is the most accessible bedside clue — and the most easily over-read.

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CHAPTER 2 PART I · MECHANISM

Baroreceptors, chemoreceptors and central regulation

The neural architecture of blood pressure control, its failure in hypertension, and its pharmacological exploitation.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The baroreceptor reflex arc** — anatomy, firing characteristics, and moment-to-moment BP buffering.
2. **Baroreceptor resetting** — how the reflex comes to perpetuate rather than correct elevated BP.
3. **NTS and RVLM** — the central integration hubs and what converges on them.
4. **Peripheral chemoreceptors** — carotid body sensitisation by hypoxia and OSA-driven hypertension.
5. **Orthostatic BP regulation** — the three-phase response to standing and where it fails clinically.
6. **Baroreflex sensitivity as a prognostic marker** — ATRAMI, BRS and heart rate variability.
7. **Central pharmacology** — how moxonidine, clonidine and methyldopa exploit this apparatus.

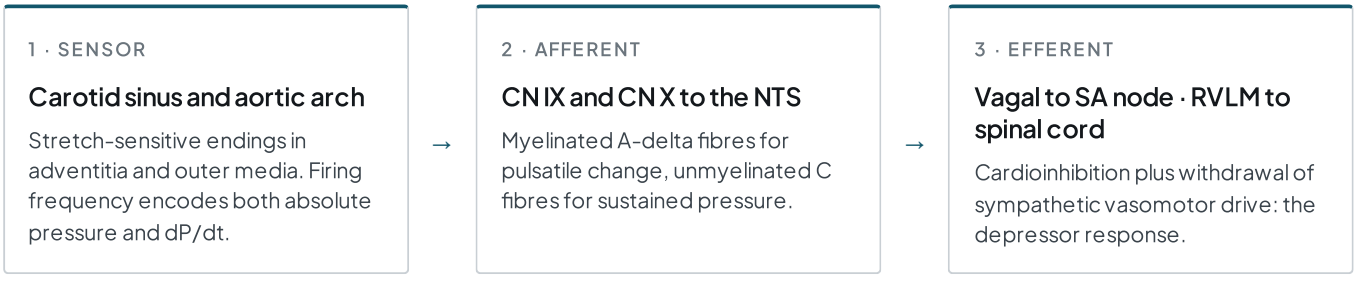
2.1 The baroreceptor reflex arc

The arterial baroreceptor reflex is the primary moment-to-moment regulator of blood pressure in mammals. It is a high-gain negative feedback loop that detects pressure changes in the arterial tree beat by beat and initiates compensatory adjustments in heart rate, cardiac contractility and peripheral vascular resistance within seconds. The arc has three anatomical components, and both its normal function and its pathological modification in hypertension follow from taking them in sequence.

High-gain negative feedback

Without it, standing up, exercise and emotional stress would each swing BP far enough to cause syncope or crisis.

FIGURE 2.1 — THE REFLEX ARC, SENSOR TO EFFECTOR



The sensors: carotid sinus and aortic arch

Arterial baroreceptors are mechanoreceptive nerve endings embedded in the adventitia and outer media of two sites: the carotid sinus, a dilatation of the internal carotid artery immediately above the common carotid bifurcation, innervated by the carotid sinus nerve, a branch of the

glossopharyngeal nerve (CN IX); and the aortic arch, innervated by the aortic depressor nerve, a branch of the vagus (CN X). Both project to the same central target.[1]

The receptors themselves are stretch-sensitive ion channels. When arterial pressure rises the vessel wall distends, stretching the adventitial nerve endings and activating mechanosensitive channels that depolarise the afferent fibre. Action potential frequency encodes the magnitude of the stimulus. Critically, baroreceptors respond to the rate of pressure change, dP/dt, as well as to absolute pressure: a rapidly rising pressure wave generates a larger afferent burst than the same pressure reached gradually, which is why pulse pressure and heart rate influence baroreceptor output independently of MAP.

Not redundant

The two sites have different pressure ranges, giving overlapping coverage across the whole physiological and pathological span.

TABLE 2.1 — CAROTID SINUS BARORECEPTOR FIRING CHARACTERISTICS

PRESSURE RANGE	MAP	REFLEX BEHAVIOUR
Firing threshold	60–70 mmHg	Below this, afferent traffic ceases; the reflex can no longer signal further pressure fall.
Steep response	80–180 mmHg	Firing rate rises steeply with pressure — the working range of the reflex.
Greatest sensitivity	100–150 mmHg	Steepest slope, and therefore maximum reflex gain, sits in the normal physiological range.
Saturation	> 180 mmHg	Firing rate plateaus. Very high pressures produce no proportionally greater compensation — which is why hypertensive emergencies do not self-correct through reflex mechanisms.

The central integration hub: nucleus tractus solitarius

The nucleus tractus solitarius is a column of neurons extending through the dorsal medulla oblongata and the primary central cardiovascular integration hub. It receives not only baroreceptor input but chemoreceptor afferents from the carotid and aortic bodies, visceral sensory input from heart and lungs via the vagus, and descending modulatory input from the hypothalamus, amygdala and prefrontal cortex. This convergence is what allows cardiovascular regulation to be integrated with the respiratory cycle, behavioural state, emotional arousal and higher cortical function.[6]

What converges on the NTS

Baroreceptors · chemoreceptors · cardiopulmonary vagal afferents · hypothalamus · amygdala · prefrontal cortex

When baroreceptor afferent firing increases, signalling a rise in arterial pressure, NTS neurons activate two parallel efferent pathways: the vagal cardioinhibitory pathway to the sinoatrial node, slowing heart rate and atrioventricular conduction, and an inhibitory projection to the rostral ventrolateral medulla that suppresses sympathetic outflow to heart and vasculature. The net result is the classical depressor response. When baroreceptor firing falls — haemorrhage, orthostasis — NTS inhibition of the RVLM is withdrawn, the RVLM increases its tonic excitatory drive to sympathetic preganglionic neurons in the intermediolateral column, and reflex tachycardia and vasoconstriction follow.

The rostral ventrolateral medulla: the sympathetic vasomotor centre

The RVLM is the principal generator of tonic sympathetic vasomotor activity. It contains glutamatergic presympathetic neurons — C1 and non-C1 populations, the former containing both adrenaline and glutamate — that maintain a tonic excitatory drive to spinal sympathetic preganglionic neurons.

Interrupting that drive by any means produces profound hypotension: bilateral RVLM lesion in animal experiments, baroreceptor activation therapy in clinical trials, central sympatholytic drugs in practice.[10]

The RVLM receives inhibitory input from the NTS and the caudal ventrolateral medulla, excitatory input from the hypothalamic paraventricular nucleus, and modulatory input from the periaqueductal grey and limbic structures — amygdala and bed nucleus of the stria terminalis — that link emotional state to cardiovascular output. That last connection explains why chronic psychosocial adversity can produce persistent elevation of resting sympathetic tone.

→ Ch. 4 and 25

The limbic–RVLM connection is the anatomical substrate for stress-induced hypertension.

2.2 Baroreceptor resetting in chronic hypertension

The most clinically important pathological modification of the reflex in hypertension is baroreceptor resetting: a gradual upward adjustment of the pressure threshold at which baroreceptors reach maximum firing, so that the reflex operates around a chronically elevated setpoint rather than restoring BP toward the normotensive range. Resetting occurs by two mechanisms on different timescales.[3]

1. **Rapid peripheral resetting — minutes to hours.** Mechanosensitive channels in the nerve endings desensitise to sustained pressure elevation, reducing firing rate at the elevated pressure and allowing the RVLM to resume baseline sympathetic output despite a raised MAP. This is the mechanism behind the acute tolerance seen when BP is elevated experimentally.

2. **Chronic structural resetting — weeks to months.** Sustained mechanical stress on the carotid sinus wall stimulates remodelling: the wall thickens, collagen is deposited in the adventitia around the nerve endings, and the wall stiffens. A stiffened wall transmits less intraluminal pressure to the endings for any given absolute pressure, reducing input signal and raising the operating threshold. Once established, pharmacologically normalising pressure does not immediately restore sensitivity — weeks of controlled normalisation are required for partial reversal.

Clinical rule

The reflex defends the hypertensive pressure, not the normal one

In established hypertension the baroreceptor reflex still functions — it still buffers acute change and still produces a normal orthostatic response. What has changed is its operating point.

Three clinical facts follow: spontaneous hypertension does not self-correct; patients feel subjectively well at chronically elevated pressures; and **rapid pharmacological BP reduction provokes reflex sympathetic activation** — tachycardia, fluid retention, renin secretion — that partially opposes the intended effect.

Baroreflex sensitivity as a prognostic marker

Baroreflex sensitivity quantifies the gain of the reflex: the change in RR interval in milliseconds per unit change in systolic BP in mmHg. What that measures is the gain of the cardiac — cardiovagal — arm. Stiffening of the carotid sinus wall reduces the mechanoreceptor input signal and lowers that gain, and central resetting contributes; in essential hypertension it is the cardiac arm that is consistently depressed, while baroreflex control of muscle sympathetic outflow and vascular resistance is relatively preserved[19]. For any given acute pressure rise the compensatory bradycardia is therefore smaller, and BP variability is correspondingly greater. The high-variability pattern seen on ABPM in some hypertensives is impaired baroreceptor buffering made visible.

How BRS is measured

Phenylephrine method · Oxford technique (phenylephrine and nitroprusside) · transfer function analysis of spontaneous 24-hour variability[14]

BAROREFLEX SENSITIVITY — REFERENCE VALUES

Healthy young adult	15–25	ms/mmHg
Essential hypertension	8–12	ms/mmHg
Heart failure with reduced EF	< 3	ms/mmHg

Evidence

ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction): post-MI patients with BRS below 3 ms/mmHg carried a relative risk of cardiac mortality of **2.8** (95% CI 1.24–6.16) against those above 3 ms/mmHg — independent of, and additive to, reduced heart rate variability and left ventricular ejection fraction. With an ejection fraction below 35% as well, the relative risk was 8.7.[13]

Heart rate variability, measured as the standard deviation of RR intervals (SDNN) or by frequency-domain analysis of LF/HF power from 24-hour Holter monitoring, provides an accessible surrogate of autonomic balance. Reduced HRV — particularly reduced high-frequency power, which reflects vagal tone — is consistently associated with elevated resting sympathetic activity, higher BP variability and increased cardiovascular risk. It requires no equipment beyond the Holter monitor, which makes it a practical tool for profiling the hypertensive patient's autonomic state.

2.3 Peripheral chemoreceptors and OSA-driven hypertension

Chemoreceptor stimuli

PaO_2 < 80 mmHg · raised $PaCO_2$ · reduced arterial pH

The peripheral chemoreceptors — carotid bodies at the common carotid bifurcation, aortic bodies adjacent to the arch — monitor the chemical composition of arterial blood. Their principal stimuli are hypoxia, hypercapnia and acidosis, and their primary physiological role is the hypoxic ventilatory response.

The cardiovascular response to chemoreceptor activation is mediated through NTS projections to the RVLM and direct projections to vagal cardiomotor neurons. Isolated chemoreceptor stimulation produces bradycardia and peripheral vasoconstriction — a diving-reflex-like response redistributing flow to heart and brain. In practice the simultaneous rise

in ventilation overrides that cardiovascular component, producing the familiar tachycardia and hypertension of hypoxic stress through indirect ventilatory effects.

Carotid body sensitisation in obstructive sleep apnoea

During each apnoeic episode oxygen saturation falls, CO_2 rises and pH falls — a combined stimulus that powerfully activates the carotid body. The resulting sympathetic surge drives a transient rise in BP and heart rate with each arousal. In moderate to severe OSA, with an AHI above 15–30 events per hour, these surges impose a cumulative nocturnal sympathetic load that holds average nocturnal BP near waking levels and produces the non-dipping or reverse-dipping pattern on ABPM.

15–30
sympathetic surges per hour through the sleep period in moderate-to-severe OSA, each raising SBP by 20–40 mmHg.

What distinguishes OSA-driven hypertension from simple sleep disruption is that the carotid body undergoes structural and functional sensitisation after chronic intermittent hypoxia. Type I glomus cells respond to repeated hypoxic episodes with greater inhibition of their oxygen-sensitive potassium channels — the channels whose closure depolarises the cell — driven by reactive oxygen species from a shifted pro-oxidant to anti-oxidant balance, and with an increased density of neurosecretory vesicles containing dopamine, ATP and substance P. The sensitised carotid body fires at higher baseline rates during normoxic wakefulness — not only during apnoeas — producing persistent daytime sympathetic overactivation measurable by microneurography as elevated resting muscle sympathetic nerve activity.[12]

Evidence

Why CPAP lowers BP only modestly — and why spironolactone is the fourth agent

Carotid body sensitisation and the central sympathetic sensitisation built up over months to years of nocturnal hypoxia persist after the apnoeas are abolished, and take weeks to months of effective therapy to partially reverse. The Fava meta-analysis accordingly found a pooled CPAP effect of only **2.6 mmHg systolic** and 2.0 mmHg diastolic — consistent with partial, delayed reversal rather than treatment failure.[8]

Intermittent hypoxia also stimulates aldosterone secretion, through hypoxia-induced renin release and direct adrenocortical stimulation, adding a volume-dependent component independent of the sympathetic mechanism. This is why aldosterone antagonists outperform other classes as a fourth agent in OSA-related resistant hypertension (PATHWAY-2 subgroup data, with independent confirmation in smaller OSA trials).

In resistant hypertension with confirmed OSA, spironolactone is the preferred fourth agent.

2.4 Orthostatic BP regulation

Standing imposes an immediate haemodynamic challenge: gravitational pooling in the venous capacitance vessels of the lower limbs and splanchnic bed within seconds of assuming an upright posture. Without compensation this reduction in venous return would lower stroke volume and cardiac output and produce syncope through falling cerebral perfusion. The normal response occurs in three overlapping phases, each mediated by distinct mechanisms.

300–800
mL of blood pools in lower-limb and splanchnic capacitance vessels within seconds of standing.

TABLE 2.2 — THE THREE-PHASE ORTHOSTATIC RESPONSE

PHASE	TIMING	MECHANISM	HAEMODYNAMIC RESULT
Phase 1 IMMEDIATE	0–6 s	Mechanical. Venous return falls as blood pools in the legs; simultaneously muscle contraction during rising compresses venous vessels, transiently increasing return before pooling takes hold.	Transient BP spike from mechanical compression, followed by a fall. HR begins to rise.[18]
Phase 2 EARLY REFLEX	6–30 s	Baroreceptor unloading. Reduced venous return lowers CO and MAP; the carotid sinus fires less; NTS inhibition of the RVLM is withdrawn; sympathetic outflow to heart and vasculature rises.	Reflex tachycardia. Arteriolar vasoconstriction raises SVR; venous constriction mobilises pooled blood. BP partially restored.
Phase 3 SUSTAINED	30 s – 5 min	Continued baroreceptor-mediated sympathetic activation, plus RAAS activation from reduced upright renal perfusion pressure, plus vasopressin release from low-pressure atrial and pulmonary artery receptors.	BP restored to near-supine levels. Normal response: SBP falls <10 mmHg, DBP may rise slightly, HR rises 10–20 bpm.

Orthostatic hypotension

Orthostatic hypotension is present in 5–10% of the general adult population but rises steeply with age and comorbidity: 20–30% of elderly hypertensives, 40–50% of patients with Parkinson's disease or Lewy body dementia, 30–40% of those with type 2 diabetes and autonomic neuropathy. It is not merely a haemodynamic inconvenience — it independently predicts falls and hip fracture (OR 1.8–2.4 in prospective studies), syncope, major adverse cardiovascular events and all-cause mortality. In ARIC, orthostatic hypotension in middle age predicted a substantially higher risk of heart failure over 17.5 years of follow-up (n = 12,363), and the association was stronger under the age of 55 than above it.[9,11,17]

Definition
SBP fall ≥20 mmHg or DBP fall ≥10 mmHg within 3 minutes of standing, or head-up tilt to 60°. Consensus 1996, unchanged since.[5]

1. **Antihypertensives are the commonest cause of iatrogenic OH.** Every class that reduces SVR or intravascular volume — diuretics, CCBs, ACE inhibitors, ARBs, alpha-blockers — can impair the compensatory vasoconstriction and volume retention that maintain BP on standing. **Alpha-blockers carry the highest risk** and should not be used as primary antihypertensives in the elderly for precisely this reason.

2. **Supine hypertension with orthostatic hypotension is a genuine dilemma.** It occurs in about half of patients with neurogenic orthostatic hypotension — 34–46% in Parkinson's disease, 37% in multiple system atrophy, 48–70% in pure autonomic failure: lowering supine BP reduces nocturnal end-organ damage but worsens daytime orthostatic falls.[7]

3. **Lying and standing BP at every visit is a mandatory safety check** — not optional — in elderly patients and in anyone on antihypertensive therapy.

2.5 Central pharmacology: exploiting the regulatory apparatus

Three classes of centrally acting antihypertensive exploit the neural architecture described above to reduce sympathetic outflow. Their mechanisms are precisely derivable from the neuroanatomy, which makes them among the best-understood drugs in cardiovascular pharmacology.

TABLE 2.3 — CENTRALLY ACTING ANTIHYPERTENSIVES

DRUG	CENTRAL TARGET	MECHANISM	CLINICAL PROFILE
moxonidine **rilmenidine** I_1 AGONISTS	Imidazoline I_1 receptors in the RVLM	Selective I_1 agonism reduces tonic excitatory drive from RVLM to sympathetic preganglionic neurons. Lower alpha-2 affinity than clonidine, so less sedation and less rebound.	Metabolic benefit: improves insulin sensitivity and reduces sympathetic-driven insulin resistance — useful in metabolic syndrome. **Avoid in HFrEF:** MOXCON showed excess mortality, attributed to excess vagal activation reducing LV function.[4]
clonidine ALPHA-2 AGONIST	Alpha-2 adrenoceptors in NTS and RVLM	Pre- and postsynaptic alpha-2 agonism hyperpolarises presympathetic neurons in NTS and RVLM and reduces noradrenaline release from sympathetic terminals throughout the body.	Potent, reliable, rapid onset. Useful in resistant hypertension and urgency. **Never stop abruptly** — rebound hypertension from sympathetic overactivity can follow sudden withdrawal; the label says to reduce the dose gradually over 2 to 4 days[20]. Sedation and dry mouth limit use.
methyldopa FALSE TRANSMITTER	Alpha-2 adrenoceptors in NTS and RVLM, via active metabolite	Converted to alpha-methylnoradrenaline by DOPA decarboxylase in CNS neurons, where it acts as a false neurotransmitter with preferential alpha-2 agonist activity, reducing central sympathetic outflow.	Drug of choice in hypertension in pregnancy — over 40 years of safety data, no fetal harm. **Avoid postpartum:** associated with postnatal depression. Coombs-positive haemolytic anaemia in under 5%. Sedation, postural hypotension and hepatotoxicity limit long-term use.

Baroreceptor activation therapy

The most direct clinical exploitation of this architecture is baroreceptor activation therapy: an implantable device that delivers continuous electrical stimulation to the carotid sinus nerve, mimicking the afferent signal of sustained pressure elevation and driving tonic sympathoinhibition through the NTS–RVLM pathway.[15]

Proof of the circuit

BAT works only because the NTS–RVLM pathway does what this chapter says it does.

DEVICE TRIALS

TRIAL	DEVICE	RESULT
Rheos Pivotal N = 265	First-generation bilateral	Mean SBP reduction of 26 mmHg at 12 months in responders; device-related complications limited enthusiasm.[2]
BAROSTIM BEYOND	Barostim Neo — unilateral	SBP −24 mmHg and DBP −12 mmHg at 6 months in resistant hypertension, with a more favourable safety profile.
BeAT-HF	Barostim Neo in HFrEF	Improved 6-minute walk distance, quality of life and NT-proBNP — consistent with the deleterious role of sympathetic overactivation in heart failure.

BAT remains a specialised intervention for refractory resistant hypertension, in centres with expertise in implantation and follow-up. Its existence is nonetheless the most direct clinical validation of the architecture described here: tonic activation of the baroreceptor afferent pathway produces sustained reduction in central sympathetic tone and blood pressure through the NTS–RVLM circuit.

2.6 Clinical implications of baroreceptor physiology

TABLE 2.4 — FIVE IMPLICATIONS FOR THE OUTPATIENT HYPERTENSIVE

IMPLICATION	PHYSIOLOGICAL BASIS	PRACTICAL APPLICATION
BP variability predicts risk independently of mean BP	Impaired BRS means transient pressure rises are less effectively buffered; each elevation produces more end-organ stress per unit pressure.	ABPM beats clinic BP for risk stratification because it captures the variability single readings miss. High SD on ABPM is an independent stroke risk marker (Rothwell, ASCOT-BPLA, 2010).[16]
Reflex tachycardia limits pure vasodilators	Arteriolar vasodilation lowers MAP, activating baroreceptors and provoking tachycardia, renin secretion and sodium retention that partially restore BP.	Hydralazine and minoxidil must be combined with a beta-blocker and a diuretic, or reflex tachycardia and sodium retention blunt the antihypertensive effect.
Counter-regulation with diuretics and RAAS blockers	Volume reduction activates baroreceptors and the RAAS; ACEi/ARB monotherapy provokes compensatory renin secretion over time.	Combination therapy attacking several mechanisms at once pre-empts these responses. This — not simple additivity — is the pharmacological rationale for combination therapy.
Evaluate OSA before adding drugs	Carotid body sensitisation by chronic intermittent hypoxia produces persistent daytime sympathetic elevation that no antihypertensive class fully reverses.	In resistant hypertension or a non-dipping ABPM pattern, investigate and treat OSA before adding a third or fourth agent. STOP-BANG in every new hypertensive.
Standing BP is mandatory	Antihypertensives impair orthostatic vasoconstriction and volume retention, with the largest effect in the elderly, whose baroreflex sensitivity is already reduced.	Measure lying and standing BP at every visit over age 65 and in all patients on antihypertensives. A fall greater than 20 mmHg SBP mandates drug review before any dose escalation.

KEY POINTS

1. **The reflex arc:** stretch endings in carotid sinus and aortic arch → NTS → RVLM → sympathetic outflow. It buffers acute change within seconds but saturates above MAP 180 mmHg, so severe hypertension cannot self-correct.
2. **Resetting:** structural stiffening of the carotid sinus wall reduces mechanoreceptor input and raises the reflex setpoint, so it defends the hypertensive pressure. This is why hypertension self-perpetuates and why patients feel well.
3. **BRS** falls to 8–12 ms/mmHg in essential hypertension (normal 15–25). ATRAMI: below 3 ms/mmHg post-MI gives RR 2.8 (1.24–6.16) for cardiac mortality, independent of LVEF and HRV; with LVEF under 35% as well, RR 8.7 (4.3–17.6).
4. **Carotid body sensitisation in OSA:** Type I glomus cell upregulation raises resting MSNA even in normoxic daytime wakefulness — hence the partial CPAP effect, and hence spironolactone as preferred fourth agent.
5. **Orthostatic hypotension** (SBP −20 or DBP −10 within 3 minutes) affects 20–30% of elderly hypertensives. ARIC: higher heart-failure risk on long follow-up. Lying-standing BP at every visit.
6. **Central agents:** moxonidine on I_1 receptors in the RVLM; clonidine on alpha-2 in NTS/RVLM; methyldopa via alpha-methylnoradrenaline. Never stop clonidine abruptly; avoid moxonidine in HFrEF; methyldopa remains first choice in pregnancy.
7. **Baroreceptor activation therapy:** carotid sinus nerve stimulation produces tonic sympathoinhibition through NTS–RVLM. Barostim Neo: SBP −24 mmHg in resistant hypertension — the clinical validation of the circuit.

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CHAPTER 3 PART I · MECHANISM

The renin–angiotensin–aldosterone system

The complete cascade, the counter-regulatory arms, tissue RAAS, and pharmacological exploitation.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The complete cascade** — angiotensinogen to aldosterone, every step and its pharmacological target.[10]
2. **The juxtaglomerular apparatus** — anatomy, the three stimuli for renin secretion, and their drug consequences.
3. **Angiotensin II beyond vasoconstriction** — fibrosis, LVH, renal damage, ROS and inflammation.
4. **AT_1 against AT_2 signalling** — the opposing arms of the angiotensin receptor system.
5. **The ACE2–Ang(1–7)–Mas axis** — the counter-regulatory arm and its emerging therapeutic significance.
6. **Aldosterone** — genomic and non-genomic actions, cardiac fibrosis, and the escape phenomenon.
7. **Local tissue RAAS** — cardiac, renal, vascular and cerebral systems acting independently of the circulation.

3.1 The complete RAAS cascade

The renin–angiotensin–aldosterone system is the dominant humoral regulator of long-term blood pressure and extracellular fluid volume.[21] Where the baroreceptor reflex operates beat to beat, the RAAS regulates pressure over minutes to days through coordinated effects on vascular tone, renal sodium handling and aldosterone secretion. Every major class of antihypertensive either blocks a RAAS component directly or reduces the input signals that activate it.

~70%

of patients with essential hypertension have renin that is not suppressed — that is, a renin–angiotensin system still contributing to the pressure rather than switched off by it. The remaining third is low-renin hypertension, volume-driven and characteristically salt-sensitive.[23]

FIGURE 3.1 — THE CLASSICAL CASCADE AND ITS COUNTER-REGULATORY ARM

SUBSTRATE	**Angiotensinogen** Liver, constitutively expressed. Substrate concentration is normally rate-limiting.
ENZYME · 1	**Renin** Juxtaglomerular cells. The rate-limiting enzyme of the cascade — target of aliskiren, now of historical interest only.
DECAPEPTIDE	**Angiotensin I** Biologically inactive; circulates briefly.
ENZYME · 2	**ACE** Lung endothelium. Also degrades bradykinin and substance P — target of the ACE inhibitors.
OCTAPEPTIDE	**Angiotensin II** The primary effector molecule of the system.
RECEPTORS	**AT_1 — pathological arm** Vasoconstriction · aldosterone secretion · LVH · fibrosis **AT_2 — counter-regulatory arm** Vasodilation · anti-proliferation · apoptosis · natriuresis
ALTERNATE ENZYME	**ACE2 → Ang(1–7)** Cleaves Ang II to the heptapeptide, which acts on the Mas receptor: vasodilation, anti-fibrosis.
STEROID	**Aldosterone** Adrenal zona glomerulosa, stimulated by Ang II and hyperkalaemia. Acts at the mineralocorticoid receptor: renal Na^+ retention, K^+ excretion, cardiac fibrosis, vascular inflammation — target of the MRAs.

The cascade has two sequential rate-limiting enzymatic steps, and both are pharmacological targets. Renin cleaves the leucine–valine bond of angiotensinogen to generate angiotensin I; its secretion from juxtaglomerular cells is the true rate-limiting step of the physiological cascade, and the target of aliskiren, the only direct renin inhibitor ever marketed — now, after ALTITUDE, essentially a historical footnote rather than a therapeutic option (see Table 3.5). ACE then cleaves two amino acids from the C-terminus of angiotensin I to generate angiotensin II. ACE is a non-specific carboxypeptidase that also degrades bradykinin, substance P and other vasoactive peptides — a dual substrate specificity responsible both for therapeutic benefit, since ACE inhibitors preserve bradykinin and its NO-mediated vasodilation, and for the principal adverse effects of cough and angioedema.

One enzyme, two substrates

ACE degrades bradykinin as well as generating Ang II. That single fact explains both the extra cardioprotection and the cough.

3.2 The juxtaglomerular apparatus and renin secretion

Renin is synthesised, stored in membrane-bound secretory granules and released by juxtaglomerular cells: specialised smooth muscle cells in the wall of the afferent arteriole at the point where it enters the glomerulus. They are anatomically and functionally coupled to the macula densa, a patch of specialised tubular epithelium in the thick ascending limb of the loop of Henle that directly contacts the afferent arteriole, and to the lacis cells, extraglomerular mesangial cells forming a cellular bridge that probably mediates paracrine signalling.

Three coupled cell types

JG cells in the afferent arteriole · macula densa in the thick ascending limb · lacis cells bridging the two

Secretion is regulated by three distinct and independent input signals, each able to activate or suppress it regardless of the others. Understanding all three is what allows you to predict how a given drug will alter RAAS activity, and to interpret a plasma renin activity measurement.

TABLE 3.1 — THE THREE RENIN SECRETION SIGNALS

SIGNAL	SENSOR	MECHANISM	CLINICAL AND DRUG IMPLICATION
Renal perfusion pressure RENAL BARORECEPTOR	JG cells themselves — intrinsic mechanosensors detecting stretch of the afferent arteriolar wall	High perfusion pressure stretches the wall and suppresses renin. Low pressure reduces stretch and stimulates secretion.	Renal artery stenosis drives sustained hypersecretion. ACEi/ARBs reduce Ang II and efferent arteriolar tone, so JG cells sense a lower pressure — hence the **reactive renin escape** that limits their long-term efficacy as monotherapy.
Tubular sodium delivery MACULA DENSA	Macula densa cells sensing luminal NaCl through the NKCC2 co-transporter	High luminal NaCl releases adenosine and TGF-β, suppressing JG cells. Low NaCl releases PGE_2 and NO, stimulating them.	Loop diuretics block NKCC2, so the macula densa perceives low delivery despite systemic volume expansion — powerful renin stimulation. This is why a loop diuretic with an ACEi/ARB is complementary rather than contradictory.
Sympathetic drive BETA-1 MECHANISM	Beta-1 adrenoceptors on the JG cell membrane	Noradrenaline from sympathetic terminals and circulating adrenaline raise cAMP, driving renin exocytosis from secretory granules.	The mechanistic basis for the RAAS-lowering effect of beta-blockers beyond heart rate and contractility — most relevant in high-renin neurogenic hypertension. Also why plasma renin activity rebounds after stopping a beta-blocker.

3.3 Angiotensin II: actions beyond vasoconstriction

Angiotensin II is the primary effector molecule of the RAAS. Its best-known action is arteriolar vasoconstriction through AT_1 receptor activation, but that represents only a fraction of its biological activity. Sustained Ang II excess produces a syndrome of end-organ damage through mechanisms entirely distinct from its haemodynamic effects.

Where Ang II excess comes from

Renovascular hypertension · primary aldosteronism · heart failure with RAAS activation · treated hypertension with ACEi escape

AT_1 receptor signalling: the pathological arm

The AT_1 receptor is a G-protein-coupled receptor — Gq/G11 primary, Gi secondary — whose activation initiates multiple intracellular cascades. The primary Gq/G11 pathway activates phospholipase C, generating inositol trisphosphate and diacylglycerol. IP_3 releases Ca^{2+} from intracellular stores, producing the immediate vasoconstriction; DAG activates protein kinase C, which initiates mitogenic signalling. Beyond that immediate haemodynamic effect, sustained AT_1 activation drives four pathological processes of critical clinical importance.[6]

TABLE 3.2 — SUSTAINED AT_1 ACTIVATION: MECHANISM TO CLINICAL CONSEQUENCE

PROCESS	MOLECULAR MECHANISM	CLINICAL CONSEQUENCE	DRUG PREVENTION
Cardiac hypertrophy and fibrosis	AT_1 → Gq → MAPK (ERK1/2, JNK) → hypertrophy transcription factors GATA-4 and MEF2C. AT_1 → NF-κB → TGF-β1 → fibroblast activation and collagen I/III deposition.	LVH, concentric initially from pressure overload, eccentric later. Cardiac fibrosis giving diastolic dysfunction, an AF substrate and arrhythmia risk. LIFE: losartan reduced ECG-LVH more than atenolol at equal BP.[5]	ACEi and ARBs block AT_1-driven hypertrophy and fibrosis beyond BP lowering. MRAs block the aldosterone-driven collagen deposition.
Glomerular hypertension and proteinuria	AT_1 constricts the efferent more than the afferent arteriole, raising intraglomerular pressure. AT_1 on mesangial cells contracts them, reducing filtration surface. TGF-β1 drives tubular and glomerular fibrosis.	Microalbuminuria → macroproteinuria → nephrosclerosis → CKD. RENAAL (losartan): 25% reduction in creatinine doubling, 28% in end-stage renal disease. IDNT (irbesartan): 23%. AASK: ramipril superior to amlodipine in Black CKD.[4,12,26]	ACEi/ARBs dilate the efferent arteriole specifically, reducing intraglomerular pressure while lowering systemic BP — the mechanistic basis for their mandatory use in proteinuric CKD.[11]
Vascular remodelling and atherosclerosis	AT_1 → NADPH oxidase → superoxide → eNOS uncoupling, so less NO and more O_2^-. AT_1 → NF-κB → VCAM-1, ICAM-1, MCP-1 → inflammatory cell recruitment. AT_1 → VSMC proliferation through MAPK.	Endothelial dysfunction with reduced FMD, accelerated atherosclerosis, inward eutrophic remodelling and permanent SVR elevation. HOPE: ramipril cut MACE by 22% with only 3 mmHg SBP reduction.[22]	ACEi add anti-atherogenic effects through bradykinin (NO, PGI_2) and AT_2 activation. ARBs leave AT_2 counter-regulation unopposed but gain no bradykinin benefit.
Aldosterone excess and mineralocorticoid damage	AT_1 on the zona glomerulosa stimulates aldosterone synthase (CYP11B2). Aldosterone then activates MR in kidney, heart and vasculature.	Renal Na^+ retention with K^+ loss, cardiac interstitial fibrosis (RALES, EPHESUS), vascular inflammatory fibrosis, endothelial dysfunction. Aldosterone escape 6–12 months after ACEi initiation.	ACEi/ARBs reduce Ang II-driven aldosterone. MRAs — spironolactone, eplerenone, finerenone — block MR directly, addressing escape and adding organ protection beyond BP.

AT_2 receptor signalling: the counter-regulatory arm

The AT_2 receptor is expressed predominantly during fetal development, where it mediates the apoptotic signalling essential for normal organ morphogenesis. It signals through Gi proteins and tyrosine phosphatase activation, opposing the mitogenic and vasoconstrictive effects of AT_1. Its biological consequences are vasodilation through NO and bradykinin release, inhibition of cell growth and proliferation, promotion of apoptosis, and natriuresis through renal tubular mechanisms — collectively counter-regulatory, buffering the pathological consequences of excessive AT_1 stimulation.

Upregulated by injury

AT_2 expression is low in healthy adult tissue but rises after tissue injury, cardiac hypertrophy and RAAS blockade.

The pharmacological significance is that ARBs, by blocking AT_1, allow accumulating Ang II to act preferentially on the unopposed AT_2 receptor, supplementing the primary antihypertensive effect with AT_2-mediated vasodilation and anti-proliferation. This is one of the proposed mechanisms for organ-protective ARB effects exceeding those predicted from BP reduction alone. ACE inhibitors, by contrast, reduce total Ang II production and therefore reduce both AT_1 and AT_2 stimulation, potentially blunting the counter-regulatory benefit.

3.4 The ACE2–angiotensin(1–7)–Mas axis

ACE2, identified in 2000, is a monocarboxypeptidase and the most important counter-regulatory arm of the RAAS at the enzymatic level. It cleaves a single amino acid from the C-terminus of angiotensin I to generate angiotensin(1-9), and more efficiently cleaves angiotensin II to generate the heptapeptide angiotensin(1-7). Ang(1-7) acts on the Mas receptor — identified in 2003 as its specific G-protein-coupled receptor — producing effects broadly counter-regulatory to AT_1 activation: vasodilation through NO and PGI_2 release, anti-proliferation, anti-fibrosis and improved insulin sensitivity.[7,19]

The axis therefore functions as an enzymatic and signalling counter-system to the classical ACE/Ang II/AT_1 axis, and this bidirectional balance is now understood to be as important as the classical cascade in determining the net cardiovascular effects of RAAS activity. Three clinical implications extend beyond BP regulation.

A self-balancing pair

When classical axis activity is high, more substrate is available for ACE2 — so counter-regulation is amplified in proportion.[20]

1. **ACE2 is the cellular entry receptor for SARS-CoV-2.** This generated concern that RAAS-blocking drugs might worsen COVID-19 outcomes by upregulating ACE2 expression. Registry data and the ACEI-COVID trial confirmed no increased mortality risk with ACEi or ARB therapy, and current guidelines recommend continuing these drugs.
2. **ACE2 downregulation in cardiac injury, obesity and diabetes** may contribute to pathological Ang II excess independent of renin levels — a mechanistic basis for the elevated cardiovascular risk in these conditions.
3. **ACE2 activators and Ang(1-7) peptide analogues** represent an emerging therapeutic strategy in hypertension and heart failure, currently in phase II development.

3.5 Aldosterone: genomic and non-genomic actions

Aldosterone is a C21 steroid synthesised in the zona glomerulosa of the adrenal cortex. Its primary physiological role is regulation of extracellular fluid volume and potassium balance through effects on renal tubular sodium and potassium transport.[1]

Three secretory stimuli

Angiotensin II — principal in most states · plasma K^+, acting directly on the zona glomerulosa · ACTH, minor basally but dominant in GRA

TABLE 3.3 — TWO MECHANISMS, TWO TIMESCALES

PATHWAY	LATENCY	MECHANISM	CLINICAL RELEVANCE
Genomic CLASSICAL RENAL MR	30–60 min lasting hours	Diffusion across the membrane, binding to cytosolic MR, nuclear translocation, and binding to hormone response elements. In the cortical collecting duct principal cell this raises apical ENaC and basolateral Na^+/K^+-ATPase expression.	Na^+ reabsorption with obligatory water, and K^+ secretion into the lumen. In pathological excess — primary aldosteronism, or secondary from heart failure, cirrhosis or nephrotic syndrome — persistent sodium retention, volume expansion and hypokalaemia.
Non-genomic VASCULAR AND CARDIAC	seconds to minutes	Membrane-associated MR coupled to EGFR transactivation, Src kinase and PI3K/Akt. Not blocked by protein synthesis inhibitors.	Rapid VSMC vasoconstriction independent of renal Na^+ handling. In cardiomyocytes, activation of Na^+/H^+ exchangers and Ca^{2+} channels raises intracellular calcium, contributing to contractile dysfunction and arrhythmia risk. **Most important: promotion of myocardial fibrosis** through fibroblast activation and collagen synthesis.

Evidence

RALES: a mortality benefit at a dose with little diuretic effect

Spironolactone in severe HFrEF produced a **30% relative risk reduction in all-cause mortality** at 25 mg — a dose with minimal diuretic effect. At 25 mg the diuretic effect is small, which is the argument for a non-diuretic mechanism — blockade of aldosterone-driven myocardial fibrosis rather than volume reduction. The trial established the benefit, not the mechanism.[18]

EPHESUS (eplerenone post-MI with LV dysfunction) and EMPHASIS-HF (eplerenone in mild HFrEF) confirmed and extended the finding.[27]

The aldosterone escape phenomenon

A clinically important limitation of ACE inhibitor and ARB therapy is aldosterone escape, or breakthrough: the return of plasma aldosterone to near-baseline or even supranormal levels 6–12 months after initiating RAAS-blocking therapy, despite continued treatment. It occurs through Ang II-independent secretion driven by potassium — the hyperkalaemia that develops with RAAS blockade directly stimulates the zona glomerulosa — by ACTH, and by other incompletely characterised stimuli.[3]

The consequence is that the expected reduction in aldosterone is not maintained long-term in a substantial proportion of patients. Escape blunts the antifibrotic and antiproteinuric benefits of RAAS blockade and contributes to the residual cardiovascular risk that persists despite apparently optimal therapy.

10–53%

is the reported range for aldosterone escape on established RAAS blockade — the spread reflects different definitions and different populations, not a settled figure.[3]

Clinical rule

Suppressing Ang II is not the same as suppressing aldosterone

Even with Ang II suppressed by an ACEi or ARB, residual or escaped aldosterone continues to drive myocardial fibrosis, proteinuria and sodium retention unless blocked directly at the receptor.

This is the principal rationale for adding an MRA — spironolactone, eplerenone or finerenone — in HFrEF, diabetic nephropathy and proteinuric CKD. FIDELIO-DKD and FIGARO-DKD gave the definitive evidence that MRA therapy on top of maximum-dose ACEi/ARB reduces cardiovascular events and CKD progression independently of residual BP reduction.[2,17]

3.6 Local tissue RAAS

Every component of the cascade — angiotensinogen, renin, ACE, angiotensin receptors, mineralocorticoid receptors — is expressed in multiple tissues independently of the circulating systemic RAAS. Local systems have been characterised in the heart, kidney, brain, vasculature and adipose tissue, and their pathological activation contributes to end-organ damage independently of circulating Ang II levels.[16]

1000×

Intrarenal Ang II concentration exceeds plasma levels a thousandfold in hypertension.

TABLE 3.4 — THE FOUR LOCAL TISSUE SYSTEMS

SYSTEM	COMPONENTS EXPRESSED	PATHOLOGICAL ROLE	CLINICAL IMPLICATION
Cardiac	Angiotensinogen in cardiomyocytes; renin in fibroblasts and mast cells; ACE in endothelium and fibroblasts; AT_1, AT_2 and MR in cardiomyocytes and fibroblasts	Local Ang II drives cardiomyocyte hypertrophy and fibroblast activation independently of plasma Ang II — which is why LVH can persist or progress despite systemic RAAS suppression.	Tissue-penetrating ACEi (ramipril, perindopril, trandolapril) may have superior cardiac effects to enalapril or lisinopril. HOPE, QUIET and EUROPA all support cardioprotection beyond BP lowering.
Renal	Angiotensinogen in proximal tubular cells — the major source of intrarenal Ang II; renin in JG cells and collecting duct; ACE on the proximal brush border; AT_1 throughout the tubule	Intrarenal Ang II drives proximal Na^+ reabsorption through NHE3 independently of systemic levels, sustaining intraglomerular hypertension even when the systemic system appears suppressed.	ACEi and ARBs reduce intrarenal Ang II and specifically dilate efferent arterioles — the mechanistic basis for renoprotection beyond systemic BP lowering in CKD.
Vascular and adipose	Angiotensinogen in VSMC and adventitial fibroblasts; renin in adventitia; ACE in endothelium — the primary site of systemic Ang I conversion; AT_1 and AT_2 in VSMC and endothelium	Local Ang II drives VSMC proliferation and hypertrophy, and NADPH oxidase-mediated oxidative stress that reduces NO. Visceral fat generates Ang II acting on perivascular adipose and systemically.	Adipose RAAS expansion contributes to the difficulty of controlling BP in obese patients despite optimal systemic blockade. Weight loss reduces adipose RAAS activity and BP independently of systemic renin change.
Cerebral	Angiotensinogen and Ang II synthesised de novo in glial cells; ACE in circumventricular organs — subfornical organ, area postrema; AT_1 in RVLM, hypothalamus, nucleus ambiguus	Central Ang II acting on RVLM AT_1 receptors increases sympathetic outflow independently of circulating Ang II, and may explain persistent sympathetic overactivation despite adequate systemic blockade.[8]	Not blocked by agents with poor CNS penetration (enalapril, losartan). Ramipril and telmisartan penetrate better and may reduce central RAAS activity more effectively — a proposed, not proven, mechanism for differential dementia risk.

3.7 Pharmacological exploitation of the RAAS

The cascade has five pharmacologically accessible intervention points. The clinical characteristics of each class — efficacy profile, adverse effects, interactions, special indications — are direct consequences of the precise biochemical step blocked and the compensatory responses that blockade provokes.

TABLE 3.5 — FIVE INTERVENTION POINTS ON ONE CASCADE

POINT	CLASS	CASCADE EFFECT	KEY CLINICAL CONSEQUENCE
Renin secretion UPSTREAM	Beta-blockers indirect	Block beta-1–mediated renin secretion from JG cells, reducing circulating renin and therefore Ang I, Ang II and aldosterone.	Most effective in high-renin neurogenic hypertension where the SNS is the primary renin driver; less effective in low-renin volume-driven hypertension — elderly, salt-sensitive, Afro-Caribbean. This is the physiology behind the AB/CD rule.
Renin enzyme DIRECT · HISTORICAL	aliskiren	Non-peptide inhibitor occupying the renin active site, blocking angiotensinogen cleavage and reducing Ang I, Ang II and aldosterone simultaneously. Plasma renin concentration rises while activity falls.	**Contraindicated with an ACEi or ARB in diabetes — that is the label wording, and ALTITUDE enrolled only diabetic patients. In renal impairment the combination is a precaution to be avoided, not a stated contraindication.** ALTITUDE: excess renal failure, hyperkalaemia, hypotension and stroke when added to existing blockade. Very limited role.[15]
ACE enzyme ANG I → ANG II	ACE inhibitors	Blocks Ang II generation and bradykinin degradation. Net effect: less vasoconstriction, plus vasodilation and organ protection from preserved bradykinin acting through NO and PGI_2. Reactive renin rise follows.	Cough in 10–35% of Asian populations; angioedema rare but life-threatening. Cardio- and renoprotective beyond BP. First-line with proteinuria, post-MI, HFrEF and high CV risk (HOPE, SOLVD, AIRE, PROGRESS).[24]
AT_1 receptor ANG II BINDING	ARBs	Competitively blocks AT_1 so Ang II cannot bind; accumulated Ang II acts on AT_2. No bradykinin accumulation, therefore no cough. Reactive renin and Ang II rise.	Equivalent outcomes to ACEi; preferred when ACEi cough is intolerable. **Do not combine an ACEi with an ARB** — ONTARGET showed more renal failure and hyperkalaemia with no CV benefit. LIFE, RENAAL, IDNT, VALUE.[9]
Mineralocorticoid receptor ALDOSTERONE EFFECT	MRAs: spironolactone, eplerenone, finerenone	Block aldosterone binding to MR, preventing genomic Na^+ retention and non-genomic fibrotic effects. Circulating aldosterone is not reduced and may rise as MR-mediated feedback is lost.	Spironolactone is the most effective fourth-line drug in resistant hypertension (PATHWAY-2, superior to doxazosin and bisoprolol)[25], limited by gynaecomastia and erectile dysfunction. Eplerenone: more selective, post-MI HFrEF. Finerenone: non-steroidal, for diabetes with CKD, lower hyperkalaemia risk.[13]

The dual ACE substrate deserves emphasis. ACE inhibitors reduce Ang II — the same effect ARBs produce — and increase bradykinin, which ARBs do not. The bradykinin component causes the cough and angioedema, but also a component of cardioprotection not reproduced by ARBs: bradykinin stimulates endothelial NO and PGI_2 release, promotes cardiac preconditioning and has direct anti-ischaemic myocardial effects. ONTARGET, comparing ramipril, telmisartan and their combination, found telmisartan non-inferior to ramipril — 16.7% against 16.5%, relative risk 1.01, 95% CI 0.94–1.09 — with no signal favouring either, and the combination arm numerically lower still at 16.3%.[14] The bradykinin difference is a real pharmacological difference and it remains the mechanistic argument sometimes made for an ACEi first. ONTARGET supplies no outcome evidence for it. The guidelines treat the two classes as equivalent first-line choices, and this book does not let a mechanism

Frequently misunderstood

An ACEi does two things an ARB does not both do: it lowers Ang II *and* raises bradykinin.

decide what the evidence leaves open: either class may be started, and where cough or angioedema makes an ACEi unsuitable an ARB is used with no expected loss of benefit.

KEY POINTS

1. **The cascade:** angiotensinogen → renin (rate-limiting) → Ang I → ACE, which also degrades bradykinin → Ang II → AT_1 (vasoconstriction, LVH, fibrosis, aldosterone) and AT_2 (counter-regulatory). Counter-arm: ACE2 → Ang(1–7) → Mas.
2. **Three renin signals:** low afferent pressure (explains reactive renin rise on ACEi/ARB); low tubular NaCl at the macula densa (explains why loop diuretics stimulate the RAAS); beta-1 receptors on JG cells (explains the renin effect of beta-blockers).
3. **Ang II beyond vasoconstriction:** LVH through MAPK/GATA-4, fibrosis through TGF-β1/NF-κB, intraglomerular hypertension through efferent constriction, and NADPH oxidase-driven oxidative stress. HOPE: 22% MACE reduction on 3 mmHg.
4. **Aldosterone escape:** aldosterone returns to baseline 6–12 months after starting an ACEi/ARB, driven by K^+ and ACTH; reported rates range from 10% to 53% and the definition drives the number. The rationale for adding an MRA in HFrEF, diabetes with CKD and resistant hypertension.
5. **ACEi against ARB:** the ACEi blocks Ang II production and preserves bradykinin; the ARB blocks AT_1 and leaves AT_2 counter-regulation unopposed. ONTARGET: equivalent outcomes — and do not combine the two for blood pressure. The one licensed exception is an ARB added to an ACEi in heart failure, under specialist supervision.
6. **Tissue RAAS** operates independently of the circulation. Intrarenal Ang II exceeds plasma levels a thousandfold, maintaining intraglomerular hypertension even under systemic blockade. Tissue-penetrating ACEi may protect better.
7. **MRAs in resistant hypertension:** spironolactone was the most effective fourth drug in PATHWAY-2. Finerenone in FIDELIO-DKD and FIGARO-DKD reduced CKD progression and CV events on top of maximal ACEi/ARB, with less hyperkalaemia.

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CHAPTER 4 PART I · MECHANISM

The sympathetic nervous system in BP regulation

Neural pathways, adrenoceptor pharmacology, the MSNA evidence, and the neurogenic basis of hypertension.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The three effector pathways** — cardiac, arteriolar and renal routes to a raised pressure.
2. **Adrenoceptor subtypes** — distribution, signalling, and the rationale for selective blockade.
3. **Direct human evidence** — microneurography, noradrenaline spillover, HRV and BRS.
4. **Why overactivation is primary** — how the circularity argument was resolved.
5. **Neurogenic hypertension across comorbidities** — obesity, OSA and CKD as one mechanism.
6. **Renal sympathetic nerves** — afferent and efferent function, and the denervation evidence.
7. **The resting heart rate** — the most accessible bedside marker of sympathetic drive.

4.1 The three sympathetic effector pathways

The sympathetic nervous system raises blood pressure through three anatomically and mechanistically distinct effector pathways, each targeting a different component of MAP = CO × SVR. Understanding all three is essential for rational drug selection in sympathetically driven hypertension, because different classes address different pathways with very different specificity.

One equation, three routes

Cardiac raises CO. Arteriolar raises SVR. Renal raises both, through the RAAS and sodium.

TABLE 4.1 — THE THREE EFFECTOR PATHWAYS

PATHWAY	EFFECTOR ORGAN	MECHANISM	BP EFFECT AND DRUG TARGET
Cardiac BETA-1	SA node · AV node · ventricular myocardium	Noradrenaline released from cardiac sympathetic terminals binds beta-1 adrenoceptors: positive chronotropy at the SA node, inotropy in the ventricular myocardium, dromotropy at the AV node. CO rises through both HR and SV.	Raises SBP and MAP through elevated CO; **elevated resting HR is the primary clinical marker.** Target: beta-1 selective blockers — bisoprolol, metoprolol, nebivolol; non-selective propranolol or carvedilol.
Arteriolar ALPHA-1	Arteriolar smooth muscle — the resistance vessels	Noradrenaline binds alpha-1 on VSMC: Gq → IP_3 → Ca^{2+} release → smooth muscle contraction → arteriolar vasoconstriction. SVR rises through reduced radius, with Poiseuille fourth-power amplification.	Raises DBP and MAP through elevated SVR; a high DBP relative to SBP marks arteriolar vasoconstriction. Target: alpha-1 blockers (doxazosin, prazosin), central sympatholytics, vasodilatory beta-blockers (nebivolol via beta-3/NO, carvedilol via alpha-1 block).
Renal BETA-1 AND ALPHA-1	Juxtaglomerular cells · tubular epithelium · renal vasculature	Three simultaneous targets: beta-1 on JG cells → renin secretion → Ang II and aldosterone; alpha-1 on the afferent arteriole → renal vasoconstriction and reduced GFR; alpha-1 on proximal tubular cells → raised Na^+/H^+ exchanger activity → sodium reabsorption.	Raises MAP through RAAS activation over hours and direct sodium retention within minutes, creating **positive feedback: SNS → RAAS → more SNS.** Target: beta-blockers for the renin limb; renal denervation ablates all three at once; ACEi/ARBs block the downstream consequence.

4.2 Adrenoceptor subtypes and drug selectivity

The cardiovascular effects of sympathetic activation are mediated by a family of G-protein-coupled adrenoceptors differing in tissue distribution, G-protein coupling and signal transduction. Pharmacological selectivity for these subtypes determines the clinical profile of each adrenergic class, and explains the substantial differences in adverse effects, efficacy patterns and special indications among drugs that share a common mechanism.

Why side effects differ

Drugs sharing one mechanism — reducing sympathetic tone — differ clinically only by which receptor subtypes they touch.

TABLE 4.2 — ADRENOCEPTOR SUBTYPES: LOCATION, SIGNALLING, PHARMACOLOGY

RECEPTOR	PRIMARY LOCATIONS	SIGNAL CASCADE	PHYSIOLOGICAL EFFECT	DRUGS
Alpha-1 GQ	Arteriolar VSMC · venous capacitance vessels · prostate · skin, gut and GU tract	PLC → IP_3 → Ca^{2+} → MLCK → smooth muscle contraction	Arteriolar vasoconstriction with rising SVR; venoconstriction; prostatic contraction	Alpha-1 blockers: doxazosin, prazosin, terazosin. Also blocked by carvedilol. Phentolamine — non-selective — for phaeochromocytoma crisis.[19]
Alpha-2 GI	Presynaptic sympathetic terminals as autoreceptors · NTS and RVLM neurons · pancreatic beta cells · platelets	Inhibits adenylyl cyclase → less cAMP → reduced Ca^{2+} influx → inhibition of noradrenaline vesicle fusion	Presynaptic autoinhibition of NA release; central RVLM sympathoinhibition	Central alpha-2 *agonists*: clonidine, methyldopa via alpha-methylnoradrenaline, guanfacine. These activate alpha-2 to produce central sympathoinhibition.
Beta-1 GS	SA node · AV node · ventricular myocardium · JG cells · adipose tissue	Adenylyl cyclase → cAMP → PKA → L-type Ca^{2+} channel phosphorylation (chronotropy, inotropy) and phospholamban phosphorylation (lusitropy)	Positive chronotropy, inotropy, dromotropy and lusitropy; renin secretion; adipose lipolysis	Beta-1 selective blockers: bisoprolol (most selective), metoprolol, nebivolol, atenolol. Nebivolol additionally releases NO through beta-3.

RECEPTOR	PRIMARY LOCATIONS	SIGNAL CASCADE	PHYSIOLOGICAL EFFECT	DRUGS
Beta-2 GS	Bronchiolar smooth muscle · arterial and skeletal muscle arterioles · liver · uterus	cAMP → PKA → smooth muscle relaxation; hepatic glycogenolysis; skeletal muscle K^+ uptake	Bronchodilation; exercise vasodilation shunting blood to working muscle; hyperglycaemia and hypokalaemia on systemic activation	Non-selective beta-blockers block beta-2 — bronchospasm in asthma is the reason they are **avoided in reversible airways disease.** The corollary matters more and is more often got wrong: **bronchospastic disease is not a listed contraindication to a beta-1 selective agent**, and such an agent should not be withheld where the indication is strong — after infarction, or in heart failure. The label is permissive on four conditions rather than none: patients with bronchospastic disease should in general not receive a beta-blocker; a beta-1 selective agent may be used where other treatment has failed or is not tolerated; beta-1 selectivity is not absolute and is dose-dependent, so the dose is the lowest possible; and a bronchodilator is readily available or given concomitantly.[27] In severe or poorly controlled asthma the risk is real and the decision is shared with the respiratory physician. Selectivity with caution is the requirement, not abstention.
Beta-3 GS AND GI	Adipose tissue · bladder detrusor · cardiac myocytes · vascular endothelium	Adipose: cAMP → HSL → thermogenesis and lipolysis. Cardiac: Gi-mediated negative inotropy. Endothelial: Gi → NOS3 phosphorylation → NO	Thermogenesis and lipolysis; a cardiac inotropic brake; endothelial NO release; detrusor relaxation	Nebivolol has partial beta-3 agonist activity giving NO-mediated vasodilation — the one beta-blocker with a vasodilatory rather than vasoconstrictive haemodynamic profile. Mirabegron, a selective beta-3 agonist for overactive bladder, may raise BP.
Dopamine D1 GS	Renal and mesenteric arteries · renal tubular cells	cAMP → renal vasodilation; cAMP → inhibition of Na^+/K^+-ATPase and Na^+/H^+ exchanger → natriuresis	Renal vasodilation and natriuresis. The 'renal-dose dopamine' concept is now largely discredited.	Fenoldopam, a selective D1 agonist, is used intravenously in hypertensive emergencies and preserves renal blood flow. Low-dose dopamine activates D1 but renal protection is unproven.

4.3 Direct human evidence for sympathetic overactivation

The neurogenic hypothesis of essential hypertension — that sympathetic overactivation is a primary causal mechanism rather than a secondary response to elevated BP — rests on a body of direct human evidence accumulated over five decades, qualitatively different from the indirect inferences available from animal models. Three measurement techniques have provided converging evidence that muscle sympathetic nerve activity is chronically elevated in human essential hypertension, and that the elevation precedes rather than follows sustained BP elevation.[20]

Microneurography and muscle sympathetic nerve activity

Muscle sympathetic nerve activity, recorded from peroneal or tibial fascicles innervating skeletal muscle vasculature, is the gold-standard direct measure of sympathetic vasomotor activity in humans. It is expressed as bursts per minute, or per 100 cardiac cycles, and has three established characteristics relevant to hypertension research.

The technique

A tungsten microelectrode inserted percutaneously into the common peroneal nerve at the fibular head, recording multiunit discharge in postganglionic fascicles. Vallbo and Hagbarth, 1960s.[14]

1. **MSNA is tightly coupled to the cardiac cycle.** Bursts occur in diastole, triggered by baroreceptor unloading during the diastolic pressure fall. Burst frequency is therefore partly determined by baroreflex gain — so the reduced BRS of Chapter 2 directly contributes to elevated resting MSNA by weakening inhibitory input to the RVLM.[13,17]
2. **MSNA is markedly elevated in untreated essential hypertension:** approximately 40–50 bursts per 100 cardiac cycles against 25–35 in age- and BMI-matched normotensives, a 40–80% elevation that persists after adjustment for age, BMI and physical fitness.[12]
3. **Normotensive offspring of hypertensive parents already have elevated MSNA** — before they have developed hypertension themselves. Replicated in multiple independent cohorts, this establishes that elevated MSNA is not simply a consequence of baroreceptor unloading by a raised pressure, but reflects an inherited or developmentally determined upregulation of central sympathetic drive that precedes the haemodynamic abnormality.

Organ-specific noradrenaline spillover

Plasma noradrenaline concentration reflects the net balance of total sympathetic firing and noradrenaline clearance, and is therefore an insensitive, non-specific index of regional activity. The isotope-dilution spillover technique developed by Esler and colleagues at the Baker Institute overcomes this by combining total-body spillover from tritiated noradrenaline infusion, regional arteriovenous concentration differences across specific organs, and organ blood flow by indicator dilution — allowing the noradrenaline released from each organ's terminals to be calculated separately.[9]

2–3×

higher cardiac noradrenaline spillover in young essential hypertensives than normotensives — with total plasma noradrenaline normal.

The key finding in essential hypertension is that cardiac and renal spillover are selectively elevated even when total plasma noradrenaline is normal or only mildly raised. Cardiac spillover is two to three times higher in young essential hypertensives, accounting for the elevated resting heart rate and the high-CO phenotype. Renal spillover is disproportionately elevated relative to other organs, driving renin secretion and tubular sodium retention. That organ-selective pattern — cardiac and renal rather than uniform global activation — is the mechanistic justification for renal denervation: if

renal overactivation is disproportionate and contributes independently, selective ablation should reduce it while leaving cardiac and systemic tone relatively unaffected.

Heart rate variability and autonomic balance

Heart rate variability provides an accessible non-invasive index of autonomic cardiovascular modulation. The RR interval fluctuates continuously under respiratory sinus arrhythmia, sympathetic vasomotor waves and very-low-frequency thermoregulatory and RAAS-mediated oscillations. The LF/HF ratio indexes sympathovagal balance, though its interpretation is debated because LF power has both sympathetic and vagal contributions.

Frequency bands

HF 0.15–0.40 Hz — vagal
LF 0.04–0.15 Hz — sympathetic vasomotor
VLF — thermoregulatory and RAAS

In essential hypertension, HRV analysis consistently shows reduced total power, reduced HF power indicating lost vagal tone, an elevated LF/HF ratio and increased LF power. SDNN — the standard deviation of all RR intervals — is the simplest and most robust measure: it integrates all frequency components and is the strongest HRV predictor of cardiovascular mortality in post-MI and heart failure populations (DIAMOND-MI, ATRAMI). In hypertension, low SDNN correlates with elevated MSNA and predicts incident cardiovascular events independently of mean BP.

4.4 Why overactivation is primary, not secondary

The central challenge in establishing sympathetic overactivation as a cause rather than a consequence is the circularity argument. Four independent lines of evidence have collectively resolved it in favour of the primary neurogenic hypothesis, and each works by establishing temporal precedence.

The circularity problem

Elevated BP unloads baroreceptors, which raises RVLM drive and MSNA. So does high MSNA cause the hypertension, or does the hypertension cause the high MSNA?

TABLE 4.3 — FOUR LINES OF EVIDENCE FOR SYMPATHETIC PRIMACY

EVIDENCE	DESIGN	FINDING	WHY IT SUPPORTS PRIMACY
Elevated MSNA in pre-hypertensive offspring	Cross-sectional microneurography in normotensive offspring of hypertensive against normotensive parents — Julius, Greenfield and Lambert cohorts	MSNA significantly elevated in offspring with a positive family history before any BP elevation; the elevation predicts subsequent hypertension at 5–10 years.	MSNA elevation precedes BP elevation, so it cannot be caused by baroreceptor unloading from a pressure that has not yet risen. Supports an inherited central sympathetic setpoint.
Resting HR predicts incident hypertension	Prospective cohorts — Framingham, HARVEST, PAMELA — measuring resting HR in normotensives and following for incident hypertension	Resting HR in the highest quartile, above 80 bpm, carried a two- to threefold risk of developing hypertension over 10–15 years.	A cardiac sympathetic marker precedes sustained BP elevation; the temporal sequence is consistent with the SNS as primary driver.
RVLM firing rates in hypertensive animals	Direct RVLM single-unit recordings in spontaneously hypertensive rats against Wistar-Kyoto controls, before hypertension develops	RVLM neurons fire faster in pre-hypertensive SHR than in normotensive controls, and the faster firing precedes the BP elevation.	RVLM overactivity is an intrinsic property of the neurogenic phenotype, not a response to elevated pressure.
Young hypertensive haemodynamics	Invasive haemodynamic studies (Julius, Lund-Johansen) in young untreated hypertensives against normotensive controls	High CO, elevated HR, normal or low SVR — the haemodynamic fingerprint of cardiac sympathetic overactivation before structural SVR elevation appears.[15]	The high-CO pattern is mechanistically consistent with cardiac overactivation as the initiating abnormality; SVR rises years later from remodelling.

4.5 Neurogenic hypertension across comorbidities

Sympathetic overactivation is not confined to idiopathic essential hypertension. It is a shared pathological mechanism running through several common conditions that cluster with hypertension, and recognising it as a common thread has direct implications for drug selection in these patients.

Obesity and the leptin–SNS axis

Adipocytes are the primary source of leptin, the satiety hormone signalling energy sufficiency to the hypothalamus. In obesity, leptin levels are chronically elevated but fail to suppress appetite — central leptin resistance. Leptin's ability to activate the sympathetic nervous system through hypothalamic and brainstem projections to the RVLM is nevertheless preserved, a dissociation termed selective leptin resistance. Obese patients therefore have persistent hyperphagia from central resistance alongside persistent sympathetic overactivation from intact leptin–SNS signalling.

Selective leptin resistance

Appetite suppression fails. Sympathetic activation does not. The obese patient gets the worst of both.

The quantitative evidence is compelling. MSNA in obese individuals is about 40% higher than in lean controls matched for age and sex; renal noradrenaline spillover is the most disproportionately elevated component; and the correlation between plasma leptin and MSNA, $r \approx 0.49$, is among the stronger predictor–MSNA relationships in human sympathetic neuroscience. Weight loss by any mechanism — diet, exercise, bariatric surgery, GLP-1 agonists, SGLT2 inhibitors — reduces MSNA in proportion to the weight lost, with large and sustained reductions after major surgical weight loss.[1,22]

Obstructive sleep apnoea

As described in Chapter 2, OSA produces sympathetic overactivation through two interacting mechanisms: acute nocturnal surges from each apnoeic episode, as intermittent hypoxia activates the carotid body and excites the RVLM, and chronic carotid body sensitisation producing persistent daytime MSNA elevation. In moderate to severe disease with an AHI above 30, daytime MSNA is approximately twice that of matched controls — the mechanism responsible for hypertension persisting through the waking hours despite no ongoing apnoeas.[24]

The haemodynamic fingerprint has two features directly attributable to the sympathetic mechanism: an elevated resting heart rate, the cardiac component, and the non-dipping or reverse-dipping pattern on ABPM, from nocturnal surges holding pressure up through the sleep period. Non-dipping is the single most important ABPM finding for identifying OSA as the dominant hypertensive mechanism.

60%

of non-dippers on ABPM have OSA confirmed on polysomnography.

Chronic kidney disease

CKD is associated with MSNA elevation among the highest recorded in any non-cardiac condition, through two distinct mechanisms. First, afferent renal nerve signals from the ischaemic or diseased kidney travel to the NTS and RVLM and sensitise central sympathetic circuits. Second, uraemic toxins including indoxyl sulphate and p-cresol directly activate central sympathetic neurons through incompletely characterised mechanisms.

The clinical implication is that in CKD with hypertension, sympathetic overactivation is a disease-specific mechanism that standard drug protocols may not adequately address. Beta-blockers — particularly the metabolically neutral carvedilol and nebivolol — are under-prescribed in CKD hypertension despite a strong mechanistic rationale. Renal denervation has shown promise in CKD-related resistant hypertension in early data, consistent with the importance of renal afferent signalling in maintaining elevated central drive — though the reductions remain modest and the evidence base small.

Converse, 1992

Bilateral nephrectomy in dialysis patients produced immediate, dramatic reductions in MSNA — proof that the kidney itself generates the afferent signal.[6]

4.6 Renal denervation: mechanism and clinical evidence

The renal sympathetic nerves run in the adventitia of the renal arteries, intermingled with connective tissue at the outer wall. They comprise efferent fibres from the RVLM to the kidney, mediating the three renal effects of section 4.1, and afferent fibres from renal mechanoreceptors and chemoreceptors to the NTS and RVLM, mediating the kidney-to-brain signalling that elevates central drive. Catheter-based renal denervation delivers radiofrequency energy or ultrasound through an endovascular catheter in the renal arteries, ablating both populations.[8]

TABLE 4.4 — THE RENAL DENERVATION TRIAL SEQUENCE

TRIAL	DESIGN	BP REDUCTION	CLINICAL IMPLICATION
SYMPLICITY HTN-1 and HTN-2 2009–2010	First-generation single-electrode catheter; unblinded; n = 106 in HTN-2[18]	SBP −32 mmHg at 6 months in the treated arm against −1 mmHg in controls[10]	Dramatic apparent efficacy generated enormous enthusiasm, but there was no sham control, and open-label design with selected patients confounded interpretation.
SYMPLICITY HTN-3 2014	First sham-controlled trial; n = 535; randomised 2:1 active to sham; primary endpoint office SBP at 6 months	Active −14.1 mmHg, sham −11.7 mmHg. Difference −2.4 mmHg; p = 0.26[4]	Failed its primary endpoint, to the field's surprise. Later analysis showed incomplete denervation, antihypertensive changes in 39% of patients, and white-coat responders confounding the result.[28]
SPYRAL HTN-OFF MED and ON MED 2017–2021	Redesigned multielectrode spiral catheter giving more complete denervation; patients off or on standardised therapy; sham-controlled; ABPM primary endpoint	OFF MED: 24-hour SBP −4.7 against −0.6 mmHg sham (p = 0.0068). ON MED: −9.0 against −1.6 mmHg (p < 0.001)[5]	Positive sham-controlled evidence with the improved catheter. ABPM confirms a genuine haemodynamic effect beyond placebo. ESC 2023: RDN may be considered in resistant hypertension as an adjunct to drug therapy.
RADIANCE-HTN TRIO 2021	Endovascular ultrasound denervation; n = 136; patients on standardised triple therapy; sham-controlled	Two-month daytime ABPM: median **−8.0 mmHg, 4.5 mmHg greater than sham**[2]	Confirms the effect with the ultrasound modality and extends the evidence to patients already on triple therapy, supporting a role as an add-on procedure in truly resistant hypertension.

Clinical rule

Where renal denervation actually sits

ESH 2023: RDN may be considered in confirmed resistant hypertension — uncontrolled on three or more drugs at optimum doses including a diuretic, with secondary causes excluded — at experienced centres with appropriate selection and follow-up. It is not a first- or second-line intervention.[3,21]

Context the magnitude honestly: **4–9 mmHg on ABPM, against the 8–10 mmHg expected from adding spironolactone** as a fourth drug in the same population.

It is not a way around non-adherence. Non-adherence is the commonest cause of apparently resistant hypertension, and the denervation trials screened it out — by witnessed dosing, pill counts or drug assay — before randomising. A patient not taking three drugs is not a denervation candidate; he is a patient whose adherence has not yet been addressed. Selection is equally strict anatomically: suitable renal artery anatomy, adequate GFR, secondary causes excluded, at a centre that does the procedure regularly.

4.7 The resting heart rate as a clinical marker

Resting heart rate is the most accessible bedside observation in this chapter, and the one most easily over-read. It is not a measurement of sympathetic drive: the relationship between resting heart rate and directly measured sympathetic nerve traffic is weak in essential hypertension, and a rate above 80 may equally reflect deconditioning, anaemia, thyrotoxicosis, fever, pain, alcohol or a drug. What it is, robustly, is an independent cardiovascular risk factor whose prognostic importance rivals that of systolic BP in several large prospective datasets — and a prompt to go looking for a driver.

Target on treatment

55–70 bpm — the ESC recommendation in established CAD, and reasonable as a general target in neurogenic hypertension.[25]

TABLE 4.5 — THE EVIDENCE ON RESTING HEART RATE

SOURCE	FINDING
Framingham Heart Study 28-YEAR FOLLOW-UP	Resting HR predicts all-cause and cardiovascular mortality independently of BP, cholesterol, smoking and physical activity.[16]
Meta-analysis 46 STUDIES · 1.25 MILLION	Each 10 bpm increment carries a **9% increase in all-cause mortality** (RR 1.09, 95% CI 1.07–1.12).[26]
Pooled placebo-arm analysis STABLE OR SUSPECTED CORONARY DISEASE	Resting HR independently predicts all-cause and cardiovascular mortality in stable CAD. Above 70 bpm identifies a high-risk subgroup with mortality equivalent to patients with substantially worse LV function.[7]
BEAUTIFUL N = 10,917 · STABLE CAD, HR > 70	Ivabradine — pure HR reduction with no antihypertensive effect — reduced MI by **36%** and coronary revascularisation by 30% in patients with HR above 70 bpm and impaired LV function, confirming that elevated HR is a mechanistic contributor to ischaemic events rather than merely a marker.[11]
HARVEST NORMOTENSIVES, PROSPECTIVE	Resting HR above 80 bpm in normotensives carried a **3.2-fold** increased risk of developing hypertension over 10 years, independent of baseline BP and other risk factors — HR elevation as a prodromal marker of neurogenic hypertension.[23]
What resting HR does and does not measure PHYSIOLOGICAL LIMITS OF THE MARKER	Resting heart rate is a chronotropic endpoint, shaped by vagal tone, fitness and drugs as well as by sympathetic outflow. It is an accessible indirect index of cardiac sympathetic drive, not a measurement of it. A numeric correlation with muscle sympathetic nerve traffic is widely quoted; it could not be traced to a source that states it, and none is given.

The clinical implication is that every hypertensive patient's resting heart rate should be documented at every visit — not merely as a vital sign but as a risk marker. Above 80 bpm in an untreated patient — once anaemia, thyroid disease, fever, pain and drugs have been excluded — the rate is consistent with sympathetic overactivation, and is a reason to look for what is driving it: stress, disrupted sleep, apnoea, deconditioning, alcohol. It also represents an independent cardiovascular risk that is *not* addressed by drugs which lower BP without lowering rate — amlodipine, diuretics, ARBs. Where the guideline permits a choice, that is an argument a beta-blocker can be weighed on. It is not, on its own, a reason to prescribe one.

KEY POINTS

1. **Three effector pathways:** cardiac (beta-1 → chronotropy and inotropy → CO); arteriolar (alpha-1 → vasoconstriction → SVR); renal (beta-1 → renin, alpha-1 → Na^+ reabsorption). Each has its own drug class.
2. **Selectivity determines profile:** beta-1 selective agents avoid beta-2 bronchospasm; nebivolol adds beta-3/NO vasodilation; carvedilol adds alpha-1 blockade; clonidine and methyldopa *activate* alpha-2 for central sympathoinhibition.
3. **MSNA is 40–80% elevated** in untreated hypertensives, and already elevated in normotensive offspring of hypertensive parents — proving temporal precedence, and answering the circularity argument.
4. **Organ-specific spillover (Esler):** cardiac and renal noradrenaline release are selectively elevated despite normal total plasma noradrenaline. Renal selectivity is the mechanistic basis for denervation.
5. **Comorbidities share the mechanism:** obesity (leptin–SNS, MSNA about 40% higher, reversible with weight loss); OSA (carotid body sensitisation, daytime MSNA doubled, 60% of non-dippers); CKD (renal afferent signalling — Converse 1992).
6. **Renal denervation:** SYMPLICITY HTN-3 failed on sham control; SPYRAL and RADIANCE with better catheters gave 4–9 mmHg on ABPM. ESC 2023: adjunct in confirmed resistant hypertension at experienced centres, with strict selection — never a substitute for adherence.
7. **Resting HR is a target, not just a vital sign.** Each 10 bpm carries 9% more mortality (meta-analysis of 46 studies); Framingham established that the relation is independent of BP. HARVEST: a resting rate in the top quartile predicted progression to sustained hypertension. BEAUTIFUL: HR reduction alone cut MI by 36% — but only in the HR > 70 subgroup; the trial's own primary endpoint was neutral. Target 55–70 bpm.

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CHAPTER 5 PART I · MECHANISM

Renal pressure-natriuresis: Guyton's infinite gain theory

The kidney as the ultimate arbiter of blood pressure, the pressure-natriuresis curve, and why all sustained hypertension is renal.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Guyton's infinite gain concept** — why only the kidney can sustain a long-term BP elevation.
2. **The pressure-natriuresis curve** — normal physiology, the rightward shift, and what it means clinically.
3. **What shifts the curve rightward** — RAAS, sympathetic drive, nephron number, immune infiltration.
4. **The Brenner hypothesis** — nephron number at birth and the lifetime consequence for BP.
5. **Renal immune mechanisms** — Th17 cells, Tregs and the salt–immune–NO pathway.
6. **Why diuretics work** — in virtually every subtype, whatever the primary mechanism.
7. **Resistant hypertension** — why volume is always involved, and the 24-hour urine sodium.

5.1 Guyton's infinite gain concept

Arthur Guyton's analysis of long-term blood pressure regulation, developed through mathematical modelling and experiment at the University of Mississippi in the 1970s and 1980s, produced one of the most important and most frequently misunderstood insights in cardiovascular physiology: the kidney is the only organ capable of sustaining a long-term elevation in blood pressure, and any mechanism causing sustained hypertension must ultimately do so by impairing renal sodium excretion.[4]

The argument develops from a conservation law that applies to any steady-state organism: at any stable blood pressure, sodium intake must equal sodium output. If more sodium is ingested than excreted, sodium and obligatory water accumulate, expanding extracellular fluid volume, increasing venous return, raising cardiac output and elevating pressure. If output exceeds intake, the reverse occurs. Stable BP requires balanced sodium homeostasis, and that requires the kidney to adjust excretion to match intake precisely.

The critical insight concerns the gain of this regulatory system. Guyton's analysis demonstrated that the renal–body fluid pressure control system has, in principle, *infinite* gain for long-term regulation: given days to weeks, the kidney can adjust sodium excretion to match any level of intake, restoring balance and therefore stable pressure. No other organ or regulatory system can achieve this.[8]

Gain, in engineering terms

The ratio of output change to input change in a feedback loop. High gain corrects deviations completely; low gain corrects partially.

FIGURE 5.1 — THE INFINITE GAIN ARGUMENT

PREMISE	For **any** stable long-term BP, sodium intake = sodium excretion. This is a conservation law, not an observation.
IF A NON-RENAL MECHANISM RAISES BP	Raised BP → higher renal perfusion pressure → pressure-natriuresis → negative sodium balance → volume contraction → CO falls → **BP returns toward normal.**
SO FOR BP TO STAY ELEVATED	The kidney must be *accepting* the higher pressure without proportionally increasing excretion — that is, the pressure-natriuresis curve must be shifted rightward, requiring a higher perfusion pressure to excrete the same sodium load.

Within Guyton's model, all sustained hypertension, whatever its initiating cause, is maintained by a rightward shift of the renal pressure-natriuresis relationship. That is a prediction of the model, not a conservation law and not a measured finding, and its universality is disputed. What is not disputed is its clinical use: it tells you to look at volume in every patient whose pressure will not settle.

Clinical rule

Final pathway, not first cause

This does not mean primary renal disease initiates all hypertension. It means the kidney is the **final pathway** through which any sustained elevation is maintained: neurogenic, RAAS-driven, obesity-related and aldosterone-driven hypertension all sustain their pressure because the specific mechanism operating in that patient has shifted the curve rightward.

Remove the shift — treat the mechanism, restrict sodium, or force natriuresis with a diuretic — and volume contraction will lower BP even where the initiating mechanism is not directly addressed.

5.2 The pressure-natriuresis curve

The pressure-natriuresis relationship describes the quantitative link between renal perfusion pressure and urinary sodium excretion in the steady state. It was characterised originally in isolated perfused kidney preparations and confirmed subsequently in intact animals and in humans with direct renal artery pressure manipulation.[9]

In the normal kidney the relationship is steeply positive: a 10 mmHg rise in perfusion pressure approximately doubles urinary sodium excretion in the short-term preparation. Over days the gain is greater still, because suppression of renin and aldosterone by the higher pressure, release of atrial natriuretic peptide and reduction of renal sympathetic tone all amplify the natriuretic response. The operating point on this curve — the MAP at which intake equals excretion at habitual sodium intake — defines the individual's stable long-term blood pressure.

In hypertension the curve is shifted rightward: the kidney requires a higher MAP to excrete the same sodium load, and the operating point is displaced upward. The magnitude of the shift corresponds precisely to the degree of stable hypertension — a curve shifted 20 mmHg rightward gives a stable MAP about 20 mmHg above the normotensive operating point. The curve

MAP 90–95

mmHg — the operating point for a normotensive adult on a typical Indian diet — a national mean of about 8 g of salt a day (Chapter 9).

also flattens, so the natriuretic response to a given pressure increment is attenuated by arteriolar remodelling, tubular transport upregulation and RAAS activation.

TABLE 5.1 — NORMAL AGAINST HYPERTENSIVE KIDNEY

PARAMETER	NORMAL KIDNEY	HYPERTENSIVE KIDNEY	CLINICAL CONSEQUENCE
Curve position	Operating point at MAP ≈ 90 mmHg — sodium balance at normal intake	Shifted rightward: operating point MAP ≈ 100–120 mmHg or above	Stable BP sits at the new operating point and cannot be lower without sodium restriction or pharmacological natriuresis.
Curve slope PRESSURE SENSITIVITY	Steep: a 10 mmHg rise roughly doubles Na^+ excretion	Reduced: the same increment gives a smaller proportional natriuresis — 'pressure-resistant'	A higher pressure is needed to excrete the same load, which is why lowering BP alone does not normalise volume status.
Response to sodium loading	Rapid natriuresis within hours; BP barely moves on normal loading	Blunted and delayed natriuresis; BP rises significantly with a sodium load	This is salt sensitivity, and it is measurable: 24-hour urine Na^+ plus the BP response to a salt challenge.[1]
Response to antihypertensive drugs	Any BP reduction lowers renal perfusion → sodium retention → partial BP restoration	The same counter-regulation, amplified; diuretics override it by forcing natriuresis directly	Explains why most drugs lose some efficacy over time without a diuretic. RAAS blockers provoke less counter-regulation than vasodilators, having less baroreceptor-driven sympathetic activation.

5.3 Mechanisms that shift the curve rightward

The rightward shift is produced by several overlapping mechanisms, each reducing the kidney's ability to excrete sodium at any given perfusion pressure. They correspond precisely to the pathophysiological processes described in the preceding chapters — confirming that all of them converge on the kidney, as Guyton's model predicts.

RAAS activation

Four renal actions, one direction

Afferent constriction · raised filtration fraction · NHE3 stimulation · aldosterone-driven ENaC — all retain sodium.

Angiotensin II acts on the kidney in four ways that collectively shift the curve rightward. At the afferent arteriole it causes vasoconstriction that reduces glomerular blood flow and GFR, lowering the filtered sodium load. At the efferent arteriole, constriction raises the filtration fraction, increasing peritubular capillary oncotic pressure and promoting proximal reabsorption. It directly stimulates the proximal tubular Na^+/H^+ exchanger through AT_1, independently of any haemodynamic effect. And the aldosterone it stimulates raises ENaC expression and Na^+/K^+-ATPase activity in the collecting duct, adding distal reabsorption.

The combined effect forces the kidney to reabsorb more sodium at any given pressure. This is why ACE inhibitors and ARBs are so effective in RAAS-driven hypertension: they remove the mechanism doing the shifting, allowing the curve to return toward its normotensive position.[7]

Sympathetic activation

Renal sympathetic nerves directly stimulate tubular sodium reabsorption through alpha-1 activation of NHE3 in the proximal tubule, independently of their effects on renin secretion and renal vascular resistance. This direct

tubular effect shifts the curve rightward by raising proximal reabsorptive capacity at any perfusion pressure, and it is additive to the RAAS effect because it works through a different cellular pathway.

Renal denervation reduces BP partly through this mechanism: ablating efferent fibres removes both the direct sodium retention drive and the renin drive, shifting the curve leftward. That SPYRAL and RADIANCE produced 4–9 mmHg on ABPM despite only 40–50% ablation of renal sympathetic fibres suggests even partial denervation shifts the curve — a real mechanistic effect, but a modest one, and an adjunct to drug therapy rather than a replacement for it (V1·Ch4).

Additive, not redundant

Alpha-1/Gq is a different pathway from AT_1/Gq — so RAAS blockade alone does not reverse the renal sympathetic contribution.

Reduced nephron number: the Brenner hypothesis

Barry Brenner proposed in 1988 that individuals born with a reduced number of nephrons have a permanently impaired capacity to excrete sodium at normal perfusion pressures — shifting their curve rightward from birth and predisposing them to salt-sensitive hypertension for life.[3]

Several independent lines of evidence support it. Autopsy studies show hypertensive individuals have fewer nephrons per kidney than normotensive controls matched for age and kidney weight. Live kidney donors with fewer nephrons, estimated by total glomerular volume at biopsy, have higher BP five years after donation than those with more — suggesting the remaining nephrons operate under higher intraglomerular pressure to maintain balance. And the conditions that reduce nephron endowment at birth are the same ones associated with increased lifetime hypertension risk.

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nephrons per kidney in hypertensives against 1,429,000 in matched normotensives at autopsy. Keller, NEJM 2003; $p < 0.0001$.

TABLE 5.2 — CONDITIONS REDUCING NEPHRON ENDOWMENT[2]

CONDITION	MECHANISM	MAGNITUDE OF EFFECT
Prematurity < 37 WEEKS	Nephrogenesis continues until 36 weeks; premature birth terminates it early. Nephron endowment tracks gestational age at birth closely (r = 0.87), and in most preterm infants glomerulogenesis stops within about forty days of delivery — though it can persist longer in some[18] — so the earlier the birth, the larger the share of the nephrogenic window that is never completed.[14]	Premature infants have 25–50% fewer nephrons than term infants. Lifetime hypertension risk two to three times higher, with earlier onset of CKD.
Low birth weight < 2.5 KG	Intrauterine growth restriction from maternal hypertension, placental insufficiency, malnutrition or smoking impairs nephrogenesis through the critical third trimester.	Each kilogram of lower birth weight is associated with roughly 1.5 mmHg higher adult systolic pressure in men and 2.8 mmHg in women. **India: about 27% of births are low birth weight on modelled UNICEF–WHO estimates, against 17% on the country's own recorded NFHS-5 figure — the gap is unweighed home births** — the highest rate of any major country, and a substantial population-level contribution.[5,12]
Maternal protein restriction	Protein restriction in pregnancy impairs glomerular formation, demonstrated in animal models and in epidemiological data from the Dutch Hunger Winter cohort.	Dutch Hunger Winter offspring showed higher BP, more CKD and more metabolic syndrome at 50-year follow-up — mechanistically consistent with the hypothesis.
Maternal hypertension and pre-eclampsia	Uteroplacental insufficiency reduces renal blood flow to the fetus during nephrogenesis.	Offspring of pre-eclamptic pregnancies — particularly those born preterm or growth-restricted — can have low nephron mass and a higher later risk of hypertension. Specific figures for the size of that reduction circulate widely and could not be traced to a source that states them, so none is given.[13]
Unilateral renal agenesis	Born with a single kidney: compensatory hypertrophy maintains GFR initially, but intraglomerular hypertension accelerates nephron loss.	Three times higher hypertension prevalence, earlier CKD onset and proteinuria at a younger age. Relevant to pre-employment and sports fitness assessment.

The Indian relevance is direct. India has the highest rate of low birth weight deliveries of any major country — about 27% of births on modelled UNICEF–WHO estimates, 17% on the recorded NFHS-5 figure, against 7% in the USA and 6% in the UK[12] — driven by maternal undernutrition, anaemia, early marriage and short interpregnancy intervals. These children are born with a reduced nephron complement, making them intrinsically salt-sensitive and predisposed to early-onset hypertension: a population-level biological substrate for India's hypertension epidemic operating entirely through the Guyton mechanism.[11]

5.4 Renal immune mechanisms: the Th17–NO pathway

A major conceptual advance came from recognising that immune cells infiltrate the renal interstitium in hypertension, and that this infiltration shifts the pressure-natriuresis curve rightward by impairing the nitric oxide pathway in renal tubular epithelium. Subsequent work identified the responsible subtype: T helper 17 cells.

The knockout experiment

RAG-1 mice, lacking B and T lymphocytes, develop far less hypertension on Ang II or DOCA-salt. Transferring T cells — not B cells — restores it.[6]

FIGURE 5.2 — THE SALT–IMMUNE–NO PATHWAY (WILCK ET AL., NATURE 2017)

1. **High dietary sodium** raises extracellular NaCl, which activates SGK1 kinase in Th17 cells and enhances Th17 differentiation.
2. **Th17 cells secrete IL-17A**, which impairs eNOS activity in renal tubular epithelial cells.[15]
3. **Reduced tubular NO impairs pressure-natriuresis.** NO normally promotes natriuresis; losing it shifts the curve rightward, retaining sodium at any given perfusion pressure.

Counter-regulation

Regulatory T cells suppress Th17 activation. Treg deficiency in obesity, metabolic syndrome and CKD leaves Th17 unopposed — exaggerated salt-sensitive hypertension.

Gut microbiome

A high-sodium diet reduces *Lactobacillus* species, increasing Th17 activity. Restoring *Lactobacillus* partially reversed the BP rise in mice and in humans.

The clinical implications sit at the research frontier but have two actionable consequences. First, the pathway explains how dietary sodium restriction reduces BP through a route entirely distinct from volume reduction: less sodium means less Th17 activation, restored tubular NO and a leftward curve shift. That is additive to the direct natriuretic effect, and it accounts for sodium restriction reducing BP by more than the change in urinary sodium output alone would predict.

Second, the Treg–Th17 imbalance of metabolic syndrome, obesity and CKD explains the particularly aggressive salt-sensitive hypertension in these groups, and their disproportionate response to spironolactone — which reduces Th17-driven vascular inflammation through MR-independent anti-inflammatory mechanisms alongside its classical aldosterone antagonism.

5.5 Why diuretics work in every subtype

Three transporters, one effect

Thiazides block NCC in the distal convoluted tubule · loop agents block NKCC2 in the thick ascending limb · MRAs block ENaC in the collecting duct.

One of the most clinically useful predictions of Guyton's model is that diuretics should be effective in virtually all forms of hypertension regardless of the primary mechanism, because they directly force the leftward curve shift that any sustained BP reduction requires.

The mechanism is straightforward. Each class blocks a specific tubular transporter responsible for a fraction of total sodium reabsorption; blocking it means the kidney excretes more sodium at any given MAP, establishing a new sodium balance at a lower operating pressure.

The counter-regulatory response is equally predictable from the model, and partially limits monotherapy: volume contraction reduces renal perfusion pressure and activates the RAAS through the macula densa mechanism of Chapter 3, which attempts to restore balance by shifting the curve rightward again. This is why diuretic monotherapy produces a large initial reduction that partly attenuates over the first six to eight weeks. Combining a diuretic with a RAAS blocker prevents the escape and sustains the full natriuretic benefit — the combination is mechanistically synergistic rather than merely additive.

Evidence

Why chlorthalidone won ALLHAT

Chlorthalidone was superior to amlodipine and lisinopril in preventing heart failure, and equivalent for coronary events and stroke, in a high-risk hypertensive population.

Mechanistically: it addresses the volume component present in *all* subtypes — including those whose primary mechanism is RAAS activation or arteriolar stiffness, which lisinopril and amlodipine respectively address by other routes. In the elderly, volume-dependent low-renin phenotype that predominated in ALLHAT, direct volume reduction was the most appropriate intervention available.

5.6 Guyton's model and resistant hypertension

By definition, a patient whose BP remains elevated on three or more appropriately dosed drugs including a diuretic has either an inadequately shifted pressure-natriuresis curve despite the diuretic, or a diuretic dose or class insufficient to force the necessary shift at their level of sodium retention. Either way, the model says: look at volume.

PATHWAY-2 provided direct experimental support. It compared four fourth-line agents — spironolactone, doxazosin, bisoprolol and placebo — as add-on therapy in resistant hypertensives already on three drugs. Spironolactone was dramatically superior to all alternatives.

−8.7

mmHg more than placebo

Home systolic, spironolactone in PATHWAY-2. It beat doxazosin by a further 4.0 mmHg and bisoprolol by 4.5.

The mechanistic interpretation follows the framework exactly: these patients have an excessive volume-dependent component, their curve substantially shifted rightward, and the thiazide in their three-drug regimen was not fully overcoming it. Adding spironolactone — which blocks the aldosterone-driven ENaC activation in the collecting duct that standard thiazide therapy leaves untouched — forced a further leftward shift, re-establishing sodium balance at a lower operating MAP.

Further support comes from renin: plasma renin activity in the PATHWAY-2 resistant hypertensives was suppressed, consistent with a volume-excess, aldosterone-driven mechanism, and the patients with the lowest renin had the greatest response. The prediction is confirmed — low renin means primary aldosterone excess, and spironolactone is the rational drug.

Clinical rule

Optimise volume before escalating drugs

Before adding a fifth drug to a resistant regimen, reassess the diuretic:

Is it the right class and the right dose for this patient? Note that the old rule to switch to a loop diuretic below an eGFR of 30 has been overturned: CLICK showed a titrated thiazide-like agent still working at a mean eGFR of 23 (V1 Ch19, Table 19.4). Reserve the loop for congestion. Is dietary sodium restriction actually being achieved, confirmed by a 24-hour urine sodium? Is spironolactone already included?

Volume optimisation precedes drug escalation in every resistant hypertension evaluation.

5.7 The 24-hour urine sodium in practice

Guyton's model generates a directly measurable clinical index. If all sustained hypertension involves a rightward curve shift, then measuring how much sodium the kidneys are retaining at a given BP tells you about the degree of shift and identifies the salt-sensitive component of that patient's hypertension. The 24-hour urine sodium is the most accurate non-invasive measure of dietary sodium intake in steady state, and the best predictor of response to both sodium restriction and diuretic therapy.

Why it works as a measure

In a weight-stable person, sodium output must equal intake — so the 24-hour collection *is* the diet, not a report of it.

TABLE 5.3 — INTERPRETING THE 24-HOUR URINE SODIUM

FINDING	INTERPRETATION	CLINICAL ACTION
> 200 mEq > 11.7 G SALT/DAY	Very high dietary intake. In a patient uncontrolled on two or three drugs, the volume component is the dominant contribution.	Intensive dietary counselling *before* adding another drug. Show the patient the number: "your urine shows 12 g of salt a day; the target is 5." Objective data drives change better than generic advice.
100–200 mEq 5.8–11.7 G SALT/DAY	Moderate to high intake, above the WHO target of under 85 mEq/day. Some contribution to the volume component.[17]	Counselling with a specific target: reduce below 100 mEq/day and reassess BP at four weeks. May reduce the drug requirement.
< 85 mEq < 5 G SALT/DAY	Adequate restriction; the dietary volume component is minimised. If BP remains uncontrolled, renal sodium retention rather than intake is the primary mechanism.	Investigate aldosterone-driven retention: aldosterone-to-renin ratio if not already done. Consider spironolactone, and optimise RAAS blockade.
< 40 mEq < 2.3 G SALT/DAY	Very low intake with hypertension persisting — significant intrinsic renal sodium retention.	High suspicion of primary aldosteronism, significant CKD with impaired natriuresis, or a structural curve shift. **Urgent secondary workup.**

KEY POINTS

1. **Infinite gain:** for any sustained hypertension the kidney must be accepting the elevated pressure without proportional natriuresis. Remove the rightward shift — diuretic, sodium restriction, or treating the cause — and volume contraction lowers BP. True of every subtype.
2. **The curve shift:** the operating point moves rightward by 10–30 mmHg and the slope flattens. The magnitude of the shift equals the degree of stable hypertension.
3. **Brenner:** nephron number at birth is a lifelong determinant of the setpoint. Keller 2003 — hypertensives have half the nephrons of normotensives at autopsy. India's low birth weight rate — about 27% of births on modelled estimates — is a population-scale salt-sensitivity substrate.[10]
4. **Th17–NO (Wilck 2017):** dietary NaCl activates Th17 through SGK1 → IL-17A impairs tubular eNOS → less NO → impaired natriuresis. Treg deficiency in obesity and CKD removes the brake; a high-sodium diet also depletes *Lactobacillus*.
5. **Diuretics work everywhere** because they force the leftward shift directly. RAAS counter-regulation attenuates monotherapy over 6–8 weeks; pairing with a RAAS blocker prevents the escape.
6. **PATHWAY-2:** spironolactone lowered home systolic 8.7 mmHg more than placebo, and beat doxazosin by 4.0 and bisoprolol by 4.5 mmHg. Lowest renin, greatest response — resistant hypertension is an undertreated volume problem.[16]
7. **24-hour urine sodium** is Guyton's model made measurable, and is mandatory in resistant or difficult hypertension. Above 200 mEq/day: counsel before prescribing. Below 85 mEq/day with persisting hypertension: intrinsic retention — check the ARR.

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CHAPTER 6 PART I · MECHANISM

The endothelium: nitric oxide, prostacyclin and endothelin-1

The vascular biology of blood pressure regulation, endothelial dysfunction in hypertension, and its pharmacological consequences.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The endothelium as an endocrine organ** — paracrine control of vascular tone.
2. **The eNOS pathway** — from shear stress to smooth muscle relaxation, step by step.
3. **NO beyond vasodilation** — anti-platelet, anti-adhesion, anti-proliferative, anti-thrombotic.
4. **How hypertension destroys NO** — NADPH oxidase, superoxide, eNOS uncoupling and ADMA.[21]
5. **Prostacyclin and thromboxane A_2** — the eicosanoid balance, and how NSAIDs disrupt it.
6. **Endothelin-1** — the most potent endogenous vasoconstrictor, and the new drug class.
7. **Flow-mediated dilation** — measurement, clinical validation, and reversibility with therapy.

6.1 The endothelium as an active endocrine organ

For most of the twentieth century the vascular endothelium was regarded as a passive, non-thrombogenic lining separating the bloodstream from the underlying smooth muscle. That view was overturned by Robert Furchgott's demonstration that the vasodilatory response of isolated aortic rings to acetylcholine depends entirely on an intact endothelial layer. Removing the endothelium abolished the response — indeed acetylcholine then *contracted* the denuded ring through direct muscarinic stimulation of smooth muscle. Furchgott named the responsible factor endothelium-derived relaxing factor; Moncada and Ignarro identified it as nitric oxide. The work earned Furchgott, Ignarro and Murad the 1998 Nobel Prize, and established the endothelium as an active endocrine organ continuously synthesising mediators that govern vascular tone, platelet function, coagulation and inflammation.[15,17,19]

Furchgott, 1980

Remove the endothelium and acetylcholine no longer dilates an aortic ring — it constricts it. The relaxing factor turned out to be nitric oxide.[8]

The endothelium is a single continuous monolayer lining every vessel from the aorta to the capillaries. It is exquisitely sensitive to mechanical forces — shear stress from flow, circumferential wall stress from intraluminal pressure — to humoral signals including vasoactive hormones, cytokines, growth factors and lipoproteins, and to metabolic signals such as hypoxia, hyperglycaemia and oxidised LDL.[1]

5,000

square metres of surface area, and about 1 kg of mass — the largest endocrine organ in the body.

The balance between vasodilatory mediators — NO, prostacyclin, endothelium-derived hyperpolarising factor — and vasoconstrictive mediators — endothelin-1, angiotensin II generated locally by endothelial ACE, thromboxane A_2 — determines the basal vascular tone that the sympathetic nervous system and circulating hormones then modulate.[4] In health the

balance favours vasodilation, anti-platelet activity and anti-inflammatory quiescence. In hypertension, in the presence of cardiovascular risk factors and in established atherosclerosis, it shifts toward vasoconstriction, platelet activation and inflammatory endothelial activation — the state termed endothelial dysfunction.[9]

6.2 The eNOS pathway: shear stress to relaxation

Nitric oxide is synthesised in endothelial cells by endothelial nitric oxide synthase — eNOS, or NOS3 — a constitutively expressed calmodulin-dependent enzyme catalysing the five-electron oxidation of the guanidino nitrogen of L-arginine to produce L-citrulline and NO.[7]

Cofactors matter clinically

O_2 · NADPH · BH_4 · FAD · FMN. BH_4 deficiency is the primary mechanism of eNOS uncoupling in hypertension.

FIGURE 6.1 — THE ENOS SIGNALLING CASCADE

STIMULUS	**Shear stress** — the primary physiological trigger — plus acetylcholine, bradykinin, substance P, histamine, thrombin, VEGF, insulin and oestrogen.
TRANSDUCTION	Shear stress opens mechanosensitive ion channels → Ca^{2+} influx. Receptor agonists act through Gq → IP_3 → ER Ca^{2+} release.
ACTIVATION	Rising $[Ca^{2+}]_i$ forms the calmodulin–Ca^{2+} complex, which displaces caveolin-1 from eNOS — caveolin-1 tonically inhibits the enzyme.
SYNTHESIS	L-arginine + O_2 + NADPH → L-citrulline + NO + $NADP^+$
SECOND MESSENGER	NO diffuses freely into the smooth muscle cell → activates soluble guanylyl cyclase → GTP to cGMP → protein kinase G.
EFFECT	PKG inactivates MLCK and opens BKCa channels → $[Ca^{2+}]_i$ falls → myosin light chain dephosphorylation → **vasodilation.**

Clinical rule

Nitrates and PDE5 inhibitors share one pathway — never combine them

Organic nitrates are exogenous NO donors: mitochondrial aldehyde dehydrogenase releases NO, which activates the sGC–cGMP cascade independently of endothelial integrity. That is why nitrates still work in vessels with severely dysfunctional endothelium.[11]

PDE5 inhibitors potentiate the same pathway from the other end, by blocking cGMP degradation.

Combining an NO donor with a cGMP-degradation inhibitor produces uncontrolled cGMP accumulation, profound vasodilation, catastrophic hypotension and death.

6.3 Non-vasodilatory functions of endothelial NO

Vasodilation is the best-known action of NO, but its other effects matter equally for cardiovascular protection — and they account for the disproportionately large event reduction seen with drugs that enhance NO production, such as ACE inhibitors acting through bradykinin, relative to the BP they lower.

TABLE 6.1 — FOUR PROTECTIVE FUNCTIONS BEYOND VASODILATION

FUNCTION	MECHANISM	RELEVANCE IN HYPERTENSION
Anti-platelet	NO activates platelet sGC → cGMP → PKG, inhibiting GPIIb/IIIa exposure, reducing P-selectin expression and blocking ADP-induced aggregation. Prostacyclin augments this through a separate cAMP pathway.	In endothelial dysfunction, reduced NO and PGI_2 give platelet hyperactivity and thrombus formation at sites of minor endothelial injury — the mechanistic basis for the high MI risk of established hypertension.
Anti-adhesion	NO suppresses NF-κB activation in endothelial cells, reducing expression of VCAM-1, ICAM-1, E-selectin and MCP-1 — the adhesion molecules required for monocyte and leucocyte attachment.	Preventing monocyte–endothelial adhesion blocks the first step of plaque formation. In NO deficiency, VCAM-1 and ICAM-1 upregulation leads to monocyte adherence, foam cell formation and the early atherosclerotic lesion.
Anti-proliferative	NO activates sGC in VSMC; cGMP inhibits migration and proliferation by blocking PDGF and FGF receptor signalling, and inhibits extracellular matrix synthesis by VSMC and fibroblasts.	Prevents the inward eutrophic remodelling that permanently raises SVR. Without it, VSMC proliferation proceeds unchecked — the irreversible component of longstanding hypertension.
Anti-thrombotic	NO inhibits endothelial tissue factor expression, promotes tPA release, and inhibits von Willebrand factor secretion from Weibel–Palade bodies.	Maintains the procoagulant–anticoagulant balance that prevents intraluminal thrombus in undamaged vessels. Losing it raises thrombotic risk at sites of minor intimal injury.

6.4 How hypertension destroys nitric oxide

Endothelial dysfunction is defined operationally as the inability to produce a normal vasodilatory response to endothelium-dependent stimuli such as acetylcholine, bradykinin or increased shear stress. The fundamental biochemical abnormality is not reduced eNOS expression or activity, but an increase in the rate at which NO is chemically inactivated before reaching sGC in smooth muscle — combined with a state of eNOS uncoupling in which the enzyme produces superoxide instead of NO.[12]

The key correction

eNOS expression is not the problem. NO is being destroyed after synthesis — and the enzyme itself starts making the destroyer.

NADPH oxidase and reactive oxygen species

The primary source of reactive oxygen species in the hypertensive vascular wall is NADPH oxidase, a membrane-bound complex transferring electrons from NADPH to molecular oxygen to generate superoxide. The vascular form is not the phagocytic oxidase of neutrophils but constitutively expressed vascular isoforms — Nox1 in VSMC, Nox2 in endothelium, Nox4 in both — activated by angiotensin II through AT_1–Rac1 signalling, by mechanical stretch, and by inflammatory cytokines.[10]

3×

faster than NO reacts with sGC — the rate at which superoxide scavenges it first.

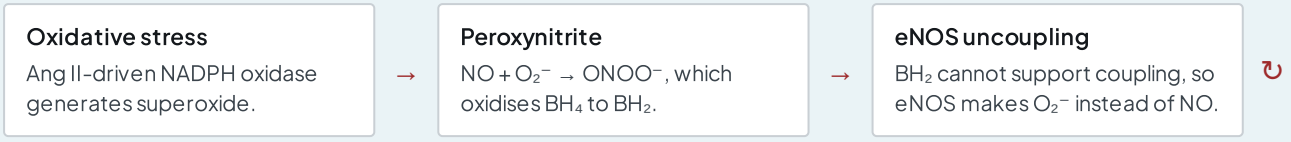
Because superoxide reacts with NO roughly three times faster than NO reacts with sGC, elevated superoxide production means the NO that eNOS makes is scavenged before it can diffuse to smooth muscle. The product is peroxynitrite, a highly reactive nitrogen species causing protein nitration,

lipid peroxidation, DNA damage and mitochondrial dysfunction. Peroxynitrite is not merely an end product of NO inactivation — it is itself a toxic oxidant contributing to the cellular damage of the hypertensive vascular wall.

eNOS uncoupling and tetrahydrobiopterin

Under BH_4 deficiency or L-arginine depletion, eNOS undergoes a conformational change that uncouples electron transfer from NO synthesis: NADPH is still oxidised, but instead of generating NO from L-arginine, molecular oxygen is reduced to superoxide. The uncoupled enzyme is therefore not merely failing to produce NO — it is actively generating the superoxide that destroys whatever NO the remaining coupled population makes.

FIGURE 6.2 — THE SELF-AMPLIFYING CYCLE



Once established, the cycle is self-sustaining — which is why the endothelial dysfunction of established hypertension reverses only slowly with antihypertensive therapy.

Asymmetric dimethylarginine provides a third mechanism of NO reduction. ADMA is an endogenous competitive inhibitor of eNOS, produced by protein arginine methyltransferases as a normal byproduct of protein catabolism and degraded by dimethylarginine dimethylaminohydrolase. In hypertension, CKD, diabetes and heart failure, oxidative stress reduces DDAH activity, ADMA accumulates, and eNOS is competitively inhibited. Its elevation correlates with the degree of endothelial dysfunction measured by flow-mediated dilation.[18]

ADMA

An independent predictor of cardiovascular events and all-cause mortality in EPIC-Norfolk and the Cardiovascular Health Study.

6.5 Prostacyclin, thromboxane A_2 and the NSAID problem

The prostaglandin pathway is a second endothelial vasodilatory and anti-platelet system operating in parallel with NO — and it is the one that non-steroidal anti-inflammatory drugs disrupt, with direct consequences for blood pressure control.

Prostacyclin is synthesised by endothelial cells from arachidonic acid through COX-1, constitutively expressed in endothelium, and prostacyclin synthase. It acts on Gs-coupled IP receptors on platelets and VSMC to raise cAMP, inhibiting platelets and dilating vessels. Its half-life of about two minutes makes its action local and paracrine. Thromboxane A_2 is synthesised predominantly by activated platelets from the same substrate, also through COX-1 but using thromboxane synthase; it acts on Gq-coupled TP receptors to raise Ca^{2+}, aggregating platelets and constricting vessels. The PGI_2/TXA_2 balance at any site of vascular injury determines whether the local response favours dilation and platelet inhibition or constriction and aggregation.[14]

Opposed pairs

PGI_2 — endothelium, COX-1, IP receptor, Gs, cAMP: dilation and platelet inhibition. TXA_2 — platelet, COX-1, TP receptor, Gq, Ca^{2+}: constriction and aggregation.

TABLE 6.2 — HOW NSAIDS RAISE BLOOD PRESSURE

MECHANISM	EFFECT ON BP	COX-1 AGAINST COX-2 RELEVANCE
Inhibition of renal PGE_2 and PGI_2	Renal PGE_2 from medullary COX-2 and PGI_2 from endothelial COX-1 normally promote natriuresis and dilate the renal vasculature. Inhibition gives sodium retention plus renal vasoconstriction — volume expansion, reduced GFR, rising BP.	Both isoforms reduce renal prostaglandins. COX-2 selective agents were hoped to spare the COX-1–dependent renal effects, but COX-2 contributes substantially to renal prostaglandin synthesis: **celecoxib and etoricoxib raise BP almost as much as non-selective agents.**
Inhibition of endothelial PGI_2	Losing prostacyclin removes a vasodilatory and anti-platelet signal.	COX-2 selective agents abolish endothelial PGI_2, which is largely COX-2 derived, while leaving platelet TXA_2 — COX-1 derived — intact. That prothrombotic shift is the mechanism behind the increased MI and stroke risk seen in VIGOR and APPROVe.[6]
Antagonism of antihypertensive drugs	NSAIDs blunt the effect of ACEi, ARBs and diuretics. ACEi/ARBs work partly by raising vasodilatory prostaglandins; NSAIDs abolish that benefit. Diuretics depend on renal prostaglandins for their natriuretic effect.	**The triple whammy:** ACEi or ARB, plus diuretic, plus NSAID — acute kidney injury risk from reduced renal perfusion, absent afferent vasodilation and direct tubular toxicity together.
Paracetamol	Regular use at full therapeutic dose — 1 g four times daily — raised ambulatory systolic pressure by several mmHg in a randomised crossover trial in treated hypertensives, an effect on the scale of adding a drug. Do not treat it as inert in a patient whose pressure will not settle. The mechanism is unsettled; probably weak COX inhibition and TRPA1 activation reducing PGI_2.[13]	Much smaller than the NSAID effect and not clinically meaningful for acute use. For a hypertensive patient needing regular analgesia, paracetamol at the lowest effective dose remains preferable to an NSAID.

6.6 Endothelin-1: the most potent endogenous vasoconstrictor

Endothelin-1 is a 21-amino-acid peptide synthesised and released by endothelial cells in response to shear stress, hypoxia, angiotensin II, thrombin, cytokines and oxidised LDL. Its plasma half-life is four to seven minutes, but its effects last hours because it dissociates from its receptor very slowly.[22]

It is synthesised from preproendothelin-1 through endothelin-converting enzyme cleavage of the intermediate big endothelin, and released predominantly *abluminally* — toward the smooth muscle rather than into the bloodstream — confirming it as a paracrine rather than circulating hormone. Plasma ET-1 levels therefore underestimate the local concentrations to which VSMC are actually exposed.

10×
the contractile potency of angiotensin II on a molar basis — the most potent endogenous vasoconstrictor identified in mammals.

TABLE 6.3 — ET-A AND ET-B: OPPOSING VASCULAR EFFECTS

RECEPTOR	LOCATION	SIGNALLING	EFFECT	CLINICAL IMPLICATION
ET-A	Vascular smooth muscle — predominant · cardiac myocardium · adrenal cortex	Gq → IP_3 → Ca^{2+} release; Gi inhibits adenylyl cyclase; Rho kinase activation gives Ca^{2+} sensitisation	Potent sustained vasoconstriction; cardiac hypertrophy; aldosterone secretion; cardiac and renal fibrosis	The primary mediator of ET-1's pressor effect. ET-A antagonists reduce pulmonary vascular resistance in PAH; in systemic hypertension, ET-A blockade lowers BP and LVH independently of other mechanisms.
ET-B	Vascular endothelium — primary site · VSMC in a minority · renal tubular cells · lung	Gs → cAMP in endothelium; Gq → Ca^{2+} in VSMC; Gi → NO and PGI_2 release from endothelium	Endothelial: NO and PGI_2 release, giving vasodilation and platelet inhibition. VSMC: minor vasoconstriction. Renal: natriuresis	Endothelial ET-B is counter-regulatory — a healthy endothelium uses it to buffer ET-1's own vasoconstriction. In endothelial dysfunction that NO release is impaired, leaving **unopposed ET-A vasoconstriction** — which is why hypertension is worse in endothelial dysfunction states.

Endothelin receptor antagonists — bosentan, a dual ET-A/ET-B agent, and the ET-A selective ambrisentan and macitentan — are established treatments for pulmonary arterial hypertension, where elevated pulmonary ET-1 is a primary mechanism. In systemic hypertension, the ET-A selective darusentan produced 10–17 mmHg systolic reduction in resistant hypertension, but its phase III programme failed — the trial that used ambulatory rather than clinic pressure as its endpoint missed, and fluid retention and oedema limited the class. (The hepatotoxicity that ended sitaxentan belonged to a different drug.)[2]

Where ET-1 is elevated

Primary hypertension, especially salt-sensitive and low-renin phenotypes · heart failure · PAH · pre-eclampsia · scleroderma vasculopathy

Evidence

Aprocitentan — the first new oral class in over a decade

Aprocitentan, a dual ET-A/ET-B antagonist, was approved by the FDA in 2024 for resistant hypertension — the first genuinely new class of oral antihypertensive to reach approval in more than ten years, and a direct clinical validation of the endothelin axis described here.[5]

6.7 Flow-mediated dilation

Flow-mediated dilation of the brachial artery is the most widely validated non-invasive clinical measure of endothelial vasodilatory function. The technique, standardised by Celermajer and colleagues in 1992, uses high-resolution B-mode ultrasonography of the brachial artery at rest and after reactive hyperaemia produced by five minutes of forearm cuff occlusion followed by deflation. The hyperaemia increases shear stress, which in a healthy endothelium produces NO-mediated dilation proportional to the shear increase. FMD is expressed as the percentage increase in diameter at peak hyperaemia relative to baseline.[3,20]

Normal 8–12%

In hypertension, diabetes, dyslipidaemia, smoking or established CAD: typically 4–7% or less.

TABLE 6.4 — THE PROGNOSTIC EVIDENCE FOR FMD

STUDY	POPULATION	FINDING
Celermajer LANCET 1994	Males at differing stages of atherosclerosis risk factor exposure	FMD progressively impaired from childhood through adolescent risk factor exposure to established adult atherosclerosis — endothelial dysfunction *precedes* structural atherosclerotic disease.
Yeboah MESA · CIRCULATION 2009	n = 3,026 asymptomatic adults; median follow-up 5.7 years	Each 1% decrease in FMD was associated with an **8% increase in cardiovascular events**, and FMD improved risk prediction beyond the Framingham risk score alone.[16]
Gokce NEJM 2002	Patients undergoing elective vascular surgery	Preoperative FMD was the strongest predictor of postoperative adverse cardiovascular events — superior to angiographic coronary disease severity.
Reversibility MULTIPLE META-ANALYSES	Hypertensive patients started on ACEi, ARBs, CCBs or exercise programmes	FMD improves with sustained BP reduction and with therapies that specifically enhance NO. The improvement with ACEi *exceeds* that predicted from BP reduction alone, confirming a pleiotropic NO-enhancing effect.

FMD is not measured routinely, requiring specialised ultrasound equipment, rigorous patient preparation and operator skill. But knowing its physiological basis is essential, because it explains three things the clinician sees constantly: why drugs that enhance the NO pathway have cardiovascular benefits beyond BP reduction; why smoking cessation, exercise and weight loss improve outcomes through restored endothelial function independently of their effect on pressure; and why endothelial dysfunction should be treated as a target of therapy rather than merely a biomarker of risk.

KEY POINTS

1. **The endothelium is an endocrine organ** — 5,000 m², about 1 kg — continuously balancing vasodilators (NO, PGI_2) against vasoconstrictors (ET-1, local Ang II). Endothelial dysfunction is a shift toward constriction, platelet activation and inflammation.
2. **eNOS pathway:** shear stress → Ca^{2+}–calmodulin → eNOS → NO → sGC → cGMP → PKG → relaxation. BH_4 is the critical cofactor; its deficiency switches eNOS from making NO to making superoxide.
3. **NO does four other jobs:** anti-platelet, anti-adhesion, anti-proliferative, anti-thrombotic. Losing all four explains the accelerated atherosclerosis and thrombotic risk of hypertension beyond the haemodynamic effect of pressure itself.
4. **The destruction cycle:** Ang II-driven NADPH oxidase → superoxide, which scavenges NO three times faster than sGC can use it → peroxynitrite oxidises BH_4 → eNOS uncouples → more superoxide. ADMA accumulation adds a third mechanism.
5. **NSAIDs raise BP** by inhibiting renal PGE_2/PGI_2, removing endothelial PGI_2, and antagonising ACEi, ARBs and diuretics. COX-2 selective agents are barely safer for BP. ACEi + diuretic + NSAID is the triple whammy for AKI.
6. **ET-1** is ten times more potent than Ang II and released abluminally. ET-A constricts and fibroses; endothelial ET-B counter-regulates through NO and PGI_2 and is lost in dysfunction. Aprocitentan was FDA-approved in 2024 for resistant hypertension.
7. **FMD:** normal 8–12%, falling to 4–7% in hypertension and diabetes. MESA — each 1% fall carries 8% more cardiovascular events, adding prognostic information beyond Framingham. It improves with ACEi by more than BP reduction predicts.

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CHAPTER 7 PART I · MECHANISM

Circadian rhythm of blood pressure

The 24-hour BP pattern, dipping physiology, morning surge mechanisms, and chronopharmacology.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The normal 24-hour profile** — pre-dawn nadir, morning surge, plateau and nocturnal dip.
2. **Dipping classification** — normal, non-dipper, extreme dipper, reverse dipper, and prognosis.
3. **Six converging mechanisms** behind the morning surge, and why events cluster at dawn.
4. **Non-dipping** — causes, mechanisms, and the clinical significance of the nocturnal pattern.
5. **White coat, masked and nocturnal hypertension** — ABPM definitions and management.
6. **Chronopharmacology** — HYGIA against TIME, bedtime dosing, and the guideline position.
7. **ABPM in practice** — indications, interpretation, and what clinic BP cannot reveal.

7.1 The normal 24-hour blood pressure profile

Blood pressure is not a static variable. In a healthy normotensive adult it follows a reproducible circadian rhythm driven by the interplay of the autonomous circadian clock, the sleep–wake cycle, the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system and the RAAS. This rhythm is not merely physiological background: it determines when cardiovascular events cluster, it explains patterns of organ damage that clinic measurement cannot reveal, and it has direct implications for the timing of drug administration.[14]

20–40
mmHg of systolic variation across 24 hours in a healthy normotensive adult.

TABLE 7.1 — THE FOUR PHASES OF THE CIRCADIAN BP PROFILE

PERIOD	BP PATTERN	DRIVING MECHANISMS	CLINICAL SIGNIFICANCE
0200–0600 PRE-DAWN NADIR	Lowest BP of the cycle — systolic typically 10–20 mmHg below daytime. HR at its lowest. This is the nocturnal dip.	Deep sleep: minimal sympathetic activity, lowest cardiac output. Lowest circulating catecholamines, renin and cortisol. Vagal dominance with maximum HRV.	**Nocturnal BP is the strongest predictor of cardiovascular outcomes** among all ABPM-derived variables.[18] The dip during this period determines dipping status.
0600–1200 MORNING SURGE	Rapid rise from nadir to the day's highest BP — systolic rises 20–30 mmHg within 30–90 minutes of waking, with HR accelerating simultaneously.	Six simultaneous mechanisms (section 7.3): sympathetic activation on waking, cortisol surge, RAAS activation, loss of recumbency, platelet activation and physical activity.	**Peak cardiac event risk.** MI, ischaemic stroke and sudden cardiac death are all more frequent in this six-hour window than in any other.[2,4]
1000–1800 DAYTIME PLATEAU	Sustained plateau near peak values, with moderate variability from activity, meals and stress.	Maintained sympathetic tone, sustained cortisol falling through the afternoon, physical activity, postprandial insulin and vasoactive peptides.	The period conventional clinic readings capture. It does *not* represent the 24-hour burden, and cannot detect white coat effect, masked hypertension or nocturnal hypertension.
1800–2400 EVENING DECLINE	Gradual fall as activity reduces and sleep approaches. Some individuals show a secondary evening surge at 1800–2000.	Declining sympathetic tone and cortisol, reduced activity, rising melatonin. RAAS activity begins to fall.	An evening surge can be unmasked by ABPM and is associated with OSA and nocturnal hypertension. Evening dosing may target this period.

7.2 Dipping classification and prognosis

The fall in BP during the nocturnal sleep period, expressed as a percentage of mean daytime BP, is the single most important categorical variable derived from ABPM, and carries prognostic significance independent of mean BP level.

EQUATION 7.1 — NOCTURNAL DIP

$$\text{Dip (\%)} = \frac{\text{mean daytime SBP} - \text{mean nocturnal SBP}}{\text{mean daytime SBP}} \times 100$$

Some guidelines use a single >10% threshold for normal dipping; the 10–20% range quoted here is the ESH 2023 definition.

TABLE 7.2 — FOUR DIPPING CATEGORIES

STATUS	DEFINITION	PREVALENCE	CARDIOVASCULAR RISK	COMMON CAUSES
Normal dipper	10–20% nocturnal SBP reduction	50–60% of normotensives; ~40% of treated hypertensives	Reference group — the best prognosis of any dipping category.	Normal autonomic function, normal sleep architecture, no significant comorbidity.
Non-dipper	< 10% reduction	30–40% of hypertensives; more common with age	HR 1.27 (1.06–1.53) for cardiovascular events. A stronger predictor of LVH, microalbuminuria and stroke than daytime BP alone.[13]	OSA — the commonest, present in about 60% — plus CKD, diabetes with autonomic neuropathy, primary aldosteronism, obesity, high evening sodium.
Extreme dipper	> 20% reduction	5–10% of hypertensives	Paradoxically elevated ischaemic stroke risk, particularly in the elderly: excessive nocturnal fall may cause cerebral hypoperfusion where carotid stenosis is tight or autoregulation shifted.[13]	Autonomic hyperactivity; aggressive antihypertensive therapy, especially bedtime dosing in the elderly; orthostatic hypotension patterns.
Reverse dipper RISER	Nocturnal BP *higher* than daytime	5–10%; more in advanced CKD, severe OSA, autonomic failure	**Highest risk category — RR 2.5–4.0.** Strongly associated with LVH, CKD progression and haemorrhagic stroke.[16]	Severe OSA with nocturnal sympathetic surges, end-stage CKD or dialysis, autonomic failure with supine hypertension, severe primary aldosteronism.

Evidence

Nocturnal BP beats daytime BP for prediction

The Dublin Outcome Study entered daytime, night-time and 24-hour values into the same analysis and found **nocturnal systolic BP the strongest predictor of cardiovascular mortality**.[1]

The Syst-Eur sub-analysis and multiple subsequent cohorts confirm that each 10 mmHg rise in mean nocturnal SBP carries a 14–19% increase in event risk, independent of the 24-hour mean.[5]

7.3 The morning surge: six converging mechanisms

The morning surge is not one phenomenon but the net result of six simultaneous biological changes, all acting in the same pressor direction within the 60–90 minutes surrounding waking. That convergence explains both the magnitude of the surge and the clustering of acute cardiovascular events at this time of day.

TABLE 7.3 — THE SIX MECHANISMS OF THE MORNING SURGE

MECHANISM	TIMING	PATHWAY	CONTRIBUTION
Sympathetic activation on waking	Begins 15–30 min before waking; peaks within 30 min of arousal	The sleep-to-wake transition activates the reticular activating system → RVLM excitation → sympathetic outflow to heart and vasculature: HR, CO and SVR all rise.	**The primary driver — about 50% of the surge.** The highest plasma noradrenaline of the 24-hour cycle occurs at 0800–0900.[7]

MECHANISM	TIMING	PATHWAY	CONTRIBUTION
Cortisol surge	Begins 1–2 hours before waking; peaks at waking	Peak pre-dawn ACTH drives the cortisol peak. Cortisol sensitises the vasculature to catecholamines by upregulating adrenoceptors, exerts mild mineralocorticoid activity, and raises angiotensinogen.	Augments the sympathetic effect and explains the diurnal sensitisation to vasopressors. Cortisol is measured most reliably at 0800 for diagnostic purposes.
RAAS activation	Peak renin secretion at night; peak Ang II and aldosterone in early morning	Nocturnal recumbency and reduced sodium delivery from overnight retention stimulate JG cell renin secretion during sleep; Ang II peaks in the early morning.	Adds sustained vasoconstriction and sodium retention. Explains why ACEi and ARBs with genuine 24-hour coverage specifically attenuate the surge.
Loss of recumbency	Immediately on standing	The orthostatic response of Chapter 2: gravitational venous pooling → baroreceptor unloading → reflex sympathetic activation, plus a transient spike from the muscle pump.	Adds 5–10 mmHg, and matters particularly in elderly patients whose orthostatic response is exaggerated or dysregulated.
Platelet hyperaggregability	Peak at 0600–1200	Highest platelet TXA_2 production and lowest prostacyclin of the day. The morning catecholamine surge activates platelets through alpha-2 stimulation.[15]	Not a BP mechanism, but it explains the concurrent thrombotic risk: peak BP surge, maximum platelet aggregability and lowest fibrinolytic activity coincide.
Physical activity	Onset of activity with waking	Exercise raises HR and CO. Even showering, dressing and walking amplify the catecholamine surge substantially in uncontrolled hypertensives.	Variable with intensity and fitness. In uncontrolled hypertension, morning exercise can trigger dangerously high peaks.

The clinical consequence is the characteristic morning clustering of acute events. MILIS for myocardial infarction, Marler for ischaemic stroke and Muller for sudden cardiac death all show a statistically robust peak in this window.[11] In MILIS the morning peak in MI incidence coincided precisely with the morning peaks in plasma catecholamines, platelet aggregability and BP — confirming that the circadian rhythm of events reflects the circadian rhythm of the mechanisms above.

49%

excess ischaemic stroke in the 6 am to noon window, with a 29% excess of sudden cardiac death in the same hours — the morning peak first described for myocardial infarction in 1985.

The therapeutic implication is that drugs should deliver their maximum effect during the highest-risk period: the six to twelve hours after waking. That requires adequate duration of action, and it should inform the timing of the morning dose. A drug taken at 0800 that peaks at 1000 and wanes by 0600 the next morning leaves the patient unprotected through the surge unless the dose is taken before getting up.

7.4 Non-dipping: causes and significance

Non-dipping is not a disease in itself but a haemodynamic signature of several conditions that impair the normal nocturnal withdrawal of sympathetic tone. It is the single most important ABPM finding that should change management, because it identifies a high-risk group in whom target organ damage — LVH, microalbuminuria, cerebrovascular disease — is

disproportionate to the daytime BP level. Anything that disrupts sleep architecture, maintains nocturnal sympathetic activation, or impairs the circadian variation in RAAS activity will produce it.

The normal mechanism

Sympathetic withdrawal during slow-wave sleep, mediated by the hypothalamic sleep switch suppressing RVLM firing in NREM stages 3 and 4.

TABLE 7.4 — SIX CAUSES OF NON-DIPPING

CAUSE	MECHANISM	CLINICAL RECOGNITION AND ACTION
Obstructive sleep apnoea MOST COMMON	Each apnoeic episode: hypoxia → carotid body activation → RVLM excitation → sympathetic surge → BP spike. Surges occur 15–30 times an hour, holding average nocturnal BP near waking levels.	STOP-BANG ≥ 3; non-dipping plus partner-reported snoring or witnessed apnoea. About 60% of non-dippers have OSA confirmed on polysomnography. CPAP reduces nocturnal BP 4–7 mmHg and partially restores dipping.[3]
Chronic kidney disease	Volume overload from impaired natriuresis maintains elevated BP through the night despite recumbency, and afferent renal nerve signals maintain elevated RVLM drive.	Non-dipping in CKD correlates with GFR decline and proteinuria severity. Treat with adequate diuretic therapy and dietary sodium restriction — a loop diuretic if eGFR is below 30.
Diabetic autonomic neuropathy	Damage to the autonomic fibres that normally mediate sympathetic withdrawal during sleep — the mechanism is structurally impaired, not merely suppressed.	Seen in long-duration diabetes with other autonomic features: postural hypotension, resting tachycardia, gastroparesis. Non-dipping is an early autonomic marker, appearing before overt neuropathy.
Primary aldosteronism	Aldosterone's genomic effects peak four to eight hours after secretion, so nocturnal aldosterone drives overnight sodium loading that blunts the dip.	Non-dipping with hypokalaemia, suppressed renin and a raised ARR should prompt adrenal imaging. Spironolactone restores dipping in aldosterone-driven cases.
Obesity	Visceral adiposity brings adipose RAAS, leptin-driven sympathetic activation and a high prevalence of OSA — all maintaining nocturnal sympathetic tone.	BMI above 30 with non-dipping: screen for OSA. Weight loss of 5–10% partially restores normal dipping.
High dietary sodium	Excess sodium impairs the nocturnal natriuresis that normally allows BP to fall during sleep; Th17-driven retention (Chapter 5) may exaggerate the effect.	A 24-hour urine sodium above 200 mEq in a non-dipper: restriction often partially restores dipping. **The most modifiable non-pharmacological intervention available.**

7.5 White coat, masked and nocturnal hypertension

Conventional clinic measurement identifies only a fraction of the information needed for complete phenotyping. Three distinct phenotypes are defined by comparing clinic BP with out-of-office BP, each with a different prognosis and different management.

TABLE 7.5 — FOUR PHENOTYPES DEFINED BY CLINIC AGAINST OUT-OF-OFFICE BP ESTABLISHED

PHENOTYPE	DEFINITION	PREVALENCE	CARDIOVASCULAR RISK	MANAGEMENT
True sustained hypertension	Clinic elevated *and* out-of-office elevated	50–55% of those with elevated clinic BP	Highest risk; the reference category for outcome trials.	Antihypertensive therapy per guidelines; both clinic and home targets apply.
White coat hypertension	Clinic ≥ 140/90 but out-of-office normal — under 135/85 home, under 130/80 ABPM[8]	15–25% of those with elevated clinic BP	Intermediate: lower than sustained hypertension, higher than normotension. Converts to sustained hypertension in 30–40% at ten years.	No immediate drug therapy in most guidelines. Annual ABPM or home monitoring to detect conversion. Lifestyle modification.
Masked hypertension	Clinic under 140/90 but out-of-office elevated — ≥ 135/85 home, ≥ 130/80 ABPM[12,17]	15–20% of those with normal clinic BP	**Risk equivalent to sustained hypertension: HR 2.0.** Frequently missed; may present with LVH, microalbuminuria or a first cardiovascular event.	Same treatment thresholds as sustained hypertension. Suspect it with high-normal clinic BP, in young adults with risk factors, and where LVH or microalbuminuria appears without clinic elevation.
Nocturnal hypertension	Mean nocturnal SBP ≥ 120 or DBP ≥ 70 on ABPM, whatever the daytime BP	In its isolated form — daytime pressure normal — 12.9% of a referred ambulatory cohort and 22.8% of an untreated general population[19,20]; higher in CKD, diabetes and the elderly[12]	Independent risk factor. Nocturnal SBP is the strongest ABPM predictor of outcomes, and is associated with LVH, albuminuria and non-dipping.	Consider moving one agent to bedtime. Investigate for OSA, CKD and primary aldosteronism. Do not over-correct in the elderly — extreme dipping carries its own risk.

7.6 Chronopharmacology: when to take the drugs

The circadian biology raises a reasonable question: should antihypertensives be taken in the morning, to cover the high-risk surge, or at bedtime, to cover nocturnal hypertension and improve dipping? The question has largely been answered. The large, independently adjudicated trial found no difference in outcomes; the trial reporting a spectacular bedtime benefit has been challenged on methodological grounds and has not been replicated. This is not a live controversy to be resolved patient by patient — but it is worth understanding why, because the disputed result is still widely quoted.

TABLE 7.6 — TIME AGAINST HYGIA

TRIAL	DESIGN	RESULT	INTERPRETATION
TIME N = 21,104 · 5.2 YR	UK. Designed to answer the question rigorously: morning against evening dosing, with primary outcome adjudication by independent reviewers blinded to allocation.	No significant difference. **HR 0.95 (95% CI 0.83–1.10); p = 0.53**[9]	Falls were in fact slightly *fewer* with evening dosing (21.1% against 22.2%, p = 0.048), and no safety concern emerged. TIME effectively refutes the claim that a simple across-the-board switch to bedtime dosing produces a large cardiovascular benefit.
HYGIA Chronotherapy N = 19,084 · 6.3 YR DISPUTED OUTLIER	Hermida, University of Vigo. All antihypertensives at bedtime against all on waking. Investigator-initiated; event verification by the trial investigators.	45% reduction in the primary composite endpoint. **HR 0.55 (95% CI 0.50–0.61); p < 0.001**[6]	The magnitude is extraordinary — larger than adding a second drug or achieving a 10 mmHg reduction in outcome trials. A 2022 *European Heart Journal* reanalysis raised concerns: no independent data monitoring, no independent event adjudication, and a benefit inconsistent with any known biological mechanism for a dosing-time effect of that size. **Treat this as a disputed outlier, not as evidence in the balance against TIME.**

Clinical rule

Not routine — but targeted bedtime dosing is rational

Consistent with ESH 2023: routine bedtime dosing is **not** recommended as a standard strategy for all hypertensive patients.[10]

Moving *one* agent to bedtime is nonetheless reasonable in three specific situations: confirmed nocturnal hypertension on ABPM; a non-dipping pattern with an identifiable cause being treated (OSA, CKD, primary aldosteronism); or a morning surge that remains uncontrolled despite adequate daytime coverage.

Trough-to-peak ratio and 24-hour coverage

Whatever the timing debate concludes, duration of action has unambiguous implications. The trough-to-peak ratio — the BP reduction just before the next dose against the peak reduction four to eight hours after dosing — determines how consistently a drug covers the full 24 hours.

The regulatory floor

FDA approval as a once-daily agent requires a T/P ratio of at least 0.5. Above 0.8 is preferred where the morning surge must be covered.

TABLE 7.7 — TROUGH-TO-PEAK RATIOS AND DURATION OF ACTION

DRUG	T/P RATIO	DURATION	CHRONOPHARMACOLOGICAL IMPLICATION
amlodipine	0.95–1.0	40–50 h	Ideal 24-hour coverage and excellent surge attenuation — clinically the longest-acting oral antihypertensive. Missing a single dose has minimal immediate effect.
telmisartan	0.90–0.95	36–40 h	Superior 24-hour coverage among the ARBs, with an effective duration specifically suited to morning surge attenuation.
chlorthalidone	0.85–0.95	48–72 h	Very long duration; covers 24 hours and attenuates nocturnal volume-driven BP. One of the reasons it is preferred over HCTZ.
perindopril	0.80–0.90	24–30 h	Good coverage and a higher T/P than enalapril — the preferred ACEi where once-daily morning dosing is used.
ramipril	0.55–0.75	24 h	Adequate but lower; may leave the morning surge partially uncovered if taken the previous evening.
losartan	0.50–0.65	18–24 h	The shortest-acting ARB; may need twice-daily dosing, or switching to telmisartan or olmesartan for full surge coverage.

DRUG	T/P RATIO	DURATION	CHRONOPHARMACOLOGICAL IMPLICATION
hydrochlorothiazide	0.40–0.60	12–18 h	Shorter than chlorthalidone with less consistent coverage — one of several reasons it is inferior in outcome trials.
atenolol	0.45–0.60	18–24 h	Low T/P; surge coverage may be inadequate with once-daily evening dosing. Also has an inferior central pressure effect (CAFE, Chapter 1).

7.7 ABPM in clinical practice

Twenty-four hour ambulatory monitoring is the gold standard for characterising blood pressure because it supplies what clinic measurement cannot: the nocturnal level and dipping status, the presence of white coat or masked hypertension, the magnitude of the morning surge, variability through the day, and the adequacy of 24-hour drug coverage.

Underused in India

Equipment cost and limited availability outside tertiary centres, despite clear clinical superiority.

TABLE 7.8 — SIX INDICATIONS FOR ABPM

INDICATION	WHY ABPM IS ESSENTIAL HERE
Suspected white coat hypertension	Elevated clinic BP without target organ damage, no compelling indication for therapy, low overall risk. ABPM separates true hypertension, which is treated, from white coat, which is monitored — avoiding unnecessary lifelong drug exposure.
Suspected masked hypertension	Normal clinic BP with unexplained target organ damage — LVH on ECG or echo, microalbuminuria, early retinopathy — or high-normal clinic readings of 135–139/85–89, or a young adult with multiple risk factors.
Suspected nocturnal hypertension	Non-dipping suspected in CKD, diabetes or OSA, or BP refractory despite adequate daytime control. ABPM quantifies the nocturnal component and guides the bedtime dosing decision.
Resistant hypertension evaluation	Distinguishes true resistance from white coat effect: **30–40% of apparent resistant hypertensives have controlled ABPM** — pseudo-resistance. Also guides timing optimisation.
Adequacy of BP control	Clinic BP appears controlled but organ damage is progressing — worsening LVH, rising creatinine, new microalbuminuria. ABPM may reveal a morning surge, nocturnal hypertension or masked uncontrolled status.
Autonomic and orthostatic assessment	Suspected orthostatic hypotension in an elderly patient on antihypertensives. ABPM with orthostatic positions at set time points identifies the diurnal pattern and guides medication adjustment.

KEY POINTS

1. **The 24-hour profile:** nadir 0200–0600, surge 0600–1200 with a 20–30 mmHg systolic rise, daytime plateau, evening decline. MI, stroke and sudden death peak in the morning window — a 49% excess of ischaemic stroke and a 29% excess of sudden cardiac death between 6 am and noon.[2,4]
2. **Dipping:** normal 10–20%; non-dipper under 10% (HR 1.27, usually OSA); extreme dipper over 20% (paradoxical stroke risk in the elderly); reverse dipper (highest risk, RR 2.5–4.0).[16] Nocturnal SBP is the strongest ABPM predictor — Dublin Outcome Study.
3. **Six surge mechanisms:** sympathetic activation on waking (~50% of it), cortisol peak, overnight RAAS activation, the orthostatic response, peak platelet aggregability, and the onset of activity. Covering this needs a T/P ratio above 0.8.
4. **Non-dipping causes:** OSA (~60% of non-dippers), CKD, diabetic autonomic neuropathy, primary aldosteronism, obesity, and high dietary sodium — the last being the most modifiable.
5. **Phenotypes:** white coat (15–25% of elevated clinic BP; monitor, don't treat)[8] against masked (15–20% of normal clinic BP; risk equals sustained hypertension, HR 2.0; treat it).[12] Nocturnal hypertension is an independent risk factor — investigate for OSA, CKD and primary aldosteronism; moving one agent to bedtime is a reasonable trial of timing, not a treatment.
6. **TIME against HYGIA:** TIME (n = 21,104, blinded adjudication) found no difference between morning and evening dosing (p = 0.53). HYGIA's 45% reduction is methodologically disputed and unreplicated.[6] ESH 2023: no routine bedtime switch.[10]
7. **T/P ratios:** amlodipine, telmisartan, chlorthalidone and perindopril all cover 24 hours well. Losartan, HCTZ and atenolol may leave the morning surge unprotected. Favour agents above 0.8 for once-daily therapy.

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CHAPTER 8 PART I · MECHANISM

Classification and definitions of hypertension

Guideline thresholds, the SPRINT controversy, phenotypic subtypes, and hypertensive crises.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Four guideline systems compared** — JNC 8 and ACC/AHA 2017 as history; ESH 2023, ESC 2024 and AHA/ACC 2025 as the current thresholds.
2. **SPRINT and the 130/80 debate** — attended against unattended measurement, and its consequences.
3. **Grades of hypertension** — the clinical significance of each stage and its treatment implication.
4. **Systolic, diastolic and combined** — four phenotypic subtypes and the drug choice each implies.
5. **Urgency against emergency** — the single most consequential binary decision in hypertension.
6. **Accelerated and malignant hypertension** — why fundoscopy changes the treatment pathway.
7. **Primary against secondary** — prevalence, red flags, and when to start the diagnostic search.

8.1 The diagnostic threshold: why numbers change

A blood pressure threshold for diagnosing hypertension is not a biological constant. It is a risk-based clinical decision: the level above which the cardiovascular risk attributable to BP elevation justifies the cost, inconvenience and risk of starting therapy. Because risk is continuous, with no threshold, down to at least 115/75 mmHg[7], any threshold is arbitrary in physiological terms and must be calibrated against randomised evidence of treatment against non-treatment at that specific level, in populations with specific risk profiles.

Lewington, Lancet 2002

Each 20 mmHg rise in systolic pressure doubles cardiovascular mortality risk, continuously, from 115 mmHg upward.[7]

This is why the threshold has changed repeatedly over four decades, and why different guideline bodies reach different conclusions from substantially the same evidence. The JNC series moved from 160/95 mmHg in 1977 to 140/90 in 1993 as outcome evidence accumulated. ACC/AHA moved to 130/80 in 2017 on the basis of SPRINT. ESH 2023 retained 140/90 as the office treatment threshold while acknowledging 130/80 as the optimal target in treated patients — on the grounds that SPRINT's measurement methodology is not equivalent to standard office measurement.[10] The 2023 guideline is the European Society of Hypertension's; the ESC published its own in 2024, keeping the 140/90 diagnostic threshold but adding a category of elevated BP for 120–139/70–89 and recommending a treated systolic target of 120–129 mmHg where tolerated.[15]

8.2 Major guideline systems compared

TABLE 8.1 — FOUR SYSTEMS, ONE BP SCALE — AND WHICH ARE CURRENT

OFFICE BP	JNC 8 (2014) — SUPERSEDED	AHA/ACC 2025	ESH 2023 · ESC 2024	CLINICAL IMPLICATION
< 120/< 80	Normal	Normal	ESH: optimal. ESC 2024: non-elevated only below 120/70 — a diastolic of 70–79 already sits in its elevated band[15]	No intervention; lifestyle optimisation in high-risk individuals.
120–129/< 80	Normal or prehypertension	Elevated BP — lifestyle measures; no drug is gated here	ESH: normal. ESC 2024: elevated BP — lifestyle measures; drug therapy is not offered below 130/80 whatever the risk[15]	Lifestyle modification on every current system. No guideline starts a drug in this band.
130–139/80–89	Prehypertension — no drug therapy[5]	**Stage 1 hypertension** — drug therapy at once with established cardiovascular disease, diabetes, chronic kidney disease or a 10-year PREVENT risk of 7.5% or more; otherwise three to six months of lifestyle therapy, then a drug if still ≥ 130/80[20]	ESH: high-normal (130–139/85–89) — **not** hypertension[8]. ESC 2024: the upper half of the elevated band — a drug after a maximum of three months of lifestyle therapy if 10-year risk is 10% or more or a high-risk condition is present[15]	**The major divergence point.** AHA/ACC labels this hypertension and treats it by risk; ESC does not call it hypertension but also treats its upper half by risk; ESH does not diagnose hypertension here — lifestyle only, unless a compelling indication applies.
140–159/90–99	Stage 1 — treat per risk	Stage 2 — drug therapy recommended	ESH: grade 1 — lifestyle with or without drugs by risk profile. ESC 2024: hypertension — drug therapy once confirmed[15]	All current systems agree the diagnosis is hypertension, and all recommend lifestyle modification. The treatment approach varies with risk.
160–179/100–109	Stage 2 — two drugs initially	Stage 2	ESH: grade 2 — drug therapy usually recommended. ESC 2024: hypertension	Drug therapy recommended by all guidelines, with combination therapy preferred.
≥ 180/≥ 110	Stage 2	Stage 2	ESH: grade 3 — immediate drug therapy. ESC 2024: hypertension	Immediate drug therapy. Assess for end-organ damage; if acute damage is present, this is a hypertensive emergency.

Two of the systems in the table are history. JNC 8 is quoted for its lineage only. The 2017 ACC/AHA guideline[14], still widely quoted as current, was replaced in 2025, and its 10% ASCVD gate went with it — the 2025 gate is a PREVENT risk of 7.5%, and the risk decides how soon the drug starts, not whether it starts.[20] The 2017 document is cited in this book only where the historical position is at issue. The ESC 2024 elevated-BP band runs from 120/70

to 139/89; drug therapy within it applies only to its upper half, 130–139/80–89, and only after up to three months of lifestyle therapy.[15] V3 Ch12 sets the thresholds out in full.

8.3 SPRINT and the 130/80 debate

SPRINT (n = 9,361; NEJM 2015) randomised high-cardiovascular-risk patients without diabetes or prior stroke to an intensive systolic target below 120 mmHg against a standard target below 140. It was stopped early at 3.26 years by the data safety monitoring board because of significantly lower rates of the primary composite endpoint in the intensive arm. All-cause mortality was also lower — 3.3% against 4.5%; HR 0.73, p = 0.003.[12]

0.75

hazard ratio for the primary composite endpoint in SPRINT's intensive arm — 5.2% against 6.8% over the trial, or 1.65% against 2.19% a year.[12]

These results appear to support strongly both a lower treatment target and a lower diagnostic threshold. Interpreting them, however, requires a methodological feature that was not widely appreciated until after publication: SPRINT used *unattended* automated office BP rather than the conventional attended measurement used in all previous outcome trials and in routine practice.

TABLE 8.2 — ATTENDED AGAINST UNATTENDED MEASUREMENT

METHOD	PROCEDURE	CONSEQUENCE
Conventional attended office BP	A physician or nurse enters the room, applies the cuff and takes two or three readings with the patient fully aware of the process.	Produces a white coat effect: anticipation triggers a sympathetic response that raises BP by an average of **5–15 mmHg** above true resting pressure.
Unattended automated office BP AOBP · USED IN SPRINT	The patient sits alone in a quiet room for five minutes, then an automated device takes three to five readings at one-minute intervals with no healthcare personnel present.[9]	Eliminates the white coat pressor response, giving readings 5–15 mmHg lower than attended ones. Comparative studies show AOBP correlates more closely with awake ABPM than attended readings do.[3]

Clinical rule

The guidelines agree more than they appear to

SPRINT's intensive target of under 120 mmHg by unattended AOBP is approximately equivalent to **130–135 mmHg by conventional attended measurement.** That translation is precisely what ACC/AHA 2017 did in setting a target of under 130/80 using conventional measurement.

The ESH position is that the methodological incompatibility means SPRINT cannot be applied directly to attended practice, and that European outcome evidence — collected with attended measurement — supports 140/90 as the office diagnostic threshold.

The practical difference is therefore smaller than it looks: **both agree that in high-risk patients — previous CVD, diabetes, CKD, high calculated risk — the optimal target is 130/80 mmHg or lower if tolerated.**[8,14]

8.4 Grading of hypertension: the ESH system

The grading system gives a clinically useful framework for communicating severity and setting initial treatment intensity. The three grades correspond to increasing cardiovascular risk, increasing urgency of initiation, and increasing likelihood of needing combination therapy from the outset.

TABLE 8.3 — THE THREE GRADES

GRADE	OFFICE BP	CHARACTERISTICS	INITIAL TREATMENT
Grade 1 MILD	SBP 140–159 and/or DBP 90–99	May have no symptoms and no target organ damage. Risk stratification by overall cardiovascular risk is essential — the same BP carries very different absolute risk in a 35-year-old non-smoker and a 65-year-old diabetic.	Lifestyle modification for three to six months at low or moderate risk. Immediate drug therapy at high or very high risk — established CVD, diabetes, CKD, or Grade 1 with three or more risk factors. Single agent, or combination if above 155/95.
Grade 2 MODERATE	SBP 160–179 and/or DBP 100–109	Higher likelihood of target organ damage, with symptoms if severe. Risk is elevated even at a low overall risk factor burden.	Immediate drug therapy alongside lifestyle modification. Two-drug combination preferred, as a single-pill combination where available and affordable. Review at four weeks.
Grade 3 SEVERE	SBP ≥ 180 and/or DBP ≥ 110	High probability of target organ damage. This is a hypertensive *emergency* if acute organ damage is present, and an *urgency* if it is not.	Immediate drug therapy, two-drug combination from day one. Urgent clinical assessment for target organ damage. If acute damage is found, refer for intravenous management.

8.5 Phenotypic subtypes

Beyond severity, hypertension is characterised clinically by *which* BP component is elevated. That pattern reflects the underlying haemodynamic and vascular mechanism, and has direct implications for drug selection.

TABLE 8.4 — FOUR PHENOTYPIC SUBTYPES DEFINITIONS ESTABLISHED TREATMENT COLUMN: PROPOSED FRAMEWORK

SUBTYPE	DEFINITION	MECHANISM	PREVALENCE	TREATMENT APPROACH
Combined SYSTOLO-DIASTOLIC	SBP ≥ 140 *and* DBP ≥ 90	Mixed: elevated CO, elevated SVR, or both. Typical of middle-aged essential hypertension with functional arteriolar vasoconstriction.	The commonest pattern at 40–65 years; about 60% of hypertensives	Most classes are effective. Choice is guided by the haemodynamic phenotype of Chapter 1, by comorbidities and by risk.
Isolated systolic ISH	SBP ≥ 140 with DBP < 90; pulse pressure ≥ 50	Aortic stiffness with Windkessel function lost (Chapter 1). Stroke volume is transmitted directly as a high-pressure wave; SVR may be normal or reduced.	Predominant above 65 — in NHANES III it accounted for about 74% of uncontrolled hypertension in adults aged 50 and over.[16] Occasionally in younger patients with a hyperdynamic circulation	CCBs and thiazide-type diuretics are most effective.[11] Record the diastolic at every visit and examine the patient if it falls low — but a low diastolic in an asymptomatic patient with stable renal function is not a reason to leave the systolic uncontrolled (V3 Ch13). Above 80, treat: HYVET showed a mortality and heart-failure benefit[4]; its 150/80 was that trial's target, not today's. The target is the ordinary one — 120–129 systolic where tolerated on ESC 2024, relaxed from age 85 or for moderate-to-severe frailty or symptomatic orthostatic hypotension.[15]
Isolated diastolic IDH	DBP ≥ 90 with SBP < 140	High SVR with preserved aortic compliance — typically neurogenic or RAAS-driven arteriolar vasoconstriction; occasionally a high-CO young adult.	10–15% of hypertensives, predominantly young adults	A guideline first-line agent — ACE inhibitor or ARB, calcium channel blocker or thiazide-type diuretic; the RAAS blocker fits the mechanism best. A beta-blocker only where a compelling indication names one — a high resting heart rate is not one, and anaemia and thyroid disease are excluded before it is interpreted at all (Chapter 1, Table 1.5). Carries a 40% increased cardiovascular risk against normotensives (Framingham).[1]
Isolated nocturnal	Clinic and daytime ABPM normal; nocturnal SBP ≥ 120 or DBP ≥ 70	OSA, CKD, primary aldosteronism or other causes of non-dipping (Chapter 7). Nocturnal RAAS and sympathetic activity uncorrected by a morning-only regimen.	Reported prevalence varies with the population and the definition used — 12.9% in a referred ambulatory cohort, 22.8% in an untreated general population; frequently missed without ABPM[17,18]	Investigate for OSA, CKD and primary aldosteronism and treat what is found — that is where the benefit is; an aldosterone antagonist where the mechanism is aldosterone-driven. Make sure the regimen is genuinely 24-hour and at full dose. Moving one agent to the evening is a safe and reasonable trial of timing, but randomised trials show the hour does not change outcomes (V2 Ch14) — describe it to the patient as a trial, not a treatment. Target organ damage is disproportionate to clinic BP.

8.6 Urgency and emergency: the critical distinction

Hypertensive crisis means a severe elevation requiring immediate attention. Whether it is an urgency or an emergency is the most clinically consequential binary decision in hypertension management, because it determines whether the patient needs intravenous drugs in a monitored setting or can be managed with oral agents.

Not the number

The distinction is made by the presence or absence of *acute* target organ damage — never by the BP value alone.

TABLE 8.5 — URGENCY AGAINST EMERGENCY

FEATURE	HYPERTENSIVE URGENCY	HYPERTENSIVE EMERGENCY
BP level	Usually SBP ≥ 180 or DBP ≥ 120; the threshold is not absolute[2]	Any level if acute damage is present — typically SBP ≥ 180, but not required
Acute target organ damage	**Absent**	**Present — this is the defining criterion**
Presentation	Elevated BP found incidentally; moderate headache; asymptomatic Grade 2; missed medication doses	Hypertensive encephalopathy, haemorrhagic or ischaemic stroke, acute coronary syndrome, aortic dissection, acute pulmonary oedema, acute kidney injury, eclampsia
Setting	Outpatient or emergency department; oral antihypertensives	ICU or high-dependency unit; intravenous antihypertensives; continuous arterial monitoring
Reduction target and rate	No acute reduction. Restart or intensify oral therapy and bring the pressure down over 24 to 48 hours, with review within a week.[2,14] Rapid lowering offers no benefit here and risks hypoperfusion in a patient whose autoregulatory range has shifted upward. **Not** to normal acutely. **Never sublingual nifedipine IR.**	Reduce MAP by 20–25% in the first hour. Two exceptions: aortic dissection — SBP under 120 and HR under 60 within 20 minutes; acute ischaemic stroke — permissive hypertension up to 220/120 if no thrombolysis is planned.[14]

Accelerated and malignant hypertension

Accelerated hypertension is defined by grade 3 Keith–Wagener–Barker retinopathy — bilateral flame haemorrhages and cotton-wool spots, with or without disc oedema — in the context of severely elevated BP. It represents severe hypertensive microvascular injury to the retinal arterioles, and is a marker of parallel injury in the renal and cerebral arterioles that may not yet be clinically apparent.

Malignant hypertension adds papilloedema — bilateral optic disc swelling from raised intracranial pressure. It is the most severe end of the emergency spectrum, with fibrinoid necrosis of arterioles throughout the body and high short-term mortality if untreated.

79%

one-year mortality in malignant hypertension before antihypertensive therapy existed — only one patient in five survived the year.[6,19] Five-year survival now exceeds 70%.

Clinical rule

Fundoscopy is not optional in the hypertensive crisis

All patients with grade 3 retinopathy — accelerated hypertension — require admission for parenteral therapy and urgent organ damage assessment: renal function, urine microscopy, ECG, chest radiograph, echocardiogram. Those with grade 4 retinopathy — malignant hypertension with papilloedema — require ICU-level care.

Fundoscopy is the single physical finding that immediately moves the treatment pathway from outpatient to inpatient.

8.7 Primary against secondary hypertension

Primary essential hypertension — the integrated haemodynamic consequence of the mechanisms of Chapters 1 to 6 without a single correctable cause — accounts for 90–95% of adult hypertension. Secondary hypertension, where a specific and potentially correctable cause can be identified, accounts for 5–10% overall but a substantially higher proportion of specific subgroups.[13]

Where secondary causes hide

Under age 40: about 30% in referred series, about 2% unselected · resistant hypertension: 30–40% · rapid-onset or severe hypertension

TABLE 8.6 — SECONDARY CAUSES: CLUES AND TESTS

CAUSE	PREVALENCE	KEY CLINICAL CLUES	DIAGNOSTIC TEST
Primary aldosteronism	5–10% overall; **20–30% of resistant hypertension**	Hypokalaemia — though absent in 40%. Non-dipping on ABPM. Resistant hypertension. Adrenal incidentaloma.	Aldosterone-to-renin ratio. Confirmatory saline infusion test. Adrenal CT with adrenal vein sampling if confirmed.
Renovascular RENAL ARTERY STENOSIS	1–5% overall; higher in elderly males and young females	Flash pulmonary oedema. Abdominal bruit. An ACEi or ARB provokes a creatinine rise above 30%. Asymmetric kidneys on ultrasound. Fibromuscular dysplasia in a young woman.	Renal Doppler ultrasound; CT renal angiography; MR angiography.
Phaeochromocytoma and paraganglioma	0.1–0.5% of hypertension; about 5% of adrenal incidentalomas	Paroxysmal hypertension, though not always. The triad of headache, palpitations and diaphoresis. BP lability. An adrenal incidentaloma above 4 cm.	24-hour urine catecholamines and metanephrines, or plasma metanephrines. Imaging: adrenal CT or MRI plus MIBG or DOTATATE PET.
Obstructive sleep apnoea	**30–40% of resistant hypertension**; about 10% of all hypertension	Non-dipping. Excessive daytime sleepiness. STOP-BANG ≥ 3. Snoring and witnessed apnoeas. Obesity, though OSA occurs at normal weight.	STOP-BANG score; overnight oximetry; polysomnography as the gold standard.
Cushing's syndrome	< 0.1%	Cushingoid features: central obesity, purple striae, easy bruising, moon face, buffalo hump, proximal myopathy.	24-hour urine free cortisol; overnight 1 mg dexamethasone suppression test; late-night salivary cortisol.
Thyroid disorders	Hypothyroidism 3–5%; hyperthyroidism 1–2%	Hypothyroid: diastolic hypertension, bradycardia, cold intolerance, constipation. Hyperthyroid: systolic hypertension, tachycardia, tremor, weight loss.	TSH and free T4 — mandatory baseline in every new hypertensive.
Chronic kidney disease	1–5% as a primary cause; very common as a co-occurring condition	Elevated creatinine. Proteinuria. Small echogenic kidneys on ultrasound. Anaemia of chronic disease.	Creatinine, eGFR and urine ACR — mandatory in every new hypertensive.

The decision to investigate is guided by clinical suspicion rather than routine screening of every patient. These features should prompt it: age below 40; resistant hypertension uncontrolled on three drugs including a diuretic; rapid onset or sudden worsening of previously controlled hypertension; hypokalaemia without diuretic use; abnormal renal function or significant

proteinuria; adrenal incidentaloma on imaging; paroxysmal symptoms consistent with phaeochromocytoma; features of Cushing's syndrome; and clinical features of fibromuscular dysplasia in a young woman.

KEY POINTS

1. **Guideline divergence:** the American guideline diagnoses hypertension at ≥ 130/80 mmHg — set in 2017 and kept by the 2025 document that replaced it, with a PREVENT risk of 7.5% now gating how soon the drug starts[20]; the European documents retain ≥ 140/90 — ESH 2023, and the 2024 ESC guideline, which adds a category of elevated BP for 120–139/70–89 and sets a treated systolic target of 120–129 mmHg.[15] SPRINT's unattended AOBP target of under 120 translates to about 130–135 attended — which reconciles the numbers in practice. Whenever a threshold is quoted in this book, the guideline it belongs to is named with it.
2. **ESH grades:** Grade 1 — lifestyle first unless high risk; Grade 2 — immediate two-drug therapy; Grade 3 — immediate combination, assess for emergency. The grade sets the urgency of initiation, not the target — under 130/80 for most patients on ESH 2023, and 120–129 systolic where tolerated on ESC 2024.[8,15]
3. **ISH** is the predominant pattern in older hypertensives — about 74% of uncontrolled hypertension over the age of 50 in NHANES III[16]; the mechanism is aortic stiffness. CCB and thiazide preferred. Record the DBP at every visit and examine the patient if it falls low, but do not leave the systolic uncontrolled for the sake of the diastolic (V3 Ch13). Above 80, treat: HYVET showed a mortality and heart-failure benefit; its 150/80 was that trial's target, not today's. The target is the ordinary one — 120–129 systolic where tolerated on ESC 2024, below 130 on AHA/ACC 2025 — relaxed from age 85, or for moderate-to-severe frailty or symptomatic orthostatic hypotension.[4,15,20]
4. **Urgency against emergency** turns on acute target organ damage, not the number. Emergency: encephalopathy, stroke, ACS, dissection, pulmonary oedema, eclampsia, AKI — IV drugs, ICU, MAP down 20–25% in the first hour. Urgency: oral drugs over 24–48 hours. Never sublingual nifedipine IR.
5. **Accelerated hypertension** — grade 3 retinopathy — means admission for IV therapy. **Malignant hypertension** — grade 4 with papilloedema — means ICU. Fundoscopy is the decisive examination finding.
6. **Secondary causes:** primary aldosteronism 5–10% overall and 20–30% of resistant cases; OSA 30–40% of resistant cases; phaeochromocytoma 0.1–0.5%. Investigate when: age under 40, resistant, rapid onset, hypokalaemia without diuretics, adrenal incidentaloma, paroxysmal symptoms.
7. **Risk is continuous from 115/75** (Lewington, Lancet 2002): each 20 mmHg systolic rise doubles cardiovascular mortality. The diagnostic threshold is a risk-based decision calibrated against trial evidence, not a biological constant — which is why it moves as evidence accumulates.[7]

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CHAPTER 9 PART I · MECHANISM

Epidemiology of hypertension: global and India

Prevalence, burden, treatment gaps, mortality contribution, and the Indian epidemic in context.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Global prevalence** — 1.28 billion adults, and what the WHO 2021 analysis established.
2. **Mortality burden** — hypertension as the leading attributable risk factor worldwide.
3. **The treatment cascade** — why only about one hypertensive in five, worldwide, has controlled BP.
4. **India's epidemic** — NFHS-5 and ICMR-INDIAB data, and the 315 million adults affected.
5. **India's control cascade** — roughly 15 per 100 hypertensives adequately controlled.
6. **The South Asian phenotype** — biological vulnerability at lower BMI and lower BP.
7. **India Hypertension Control Initiative** — and the path toward population-level control.

9.1 The global burden: 1.28 billion adults

The most comprehensive global analysis of hypertension prevalence to date established the scale of the epidemic with unprecedented precision, and revealed trends that challenge conventional assumptions about where the problem is concentrated.

In 2019 an estimated 1.28 billion adults aged 30 to 79 had hypertension worldwide, defined as office SBP ≥ 140 or DBP ≥ 90 or current antihypertensive use. A separate analysis running from 1975 counts 594 million then and 1.13 billion by 2015 — a doubling, driven predominantly by population growth and ageing rather than by rising age-standardised prevalence — which remained relatively stable in high-income countries while rising substantially in low- and middle-income countries.[15,16]

NCD-RisC, Lancet 2021

1,201 population-based studies · 184 countries · 104 million individuals with measured BP · 1990 to 2019.

TABLE 9.1 — REGIONAL DISTRIBUTION, 2019

REGION	AFFECTED ADULTS	AGE-STANDARDISED PREVALENCE	CHANGE 1990–2019
South Asia INDIA, PAKISTAN, BANGLADESH, NEPAL	~450 million India alone: 200–220 m	32–36% men 30–34% women	Rising, driven by urbanisation, dietary transition and reduced physical activity. India's urban prevalence now approaches European levels.
Sub-Saharan Africa	~130 million	30–40% highest globally	The largest proportional increase of any region, with the poorest treatment and control rates worldwide.
East Asia and Pacific	~400 million	25–35%	Stable or slightly declining in China following national programmes; rising in Pacific island nations.
High-income countries EUROPE, NORTH AMERICA, AUSTRALIA	~220 million	22–30%	Age-standardised prevalence stable and cardiovascular mortality from hypertension declining through treatment — but absolute numbers rising as populations age.
Latin America and Caribbean	~130 million	28–34%	Rising with urbanisation and increasing dietary salt, with large urban–rural gaps.

TABLE 9.2 — THE GLOBAL TREATMENT CASCADE

STEP	GLOBAL, 2019	HIGH-INCOME COUNTRIES	LOW- AND MIDDLE-INCOME
Aware of their hypertension	~580 million (45%)	75–80%	40–50%
Receiving treatment OF THOSE AWARE	~440 million 76% of aware; 34% of all	85–90% of aware	50–60% of aware
BP controlled on treatment UNDER 140/90	~175 million 14% of all hypertension	50–60% of treated ~45% of all	20–30% of treated 8–12% of all

The cascade shows that only about one in five of the world's 1.28 billion hypertensives has controlled blood pressure — the WHO global report puts it at approximately one in five, and older figures of one in seven reflect an earlier vintage of the same cascade — a figure reflecting failures at several distinct points in the pathway: inadequate screening and awareness, poor access to diagnosis, inadequate treatment initiation, insufficient follow-up, non-adherence, and underdosing.[20]

9.2 The leading global mortality risk factor

WHO's 2023 global report on hypertension, drawing on Global Burden of Disease estimates for 2019, ranked elevated systolic blood pressure as the single leading risk factor for all-cause mortality worldwide, attributable to an estimated 10.8 million deaths and 235 million disability-adjusted life years annually. The attributable diseases are ischaemic heart disease (4.9 million deaths, 47% of the total), haemorrhagic stroke (2.0 million), ischaemic stroke (1.5 million), hypertensive heart disease (0.7 million) and CKD (0.5 million).[20]

10.8 m

deaths annually attributable to elevated systolic BP — more than smoking (7.7 m), air pollution (6.7 m) or high fasting glucose (6.5 m).

Clinical rule

Most attributable risk sits below the diagnostic threshold

The risk attributable to elevated BP is not confined to those who meet a diagnostic threshold. It is continuous from systolic pressures well below 140 mmHg, and a substantial fraction of population-attributable risk comes from the very large number of people in the 120–140 mmHg range.

Summed across hundreds of millions, their collective risk exceeds the absolute risk carried by the much smaller number above 180 mmHg. **This is the statistical basis for population-level sodium reduction: even a 1–2 mmHg shift in the whole population distribution prevents more events than treating only those above the threshold.**[6]

9.3 India: the scale of the epidemic

India faces an epidemic of extraordinary scale, defined not merely by absolute numbers — the largest in any single country — but by the combination of high prevalence, very low treatment rates, and the biological vulnerabilities of the South Asian phenotype that make untreated hypertension disproportionately damaging.

NFHS-5 reported that 24% of men and 21% of women aged 15 and above had hypertension. Age-standardising those figures to the adult population above 30 — an estimate made here, not a published one — gives roughly a third of adults. The two surveys use different age ranges and definitions, so their headline numbers are not directly comparable; ICMR-INDIAB's 315 million is the figure to quote. ICMR-INDIAB (113,043 participants) reported a hypertension prevalence of **35.5%**, an estimated **315 million adults**, with substantial inter-state variation from 20% in rural Uttar Pradesh to over 40% in urban Kerala and Goa.[1,14]

Two national datasets

NFHS-5 (2019–21): over 600,000 households, all states and union territories. ICMR-INDIAB (2023): standardised methodology across all Indian states.

TABLE 9.3 — INDIA'S CONTROL CASCADE AGAINST THE UNITED STATES

STEP	INDIA — NFHS-5 AND ICMR-INDIAB HYPERTENSION ≥ 140/90 OR ON TREATMENT	USA — NHANES 2019 ≥ 130/80 OR ON TREATMENT (ACC/AHA) — A LOWER THRESHOLD, NOT COMPARABLE WITH THE INDIAN FIGURE
Prevalence in adults	~315 million affected (35.5%)	116 million (~45%) — at the American ≥ 130/80 definition, which inflates the count; the comparison that holds across the two definitions is the control rate
Aware of the diagnosis	~45–50% of those affected[17]	~85%
On treatment OF THOSE AWARE	~65–70% of those aware — 60 to 65 million in total	~75%
BP controlled OF THOSE TREATED	~20–25% — 13 to 16 million, about 7% of all hypertension	~54%
Overall control rate	~17 per 100 hypertensives POOLED 17.5% FOR 2001–2020, RISING TO 22.5% IN 2016–2020; SOUTHERN REGION 23.5%, EASTERN LOWEST[11]	~45 per 100

Clinical rule

What ten hypertensive patients in an Indian OPD actually look like

On average: **five** are unaware they have the condition or have never been formally diagnosed; **three** are aware but untreated or inadequately treated; **one or two** are on treatment but uncontrolled; and **one** has controlled BP.

This is the population every Indian clinician is actually serving.

9.4 Urban–rural and regional patterns

The geography of hypertension in India reflects the differential pace of epidemiological transition across regions, and the interaction of income, urbanisation, diet and physical activity.

TABLE 9.4 — FOUR PATTERNS IN THE INDIAN DATA

PATTERN	DATA	DRIVERS	CLINICAL IMPLICATION
Urban–rural gap NARROWING	Urban 32–38%, rural 25–30%. The gap has narrowed from about 15 percentage points in 2000 to 8 in 2021; NFHS-5 shows rural prevalence rising faster than urban.[2]	Rural: rapid transition to processed and ultra-processed foods, less agricultural labour, salt in preserved foods, an awareness deficit. Urban: awareness and treatment improving, but not enough.	Rural hypertension is now larger in absolute numbers than urban, simply because more people live in rural India. Sub-health-centre screening and ASHA worker involvement are the critical delivery points.
North–South gradient	The gradient is real but less clean than often drawn. A district-level analysis of all 707 districts gives an age-standardised prevalence of 22.4% overall, highest in western and southern districts — but Punjab and Sikkim, in the north and northeast, are among the highest-prevalence states, and better-developed districts show *higher*, not lower, prevalence.[5]	South: earlier urbanisation, higher fat intake, lower physical activity, longer survival and therefore more elderly. North: more smoking, different dietary patterns, and a younger population structure that limits the age-adjusted burden.	The states with the highest prevalence — Kerala, Goa, Mizoram — also have higher cardiovascular mortality, confirming that the prevalence gradient translates into outcome differences.
Young adult hypertension RISING SHARPLY	Hypertension in young Indian adults is rising, but the size of the rise should be quoted carefully. The published NFHS analysis this book could verify covers ages 15–24, where prevalence in men rose from 5.2% to 6.2% between the two survey rounds while remaining near 4.0% in women; prehypertension rose more steeply, from 38.9% to 44.5% in men. Figures for the 20–39 band circulate widely and could not be traced to a source.[10]	The obesity epidemic — BMI above 25 now affects 26% of urban adults — plus sleep deprivation and shift work, processed and fast food, physical inactivity (India is among the most inactive nations in WHO data), and psychosocial stress in the urban service economy.	Young adult hypertension is predominantly neurogenic and high-CO (Chapter 1). Early diagnosis prevents decades of cumulative organ damage. **Occupational medicine is a key intervention point** — workplace screening reaches employed young adults who access healthcare no other way.
Gender patterns	Men have higher prevalence below 60; women higher above 60, the post-menopausal shift. Rural women have worse awareness and treatment rates than men.[18]	Oestrogen's protective vascular effects pre-menopause. The post-menopausal rise reflects lost oestrogen-mediated NO production and favourable lipid effects. Rural women: lower healthcare utilisation and less screening.	Post-menopausal women are the fastest-growing hypertensive demographic in India. Review BP at every HRT prescription, transdermal preferred. Dedicated women's health screening programmes are needed.

9.5 The South Asian phenotype

South Asians have a well-documented susceptibility to cardiovascular disease at lower BMI, lower BP and earlier ages than Europeans, reflecting distinct body composition, metabolic and vascular characteristics that interact with hypertension to amplify risk. Three features matter clinically.

WHO thresholds for South Asians

Overweight: BMI ≥ 23. Obese: BMI ≥ 27.5. Both lower than the European cut-offs, for the reason described here.

1 **Central obesity at lower absolute BMI.** South Asians accumulate proportionally more visceral adipose tissue than Europeans at the same BMI — a South Asian at BMI 23 typically carries the visceral fat mass of a European at BMI 26. The metabolic consequences of adiposity — insulin resistance, adipose RAAS expansion, leptin-driven sympathetic overactivation — therefore occur at lower absolute weight.

2 **High salt sensitivity.** Reduced average nephron number from the high prevalence of low birth weight (Chapter 5) combined with the high dietary sodium of Indian cooking — a mean of 8.0 g of salt a day in adults aged 18 to 69 in the National NCD Monitoring Survey of 2017–18, estimated from spot urine sodium — creates a high-intake, low-capacity mismatch producing salt-sensitive hypertension at population scale. *This substrate is not repairable by drug therapy; only population-level sodium reduction addresses it.*[13]

3 **Earlier events at lower risk factor burden.** The INTERHEART South Asia sub-study and multiple Indian cohorts show South Asians having a first myocardial infarction younger: in INTERHEART the mean age of first MI was **53.0 years** in South Asian countries against **58.8 years** elsewhere.[7] Whether a given blood pressure carries greater absolute risk in an Indian patient than in a European with otherwise identical risk factors is a separate question, and one this book does not have a source for.

9.6 India Hypertension Control Initiative

The India Hypertension Control Initiative, launched in 2017 by ICMR, the Ministry of Health and Family Welfare, WHO and state governments, is the most significant programmatic effort to address the treatment cascade at scale. Modelled on the WHO HEARTS package, it operates through the government primary healthcare system — sub-centres, primary health centres and community health centres — India's largest healthcare delivery network.

Evidence

What IHCI achieved, and what it proves

Across phase I states — Punjab, Kerala, Himachal Pradesh, Maharashtra, Madhya Pradesh and six others — BP control among registered patients reached **47%** by early 2021, and **55%** at health and wellness centres, against a national baseline of about **12%** before the programme.[3,8]

Three lessons follow for clinical practice. **Treatment simplification** — one algorithm rather than individualised prescribing for every patient — dramatically improves population-level outcomes even at some cost in individual optimisation. **Patient-held records and community health worker involvement** are independently effective without complex health system change.

And most importantly: **the barrier to BP control in India is not pharmacological complexity. It is drug availability, cost and follow-up continuity — systems problems, not clinical ones.**[12]

The protocol

Amlodipine 5 mg first-line for all, *except in chronic kidney disease, where telmisartan is recommended instead* · fixed escalation steps — amlodipine 10 mg, then telmisartan 40 and 80 mg, then chlorthalidone · three drugs procured for the whole programme, given free of cost at every clinic · patient-held BP passports[9] · ASHA workers in the community care team[8]

30–40 m

organised-sector workers in factories, mines, construction and utilities are legally required to have annual health examinations.

9.7 The occupational physician's role

Occupational health physicians and factory medical officers occupy a strategically important position in India's hypertension control effort that is systematically underused. Organised workplaces give access to a population predominantly in the highest-risk demographic — working-age adults aged 25 to 60 — in a setting that already requires medical engagement through pre-employment examinations, periodic health examinations and fitness-for-duty assessments mandated by the Factories Act.

NFHS-5 data suggest employed adults in the organised sector have only marginally better awareness and treatment rates than the general population, despite regular contact with healthcare through occupational health services. That is a missed opportunity of considerable scale: if BP measurement, diagnosis and treatment initiation were systematically integrated into these mandatory examinations, the workplace would become a major entry point into the control cascade.

Implementation requires three additions to existing practice, none needing equipment beyond what occupational health facilities already possess: standardised BP measurement at every examination using a validated automated device and an appropriately sized cuff; a documented action protocol distinguishing employees needing same-visit referral (Grade 3), follow-up measurement within four weeks (Grade 1–2), and ABPM or home monitoring (borderline or variable readings); and a referral pathway to the company clinic or nearest primary health centre for treatment initiation.

KEY POINTS

1 **Global burden:** 1.28 billion adults in 2019 (NCD-RisC, Lancet 2021). Of all hypertensives, roughly 45% are aware and 34% treated; WHO puts control at **about one in five**. Sub-Saharan Africa has the worst control; South Asia the largest absolute burden.

2 **GBD 2019:** elevated systolic BP is the leading global mortality risk factor — 10.8 million deaths and 235 million DALYs annually, more than smoking, high glucose or air pollution. Risk is continuous from 115/75 mmHg.[4]

3 **India:** about 315 million affected adults; ICMR-INDIAB prevalence 35.5%. The cascade — about 50% aware, 65% of those treated, 20–25% of those controlled — leaves roughly 17 per 100 controlled on the best pooled estimate for 2001–2020 — rising to about 22 per 100 in 2016–2020[11] — against 45 per 100 in the USA.

4 **Patterns:** the urban–rural gap is narrowing as rural prevalence rises fastest. North–South gradient: real but less clean than it is drawn — district-level age-standardised prevalence is 22.4% overall, highest in western and southern districts, but Punjab and Sikkim are among the highest-prevalence states and better-developed districts run higher, not lower.[5] Young-adult prevalence is rising but not doubling — 5.2% to 6.2% in men aged 15–24 across the two NFHS rounds, with prehypertension rising more steeply, from 38.9% to 44.5%; the figures for the 20–39 band that circulate widely have no traceable source.[10]

5 **South Asian phenotype:** more visceral fat at lower BMI — overweight from a BMI of 23, obesity from 27.5, both lower than the European cut-offs; salt sensitivity from low birth weight reducing nephron endowment — about 27% of births on modelled UNICEF–WHO estimates, 17% on NFHS-5's recorded figure (V1 Ch05); first MI at a mean of 53.0 years against 58.8 elsewhere (INTERHEART).[7]

6 **IHCI (2017):** a simplified protocol — amlodipine first-line, patient-held BP card, ASHA support, free drugs — raised control among registered patients to **47%**, and to **55%** at health and wellness centres, against a national baseline of about **12%**. It demonstrates that systems barriers, not clinical complexity, are the bottleneck.[19]

7 **The occupational opportunity:** 30–40 million organised-sector workers have mandatory annual examinations. Systematic BP measurement, documentation and referral there would reach the highest-risk demographic at a point of guaranteed healthcare contact.

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CHAPTER 10 PART I · MECHANISM

The mosaic theory of essential hypertension

Page's integrated model, the eight mechanisms, haemodynamic transition, vascular remodelling, and epigenetics.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Page's Mosaic Theory (1949)** — why no single mechanism explains essential hypertension.
2. **The eight mosaic tiles** — neural, humoral, mechanical, renal, vascular, endothelial, genetic, immune.
3. **The haemodynamic transition** — from high-CO neurogenic to high-SVR structural hypertension.
4. **Vascular remodelling** — eutrophic, hypertrophic, rarefaction and atherosclerotic patterns.
5. **Epigenetics** — DNA methylation, histone modification, microRNAs and the 1,000-day window.
6. **Fetal programming** — the Barker hypothesis and the developmental origins of adult hypertension.
7. **Why monotherapy has a ceiling** — and why combination therapy is mechanistically superior.

10.1 Page's Mosaic Theory: the conceptual foundation

Irvine Page, working at the Cleveland Clinic in the 1940s, proposed the mosaic theory in 1949 as an explicit rejection of the prevailing tendency to seek a single dominant cause for elevated blood pressure. Having observed that essential hypertension could not be attributed solely to renal disease, nor to excess catecholamines, nor to volume overload, nor to arteriolar structural change alone, Page argued that sustained elevation required the simultaneous contribution of multiple interacting mechanisms — each a tile in a mosaic.[7]

Page's original mosaic included neural, humoral, mechanical and renal factors. Over seven decades the model has been progressively validated and expanded: vascular biology, endothelial function, genetic determinants and immune mechanisms have each been added as distinct tiles with established evidence for independent contribution. The modern mosaic has eight principal components, each corresponding to a mechanistic pathway described elsewhere in this book.[7,8]

The image itself

Remove one tile and the pattern is distorted but not eliminated. Remove several and the picture degrades substantially.

TABLE 10.1 — THE EIGHT TILES OF THE MODERN MOSAIC PROPOSED FRAMEWORK

TILE	CORE MECHANISM	KEY EVIDENCE	DRUG CLASSES ADDRESSING IT
Neural SNS OVERACTIVATION	RVLM-mediated sympathetic overactivation: elevated resting MSNA, high resting HR, the neurogenic high-CO phenotype (Chapter 4).	Microneurography in offspring of hypertensives (Julius); HARVEST; RVLM firing in pre-hypertensive SHR.	Beta-blockers, central sympatholytics, renal denervation.

TILE	CORE MECHANISM	KEY EVIDENCE	DRUG CLASSES ADDRESSING IT
Humoral RAAS ACTIVATION	Angiotensin II: vasoconstriction, aldosterone secretion, LVH, renal damage. Aldosterone: Na^+ retention, cardiac fibrosis, vascular inflammation (Chapter 3).	HOPE, LIFE, RENAAL, IDNT; PATHWAY-2; FIDELIO-DKD.	ACE inhibitors, ARBs, MRAs. (Aliskiren is of mechanistic interest only — see V1·Ch3.)
Mechanical HAEMODYNAMIC FORCES	Elevated pressure directly injures endothelium, hypertrophies smooth muscle, raises LV wall stress and accelerates arteriolar remodelling through Laplace's Law (Chapter 1).	Pressure-induced remodelling in organ bath studies; event clustering at the morning surge; LVH regression with BP control.	All classes; ACEi and ARBs most effective for LVH and arteriolar regression.
Renal PRESSURE-NATRIURESIS SHIFT	Rightward shift of the curve: reduced nephron number, intrarenal RAAS and tubular Na^+ retention maintain volume expansion at elevated BP (Chapter 5).	Guyton's model; Brenner hypothesis (Keller, NEJM 2003 — halved nephron number); PATHWAY-2.[11]	Diuretics, ACEi and ARBs, renal denervation, dietary sodium restriction.
Vascular STRUCTURAL REMODELLING	Inward eutrophic arteriolar remodelling raising the wall-to-lumen ratio without net growth, permanently elevating the SVR floor; plus aortic stiffness giving ISH.	Media–lumen ratio studies (Mulvany, Heagerty); pulse-wave-velocity cohort data; CAFE (central pressure).	ACEi and ARBs give the best regression; CCBs modest; diuretics aid it through volume reduction.
Endothelial DYSFUNCTION	Reduced NO bioavailability through NADPH oxidase, eNOS uncoupling, BH_4 oxidation and ADMA; endothelin-1 excess; PGI_2/TXA_2 imbalance (Chapter 6).	FMD studies (Celermajer, MESA); ADMA as an independent mortality predictor; ACEi pleiotropic effects beyond BP.	ACEi through bradykinin and NO; CCBs reduce oxidative stress; statins upregulate eNOS.
Genetic INHERITED SUSCEPTIBILITY	Heritability 30–50%. Polygenic: hundreds of common small-effect variants. Monogenic: rare large-effect mutations — Liddle, Gordon, GRA. Pharmacogenomic variants affecting drug response.	Twin studies; GWAS with over 1,500 SNPs from UK Biobank; monogenic syndrome series; ACE I/D polymorphism data.	Genotype-guided prescribing is emerging. Treat monogenic causes specifically — amiloride in Liddle, surgery in GRA.
Immune TH17 INFLAMMATION	T-cell infiltration of the renal interstitium; Th17–IL-17A impairment of pressure-natriuresis; Treg deficiency in metabolic syndrome; the microbiome–salt interaction (Chapter 5).[3,6,9]	RAG-1 knockout mice; T-cell transfer experiments; Wilck human data on *Lactobacillus* and sodium; RALES antifibrotic MRA effects.[17]	MRAs, with anti-inflammatory effects beyond MR blockade; sodium restriction; microbiome modulation (emerging).

10.2 The haemodynamic transition

One of the most important clinical insights emerging from the mosaic framework is the haemodynamic transition: the progressive shift in dominant mechanism that occurs over years to decades as untreated or inadequately treated hypertension evolves.

In the early stages — typically young adults in their twenties and early thirties with a neurogenic phenotype — the dominant abnormality is elevated cardiac output. Resting heart rate is high, stroke volume is large relative to vascular calibre, and SVR is initially normal or even below average as the

body attempts to compensate by peripheral vasodilation. This is the high-CO phase characterised by Julius and Lund-Johansen, in which the neural tile is most active.

Over years, the sustained high-pressure environment produces structural change in the resistance arterioles. Smooth muscle cells rearrange around a smaller lumen, medial thickness increases, and collagen is deposited in the adventitia. These changes permanently raise arteriolar resistance, so SVR rises. The baroreceptors reset to defend the higher pressure. The RAAS adapts to the new operating point. Cardiac output, now working against elevated SVR, may normalise or even fall as the left ventricle hypertrophies and diastolic compliance falls.

The 55-year-old who has been poorly controlled since their thirties has therefore completed the transition: SVR is structurally elevated, baroreceptors are reset, renin may now be suppressed from volume loading, and the heart is hypertrophied with early diastolic dysfunction. The drug choice that was rational at 30 — a beta-blocker for a high-CO neurogenic pattern — may be irrational at 55, where the structural high-SVR low-renin phenotype responds better to a diuretic or a CCB. **Reassessing the haemodynamic phenotype when BP becomes difficult to control is a clinical imperative that the mosaic framework makes explicit.**

Two different diseases

The hypertension of a poorly controlled 55-year-old is not the same disease as the hypertension of a newly presenting 30-year-old — and does not respond to the same drug.

10.3 Vascular remodelling: four patterns

Vascular remodelling refers to the structural changes in vessel walls that develop in response to sustained haemodynamic stress and to the chronic action of Ang II, ET-1 and aldosterone on smooth muscle and connective tissue. Four distinct patterns have been characterised in different vascular segments and at different stages, each with its own functional consequence.

TABLE 10.2 — FOUR REMODELLING PATTERNS

PATTERN	VASCULAR SITE	STRUCTURAL CHANGE	FUNCTIONAL CONSEQUENCE
Inward eutrophic remodelling	Small resistance arterioles, 50–200 µm — the dominant pattern in essential hypertension	Smooth muscle cells rearrange around a smaller lumen with no net increase in total wall volume. Wall-to-lumen ratio rises; lumen narrows by 10–15%.	Permanent SVR elevation — by Poiseuille, a 10% lumen reduction raises resistance 52%. Cannot be fully reversed by vasodilators. Partial regression follows two to five years of ACEi or ARB therapy (LIVE trial: indapamide superior to enalapril in diabetic hypertension).
Hypertrophic remodelling	Larger arterioles and small arteries, 200–500 µm; also in severe or longstanding disease	A true increase in smooth muscle mass — hypertrophy and hyperplasia driven by Ang II, ET-1 and mechanical stretch. The lumen narrows *and* wall mass increases.	Contributes structurally to both SVR elevation and reduced compliance. Worse prognosis than the eutrophic pattern: target organ damage occurs at lower absolute pressures when it is present.
Microvascular rarefaction	Capillary and arteriolar beds in skeletal muscle, heart and skin	Reduced capillary density. Functional rarefaction: capillaries present but unperfused. Structural rarefaction: vessel dropout with apoptosis.	Reduced skeletal muscle oxygen delivery gives exercise intolerance; increased diffusion distance contributes to insulin resistance. In the heart, microangiopathy without obstructive CAD — **angina with normal coronaries.**
Atherosclerotic remodelling	Medium and large arteries: coronary, carotid, femoral, renal	Endothelial dysfunction → monocyte adhesion → foam cell formation → lipid-rich plaque. Smooth muscle migrates from media to intima; advanced plaques calcify.	Plaque vulnerability to rupture giving ACS; flow limitation giving stable angina and claudication; thromboembolism giving ischaemic stroke and renal artery thrombosis. Accelerated by hypertension through NO depletion and VCAM-1 upregulation.

10.4 Epigenetics and the 1,000-day window

The genetic contribution includes not only fixed DNA sequence variation but epigenetic modification — heritable changes in gene expression that do not alter the sequence itself. Epigenetic mechanisms explain how environmental exposures during critical developmental periods produce persistent changes in cardiovascular phenotype, transmitted across cell divisions and potentially across generations.

TABLE 10.3 — THREE EPIGENETIC MECHANISMS

MECHANISM	MOLECULAR BASIS	RELEVANCE TO HYPERTENSION
DNA methylation	Methyl groups added to cytosine residues in CpG dinucleotides by DNMT enzymes; promoter methylation generally silences expression. TET enzymes catalyse demethylation.	Differential methylation of the renin, ACE and AGT genes has been identified in hypertensive patients. Prenatal protein restriction hypomethylates the glucocorticoid receptor gene in offspring kidney, reducing RAAS counter-regulation. 11β-HSD2 methylation in the fetal kidney explains how maternal glucocorticoid excess produces offspring hypertension.
Histone modifications	Post-translational modification of histone proteins — acetylation, methylation, phosphorylation, ubiquitination — altering chromatin structure and transcriptional accessibility.	Ang II activates histone acetyltransferases in VSMC, facilitating inflammatory gene transcription. HDAC inhibitors reduce BP in experimental models by suppressing Ang II-induced inflammatory expression, with early human evidence in essential hypertension.
MicroRNAs	Small non-coding RNAs of about 22 nucleotides binding complementary sequences in 3′ UTRs of target mRNAs, causing degradation or translational repression.	miR-155 regulates AT_1R expression and is elevated in hypertension; miR-21 promotes VSMC proliferation and fibrosis; miR-126 maintains endothelial integrity and is reduced. Circulating miRNAs are measurable in plasma and under evaluation as biomarkers of hypertensive end-organ damage.

The Barker hypothesis and three programming mechanisms

David Barker's observation in the 1980s that English regions with the highest early-twentieth-century infant mortality from poor nutrition also had the highest adult cardiovascular mortality sixty years later led to the developmental origins of health and disease hypothesis: that nutritional and hormonal conditions during fetal development and early infancy programme cardiovascular and metabolic phenotype in ways that persist for life. Three programming mechanisms are established for hypertension.[4]

The 1,000 days
Conception to 24 months — the period in which cardiovascular phenotype is most plastic and most susceptible to epigenetic modification.

1. **Reduced nephron endowment.** Intrauterine growth restriction reduces nephron formation during the critical third-trimester window. The deficit is permanent and shifts the pressure-natriuresis curve rightward for life — the Brenner hypothesis of Chapter 5, operating through an epigenetically determined structural deficit.[13]

2. **HPA axis programming.** Intrauterine glucocorticoid excess — from maternal stress, placental 11β-HSD2 deficiency, or exogenous corticosteroids — programmes the fetal HPA axis toward a higher cortisol setpoint that persists postnatally. Elevated cortisol sensitises the vasculature to catecholamines, promotes renal sodium retention, and raises angiotensinogen synthesis: *three mosaic tiles programmed simultaneously.*

3 **Sympathetic programming.** Postnatal undernutrition followed by catch-up growth — a common trajectory in Indian children born with low birth weight — sustainedly upregulates the sympathetic nervous system through leptin. The malnourished infant has very low leptin; the surge during catch-up growth activates central circuits that remain sensitised. This programming of the neural tile in early life produces the high-MSNA phenotype that presents clinically as young adult hypertension with an elevated resting heart rate.

10.5 Why monotherapy has a ceiling

The mosaic theory has a direct pharmacological consequence that is among the most practically important insights in the field: because sustained hypertension is maintained by multiple simultaneously active mechanisms, blocking only one will always produce an incomplete reduction — limited by counter-regulatory activation of the others.

FIGURE 10.1 — THE ARITHMETIC OF THE CEILING

Suppose SVR is elevated 40% through four mechanisms contributing roughly equally:

10% RAAS	10% Sympathetic	10% Structural remodelling	10% Endothelial dysfunction

An ACE inhibitor can reduce SVR by about 10%, giving a MAP reduction of roughly 8–10 mmHg — exactly what trials show for ACEi monotherapy. **The other 30% is untouched.**[12]

The ceiling is not a pharmacological limitation of the drug. It is a mathematical consequence of the mosaic.

Worse, blocking one mechanism activates the others. A diuretic that reduces volume and lowers CO activates the baroreceptor–RVLM–sympathetic axis, stimulates the RAAS by reducing perfusion pressure, and activates the macula densa. These counter-regulatory responses partially restore BP through other tiles even as the targeted mechanism is suppressed.

Combination therapy addressing several tiles at once is therefore not merely an empirical observation that two drugs lower BP more than one: it is a mechanistically predicted necessity following directly from the framework. The most effective pairings address complementary mechanisms with minimal counter-regulatory overlap.[16]

Counter-regulation, concretely

A diuretic that lowers CO activates the baroreflex, stimulates renin through reduced perfusion pressure, *and* stimulates the macula densa through low NaCl delivery — three tiles at once.

Clinical rule

The wrong drug does not merely underperform — it can worsen control

A drug mismatched to the dominant tile may actively worsen BP control by potently activating counter-regulatory mechanisms while only partially suppressing its target.

A beta-blocker given to an elderly, low-renin, volume-dependent hypertensive reduces renin secretion that was already low and slows a heart rate that was not elevated, while reflex sodium retention from reduced CO activates volume mechanisms further. **The result is minimal BP reduction, bradycardia and worsening fluid retention.**

Understanding the mosaic ensures drug choice is matched to the dominant active tile, not simply drawn from a generic algorithm.

TABLE 10.4 — RATIONAL COMBINATIONS AND THEIR MECHANISTIC BASIS

COMBINATION	MECHANISTIC BASIS	TRIAL EVIDENCE
ACEi or ARB + CCB MOST EVIDENCE-BASED	The RAAS blocker addresses the humoral tile and reduces endothelial dysfunction; the CCB addresses the vascular and mechanical tiles through arteriolar vasodilation. No shared counter-regulatory pathway: the CCB does not significantly activate the RAAS, and the RAAS blocker causes no reflex tachycardia because SVR and CO changes are balanced.	ACCOMPLISH: amlodipine–benazepril superior to HCTZ–benazepril for cardiovascular outcome. ASCOT-BPLA: amlodipine–perindopril against atenolol–bendroflumethiazide gave **23% fewer cardiovascular events.**[5,10]
ACEi or ARB + thiazide	The RAAS blocker reduces Ang II and aldosterone (humoral tile); the thiazide reduces volume (renal tile). The synergy runs both ways: the thiazide activates the RAAS through the macula densa, providing more substrate for the blocker to suppress, while the blocker prevents diuretic-induced hypokalaemia through aldosterone suppression.	ADVANCE: perindopril–indapamide in diabetes reduced cardiovascular and renal outcomes. PROGRESS: perindopril–indapamide reduced recurrent stroke by 43%.[1,15]
CCB + thiazide	Both address structural SVR — the CCB by functional vasodilation, the thiazide by volume reduction. Particularly rational in elderly ISH, where renin is low, the picture volume-dependent and structural SVR elevation dominant.	ALLHAT: chlorthalidone equivalent to amlodipine for coronary outcomes and superior for heart failure prevention. SHEP: chlorthalidone-based therapy in ISH.[2]
ACEi or ARB + CCB + thiazide THE EVIDENCE-BASED TRIPLE	Addresses all three principal BP-raising mechanisms at once — RAAS, SVR and volume — with complementary counter-regulatory profiles: neither the CCB nor the RAAS blocker significantly activates the RAAS the thiazide inhibits, and the thiazide causes no reflex tachycardia because RAAS and sympathetic counter-regulation are partly blocked.	ESH 2023 recommends triple combination for Grade 2 and above. Multiple ABPM and office studies show triple therapy achieves control in 70–80% of patients against about 50% with two drugs.[14]

KEY POINTS

1. **Page's Mosaic Theory (1949):** no single cause explains essential hypertension. Eight tiles — neural, humoral, mechanical, renal, vascular, endothelial, genetic, immune — each independently validated with trial evidence.
2. **Haemodynamic transition:** early hypertension is high-CO neurogenic; years of remodelling convert it to high-SVR structural, low-renin and volume-dependent. The beta-blocker rational at 30 may be wrong at 55 — reassess the phenotype when control becomes difficult.
3. **Four remodelling patterns:** inward eutrophic (dominant; 10–15% lumen loss gives 52% more resistance; partly reversible with ACEi/ARB), hypertrophic (worse prognosis), microvascular rarefaction (exercise intolerance, insulin resistance, angina with normal coronaries), and atherosclerotic.
4. **Epigenetics:** DNA methylation of RAAS promoters and fetal 11β-HSD2, histone modification driving Ang II inflammatory expression, and microRNAs — miR-155 raising AT_1R, miR-21 promoting fibrosis, miR-126 lost from endothelium.
5. **Barker and DOHaD:** three programming routes from low birth weight to adult hypertension — reduced nephron endowment, a raised lifelong cortisol setpoint, and leptin-driven sympathetic programming during catch-up growth. India's low birth weight rate — about 27% on modelled estimates — makes this population-scale.
6. **The monotherapy ceiling is predicted, not observed:** blocking one tile activates counter-regulation through the others. A diuretic activates the RAAS; a vasodilator activates the sympathetic system; a RAAS blocker is partly countered by it. Not a drug limitation — a mosaic consequence.
7. **Rational combinations:** ACEi/ARB + CCB (ACCOMPLISH, ASCOT); ACEi/ARB + thiazide (ADVANCE, PROGRESS); the triple recommended by ESH 2023, achieving control in 70–80%. The best pairings target complementary tiles with minimal shared counter-regulation.

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Ten mechanisms, one clinical method

Part I has established a single proposition in ten instalments: blood pressure is elevated only because cardiac output is high, systemic vascular resistance is high, or both — and every mechanism in this Part acts by moving one of those two terms. Nothing in the remainder of this series departs from that framework.

What follows is its application. Part II takes the aetiologies that drive each mechanism in the individual patient. Part III applies the framework to special populations, where the same reading demands a different drug. Volume 2 analyses every drug class by the variable it addresses; Volume 3 carries the method from the clinic door to the emergency room.

THE CHAIN OF REASONING, CHAPTER BY CHAPTER

1	**The equation**	MAP = CO × SVR. There is no third mechanism, and no antihypertensive acts outside it.
2	**The neural reflex**	The baroreflex still works in hypertension — it has simply reset to defend the higher pressure.
3	**The humoral axis**	Angiotensin II and aldosterone raise SVR and retain sodium, and damage organs independently of pressure.
4	**The sympathetic drive**	Overactivation precedes the pressure rise rather than following it — MSNA is raised before hypertension appears.
5	**The renal arbiter**	Whatever starts it, sustained hypertension is maintained by a rightward-shifted pressure-natriuresis curve.
6	**The endothelium**	Losing nitric oxide costs vasodilation and three protections besides — anti-platelet, anti-adhesion, anti-proliferative.
7	**The 24-hour clock**	Nocturnal pressure predicts outcome better than daytime pressure, and clinic readings cannot see it.
8	**The definitions**	Thresholds are risk-based decisions, not biological constants. Acute organ damage, not the number, defines an emergency.
9	**The scale**	1.28 billion adults; one in seven controlled. In India, roughly one patient in ten. Systems, not pharmacology, is the bottleneck.
10	**The mosaic**	Because several tiles are active at once, monotherapy has a mathematical ceiling — and combination therapy is a prediction, not a preference.

CARRY THESE THREE FORWARD

Identify the dominant mechanism alongside starting guideline-directed treatment, never as a gate in front of it — the resting heart rate, the pulse pressure and the 24-hour urine sodium will usually tell you. Reassess the phenotype when control becomes difficult, because the haemodynamic transition changes the right answer over decades. And treat volume in every resistant case before reaching for a fifth agent.

VOLUME ONE · PART II

Aetiology of essential hypertension

Genetics, salt sensitivity, the renin phenotypes, sympathetic overactivation and the vascular biology that turns a functional rise into fixed disease.

Hypertension: A Phenotype-Based Approach

Volume 1 · Why Is This Patient Hypertensive?

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5 chapters

Part II of five

CHAPTER 11 PART II · AETIOLOGY

Genetics of hypertension

Heritability, the monogenic syndromes every physician must recognise, the polygenic architecture, and the pharmacogenomics that hint at individualised therapy.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Heritability** — 30–60% of blood-pressure variation is genetic, pooled at about 54% systolic and 49% diastolic, and what twin, family and adoption studies each contribute.[12,18]
2. **The monogenic syndromes** — six rare but curable causes, and the single mechanism all of them share.
3. **Liddle versus Gordon** — why one needs amiloride and the other a thiazide, and why potassium tells them apart.
4. **Liquorice and mulethi** — an acquired, entirely reversible phenocopy of a genetic syndrome, frequently missed in India.
5. **Polygenic architecture** — 2,103 signals, all from European genomes, and what a polygenic risk score can and cannot yet do.
6. **AGT M235T** — a candidate gene at high frequency in South Asians, and the phenotype it helps explain.
7. **The AB/CD rule** — pharmacogenomics as it already exists in everyday practice.

11.1 Heritability of blood pressure

Blood pressure is substantially heritable. Twin studies, comparing concordance in identical (monozygotic) and fraternal (dizygotic) twins, consistently estimate the heritability of both systolic and diastolic pressure at 30–60% — pooled across seventeen twin studies at 54% for systolic and 49% for diastolic pressure — meaning that genetic factors account for roughly a third to three-fifths of the variation in blood pressure across the population, with the remainder environmental.[18]

Family studies reinforce this: first-degree relatives of a hypertensive have a two- to fourfold increased risk of developing hypertension. Adoption studies — in which children raised apart from their biological parents track more closely with the biological than the adoptive parents' blood pressure — confirm that the effect is genuinely genetic rather than merely a shared household environment.

The practical corollary is that a family history of early hypertension is a real and useful risk marker, and that the children of hypertensive parents warrant earlier screening.

~54%
Pooled twin-study heritability of systolic pressure (49% diastolic). The remainder is environmental — which is where treatment acts.

11.2 Monogenic (Mendelian) hypertension syndromes

The monogenic hypertension syndromes are individually rare, but they are important out of all proportion to their frequency for three reasons: each is specifically treatable or curable when identified; each illuminates a pathway

that also operates in common essential hypertension; and each should be considered in the young patient with severe hypertension, spontaneous hypokalaemia, or a strong family history of early severe disease.

A unifying feature — which reinforces Guyton's principle (V1·Ch5) that the kidney is the final common pathway of sustained hypertension — is that every one of these syndromes acts by increasing sodium reabsorption in the distal nephron.

When to think of one

Young patient · severe hypertension · spontaneous hypokalaemia · strong family history of early severe disease.

TABLE 11.1 — THE MONOGENIC HYPERTENSION SYNDROMES

SYNDROME	MOLECULAR DEFECT	POTASSIUM	RECOGNITION AND TREATMENT
Liddle ENAC GAIN OF FUNCTION	Constitutively active epithelial sodium channel	Low	Early severe hypertension, metabolic alkalosis, **low renin and low aldosterone**. Responds to **amiloride or triamterene** — not spironolactone, because the defect is downstream of the mineralocorticoid receptor.[15]
Gordon PHA TYPE II	WNK kinase mutations increase sodium–chloride cotransporter (NCC) activity[11]	High	The one syndrome with **hyperkalaemia**, and with metabolic acidosis. Responds dramatically to low-dose **thiazide**, which blocks NCC.
GRA GLUCOCORTICOID-REMEDIABLE ALDOSTERONISM	Chimeric CYP11B1/CYP11B2 gene places aldosterone under ACTH control[6]	Low	Early-onset hypertension, family history, often **early stroke**. Treated with low-dose **dexamethasone** (suppressing ACTH) or a mineralocorticoid antagonist.
AME APPARENT MINERALOCORTICOID EXCESS	Loss of 11-beta-hydroxysteroid dehydrogenase type 2; cortisol activates the mineralocorticoid receptor[1]	Low	Severe hypertension with low renin and aldosterone. Acquired form from liquorice — in India *mulethi*, common in Ayurvedic churnas — inhibits the same enzyme (V1·Ch30). Frequently missed, entirely reversible.
CAH 11-BETA-HYDROXYLASE DEFICIENCY	Enzyme block diverts synthesis to the mineralocorticoid 11-deoxycorticosterone[2]	Low	Hypertension with **virilisation**. Treated by glucocorticoid replacement.
Familial phaeo PHAEOCHROMOCYTOMA-PARAGANGLIOMA	Germline VHL, RET, NF1, and succinate dehydrogenase SDHB/C/D[3]	Variable	Catecholamine-secreting tumours; screening and management in V1·Ch26.

Two of these are worth committing to memory as a pair, because they are the ones a physician will actually meet and because they are opposites. Liddle and Gordon both act on distal sodium handling, but potassium separates them at a glance — low in Liddle, high in Gordon — and the treatments are not interchangeable.

11.3 The polygenic architecture

The great majority of hypertension is not monogenic but polygenic: it results from the combined effect of a very large number of common genetic variants, each contributing a tiny increment to blood pressure, interacting with the environment.[4] Genome-wide association studies have mapped this architecture in increasing detail.[8]

The largest single-stage study to date, published in 2024, identified 2,103 independent genetic signals across more than a thousand loci associated with blood pressure, together explaining more than 60% of the heritability attributable to common variants.[7] Its 1,028,980 participants were all of European ancestry, and in a book written for Indian practice that is the point: no study of comparable size exists in South Asians,[9] and polygenic scores built on European data transfer poorly across ancestries. No single variant is necessary or sufficient; it is the cumulative burden that matters.[17]

The spironolactone trap

Liddle looks like hyperaldosteronism and is not. The channel is active independently of the receptor, so blocking the receptor achieves nothing. Block the channel.

GWAS 2024

1,028,980 individuals, all of European ancestry.

2,103

independent signals across more than a thousand loci, explaining >60% of common-variant heritability.[7]

TABLE 11.2 — WHAT A POLYGENIC RISK SCORE SEPARATES

COMPARISON	SYSTOLIC DIFFERENCE	ODDS OF HYPERTENSION	STATUS IN PRACTICE
Top decile of score vs bottom decile GWAS 2024, N > 1 MILLION	~17 mmHg	> 7-fold	Not yet part of routine practice. The finding establishes that genetic susceptibility is real, measurable and substantial, and points toward identifying high-risk individuals for prevention **before the pressure has risen**.

11.4 Candidate-gene polymorphisms

Before the genome-wide era, research focused on candidate genes in the pathways known to control blood pressure. Several of these remain clinically illuminating, particularly in the renin–angiotensin system. Individually the effects are small, but together they help explain why the renin–angiotensin system is so central in some populations, and why drug responses vary between individuals.

Why this matters in India

AGT 235T is present at **high frequency in South Asians** — a genetic contribution to the salt-sensitive, RAAS-active phenotype (V1·Ch9 and Ch12).

TABLE 11.3 — CANDIDATE GENES IN THE RENIN–ANGIOTENSIN AND SODIUM-HANDLING PATHWAYS

GENE AND VARIANT	ASSOCIATION	CLINICAL RELEVANCE
ACE INSERTION/DELETION (I/D)	The D allele is associated with higher ACE activity[13]	Slightly higher blood pressure.
AGT ANGIOTENSINOGEN M235T	The 235T allele is associated with higher circulating angiotensinogen[14]	**High frequency in South Asians** — a genetic contribution to the salt-sensitive, RAAS-active phenotype prevalent in the Indian population.
AGTR1 ANGIOTENSIN II TYPE 1 RECEPTOR A1166C	Augmented angiotensin II responses[5]	Part of the explanation for variable RAAS-blocker response.
ADD1 ALPHA-ADDUCIN G460W	Salt-sensitive hypertension	Long associated with salt sensitivity and a better diuretic response, but a meta-analysis of 22 studies and 14,303 cases found **no significant association with hypertension overall** (OR 1.02) and describes the diuretic-response evidence as inconsistent across populations. Treat this row as unsettled.[10]

11.5 Pharmacogenomics and the AB/CD rule

The observation that the same antihypertensive drug at the same dose produces a large blood-pressure fall in one patient and almost none in another has a substantial genetic basis, and the study of this is pharmacogenomics. Routine pharmacogenomic testing is not yet standard in hypertension, but its central insight is already embedded in clinical practice as the AB/CD rule, a long-standing heuristic for thinking about first-drug selection in terms of the dominant mechanism, within what the guideline permits.

Mechanism, not demography

The rule reflects the dominant blood-pressure-maintaining mechanism in each group — **not** a rigid rule of age or ethnicity.

TABLE 11.4 — THE AB/CD RULE, AND THE PHYSIOLOGY UNDER IT

ARM	PATIENT	DOMINANT MECHANISM	DRUGS
A / B	Younger, higher-renin patients (and, historically in the framework, white patients)	An **activated renin–angiotensin system**	**A**CE inhibitors and ARBs, or **B**eta-blockers — drugs that block that system.
C / D	Older, lower-renin patients; patients of African ancestry; salt-sensitive patients	**Volume and resistance**, low-renin physiology	**C**alcium channel blockers or **D**iuretics — drugs that reduce volume and resistance.

The rule was supported by the ALLHAT trial, in which the diuretic and calcium channel blocker arms outperformed the ACE inhibitor in reducing events in Black patients, consistent with their predominantly low-renin,

volume-dependent physiology.

The AB/CD rule is the everyday, practical expression of pharmacogenomics and of the phenotype approach: match the drug to the mechanism.

ALLHAT

Diuretic and calcium-channel-blocker arms outperformed the ACE inhibitor for events in Black patients — low-renin, volume-dependent physiology.[16]

KEY POINTS

1. **Heritability of blood pressure is 30–60%, pooled at about 54% systolic** across seventeen twin studies. A family history of early hypertension is a real risk marker, and the children of hypertensive parents warrant earlier screening.
2. **All six monogenic syndromes increase distal-nephron sodium reabsorption**, reinforcing Guyton's kidney-centred model. They are rare, but each is specifically treatable and each illuminates a pathway operating in essential hypertension.
3. **Potassium separates Liddle from Gordon.** Liddle is hypokalaemic and needs **amiloride or triamterene**, never spironolactone — the ENaC defect is downstream of the mineralocorticoid receptor. Gordon is the **hyperkalaemic** one and responds to low-dose thiazide.
4. **Liquorice — mulethi — reproduces AME.** It inhibits 11-beta-HSD2, letting cortisol act at the mineralocorticoid receptor. Common in Ayurvedic churnas, frequently missed, and **entirely reversible** on withdrawal.
5. **Hypertension is overwhelmingly polygenic.** The 2024 genome-wide study in over a million people found 2,103 independent signals explaining more than 60% of common-variant heritability.[7]
6. **Polygenic risk scores separate top from bottom decile by ~17 mmHg systolic** and a more than sevenfold odds of hypertension — not yet routine, but pointing to risk identification before the pressure rises.[7]
7. **The AB/CD rule is pharmacogenomics as it already exists.** A/B for younger, higher-renin patients; C/D for older, lower-renin, salt-sensitive patients and those of African ancestry — supported by ALLHAT. It reflects mechanism, not demography.[19]

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CHAPTER 12 PART II · AETIOLOGY

Salt sensitivity: the renal–genetic axis

Why the same salt intake raises blood pressure in some people and not others — the four mechanisms, the India context, and the therapeutic consequences.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Salt sensitivity as a spectrum** — the Weinberger definition, and why it is continuous rather than a category.
2. **The four mechanisms** — nephron number, RAAS suppression failure, the salt-immune pathway, and renal sympathetic tone.
3. **The Th17–IL-17 pathway** — a route to sodium retention independent of the RAAS and sympathetic systems.
4. **Why India is different** — low birth weight, AGT 235T and hidden dietary sodium converging on one population.
5. **Recognition without a metabolic ward** — renin, 24-hour urine sodium, dipping status, and the diuretic response.
6. **Potassium as the counter** — INTERSALT, DASH-Sodium and the SSaSS outcome data, and who must not have it.
7. **Matching drug to mechanism** — chlorthalidone, spironolactone and the SGLT2 inhibitors.

12.1 Definition — a continuous trait

Blood pressure does not respond uniformly to dietary sodium. In some individuals a rise in salt intake produces a large, reproducible rise in blood pressure, and salt restriction a corresponding fall; in others, blood pressure is stable across a wide range of intakes. Salt sensitivity is the degree to which an individual's blood pressure tracks their sodium intake, and it is a continuous trait, not a binary category.[3]

The underlying physiology is the rightward-shifted pressure–natriuresis curve of V1·Ch5: the salt-sensitive kidney cannot excrete a sodium load without a rise in pressure to drive the natriuresis.

10

mmHg — the Weinberger threshold

A person is classed salt-sensitive if mean arterial pressure rises by 10 mmHg or more on sodium loading and falls correspondingly on restriction, under controlled conditions.

12.2 The four mechanisms

Salt sensitivity is a phenotype produced by any combination of four distinct mechanisms, which coexist in varying proportions in different patients. They are worth separating because each points to a different intervention.

Not one disease

The four mechanisms coexist. Which dominates decides whether the answer is sodium restriction, a diuretic, an aldosterone antagonist, or all three.

TABLE 12.1 — THE FOUR MECHANISMS OF SALT SENSITIVITY

MECHANISM	HOW IT PRODUCES SALT SENSITIVITY	EVIDENCE AND CONSEQUENCE
Reduced nephron number BRENNER HYPOTHESIS	Fewer nephrons mean each handles a greater sodium load and operates closer to its excretory ceiling, so a higher pressure is needed to excrete a given intake (V1·Ch5).	Autopsy evidence (Keller and colleagues, *NEJM* 2003) found hypertensives had roughly **half the glomeruli** of normotensives. Nephrogenesis ends at ~36 weeks, so prematurity and low birth weight **fix a low nephron number for life**.[5]
RAAS suppression failure	A sodium load normally suppresses renin and aldosterone promptly, allowing the load to be excreted. Where suppression is blunted, aldosterone-driven retention continues inappropriately.	A spectrum running from subtle blunting to frank **primary aldosteronism** (V1·Ch13). Where this dominates, an aldosterone antagonist is the mechanistically matched drug.
The salt–immune pathway TH17 · IL-17 · NITRIC OXIDE	High extracellular sodium activates T-helper-17 lymphocytes to secrete interleukin-17, which suppresses nitric oxide production in the renal tubule and impairs sodium excretion.[6,12]	Wilck and colleagues, *Nature* 2017. Regulatory T cells oppose this, and their deficiency in obesity, diabetes and CKD leaves the pathway unopposed. The same work linked high sodium to depletion of gut *Lactobacillus* — a mechanism **independent of the RAAS and sympathetic systems**.
Renal sympathetic overactivation	Renal sympathetic tone fails to withdraw appropriately during a sodium load, maintaining proximal tubular reabsorption.[1]	Sustains retention (V1·Ch4).

12.3 The India context — a salt-sensitive population

Several factors converge to make the Indian population unusually salt-sensitive at a scale with few parallels. India has among the highest rates of low birth weight of any large country, reducing nephron endowment across millions of people. The AGT 235T allele, associated with higher angiotensinogen, is present at high frequency in South Asians, amplifying the RAAS.[11] And dietary sodium intake is high, much of it hidden in cooking salt, pickles, papad, salted snacks and processed foods, while dietary potassium is often low.

The combination means that salt sensitivity is not an occasional trait to be sought in selected patients but a near-universal biological substrate that should be assumed in most Indian hypertensives — which makes sodium restriction a mechanistically fundamental intervention rather than incidental lifestyle advice.

Where the salt hides

Cooking salt · pickles · papad · salted snacks · processed foods. The patient reports less than the urine shows, every time.

12.4 Identifying the salt-sensitive patient

Formal salt-sensitivity testing is impractical, so the phenotype is recognised from accessible surrogates. Together these identify the patient in whom the volume–sodium mechanism dominates.

The most useful single test

A 24-hour urine sodium in an uncontrolled patient. It identifies the phenotype *and* quantifies true intake — invariably higher than reported.

TABLE 12.2 — RECOGNISING SALT SENSITIVITY WITHOUT A METABOLIC WARD

SURROGATE	FINDING	WHAT IT INDICATES
Plasma renin activity ON A NORMAL-SODIUM DIET	**Suppressed**	A volume-dependent, low-renin state.
24-hour urine sodium IN AN UNCONTROLLED PATIENT	**High**	Confirms the phenotype and **objectively quantifies intake**, invariably higher than the patient reports.
Ambulatory monitoring	**Non-dipping**	Impaired nocturnal natriuresis.
Sequential drug trial	Better response to a **diuretic** than to a RAAS blocker	The volume-sodium mechanism dominates over the renin-angiotensin one.

12.5 Potassium — the physiological counter

Higher potassium intake lowers blood pressure through mechanisms that directly oppose sodium: it promotes urinary sodium excretion and relaxes vascular smooth muscle.

Indian sources

Banana · coconut water · tomato · green leafy vegetables · pulses such as rajma. Abundant and affordable.

TABLE 12.3 — THE EVIDENCE FOR POTASSIUM

STUDY	DESIGN	FINDING
INTERSALT	Observational, cross-population	Higher urinary potassium independently associated with **lower blood pressure**.[4]
DASH-Sodium	Randomised feeding trial	Reduced sodium combined with increased potassium produced **large reductions** in blood pressure.[9]
SSaSS SALT SUBSTITUTE AND STROKE STUDY	Large randomised trial, rural China	Replacing some sodium chloride with potassium chloride in household salt **reduced stroke, major cardiovascular events and death** — hard-outcome evidence for population-level salt substitution.[7]

Reflecting this, the 2024 ESC guideline now recommends potassium supplementation or substitution for most patients.[2]

The essential caution is that potassium loading and salt substitutes must be avoided in chronic kidney disease and in patients on ACE inhibitors, ARBs or mineralocorticoid antagonists, because of the risk of hyperkalaemia.

The one hard caution

Avoid potassium loading and salt substitutes in CKD, and in patients on ACE inhibitors, ARBs or mineralocorticoid antagonists

— risk of hyperkalaemia.

12.6 Therapeutic implications

In the salt-sensitive patient, treatment is directed at reducing the sodium load and enhancing its excretion. Dietary sodium restriction produces blood-pressure falls of a magnitude equivalent to a drug in this group, and confirming intake with a 24-hour urine sodium before escalating drug therapy is often the highest-value step.

TABLE 12.4 — MATCHING THE DRUG TO THE DOMINANT MECHANISM

AGENT	MECHANISM IT ADDRESSES	NOTE
Thiazide-type diuretics	Forced natriuresis	**Chlorthalidone preferred** over hydrochlorothiazide for its longer action and better outcome data — and effective even in advanced CKD (CLICK, V1·Ch19).
Aldosterone antagonists	RAAS suppression failure	Spironolactone was the **most effective fourth drug** in resistant hypertension in PATHWAY-2.[13]
SGLT2 inhibitors	Proximal-tubular natriuresis	Well matched to the salt-sensitive **diabetic** patient, and add renal and cardiovascular protection (V1·Ch19 and Ch20).

KEY POINTS

1. **Salt sensitivity is a continuous trait** — the degree to which blood pressure tracks sodium intake — reflecting the rightward-shifted pressure-natriuresis curve. Commonest in the elderly, obese, diabetic, those with CKD, and people of African and South Asian ancestry.[10]
2. **Four interacting mechanisms:** reduced nephron number (Brenner; Keller *NEJM* 2003; fixed by low birth weight), RAAS suppression failure (a spectrum up to primary aldosteronism), the salt–immune Th17–IL-17–nitric-oxide pathway (Wilck *Nature* 2017), and renal sympathetic overactivation.
3. **India is a salt-sensitive population** — very high low-birth-weight rates, high AGT 235T frequency, and high hidden sodium with low potassium. Assume salt sensitivity in most Indian hypertensives.
4. **That makes sodium restriction fundamental, not incidental.** In this group its effect is of a magnitude equivalent to a drug.
5. **Surrogates only, and imperfect ones:** suppressed plasma renin activity, high 24-hour urine sodium, non-dipping on ambulatory monitoring, and a better response to a diuretic than a RAAS blocker. A 2022 review states plainly that *no* clinical approach yet has sufficient sensitivity and specificity to identify salt sensitivity, and that plasma renin in particular is unreliable — salt-sensitive patients may have normal or low levels.[8]
6. **Potassium is the counter.** INTERSALT and DASH-Sodium show benefit; **SSaSS** showed potassium-based salt substitution reduced stroke, cardiovascular events and death. 2024 ESC now recommends it — but **avoid in CKD or on ACEi/ARB/MRA**.
7. **Match the drug to the mechanism:** chlorthalidone (effective even in advanced CKD — CLICK), spironolactone where RAAS suppression failure dominates (PATHWAY-2), SGLT2 inhibitors for the salt-sensitive diabetic.

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CHAPTER 13 PART II · AETIOLOGY

RAAS dysregulation and primary aldosteronism

The renin phenotypes, the most common and most under-diagnosed correctable cause of hypertension, and the shift to universal screening.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Renin heterogeneity** — why essential hypertension is three physiologies, not one, and what each responds to.
2. **Primary aldosteronism as a spectrum** — 5–10% of all hypertensives, a third of resistant cases, up to 18% of new diagnoses.[14]
3. **The hypokalaemia dogma** — why a normal potassium excludes nothing, and why most cases are normokalaemic.
4. **The move toward universal screening** — 2024 ESC and 2025 Endocrine Society, where 2025 AHA/ACC stopped, and why fewer than 15% are screened.
5. **Reading the aldosterone-to-renin ratio** — which drugs raise it, which lower it, and which are safe cover during testing.
6. **Confirm, subtype, treat** — and why adrenal vein sampling, not CT, decides who gets an operation.
7. **Laragh's renin profiling** — measuring the renin to pick the first drug.

13.1 The renin heterogeneity of essential hypertension

A fundamental error is to treat essential hypertension as a single, uniform disorder. Its renin–aldosterone profile is widely heterogeneous, and this heterogeneity maps onto the phenotypes and the drug logic of this book.

One disease, three physiologies

Where a patient sits on the renin spectrum is the basis of Laragh profiling (13.7) and of the AB/CD rule (V1·Ch11).

TABLE 13.1 — THE RENIN PROFILE OF ESSENTIAL HYPERTENSION

PROFILE	SHARE OF PATIENTS	PHYSIOLOGY AND TYPICAL PATIENT	RESPONDS TO
High renin	**~ one third**	RAAS-driven, often neurogenic; typically the younger patient.	ACE inhibitors, ARBs or beta-blockers.
Normal renin	**~ one half**	Mixed physiology.	Combination therapy targeting both mechanisms.
Low renin	**~ one sixth**	Volume-dependent, salt-sensitive; older patients, those of African ancestry, the salt-sensitive.	Diuretics and calcium channel blockers.

At the extreme low-renin end of the spectrum lies primary aldosteronism, the subject of most of this chapter.

13.2 Primary aldosteronism is a spectrum, and it is common

Primary aldosteronism is the autonomous secretion of aldosterone that is inappropriately high for the renin level. It was long conceived as a rare, discrete disease defined by the triad of hypertension, hypokalaemia and an adrenal adenoma — Conn's syndrome. This conception is now known to be wrong on two counts.

5–10%

of all hypertensives

Not a rare tumour. A common condition on a continuum, and one that damages heart and kidney more than essential hypertension at the same pressure.

TABLE 13.2 — HOW COMMON PRIMARY ALDOSTERONISM ACTUALLY IS

POPULATION	PREVALENCE
All hypertensives	5–10%
Resistant hypertension	around a third
Treatment-naïve, newly diagnosed PRIMARY-CARE COHORTS	up to 18%

Second, it is not a discrete disease but a spectrum of renin-independent aldosterone production, ranging from mild, subclinical autonomy through to the classic florid adenoma. This reconception is one of the most important shifts in modern hypertension, because primary aldosteronism causes more cardiovascular and renal damage than essential hypertension at the same blood pressure, and because it is specifically and often curably treatable.[10]

13.3 The collapse of the hypokalaemia dogma

The single most damaging misconception in this area is the belief that primary aldosteronism can be excluded by a normal serum potassium. In fact only about 9–37% of confirmed cases are hypokalaemic; the majority are normokalaemic. Restricting screening to patients with low potassium therefore misses most cases.

Hypokalaemia, when present, also interferes with aldosterone secretion and can artificially lower the aldosterone-to-renin ratio, so it should be corrected before testing.

13.4 The shift to universal screening

Because primary aldosteronism is common, damaging, treatable, and frequently normokalaemic, yet fewer than 15% of eligible patients are ever screened, the guidelines have moved toward broader case detection — universal in the Endocrine Society and ESC documents, resistant and stage 2 disease in the American one — and this book takes its own position on the question in Chapter 37.

Whether to act on this in an Indian clinic is a separate question from what the guidelines say, and Chapter 37 argues it in full — landing, on health-system grounds, on screening the high-yield groups first (Ch37, *Whether to screen every hypertensive*). Read the two together before deciding your own practice.

The rule to remember

A normal potassium does not exclude primary aldosteronism.

It should not discourage screening.[5]

< 15%

of eligible patients are ever screened. The commonest correctable cause of hypertension is also the least looked for.[3]

TABLE 13.3 — THE GUIDELINE SHIFT TOWARD UNIVERSAL SCREENING

GUIDELINE	RECOMMENDATION
2024 ESC	Class IIa — **consider screening all adults with confirmed hypertension** by measuring renin and aldosterone.[9]
2025 Endocrine Society	Screen **all patients with hypertension**.
2025 AHA/ACC	Screen every adult with resistant hypertension, whether or not the potassium is low, and stage 2 hypertension besides, together with the established high-yield groups.[6] It did not follow the Endocrine Society to universal screening, and the disagreement is real.
The older selective approach	Limited screening to resistant hypertension, hypokalaemia, adrenal incidentaloma or young-onset disease. Those categories should **certainly still be screened** — but they capture only a fraction of cases.

A practical enabler of this shift is the evidence that the aldosterone-to-renin ratio retains high sensitivity and a very high negative predictive value even without full withdrawal of interfering medications, making screening feasible in ordinary practice.

13.5 Performing and interpreting the aldosterone-to-renin ratio

The screening test is the aldosterone-to-renin ratio — the plasma aldosterone concentration divided by the renin, activity or concentration. A raised ratio, with an aldosterone that is elevated or inappropriately non-suppressed relative to a low renin, is a positive screen and requires confirmation. The number is meaningless without its units. Current guidance takes a ratio above 20 where aldosterone is in ng/dL and renin is a plasma renin activity in ng/mL/h, or above 70 where aldosterone is in pmol/L and renin is a direct concentration in mU/L, and about a quarter lower where aldosterone is measured by mass spectrometry — but the laboratory's own cut-off, for its own assay, is the one to use.[1]

TABLE 13.4 — WHAT MOVES THE RATIO, AND WHAT TO DO ABOUT IT

INTERFERENCE	EFFECT ON THE RATIO	ACTION
Beta-blockers	Lower renin → **falsely raise** the ratio	Account for it; a positive result may be spurious.
ACE inhibitors, ARBs	Raise renin → **falsely lower** the ratio	A negative result on these is less reassuring.
Mineralocorticoid antagonists	Raise renin → **falsely lower** the ratio	**Withhold for several weeks** before testing.
Hypokalaemia	Suppresses aldosterone → lowers the ratio	**Correct it first.**
Thiazide, thiazide-like and loop diuretics	Raise renin → **falsely lower** the ratio	The drug most often forgotten. A potassium-wasting diuretic interferes, and it is the one most often left running.[5]
Dihydropyridine calcium channel blockers	Raise renin → **falsely lower** the ratio	A negative result on these is less reassuring.[5]
NSAIDs, including over-the-counter ones	Lower renin → **falsely raise** the ratio	Ask; patients do not report them as medicines.[5]
Doxazosin, slow-release verapamil, hydralazine	Relatively **neutral**	Use for blood-pressure cover during testing where drugs must be maintained.[5]

The pragmatic modern position is that an abnormal ratio on background therapy is informative and should prompt confirmation rather than be dismissed, given the sensitivity of the test even without washout.

13.6 Confirmation, subtyping and treatment

A positive screen is confirmed by a suppression test — saline infusion or fludrocortisone suppression — demonstrating that aldosterone fails to suppress normally with sodium loading.[11] Once confirmed, subtyping distinguishes the two treatment-determining categories.

Imaging is not enough

A visible nodule may be non-functioning, and bilateral disease may look normal. **Adrenal vein sampling** is the definitive lateralisation test.[7]

TABLE 13.5 — SUBTYPE DECIDES TREATMENT

SUBTYPE	HOW IT IS ESTABLISHED	TREATMENT
Unilateral ALDOSTERONE-PRODUCING ADENOMA	Adrenal CT **plus adrenal vein sampling** in surgical candidates — imaging alone is unreliable for lateralisation.	**Laparoscopic adrenalectomy** — cures or substantially improves the hypertension in most patients.
Bilateral ADRENAL HYPERPLASIA	As above; sampling shows no lateralisation.	Medical: a **mineralocorticoid receptor antagonist**. The 2025 guideline suggests spironolactone over the other agents, started at 12.5–25 mg daily and titrated; eplerenone (25 mg once or twice daily) is the alternative where gynaecomastia is limiting.[1] Finerenone is not a treatment for primary aldosteronism: its licence and its trials are in chronic kidney disease with type 2 diabetes and in heart failure, and its label does not name primary aldosteronism.[2,16]

The direct cardiovascular toxicity of aldosterone (V1·Ch3) means treatment benefits the heart and kidney beyond the blood-pressure effect; RALES and EPHESUS established the mortality benefit of mineralocorticoid antagonism in heart failure.[12,13,15]

13.7 Laragh's renin-profiling approach

John Laragh's framework applies the renin heterogeneity of 13.1 to drug selection: measure the renin, and choose the drug most likely to work.[8]

A guide, not a rule

Renin profiling is probabilistic — it raises the chance of a good first-drug response. It dovetails with the AB/CD rule and the phenotype approach.

TABLE 13.6 — RENIN PROFILING AND THE FIRST DRUG

RENIN	HYPERTENSION IS	CHOOSE
High	RAAS-driven	ACE inhibitor, ARB, or a beta-blocker (which lowers renin).
Low	Volume-dependent	A diuretic or calcium channel blocker — and, if the ARR is positive, a **mineralocorticoid antagonist**.
Normal	Mixed	Combination therapy targeting both mechanisms.

KEY POINTS

1. **Essential hypertension is heterogeneous by renin:** roughly a third high-renin (RAAS-driven, younger, responds to A/B drugs), half normal-renin, a sixth low-renin (volume-dependent, older, African-ancestry or salt-sensitive, responds to C/D drugs). Primary aldosteronism sits at the extreme low-renin end.[4]
2. **Primary aldosteronism is common and a spectrum**, not a rare discrete tumour: ~5–10% of all hypertensives, ~30% of resistant hypertensives, up to 18% of treatment-naïve new diagnoses.
3. **It damages more than essential hypertension at the same pressure** — and is specifically, often curably, treatable.
4. **The hypokalaemia dogma is wrong.** Only ~9–37% of confirmed cases are hypokalaemic; most are normokalaemic. A normal potassium does **not** exclude the diagnosis. Correct hypokalaemia before testing.
5. **Screening has shifted toward universal** in the 2024 ESC (Class IIa) and 2025 Endocrine Society documents; the 2025 AHA/ACC stopped at resistant and stage 2 hypertension. Chapter 37 sets out which groups this book recommends screening first. Fewer than 15% of eligible patients are currently screened. The ratio holds its sensitivity even without full drug washout.
6. **Reading the ratio:** beta-blockers falsely raise it; ACEi, ARBs and MRAs falsely lower it (withhold MRAs several weeks); doxazosin and verapamil are relatively neutral cover. An abnormal ratio on background therapy should prompt confirmation, not dismissal.
7. **Confirm, subtype, treat:** saline or fludrocortisone suppression; then **unilateral adenoma** (adrenalectomy) versus **bilateral hyperplasia** (MRA), decided by adrenal vein sampling — imaging alone is unreliable. Treatment protects heart and kidney beyond BP (RALES, EPHESUS).

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CHAPTER 14 PART II · AETIOLOGY

Sympathetic overactivation in essential hypertension

The neurogenic phenotype, the human evidence, the psychosocial and occupational drivers, and where it bears on treatment the guideline already permits.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The neurogenic phenotype** — a resting heart rate above 80 as the most accessible marker, and what else travels with it.
2. **The direct human evidence** — microneurography, noradrenaline spillover, and why the finding precedes the disease.
3. **Central sensitisation** — how chronic stress reprograms the brainstem set point upward, and why it stays up.
4. **Job strain and effort–reward imbalance** — the two occupational models and the risk each carries.
5. **The Indian occupational profile** — IT and BPO work, night shifts, and the hypertension daytime readings miss.
6. **One mechanism, many comorbidities** — obesity, apnoea, kidney disease, heart failure and the metabolic syndrome.
7. **Matched treatment** — the guideline first-line classes first; where a beta-blocker is indicated, bisoprolol or nebivolol and why not atenolol; and the non-drug measures that are mechanistically targeted.

14.1 The neurogenic phenotype

V1·Ch4 established the mechanisms; this chapter treats neurogenic hypertension as a recognisable clinical entity. Its most accessible clue is the resting heart rate — a clue, and not more than that.

> 80
bpm at rest, untreated
Consistent with sympathetic cardiac overactivation once anaemia, thyroid disease and deconditioning have been excluded — and an independent predictor of cardiovascular mortality in its own right.

TABLE 14.1 — RECOGNISING THE NEUROGENIC PHENOTYPE PROPOSED FRAMEWORK

FEATURE	FINDING
Resting heart rate	Persistently **above 80 bpm** in an untreated hypertensive — an independent predictor of cardiovascular mortality.[16,17]
Cardiac output	High or high-normal.
Ambulatory monitoring	High blood-pressure variability and a **large morning surge**.
Plasma renin activity	Elevated.
The patient	Younger, often lean, frequently reports palpitations, commonly works under chronic stress or disrupted sleep.

This high-output, sympathetically driven pattern is the earliest haemodynamic stage of essential hypertension (V1·Ch1). Recognising it matters because the standard age-and-ethnicity drug algorithm does not specifically address the sympathetic overactivity driving the disease.

14.2 The direct human evidence

The claim that sympathetic overactivation causes human hypertension rests on direct measurement, not inference.

It precedes the disease

Muscle sympathetic nerve activity is already raised in the **still-normotensive offspring** of hypertensive parents — so it is not a consequence of high pressure.

TABLE 14.2 — WHAT EACH METHOD SHOWS

METHOD	FINDING	WHY IT MATTERS
Microneurography	Muscle sympathetic nerve activity **2–3× higher** than in matched controls, correlated with severity and target-organ damage.	Already elevated in normotensive offspring of hypertensives — it **precedes and predicts** the disease.
Noradrenaline spillover	Overactivation is **organ-selective**.	Disproportionately affects the heart and the kidneys.[9]
Heart-rate variability	Reduced — vagal withdrawal.	An accessible clinical correlate; predicts adverse outcome.
Baroreflex sensitivity	Reduced.	Also predicts adverse outcome; reflected clinically in resting heart rate and BP variability.[13]

14.3 Central sensitisation by chronic stress

The pathway from chronic psychosocial stress to sustained hypertension runs through the brainstem. Repeated stressors chronically activate the amygdala and the hypothalamic–pituitary–adrenal axis, which drive the rostral ventrolateral medulla — the sympathetic vasomotor centre (V1·Ch2).

Over months to years the rostral ventrolateral medulla undergoes central sensitisation: its firing threshold falls and its baseline output rises, while the prefrontal cortex that normally restrains it loses volume and connectivity. The consequence is a sympathetic set point reprogrammed upward, which remains elevated even after the original stressor is removed — and which explains why interventions that strengthen prefrontal inhibitory control, such as slow breathing, meditation and yoga, are specifically effective in this phenotype.

Why leaving the job is not enough

The set point is reprogrammed upward and stays elevated after the stressor is removed. This is why blood pressure does not simply normalise on escaping a stressful situation.

14.4 Job strain, effort–reward imbalance, and the occupational dimension

Two psychosocial models frame the occupational contribution, of particular relevance to the occupational-health physician and developed further in V1·Ch25.

India specifically

IT and BPO work combines high demand, low control, night shifts and a young workforce — a high-risk profile behind the rising young-adult hypertension of V1·Ch9 and Ch16.

TABLE 14.3 — THE TWO OCCUPATIONAL MODELS

MODEL	THE HAZARDOUS CONFIGURATION	RISK
Job strain KARASEK	High psychological demand combined with **low control**.	A pooled analysis of nearly 200,000 workers (Kivimäki and colleagues, *Lancet* 2012) found a **23% excess risk of coronary heart disease**, and an increased risk of incident hypertension.[12]
Effort–reward imbalance SIEGRIST	Sustained mismatch between effort invested and reward received.[10]	Associated with roughly a **doubling** of hypertension risk.

Rotating shift work independently raises hypertension incidence by disrupting the circadian control of blood pressure, and daytime clinic readings often miss the resulting nocturnal and post-shift hypertension.

14.5 The common sympathetic thread

Sympathetic overactivation is the shared mechanism linking hypertension to the conditions that cluster with it — so that treating those conditions lowers the sympathetic drive.

TABLE 14.4 — ONE MECHANISM, MANY COMORBIDITIES

CONDITION	HOW IT RAISES SYMPATHETIC DRIVE	CONSEQUENCE
Obesity	Leptin drives central sympathetic activation (V1·Ch21).[11]	Weight reduction lowers the drive.
Obstructive sleep apnoea	Intermittent hypoxia sensitises the carotid-body chemoreflex (V1·Ch2, Ch24).[15]	Treating the apnoea treats the mechanism.
Chronic kidney disease	Afferent renal-nerve signals raise central outflow (V1·Ch4).[6]	The rationale for renal denervation.
Heart failure	Baroreceptor unloading triggers maladaptive activation.	Beta-blockade counteracts it and **reduces mortality**.
Metabolic syndrome	Sympathetic overactivation and insulin resistance reinforce one another in a self-worsening loop.	Avoid non-vasodilatory beta-blockers (atenolol, metoprolol) as primary agents — they worsen insulin resistance and lipids, and the guidelines already caution against the beta-blocker/thiazide pairing in metabolic syndrome. Where a beta-blocker is indicated, prefer nebivolol or carvedilol.[2]

14.6 Treatment matched to the phenotype

Drug selection targets the sympathetic drive directly. For the patient with a clearly elevated resting heart rate, beta-1 blockade lowers both the rate and the sympathetically driven renin secretion, and that is a real mechanistic argument. It is not, by itself, an indication. Beta-blockers are not first-line therapy for uncomplicated hypertension in the current guidelines; where the guideline calls for an added or alternative agent, or where a compelling indication for beta-blockade already exists, this is the reasoning that would favour a cardioselective agent such as bisoprolol, or the vasodilatory and metabolically neutral nebivolol, over the alternatives it permits.

Not atenolol

Inferior in outcome trials (LIFE, ASCOT) and adverse in its central-pressure profile (V1·Ch15).[7,8]

TABLE 14.5 — MATCHED TREATMENT, DRUG AND NON-DRUG

INTERVENTION	WHY IT FITS THIS PHENOTYPE
Bisoprolol or nebivolol	Beta-1 blockade lowers heart rate **and** sympathetically driven renin secretion. Nebivolol is vasodilatory and metabolically neutral.
ACE inhibitor or ARB	A rational alternative or addition where the RAAS is also activated, as in the young high-renin patient.
Aerobic and isometric exercise	Reduces central sympathetic drive. **Isometric exercise is the most effective single exercise mode.**
Mindfulness, yoga, slow pranayama	Strengthen prefrontal inhibitory control over the sensitised set point — mechanistically targeted, not generic advice.
Treat coexisting OSA; modify workplace stressors	Addresses the drivers at source.
Renal denervation	An adjunctive option in selected patients with genuine drug-resistant sympathetically driven hypertension (V1·Ch4).[1,3,4,5,14]

KEY POINTS

1. **The neurogenic phenotype** is recognised by a resting heart rate persistently above 80 bpm — itself an independent mortality predictor — with high cardiac output, high BP variability, a large morning surge and raised renin, typically in younger, leaner, stressed patients.
2. **The standard drug algorithm does not address the sympathetic drive**, which is why recognising this phenotype changes the prescription.
3. **Direct human evidence:** microneurography shows sympathetic nerve activity 2–3× elevated and **already raised in normotensive offspring** of hypertensives, so it precedes the disease; spillover shows cardiac and renal selectivity; reduced heart-rate variability and baroreflex sensitivity are the accessible correlates.
4. **Chronic stress sensitises the brainstem set point upward** (amygdala and HPA drive, prefrontal disinhibition), so pressure does not fully normalise on removing the stressor — the basis for the specific efficacy of central-drive-reducing interventions.
5. **Occupational drivers:** job strain (Karasek) carried a 23% excess coronary risk in nearly 200,000 workers (Kivimäki, *Lancet* 2012); effort–reward imbalance (Siegrist) is associated with hypertension more modestly (pooled $r \approx 0.26$), not a doubling. Indian IT and BPO work and rotating shifts concentrate both, and daytime readings miss the result.
6. **Sympathetic overactivation links hypertension to its comorbidities** — obesity via leptin, apnoea via the chemoreflex, kidney disease via afferent renal nerves, heart failure via baroreceptor unloading, metabolic syndrome via the insulin-resistance loop. **Avoid atenolol and metoprolol in metabolic syndrome**; prefer ACEi, ARB, nebivolol or carvedilol.
7. **Matched treatment:** a guideline first-line class first — an ACEi or ARB fits the high-renin physiology, or a calcium channel blocker; a beta-blocker is not first-line for uncomplicated hypertension and is reserved for a compelling indication, and where one exists it is bisoprolol or nebivolol, never atenolol (LIFE, ASCOT); aerobic and isometric exercise, mindfulness and yoga as mechanistically targeted measures; treat coexisting apnoea; renal denervation as an adjunct in genuine resistant disease.

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CHAPTER 15 PART II · AETIOLOGY

Vascular biology of essential hypertension

From functional vasoconstriction to fixed structural disease, and why central aortic pressure — not the brachial cuff — determines outcome.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Two phases of resistance** — functional and reversible, then structural and not, and why that decides what treatment can achieve.
2. **Inward eutrophic remodelling** — the media-to-lumen ratio, and the fourth-power law that gives it force.
3. **Aortic stiffness** — the loss of Windkessel buffering and the origin of isolated systolic hypertension.
4. **Pulse wave velocity** — the 10 m/s threshold and the risk each additional metre per second carries.
5. **Central aortic pressure** — what CAFE showed, and why identical cuff readings can mean different hearts.
6. **Microvascular rarefaction** — exercise intolerance, insulin resistance and angina with clean coronaries.[13]
7. **How the classes differ** — and why three independent lines of evidence converge on one combination.

15.1 Two phases of resistance

The sustained rise in systemic vascular resistance evolves through two overlapping phases, and the distinction defines what treatment can achieve.

Why early matters

Acting in the functional phase is disproportionately valuable, because the disease is still reversible. Once the wall has remodelled, it is not.

TABLE 15.1 — FUNCTIONAL AND STRUCTURAL RESISTANCE

PHASE	THE VESSEL WALL	REVERSIBILITY	CLINICAL CONSEQUENCE
Functional	Arterioles actively constricted by neural, humoral and endothelial signals; the wall is **structurally normal**.	Fully reversible	Recent-onset hypertension in a young patient often normalises on a single well-chosen drug.
Structural	Sustained constriction has driven remodelling — smooth muscle rearranged around a narrower lumen, collagen deposited, elastin degraded.[2,4,9,12]	The resistance floor	No longer fully reverses even with complete pharmacological vasodilation. Long-standing hypertension is harder to control and needs more drugs.

15.2 Inward eutrophic remodelling

The characteristic structural change of essential hypertension is inward eutrophic remodelling: the smooth-muscle cells rearrange around a smaller lumen without a net increase in wall mass. It is measured directly by the media-to-lumen ratio on small-artery biopsy.[10,11]

The clinical force of this modest-sounding change comes from the fourth-power law (V1·Ch1): a 20% reduction in lumen radius more than doubles the resistance of the vessel, so structural remodelling alone can sustain a large pressure elevation independent of any ongoing vasoconstriction.[14]

Inward eutrophic remodelling is more reversible than the hypertrophic remodelling seen in obesity and diabetes, and it responds best to RAAS blockade. Non-invasive surrogates for arteriolar structure include the retinal arteriolar-to-venular ratio and the carotid intima-media thickness — the latter regressing more with ACE inhibitors and calcium channel blockers than with beta-blockers at equal blood pressure, in the ELSA trial.

5–6 → 14%

media-to-lumen ratio

From health to established or diabetic hypertension. A modest-sounding change with a fourth-power consequence.

ELSA

Carotid intima-media thickness regressed more with ACE inhibitors and calcium channel blockers than with beta-blockers — **at equal blood pressure**

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15.3 Aortic stiffness and isolated systolic hypertension

Distinct from arteriolar remodelling is the stiffening of the large elastic arteries, principally the aorta, which drives a different pattern of disease. A healthy aorta buffers the stroke volume — the Windkessel function of V1·Ch1; as it stiffens with age and hypertension, elastin fracturing and collagen and calcium replacing it, it can no longer do so. Systolic pressure rises while diastolic falls, widening the pulse pressure. This is the mechanism of isolated systolic hypertension, the dominant pattern in the elderly (V1·Ch17).[6,8,15,20,21]

TABLE 15.2 — CAROTID–FEMORAL PULSE WAVE VELOCITY[7]

MEASURE	THRESHOLD OR INCREMENT	MEANING
Pulse wave velocity	**above 10 m/s**	Indicates significant arterial stiffness.[17]
Each 1 m/s increment	14% more cardiovascular events; 15% higher cardiovascular and all-cause mortality ADJUSTED; 17 STUDIES, 15,877 SUBJECTS[18]	Stiffness is not a marker of risk — it carries risk.

The consequences reach the heart directly: a higher systolic load drives left ventricular hypertrophy, while the lower diastolic pressure reduces coronary perfusion, producing relative myocardial ischaemia even without obstructive coronary disease — the basis of the adverse prognosis of a wide pulse pressure.

Both ends hurt

The systole loads the ventricle; the low diastole starves the coronaries. A wide pulse pressure is doubly damaging.

15.4 Central aortic pressure and the CAFE trial

The pressure the heart and coronary arteries actually experience is the central aortic pressure, which is not identical to the brachial cuff reading and can be modified by drug choice independently of the brachial effect.

4.3

mmHg — invisible to the cuff

The central systolic difference between amlodipine- and atenolol-based regimens in CAFE, at identical brachial pressures.

TABLE 15.3 — CAFE: IDENTICAL CUFF, DIFFERENT HEART

	AMLODIPINE-BASED	ATENOLOL-BASED
Brachial blood pressure	Essentially identical	Essentially identical
Central aortic systolic	Lower by ~4.3 mmHg	Higher
Augmentation index	Lower	Higher
Mechanism	Reduces the amplitude of the reflected wave.	Slows the heart rate and **prolongs systole**, so the reflected wave returns earlier and augments central systolic pressure.

CAFE — the Conduit Artery Function Evaluation sub-study of ASCOT — measured central aortic pressure non-invasively in over 2,000 patients.[19] The difference, invisible to the cuff, substantially explained the superior cardiovascular outcomes of the amlodipine-based regimen in the main ASCOT trial. This makes atenolol uniquely disadvantageous: it can control the brachial pressure while leaving an unfavourable central pressure, and it is a principal reason atenolol is no longer a preferred agent.

15.5 Microvascular rarefaction

Longstanding hypertension reduces the density of capillaries and small arterioles — microvascular rarefaction — with three under-appreciated consequences.[3]

Functional vs structural

Non-perfused vessels can be recruited again. **Physically lost vessels largely cannot** — a further argument for early treatment.

TABLE 15.4 — THREE CONSEQUENCES OF RAREFACTION

CONSEQUENCE	MECHANISM
Exercise intolerance	A greater diffusion distance for oxygen to reach the muscle.
Insulin resistance	A reduced capillary surface limits delivery of insulin and glucose to skeletal muscle — **a mechanism linking hypertension to later type 2 diabetes**.
Microvascular angina	Chest pain with myocardial ischaemia despite normal coronary arteries.

ACE inhibitors and ARBs partially restore capillary density through their nitric-oxide-enhancing and anti-proliferative effects.

15.6 Drug effects on vascular structure

The drug classes differ substantially in their effect on vascular structure, so that two drugs producing equal blood-pressure reduction can have different long-term structural and outcome effects.

TABLE 15.5 — WHAT EACH CLASS DOES TO THE VESSEL

CLASS	ARTERIOLAR STRUCTURE	CENTRAL PRESSURE	EVIDENCE
ACE inhibitors, ARBs	**Best regression** of media-to-lumen ratio — anti-proliferative and anti-fibrotic.	Favourable.	ARBs give the best regression of left ventricular hypertrophy — **LIFE**, losartan superior to atenolol.[1]
Calcium channel blockers	Good intima-media regression.	**Best reduction**.	CAFE for central pressure; ELSA for intima-media thickness.
Beta-blockers PARTICULARLY ATENOLOL	Little structural regression.	**Worsened**.	The outlier on both counts.

The evidence therefore converges — from haemodynamics, from vascular biology, and from the outcome trials ACCOMPLISH and ASCOT — on one pairing: where a second drug is being chosen and no diuretic is yet established, an ACE inhibitor or ARB with a calcium channel blocker has the best outcome evidence, the RAAS blocker giving arteriolar regression and the calcium channel blocker giving central-pressure reduction.[5] Note the boundary. ACCOMPLISH's comparator was hydrochlorothiazide; the question has never been asked against chlorthalidone, and CAFE measured pressure, not outcomes. "Preferred where a diuretic is not already established" is what the evidence supports; "optimal" is not. Do not switch a patient who is controlled on a chlorthalidone-based regimen (V2 Opening 2).

Three roads, one answer

Haemodynamics, vascular biology and the outcome trials converge on ACEi/ARB + CCB as the pairing to choose when no diuretic is established — one of the most internally consistent stories in cardiovascular pharmacology, with one untested comparator.

KEY POINTS

1. **Two phases of resistance:** functional (reversible neural and humoral vasoconstriction, normalising easily in young recent-onset disease) and structural (partially irreversible inward remodelling — the resistance floor). Acting in the functional phase is disproportionately valuable.
2. **Inward eutrophic remodelling** — media-to-lumen ratio rising measurably in small resistance arteries — sustains large pressure elevations via the fourth-power law, where a 20% lumen reduction more than doubles resistance. Best regressed by RAAS blockade.
3. **Aortic stiffness abolishes Windkessel buffering**, producing isolated systolic hypertension with a wide pulse pressure. Pulse wave velocity above 10 m/s is significant; higher velocity carries higher risk independently of brachial pressure.[16]
4. **A wide pulse pressure damages at both ends:** the higher systolic load drives left ventricular hypertrophy while the lower diastolic pressure reduces coronary perfusion, producing ischaemia without obstructive coronary disease.
5. **Central aortic pressure, not the brachial cuff, determines outcome**, and drug choice modifies it independently. CAFE: amlodipine and atenolol gave identical brachial pressures but ~4.3 mmHg lower central systolic with amlodipine, which explains the outcome difference in ASCOT.[19]
6. **Atenolol is uniquely disadvantageous** — it prolongs systole so the reflected wave augments central pressure. It can control the cuff while leaving the heart worse off.
7. **Where a second drug is chosen and no diuretic is yet established, ACEi/ARB + CCB is the pairing with the best outcome evidence** — arteriolar regression from the RAAS blocker, central-pressure reduction from the calcium channel blocker — a conclusion on which haemodynamics, vascular biology and the ACCOMPLISH and ASCOT trials converge. ACCOMPLISH's comparator was hydrochlorothiazide, never chlorthalidone: do not switch a patient controlled on a chlorthalidone-based regimen (V2 Opening 2). Rarefaction adds a further argument for early treatment.

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VOLUME ONE · PART III

Special populations

The young, the old, pregnancy, kidney disease, diabetes and obesity — where the phenotype, the target and the drug all change.

Hypertension: A Phenotype-Based Approach

Volume 1 · Why Is This Patient Hypertensive?

Dr Ravikiran Jadhav

MBBS · AFIH · Occupational Health Physician

6 chapters

Part III of five

CHAPTER 16 PART III · SPECIAL POPULATIONS

Hypertension in young adults

Why the young hypertensive needs a different approach: high secondary yield, a neurogenic phenotype, and reproductive considerations.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why under-40 is different** — secondary yield, dominant mechanism, and the decisive weight of exposure duration.
2. **The rising Indian burden** — and why it puts young-adult hypertension at the centre of occupational practice.
3. **The structured secondary screen** — six causes, the clue that raises each, and what to do about it.
4. **Fibromuscular dysplasia** — the young woman with resistant hypertension, and a lesion angioplasty often cures.
5. **The neurogenic high-renin phenotype** — and why it is the mirror image of the elderly patient.
6. **Reproductive considerations** — why contraception is discussed before the prescription, not after.
7. **Athletes, the contraceptive pill and stimulant use** — three situations that overturn the usual choice.

16.1 Why the young hypertensive is different

Hypertension under 40 is not simply early essential hypertension; it warrants a distinct approach for three reasons.

30%

secondary cause in referred young adults

Against 5–10% in hypertension generally — and only about 2% in an unselected young cohort.[2,4] The yield depends on who is in front of you.

TABLE 16.1 — THREE REASONS THE YOUNG ARE DIFFERENT

	WHY IT MATTERS
Secondary yield	Secondary causes are far commoner in the young than in hypertension at large, which runs at 5–10%: referral series of young adults report about **30%**, and a tertiary series of 16- to 30-year-olds as much as **40%**, while an unselected young cohort — Korean military conscripts — yields about **2%**.[2,4,19] The consequence is not that every young hypertensive is screened for everything, but that screening is directed by the features which raise the yield: onset before 30, severe or resistant hypertension, hypokalaemia, a suggestive history or examination finding, and a sudden rise in a previously stable patient.
Dominant mechanism	Young hypertension is predominantly **neurogenic and high-output** (V1·Ch1, Ch14).[3] The drugs suited to it differ from those suited to the low-renin, volume-dependent physiology of the elderly.
Duration of exposure	A 30-year-old with uncontrolled hypertension accumulates decades of target-organ damage before old age, so effective treatment now is **among the highest-yield cardiovascular interventions in all of medicine**.[5,7,17]

16.2 The rising burden in young Indian adults

Hypertension is common among young Indian adults and much of it is undiagnosed — the National Family Health Survey of 2019–21 found a substantial burden in the 15–49 age group[13,16] — and the drivers are obesity, sedentary urban life, high-sodium processed food, sleep deprivation and occupational stress (V1·Ch9, Ch14 and Ch25).

16.3 Secondary causes and their yield

Because the yield is high, every young hypertensive warrants a structured secondary screen.[10] The younger and more severe or resistant the hypertension, the higher the index of suspicion.[18]

For the occupational physician

A predominantly young workforce makes young-adult hypertension a central concern, not a peripheral one.

TABLE 16.2 — THE STRUCTURED SECONDARY SCREEN IN THE YOUNG

SECONDARY CAUSE	KEY CLUE	INVESTIGATION AND MANAGEMENT
Fibromuscular dysplasia RENOVASCULAR	Young women; resistant hypertension; abdominal bruit; "string of beads".[9,11]	Renal Doppler, CT or MR angiography. **Angioplasty often curative.**
Primary aldosteronism	Hypokalaemia — but often normokalaemic; muscle weakness, polyuria.	Aldosterone–renin ratio → confirmation → CT and adrenal vein sampling (V1·Ch13). Adrenalectomy or MRA.[1]
Phaeochromocytoma	Paroxysmal hypertension with headache, palpitations, sweating; labile pressure.	Plasma or urine metanephrines; imaging; genetic testing. **Alpha-block before beta-block**, then excision.[6]
Coarctation of the aorta	Radio-femoral delay; arm–leg pressure difference; rib notching.	Echocardiography, CT or MR aortography. Stent or surgical repair.[15]
Obstructive sleep apnoea	Snoring, daytime sleepiness, STOP-BANG ≥ 3, non-dipping.	Oximetry or polysomnography; CPAP; weight loss (V1·Ch24).
Oral contraceptive–related	Onset temporally linked to the combined pill.	Trial off the combined pill; switch to progestogen-only or non-hormonal.

16.4 The dominant mechanisms

Once secondary causes are excluded, the essential hypertension of the young is dominated by the neurogenic high-output and high-renin phenotypes (V1·Ch13, Ch14): a resting heart rate at the upper end of or above normal, high cardiac output, elevated plasma renin activity, and often a disproportionately raised diastolic pressure reflecting angiotensin II–driven arteriolar constriction.[3]

16.5 Drug selection

Drug selection is guided by the haemodynamic phenotype, by comorbidities, and — critically in women of childbearing age — by reproductive considerations.

The highest-yield intervention in the young workforce is often not a drug at all but addressing the neurogenic drivers — sleep, shift patterns, workload and stress — and confirming the diagnosis with ambulatory monitoring before committing a young person to lifelong pharmacotherapy.[8]

The mirror image of the elderly

High renin, high output here; low renin, stiff aorta there. Reading which one you are looking at is what makes rational first-drug choice possible.

Before any drug

In a woman who may become pregnant, discuss contraception **before** initiating. ACE inhibitors and ARBs cause fetal injury and death (V1·Ch18).

TABLE 16.3 — CHOOSING THE DRUG IN THE YOUNG PATIENT

SITUATION	CHOOSE	AVOID
Neurogenic pattern HIGH HEART RATE, HIGH VARIABILITY, HIGH RENIN	**An ACE inhibitor / ARB or a dihydropyridine calcium channel blocker** — the guideline first-line classes, and the ACEi/ARB fits the high-renin physiology well.[20] A beta-blocker is not first-line for uncomplicated hypertension at any age or heart rate; reserve it for a compelling indication (ischaemic heart disease, heart failure, rate control), and where one exists choose bisoprolol or nebivolol, which address both heart rate and renin. Where the resting tachycardia itself is the problem, look for its cause — anxiety, thyrotoxicosis, anaemia, alcohol, stimulants — before treating it with a drug.	**A beta-blocker as monotherapy on the strength of a heart rate** — the phenotype does not override the guideline. **Atenolol** in particular — inferior in LIFE and ASCOT, adverse central pressure (V1·Ch15).
Women who may become pregnant	**Amlodipine, methyldopa or labetalol** where pregnancy is planned or not excluded.	**ACE inhibitors and ARBs** — the label's boxed warning is not confined to a trimester: drugs acting on the renin–angiotensin system can injure and kill the developing fetus, and the label directs discontinuation as soon as pregnancy is detected. The fetal renal injury is best documented from the second trimester, but the contraindication runs throughout (V3·Ch35). In a woman who may conceive, switch before conception rather than after a positive test.
Athletes and highly active patients	ACE inhibitor / ARB or a calcium channel blocker.	Beta-blockers blunt exercise capacity and are banned in some sports; diuretics risk dehydration and are also banned in some sports.
Oral contraceptive–related	Discontinue the combined pill — the oestrogen-driven rise in angiotensinogen resolves within a few months.	—
Substance use COCAINE, AMPHETAMINES	A **benzodiazepine first**, with a nitrate, labetalol or phentolamine (V1·Ch30).	**Not the first drug** — a beta-blocker alone risks unopposed alpha-vasoconstriction, and guidance has not moved (V1·Ch30).[12]

KEY POINTS

1. **Secondary causes are far commoner in the young** — about 30% in referral series and up to 40% in tertiary practice, but only about 2% in an unselected young cohort, against 5–10% in hypertension generally.[2,4,19] Screen on onset before 30, severe or resistant disease, hypokalaemia or a clue, rather than by reflex. Highest-yield: fibromuscular dysplasia, primary aldosteronism, phaeochromocytoma, coarctation, apnoea and the contraceptive pill.[14]
2. **India's young-adult burden is rising** (2015–2021) on obesity, sedentary life, processed food, sleep loss and stress.
3. **Long exposure makes early treatment one of the highest-yield interventions in medicine** — decades of organ damage are prevented, not merely postponed.
4. **The dominant mechanism is neurogenic, high-output, high-renin:** raised resting heart rate, high output, elevated renin, disproportionately high diastolic pressure. The drug is still a guideline first-line class — an ACEi/ARB, which fits the high-renin physiology, or a calcium channel blocker; a beta-blocker only where a compelling indication exists, never on the heart rate alone.
5. **Women of childbearing age:** ACE inhibitors and ARBs cause fetal injury and death — the label's boxed warning is not confined to a trimester — and the label directs that they be stopped as soon as pregnancy is detected. In a woman planning pregnancy, change in advance to amlodipine, methyldopa or labetalol, and discuss contraception **before** starting any drug.
6. **Three situations overturn the usual choice:** athletes (prefer ACEi/ARB or CCB); contraceptive-related (discontinue the combined pill); cocaine or amphetamine (benzodiazepine first, then a vasodilator, labetalol or phentolamine — **a beta-blocker is not the first drug**).
7. **Confirm with ambulatory monitoring and address the neurogenic drivers** — sleep, shifts, workload, stress — before committing a young person to lifelong pharmacotherapy.

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CHAPTER 16A PART III · SPECIAL POPULATIONS

Hypertension in children and adolescents

A short chapter, written for a doctor who does not treat children — how to recognise it, why the numbers work differently, and when to hand the patient on.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why a number will not do** — blood pressure in a child is read against a percentile for age, sex and height, and the reason that is not bureaucratic pedantry.
2. **The categories** — elevated, stage 1 and stage 2, and why they simplify into adult numbers at thirteen.
3. **The proportion that is secondary** — the single largest difference from adult practice, and how it moves with age.
4. **Who to screen, and how often** — and the cuff, which is where most paediatric readings go wrong.
5. **What the Indian data show** — and why the numbers vary so widely between studies.
6. **When to refer, and what this chapter deliberately does not print.**

Forty-three times in these three volumes a child is mentioned in passing — a coarctation, a reflux nephropathy, a steroid, a growth chart. This chapter exists so that those mentions have somewhere to point.

What this chapter does not do

It prints no paediatric drug doses and no paediatric treatment algorithm. That is a deliberate decision, not a gap. This is a book written for adult practice; a child who needs an antihypertensive needs a paediatrician, a weight-based dose from a paediatric formulary, and an evaluation for a cause. What an adult physician needs from a paediatric chapter is the ability to recognise the problem, to avoid the two errors that matter, and to know when to refer. That is what is here.

16A.1 Why a number will not do

In an adult, 140/90 means the same thing at thirty and at seventy. In a child it means nothing until you know how old the child is, whether the child is a boy or a girl, and how tall the child is. Blood pressure rises through childhood with body size, and the reference is a **percentile** drawn from a healthy population of the same age, sex and height.

The percentile is an American one. The 2017 tables were built from North American children and exclude every child at or above the 85th percentile for body mass index, so they describe normal-weight American children[1]; no Indian normative table is in national use. Classifying an Indian child against them is a substitution, not a validation, and it is part of why Indian prevalence estimates vary as widely as they do.

Height enters twice. It sets the percentile — and short stature is itself a clue. A child below the expected height centile with a raised pressure raises chronic kidney disease, long-standing steroid exposure and Turner syndrome, all at once. **Plot the growth before interpreting the pressure.**

That is why 118/76 can be an unremarkable reading in a tall fifteen-year-old and stage 2 hypertension in a small six-year-old. The number has not changed; the population it is being read against has. A clinician who carries adult thresholds into a paediatric consultation will miss the six-year-old entirely.

16A.2 The categories, and what changes at thirteen

The 2017 American Academy of Pediatrics guideline sets the categories used here[1]. Europe does not agree: the European Society of Hypertension's paediatric scheme keeps percentiles to sixteen rather than thirteen and then uses the older adult numbers, so a seventeen-year-old at 135/85 is stage 1 under the American definition and high-normal under the European one. Neither is wrong. Say which you are quoting. Below thirteen they are percentile-based; from thirteen they become the adult numbers, so that an adolescent moving into adult care does not change diagnosis on a birthday.

The practical objection to a percentile system is obvious and worth stating: nobody computes a percentile from memory in a busy clinic. In practice the tables are consulted, or a calculator is, and the reading that prompts the lookup is usually one that already looked high for the child in front of you. That is the right way round. **The categories exist to settle a threshold decision — is this normal, does it need repeating, does it need referral — not to grade severity to a decimal place.**

Note also what the table does not contain. There is no paediatric equivalent of the adult "grade 3", and no category above stage 2. A child whose pressure is far above the stage 2 threshold is not in a further category; that child is an emergency, and belongs in Volume 3.

TABLE 16A.1 — THE CATEGORIES

CATEGORY	AGE 1 TO UNDER 13	AGE 13 AND OVER
Normal	Below the 90th percentile for age, sex and height[1]	Below 120/80[1]
Elevated	At or above the 90th percentile and below the 95th, **or** 120/80 up to the 95th percentile — whichever is lower[1]	120–129 with a diastolic below 80[2]
Stage 1	At or above the 95th percentile — the line at which a child is hypertensive — up to the 95th percentile plus 12 mmHg, **or** 130/80 to 139/89 — whichever is lower[1]	130–139 / 80–89[2]
Stage 2	95th percentile plus 12 mmHg, **or** 140/90 — whichever is lower[2]	140/90 and above[2]

Read the "whichever is lower" carefully. It exists so that a large adolescent under thirteen cannot be reassured by a percentile that has drifted above adult thresholds. The lower of the two rules always wins.

16A.3 The proportion that is secondary

This is the difference that matters most, and the one an adult physician is least prepared for. In adult hypertension, 5 to 10% is secondary. In childhood, where you are standing changes the answer. In children newly diagnosed at school or in primary care — which is where an adult physician meets them — a secondary cause is found in about **4%**; in paediatric referral clinics it is about **20%**[4]. What raises the probability is youth, severity and the red flags below: one small study puts primary hypertension at **17% under six** against about **60% at thirteen and over**[2], and that age gradient, rather than any single figure, is what should be carried away.

Turn that around. In a child under six with a confirmed raised pressure, the odds are about five to one that there is a cause to be found. The younger the child, the higher the pressure, and the less the child weighs, the harder you look. Renal parenchymal disease and renovascular disease dominate; coarctation must be excluded by femoral pulses and four-limb pressures in any child, at any age, at the first raised reading.

Primary hypertension in a child is not a diagnosis of first resort. It becomes plausible in an older adolescent, with obesity, with a family history, with a pressure only modestly above the threshold, and after the causes above have been considered.

The one examination step never to skip

Feel the femoral pulses and put a cuff on a leg. Palpation alone does not exclude a coarctation — collaterals can keep the femoral pulse palpable — so the arm-to-leg gradient is measured, not inferred. It is the secondary cause that is missed for decades, and it is missed because nobody went below the waist. V1·Ch37.

16A.4 Who to screen, and how

Screen annually from **age three**. Screen at **every** encounter in a child with obesity, kidney disease, diabetes, aortic arch obstruction or coarctation, or taking a drug that raises pressure[1,2]. Below three, blood pressure is not screened routinely but is measured in defined groups — congenital heart disease, recurrent urinary tract infection or a urological malformation, a solid-organ or marrow transplant, malignancy, neurofibromatosis, tuberous sclerosis or sickle cell disease[1].

Then measure it properly, which in children is where most of the error lives. **A cuff that is too small over-reads** — and in a country where paediatric cuffs are often the one size the clinic owns, that error is systematic rather than random. Measure the mid-arm circumference, midway between acromion and olecranon, and choose the cuff from it: the bladder's width should be at least 40% of that circumference, and its length should wrap 80 to 100% of the way round the arm[1]. If the child falls between two cuffs, use the larger. Use the right arm — the percentile tables were built from right-arm readings, and a left-arm reading can be falsely low if the narrowing of a coarctation involves the left subclavian[1]. If the first reading is high, measure both arms and a leg. An automated device that flags a raised reading should be repeated by auscultation.

One raised reading is not a diagnosis. Hypertension is diagnosed on auscultation-confirmed readings at or above the 95th percentile on three separate visits[1], and three properly taken sets are a diagnosis, not a compromise. Ambulatory monitoring confirms it where a paediatric monitor exists but is not required to make it[1] — and it is separately indicated, whatever the clinic reading, in a child with chronic kidney disease, diabetes, a transplant, severe obesity or a repaired coarctation, because in those children the hypertension is often masked[2]. The white-coat effect is at least as strong in children as in adults, and the consequence of a false label — a lifetime of investigations, an insurance note, a sporting restriction — is longer.

16A.5 What the Indian data show

A systematic review of 25 cross-sectional studies covering **27,682 Indian adolescents** aged 10 to 19 found a pooled hypertension prevalence of **7.6%** (95% CI 6.1 to 9.1), with individual studies ranging from **2% to 20.5%**[3].

That ten-fold spread between studies is the finding, as much as the pooled number is. It reflects different reference tables, different cuffs, different numbers of visits before a label was applied, and different populations — urban private schools against rural government ones. A prevalence figure quoted from a single Indian school survey should be read with that spread in mind.

16A.6 When to refer

TABLE 16A.2 — REFER, AND HOW URGENTLY

THE FINDING	URGENCY	WHY
Any confirmed hypertension under six	**Refer**	The odds favour a secondary cause by roughly five to one[2]
Stage 2 at any age	**Refer promptly**	Higher pressures carry a higher secondary yield and a shorter safe interval
Absent or delayed femoral pulses, or an arm–leg gradient	**Refer**	Coarctation until proven otherwise
Raised pressure with short stature, poor growth or abnormal urinalysis	**Refer**	Chronic kidney disease is the commonest secondary cause in childhood
Headache, visual change, seizure or heart failure with a raised pressure	**Emergency**	Hypertensive emergency in a child. **The adult protocols in V3·Part Five do not apply.** In a child the pressure is brought down by no more than a quarter of the intended fall over the first eight hours, the rest over the following twelve to twenty-four, on weight-based intravenous doses[1]. Paediatrics and critical care are involved at once.
Any confirmed hypertension in a child who is not overweight, at any age	**Refer**	Primary hypertension in a thin child is a diagnosis of last resort[1]
Born preterm, or hypokalaemia, an abdominal bruit or unequal kidney sizes	**Refer**	Renovascular and renal parenchymal disease[1]
Stage 2, or stage 1 with symptoms	**Within one week**, sooner if symptomatic	The AAP interval for stage 2; a symptomatic child is seen the same day[1]
Confirmed stage 1 in a child under thirteen	Recheck within one to two weeks; refer once confirmed across three visits	Only the child of six or over who is overweight or obese, has a family history and has a normal history and examination is exempt from a secondary work-up[1]
An older adolescent, obese, family history, stage 1, normal history and examination	Lifestyle, recheck, and refer if it persists over three visits	The one group where primary hypertension is the likely answer — and even there, urinalysis, a chemistry panel and lipids are done in every hypertensive child[1]

An adult physician meets this most often in two places: the eighteen-year-old at a pre-employment medical, and the adolescent brought to a general clinic because there is no paediatrician nearby. In the first, adult thresholds apply and V1·Ch16 is the chapter that governs. In the second, the honest answer is usually a properly taken reading, a urinalysis, femoral pulses, and a referral — not a prescription.

KEY POINTS

1. **A child's blood pressure is read against a percentile** for age, sex and height, not against a fixed number. The same 118/76 is normal in a tall fifteen-year-old and stage 2 hypertension in a small six-year-old.
2. **At thirteen the system changes to fixed adult numbers** — elevated 120–129 with a diastolic below 80, stage 1 at 130–139/80–89, stage 2 at 140/90 and above.[1,2]
3. **About half of childhood hypertension is secondary**, and the younger the child the likelier that is: roughly 17% of hypertension under six is primary, against about 60% at thirteen and over.[2] In adult practice the proportion is 5 to 10%. That inversion is the whole difference.
4. **Screen annually from age three**, and at every encounter in a child with obesity, kidney disease, diabetes, aortic arch obstruction or coarctation, or on a drug that raises pressure.[1,2]
5. **The commonest error is the cuff.** A cuff too small over-reads. The bladder's width should be at least 40% of the mid-arm circumference and its length should wrap 80 to 100% of the way round; between two cuffs, use the larger. Right arm.
6. **One raised reading is not a diagnosis.** Confirm on repeated visits; ambulatory monitoring is the confirmatory test where it is available.[2]
7. **In India, pooled adolescent prevalence is 7.6%** (95% CI 6.1 to 9.1) across 25 studies and 27,682 participants aged 10 to 19, with individual studies ranging from 2% to 20.5%.[3] The spread is a measurement and definition problem as much as a real one.
8. **This chapter prints no paediatric drug doses.** That is deliberate. A child who needs an antihypertensive needs a paediatrician, a weight-based dose from a paediatric formulary, and a search for the cause — not a dose taken from a book written for adult practice.
9. **The adolescent who reaches an adult clinic is the one this book is for.** At eighteen the thresholds are adult thresholds, but the pre-test probability of a secondary cause is still that of a young adult, not of a sixty-year-old — V1·Ch16.
10. **Height matters twice.** It enters the percentile, and short stature is itself a clue — to chronic kidney disease, to Turner syndrome, to long-standing steroid exposure.

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CHAPTER 17 PART III · SPECIAL POPULATIONS

Hypertension in the elderly

Isolated systolic hypertension, the trial evidence for treating even the very old, the targets, the J-curve, and the balance against falls.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Isolated systolic hypertension** — why aortic stiffness makes it the dominant pattern after 65, and what physiology follows.
2. **The trial evidence** — SHEP, Syst-Eur, HYVET, SPRINT and STEP, and what each established.
3. **HYVET** — the first demonstration that treating the over-80s reduces mortality.
4. **Targets by fitness, not by age alone** — the current guideline number, and the short list of patients for whom a more lenient one is permitted.
5. **The J-curve** — why the observation is real and largely not causal, and why a low diastolic is a reason to examine the patient rather than to leave the systolic high.
6. **Falls and orthostasis** — the standing pressure at every visit, and the drugs to avoid.
7. **Pseudohypertension and cognitive protection** — over-treating a calcified artery, and what the dementia trials did and did not show.

17.1 Isolated systolic hypertension

In the elderly, the dominant pattern is isolated systolic hypertension — a raised systolic with a normal diastolic pressure — the direct consequence of aortic stiffness and the loss of Windkessel buffering (V1·Ch1, Ch15). It affects the majority of hypertensives over 65 and the great majority over 75, and it produces the wide pulse pressure that is itself an independent risk marker.

Physiologically these patients have a low-renin, often normal-resistance state with concentric left ventricular hypertrophy, diastolic dysfunction, and a coronary circulation perfused against an already-low diastolic pressure — a physiology that directly shapes both drug choice and the setting of targets.

A physiology that dictates the drug

Low renin, often normal resistance, concentric LVH, diastolic dysfunction, and coronaries perfused against an already-low diastolic pressure.

17.2 The evidence for treatment

A series of landmark trials established that treating hypertension in the elderly, including the very old, substantially reduces stroke, cardiovascular events and mortality.

21%

mortality reduction over 80

HYVET — the first demonstration of a mortality benefit from treating hypertension in this age group.[3]

TABLE 17.1 — THE TRIAL EVIDENCE IN THE ELDERLY

TRIAL	POPULATION AND REGIMEN	RESULT
SHEP	Isolated systolic hypertension; chlorthalidone-based.	Stroke reduced by **36%**.[10]
Syst-Eur	Nitrendipine, a calcium channel blocker.	Stroke reduced by **42%**; dementia by **50%** in a sub-analysis.[6,11]
HYVET	Over 80, systolic ≥ 160; indapamide ± perindopril to a target below 150/80.	Stroke **−30%** — the primary endpoint, but **p = 0.06** (HR 0.70, 0.49–1.01), short of conventional significance. All-cause mortality **−21%** (HR 0.79, 0.65–0.95; p = 0.02) and heart failure **−64%** (HR 0.36, 0.22–0.58; p < 0.001) were significant. **The first mortality benefit shown in this age group.**[3]
SPRINT ELDERLY SUBGROUP	Intensive target below 120 by **unattended automated** measurement — equivalent to roughly **130–135 attended** in an ordinary clinic (V1·Ch8).[12,16]	Benefit in the over-75s, with serious adverse events at similar overall rates in the two arms — **48.4% against 48.3%**. Hypotension, syncope, electrolyte disturbance and acute kidney injury were numerically higher on intensive treatment but none reached significance, and injurious falls were non-significantly fewer (HR 0.91).[16] The caution about SPRINT in an elderly patient is about the measurement method, not a demonstrated excess of harm.
STEP	China, ages 60–80.	Supported a target below 130 **in the fit**.[17]

Treatment is therefore firmly indicated; the question is how intensively, and in whom.

17.3 Targets in the fit and the frail

The evidence supports one target for the fit, a more lenient one for a defined minority — and no diastolic constraint that overrides the systolic. The guidelines moved between 2017 and 2024, and this chapter follows the current ones.

What "below 120" means

SPRINT's target was unattended automated office BP, which reads 5–15 mmHg below an ordinary attended reading. A patient sitting at 130–135 on your clinic cuff has already reached it. Treating an attended reading down to 120 in an 80-year-old is not intensive control — it is over-treatment, and it is the route to the hypotension, syncope and kidney injury that the trial itself, properly measured, did not show in excess.

TABLE 17.2 — TARGETS BY FITNESS AND AGE

PATIENT	SYSTOLIC TARGET	BASIS
Fit, non-frail ANY AGE	**120–129 where tolerated** (ESC 2024)[18], or **below 130** on the American guideline[14] — measured rested, correctly cuffed and averaged; **not below about 120**.	STEP; the non-frail SPRINT subgroup — read as attended-equivalent values.[16,17] HYVET established benefit below 150/80 in the over-80s[3]; that was the edge of the evidence at the time, not a ceiling, and no current guideline sets a separate, higher target for a fit octogenarian.[18]
Age 85 or over, moderate-to-severe frailty, symptomatic orthostatic hypotension, or limited life expectancy	**A more lenient target** — as low as is reasonably achievable and tolerated.[18]	These are the ESC 2024 exceptions, and the only ones: mild frailty at any age is not one. Frailty scales (Clinical Frailty Scale, FRAIL) identify the patient who derives less benefit and more harm.[9] Use shared decision-making and single-pill combinations to limit pill burden, and weigh time to benefit (V3·Ch14).
Diastolic ALL ELDERLY	**No floor overrides the systolic.** ESC 2024 gives 70–79 as a target, not as a line at which systolic lowering stops.[18]	See 17.4. A low on-treatment diastolic is a marker, not a mechanism — reduce the drug for symptoms, not for a number (V3·Ch13).

17.4 The J-curve and the diastolic

The J-curve describes the observation that below a certain diastolic pressure, cardiovascular risk rises again rather than continuing to fall — the proposed mechanism being that the coronary arteries fill during diastole, and an excessively low diastolic pressure reduces coronary perfusion, most of all in a hypertrophied ventricle with high oxygen demand.[4,13] The observation is real; on the best available analysis it is largely not causal. In SPRINT the lowest on-treatment diastolic quintile had the most events, and the association vanished on adjustment — HR 0.99 (0.98 to 1.00).[19] A low diastolic marks the sick patient; it does not make him sick.

The practical rule follows. Do not withhold systolic lowering from an elderly patient with a wide pulse pressure because the diastolic is low — a 74-year-old at 172/66 is the patient at highest absolute stroke risk in this chapter, and SHEP was conducted in exactly that population.[10] Watch the diastolic at every titration step, but examine the patient rather than the number: reduce or space the drugs for symptoms — dizziness, falls, fatigue, an orthostatic drop, a rising creatinine — not because a diastolic crossed a line that no randomised evidence supports. The 2024 ESC diastolic figure of 70–79 is a target, not a stop-line.[18] Volume 3 sets out the evidence in full (V3·Ch13).

The bind, resolved

Bringing a high systolic to target necessarily drives an already-low diastolic lower. In wide-pulse-pressure ISH the two goals appear to fight each other — and the systolic wins, because that is where the randomised benefit is.

17.5 Falls, orthostatic hypotension and drug selection

The elderly are uniquely vulnerable to the harms of treatment, chief among them falls from orthostatic hypotension.

A fall can cause a hip fracture or subdural haematoma more harmful than the hypertension being treated. Drug selection follows the low-renin physiology.

Every visit

Lying and standing pressure at one and three minutes. A fall of **20 systolic or 10 diastolic** mandates a regimen review **before** any escalation.[5]

TABLE 17.3 — DRUG SELECTION IN THE ELDERLY

AGENT	PLACE	BASIS
Thiazide-type diuretics AND CALCIUM CHANNEL BLOCKERS	First-line	Guideline first-line choice in this age group, established by SHEP and Syst-Eur.[10,11] The low-renin physiology explains *why* these classes perform well here — it is not the reason to choose them.
ACE inhibitors, ARBs	Where there is a compelling indication	Heart failure, CKD with proteinuria, post-infarction.
Alpha-1 blockers	Not as primary agents	Orthostasis risk. The ALLHAT doxazosin arm was stopped early for excess heart failure; the Beers Criteria flag alpha-blockers and high-dose diuretics as potentially inappropriate in the elderly.[1]

17.6 Pseudohypertension and cognitive protection

Pseudohypertension — a falsely elevated cuff reading caused by an incompressible, medially calcified brachial artery (Monckeberg sclerosis) — should be suspected in an elderly patient with apparently severe hypertension but no target-organ damage, or one who develops hypotensive symptoms while the cuff pressure remains high.[7] It can lead to harmful over-treatment.

Suspect it when

Severe readings but **no target-organ damage** — or hypotensive symptoms while the cuff still reads high.

TABLE 17.4 — TREATMENT AND COGNITION: WHAT THE TRIALS SHOWED

EVIDENCE	FINDING
ARIC, Framingham	Midlife treatment associated with **reduced dementia risk**.
Syst-Eur	**50% reduction** in dementia incidence — on 32 cases.[6]
HYVET-COG	**No significant reduction** in incident dementia (HR 0.86, 95% CI 0.67–1.09). The null result from the trial this chapter otherwise leans on most for the over-80s.[8]
SPRINT-MIND	**Probable dementia, the primary outcome, was not significantly reduced** — HR 0.83 (95% CI 0.67–1.04). Mild cognitive impairment was, HR 0.81 (0.69–0.95), as was the composite of MCI or probable dementia, HR 0.85 (0.74–0.97) — both secondary outcomes.[15]

Treatment can therefore reasonably be offered as protection against cognitive decline. It should not be sold as dementia prevention: the two trials with dementia as a stated outcome, HYVET-COG and SPRINT-MIND, were

both null on it, and Syst-Eur's halving rests on 32 cases.[6,8,15] And the offer holds only where treatment does not cause the falls that would offset the benefit.

KEY POINTS

1. **Isolated systolic hypertension dominates in the elderly** — raised systolic, normal diastolic, wide pulse pressure — reflecting aortic stiffness, with LVH, diastolic dysfunction and marginal coronary perfusion. First-line: thiazide-type diuretic or calcium channel blocker.
2. **Treatment is firmly indicated even over 80:** SHEP (–36% stroke), Syst-Eur (–42% stroke, –50% dementia), HYVET (–21% mortality, –64% heart failure), with SPRINT and STEP supporting intensive targets in the fit — SPRINT's "below 120" being unattended, about 130–135 attended.[3,6,10,11,12,17]
3. **Targets follow fitness, not age alone:** fit at any age, 120–129 where tolerated (ESC 2024) or below 130 on the American guideline, properly measured and not below about 120; a more lenient target only for age 85 or over, moderate-to-severe frailty, symptomatic orthostatic hypotension or limited life expectancy — individualised with frailty scales and single-pill combinations. Mild frailty is not an exception.[14,18]
4. **There is no diastolic floor that overrides the systolic.** The J-curve is real as an observation and largely not causal: in SPRINT the association between a low on-treatment diastolic and events disappeared on adjustment. Do not withhold systolic lowering from a wide-pulse-pressure patient because the diastolic is low.[4,13,19]
5. **The J-curve:** below a diastolic threshold observed risk rises again, and the proposed mechanism is coronary filling in diastole — most relevant in wide-pulse-pressure ISH, where the two targets appear to fight each other. Treat the systolic. Examine the patient, and reduce or space the drugs for symptoms — dizziness, falls, an orthostatic drop, a rising creatinine — not for a number (V3·Ch13).
6. **Falls and orthostasis:** measure standing pressure at every visit; a 20/10 mmHg drop mandates drug review before escalation. **Avoid alpha-1 blockers as primary agents** — the ALLHAT doxazosin arm stopped early; Beers Criteria.[2]
7. **Pseudohypertension** (Monckeberg calcification) causes falsely high readings and over-treatment — suspect it with severe readings but no organ damage. **Cognitive protection** is plausible but not settled: Syst-Eur –50% on 32 dementia cases; HYVET-COG and SPRINT-MIND both null on dementia itself, SPRINT-MIND positive only on the secondary outcome of mild cognitive impairment. Offer it as protection against cognitive decline, not as dementia prevention, and only where treatment does not cause falls.[8]

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CHAPTER 18 PART III · SPECIAL POPULATIONS

Hypertension in pregnancy

Classification, the CHAP shift in treatment thresholds, safe and contraindicated drugs, pre-eclampsia, and the eclamptic emergency.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The six categories** — why superimposed pre-eclampsia is the one that gets missed, and why HELLP can arrive with only modest hypertension.
2. **CHAP** — the 2022 trial that moved the threshold for treating chronic hypertension in pregnancy from 160/105 down to 140/90.
3. **Why the old fear was wrong** — active treatment did not restrict fetal growth.
4. **Safe and contraindicated drugs** — methyldopa, labetalol and nifedipine, and the absolute bar on RAAS blockade.
5. **Pre-eclampsia pathophysiology** — spiral-artery failure, sFlt-1, and maternal endothelial injury.[21]
6. **Aspirin from 12 weeks** — the prevention that is most often simply not started.
7. **Magnesium, delivery, and lifelong risk** — the emergency, the cure, and what pre-eclampsia predicts decades later.

18.1 Classification

Hypertension complicates 5–10% of pregnancies and remains a leading cause of maternal and fetal morbidity and mortality.[23,25] Five categories are distinguished, with one severe variant — and the fifth, pre-eclampsia superimposed on chronic hypertension, is the one most often missed, because her pressure was never normal to begin with.

HELLP

Haemolysis, elevated liver enzymes, low platelets. May occur with **only modest blood-pressure elevation** — the pressure does not tell you how sick she is.[16]

TABLE 18.1 — THE HYPERTENSIVE DISORDERS OF PREGNANCY[7,9,29]

CATEGORY	DEFINITION
Chronic hypertension	Predates pregnancy, or is diagnosed **before 20 weeks**.
Gestational hypertension	New hypertension **after 20 weeks** without proteinuria or organ dysfunction. A proportion progress to pre-eclampsia.
Pre-eclampsia	New hypertension after 20 weeks **with proteinuria or maternal organ dysfunction** — thrombocytopenia, renal or hepatic impairment, pulmonary oedema, or neurological features. Proteinuria means **300 mg or more in 24 hours**, a protein:creatinine ratio of **0.3 or more**, or **2+ on dipstick** where no quantitative test is available.[7]
Superimposed pre-eclampsia	Chronic hypertension in which, after 20 weeks, **new proteinuria, new maternal organ dysfunction or evidence of uteroplacental dysfunction** appears. The highest-risk category, and the one most often missed, because her pressure was never normal to begin with. She goes on the pre-eclampsia pathway, not the chronic-hypertension one.[10]
Eclampsia	Generalised seizures in a woman with pre-eclampsia. A life-threatening emergency.[5,26,28]
HELLP syndrome	Haemolysis, elevated liver enzymes, low platelets — a severe variant that may occur with only modest blood-pressure elevation.[16]

18.2 The CHAP shift in treatment threshold

For decades, mild chronic hypertension in pregnancy was left untreated until the pressure reached severe levels — 160/105 to 110 — on the basis of old concerns that lowering it might impair fetal growth. The CHAP trial overturned this.

<140/90

the new target

CHAP: Tita and colleagues, *New England Journal of Medicine*, 2022. A genuine, recent change in obstetric practice.

TABLE 18.2 — CHAP: WHAT CHANGED AND WHY

	DETAIL
Design	2,408 women with mild chronic hypertension randomised to active treatment to a target **below 140/90**, versus treatment only for severe hypertension.[3]
Primary result	Active treatment reduced the composite of pre-eclampsia with severe features, medically indicated preterm birth before 35 weeks, placental abruption, and fetal or neonatal death — **30.2% versus 37.0%, risk ratio 0.82**.[3]
The old fear, tested	No increase in small-for-gestational-age births.[2] The concern that had governed practice for decades did not materialise.
Now recommended by	ACOG, the Society for Maternal-Fetal Medicine, and the 2023 ESH guideline — treat to below 140/90 using **labetalol or extended-release nifedipine**.[3,6,19]
Residual caution	CHIPS compared a target diastolic of **85** against **100** mmHg and found the same pregnancy-loss and neonatal outcomes with significantly less severe hypertension in the tighter arm, and no signal of fetal harm[17] — but it did not titrate without a floor. Its algorithm reduced or stopped the drug whenever the diastolic fell to **80 mmHg or below**, and raised or started it above 85. Three positions stand: CHAP treated at a threshold of 140/90, NICE aims at **135/85**, and ISSHP at a **diastolic of 85** whatever the systolic, quoting the CHIPS algorithm as part of the recommendation[10,19]. Aim for a diastolic of 85, avoid an abrupt fall, and step the dose down if the diastolic reaches 80.

18.3 Safe and contraindicated drugs

Drug selection is dominated by fetal safety, and the single most important rule is that ACE inhibitors, ARBs and direct renin inhibitors must not be used in pregnancy. Their second- and third-trimester effect is fetal toxicity rather than teratogenesis — loss of fetal renal function, oligohydramnios, skull ossification defects, growth restriction and death — and ISSHP bars them on that ground, noting that they do not appear to be teratogenic.[10,31] Note where the bar sits on the label: it is a boxed warning of fetal injury and death, and a paragraph on pregnancy in Use in Specific Populations, not an entry under Contraindications[37] — a reader who checks a label and finds pregnancy absent from the contraindications section has not found a loophole. The absolute prohibition is the guideline position, and it is the one to follow.

Before conception, not after

The label directs that the drug be stopped as soon as pregnancy is detected, and NICE within two working days of being notified. Better still, in a woman planning pregnancy, counsel and switch **before** conception — that is prudence rather than a guideline rule, and it is the one that avoids the exposure altogether.

TABLE 18.3 — ANTIHYPERTENSIVE DRUGS IN PREGNANCY

DRUG	STATUS	NOTES
Methyldopa	Safe — first-line	Longest safety record.[22] May cause sedation; the label reports a positive direct Coombs test in **10–20%**, usually between 6 and 12 months of treatment. The direct test alone does not interfere with typing or cross-matching — it is a positive indirect test alongside it that can complicate the cross-match — and haemolysis itself is rare.[38]
Labetalol	Safe — first-line	Oral and intravenous; used for chronic control and acute severe hypertension. Avoid in asthma.
Nifedipine MODIFIED RELEASE	Safe — first-line	Effective oral agent; also for acute control. **Avoid sublingual immediate-release.**
Hydralazine INTRAVENOUS	Safe — acute	For acute severe hypertension. Long obstetric track record.
ACE inhibitors, ARBs, DRIs	Contraindicated	**Contraindicated throughout pregnancy** — the label's boxed warning names no trimester. The classical fetopathy follows second- and third-trimester exposure; the first-trimester malformation risk is disputed (V3·Ch23). Stop as soon as pregnancy is detected; better, switch before conception.
Atenolol	Avoid	Fetal growth restriction.
Diuretics	Caution	Pre-eclampsia is a volume-contracted state. Avoid unless already established for a compelling indication. **Spironolactone is not one to continue with caution** — its label warns that it may affect sex differentiation of the male fetus during embryogenesis, so stop it.

18.4 Pre-eclampsia: pathophysiology and prevention

Pre-eclampsia originates in the placenta. Deficient trophoblastic remodelling of the maternal spiral arteries leaves them narrow and high-resistance, and the resulting placental ischaemia releases anti-angiogenic factors — chiefly soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin — that antagonise vascular endothelial and placental growth factors, producing widespread maternal endothelial dysfunction.[24]

This endothelial injury manifests as hypertension, proteinuria, thrombocytopenia, hepatic and renal impairment, and the neurological features that culminate in eclampsia.[24,34]

sFlt-1/PlGF

Used in some settings to aid diagnosis and risk stratification.[1]

TABLE 18.4 — PREVENTION IN HIGH-RISK WOMEN

INTERVENTION	DETAIL	WHO
Low-dose aspirin	**75–150 mg daily, started from 12 weeks and continued to delivery.**[33] NICE and the USPSTF both put the start at 12 weeks; the USPSTF specifies 81 mg, the US tablet strength[19,32]. Where 150 mg is available, prefer it, and give it at night: ISSHP specifies 150 mg at bedtime after multivariable screening, 100 to 162 mg daily after risk-factor screening, and bedtime dosing either way — which is how ASPRE gave it[10,12]. In India the 75 mg tablet is the one on the shelf; two of them at bedtime is closer to the evidence than one in the morning. ACOG gives the window as **12 to 28 weeks, optimally before 16**, and ISSHP says preferably before 16 weeks and stopped by 36[7,10] — so 16 weeks is a preference for starting early, not a deadline after which aspirin is pointless. The USPSTF's stratified analysis found no consistent difference in effect by the timing of initiation.[33] A HIGH-RISK WOMAN FIRST SEEN AT 18 OR 20 WEEKS IS STILL INSIDE ACOG'S WINDOW AND SHOULD BE STARTED. Start it at the visit where the decision is made; the commonest failure is not refusal but drift.[12]	There are two routes onto aspirin, and the second is the one that gets missed. **Any one high-risk factor** (ACOG): previous pre-eclampsia, chronic hypertension, chronic kidney disease, type 1 or type 2 diabetes, autoimmune disease (SLE, antiphospholipid syndrome), multiple pregnancy.[7] **Or any two moderate-risk factors** (ACOG): first pregnancy, BMI above 30, family history of pre-eclampsia, age 35 or over, sociodemographic risk, and personal-history factors such as a previous low-birth-weight or adverse pregnancy outcome or a pregnancy interval over ten years.[7] NICE DRAWS THE SAME TWO LINES IN DIFFERENT PLACES — IT SETS AGE AT 40 AND BMI AT 35, AND PUTS A MULTI-FETAL PREGNANCY AMONG THE MODERATE FACTORS RATHER THAN THE HIGH. SO ACOG COUNTS TWINS ALONE AS ENOUGH AND NICE ASKS FOR A SECOND FACTOR; WHERE THE TWO DISAGREE, START THE ASPIRIN — THE HARM OF AN UNNECESSARY 75 MG IS SMALL AND THE HARM OF A MISSED ONE IS NOT.[19] USPSTF CLASSES ASSISTED REPRODUCTION AS A *MODERATE*-RISK FACTOR, REQUIRING A SECOND FACTOR BEFORE ASPIRIN IS INDICATED ON RISK GROUNDS ALONE.[32] Volume 3 sets the two lists side by side (V3·Ch23).
Calcium supplementation	**1.5 to 2.0 g of elemental calcium daily**, in divided doses — the WHO figure.[35] ISSHP sets the floor lower, at 500 mg a day.[10] The figure is elemental calcium, not the salt: a 500 mg calcium carbonate tablet carries 200 mg of elemental calcium, so "500 mg twice daily" of the carbonate is a quarter or less of the WHO dose.	Women with low dietary calcium — **of particular relevance in parts of the Indian population**.[12,35]

18.5 Severe features, magnesium sulphate and delivery

Severe features — systolic ≥ 160 or diastolic ≥ 110 (confirmed on two occasions four hours apart for the diagnosis, but treated once it has persisted fifteen minutes — Table 18.5), platelets below 100,000 per microlitre, transaminases above twice the upper limit of normal or severe right-upper-quadrant pain, creatinine above 1.1 mg/dL or doubled from baseline, pulmonary oedema, or new headache unresponsive to analgesia or visual disturbance — mandate blood-pressure control and seizure prophylaxis.[7] The thresholds are ACOG's; a platelet count of 130,000 is not thrombocytopenia for this purpose, and one of 85,000 is a severe feature whatever the pressure.[20]

Magnesium toxicity

Monitor respiratory rate, reflexes and urine output.

Calcium gluconate

is the antidote and should be available.

TABLE 18.5 — MANAGING SEVERE DISEASE

ELEMENT	MANAGEMENT
Seizure prophylaxis and treatment	**Magnesium sulphate** — the agent of choice (Magpie trial; superior to diazepam and phenytoin in the Collaborative Eclampsia Trial).[11,18,30] NICE prints the regimen: a loading dose of **4 g intravenously over 5 to 15 minutes**, then **1 g per hour for 24 hours** — or for 24 hours after the last fit, if one has occurred — and a recurrent fit treated with a further **2 to 4 g over 5 to 15 minutes**[19]. Monitor deep tendon reflexes, respiratory rate and urine output throughout; the label sets the floors at a knee-jerk reflex that must still be present, a respiratory rate of at least 16 a minute, and at least 100 mL of urine over each four hours, and an injectable calcium salt must be immediately to hand.[18]
Acute severe hypertension	**A systolic of 160 or a diastolic of 110, persisting fifteen minutes, is the trigger; the first dose is given within thirty to sixty minutes. Labetalol** 10 to 20 mg intravenously, then 20 to 80 mg every 10 to 30 minutes to a cumulative 300 mg, or an infusion of 1 to 2 mg per minute. **Hydralazine** 5 mg intravenously or intramuscularly, then 5 to 10 mg intravenously every 20 to 40 minutes to a cumulative 20 mg — a quarter of the general adult dose, and the two must never be confused. **Immediate-release nifedipine** 10 to 20 mg by mouth, swallowed — never sublingual — repeated after 20 minutes if needed, then 10 to 20 mg every 2 to 6 hours to a daily maximum of 180 mg.[7,14] Aim below 160/110 by a **controlled** reduction that does not compromise placental perfusion; the general rule of a 25% fall in the first hour does not apply here. Magnesium sulphate is for the seizure and does not replace the antihypertensive.[13,14] Table 23.1 in Volume 3 sets the regimens out in full (V3·Ch23).
Definitive treatment	Delivery. The gestation depends on the category. **Chronic or gestational hypertension below 160/110:** not before 37 weeks unless there is another indication.[19] **Pre-eclampsia, or superimposed pre-eclampsia, without severe features:** deliver at 37 weeks. **Pre-eclampsia with severe features at 34 weeks or beyond:** deliver, after stabilising the mother. **Below 34 weeks:** expectant management only where mother and fetus can be watched continuously and there is no eclampsia, HELLP, pulmonary oedema, abruption, uncontrollable hypertension or non-reassuring fetal status — and deliver at any point if she deteriorates.[7] Antenatal corticosteroids if delivery before 34 weeks is anticipated.[4]

18.6 Postpartum and lifelong risk

Blood pressure may peak in the days after delivery — NICE directs a measurement at least once between day 3 and day 5 — so monitoring continues into the puerperium.[19] Several drugs are compatible with breastfeeding: labetalol, nifedipine, enalapril and methyldopa[15], though NICE directs that methyldopa be stopped within two days of the birth and something else substituted, and the label lists depression among its psychic disturbances. The ACE inhibitors are barred in pregnancy but not after it, and enalapril is the one to reach for — it is the agent NICE names for the postnatal period and it has the best lactation record of the class. Do not read that as a class permission: the lisinopril label advises against breastfeeding on treatment.[37] Avoid diuretics and ARBs while she is feeding.

A history of pre-eclampsia or gestational hypertension is a powerful lifelong cardiovascular risk marker.[36] It should be recorded as a sex-specific cardiovascular risk factor, and these women followed with long-term risk-factor surveillance — a point of importance for primary-care and occupational-health practice.[27]

3.7×

risk of later hypertension

The risk is not uniform across outcomes: after pre-eclampsia the relative risk is **3.70** for chronic hypertension, **2.16** for ischaemic heart disease and **1.81** for stroke.[8] Quoting a single "doubling" understates the hypertension risk and overstates the stroke risk.

KEY POINTS

1. **Six categories:** chronic hypertension (before 20 weeks), gestational hypertension (after 20 weeks, no proteinuria), pre-eclampsia (with proteinuria or organ dysfunction), pre-eclampsia superimposed on chronic hypertension (new proteinuria or organ dysfunction after 20 weeks in a woman whose pressure was already raised — the one most often missed), eclampsia (seizures), and HELLP. Pre-eclampsia is a placental multi-system disorder; delivery is the only cure.
2. **CHAP changed practice:** treat mild chronic hypertension to **below 140/90**, not the old ≥160/105 threshold — reducing severe pre-eclampsia, preterm birth before 35 weeks, abruption and fetal or neonatal death (30.2% vs 37.0%, RR 0.82), **without harming fetal growth**.
3. **Use labetalol or extended-release nifedipine** for that target. NICE aims at **135/85** and ISSHP at a diastolic of **85**; step the dose down if the diastolic reaches **80**, as CHIPS did.
4. **Safe:** methyldopa, labetalol, modified-release nifedipine. **Acutely:** intravenous labetalol, intravenous hydralazine, or immediate-release nifedipine by mouth — swallowed, never sublingually, and note that the immediate-release capsule's own label bars it for acute blood-pressure reduction. Treat 160/110 once it has persisted fifteen minutes, and give the first dose within thirty to sixty minutes. Contraindicated: ACE inhibitors, ARBs, direct renin inhibitors — throughout pregnancy, not only the second and third trimesters, though that is where the fetopathy is documented. Avoid atenolol (growth restriction), spironolactone (antiandrogenic to a male fetus) and diuretics (volume-contracted state).
5. **Pathophysiology:** deficient spiral-artery remodelling → placental ischaemia → anti-angiogenic factors (sFlt-1, soluble endoglin) → maternal endothelial dysfunction. The sFlt-1/PlGF ratio aids risk stratification.
6. **Prevention:** low-dose aspirin 75–150 mg — 150 mg at bedtime where it can be had — in high-risk women, **started from 12 weeks** and continued to delivery. Two routes qualify her: any one high-risk factor, or any two moderate ones; the second route is the one that gets missed. ACOG gives the window as 12 to 28 weeks, optimally before 16 — earlier is better, but 16 weeks is not a deadline, and a woman first seen at 18 weeks should still be started. Calcium 1.5 to 2.0 g of elemental calcium daily, in divided doses, where dietary intake is low — relevant in parts of India — and count the elemental calcium, not the weight of the salt.
7. **Severe disease:** magnesium sulphate (Magpie; superior to diazepam and phenytoin) with calcium gluconate as antidote; controlled BP reduction; delivery is definitive. **Postpartum:** pressure may peak in the first days after delivery, and NICE directs a measurement at least once between day 3 and day 5; labetalol, nifedipine and enalapril are breastfeeding-safe; a pre-eclampsia history carries a relative risk of **3.70 for later hypertension**, 2.16 for ischaemic heart disease and 1.81 for stroke, and warrants long-term surveillance. Do not compress it to a doubling — that understates the hypertension and overstates the stroke.

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CHAPTER 19 PART III · SPECIAL POPULATIONS

Hypertension in chronic kidney disease

A near-universal, bidirectional and mechanistically shifting problem — and a drug landscape transformed by SGLT2 inhibitors, finerenone, and the overturning of old dogmas.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The bidirectional cycle** — and why the dominant mechanism shifts from RAAS to volume as function declines.
2. **The KDIGO below-120 target** — why it is inseparable from how the pressure is measured, and why it is contested.
3. **The expected creatinine rise** — up to 30%, stabilising, and why stopping the drug is the error.
4. **CLICK** — the trial that overturned the rule against thiazides below an eGFR of 30.
5. **SGLT2 inhibitors** — CREDENCE, DAPA-CKD and EMPA-KIDNEY, and why diabetes status no longer decides.
6. **Finerenone and potassium** — the residual mineralocorticoid injury, and what keeps the regimen possible.
7. **Dialysis and transplant hypertension** — volume before drugs, and the calcineurin interaction.

19.1 A near-universal, bidirectional relationship

Hypertension is present in the great majority of patients with chronic kidney disease, and its prevalence rises steadily as kidney function falls, approaching universality in stage 4–5 disease and in patients on dialysis. The two conditions are locked in a bidirectional relationship in which each causes and worsens the other.

For the non-nephrologist

In stage 3 CKD the risk of **dying from cardiovascular disease far exceeds** the risk of ever reaching end-stage failure. BP control here is a cardiovascular intervention at least as much as a renal one.

TABLE 19.1 — THE SELF-REINFORCING CYCLE

DIRECTION	MECHANISM
Hypertension → kidney	The elevated systemic pressure is transmitted to the glomerular capillaries, producing glomerular hypertension, hyperfiltration and progressive glomerulosclerosis.
Kidney → hypertension	Four mechanisms operating together: impaired pressure–natriuresis with sodium and volume retention (V1·Ch5); RAAS activation (V1·Ch3); sympathetic overactivation driven by afferent signals from the diseased kidney (V1·Ch4); and increased endothelin activity (V1·Ch6).[5]

An important organising insight is that the dominant mechanism shifts as the disease progresses. In earlier CKD the renin–angiotensin and sympathetic mechanisms are relatively more prominent, and RAAS blockade is correspondingly central. As kidney function declines and the capacity to excrete sodium falls, the disease becomes progressively more volume-dependent and salt-sensitive, and diuretics and sodium restriction become decisive. Recognising where a patient sits along this shift is the key to choosing the right drug.

The shift

Early CKD: RAAS and sympathetic. Late CKD: **volume and salt**. The drug follows the stage.

19.2 Blood pressure targets: the 2021 KDIGO target and its controversy

The 2021 KDIGO guideline recommended a target systolic pressure of less than 120 mmHg for most adults with non-dialysis chronic kidney disease — provided the pressure is measured by the standardised technique used in the trials: rested, unobserved, correctly performed, not a routine clinic reading.[4]

<120

KDIGO 2021 — with a condition

The target is **inseparable from the measurement method**. Applying it to an ordinary clinic reading risks over-treatment, hypotension and falls.

TABLE 19.2 — TARGETS, AND THE QUALIFICATIONS THAT TRAVEL WITH THEM

SOURCE	TARGET	QUALIFICATION
KDIGO 2021 NON-DIALYSIS CKD	Systolic **below 120**	Standardised measurement only. KDIGO states it is potentially hazardous to apply this to non-standardised readings.[4] Derived largely from the SPRINT CKD subgroup; evidence that below 120 specifically slows progression is weak except perhaps with proteinuria — and SPRINT itself excluded heavy proteinuria, so that qualification rests on the older MDRD and AASK subgroups.[15] Few patients in ordinary practice reach it; no published achievement rate was found to put a figure on that.
2023 ESH / 2024 ESC	120–129	Less aggressive. THE 120–129 BAND IS THE ESH AND ESC POSITION FOR HYPERTENSION IN GENERAL; NEITHER STATES A SEPARATE FIGURE FOR CHRONIC KIDNEY DISEASE.[10]
ACC/AHA	Below 130	Less aggressive.
Kidney transplant	Below **130/80**	More conservative than the native-kidney target.

KDIGO itself allows less intensive treatment for patients with very limited life expectancy or symptomatic postural hypotension. The practical synthesis is to pursue tight control, individualised for frailty, orthostatic symptoms and the degree of proteinuria — and, critically, to measure the blood pressure properly before applying any low target to it.

19.3 RAAS blockade: the cornerstone, and the expected fall in filtration

For the patient with chronic kidney disease and albuminuria, an ACE inhibitor or ARB is the cornerstone of therapy, because these drugs provide renoprotection beyond their blood-pressure effect. They preferentially dilate the efferent glomerular arteriole (V1·Ch3), reducing intraglomerular pressure and thereby the glomerular hypertension and hyperfiltration that drive progressive sclerosis. The landmark trials are RENAAL and IDNT (ARBs in diabetic nephropathy) and AASK and REIN (ACE inhibitors in non-diabetic disease).[9,16]

Stopping a renoprotective drug because of the expected creatinine rise removes the most protective agent from precisely the patient who needs it most. KDIGO is explicit on two further points that are as often got wrong: the drug is **continued as the eGFR falls below 30**, not stopped at that line; and the reasons to reduce or stop it are **symptomatic hypotension** and **hyperkalaemia that cannot be controlled**, not the creatinine number alone.[8]

TABLE 19.3 — THE CREATININE RISE: WHAT TO DO

OBSERVATION	INTERPRETATION	ACTION
Rise up to 30% STABILISING WITHIN 2–4 WEEKS	Expected and acceptable. It reflects the very haemodynamic change that confers the long-term renoprotection.	**Continue the drug.** Monitor creatinine and expect it to plateau.
Rise greater than 30% OR NOT STABILISING	Warrants investigation.	Investigate — chiefly for **bilateral renal artery stenosis** — and consider withdrawal.

19.4 Diuretics, and the overturning of the eGFR-30 rule

Because chronic kidney disease is a volume-expanded, sodium-retentive state, a diuretic is almost always necessary, and dietary sodium restriction is a powerful co-intervention. For many years the teaching was categorical: thiazide-type diuretics lose efficacy once the eGFR falls below about 30, and must be replaced by loop diuretics. This dogma has been overturned.

Two firm cautions

Monitor **potassium** — reduced aldosterone activity and limited excretory capacity predispose to hyperkalaemia. And **do not combine an ACE inhibitor with an ARB for blood pressure — the licensed exception is an ARB added to an ACE inhibitor in heart failure, under specialist supervision**: ONTARGET showed dual blockade increases acute kidney injury and hyperkalaemia without added benefit.[11,12]

11.0 mmHg — CLICK, stage 4 CKD

24-hour systolic reduction with chlorthalidone versus 0.5 mmHg with placebo, in patients already on a mean of 3.4 drugs.[1]

TABLE 19.4 — CLICK: THIAZIDES DO WORK IN ADVANCED CKD

	DETAIL
Design	Agarwal and colleagues, *New England Journal of Medicine* 2021. 160 patients with **stage 4 CKD** (mean eGFR 23.2) and poorly controlled hypertension despite a mean of 3.4 antihypertensive drugs, randomised to chlorthalidone (from 12.5 mg daily) or placebo.
Result	24-hour systolic reduction of **11.0 mmHg** versus 0.5 mmHg with placebo over 12 weeks, together with a reduction in albuminuria.[1]
Consequence	Chlorthalidone is now a rational agent for resistant hypertension **even at low eGFR** — alongside, not necessarily instead of, a loop diuretic used for volume and oedema control.
Trade-off	A higher rate of electrolyte disturbance and reversible falls in eGFR. Monitor potassium, sodium and renal function.

19.5 SGLT2 inhibitors: the transformation of CKD care

The most important change in the management of chronic kidney disease in a generation is the arrival of the SGLT2 inhibitors as renoprotective and blood-pressure-lowering agents in both diabetic and non-diabetic disease. By blocking sodium–glucose co-transport in the proximal tubule they increase distal sodium delivery, restore the tubuloglomerular feedback that reduces

intraglomerular pressure, and produce an osmotic and natriuretic diuresis. The blood-pressure effect is modest — of the order of 3–4 mmHg systolic — but the renal and cardiovascular protection is substantial and largely independent of it.

A practical bonus

They **reduce hyperkalaemia**, which helps keep patients on their renoprotective RAAS blockade.

TABLE 19.5 — THE SGLT2 INHIBITOR TRIALS IN KIDNEY DISEASE

TRIAL	DRUG AND POPULATION	RESULT
CREDENCE	Canagliflozin, diabetic proteinuric CKD.	Primary renal outcome reduced by about **30%**.
DAPA-CKD	Dapagliflozin. Extended benefit to **non-diabetic as well as diabetic** CKD with UACR ≥ 200 mg/g.	Composite of sustained 50% eGFR decline, end-stage kidney disease, or renal or cardiovascular death reduced by about **40%**.
EMPA-KIDNEY 2023	Empagliflozin. Broadened further — including lower albuminuria and a wide range of causes.	CKD progression or cardiovascular death reduced by about **28%**.[13]

SGLT2 inhibitors are now recommended in chronic kidney disease **regardless of diabetes status** — and the guideline says who. KDIGO 2024 recommends one for type 2 diabetes with CKD at an **eGFR of 20 or above**, and for CKD of any cause at an eGFR of 20 or above with an **ACR of 200 mg/g or more**, or with heart failure at any level of albuminuria; it suggests one at an eGFR of 20 to 45 with a lower ACR.[8] The dapagliflozin label does not recommend initiation below an eGFR of 25, nor the drug at all for CKD in polycystic kidney disease or in patients on, or recently on, immunosuppression for kidney disease.[18] Once started, the drug is continued as the eGFR falls. Expect a small early fall in filtration that settles within about two weeks — it is not injury and not a reason to stop — and hold the drug during any dehydrating illness.[18]

19.6 Finerenone: the non-steroidal mineralocorticoid antagonist

Aldosterone drives inflammation and fibrosis in the kidney and heart through the mineralocorticoid receptor, and this residual injury continues even in patients already on RAAS blockade. Finerenone, a non-steroidal mineralocorticoid receptor antagonist, blocks this pathway without the anti-androgenic effects of spironolactone. It still raises potassium — that remains its principal labelled hazard, and there is no head-to-head trial against spironolactone to say it does so less.[17]

Added, not substituted

Finerenone goes **on top of** an ACE inhibitor or ARB, never instead of one — in its trials virtually every patient was already on one at the maximum tolerated dose. The label requires potassium and eGFR before starting, bars initiation above **5.0 mEq/L**, and has the drug withheld above **5.5 mEq/L**.[17]

TABLE 19.6 — THE FINERENONE EVIDENCE

TRIAL	FINDING
FIDELIO-DKD	Reduced **kidney disease progression** in CKD with type 2 diabetes.[3]
FIGARO-DKD	Reduced **cardiovascular events** in the same population.[14]
FIDELITY PRE-SPECIFIED POOLED ANALYSIS	Over 13,000 patients — **confirmed both benefits**.[2]

Its trial evidence base is chiefly in diabetic kidney disease, though the label now also carries a heart-failure indication at an ejection fraction of 40% or above.[17] Its role in non-diabetic CKD, and its combination with SGLT2 inhibitors — which mitigate its hyperkalaemia risk and appear to add to its anti-albuminuric effect — are active areas of study.[7]

19.7 Potassium management — what makes the regimen possible

The recurring obstacle to optimal therapy in CKD is hyperkalaemia, because the most renoprotective drug classes all raise potassium in a kidney already limited in its capacity to excrete it. The modern approach does not accept hyperkalaemia as a reason to abandon renoprotection but manages it directly.

Where CKD advice diverges

The general hypertensive is told to eat more potassium (V1·Ch12). The CKD patient is told the opposite. Do not carry one rule into the other clinic.

TABLE 19.7 — KEEPING THE RENOPROTECTIVE DRUGS ON BOARD

MEASURE	HOW IT HELPS
Dietary potassium restriction	A point where CKD advice **deliberately diverges** from the potassium-rich guidance given to the general hypertensive population.
SGLT2 inhibitors	Lower potassium — a reason to co-prescribe beyond their renal benefit.
Potassium binders PATIROMER, SODIUM ZIRCONIUM CYCLOSILICATE	Control serum potassium and thereby **allow RAAS blockade and mineralocorticoid antagonism to be continued** in patients who would otherwise have to stop them.

19.8 Resistant hypertension in CKD, and the newer options

Resistant hypertension is common in CKD. Throughout, the correction of volume overload and the confirmation of adherence remain the first steps before any agent is added.

TABLE 19.8 — OPTIONS IN RESISTANT CKD HYPERTENSION

OPTION	PLACE AND CAUTION
Mineralocorticoid antagonist	Spironolactone, or finerenone in diabetic disease — often the most effective added agent, but spironolactone carries a real hyperkalaemia risk. The label sets no eGFR floor: between 30 and 50 it directs a reduced start of 25 mg on alternate days, no start above a potassium of 5.0, and a potassium check within one week of starting or increasing.[19] Practice, following ESH 2023, makes it the preferred fourth drug at an eGFR of 30 or above with a normal potassium — while warning that it is not the default below 45, because PATHWAY-2 excluded that group — and below 30 prefers chlorthalidone as the addition, with spironolactone only under a potassium plan or a binder.[10,20]
Chlorthalidone	On the CLICK evidence, an option **even in advanced disease**.
Aprocitentan DUAL ENDOTHELIN RECEPTOR ANTAGONIST, APPROVED 2024	Reported in PRECISION to be particularly effective in **advanced CKD** and to reduce proteinuria (V1·Ch6). A genuinely new option here, with **fluid retention** as the main caution.
Renal denervation	An adjunctive option for selected patients with genuine resistant hypertension, after shared decision-making (V1·Ch4).

19.9 Dialysis hypertension

In patients on haemodialysis, hypertension is driven predominantly by volume overload, and its most effective treatment is achievement of the correct dry weight — through adequate fluid removal, dietary sodium and fluid restriction, and limitation of interdialytic weight gain.

When drugs are needed, agents not removed by dialysis and dosed around the dialysis schedule are preferred, and the timing must account for the blood-pressure fall during fluid removal. Blood pressure is best assessed by home or interdialytic readings rather than the peridialytic readings taken in the unit, which correlate poorly with the true ambulatory burden.[6]

A common error

Reaching for antihypertensive drugs in a patient who is simply fluid-overloaded. Many dialysis patients can be controlled by volume management alone.

19.10 Transplant hypertension

Hypertension is very common after kidney transplantation, driven by the calcineurin inhibitors ciclosporin and tacrolimus — which cause vasoconstriction and sodium retention, ciclosporin more so than tacrolimus — by corticosteroids, and by the function of the transplanted and any remaining native kidneys.

Calcium channel blockers are often preferred because they directly counteract the calcineurin-inhibitor–induced vasoconstriction. The target is below 130/80 mmHg.

An interaction to manage

Diltiazem and verapamil inhibit CYP3A4 metabolism of the calcineurin inhibitors and **raise their levels** — sometimes exploited deliberately with drug-level monitoring, otherwise avoided by using amlodipine.

KEY POINTS

1 **Hypertension approaches universality in advanced CKD**, and the relationship is bidirectional — glomerular hypertension and sclerosis one way; volume retention, RAAS, afferent-nerve sympathetic activation and endothelin the other.

2 **In stage 3 CKD, cardiovascular death risk exceeds the risk of ever reaching end-stage failure**, so BP control is as much a cardiovascular as a renal intervention. The dominant mechanism shifts from RAAS and sympathetic early to volume-dependent and salt-sensitive late.

3 **KDIGO 2021 targets systolic below 120 — but only by standardised measurement**, and it is hazardous to apply to routine clinic readings. Contested: it rests largely on one trial, the evidence that below 120 specifically slows kidney disease is weak except perhaps with proteinuria, and few patients in ordinary practice reach it. Transplant target is below 130/80.[8]

4 **RAAS blockade is the cornerstone with albuminuria** (RENAAL, IDNT, AASK, REIN). A creatinine rise **up to 30% that stabilises within 2–4 weeks of starting or increasing the dose is expected — do not stop the drug**. Only a greater or non-stabilising rise warrants investigation for bilateral renal artery stenosis. Continue it as the eGFR falls **below 30**; reduce or stop only for symptomatic hypotension or uncontrolled hyperkalaemia.[8] Do not combine ACEi and ARB for blood pressure (ONTARGET) — the only licensed exception is heart failure, under specialist supervision.

5 **The eGFR-30 rule for thiazides is overturned.** CLICK: chlorthalidone 12.5 mg in stage 4 CKD cut 24-hour systolic by 11 mmHg and lowered albuminuria — a rational add-on even in advanced disease, with electrolyte and renal monitoring.[1]

6 **SGLT2 inhibitors have transformed CKD care regardless of diabetes status:** CREDENCE ~30%, DAPA-CKD ~40%, EMPA-KIDNEY ~28%. Modest BP effect, large renoprotection — and they reduce hyperkalaemia, helping keep patients on RAAS blockade. **Finerenone** adds kidney and cardiovascular benefit in diabetic CKD (FIDELIO, FIGARO, FIDELITY).

7 **Hyperkalaemia is the barrier, not a reason to abandon therapy** — dietary restriction (CKD advice diverges from the general population), SGLT2 inhibitors, and binders. **Dialysis** hypertension is volume-driven: achieve dry weight before adding drugs. **Transplant** hypertension is calcineurin-driven: prefer amlodipine, and mind the diltiazem and verapamil interaction.

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CHAPTER 20 PART III · SPECIAL POPULATIONS

Hypertension in diabetes mellitus

The dangerous synergy, the targets, mandatory RAAS blockade, and the modern agents — SGLT2 inhibitors, incretin therapies and finerenone — that treat blood pressure and the disease together.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why the combination is more than additive** — the same target organs, damaged synergistically.
2. **The target** — below 130/80, lower still where risk is high, and what ACCORD-BP and BPROAD each showed.
3. **Mandatory RAAS blockade** — why an albumin-to-creatinine ratio of 30 mg/g settles the class in a hypertensive diabetic, and where the obligation stops.
4. **SGLT2 inhibitors** — blood pressure, glucose, heart and kidney from a single mechanism.
5. **Incretin agents** — what semaglutide and tirzepatide do to the cuff, and the heart-rate rise to expect.
6. **Finerenone** — residual mineralocorticoid injury on top of RAAS blockade.
7. **The hypoglycaemia problem with beta-blockers** — and which drugs to favour instead.

20.1 The scale and danger of the combination

Hypertension is present in 70–80% of patients with type 2 diabetes, the two sharing the common soil of insulin resistance, central obesity, sympathetic overactivation and salt sensitivity (V1·Ch12, Ch14).

The combination is especially dangerous because the two conditions damage the same target organs synergistically: together they are the leading cause of end-stage kidney disease, they multiply the risk of myocardial infarction and stroke, they are a leading cause of blindness, and they damage the peripheral and autonomic nerves. Controlling blood pressure in a diabetic is at least as important as controlling glucose for preventing vascular complications — and in some analyses more so.

70–80%

of type 2 diabetics are hypertensive

Not a coincidence — a shared substrate of insulin resistance, central obesity, sympathetic drive and salt sensitivity.

20.2 Blood pressure targets

The target in diabetes has been debated, balancing the clear benefit of lowering pressure for stroke and kidney disease against the diminishing cardiac returns of very intensive control seen in some trials.

Worth saying plainly

For vascular complications, the cuff matters at least as much as the HbA1c.[14]

TABLE 20.1 — THE TARGET AND THE EVIDENCE BEHIND IT

	DETAIL
Current position	**Below 130/80** for most patients with diabetes, achieved without unacceptable side effects or pill burden[2,8] — and a **systolic below 120** where cardiovascular or kidney risk is high and the pressure can be got there safely. That is the position of the ADA Standards of Care 2026, taken on the strength of BPROAD (Bi and colleagues, *New England Journal of Medicine*, 2025): 12,821 patients with type 2 diabetes randomised to a systolic target below 120 had a 21% lower rate of major cardiovascular events than those targeted below 140 (HR 0.79, 95% CI 0.69–0.90), at the cost of more symptomatic hypotension and hyperkalaemia. Where health is poor or life expectancy limited, below 140/90 is enough.
ACCORD-BP THE HISTORY	An intensive target below 120 **did not** reduce the primary composite cardiovascular outcome — though it **did reduce stroke**. For a decade this was the reason not to go lower in diabetes; BPROAD, a far larger trial, is the reason the position moved.
Individualise for	**Orthostatic hypotension** — more common in diabetics because of autonomic neuropathy. A low diastolic in an older patient with isolated systolic hypertension is a reason to examine the patient for symptoms, not a floor that stops systolic lowering (V1·Ch17).

20.3 RAAS blockade: mandatory with albuminuria and hypertension

Once albuminuria is present — a urinary albumin-to-creatinine ratio of **30 mg/g or more**, the moderately increased category (A2, 30–299 mg/g) that used to be called microalbuminuria — an ACE inhibitor or ARB in the hypertensive diabetic is mandatory, not merely preferred, because it slows the progression of diabetic nephropathy by reducing intraglomerular pressure and proteinuria (V1·Ch19).[5,17] Where there is no albuminuria the class is not fixed: a dihydropyridine calcium channel blocker or a thiazide-like diuretic is an equally acceptable first choice.

The trials RENAAL and IDNT established this in overt nephropathy, and IRMA-2 at the moderately increased level. As elsewhere, the expected creatinine rise of up to 30% should not prompt discontinuation, potassium must be monitored, and ACE inhibitors and ARBs must not be combined (ONTARGET).[6,11]

20.4 SGLT2 inhibitors: four benefits in one drug

The SGLT2 inhibitors — empagliflozin, dapagliflozin, canagliflozin — are among the most valuable agents in the diabetic hypertensive because they act on blood pressure, glucose, heart failure and kidney disease simultaneously.

Whatever the pressure above threshold

In a hypertensive patient with diabetes, an albumin-to-creatinine ratio of **30 mg/g** settles the class: the blocker is obligatory, titrated to the highest tolerated dose, however modest the pressure — it marks the earliest stage of diabetic kidney disease. In a genuinely normotensive patient with albuminuria KDIGO makes it an option rather than a recommendation, and the trial evidence is thinner.[5,13] And in a woman who could become pregnant, neither drug is started without contraception and a plan — they are fetotoxic (V1·Ch18).

TABLE 20.2 — FOUR BENEFITS FROM ONE MECHANISM

BENEFIT	MAGNITUDE AND EVIDENCE
Blood pressure	Osmotic and natriuretic diuresis from blocking proximal-tubular sodium–glucose co-transport lowers systolic pressure by roughly **3–4 mmHg** — a volume-reducing mechanism well matched to the salt-sensitive physiology of the diabetic patient.[3]
Glucose	Lowered by the same transport block.
Heart	Large reductions in cardiovascular death and heart-failure hospitalisation — EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI.[15,16]
Kidney	Slowed disease progression — CREDENCE, DAPA-CKD, EMPA-KIDNEY (V1·Ch19).
And one more	They reduce hyperkalaemia, helping to maintain RAAS blockade.[10]

20.5 GLP-1 receptor agonists and tirzepatide

The GLP-1 receptor agonists — liraglutide, semaglutide, dulaglutide — lower blood pressure modestly alongside substantial glucose-lowering and weight loss, and reduce major adverse cardiovascular events.

Expect it

A modest rise in heart rate is an expected class effect of the incretin agents.

TABLE 20.3 — BLOOD-PRESSURE EFFECT OF THE INCRETIN AGENTS

AGENT	SYSTOLIC REDUCTION	NOTE
GLP-1 receptor agonists LIRAGLUTIDE, SEMAGLUTIDE, DULAGLUTIDE	~2–3 mmHg	Semaglutide reduced cardiovascular events even in obese patients **without** diabetes — SELECT.[7]
Tirzepatide DUAL GIP/GLP-1 RECEPTOR AGONIST	About **5–7 mmHg** in type 2 diabetes (SURPASS)	Pooled systolic reductions of 4.8, 5.8 and 7.0 mmHg at 5, 10 and 15 mg.[18] Considerably more in obesity (V1·Ch21). Greater weight loss than the GLP-1 agonists.

These agents lower pressure through both weight-mediated and possibly direct mechanisms, and are valuable additions in the obese diabetic hypertensive. Before prescribing either class, ask about medullary thyroid carcinoma in the patient or the family, and about multiple endocrine neoplasia type 2: the tirzepatide label carries a boxed warning on thyroid C-cell tumours and makes both a contraindication, and the GLP-1 receptor agonists carry the same class warning.[19] The point matters in this book, because 30 to 40% of phaeochromocytomas are hereditary and MEN 2 is among the syndromes (V1·Ch34). And warn the patient that as the weight falls the existing antihypertensives become too strong: on the tirzepatide label hypotension was seen in 2.2% of patients on concomitant antihypertensive therapy against 1.2% of those not on it, so review the doses at each visit rather than at the end.[19]

20.6 Finerenone, and the drugs to favour and avoid

Finerenone, a non-steroidal mineralocorticoid receptor antagonist, reduces kidney-disease progression (FIDELIO-DKD) and cardiovascular events (FIGARO-DKD; pooled FIDELITY) in diabetic kidney disease, added on top of RAAS blockade with potassium monitoring (V1·Ch19).[1,4,12]

The hypoglycaemia problem

Non-vasodilatory beta-blockers **mask the adrenergic warning symptoms** — tremor, palpitations — leaving sweating as the only warning left.

TABLE 20.4 — FAVOUR AND AVOID IN THE DIABETIC HYPERTENSIVE

AGENT	VERDICT	REASON
Indapamide	Preferred over hydrochlorothiazide	Metabolic neutrality and vascular effects.
Atenolol, metoprolol	Avoid as primary agents	Worsen insulin resistance and lipids, and — importantly — **mask the adrenergic warning symptoms of hypoglycaemia** (tremor, palpitations), leaving sweating as the only remaining warning.
Nebivolol, carvedilol	Preferred if beta-blockade is needed	Vasodilatory and metabolically kinder.

KEY POINTS

1. **Hypertension affects 70–80% of type 2 diabetics**, sharing insulin resistance, obesity, sympathetic overactivation and salt sensitivity — and the two synergistically damage kidney, arteries, retina and nerves.[9]
2. **BP control is at least as important as glucose control** for preventing vascular complications, and in some analyses more so.
3. **Target below 130/80** for most diabetics, and a systolic below 120 where cardiovascular or kidney risk is high and it can be reached safely — the current ADA position, on BPROAD, which found fewer major cardiovascular events at the lower target than at a target below 140 — bought with more hypotension and hyperkalaemia. ACCORD-BP, the older and smaller trial, had not shown it: an intensive target below 120 did not reduce the primary composite but did reduce stroke. Individualise for autonomic-neuropathy orthostasis; a low diastolic in the elderly is a reason to examine, not a floor that overrides the systolic.
4. **In the hypertensive diabetic, RAAS blockade is mandatory once the albumin-to-creatinine ratio reaches 30 mg/g — the A2 band once called microalbuminuria — however modest the pressure** (RENAAL, IDNT, IRMA-2); in a normotensive patient with albuminuria it is an option, not an obligation, and in a woman who could become pregnant it waits for contraception and a plan. Without albuminuria, a dihydropyridine calcium blocker or a thiazide-like diuretic serves equally well.[17] The expected ≤30% creatinine rise is acceptable; monitor potassium; do not combine ACEi and ARB for blood pressure.
5. **SGLT2 inhibitors give four benefits in one drug:** about 3–4 mmHg systolic via natriuresis, glucose control, heart-failure protection and slowed kidney progression (EMPA-REG, CANVAS, CREDENCE, DAPA-CKD, EMPA-KIDNEY) — and they lower hyperkalaemia risk.[3,10]
6. **Incretin agents lower pressure with weight:** GLP-1 agonists ~2–3 mmHg (semaglutide reduced events even without diabetes — SELECT); tirzepatide about 5–7 mmHg in diabetes and more in obesity. Expect a small heart-rate rise.
7. **Finerenone** reduces kidney and cardiovascular events on top of RAAS blockade (FIDELIO, FIGARO).[4,12] Prefer **indapamide over hydrochlorothiazide**; avoid atenolol and metoprolol — they worsen insulin resistance and mask the adrenergic warning signs of hypoglycaemia.

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CHAPTER 21 PART III · SPECIAL POPULATIONS

Hypertension in obesity

The multiple mechanisms, the power of weight loss, and the new pharmacological weight-loss agents that lower blood pressure like a drug.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Five mechanisms** — adipose RAAS, leptin, insulin resistance, sleep apnoea, and the kidneys under physical compression.
2. **Selective leptin resistance** — why the appetite effect is lost while the sympathetic one persists.
3. **Weight loss, quantified** — about 1 mmHg systolic per kilogram[11], and why that makes it a treatment rather than advice.
4. **South Asian waist thresholds** — 90 and 80 cm, and the risk they reflect.
5. **Drug selection by mechanism** — and the beta-blockers that make the problem worse.
6. **The incretin agents** — tirzepatide lowering systolic pressure by up to 10.6 mmHg in SURMOUNT-1.
7. **Bariatric surgery** — durable remission, and why the pressure falls before the weight does.

21.1 The mechanisms

Obesity is among the most powerful and most modifiable causes of hypertension, and the relationship is mechanistic and multifactorial.

Selective leptin resistance

Leptin stops suppressing appetite but **keeps driving sympathetic outflow**. The useful effect is lost; the harmful one persists.[1]

TABLE 21.1 — FIVE MECHANISMS, ONE CAUSE

MECHANISM	HOW IT RAISES PRESSURE
Adipose renin–angiotensin system	Adipose tissue is an active endocrine organ with its own RAAS, so a greater fat mass generates **more local angiotensin II**.[5]
Leptin	Secreted in proportion to fat mass; activates hypothalamic sympathetic pathways and raises sympathetic outflow — **preserved even when the appetite-suppressing action is lost** through selective resistance (V1·Ch14).[12]
Insulin resistance	Promotes renal sodium retention and reduces endothelial nitric-oxide restraint on vascular tone.[4]
Obstructive sleep apnoea	Drives sympathetic activation through chemoreflex sensitisation (V1·Ch2, Ch24).[15]
Renal compression	Visceral and retroperitoneal fat physically compresses the kidneys, raising intrarenal pressure and impairing pressure–natriuresis — giving the salt sensitivity of obesity a **genuine mechanical component** alongside the hormonal and neural ones.[3,6]

21.2 Weight loss as the primary intervention

Because obesity causes hypertension through several mechanisms all traceable to the excess adipose tissue, weight loss is the single most effective intervention and addresses them all at once.[7]

Weight loss should therefore be presented as a specific, quantified treatment, not vague advice.

1 kg

= about 1 mmHg systolic

−1.05 mmHg systolic per kilogram (95% CI −1.43 to −0.66) across randomised trials[11]. So 5–10 kg is worth 5–10 mmHg — equivalent to adding a drug — while also improving glucose, lipids and sleep apnoea.

TABLE 21.2 — WHAT TO MEASURE

MEASURE	THRESHOLD	WHY
Waist circumference	**South Asians: 90 cm men, 80 cm women**	Reflects metabolically active visceral fat, and is the most useful measure to track. South Asian thresholds are **lower**, reflecting greater cardiometabolic risk at any given adiposity.[16]

21.3 Drug selection

The guideline sets the pathway. Within it, the mechanisms below explain why some permitted options suit the obese phenotype better than others — and, more often, what to address alongside the prescription.

TABLE 21.3 — HOW THE OBESE PHENOTYPE BEHAVES ON EACH GUIDELINE-PERMITTED CLASS INTERPRETATION

AGENT	VERDICT	REASON
ACE inhibitors, ARBs	Rational first-line	The adipose renin–angiotensin system and insulin resistance both implicate angiotensin II — with the added benefit of **improving insulin sensitivity**.
Thiazide-type diuretics	Effective	Obesity is a salt-sensitive, volume-expanded state. **Indapamide preferred** for metabolic neutrality.
Calcium channel blockers	Effective and neutral	Combine well.
Atenolol, metoprolol	Caution	Worsen insulin resistance and dyslipidaemia, and promote weight gain. Prefer **nebivolol or carvedilol** where beta-blockade is needed.[14]
Mineralocorticoid antagonists	Particularly effective	In the resistant hypertension that accompanies obesity and sleep apnoea. Treating coexisting apnoea is itself an important part of blood-pressure control.

21.4 The incretin weight-loss agents

A major recent development is the arrival of highly effective pharmacological weight-loss agents that lower blood pressure substantially as a consequence.

10.6

mmHg — tirzepatide 10 mg

SURMOUNT-1 ambulatory substudy, over 36 weeks, reducing both daytime and night-time pressure by an amount that rivals many antihypertensive drugs.

TABLE 21.4 — THE INCRETIN AGENTS IN OBESITY

AGENT	WEIGHT LOSS	BLOOD PRESSURE
Semaglutide GLP-1 RECEPTOR AGONIST	Significant — the STEP programme.[17]	Reduced cardiovascular events in obese patients **without diabetes** — SELECT.[9]
Tirzepatide DUAL GIP/GLP-1 RECEPTOR AGONIST	**15–21% of body weight** — SURMOUNT.[8]	SURMOUNT-1 ambulatory substudy over 36 weeks: systolic reduced by about **7.4 mmHg** (5 mg), **10.6 mmHg** (10 mg) and **8.0 mmHg** (15 mg), day and night.[2]

These reductions are driven substantially by weight loss but may include weight-independent effects; a modest rise in heart rate is an expected class effect. They represent a genuinely new option for the obese hypertensive in whom weight is the dominant driver. Before prescribing either class, ask about medullary thyroid carcinoma in the patient or the family, and about multiple endocrine neoplasia type 2: the tirzepatide label carries a boxed warning on thyroid C-cell tumours and makes both a contraindication, and the GLP-1 receptor agonists carry the same class warning.[18] The point matters in this book, because 30 to 40% of phaeochromocytomas are hereditary and MEN 2 is among the syndromes (V1·Ch34). And warn the patient that as the weight falls the existing antihypertensives become too strong: on the tirzepatide label hypotension was seen in 2.2% of patients on concomitant antihypertensive therapy against 1.2% of those not on it, so review the doses at each visit rather than at the end.[18]

21.5 Bariatric surgery

For severe obesity in which lifestyle and pharmacological weight loss have failed, bariatric surgery — sleeve gastrectomy or Roux-en-Y gastric bypass — produces substantial and durable weight loss with profound effects on blood pressure and the whole metabolic syndrome. Many patients achieve remission or substantial improvement of hypertension and are able to reduce or stop antihypertensive drugs.[13]

Bariatric surgery also produces remission of type 2 diabetes in many patients and improves or resolves obstructive sleep apnoea, so its benefit spans the whole cluster of associated conditions. It should be considered in patients meeting the criteria for severe obesity, particularly when hypertension, diabetes and sleep apnoea coexist and have proved difficult to control — and the thresholds are lower than most physicians remember, and lower again for

Indian patients. The 2022 ASMBS/IFSO statement recommends surgery at a **BMI of 35 or above** whatever the comorbidity, and says it should be considered from **30** with metabolic disease; for Asian populations it adjusts both, so that a BMI of 25 already indicates clinical obesity and surgery should be offered from **27.5.**[19] The waist thresholds earlier in this chapter and these BMI thresholds move in the same direction, for the same reason.

Before the weight goes

The blood-pressure benefit **begins early**, before much weight is lost — reflecting rapid improvement in the hormonal and neural drivers.

KEY POINTS

1. **Obesity causes hypertension through five converging mechanisms:** the adipose renin–angiotensin system, leptin-driven sympathetic activation (persisting despite selective leptin resistance), insulin resistance, obstructive sleep apnoea, and physical renal compression by visceral fat impairing pressure–natriuresis.
2. **Weight loss is the single most effective intervention** and addresses all five at once — about **1 mmHg systolic per kilogram**, so 5–10 kg equals a drug, plus improved glucose, lipids and apnoea.[7,11]
3. **Track waist circumference, not BMI alone** — South Asian thresholds are 90 cm in men and 80 cm in women, reflecting greater cardiometabolic risk at any given adiposity.[10]
4. **Drug selection:** ACE inhibitors and ARBs first-line (adipose RAAS, improved insulin sensitivity); thiazide-type diuretics with indapamide preferred; calcium channel blockers neutral and combine well.
5. Avoid atenolol and metoprolol — they worsen insulin resistance and promote weight gain. Prefer nebivolol or carvedilol. Treat coexisting apnoea; mineralocorticoid antagonists are effective in obesity-related resistant hypertension.
6. **The incretin agents lower pressure substantially:** semaglutide (STEP weight loss; SELECT cardiovascular benefit without diabetes) and **tirzepatide** (15–21% weight loss; systolic 7.4 to 10.6 mmHg lower in the SURMOUNT-1 ambulatory substudy, day and night). Expect a small heart-rate rise.[9]
7. **Bariatric surgery** produces durable weight loss with remission or major improvement of hypertension, diabetes and apnoea. The blood-pressure benefit begins **before much weight is lost**, and is sustained.

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VOLUME ONE · PART IV

Contributing factors

Sodium, alcohol, tobacco, sleep, work and the endocrine causes worth looking for — the drivers that sit behind the number.

Hypertension: A Phenotype-Based Approach

Volume 1 · Why Is This Patient Hypertensive?

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MBBS · AFIH · Occupational Health Physician

CHAPTER 22 PART IV · CONTRIBUTING FACTORS

Dietary sodium and the salt–hypertension link

The evidence, the mechanisms, the hidden sodium of the Indian diet, potassium, and practical counselling.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The evidence** — INTERSALT, DASH-Sodium and the dose-response, and what PURE did and did not establish.
2. **Three mechanisms** — volume, immunity and the vessel wall — and why restriction works across phenotypes.
3. **Where the sodium hides** — above 80% is salt added in the kitchen and at the table, and what carries the rest.
4. **The 24-hour urine sodium** — why what the patient reports is always less than what the patient eats, and what to do about it.
5. **DASH in Indian terms** — dal, millets and curd rather than an imported diet sheet.
6. **Potassium as the counter** — and the patients who must not have more of it.
7. **Salt substitution** — SSaSS, the 2024 ESC position, and the population case.

22.1 The evidence

The relationship between dietary sodium and blood pressure is among the most thoroughly investigated in medicine, and the weight of evidence is causal.

5

mmHg per 4.6 g of salt

Systolic reduction in hypertensives — He and MacGregor 2002, 17 trials. A 6 g reduction predicts about 7 mmHg. The WHO target is under 5 g of salt daily.[5]

TABLE 22.1 — THE EVIDENCE BASE

STUDY	DESIGN	FINDING
INTERSALT	Over 10,000 people across 52 population samples in 32 countries.[6]	Within individuals, sodium was associated with the **level** of blood pressure. Across the other 48 centres it was associated with the **rise of pressure with age**, but not with median pressure. The four isolated low-sodium populations had low pressures with **no age-related rise**.
DASH-Sodium	Controlled feeding trial.	Lowering sodium reduced pressure in a **dose-dependent** manner, greatest in hypertensives.[11]
Meta-analyses HE AND MACGREGOR	Pooled.	Dose–response: a median reduction of **4.6 g of salt daily** lowered pressure by **4.96/2.73 mmHg** in hypertensives across 17 trials; a 6 g reduction predicts **7.11/3.88 mmHg**.[5]
PURE	Observational.	Suggested a J-shaped relationship at the extremes, but **criticised on methodological grounds**. The mainstream consensus — WHO under 5 g salt daily — is that reducing the high intake typical of most populations lowers pressure and cardiovascular risk.[2,10]

22.2 The mechanisms, revisited

The mechanisms of V1·Ch12 are summarised here for counselling. Their multiplicity explains why sodium restriction is effective across phenotypes.

Three routes, one advice

Volume, immunity and the vessel wall. Restriction works across phenotypes because it acts on all three.

TABLE 22.2 — WHY RESTRICTION WORKS WHATEVER THE PHENOTYPE INTERPRETATION

MECHANISM	HOW IT OPERATES
Volume THE PRIMARY ONE	A sodium load that cannot be excreted at the current pressure expands extracellular fluid and, in the salt-sensitive kidney with an impaired pressure–natriuresis relationship, **drives the pressure up until the sodium can be excreted**.[3,12]
Immune	T-helper-17 activation and suppression of tubular nitric oxide (Wilck, *Nature* 2017) connects high sodium to renal retention through inflammation — **independent of volume**.[15]
Vascular	Direct stiffening of the endothelial glycocalyx and impairment of endothelial nitric oxide.

22.3 Hidden sodium in the Indian diet

Effective counselling requires knowing where the sodium actually comes from. In India the pattern is the opposite of the Western one: discretionary salt — what goes in during cooking and what is added at the table — supplies above **80%** of intake, 83.45% in the North and 87.71% in the South on 24-hour dietary recall, while processed and restaurant food, though rising fast in urban diets, still carries the smaller share.[17] The cooking pot is therefore where counselling has to start, with pickles, papad, namkeen, packaged snacks, biscuits and bread the next target.

What the patient reports

What the patient reports is always less than what the patient eats — no published figure for the size of that gap was found, so none is printed here. The **24-hour urine sodium** captures every source at once and is the only reliable measure — and a powerful motivator.

TABLE 22.3 — WHERE THE SODIUM ACTUALLY IS

SOURCE	SHARE	EXAMPLES
Table salt	**Part of the 83–88%**	The source most patients think of. On 24-hour dietary recall, table and cooking salt together supply **83.45%** of intake in North India and **87.71%** in the South.[17]
Salt added in cooking	**The rest of it**	The largest single controllable source in the Indian kitchen — and where counselling starts, before any food label.
Preserved and processed foods	**The smaller share, and rising fast**	Pickles, papad, chutneys, namkeen, packaged foods, instant noodles, biscuits and bread, and increasingly restaurant and fast food. Some are **surprisingly high despite not tasting salty** — bread, biscuits, breakfast cereals. Additives such as papad khar and baking soda add further sodium.

22.4 The DASH pattern and its Indian adaptation

The DASH eating pattern is the best-evidenced dietary intervention, having lowered systolic pressure by about 11 mmHg in hypertensives in the original trial. Its benefit derives from the combination of reduced sodium with increased potassium, magnesium, calcium and fibre.

Not a foreign prescription

Presented in familiar terms — dal, sabzi, roti, curd — DASH is far more likely to be adopted than as an imported diet sheet.

TABLE 22.4 — DASH IN INDIAN TERMS

INCREASE	REDUCE
Dals and pulses; generous vegetables and fruit; whole grains such as whole wheat, brown rice and **millets**; low-fat curd and buttermilk; nuts.	Pickles, papad, fried snacks and processed foods — the items carrying the hidden sodium. Also red meat and sugar.

22.5 Potassium as the counter

Dietary potassium opposes sodium (V1·Ch12): it promotes urinary sodium excretion and relaxes vascular smooth muscle. INTERSALT showed higher urinary potassium associated with lower pressure, and supplementation trials show a systolic reduction of about **3.11 mmHg** (1.91–4.31) and a diastolic reduction of 1.97 mmHg, across 33 trials and 2,609 participants.[14]

The dietary prescription is therefore not simply "reduce salt" but "reduce sodium and increase potassium-rich foods" — bananas, coconut water, tomatoes, green leafy vegetables and pulses such as rajma.[13]

22.6 Salt substitutes and the population perspective

Potassium-based salt substitutes reduce sodium and raise potassium simultaneously without changing taste greatly. The Salt Substitute and Stroke Study (SSaSS), a large randomised trial in rural China, showed that a potassium-enriched salt substitute reduced stroke, major cardiovascular events and death — hard-outcome evidence for salt substitution as a population intervention, with the same hyperkalaemia caveat.[9]

At the population level, reducing sodium in the food supply through reformulation and labelling is among the most cost-effective public-health interventions available — of particular importance in India, where measured intake runs at about **8–10 g of salt a day** — roughly twice the WHO limit, on 24-hour urine collections in Delhi and Haryana (8.6 g) and Andhra Pradesh (9.5 g), and about 8 g in the National NCD Monitoring Survey[7,16,18] — and the hypertension burden is large and rising.

The caution

Patients with CKD, or on ACE inhibitors, ARBs or mineralocorticoid antagonists, must **not** increase potassium substantially or use potassium salt substitutes without monitoring.

2024 ESC

Recommends sodium below 2 g a day and raising dietary potassium — by potassium-rich food or a potassium-based salt substitute — particularly where potassium intake is low. Not in advanced kidney disease, hyperkalaemia, or on potassium-retaining drugs.[8]

KEY POINTS

1 **The evidence is causal:** INTERSALT linked sodium to pressure within individuals and to its rise with age across populations; DASH-Sodium showed a dose-dependent fall greatest in hypertensives; meta-analyses give about 5 mmHg systolic for a 4.6 g salt reduction (He and MacGregor 2002). WHO target: under 5 g salt daily.

2 **Three mechanisms:** volume expansion via impaired pressure-natriuresis (primary), the salt-immune Th17 pathway (independent of volume), and direct vascular effects — which is why restriction works across phenotypes.

3 **Above 80% of Indian sodium intake is discretionary salt** — 83.45% in the North and 87.71% in the South, cooking and table salt together[17] — and processed food carries the smaller share: pickles, papad, namkeen, biscuits, bread and restaurant meals, some surprisingly high without tasting salty. Counsel the cooking pot first.

4 **What the patient reports is always less than what the patient eats**, and no published figure was found for the size of that gap. The 24-hour urine sodium captures every source, and spot-urine formulas do not substitute for it.[4]

5 **DASH lowered systolic pressure by about 11 mmHg** and adapts readily to Indian food — dals, vegetables, fruit, millets, curd and nuts — while cutting the pickles, papad and fried snacks that carry the hidden sodium.[1]

6 **Potassium counters sodium** — about **3.11 mmHg** systolic and 1.97 diastolic across 33 trials[14]: banana, coconut water, tomato, greens, rajma. **Avoid increased potassium and salt substitutes in CKD or on ACEi, ARB or MRA.**

7 **Salt substitutes reduced stroke, events and death (SSaSS)**, and the 2024 ESC guideline recommends raising dietary potassium where intake is low, by food or substitute. Population-level sodium reduction through reformulation and labelling is among the most cost-effective public-health measures available — especially in India.

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CHAPTER 23 PART IV · CONTRIBUTING FACTORS

Alcohol, smoking and caffeine

Three everyday exposures with three quite different relationships to blood pressure — and one that is routinely under-reported.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Alcohol, quantified** — about 1 mmHg per daily drink, and when it explains the whole diagnosis.
2. **Alcohol withdrawal hypertension** — a dangerous sympathetic surge that hospital admission can precipitate.
3. **Why a smoker\u2019s clinic reading misleads** — the transient pressor effect and what ambulatory monitoring reveals.
4. **Why cessation still matters most** — as a risk multiplier removed, not a pressure lowered.
5. **Caffeine and tolerance** — why habitual coffee rarely causes sustained hypertension.
6. **Energy drinks** — a distinct concern in the young, and a question worth asking.

23.1 Alcohol

Alcohol has a clear dose-dependent effect on blood pressure and is one of the most important — and most under-reported — modifiable contributors.[3,9] The relationship is roughly linear, and the best dose–response evidence finds no threshold: systolic pressure rises about 1.25 mmHg per 12 g of alcohol a day, measured from zero.[15] The observational finding that any intake counts and the trial finding that cutting down from below two drinks a day does not measurably lower pressure are both true[12]; the practical instruction is the 2024 ESC guideline's — keep intake below about 100 g of pure alcohol a week, roughly ten standard drinks, and less is better.

1 mmHg
per daily drink
From the first drink, not from the third. In a heavy drinker — more than four or five daily — the hypertension may be **largely explained by the alcohol**.

TABLE 23.1 — ALCOHOL AND BLOOD PRESSURE

	DETAIL
Dose–response	Roughly linear above 1–2 standard drinks daily; each additional daily drink raises systolic pressure by about **1 mmHg**. Heavy drinkers may have their hypertension largely explained by alcohol.[13]
Mechanisms	Sympathetic activation, increased cortisol, an effect on the renin–angiotensin system, increased intracellular calcium in vascular smooth muscle, and impaired baroreflex sensitivity.[6]
Reduction	Produces a dose-dependent fall **proportional to the reduction achieved**.[12] Frame it as a direct and effective treatment, expressed as a specific achievable target — below about 100 g of pure alcohol a week, roughly ten standard drinks, on the 2024 ESC figure — not an unrealistic demand for abstinence, unless the pattern indicates dependence requiring structured, supported withdrawal. Say the number; a target the patient cannot repeat is not a target.

Alcohol withdrawal hypertension is a clinically dangerous phenomenon. When a heavy drinker abruptly stops, the loss of alcohol's central depressant effect produces a sympathetic surge that can cause a marked, sometimes severe rise in blood pressure with tremor, sweating, tachycardia and, in severe cases, seizures and delirium tremens.[2]

Precipitated by admission

Hospital is where alcohol becomes unavailable. Recognising withdrawal prevents misattribution to primary hypertension and directs attention to managing the withdrawal.

23.2 Smoking and blood pressure

The relationship between smoking and blood pressure is subtler and often misunderstood. Each cigarette produces an acute transient rise lasting 15–30 minutes, mediated by nicotine-induced catecholamine release.[10]

Because of this transient effect, a regular smoker's clinic blood pressure may appear normal while their true ambulatory pressure through the smoking day is higher; ambulatory monitoring may therefore reveal hypertension the clinic readings miss.

The clinic lies

A smoker measured when they have not just smoked may read normal, while the true **ambulatory** pressure through the smoking day is higher.

The more important harm, however, is the profound cumulative damage smoking does to the vascular endothelium, accelerating atherosclerosis and arterial stiffening and multiplying the cardiovascular risk of any given blood pressure. A smoker with hypertension has far higher absolute risk than a non-smoker with the same pressure — so cessation is among the most important interventions in the hypertensive smoker, **not** because it substantially lowers the pressure, which it does only modestly, but because it removes a powerful independent risk multiplier.[1,7]

Ask about tobacco, not about cigarettes. In India the commoner exposure is smokeless — khaini, zarda, gutka, paan masala, mishri — and it is held in the mouth for hours rather than smoked in pulses, so a patient using it will answer no to “do you smoke?” and yes to “do you take tobacco in any form, including chewing?” Bidis are the other omission the narrower question produces. The pressor mechanism is the same nicotine-driven catecholamine release, the vascular harm is cumulative in the same way, and the cessation argument is the same.

23.3 Caffeine and energy drinks

Caffeine acutely raises blood pressure by antagonising adenosine receptors, and a single dose can raise systolic pressure by 3–8 mmHg for one to three hours in a non-habitual user.[4,8] Regular consumers, however, develop substantial

tolerance, so the chronic blood pressure of a habitual coffee or tea drinker is little affected by their usual intake.[14]

Still worth one rule

Avoid caffeine before a blood-pressure measurement, and stay alert to the occasional unusually sensitive patient.[11]

TABLE 23.2 — CAFFEINE VERSUS ENERGY DRINKS

	EFFECT	CLINICAL POSITION
Habitual coffee or tea	Acute 3–8 mmHg systolic rise in a **non-habitual** user, lasting 1–3 hours. Tolerance develops with regular use.	Not an important cause of sustained hypertension in most people. Avoid before measurement.
Energy drinks	High caffeine doses combined with taurine, sugar and other stimulants.	**A distinct and growing concern**, especially in young adults — associated with marked pressure rises, arrhythmias and, rarely, serious cardiovascular events, particularly in quantity, with alcohol, or during exertion. **Ask about them specifically** in young patients with hypertension or palpitations (V1·Ch16).[5]

KEY POINTS

1. **Alcohol is dose-dependent, with no threshold:** about 1 mmHg systolic per daily drink from the first, and heavy drinking can wholly explain a patient\u2019s hypertension. The target to say aloud is below about 100 g of pure alcohol a week \u2014 roughly ten standard drinks \u2014 and less is better. Mechanisms: sympathetic activation, cortisol, RAAS, vascular smooth-muscle calcium, impaired baroreflex.
2. **Patients under-report it**, and reduction gives a proportional fall — so frame reduction as a specific, achievable treatment target rather than a demand for abstinence.
3. **Alcohol withdrawal hypertension:** abrupt cessation causes a sympathetic surge with marked pressure rise and risk of seizures and delirium tremens. **Hospital admission can precipitate it** — recognise it rather than misattributing it to primary hypertension.
4. **Smoking causes a transient 15–30 minute pressor effect**, so a clinic reading taken when the patient has not just smoked may be falsely reassuring. Ambulatory monitoring may reveal the true hypertension.
5. **The major harm of smoking is cumulative vascular damage**, multiplying the cardiovascular risk of any given pressure. Cessation matters chiefly as removal of a powerful independent risk multiplier — its own BP effect is modest.
6. **Caffeine raises pressure 3–8 mmHg acutely in non-habitual users**, but tolerance means habitual coffee or tea rarely causes sustained hypertension. Avoid it before a measurement.
7. **Energy drinks are a distinct and growing concern in young adults** — high caffeine plus stimulants, with marked pressure rises, arrhythmias and rare serious events, especially with alcohol or exertion. Ask about them specifically in young patients with hypertension or palpitations.

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CHAPTER 24 PART IV · CONTRIBUTING FACTORS

Obstructive sleep apnoea

A common, treatable and frequently missed cause — the chemoreflex mechanism, the screening, and an honest account of what CPAP does.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **How common it is in resistant hypertension** — and why the link is mechanistic rather than merely shared with obesity.
2. **Carotid-body sensitisation** — why a nocturnal problem produces daytime hypertension.
3. **The non-dipping pattern** — an ambulatory finding that should prompt the diagnosis.
4. **STOP-BANG** — eight items, and the score that warrants evaluation.
5. **What CPAP does to blood pressure** — modest, nocturnal, and adherence-dependent.
6. **What CPAP did not do** — SAVE, RICCADSA and ISAACC, and the most likely reason.
7. **The aldosterone connection** — why spironolactone treats both the pressure and the apnoea.

24.1 The link

Obstructive sleep apnoea is among the most common and most under-diagnosed contributors to hypertension, and its recognition matters because it is treatable and frequently missed. In sleep apnoea the upper airway repeatedly collapses, producing recurrent obstruction terminated by an arousal, accompanied by intermittent hypoxia and surges of sympathetic activity that over time produce sustained daytime hypertension.

Its prevalence is high in hypertensive populations and rises further in resistant hypertension. The association is mechanistic, not merely a shared link with obesity, because the sympathetic and vascular effects of the apnoeic episodes drive blood pressure independently of weight — although obesity is a common amplifying factor.[9]

30–40%

of resistant hypertensives

Or more — where sleep apnoea is a **leading identifiable cause**.[10,13] The link is mechanistic, not merely a shared association with obesity.

24.2 The mechanism

The mechanism centres on the intermittent hypoxia of the repeated apnoeic episodes. Each obstruction produces a fall in arterial oxygen saturation that powerfully stimulates the peripheral chemoreceptors of the carotid body (V1·Ch2).

Over time the repeated hypoxic stimulation sensitises the carotid body, so it becomes chronically over-responsive and drives a sustained increase in sympathetic outflow that persists into the daytime waking hours — producing daytime hypertension. The repeated arousals additionally fragment sleep and activate the hypothalamic–pituitary–adrenal axis, and the large intrathoracic pressure swings impose mechanical stress on the heart and great vessels.[1]

The characteristic result is a **non-dipping or reverse-dipping** ambulatory pattern (V1·Ch7), because the nocturnal apnoeas prevent the normal sleep-time fall in pressure — so a non-dipping pattern should prompt consideration of sleep apnoea.

Why it persists by day

Repeated hypoxic stimulation **sensitises** the carotid body. It becomes chronically over-responsive, and the sympathetic outflow persists into waking hours long after the night ends.[15]

24.3 Screening and diagnosis

Because sleep apnoea is common, treatable and often missed, systematic screening of hypertensive patients for its features is valuable — particularly in those with resistant hypertension, obesity, a non-dipping pattern, or characteristic symptoms.[7]

TABLE 24.1 — STOP-BANG

LETTER	ITEM
S	Snoring
T	Tiredness
O	Observed apnoeas
P	High blood pressure
B	BMI above 35
A	Age above 50
N	Neck circumference above 40 cm
G	Male gender

A score of three or more indicates intermediate-to-high risk and warrants evaluation.[3] A caution for Indian practice: the BMI item is set at 35, a threshold derived in North American surgical populations and rarely met in an Indian outpatient department, in a population where obesity begins at 27.5 (V1·Ch9) — so in an Indian patient the score understates risk, and a score of 2 driven by snoring and tiredness deserves more attention than the instrument gives it. Weight the neck circumference and the observed apnoeas, and in a resistant hypertensive investigate on the history whatever the score. The definitive diagnosis is by polysomnography, quantifying the apnoea–hypopnoea index, or by simpler home sleep studies and overnight oximetry, which are more accessible and sufficient in many cases.[8]

24.4 What CPAP does — and does not do

The mainstay of treatment for moderate-to-severe sleep apnoea is continuous positive airway pressure, which splints the upper airway open during sleep, abolishing the apnoeas, the intermittent hypoxia and the arousals, and thereby reducing the sympathetic overactivation. The honest, evidence-based position has two parts, and they must be held together.

Occupational relevance

Untreated apnoea causes daytime sleepiness that impairs **safety-critical work and driving** — bearing directly on fitness to perform a role safely (V1·Ch25).

TABLE 24.2 — CPAP: THE TWO HALVES OF THE EVIDENCE

	WHAT THE EVIDENCE SHOWS
Blood pressure	A **modest** reduction — meta-analyses show mean systolic falls of roughly **2–3 mmHg** overall, larger for **nocturnal** pressure, larger in **resistant hypertension** where the reduction is more clinically meaningful, and larger with good adherence. HIPARCO, the largest trial in resistant hypertension with sleep apnoea, reduced 24-hour *mean* and diastolic pressure significantly; the 24-hour systolic reduction did not reach significance on intention-to-treat. The nocturnal effect was larger, and more CPAP patients recovered a dipping pattern.[2,11]
Cardiovascular outcomes	The major randomised trials have been neutral. SAVE (McEvoy, *NEJM* 2016), RICCADSA and ISAACC did **not** show that CPAP reduces cardiovascular events. The most likely explanation is **poor adherence** — average use in SAVE was only about 3.3 hours per night, below the threshold generally needed for benefit — together with exclusion of the very sleepy patients who benefit most symptomatically.[12,14,16]
The practical position	CPAP is firmly indicated to relieve symptoms and improve quality of life and driving safety. It modestly lowers blood pressure — most in resistant hypertension and at night — **provided it is used consistently**. Its blood-pressure and cardiovascular benefit depends critically on adherence, which is the principal limitation of the therapy.[17]
Adjuncts and alternatives	Weight loss reduces severity and is an important adjunct. Mandibular advancement devices and, in selected cases, surgery are alternatives for CPAP-intolerant patients.[4,6]

24.5 The aldosterone connection

A specific and useful point is the bidirectional relationship between aldosterone and sleep apnoea: aldosterone-driven fluid retention contributes to the upper-airway oedema that worsens the apnoea, while the apnoea contributes to aldosterone excess.

This makes the mineralocorticoid receptor antagonists — spironolactone in particular — especially effective in the resistant hypertension associated with sleep apnoea. Screening for primary aldosteronism (V1·Ch13) is especially worthwhile in the patient with both resistant hypertension and sleep apnoea.

Two problems, one drug — and one of them unproven

Spironolactone is the best-evidenced fourth drug in resistant hypertension (PATHWAY-2), and there is a mechanistic case, on small uncontrolled studies only, that reducing fluid retention also reduces upper-airway oedema and the severity of the apnoea.[5] Treat the pressure with it; treat the apnoea with CPAP. Before starting it, check potassium and creatinine — do not start above a potassium of 5.0, reduce the starting dose at an eGFR of 30 to 50, and below 30 only with a potassium plan (V1·Ch19) — and recheck potassium within one week.[18]

KEY POINTS

1. **Sleep apnoea is a common, treatable, frequently missed cause of hypertension**, present in 30–40% or more of resistant hypertensives across cohorts — and in 64% of a series of 125 patients investigated systematically for every secondary cause irrespective of symptoms (V3·Ch19): the higher figure is what you find when you look at everyone rather than at the patients who look apnoeic. It is a leading identifiable cause. The link is mechanistic and independent of obesity, though obesity amplifies it.
2. **Mechanism:** intermittent hypoxia sensitises the carotid-body chemoreflex, producing sustained **daytime** sympathetic overactivation from a nocturnal problem.
3. **A non-dipping or reverse-dipping ambulatory pattern should prompt consideration of sleep apnoea**, because the nocturnal apnoeas prevent the normal sleep-time fall.
4. **Screen with STOP-BANG** — snoring, tiredness, observed apnoeas, pressure, BMI above 35, age above 50, neck above 40 cm, male gender; a score of three or more warrants evaluation. Diagnose by polysomnography or accessible home oximetry.
5. **CPAP lowers blood pressure modestly** — around 2–3 mmHg overall, more nocturnally and in resistant hypertension, more with good adherence (HIPARCO).
6. **But the cardiovascular outcome trials were neutral** — SAVE, RICCADSA and ISAACC — most likely because of poor adherence, averaging about 3.3 hours a night in SAVE. CPAP is firmly indicated for symptoms and driving safety; its BP and cardiovascular benefit depends critically on consistent use.
7. **The aldosterone connection is bidirectional:** aldosterone worsens upper-airway oedema and the apnoea, and the apnoea raises aldosterone. **Spironolactone is the best-evidenced fourth drug** in apnoea-associated resistant hypertension; its effect on the apnoea itself rests on small uncontrolled studies, so treat the pressure with it and the apnoea with CPAP. Check potassium and creatinine before starting and potassium within a week — and primary aldosteronism is worth screening for in these patients.

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CHAPTER 25 PART IV · CONTRIBUTING FACTORS

Psychological stress and occupational hypertension

The physiology of chronic stress, the two occupational models, the exposures within the physician\u2019s remit, and the workplace as a place to find and treat hypertension.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why chronic stress differs from acute** — cortisol dysregulation and a permanently raised sympathetic set point.
2. **Job strain and effort–reward imbalance** — two complementary models, and the risk each carries.
3. **Iso-strain** — what low social support adds to high demand and low control.[6]
4. **Exposures within your remit** — noise, shift work, lead, cadmium and carbon disulphide.
5. **The Indian occupational landscape** — IT and BPO, manufacturing, and the informal sector.
6. **The periodic examination** — screening a population with little other health-system contact.
7. **Three roles** — fitness for work, primary prevention, and return to work.

25.1 The physiology of chronic stress

The pathway from psychosocial stress to sustained hypertension (V1·Ch14) exerts its greatest and most modifiable effect on the working population. The acute stress response — amygdala activation driving the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system — is adaptive and self-limiting. The problem is chronic, repeated stress.

Only partly reversible

This is why blood pressure often does **not** fully normalise on leaving a stressful environment — and why interventions strengthening prefrontal control are valuable.

TABLE 25.1 — TWO FORMS OF LASTING DYSREGULATION

DYSREGULATION	CONSEQUENCE
Cortisol	Sustained, dysregulated exposure promoting **sodium retention, visceral fat, insulin resistance and endothelial dysfunction**.
Central sensitisation	The firing set point of the rostral ventrolateral medulla is raised, generating a higher baseline sympathetic output **even at rest and even after the stressor is removed**. The prefrontal cortex that normally restrains it loses volume and connectivity while the amygdala becomes hyper-responsive.

25.2 The job-strain and effort–reward models

Two models frame the occupational contribution, and they are complementary — acute task-level strain and chronic relational unfairness. The occupational physician assesses both.

23%

excess coronary risk

Job strain, in a pooled analysis of nearly 200,000 workers — Kivimäki, *Lancet* 2012.

TABLE 25.2 — THE TWO OCCUPATIONAL MODELS

MODEL	WHAT IT CHARACTERISES	THE HAZARDOUS CONFIGURATION AND ITS RISK
Job strain KARASEK	A job by psychological **demand** and **control** (decision latitude).[7]	High demand with low control — "high strain". Adding low social support gives the most hazardous **iso-strain**. Kivimäki (*Lancet* 2012, 197,473 workers): **a 23% excess of coronary heart disease** (HR 1.23, 95% CI 1.10–1.37). That study measured coronary events only; the association of job strain with incident hypertension rests on separate and weaker literature.[9]
Effort–reward imbalance SIEGRIST	The mismatch between effort invested and reward received — salary, esteem, security, prospects.[5,14]	Sustained imbalance is associated with higher blood pressure and incident hypertension, though the size of the effect is unsettled — a doubling of incidence in one prospective white-collar cohort[5], but only a modest pooled association across the meta-analytic literature[3]. Independent of job strain, and amplified by the personal disposition of **overcommitment**.

25.3 Specific occupational exposures

Several occupational exposures contribute directly to hypertension and are within the occupational physician's remit to identify and control. Identifying and controlling them through hygiene, engineering controls and substitution is a core occupational-health function.

TABLE 25.3 — EXPOSURES THAT RAISE BLOOD PRESSURE

EXPOSURE	EFFECT	WHERE
Noise ABOVE 80 DB(A), STEEPLY ABOVE 85	Independently raises hypertension risk through repeated sympathetic activation — **persisting even after conscious habituation**.[17] Pooled effect 1.75 (95% CI 1.46–2.10) at 80 dB(A) or above, with a dose-response: 1.66 between 80 and 85 dB(A), 3.38 between 85 and 90.[1] Note that 85 dB(A) is the hearing-conservation limit, not the threshold for the pressure effect — a worker at 82 dB(A) is compliant and still exposed.	Manufacturing, process industries.
Shift work ROTATING ROSTERS	Disrupts circadian regulation (V1·Ch7, Ch14), producing **non-dipping**. Rotating shift work carries about **30% higher odds of hypertension** (OR 1.31, 95% CI 1.07–1.60; 1.34 in cohort studies alone); night-shift status by itself did not reach significance in the same analysis (OR 1.10, 95% CI 1.00–1.20; 1.07, 0.85–1.35 in cohorts) — and eighteen of its 27 studies were cross-sectional, so "incidence" overstates the design.[12] It is the rotation, not the darkness, that the evidence indicts.	Manufacturing, healthcare, security, transport, outsourcing.
Prolonged sedentary work	Contributes through deconditioning.[4]	Office and IT work.
Lead	A weak but consistent pressure effect — about 1 mmHg systolic and 0.6 diastolic per doubling of blood lead in meta-analysis — and, at high chronic exposure, **nephropathy**, which is the clinically important lesion. Removal from exposure is justified on renal and neurological grounds; do not expect it to normalise the pressure.[13]	Battery manufacturing, smelting, informal recycling.
Cadmium	Damages the kidney and raises pressure.[16]	Various process industries.
Carbon disulphide	Accelerates atherosclerosis.	Viscose rayon industry.[2]

25.4 The India occupational context

The Indian occupational landscape presents particular risks. The information-technology and business-process-outsourcing sectors, employing millions of young adults, combine high demand, low control, night shifts aligned to overseas time zones, sedentary posture, and a young workforce in whom the neurogenic mechanism predominates — a combination contributing to the rising young-adult hypertension of V1·Ch9 and Ch16.

The manufacturing and process industries add noise, shift work and the chemical agents above, and the large informal sector adds physical strain and limited health-system access. Heat belongs in a different column: it lowers pressure acutely through vasodilatation and volume loss, and the occupational hazard it carries is syncope and acute kidney injury, particularly in a worker on a diuretic (V3·Ch33) — not hypertension. Across all these settings the workplace offers a valuable, under-used opportunity to detect and manage hypertension.

An under-used opportunity

The workplace reaches a population that may otherwise have **little health-system contact at all**.

25.5 Workplace screening

The workplace is an efficient setting for detection, bringing the physician into regular contact with large numbers of apparently healthy working adults. A camp-based screening of 2,588 factory workers in Faridabad found raised

blood pressure in 30.9% — 34.6% of the men and 18.4% of the women.[10] A larger North Indian study of 15,527 workers found 22% (V3·Ch33); the spread between the two is a reminder that a workplace prevalence figure describes that workforce, not Indian industry. The periodic health examination — statutory for workers in certain hazardous processes and good practice for many others — provides a structured opportunity to measure blood pressure, identify the undiagnosed and monitor the known hypertensive. Note that the statutory examination is hazard-specific: blood-pressure screening of the general workforce is usually an addition to it, requiring the employer's agreement, the worker's consent, and a clear statement of who sees the result.

Measurement should follow the same standards of technique as the clinic — cuff size, rest, avoidance of caffeine and recent activity — and an elevated screening reading should be confirmed on repeat and, where appropriate, by ambulatory or home monitoring rather than acted on from a single reading. Ambulatory monitoring is particularly valuable in shift workers.

Free information

The **resting heart rate**, recorded at no extra cost, helps identify the neurogenic phenotype that predominates in a young workforce.

25.6 Workplace interventions

Because the mechanism is central sympathetic sensitisation, interventions that reduce central sympathetic drive are mechanistically targeted rather than generic wellness measures.

TABLE 25.4 — INTERVENTIONS, INDIVIDUAL AND ORGANISATIONAL

LEVEL	INTERVENTION	WHY IT WORKS HERE
Individual	Structured **mindfulness-based stress reduction**	Strengthens prefrontal control. In meta-analysis of 12 trials it lowered pressure by about 7/2 mmHg — a real effect, roughly half that of a standard-dose drug, on evidence in which only one trial was at low risk of bias. **An addition to treatment, not a substitute for it.**[11]
Individual	**Yoga and slow pranayama**, around six breaths per minute	A sympathoinhibitory effect, with cultural acceptability in the Indian workforce.[15]
Individual	**Isometric and aerobic exercise**	Effective, and mechanistically targeted (V1·Ch14).[8]
Organisational	Increase worker control over pace and organisation; realistic deadlines and staffing; social support; shift schedules that minimise circadian disruption	Addresses the **root drivers** — primary prevention within the influence of the occupational-health function.

25.7 The occupational physician's role

The physician with occupational-health training occupies a distinctive position, bridging the clinical management of the individual and the prevention-oriented management of the workforce.

TABLE 25.5 — THREE ROLES

ROLE	WHAT IT INVOLVES
Fitness-for-work assessment	Determining whether a worker with hypertension is fit to perform a role safely — especially **safety-critical roles** (driving, working at height, heavy machinery, aviation, security, process industries) where a hypertensive emergency or treatment-related syncope could endanger the worker and others. The determination balances cardiovascular risk against the safety demands of the specific role. Volume 3 sets out how to make and record that determination, and why no Indian statutory figure is reproduced there — the governing rule must be obtained for the specific job (V3·Ch33).
Health promotion and primary prevention	Using workplace access to detect hypertension early and address the workplace factors that contribute to it.
Return to work	After a hypertension-related event — emergency, stroke, myocardial infarction — assessing recovery, timing and any workplace accommodations.

KEY POINTS

1. **Chronic occupational stress causes sustained hypertension** through HPA dysregulation and central sympathetic sensitisation — a permanently raised set point, only partially reversible on removing the stressor. Central-drive-reducing interventions therefore matter.
2. **Job strain** (Karasek: high demand with low control) carried a **23% excess coronary risk** in 197,473 workers (Kivimäki, *Lancet* 2012) — a study of coronary events only; its link to incident hypertension rests on separate and weaker literature. Low social support adds **iso-strain**, the most hazardous configuration.[9]
3. **Effort–reward imbalance** (Siegrist) is associated with hypertension, but the size of the effect is unsettled — a doubling of incidence in one prospective white-collar cohort, a modest pooled association of about 0.26 across the meta-analytic literature — independent of job strain and amplified by overcommitment. Assess both models.[3]
4. **Occupational exposures:** noise from 80 dB(A) and steeply above 85 (independent risk, persisting after habituation — 85 dB(A) is the hearing limit, not the pressure threshold), rotating shift work (non-dipping; about 30% higher odds of hypertension, with fixed night work alone not significant), sedentary work, and the chemicals — lead (a weak pressure effect; nephropathy is the lesion that matters), cadmium (kidney damage and raised pressure), carbon disulphide (accelerated atherosclerosis).[1]
5. **India:** IT and BPO combine high demand, low control, night shifts and a young neurogenic-predominant workforce; manufacturing adds noise, shifts, heat and chemicals; the informal sector adds strain and poor health-system access.
6. **The workplace is an under-used detection opportunity.** The periodic health examination reaches workers with little other health-system contact — use proper technique, confirm elevated readings, record the resting heart rate, and use ambulatory monitoring in shift workers.
7. **Three roles for the occupational physician:** fitness-for-work assessment, especially in safety-critical roles; health promotion and primary prevention; and management of return to work after a hypertension-related event — bridging individual care and workforce prevention.

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CHAPTER 26 PART IV · CONTRIBUTING FACTORS

Endocrine and secondary causes: when to suspect one

A short chapter with one job — to make you stop and think. Each cause is then treated properly in Part VI.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The moments** in a consultation when a secondary cause becomes likely enough to look for.
2. **The pattern-to-cause map** — which finding should make you think of which disease first.
3. **The basic panel** that every hypertensive should have, and what each test is for.
4. **Where to go next** — the chapter in Part VI that treats each cause in full.

26.1 Why this chapter is short

A quarter of a page on Cushing's syndrome teaches nobody anything. Each of the major secondary causes needs room to be explained properly — the mechanism by which it raises pressure, how it declares itself clinically, and what to order — and each gets that room in Part VI. The job of this chapter is narrower and comes first: to make you suspect, and to tell you where to turn.

Each of those causes now has its own chapter in **Part VI**, with the mechanism, the clinical detection, the investigation and its performance, and what the diagnosis changes. This chapter does the one thing those chapters cannot do from where they sit: it catches you in the middle of an ordinary consultation and tells you to look.

26.2 The moments that should stop you

The failure this chapter addresses

Secondary hypertension is rarely missed because the tests are unavailable. It is missed because nobody thought of it. The tests in Table 26.2 are cheap and ordinary; the barrier is entirely one of suspicion.

TABLE 26.1 — PATTERN TO CAUSE, AND WHERE TO READ ABOUT IT

WHAT YOU FIND	THINK FIRST OF	CHAPTER
Hypertension beginning before 30	Renal parenchymal disease; renovascular disease; coarctation. In this age group a secondary cause is present in around a third	31, 32, 37

WHAT YOU FIND	THINK FIRST OF	CHAPTER
Resistant — uncontrolled on three drugs including a diuretic	Primary aldosteronism; obstructive sleep apnoea; renal parenchymal disease; and non-adherence, which is commoner than all of them	33, 24, 31
Hypokalaemia, spontaneous or after a diuretic	Primary aldosteronism. If the renin is *also* high, a renin-secreting tumour	33, 32
Creatinine rises sharply after a RAAS blocker is started	Bilateral renal artery stenosis, or stenosis in a single functioning kidney	32
Abrupt onset, or a stable hypertensive who accelerates	Renovascular disease; phaeochromocytoma	32, 34
Paroxysms of headache, palpitations and sweating	Phaeochromocytoma — and not panic disorder until the pressure has been measured during an episode[6]	34
Easy bruising, proximal myopathy, violaceous striae	Cushing's syndrome. Obesity and diabetes alone do not discriminate[8]	35
Isolated systolic hypertension with atrial fibrillation in a younger patient	Thyrotoxicosis[3]	36
Diastolic hypertension with bradycardia and fatigue	Hypothyroidism[3]	36
Absent or asymmetric pulses, or a difference between the arms	Coarctation; Takayasu arteritis — and the arm pressure may be falsely normal	37, 32
Snoring, witnessed apnoea, daytime sleepiness, non-dipping	Obstructive sleep apnoea	24
Target-organ damage out of proportion to the pressure or its duration	Primary aldosteronism	33
The pressure rose when something was started	Drug-induced — including agents the patient does not consider medicines	27–30, App B
Recurrent flash pulmonary oedema	Bilateral renovascular disease	32

26.3 The basic panel

These tests belong to every hypertensive patient, not to a selected few. They are inexpensive, they are widely available, and between them they identify the majority of secondary hypertension that exists to be found in the young, where renal disease accounts for roughly four-fifths of it. In the adult clinic the commonest correctable cause is primary aldosteronism, and nothing in the first seven rows finds it — which is why the eighth is there.

TABLE 26.2 — WHAT EVERY HYPERTENSIVE SHOULD HAVE, AND WHY

TEST	WHAT IT IS FOR
Urinalysis with microscopy	Glomerular disease. Dysmorphic red cells and red-cell casts are close to diagnostic of glomerular bleeding when present, though frequently absent when it is there
Urine albumin–creatinine ratio	Renal injury, and independently a cardiovascular risk marker
Serum creatinine and eGFR	Renal function, and the baseline against which a post-RAAS-blocker rise is judged
Serum potassium and sodium	Hypokalaemia points at aldosteronism; it is present in only a minority, so a normal result excludes nothing
Renal ultrasound	Size, symmetry, scarring, cysts, obstruction. Asymmetry beyond about 1.5 cm turns attention to the renal arteries
Four-limb blood pressure, both arms	Coarctation and Takayasu — the only way to find either, and it costs a few minutes
A full drug and supplement history	The commonest reversible cause in a general clinic, and the one least often taken properly
Aldosterone and renin — the ratio	The commonest correctable cause, and the only test that finds it. Send it on the patient's existing drugs where withdrawal is unsafe or impractical — the 2025 guidance allows a minimal-withdrawal or no-withdrawal strategy — and read the result against them (Chapter 33). Whether every hypertensive gets it, or only the high-yield groups, is argued in Chapter 37[1]

Beyond this panel, testing should be directed rather than routine. Guideline positions are explicit that TSH, calcium and IGF-1 are **not** routine investigations in hypertension; they are ordered when something specific points there. A test ordered without a reason produces a result without a meaning, and in a population where mild abnormalities are common it generates more consultations than it resolves.

Where the argument continues

Chapter 37 sets out how common secondary hypertension actually is by age and by presentation, ranks the causes by yield, and gives both sides of the argument about screening every hypertensive for primary aldosteronism.[7]

KEY POINTS

1. **Secondary hypertension is missed for want of suspicion, not for want of tests.** Everything in the basic panel is cheap and ordinary.
2. **Age is the strongest modifier.** Around a third of confirmed hypertensives aged 18 to 40 in referred series have a secondary cause — about 2% in an unselected young cohort (Ch 16) — against 5 to 10% of adults generally.[10]
3. **In the young, renal disease is about four-fifths of it.** Start with the urine and the kidney.[4]
4. **A normal potassium does not exclude primary aldosteronism** — only a minority of cases are hypokalaemic.[1,5]
5. **Four-limb blood pressure in both arms is the only way to find a coarctation or a Takayasu**, and it takes a few minutes.[2]
6. **Resistant hypertension has four common explanations**: aldosteronism, sleep apnoea, renal disease, and non-adherence — and the last is the commonest.[9]
7. **Each cause is treated in full in Part VI.** This chapter exists to make you turn to it.

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VOLUME ONE · PART V

Drug-induced hypertension

The analgesics, hormones, immunosuppressants, stimulants and herbal preparations that raise blood pressure — and the ones patients never mention.

Hypertension: A Phenotype-Based Approach

Volume 1 · Why Is This Patient Hypertensive?

Dr Ravikiran Jadhav

MBBS · AFIH · Occupational Health Physician

4 chapters

Part V of five

CHAPTER 27 PART V · DRUG-INDUCED HYPERTENSION

NSAIDs, COX-2 inhibitors and analgesics

The prostaglandin mechanism, the triple whammy, and the surprising truth about paracetamol.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The renal prostaglandin mechanism** — sodium retention, reduced renal blood flow, and a vascular shift toward constriction.
2. **Why COX-2 selectivity does not help** — the renal effects are themselves COX-2–mediated.
3. **Which antihypertensives are blunted** — and the one class that is relatively preserved.
4. **The triple whammy** — three individually appropriate drugs converging on filtration pressure.
5. **PATH-BP** — the trial that removed paracetamol\u2019s reputation for neutrality.
6. **Why paracetamol is still preferred** despite that finding.

27.1 Why NSAIDs raise blood pressure

Non-steroidal anti-inflammatory drugs are among the most widely used medications, available over the counter and taken by many hypertensive patients. They are an important, frequently overlooked cause of raised blood pressure and of lost control in a previously well-controlled patient.

They inhibit the cyclo-oxygenase enzymes and thereby reduce prostaglandin production. In the kidney, prostaglandins — particularly PGE2 and prostacyclin — promote natriuresis, maintain renal blood flow by dilating the afferent arteriole when perfusion is threatened, and modulate renin. Inhibiting them causes sodium and water retention, expanding volume and raising pressure, and reduces renal blood flow, which in vulnerable patients can precipitate a fall in filtration rate. Systemically, the reduction of vasodilator prostacyclin relative to vasoconstrictor thromboxane shifts the vascular balance toward vasoconstriction (V1·Ch6).[14]

Where control goes

A patient stable for years loses control. Ask what they bought for their knee.

27.2 COX-2 selectivity, magnitude, and drug interactions

The COX enzyme exists as COX-1 and COX-2, and selectivity influences both gastrointestinal safety and blood-pressure effects.

3–5

mmHg systolic, on average

Concealing wide variation. Enough to convert controlled into uncontrolled hypertension.

TABLE 27.1 — MAGNITUDE, AND WHO IS MOST AFFECTED

	DETAIL
COX-2 selectivity	Both non-selective NSAIDs and selective COX-2 inhibitors raise blood pressure. **The COX-2–selective agents are not blood-pressure–neutral**, because the renal effects are substantially COX-2–mediated, and none of them may be assumed safe in a hypertensive patient. The ambulatory data do separate them: in the PRECISION substudy 24-hour systolic pressure moved by −0.3 mmHg on celecoxib against +3.7 mmHg on ibuprofen, with new hypertension in 10.3% against 23.2%.[2,3,6,8,10,11,12,15]
Average effect	About **3–5 mmHg of mean arterial pressure** — not systolic, and concealing wide variation, with some patients experiencing a much larger rise.[6,11]
Greater in	Those already hypertensive, the salt-sensitive, the elderly, and those with CKD.[5]

TABLE 27.2 — WHICH ANTIHYPERTENSIVES NSAIDS BLUNT

CLASS	EFFECT OF AN NSAID	CONSEQUENCE
ACE inhibitors, ARBs, diuretics	**Blunted** — their effect depends partly on prostaglandins.	Control is lost while the patient takes the NSAID.
Calcium channel blockers	**Relatively preserved** — a prostaglandin-independent mechanism.	A calcium channel blocker is the more reliable choice in a hypertensive patient who **cannot avoid** regular NSAIDs.
Mineralocorticoid receptor antagonists, and the potassium	**Additive on potassium** — NSAIDs reduce renin and aldosterone and raise potassium in their own right; the spironolactone label lists them among the drugs that increase serum potassium.[16]	An NSAID is on the list of drugs to review when a patient on a RAAS blocker or an MRA will not settle below 5.5 (V2·Ch7).

27.3 The triple whammy

The most dangerous consequence of NSAID use in the hypertensive patient is the triple whammy — an NSAID taken together with an ACE inhibitor or ARB and a diuretic — which can precipitate acute kidney injury, particularly with any additional stress such as dehydration or intercurrent illness.[7]

Why it is common

Each component is **individually appropriate** and widely used. The risk arises from their unrecognised concurrence — often an over-the-counter purchase for unrelated pain.

TABLE 27.3 — THREE INSULTS CONVERGING ON FILTRATION PRESSURE

AGENT	WHAT IT DOES TO THE GLOMERULUS
The NSAID	**Constricts the afferent arteriole** — removing the vasodilator prostaglandins that keep it open.
The ACE inhibitor or ARB	**Dilates the efferent arteriole** — reducing intraglomerular pressure.
The diuretic	**Depletes intravascular volume** — reducing renal perfusion.
Together	Filtration can fall precipitously.

Counselling hypertensive patients on RAAS blockers and diuretics to avoid over-the-counter NSAIDs is an important preventive measure.

One exclusion, stated plainly. This chapter is about analgesic doses. Low-dose aspirin taken for secondary prevention is not what is meant, and a patient must not be told to stop it on the strength of this advice — say "painkillers such as ibuprofen and diclofenac", never "NSAIDs". If such a patient genuinely needs a regular NSAID, remember that ibuprofen taken regularly interferes with aspirin's antiplatelet effect, and choose otherwise.

27.4 Paracetamol re-examined, and the safest strategy

Paracetamol was traditionally regarded as the safe analgesic alternative to NSAIDs in hypertensive patients, on the assumption that it has little effect on blood pressure. This has been overturned.

4.7

mmHg — PATH-BP

Placebo-corrected rise in daytime systolic pressure on regular 4 g/day paracetamol. Similar in magnitude to an NSAID.

TABLE 27.4 — PATH-BP

	DETAIL
Design	MacIntyre and colleagues, *Circulation* 2022. Double-blind, placebo-controlled crossover study of 110 hypertensive patients randomised to 1 g paracetamol four times daily (4 g/day) or placebo for two weeks each.[9]
Result	Placebo-corrected rise in daytime systolic pressure of about **4.7 mmHg**, with a smaller diastolic rise — an effect similar in magnitude to that of NSAIDs, in **both treated and untreated** hypertensives.
But still preferred	Paracetamol remains the **first-line analgesic** in hypertension because it lacks the renal, triple-whammy and gastrointestinal risks of NSAIDs.

The safest analgesic strategy is to prefer paracetamol at the lowest effective dose for the shortest duration, to monitor blood pressure when regular analgesia is required, and — when an NSAID is genuinely necessary — to use it at the lowest dose for the shortest time, to avoid it in patients on the triple-whammy combination or with CKD, and to monitor blood pressure and renal function during its use.[1,13]

KEY POINTS

1 **NSAIDs raise blood pressure by inhibiting renal prostaglandins** (PGE2, prostacyclin) — sodium and water retention, reduced renal blood flow, and a vascular shift toward vasoconstriction. A common, overlooked cause of lost control.

2 **COX-2–selective agents are not blood-pressure-neutral**, because the renal effects are substantially COX-2–mediated — though celecoxib raised ambulatory pressure less than ibuprofen. The average rise is 3–5 mmHg of mean arterial pressure, larger in hypertensives, the salt-sensitive, the elderly and those with CKD.[6,11,15]

3 **NSAIDs blunt ACE inhibitors, ARBs and diuretics but not calcium channel blockers** — so a CCB is the more reliable choice when NSAIDs are unavoidable.

4 **The triple whammy** — NSAID plus ACEi/ARB plus diuretic — can cause acute kidney injury: afferent constriction, efferent dilation and volume depletion converging on filtration pressure.[4]

5 **It is common precisely because each component is individually appropriate.** Counsel patients on a RAAS blocker plus a diuretic to avoid over-the-counter NSAIDs.

6 **Paracetamol is not blood-pressure-neutral:** regular 4 g/day raised systolic pressure about 4.7 mmHg in PATH-BP (*Circulation* 2022), similar to an NSAID, in both treated and untreated hypertensives.

7 **It remains preferred over NSAIDs** — no renal, triple-whammy or gastrointestinal risk — but at the lowest effective dose for the shortest time, with BP monitoring for regular use.

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CHAPTER 28 PART V · DRUG-INDUCED HYPERTENSION

Hormonal agents

Oral contraceptives, hormone replacement therapy, anabolic steroids, and corticosteroids.[3,4,10]

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The oestrogen–angiotensinogen mechanism** — how the combined pill activates the RAAS.
2. **Who is at greater risk** — and why a history of hypertension in pregnancy matters here.
3. **Why the route decides HRT** — first-pass metabolism, and the case for transdermal.
4. **Anabolic steroids in young men** — the concealed cause, and the two laboratory clues.
5. **Corticosteroids by agent** — why dexamethasone differs from prednisolone here.

28.1 Combined oral contraceptives

Combined oral contraceptives, containing an oestrogen and a progestogen, are a recognised cause of hypertension in women of reproductive age. The principal mechanism is the effect of the oestrogen component on hepatic synthesis of angiotensinogen, the substrate of the renin–angiotensin system: raised angiotensinogen provides more substrate for angiotensin II generation, activating the RAAS and raising pressure through vasoconstriction and sodium retention.[7]

Diagnosis and treatment in one

The hypertension is usually **reversible**, resolving within a few months of discontinuation — which both confirms the cause and treats it.

TABLE 28.1 — THE COMBINED PILL AND BLOOD PRESSURE

	DETAIL
Greater risk in	Higher-oestrogen formulations, older women, smokers, the obese, those with a family history of hypertension, and those with a **history of hypertension in pregnancy**.
Course	Most women experience a small rise within the normal range; a minority develop frank hypertension. Usually reversible within a few months of stopping.[5]
Management	Measure blood pressure before starting and monitor during use. If hypertension develops, stop the combined preparation and replace it at the same consultation. Progestogen-only preparations lack the oestrogen effect, but they are not one class for this purpose: the **progestogen-only pill and the implant** are category 1 below 160/100 and category 2 above it, while the **depot injectable** is category 2 below and category 3 above — which matters in India, where the injectable is the method most often available free. A **copper intrauterine device** is category 1 at any pressure and is the method to offer first where she will accept it; the levonorgestrel device is category 1 below 160/100 and category 2 above. In pre-existing hypertension the eligibility criteria are categorical, and the numbers matter. For the combined pill, adequately controlled hypertension, or a pressure of 140–159 systolic or 90–99 diastolic, is **category 3** — the risks usually outweigh the advantages. A systolic of 160 or more, a diastolic of 100 or more, or established vascular disease is **category 4** — an unacceptable health risk, not a matter of weighing other risk factors. Migraine with aura is category 4 at any age. The WHO and the 2024 US criteria give the same numbers.[2,6,11,13]
After a hypertensive pregnancy	A history of gestational hypertension or pre-eclampsia, with a currently normal and measurable pressure, is **category 2** for the combined pill — a reason to measure and to follow up, not a bar. Every progestogen-only method and both intrauterine devices are category 1. Measure her pressure before she chooses, and record the pregnancy as a lifelong cardiovascular risk factor while she is in front of you (V3·Ch23).[13]

28.2 Hormone replacement therapy

Hormone replacement therapy has a more nuanced relationship with blood pressure, and the route is the key determinant.

Route

decides the effect

Whether a hormone raises blood pressure depends on whether it reaches the liver in high concentration.

TABLE 28.2 — ORAL VERSUS TRANSDERMAL OESTROGEN

ROUTE	WHAT HAPPENS	POSITION
Oral	Undergoes **first-pass hepatic metabolism** and stimulates angiotensinogen production, so it can raise blood pressure by the same mechanism as the combined pill — though doses are lower than in older contraceptives and the effect smaller.	Avoid where a lower-risk route exists.
Transdermal PATCH OR GEL	**Bypasses first-pass hepatic metabolism** and does not stimulate angiotensinogen to the same degree.[1]	Minimal blood-pressure effect — the preferred route in a hypertensive woman requiring HRT.

28.3 Anabolic androgenic steroids

Anabolic androgenic steroids, used illicitly to enhance muscle and performance, are an increasingly important cause of hypertension and cardiovascular harm in young men, particularly in gymnasium and bodybuilding culture.

They raise blood pressure through sodium and fluid retention, an increase in red-cell mass that raises viscosity, direct vascular effects, and adverse lipids that accelerate atherosclerosis. Beyond hypertension they are associated with cardiomyopathy, myocardial infarction and sudden cardiac death. Management centres on cessation, after which the hypertension frequently improves, together with management of any established cardiovascular harm.[9]

Ask specifically

Use is often concealed. Enquire in a young, muscular man with hypertension — especially with a **low HDL cholesterol or raised haematocrit**.

28.4 Corticosteroids

Corticosteroids raise blood pressure partly through a mineralocorticoid effect — cortisol saturating 11-beta-HSD2 and reaching the mineralocorticoid receptor — producing sodium and fluid retention. That is not the whole mechanism, and a review of glucocorticoid-induced hypertension states plainly that it *remains unknown* and is multifactorial, involving enhanced vascular reactivity to pressors, suppression of vasodilator systems, and insulin resistance.[8] The practical consequence is that a mineralocorticoid receptor antagonist does **not** reliably control it. The effect is dose- and duration-dependent, with risk beginning above about 7.5 mg prednisolone-equivalent daily — below that dose no excess risk of hypertension has been demonstrated — and forms part of the broader picture of iatrogenic Cushing's syndrome (V1·Ch35).[12]

TABLE 28.3 — MINERALOCORTICOID ACTIVITY DIFFERS BY AGENT

AGENT	MINERALOCORTICOID ACTIVITY	CONSEQUENCE
Hydrocortisone, prednisolone	Appreciable	More likely to cause hypertension.
Dexamethasone	Minimal	The choice of steroid influences the likelihood of hypertension.

Management centres first on minimising corticosteroid exposure — lowest effective dose, shortest duration, steroid-sparing agents where appropriate — and, where the steroid cannot be reduced, on controlling the pressure with attention to the underlying sodium retention, so that a low-sodium diet and, where drug treatment is needed, a diuretic are the logical components.

KEY POINTS

1. **Combined oral contraceptives raise blood pressure via oestrogen-driven hepatic angiotensinogen** and RAAS activation. Most women have a small rise; a minority develop frank hypertension — greater risk with higher-oestrogen formulations, older age, smoking, obesity, family history and prior hypertension in pregnancy.
2. **It is usually reversible within months of stopping**, which both confirms the diagnosis and provides the treatment. Measure BP before and during use; if hypertension develops, replace the combined pill by eligibility category — the copper device, the progestogen-only pill or the implant first, the depot injectable last — and above 160/100 the combined pill is category 4.
3. **For HRT the route determines the effect:** oral oestrogen undergoes first-pass hepatic metabolism, raises angiotensinogen and can raise pressure; **transdermal bypasses it and has minimal effect — the preferred route** in a hypertensive woman.
4. **Anabolic androgenic steroids cause hypertension in young men** through sodium and fluid retention, raised red-cell mass and viscosity, and adverse lipids — alongside cardiomyopathy and increased infarction and sudden-death risk.
5. **Ask about them specifically** in a muscular young man with hypertension, a low HDL or a raised haematocrit. Use is often concealed, and cessation usually improves the pressure.
6. **Corticosteroids raise pressure through a mineralocorticoid sodium-retaining effect** that is agent-dependent — appreciable for hydrocortisone and prednisolone, minimal for dexamethasone — and dose- and duration-dependent.
7. **Minimise exposure first** — lowest effective dose, shortest duration, steroid-sparing agents — then address the sodium retention with a low-sodium diet and, if needed, a diuretic.

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CHAPTER 29 PART V · DRUG-INDUCED HYPERTENSION

Immunosuppressants and oncology drugs

Calcineurin inhibitors, VEGF inhibitors, and erythropoiesis-stimulating agents.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why calcineurin inhibitors damage and raise pressure together** — one afferent lesion, two harms.
2. **The CYP3A4 interaction** — when it is exploited deliberately, and when to prefer amlodipine.
3. **VEGF-inhibitor hypertension** — rapid, sometimes severe, and mechanistically distinct.
4. **Why its severity is a good sign** — and why that means treating rather than stopping.
5. **Erythropoiesis-stimulating agents** — viscosity, and why the rate of correction matters.

29.1 Calcineurin inhibitors

The calcineurin inhibitors ciclosporin and tacrolimus are the mainstay of immunosuppression in solid-organ transplantation and are used in various autoimmune conditions. They cause hypertension in the great majority of transplant recipients, chiefly through renal and systemic vasoconstriction — driven by increased vasoconstrictor endothelin and reduced vasodilator nitric oxide — together with sympathetic activation and renal sodium retention.

Ciclosporin has a somewhat greater hypertensive effect than tacrolimus, so switching from ciclosporin to tacrolimus is sometimes used to mitigate the hypertension.

One lesion, two harms

The vasoconstriction affects the **afferent** arteriole, so the drug damages the kidney at the same time as it raises the pressure.

TABLE 29.1 — CALCIUM CHANNEL BLOCKERS AND THE CYP3A4 INTERACTION

AGENT	EFFECT ON CALCINEURIN-INHIBITOR LEVELS	POSITION
Amlodipine DIHYDROPYRIDINE	Usually described as not sharing the effect to the same degree — but this is not absolute: in a paediatric transplant study, dose-normalised ciclosporin trough concentrations rose significantly with amlodipine as well as nicardipine, while remaining stable with lacidipine. Monitor levels rather than assume safety.	Preferred. Directly counteracts the vasoconstriction that is the principal mechanism; effective and well tolerated.
Diltiazem, verapamil NON-DIHYDROPYRIDINE	Inhibit CYP3A4, raising calcineurin-inhibitor blood levels and increasing toxicity.	Sometimes exploited **deliberately** to reduce the required dose and cost of the calcineurin inhibitor — but then managed with careful drug-level monitoring. Otherwise avoided.
Lercanidipine DIHYDROPYRIDINE	Its own Summary of Product Characteristics lists ciclosporin as a contraindication: the two should not be given together.[9]	Excluded outright with ciclosporin. "A dihydropyridine" does not mean any dihydropyridine (V2·Ch4).

And the potassium. Calcineurin inhibitors impair distal potassium secretion in their own right, so a RAAS blocker or a mineralocorticoid receptor antagonist added for a proteinuric graft is a second potassium-raising drug rather than the first, in a patient whose filtration is already reduced. Check the potassium one to two weeks after any such addition.

29.2 VEGF inhibitors

The inhibitors of vascular endothelial growth factor signalling, used in oncology, are a distinctive and important cause of hypertension, with features that set it apart. The class includes the monoclonal antibody bevacizumab and tyrosine kinase inhibitors such as sunitinib, sorafenib and pazopanib.

The hypertension means it is working

Severity correlates with anti-tumour efficacy — both reflect the degree of VEGF inhibition. That is a reason to treat the pressure, not to stop the drug.[7,8]

TABLE 29.2 — WHAT MAKES VEGF-INHIBITOR HYPERTENSION DISTINCTIVE

FEATURE	DETAIL
Mechanism	VEGF also maintains endothelial health and nitric oxide production. Inhibiting it impairs endothelial function, reduces nitric oxide, causes vasoconstriction and promotes **microvascular rarefaction**.
Onset	Characteristically **rapid** — within days to weeks.
Severity	Can be severe, sometimes reaching emergency levels.
A useful correlation	Severity correlates with the anti-tumour efficacy of the drug, both reflecting the degree of VEGF inhibition — so the hypertension is, in a sense, a marker of the drug working.
Management	Prompt, effective antihypertensive treatment — RAAS blockers and calcium channel blockers are most used — **to allow the cancer therapy to continue**. It usually resolves when the cancer treatment ends.[1,4,5]

29.3 Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents — erythropoietin and its longer-acting analogues, used for the anaemia of chronic kidney disease and cancer — cause hypertension in a substantial proportion of recipients. The principal mechanism is the increase in red-cell mass and blood viscosity, which raises the resistance to flow, together with a direct vasoconstrictor effect and reversal of the vasodilatation that accompanies anaemia.[3]

Management involves controlling the rate of haemoglobin rise, adjusting the dose, and treating the blood pressure — with attention in the dialysis population to the volume status that frequently contributes.

Rate matters

The hypertension relates to the **rate and extent** of the haemoglobin rise — one reason guidelines recommend a conservative target and gradual correction.

KEY POINTS

1. **Calcineurin inhibitors cause hypertension in most transplant recipients** through renal and systemic vasoconstriction (increased endothelin, reduced nitric oxide), sympathetic activation and sodium retention.[6]
2. **The afferent-arteriolar vasoconstriction causes both the hypertension and the nephrotoxicity** — one lesion, two harms. Ciclosporin is more hypertensive than tacrolimus, so a switch is sometimes used.
3. **Calcium channel blockers are preferred** because they counteract the vasoconstriction directly. **But diltiazem and verapamil inhibit CYP3A4** and raise calcineurin-inhibitor levels — sometimes exploited deliberately with monitoring; otherwise prefer amlodipine.[2]
4. **VEGF inhibitors** (bevacizumab, sunitinib, sorafenib, pazopanib) cause rapid-onset, sometimes severe hypertension by impairing endothelial function, reducing nitric oxide, causing vasoconstriction and microvascular rarefaction.
5. **Severity correlates with anti-tumour efficacy**, both reflecting the degree of VEGF inhibition — so the hypertension is a marker of the drug working.
6. **Treat it promptly** with a RAAS blocker or calcium channel blocker so the cancer therapy can continue; it usually resolves when treatment ends.
7. **Erythropoiesis-stimulating agents raise pressure** through increased red-cell mass and viscosity, direct vasoconstriction and reversal of anaemic vasodilatation. Risk relates to the rate and extent of the haemoglobin rise — use conservative targets and gradual correction, and mind volume status in dialysis patients.

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CHAPTER 30 PART V · DRUG-INDUCED HYPERTENSION

Sympathomimetics, stimulants and herbal agents

Decongestants, cocaine and amphetamines, and the Indian herbal context including mulethi.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Over-the-counter decongestants** — why the vasoconstriction is not confined to the nose.
2. **The cocaine beta-blocker trap** — and how much of it survives the evidence.
3. **The benzodiazepine-first approach** — and its parallel with phaeochromocytoma.
4. **Herbal pressor agents** — six to ask about, and one that acts through drug metabolism instead.
5. **Liquorice and mulethi** — 11β-HSD2 inhibition and acquired apparent mineralocorticoid excess.
6. **The distinguishing laboratory clue** — and why it turns a lifelong diagnosis into a cure.

30.1 Sympathomimetic decongestants

The sympathomimetic decongestants pseudoephedrine and phenylephrine are found in many over-the-counter cold and flu remedies and are taken widely, often without awareness that they raise blood pressure. They act as agonists at alpha-adrenergic receptors, producing the nasal vasoconstriction that relieves congestion — but this vasoconstriction is not confined to the nose, and the systemic alpha stimulation raises systemic vascular resistance and pressure.

In a normotensive person the effect is usually modest, but in a hypertensive patient — particularly one with marginal control — a decongestant can produce a clinically significant rise and can interfere with antihypertensive drugs.[8]

Read the label
Combination cold remedies frequently contain a decongestant alongside analgesics and antihistamines. Advise saline nasal sprays instead.

30.2 Cocaine and amphetamines

Cocaine and the amphetamines, including methamphetamine and MDMA, are powerful sympathomimetics that raise blood pressure acutely and sometimes dramatically, and can precipitate a hypertensive emergency with its risks of stroke, myocardial infarction, aortic dissection and death. Cocaine blocks the reuptake of noradrenaline and dopamine at the nerve terminal, prolonging and intensifying their action; amphetamines promote their release. Chronic use also damages the vasculature and accelerates cardiovascular disease.[9]

TABLE 30.1 — THE COCAINE BETA-BLOCKER TRAP

	DETAIL
The error	Giving a **beta-blocker alone**. Cocaine produces both beta-mediated cardiac stimulation and alpha-mediated vasoconstriction; blocking the beta-mediated vasodilatation of the skeletal-muscle vasculature leaves the alpha-mediated vasoconstriction **unopposed**.
The consequence	A paradoxical worsening of the hypertension and coronary vasoconstriction — "unopposed alpha stimulation". **How large this risk is in practice is now disputed.** A meta-analysis of five studies and 1,794 subjects found no significant difference in myocardial infarction or mortality between patients given a beta-blocker and those not; a pooled analysis of eight studies and 2,048 patients with cocaine-associated chest pain found no excess of death or infarction; and a 2026 review concludes the risk "may be overstated". Guidance has not moved, and the case for relaxing the rule rests on reviews rather than on a trial. The rule is retained here because the physiology is sound and a benzodiazepine-first approach costs nothing — but it should be taught as a preference, not as an absolute prohibition.[4,7,11]
The correct approach	A **benzodiazepine first-line**, reducing central sympathetic drive and agitation, then a titratable vasodilator if the pressure remains dangerous — a **nitrate**, the combined alpha-and-beta blocker **labetalol**, or **phentolamine** where the picture is one of pure catecholamine excess — so the alpha-mediated vasoconstriction is addressed rather than left unopposed. A beta-blocker is not the first drug here, and that is not because it is proven dangerous but because the benzodiazepine and the vasodilator work better.
The parallel	This is the same logic as the alpha-before-beta rule of phaeochromocytoma (V1·Ch26), and it applies to the **acutely intoxicated** patient, in whom the instinctive reach for a beta-blocker to treat tachycardia and hypertension is the wrong first move. It is a different question from whether a patient with *past* cocaine exposure may take a beta-blocker for a compelling long-term indication such as heart failure or a previous infarct. There the long-term data show no signal of harm, and the drug should not be withheld on this account.[4,11]

30.3 Herbal agents and the Indian context

Herbal and traditional medicines are widely used in India, frequently alongside conventional treatment and often without the physician's knowledge, and several raise blood pressure or interfere with its control.

Why they go unmentioned

Patients often do not regard a traditional preparation as a **medicine**, and will not mention it unless asked — explicitly and without judgement.

TABLE 30.2 — HERBAL AGENTS TO ASK ABOUT

AGENT	EFFECT
Bitter orange	Contains **synephrine**; found in some weight-loss and energy products.[5]
Yohimbe	Alpha-adrenergic.[3]
Ginseng	Effect on blood pressure is **not settled**. A pressor effect is often quoted; the available systematic review examines ginseng for *lowering* pressure in hypertensives. Ask about it, but do not assume the direction.[2]
Guarana	A caffeine source.
Ephedra MA HUANG	A **powerful sympathomimetic**.[1]
St John's wort	Does **not** itself raise blood pressure, but **induces the metabolism of many drugs** and can thereby reduce the levels and effectiveness of some antihypertensives.[6]

30.4 Liquorice and mulethi

The most important herbal cause of hypertension in the Indian context, and one frequently missed, is liquorice — *mulethi* — a common ingredient of Ayurvedic preparations, powdered churnas, throat and cough remedies, and some confectionery.

When this enzyme is inhibited, cortisol accumulates at the receptor and — because cortisol activates the mineralocorticoid receptor with a potency similar to aldosterone — produces the full picture of mineralocorticoid excess: sodium retention, volume expansion, hypertension, potassium loss with hypokalaemia, and suppression of renin and aldosterone. This acquired state reproduces the inherited syndrome of apparent mineralocorticoid excess (V1·Ch11).

11β-HSD2

the enzyme inhibited

Glycyrrhizin\u2019s active metabolite blocks the enzyme that normally protects the mineralocorticoid receptor by converting cortisol to inactive cortisone.

TABLE 30.3 — TELLING IT FROM PRIMARY ALDOSTERONISM

	PRIMARY ALDOSTERONISM	LIQUORICE / MULETHI
Blood pressure	Raised	Raised
Potassium	Often low	Low
Renin	Suppressed	Suppressed
Aldosterone	Elevated	Also suppressed — the crucial distinguishing feature
Treatment	Adrenalectomy or a mineralocorticoid antagonist	Entirely reversible on stopping the preparation

The hypertensive patient with hypokalaemia and suppressed renin *and* aldosterone should always be asked specifically about liquorice, mulethi, Ayurvedic churnas and traditional remedies. Identifying this cause allows a simple, curative intervention in place of the unnecessary investigation and lifelong treatment that would follow a misdiagnosis — a particularly valuable point in Indian practice, given the widespread and often unmentioned use of these preparations. No dose is safe for every patient: caution is conventionally advised above about 2.5 g of liquorice daily, and thresholds as low as 1.125 g daily have been proposed, while the elderly, the hypoalbuminaemic, the constipated and those taking a loop diuretic or a glucocorticoid can develop severe hypokalaemia on far less. Recovery is also slower than the word *curative* suggests — chronic exposure depletes the enzyme rather than merely blocking its active site, so pressure and potassium may take weeks to months to normalise after the preparation is stopped.[10]

KEY POINTS

1. **Sympathomimetic decongestants** (pseudoephedrine, phenylephrine) in over-the-counter cold remedies raise blood pressure via alpha-adrenergic vasoconstriction and interfere with antihypertensive drugs. Advise avoidance, saline sprays, and label-reading of combination products.
2. **Cocaine and amphetamines cause intense sympathetic activation** — cocaine blocks noradrenaline and dopamine reuptake, amphetamines promote release — with severe acute hypertension that can precipitate stroke, infarction, aortic dissection and death.
3. **The cocaine beta-blocker trap:** in acute intoxication a beta-blocker is not the first drug, and never the only one — unopposed alpha stimulation may worsen vasoconstriction and coronary spasm. Guidance has not moved, though the pooled data show no excess of death or infarction and the case for relaxing the rule rests on reviews rather than on a trial.[7,11]
4. **Use a benzodiazepine first**, then a nitrate, labetalol or phentolamine — the same alpha-before-beta logic as phaeochromocytoma. A patient with *past* cocaine use and a compelling long-term indication for a beta-blocker is a different question, and the drug should not be withheld on that account.[11]
5. **Herbal pressor agents to ask about:** bitter orange (synephrine), yohimbe, ginseng, guarana and ephedra (ma huang). **St John\u2019s wort** does not raise pressure itself but induces drug metabolism and can lower antihypertensive levels. Ask explicitly — patients rarely volunteer traditional preparations.
6. **Liquorice and mulethi** (glycyrrhizin) inhibit 11β-HSD2, so cortisol activates the mineralocorticoid receptor, producing acquired **apparent mineralocorticoid excess**: sodium retention, hypertension, hypokalaemia, and suppressed renin *and* aldosterone. Common and frequently missed in Indian practice.
7. **The key clue is that both renin and aldosterone are low** — unlike primary aldosteronism, where aldosterone is high. It reverses completely on stopping the preparation, turning unnecessary investigation and lifelong treatment into a simple cure.

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CHAPTER — DEDICATED CHAPTER

Elevated blood pressure

The 130–139 / 80–89 range — the window in which hypertension is still reversible, and what the evidence supports doing in it.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why this range matters** — risk is already raised, and the disease is still functional rather than structural.
2. **What the guidelines call it** — and why ACC/AHA and ESC 2024 differ in the name but converge on acting.
3. **Confirming it properly** — out-of-office measurement before anyone is labelled.
4. **What lifestyle change achieves here** — quantified, and comparable to a drug in this range.
5. **Isometric exercise** — the most effective single exercise mode.
6. **When drug treatment is justified** — and the risk thresholds that justify it.
7. **The case for acting early** — the functional phase, before the resistance floor is laid down.

Part A — What is happening inside the body

A.1 One set of numbers, four names — the source of the confusion

A patient is found to have a blood pressure of 134/86 mmHg. Whether this is called a disease, a warning, or nothing at all depends entirely on which guideline the physician happens to follow, and the disagreement between the major bodies is the direct cause of the therapeutic paralysis that this chapter exists to resolve.

TABLE —.1

GUIDELINE	NAME FOR 130–139 / 80–89	WHAT IT RECOMMENDS
JNC 7 (2003)	"Prehypertension" (120–139/80–89)	Lifestyle; drugs only with compelling indication[2]
ACC/AHA 2017 SUPERSEDED 2025	**"Stage 1 hypertension"** (130–139/80–89)	Lifestyle for all; **drugs if 10-year ASCVD risk ≥10%** or established CVD, diabetes, or CKD[12] Replaced by the 2025 AHA/ACC guideline, which keeps the name and the band but gates the drug on established CVD, diabetes, CKD or a 10-year PREVENT risk of 7.5% or more — otherwise after three to six months of lifestyle therapy (V3 Ch12)
ESC 2024	**"Elevated BP"** (120–139/70–89)	Lifestyle 3 months; **drugs if 10-year CVD risk ≥10% and BP confirmed ≥130/80**
ESH 2023	"High-normal" (130–139/85–89)	Lifestyle; drugs in very-high-risk patients only[11]
WHO 2021 / Chinese 2018	Non-hypertensive, but treat if high-risk	**Drug treatment for those with ≥3 risk factors or established complications**[13]

The four labels describe the same person. The confusion they generate is not academic: because one respected body calls it a disease requiring treatment and another calls it a non-disease requiring only lifestyle advice, the practical result at the bedside is that the physician, uncertain which framing is correct, defaults to the one action that offends no guideline and commits to nothing — "reduce your salt and try to lose some weight" — and the patient leaves with no understanding of what is happening to them and no specific plan.

The resolution is to stop treating the name as the clinical question. The relationship between blood pressure and cardiovascular risk is continuous and begins far below any of these thresholds: the pooled analysis of 61 prospective studies (about one million adults aged 40 to 89) showed that death from ischaemic heart disease and from stroke rises steadily with usual blood pressure down to at least 115 mmHg systolic and 75 mmHg diastolic, roughly doubling for each 20/10 mmHg — an association, in middle-aged and older adults, and one whose proportional size falls with age. There is no biological threshold at which risk suddenly begins. The 130–139/80–89 band is therefore not a diagnostic label to be argued over but a **checkpoint**: the point at which the underlying processes have become detectable and at which they are still, crucially, reversible.[8]

A.2 The reversible window — why this stage is different from established hypertension

The single most important biological fact about this band, and the one that transforms the clinical conversation, is that the blood pressure elevation here is predominantly **functional** rather than **structural**. As set out in Chapters 1 and 15, sustained vascular resistance rises in two phases: an early functional phase, in which the arterioles are actively constricted by neural and humoral signals but the vessel wall is structurally normal, and a later structural phase, in which the wall has remodelled — smooth muscle rearranged around a narrower lumen, collagen laid down, the lumen permanently reduced. In the functional phase the elevation reverses completely when the driving stimulus is removed. In the structural phase it does not, because the narrowing has become built into the architecture of the vessel.

The 130–139/80–89 band is, for most people, the functional phase. This is the window in which the process can be turned back rather than merely slowed, in which the patient can be returned to a normal blood pressure without lifelong medication. The value of acting here is not that the interventions work better — measured in millimetres they work rather less at 136 than at 160, because the fall is proportional to the starting pressure, and the chapter's own table says so for DASH and for sodium. It is that the change being reversed is still functional. Once the band is crossed into sustained established hypertension and the structural remodelling sets in, the same lifestyle change still lowers the pressure, and by more, but it can no longer fully reverse the disease or keep the patient off medication. The clinical value of acting in this band is therefore disproportionate to the modest height of the numbers, and the failure to explain this to the patient — the failure to convey that they are standing at the one point where the disease is still reversible — is the central missed opportunity of routine practice.

A.3 What is actually happening inside the body

At this stage the machinery of hypertension has begun to shift, but no single mechanism has yet run to completion. Page's mosaic (V1·Ch10) is assembling: several early processes are usually present together, with one or two dominant. The processes below are what the patient should have explained to them, because the explanation is both true and motivating, and because each process maps directly onto an intervention that reverses it.

Early endothelial dysfunction. The endothelium is the single layer of cells lining every blood vessel, and its production of nitric oxide is what keeps the arteries relaxed and open. Reduced nitric-oxide availability — from oxidative stress, from a diet high in sodium and low in potassium, from physical inactivity, from visceral fat — is one of the earliest measurable abnormalities, detectable as reduced flow-mediated dilation before the blood pressure has risen at all. In plain terms: the vessels have begun to lose their ability to relax. This is reversible; nitric-oxide function improves with exercise, weight loss, sodium reduction and increased dietary potassium.

Early sympathetic activation. In many people, particularly the young and the stressed, the earliest driver is an increase in the tone of the sympathetic nervous system — the "fight or flight" system running slightly too high, all the time. Its fingerprint is a resting heart rate at the upper end of or above the normal range, a high-output haemodynamic pattern (V1·Ch14), and often a history of chronic stress or disrupted sleep. In plain terms: the body is being held in a low-grade state of alarm, and the heart and vessels are responding accordingly. This is reversible; sympathetic tone falls with aerobic and isometric exercise, with sleep, with treatment of sleep apnoea, and with the structured reduction of chronic stress.

Early salt sensitivity and a subtle volume load. In the salt-sensitive person — and, for the reasons set out in V1·Ch12, a large proportion of the South Asian population is salt-sensitive because of a low nephron endowment from high rates of low birth weight — the kidney cannot excrete a high sodium load without a small rise in pressure. At this stage the volume expansion is subtle and the pressure–natriuresis curve has shifted only slightly, but the process has begun. In plain terms: the body is holding on to a little too much salt and water, and the pressure has risen to push it out. This is reversible; it responds directly to sodium reduction and to increased dietary potassium.

Early activation of the renin–angiotensin system and early arterial stiffening. The renin–angiotensin system may be modestly activated, contributing vasoconstriction and further sodium retention, and the large arteries have begun — but only begun — to stiffen. At this stage the stiffening is functional and reversible; left for years, it becomes the fixed structural stiffness that produces the isolated systolic hypertension of later life (V1·Ch15).

Insulin resistance and the metabolic connection. Where central obesity is present, insulin resistance ties the blood pressure to the whole metabolic syndrome: insulin promotes renal sodium retention and sympathetic activation, and the visceral fat itself behaves as an endocrine organ generating angiotensin and leptin (V1·Ch21). In plain terms: the same visceral fat that is raising the blood sugar and the cholesterol is also raising the blood pressure,

through shared machinery. This is why weight loss is genuinely powerful here — not as a vague virtue but because it removes the organ driving several mechanisms at once.

The unifying message, for both the physician and the patient, is that at this stage these processes are **functional adaptations, not fixed damage**, and that each of them can be reversed by a specific and identifiable action. The body is not yet diseased; it is responding, and the response can be redirected.

A.4 The risk, and the rate of progression — why this is not "nothing"

The other half of the confusion is the belief that because the numbers are only modestly raised, the band is benign and can be safely ignored. The outcome data refute this directly.

In the CARDIA study, which followed young adults (aged 18–30 at entry) for nearly 19 years, the rate of cardiovascular events rose stepwise with the baseline category: **1.37 per 1,000 person-years** with normal BP, **2.74** with elevated BP, **3.15** with stage 1 hypertension (130–139/80–89) and **8.04** with stage 2 hypertension. Stage 1 hypertension developing before the age of 40 carried an adjusted hazard ratio of 1.75 (95% CI 1.22–2.53) for cardiovascular disease compared with normal blood pressure — 228 events among 4,851 people over a median of 18.8 years, an association in an observational cohort, adjusted for the usual confounders and not proof that the pressure caused the events. A large Korean cohort of young adults and a UK analysis of 1.3 million adults are consistent with it in direction, the UK analysis finding both systolic and diastolic pressure independently associated with myocardial infarction and stroke down to 130/80; neither effect size is printed here. Beyond the direct risk, this band progresses: a substantial proportion of people in it develop established stage 2 hypertension within a few years, and the earlier the band is reached, the longer the lifetime exposure and the greater the accumulated damage.[9,14]

The band is therefore neither a disease to be medicated reflexively nor a non-event to be dismissed. It is a genuine, quantified elevation in risk arising from reversible processes — which is precisely the situation in which intervention has the highest value.

Part B — How to manage it

B.1 First, confirm it is real — out-of-office measurement

Before anything is done, the elevation must be confirmed outside the clinic, because this band is where **masked hypertension** (normal clinic readings, high out-of-office readings) and **white-coat elevation** (the reverse) are most common, and because a management plan built on a single clinic reading in this range is built on sand. Home blood-pressure monitoring over seven days, or 24-hour ambulatory monitoring, establishes the true average and reveals the night-time and morning pattern that points toward the dominant mechanism (a high morning surge and non-dipping pattern suggest sympathetic overactivity or sleep apnoea). The out-of-office thresholds are lower than the clinic thresholds: an average home or daytime ambulatory pressure of 135/85 corresponds to a clinic 140/90.

B.2 The decision — lifestyle alone, or lifestyle plus a drug

Once the elevation is confirmed, the treatment decision in this band is **risk-stratified, not uniform.** This is the point on which the guidelines actually agree once the labels are set aside: the higher the total cardiovascular risk, the lower the blood-pressure threshold at which a drug is justified.

- **Lower-risk patient** (no established cardiovascular disease, no diabetes, no chronic kidney disease, estimated 10-year risk below about 10%): a structured trial of lifestyle intervention for three to six months is the correct first step, with the specific, quantified programme set out below, and reassessment on out-of-office measurement. Most people in this group can be returned toward normal without a drug.
- **Higher-risk patient** (established cardiovascular disease, diabetes, chronic kidney disease, or a high estimated 10-year risk): the evidence — reflected in the ACC/AHA 2017, WHO 2021, Chinese, and 2024 ESC positions — supports starting drug treatment in this band alongside lifestyle, because the absolute benefit of lowering the pressure is large when the underlying risk is high. In this group the lifestyle programme is not an alternative to the drug but an addition to it.

Lifestyle intervention is therefore never the fallback default it is so often used as; it is the specific, evidence-based first-line treatment in the lower-risk patient and an essential co-treatment in the higher-risk one.

B.3 The complete toolkit — with magnitudes

This is the antidote to "lose some weight." Each intervention below has a mechanism that maps onto the processes of Part A and a quantified effect on systolic pressure from randomised trials and meta-analyses. Presented together, and honestly, they change the conversation entirely: the patient is not being given a vague instruction but a menu of specific, measurable treatments, several of which rival a drug.

TABLE —.2

INTERVENTION	MECHANISM IT REVERSES	TYPICAL SYSTOLIC REDUCTION	NOTES / EVIDENCE
Isometric exercise (wall squat or handgrip, ~4 × 2 min, 3×/week)	Sympathetic tone; endothelial/NO function; baroreflex	**−8 mmHg** (−8.2/−4.0)	The **most effective** single mode in a 270-trial network meta-analysis (BJSM 2023); wall squat ranked highest for systolic. Almost never prescribed.[3]
DASH dietary pattern	Sodium load; low potassium/magnesium; endothelial function	**−5 to −11 mmHg**	−5.5 overall, up to −11.4 in established hypertension; comparable to a drug. Adapts to Indian food (dals, vegetables, fruit, millets, curd, nuts).[1]
Sodium reduction (toward <5 g salt/day, confirmed by 24-hr urine)	Salt sensitivity; subtle volume load; vascular sodium effects	**−4 to −5 mmHg** (more in the salt-sensitive)	Larger effect in South Asians, the elderly, the obese, and the diabetic. Hidden sodium (pickles, papad, namkeen, processed food) must be named specifically.[4]

INTERVENTION	MECHANISM IT REVERSES	TYPICAL SYSTOLIC REDUCTION	NOTES / EVIDENCE
Increased dietary potassium / potassium-based salt substitute	Opposes sodium; VSMC relaxation	Adds to sodium reduction	The Salt Substitute and Stroke Study showed reduced stroke and death; 2024 ESC now recommends potassium supplementation/substitutes. **Avoid in CKD or on ACEi/ARB/MRA** (hyperkalaemia).[5,6]
Combined aerobic + resistance training	Sympathetic tone; insulin resistance; weight	**−6 mmHg** (−6.0/−2.5)	Second-ranked mode in the same 270-trial network meta-analysis (BJSM 2023) as the isometric row.[3]
Aerobic exercise (≥150 min/week moderate)	Sympathetic tone; endothelial function; weight	**−4.5 mmHg** (−4.5/−2.5)	The guideline baseline, but not the most effective mode; the figure is from the same network meta-analysis.[3]
Weight loss	Visceral-fat RAAS/leptin; insulin resistance; OSA	**~1 mmHg per kg** lost	Powerful because it removes an organ driving several mechanisms — but it is one tool among many, not the whole prescription.[7]
Alcohol reduction	Sympathetic activation; direct pressor effect	**−3.8 mmHg**	Dose-dependent; largest effect in heavier drinkers.[10]
Treating sleep / OSA; stress reduction	Chemoreflex and sympathetic drive; RVLM sensitisation	Variable, can be large in OSA	Screen with STOP-BANG (V1·Ch24); mindfulness and slow (≈6/min) breathing reduce central sympathetic drive (V1·Ch14).

The decisive point is that these effects **combine**, though they do not simply add. A motivated patient who adopts an isometric-exercise routine, moves toward a DASH pattern, cuts hidden sodium and raises dietary potassium, and loses several kilograms will do better than one who adopts any single measure — but combined lifestyle programmes in trials deliver rather less than the sum of the rows above, and less at 136 mmHg than at 160, because every effect in the table is smaller at a lower starting pressure. A figure of 15 to 20 mmHg is sometimes quoted for combined change. It is obtained by adding the rows above together, each measured in a different population; nobody has shown it from a starting point of 136/88, so no such figure is printed here. What can be said is that a patient in this band can be returned to a genuinely normal pressure and kept off medication, and that this is worth having — and that it is not a substitute for a drug in a patient whose risk already justifies one, as set out above. That is a specific, achievable outcome, and it is the outcome that "lose some weight" fails to describe.

B.4 Match the intervention to the dominant driver

Even in this early band the phenotype can be read, and directing the programme at the dominant driver makes it more effective and more persuasive.

- **Sympathetic/neurogenic pattern** (young, lean, stressed, resting heart rate above 80, high morning surge): lead with isometric and aerobic exercise, sleep and stress management, and treatment of any sleep apnoea. This is the group in whom the resting heart rate is the clue and in whom exercise has the largest effect.
- **Salt-sensitive/volume pattern** (South Asian, family history, high dietary salt, non-dipping pattern, older): lead with sodium reduction, potassium, and the DASH pattern, and confirm intake with a 24-hour urine sodium.
- **Metabolic pattern** (central obesity, high waist circumference, impaired glucose, dyslipidaemia): lead with weight loss and combined exercise, and address the whole metabolic syndrome — because in this patient the blood pressure is one facet of a single disorder.

B.5 Monitoring and when to escalate

The lifestyle programme is reviewed on out-of-office measurement at three months (sooner in the higher-risk patient). If the pressure has fallen into the normal range, the programme is continued and the pressure rechecked periodically, since the band tends to recur if the intervention lapses. If the pressure remains in the elevated band or has risen into established hypertension despite a genuine and confirmed lifestyle effort — or if the patient was higher-risk from the outset — drug treatment is added, chosen by the phenotype and the comorbidities as set out in the drug chapters. The lifestyle programme continues regardless, because its benefit is additive to the drug and extends beyond blood pressure to the whole of cardiovascular risk.

B.6 What to actually tell the patient

The failure this chapter addresses is, in the end, a failure of explanation. The patient in this band is almost always told what *not* to do (too much salt, too much weight) and almost never told what is happening to them or what specifically to do about it. A short, honest explanation changes the encounter, and it need take only a few minutes:

"Your blood pressure is 136/86. That is not yet a disease, but it is a warning stage — your body has started down a road that leads to high blood pressure, and I can show you exactly what is happening. Right now the change is still in how your blood vessels are behaving, not in how they are built — which means it can still be reversed. Inside your body, [the one or two dominant processes, in plain terms: your vessels have started losing their ability to relax / your system is running in a state of low-grade alarm / your body is holding on to a little too much salt and water]. The good news is that at this stage, before it becomes fixed, the right changes can turn it around completely — and I don't mean only losing weight. Here are the specific things that work and how much each one lowers pressure [name two or three, with the numbers, matched to their pattern]. Together these can lower your pressure by more than a tablet would, and if we do this now, you may never need a tablet at all. I'd like to see you in three months, and I'll give you a home blood-pressure target to track."

This is more time than the six-minute encounter usually allows, and it is the single most valuable thing that can be done for a patient in this band. It converts a vague and forgettable instruction into an understood diagnosis, a

specific plan, and a reason to act while acting still reverses the disease.

KEY POINTS

1. **The 130–139 / 80–89 range carries real excess cardiovascular risk**, and is where the disease is still functional and reversible rather than structurally fixed.
2. **The guidelines differ in nomenclature but converge on action:** ACC/AHA classes 130–139/80–89 as stage 1 hypertension; ESC 2024 introduced the category of **Elevated BP** for 120–139/70–89.
3. **Confirm before labelling.** Out-of-office measurement — home or ambulatory — separates sustained elevation from white-coat effect.
4. **Lifestyle change is the primary intervention here**, and in this range its effect is comparable to a drug: weight loss, sodium restriction, potassium, the DASH pattern, alcohol reduction and exercise.
5. **Isometric exercise is the most effective single exercise mode** for blood-pressure reduction.
6. **Drug treatment is reserved for those at higher total cardiovascular risk**, or with established disease, diabetes or kidney disease — not applied across the whole range.
7. **Acting in this window is disproportionately valuable**, because the arterioles have not yet remodelled and the resistance floor of V1·Ch15 has not yet been laid down.

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CHAPTER — DEDICATED CHAPTER

Understanding clinical trials and research papers

What a trial is, why it is done, how to read one, and the landmark trials this book relies on.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why this chapter exists** — every recommendation here rests on trial evidence a reader should be able to interrogate.
2. **Trial architecture** — randomisation, blinding, control, and what each protects against.
3. **The statistics that carry weight** — and the ones that mislead.
4. **Relative versus absolute** — why the same result can be presented two very different ways.
5. **Where scepticism is warranted** — subgroups, surrogate endpoints, and early stopping.
6. **The landmark hypertension trials** — each in one structured format.
7. **Reading as practice** — applying the method of Part A to the trials of Part B.

PART A — How to read a clinical trial

A.1 Why trials exist — the aim

Medicine must answer a simple but hard question for every treatment: *does it actually help, and is the benefit worth the harm*? For most of history this was answered by anecdote ("the patients I gave it to improved"), by authority ("my professor always used it"), and by mechanism ("it should work because of how the body functions"). Each of these is unreliable. Patients often improve anyway; authorities are often wrong; and drugs that should work by their mechanism frequently fail, or cause unexpected harm, when actually tested. The purpose of a **clinical trial** is to answer the question reliably by *comparing* the treatment against an alternative in a way that removes, as far as possible, the two great enemies of truth in medicine: **bias** (systematic error that pushes the answer in one direction) and **chance** (random error). This is the foundation of **evidence-based medicine**: making decisions from the best available evidence, generated by studies designed to minimise bias and chance, rather than from anecdote or authority alone.

The **aim of a trial**, stated precisely, is to estimate the effect of an intervention on an outcome that matters, in a defined group of patients, with enough participants and enough rigour that the result is unlikely to be due to bias or chance. Everything about how trials are designed follows from that single aim.

A.2 The hierarchy of evidence

Not all evidence is equally trustworthy. Study designs form a hierarchy, from weakest to strongest for questions about whether a treatment works:

- **Case report / case series** — a description of one or a few patients. Useful for raising a hypothesis or flagging a rare harm, but no comparison group, so it cannot show a treatment works.
- **Case–control study** — starts with people who have an outcome (cases) and people who do not (controls), and looks backward for exposures. Efficient for rare diseases, but prone to bias.
- **Cohort study** — follows groups with and without an exposure forward in time to see who develops the outcome. Better, but the groups may differ in ways that confuse the result (**confounding**).
- **Randomised controlled trial (RCT)** — allocates patients *by chance* to the treatment or the comparison, then follows them forward. This is the reference standard for treatment questions (explained below).
- **Systematic review and meta-analysis** — a rigorous synthesis of all the trials on a question, statistically combining them. At the top of the hierarchy when the underlying trials are good.

The reason the RCT sits near the top is randomisation, which is the single most powerful idea in clinical research.

A.3 The anatomy of a randomised controlled trial

Every term below appears in the trials cited in this book. Understanding them is most of the battle.

The question and the population. A good trial begins with a precise question, often framed as **PICO**: in this **P**opulation, does this **I**ntervention, compared with this **C**omparator, change this **O**utcome? The population is defined by **inclusion and exclusion criteria** — for example, SPRINT included adults with a systolic pressure of 130 mmHg or above at increased cardiovascular risk, and *excluded* those with diabetes or a prior stroke. These criteria matter enormously, because a trial's result strictly applies only to the kind of patient it enrolled (see generalisability, A.6).

Randomisation. Participants are allocated to the treatment or the comparator *by chance* (like a coin toss, done by computer). This is the heart of the RCT. Its purpose is to make the two groups alike in every respect — known and unknown, measured and unmeasured — *except* the treatment. If the groups start out identical and differ only in the treatment, any difference in outcome can be attributed to the treatment. Randomisation is what removes **confounding**, the problem that ruins observational studies (in which sicker or healthier patients may be selectively given the treatment).

Allocation concealment. The randomisation must be concealed from the people enrolling patients, so they cannot steer a particular patient into a particular group. This protects the randomisation itself.

Blinding (masking). After allocation, it is best if people do not know which group a patient is in, because knowing can bias behaviour and assessment. In a **double-blind** trial, neither the patient nor the treating clinician knows. In a **single-blind** trial, only one of them is unaware. An **open-label** trial has no blinding — everyone knows the allocation — which is sometimes unavoidable (you cannot easily blind a surgical procedure or a dosing-time comparison). A

useful compromise is the **PROBE** design (Prospective Randomised Open, Blinded Endpoint), in which treatment is open-label but the *outcomes are judged by assessors who are blinded* — this is how the TIME dosing-time trial was run.

The comparator (control). The treatment is compared against something: an inactive **placebo** (a dummy pill, to control for the act of being treated), an **active comparator** (another real drug, to see which is better), or a **sham procedure** (a fake procedure, essential in device trials — the renal denervation trials used a sham catheterisation, and this is why the early unblinded results proved misleading). A **control group** is what makes a trial a trial; without it, you cannot know what would have happened anyway.

Follow-up. Patients are followed for a defined period to see who develops the outcomes. Longer follow-up detects effects on slow outcomes such as death and stroke.

Outcomes (endpoints). The **primary outcome** is the single main question the trial was designed and powered to answer, specified *before* the trial begins (to prevent cherry-picking afterwards). **Secondary outcomes** are additional questions, treated more cautiously. A crucial distinction is between a **hard (clinical) endpoint** — something that matters directly to the patient, such as death, stroke or myocardial infarction — and a **surrogate endpoint** — a substitute measurement, such as the blood-pressure number itself or a laboratory value, that is *assumed* to predict the hard outcome but sometimes does not. A drug can lower a surrogate (blood pressure) yet fail to improve, or even worsen, the hard outcome (events) — which is exactly why outcome trials, not just blood-pressure measurements, are needed. Many trials use a **composite endpoint** that combines several hard outcomes (for example "cardiovascular death, myocardial infarction, or stroke") to accumulate enough events; this is efficient but must be read carefully (A.6).

Intention-to-treat versus per-protocol. In the **intention-to-treat** analysis, patients are analysed in the group they were *randomised* to, regardless of whether they actually took the treatment or dropped out. This sounds odd but it preserves the benefit of randomisation and gives a realistic estimate of the effect in practice; it is the trustworthy primary analysis. A **per-protocol** analysis includes only those who completed the treatment as intended — it can look more impressive but reintroduces bias, because the patients who complete treatment differ from those who do not.

Power and sample size. A trial must be large enough to detect a real effect if one exists. **Statistical power** is the probability of finding a true effect; trials are designed with enough participants (the **sample size**) to have adequate power (usually 80–90%). An underpowered trial that finds "no difference" may simply have been too small to detect one — *absence of evidence is not evidence of absence*.

Stopping early. Trials are monitored by an independent board, and may be **stopped early** for overwhelming benefit (as SPRINT was), for harm, or for futility. Early stopping for benefit can exaggerate the effect size and is interpreted with some caution.

A.4 How to read a research paper — the IMRAD structure

A trial is reported as a paper with a standard structure, **IMRAD**:

- **Introduction** — why the study was done and the precise question (the last paragraph usually states the aim).
- **Methods** — *how* it was done: the population, randomisation, blinding, intervention, comparator, outcomes and analysis. **This is the most important section for judging whether to believe the result**, yet it is the one beginners skip. A beautiful result from a flawed method is worthless.
- **Results** — *what happened*: the baseline characteristics of the groups (check they were balanced), the primary outcome, then the secondary outcomes and harms. The key numbers live here.
- **And Discussion** — what the authors think it means. Read this *critically and last*, because it is where enthusiasm and **spin** can creep in; authors may emphasise favourable secondary findings or downplay harms.

A practical **order to read** a paper is: read the **abstract** for the gist; jump to the **methods** to see if the design is sound and who was enrolled; look at the **primary outcome** in the results and its confidence interval; check the **harms**; and only then read the **discussion**, keeping your own judgement. The **title** and **abstract** alone are never enough — they are a summary written by people who want their work to matter.

A.5 The statistics you actually need

You do not need to be a statistician. You need to understand a handful of measures, which are best learned from a real example. In **SPRINT**, treating to a systolic target below 120 mmHg (intensive) rather than below 140 mmHg (standard) reduced the primary cardiovascular composite, with the event rate falling from about **2.2% per year to about 1.65% per year**.

Relative risk (RR) and relative risk reduction (RRR). The relative risk is the risk in the treated group divided by the risk in the control group. In SPRINT the intensive group had about **25% lower relative risk** of the primary outcome (reported as a hazard ratio of 0.75 — see below). "A 25% reduction" sounds dramatic, and it is the number most often quoted in headlines — but it is *relative*, and relative numbers can mislead (see the trap below).

Absolute risk reduction (ARR). This is the plain difference in risk: about 2.2% per year minus about 1.65% per year, roughly **0.55% per year** — or, over the trial, an absolute difference of a few percent. This is the number that tells a patient their actual benefit, and it is far less dramatic than the relative figure while being more honest.

Number needed to treat (NNT). The NNT is 1 divided by the absolute risk reduction, and it answers the most clinically useful question: *how many patients must I treat, for how long, to prevent one event*? A small ARR means a large NNT (many patients treated per event prevented); a large ARR means a small NNT. The NNT turns statistics into something a clinician and patient can weigh against cost and side effects.

The relative-versus-absolute trap. The same result can be presented as "a 25% reduction in risk" (relative, impressive) or "a 0.55% per year reduction in risk" (absolute, modest) — both true, describing the same data. A treatment

that halves a risk sounds wonderful, but halving a risk from 2 in a million to 1 in a million is trivial, whereas halving it from 40% to 20% is enormous. **Always ask for the absolute numbers**; a relative reduction alone, without the baseline risk, cannot tell you whether a treatment matters for your patient.

Hazard ratio (HR). Most cardiovascular trials measure *time to an event* and summarise the effect as a hazard ratio — roughly, the rate of events in the treated group relative to the control group over time. An HR of **1.0** means no difference; **below 1.0** means the treatment reduces events (SPRINT's HR of 0.75 = a 25% reduction); **above 1.0** means it increases them. The HR is essentially a relative measure and carries the same caution.

Confidence interval (CI). No trial measures the true effect exactly; it estimates it, with uncertainty. The 95% confidence interval is the range within which the true effect very probably lies. Its width tells you the **precision** (a narrow interval is precise, a wide one uncertain). Crucially, **if the confidence interval for a hazard ratio or relative risk crosses 1.0, the result is not statistically significant** — the treatment might help, do nothing, or harm. A result of "HR 0.75 (95% CI 0.64–0.89)" is significant because the whole interval is below 1; "HR 0.95 (95% CI 0.83–1.10)" — the TIME dosing-time result — is *not* significant, because the interval straddles 1.

p-value. The p-value is the probability of seeing a difference at least as large as the one observed *if the treatment truly had no effect*. By convention, $p < 0.05$ is called "statistically significant." But the p-value is widely misunderstood: it does **not** tell you the size or importance of an effect, only how likely the result is to be a fluke of chance. A tiny, clinically meaningless difference can be "highly significant" in a huge trial, and an important effect can be "non-significant" in a small one. Read the p-value alongside the effect size and the confidence interval, never alone.

Odds ratio (OR). In case–control studies (and some others) the effect is expressed as an odds ratio, interpreted like a relative risk (1.0 = no effect, below 1 = protective, above 1 = harmful). For rare outcomes it approximates the relative risk.

A.6 How to be a skeptic — critical appraisal

Believing a trial requires checking that its result is not an artefact. The main threats:

Bias. *Selection bias* — the groups differed at the start (prevented by randomisation and concealment). *Performance bias* — the groups were treated differently apart from the intervention (prevented by blinding). *Detection bias* — outcomes were assessed differently between groups (prevented by blinded endpoint assessment). *Attrition bias* — patients dropped out differentially (check how many were lost and whether intention-to-treat was used). *Reporting bias* — favourable outcomes were emphasised and unfavourable ones buried (check that the primary outcome was pre-specified and that harms are reported).

The composite-endpoint trap. A composite of "death, myocardial infarction, stroke and hospitalisation for heart failure" may show a benefit driven almost entirely by the *softest, most subjective* component

(hospitalisation) while the hard components (death) show nothing. Always look at which component drove a composite result.

The subgroup trap. Trials report effects in subgroups (by age, sex, ethnicity). With enough subgroups, some will show a "significant" effect by chance alone. Subgroup findings are hypothesis-generating, not conclusions, unless pre-specified and confirmed.

The surrogate-endpoint trap. A drug that improves a surrogate (blood pressure, a lab value) has not been shown to improve the outcomes that matter until a hard-endpoint trial proves it. History is full of drugs that improved a surrogate and harmed patients.

Funding and conflicts. Industry-funded trials are not automatically wrong, but funding and author conflicts should be noted, and independent replication valued.

The HYGIA lesson. A published trial can simply be wrong. The HYGIA chronotherapy trial reported that bedtime dosing of antihypertensives halved cardiovascular events — an effect so large it invited scrutiny; serious questions were raised about its conduct, a journal issued an expression of concern, and the rigorous, independent **TIME** trial then found *no difference* by dosing time (V1·Ch7). The lesson is that a single trial, however dramatic, is not the truth; the truth emerges from rigorous, replicated evidence, and extraordinary claims deserve extraordinary scrutiny.[17,38,39]

Generalisability (external validity). Finally, ask: *does this trial apply to my patient*? A trial in 60-year-old Europeans without diabetes may not translate directly to a 40-year-old Indian with diabetes. The strict inclusion and exclusion criteria that make a trial internally valid also limit whom its result applies to. This is a particular consideration when applying trials conducted in Western populations to Indian practice.

A.7 A worked example — reading SPRINT

Putting it together with the trial you will meet most often in this book:

- **Question (PICO):** In adults with systolic BP ≥130 mmHg at increased cardiovascular risk but *without* diabetes or prior stroke (**P**), does an intensive target of <120 mmHg (**I**) versus a standard target of <140 mmHg (**C**) reduce major cardiovascular events and death (**O**)?
- **Design:** Randomised, controlled, open-label with blinded endpoint adjudication; 9,361 participants; multicentre; median follow-up 3.26 years; stopped early for benefit.
- **Result:** Achieved systolic pressures were about 121 versus 136 mmHg (a ~15 mmHg separation). The primary composite fell with intensive treatment — **hazard ratio 0.75 (25% relative reduction), p < 0.001** — and all-cause mortality fell (**HR 0.73, 27% reduction**). Absolute event rates were about 1.65% versus 2.2% per year. Harms were higher in the intensive group: hypotension, syncope, electrolyte disturbance and acute kidney injury.
- **Appraisal:** Large, well-conducted, intention-to-treat, hard composite endpoint with blinded adjudication — strong internal validity. But *note the exclusions* (no diabetes, no prior stroke) and *note the measurement method* — SPRINT used a careful, standardised, often unobserved blood-pressure

technique that reads lower than a routine clinic measurement, so the "<120" target is not the same as <120 on a busy clinic machine — the gap is **5–15 mmHg**, so SPRINT's target corresponds to about **130–135 mmHg attended**. This is why guidelines that adopt the SPRINT target also insist on standardised measurement (Chapters 8 and 19).

- **What it changed**: SPRINT drove the intensive systolic targets in the 2017 ACC/AHA, 2024 ESC and 2021 KDIGO guidelines.

You have now appraised a landmark trial. The template you just used — question, design, result with numbers, appraisal, impact — is the template of Part B.

PART B — The landmark hypertension trials

Each trial below is given in the same structure: the **question**, the **design**, the **result**, **why it matters**, and **where it is cited in this book**. Read a few and the pattern becomes second nature. (Any one of these can be expanded to a fuller deep-dive on request.)

Blood-pressure targets

SPRINT (Systolic Blood Pressure Intervention Trial, 2015). *Question*: does treating to <120 vs <140 mmHg systolic reduce events in high-risk non-diabetics? *Design*: RCT, 9,361 patients, open-label/blinded-endpoint, stopped early at 3.26 years. *Result*: primary composite HR 0.75 (25% reduction), mortality HR 0.73 (27%); more hypotension and acute kidney injury. *Why it matters*: the basis of modern intensive targets — but only by unattended standardised measurement, which is about 5–15 mmHg below an attended reading, so <120 unattended is roughly 130–135 attended. *Cited in*: Chapters 8, 17, 19.[32]

ACCORD-BP (2010). *Question*: does intensive (<120) vs standard (<140) systolic control help in type 2 diabetes? *Design*: RCT in diabetics. *Result*: the intensive target did **not** reduce the primary cardiovascular composite, though it reduced stroke. *Why it matters*: tempered enthusiasm for very intensive targets in diabetes; contributed to the <130/80 diabetic target. *Cited in*: V1·Ch20.[27]

STEP (2021, China). *Question*: <130 vs <150 systolic in adults aged 60–80? *Result*: the intensive target reduced cardiovascular events by about a quarter (HR 0.74, 95% CI 0.60–0.92); safety and renal outcomes did not differ significantly, except for hypotension, which was more frequent in the intensive group — so monitor for it. *Why it matters*: supports intensive targets in the fit elderly. *Cited in*: Chapters 8, 17.[36]

HYVET (Hypertension in the Very Elderly Trial, 2008). *Question*: should we treat hypertension in the over-80s? *Design*: RCT, patients ≥80 with systolic ≥160, indapamide ± perindopril, target <150/80. *Result*: stroke reduced ~30% but at p = 0.055 — the primary endpoint did not reach conventional significance; all-cause mortality ~21% (p = 0.05) and heart failure ~64% (p < 0.001) did. *Why it matters*: the first randomised evidence that treating hypertension over the age of 80 reduces mortality — on a secondary endpoint, in a trial whose primary endpoint fell just short. The direction is believed; the size should not be quoted as settled. *Cited in*: V1·Ch17.[6]

SHEP (1991) and **Syst-Eur** (1997). *Question*: does treating isolated systolic hypertension in the elderly help? *Design*: RCTs — SHEP chlorthalidone-based, Syst-Eur nitrendipine-based, vs placebo. *Result*: SHEP reduced stroke by 36%; Syst-Eur by 42% (and dementia by 50% in a sub-analysis). *Why it matters*: established treatment of elderly isolated systolic hypertension, and the diuretic and calcium channel blocker as first-line for it. *Cited in*: V1·Ch17.[12,25,26]

Drug classes and combinations

ALLHAT (2002). *Question*: in a very large, diverse population, is a diuretic, a calcium channel blocker, an ACE inhibitor or an alpha-blocker best as first-line? *Design*: the largest antihypertensive trial ever, over 40,000 patients, randomised to chlorthalidone, amlodipine, lisinopril or doxazosin. *Result*: the **doxazosin (alpha-blocker) arm was stopped early** for excess heart failure; among the other three, chlorthalidone was at least as good as amlodipine and lisinopril for the primary coronary outcome and *better* for some outcomes including heart failure, and performed particularly well in Black patients. *Why it matters*: cemented the thiazide-type diuretic as a first-line agent and demoted alpha-blockers to add-on use. *Cited in*: Chapters 11, 17.[2]

ASCOT (2005) and its **CAFE** sub-study. *Question*: is an amlodipine ± perindopril regimen better than an atenolol ± thiazide regimen? *Result*: the primary endpoint — non-fatal myocardial infarction plus fatal coronary disease — did not differ significantly (HR 0.90, 95% CI 0.79–1.02, p = 0.1052). Stroke (HR 0.77), total cardiovascular events (HR 0.84), new-onset diabetes (HR 0.70) and all-cause mortality (HR 0.89) were all lower on the amlodipine-based regimen — every one of them a secondary endpoint. In the CAFE sub-study, where the two arms' *brachial* pressures were similar, amlodipine produced a lower *central aortic* pressure (by about 4.3 mmHg) than atenolol. *Why it matters*: the trial that moved the beta-blocker/thiazide combination out of first place — on secondary endpoints, which is the honest reading — and the source of the concept that central pressure, not the cuff reading, drives outcome. *Cited in*: V1·Ch15.[11,35]

ACCOMPLISH (2008). *Question*: with an ACE inhibitor, is a calcium channel blocker or a thiazide the better partner? *Result*: benazepril + amlodipine reduced cardiovascular events more than benazepril + hydrochlorothiazide at similar blood pressure. *Why it matters*: made the ACE inhibitor/ARB + calcium channel blocker pairing the preferred combination. *Cited in*: V1·Ch15.[14]

LIFE (2002). *Question*: losartan (an ARB) versus atenolol (a beta-blocker) at equal blood pressure? *Result*: losartan produced greater stroke reduction and left ventricular hypertrophy regression. *Why it matters*: showed effects beyond blood pressure, and contributed to atenolol's demotion. *Cited in*: Chapters 3, 14, 15.[10]

HOPE (2000). *Question*: does the ACE inhibitor ramipril reduce events in high-risk patients beyond its blood-pressure effect? *Result*: significant reductions in cardiovascular death, myocardial infarction and stroke. *Why it matters*: a foundation of RAAS blockade for cardiovascular protection. *Cited in*: V1·Ch3.[29]

ONTARGET (2008). *Question*: is combining an ACE inhibitor and an ARB (dual RAAS blockade) better than either alone? *Result*: **no added benefit, and more harm** — acute kidney injury, hyperkalaemia, hypotension. *Why it matters*: *do not combine an ACE inhibitor with an ARB for blood pressure*. The regulators stop short of a ban — the label says to avoid combined RAAS blockade in general, and the licensed exception is candesartan or valsartan added to an ACE inhibitor in heart failure, under specialist supervision with close monitoring of renal function, potassium and pressure.[37] *Cited in*: Chapters 3, 19, 20.[31]

Resistant hypertension and the aldosterone/endothelin pathways

PATHWAY-2 (2015). *Question*: what is the best fourth drug for resistant hypertension? *Design*: RCT comparing spironolactone, bisoprolol, doxazosin and placebo as add-on. *Result*: **spironolactone was clearly the most effective**, confirming that resistant hypertension is often driven by sodium retention and aldosterone. *Why it matters*: made spironolactone the standard fourth-line agent. *Cited in*: Chapters 12, 13.[34]

RALES (1999) and **EPHESUS** (2003). *Question*: do mineralocorticoid antagonists help in heart failure? *Result*: spironolactone (RALES) and eplerenone (EPHESUS, post-infarction) reduced mortality. *Why it matters*: established the cardiovascular, not merely diuretic, benefit of blocking aldosterone. *Cited in*: Chapters 3, 13.[21,22]

PRECISION (2022). *Question*: does the dual endothelin antagonist aprocitentan lower blood pressure in resistant hypertension? *Design*: phase 3 RCT, on top of three-drug therapy. *Result*: significant additional reduction (~4 mmHg office, ~5 mmHg ambulatory systolic), sustained to 40 weeks; main adverse effect oedema. *Why it matters*: led to the 2024 FDA approval of aprocitentan — the first new antihypertensive mechanism in about three decades. *Cited in*: Chapters 6, 19.[24]

SYMPLICITY HTN-3 / SPYRAL / RADIANCE (renal denervation). *Question*: does catheter ablation of the renal nerves lower blood pressure? *Design*: sham-controlled RCTs. *Result*: the first (SYMPLICITY HTN-3, 2014) was **neutral**; improved second-generation trials (SPYRAL, RADIANCE) showed consistent modest reductions over sham. *Why it matters*: a lesson in the value of sham controls, and the basis for the 2023 FDA approval and current guideline role of renal denervation as an adjunct. *Cited in*: V1·Ch4.[4,7,8]

Kidney protection

RENAAL and **IDNT** (2001). *Question*: do ARBs protect the kidney in diabetic nephropathy? *Result*: losartan (RENAAL) and irbesartan (IDNT) slowed progression to kidney failure. *Why it matters*: made RAAS blockade mandatory in diabetic kidney disease with albuminuria. *Cited in*: Chapters 19, 20.[9,40]

CREDENCE, DAPA-CKD, EMPA-KIDNEY (2019–2023). *Question*: do SGLT2 inhibitors protect the kidney? *Result*: canagliflozin (CREDENCE, diabetic), dapagliflozin (DAPA-CKD, diabetic *and non-diabetic*) and empagliflozin (EMPA-KIDNEY, broad CKD) each reduced its own primary kidney composite — canagliflozin by about 30%, dapagliflozin by about 40%, empagliflozin by about 28% (Table 19.5). Quote the kidney composite, which is what each trial was powered for; cardiovascular death on its own is a smaller and separate

question, and no single figure spans the three trials. *Why it matters*: transformed CKD care and extended SGLT2 inhibitors to non-diabetic kidney disease. *Cited in*: Chapters 19, 20.[20,28]

CLICK (2021). *Question*: do thiazide-type diuretics work in advanced (stage 4) CKD, where they were thought ineffective? *Design*: RCT of chlorthalidone against placebo in stage 4 CKD with poorly controlled hypertension confirmed by 24-hour ambulatory monitoring — not formally resistant hypertension. *Result*: a 24-hour systolic reduction of about 11 mmHg versus placebo, with reduced albuminuria. *Why it matters*: the first randomised evidence that a thiazide-type diuretic still lowers pressure below an eGFR of 30 — 160 patients, twelve weeks, a blood-pressure endpoint, and more hypokalaemia, reversible creatinine rise, hyperglycaemia, dizziness and hyperuricaemia on the active arm (Table 31.5). It reopens a question the field had closed; it does not close it the other way. *Cited in*: Chapters 12, 19.[1]

FIDELIO-DKD / FIGARO-DKD (2020–2021). *Question*: does the non-steroidal mineralocorticoid antagonist finerenone help in diabetic kidney disease? *Result*: reduced kidney progression (FIDELIO) and cardiovascular events (FIGARO), on top of RAAS blockade. *Why it matters*: added a new agent for diabetic kidney disease. *Cited in*: Chapters 19, 20.[5,13]

Heart failure

PARADIGM-HF (2014). *Question*: is the ARB–neprilysin inhibitor sacubitril/valsartan better than enalapril in heart failure with reduced ejection fraction? *Result*: reduced cardiovascular death and heart-failure hospitalisation. *Why it matters*: established ARNI therapy and is the exception to the "no dual RAAS" rule (a distinct pharmacology). *Cited in*: V1·Ch3.[18]

Pregnancy

CHAP (Chronic Hypertension and Pregnancy, 2022). *Question*: should mild chronic hypertension in pregnancy be treated to <140/90, or left until severe? *Design*: RCT, 2,408 women. *Result*: treating to <140/90 reduced the composite of severe pre-eclampsia, preterm birth <35 weeks, abruption and fetal/neonatal death (30.2% vs 37.0%, RR 0.82) without harming fetal growth. *Why it matters*: changed obstetric practice to a <140/90 threshold. *Cited in*: V1·Ch18.[33]

Magpie (2002). *Question*: does magnesium sulphate prevent eclamptic seizures in pre-eclampsia? *Result*: it more than halved the risk of eclampsia. *Why it matters*: established magnesium sulphate as the seizure-prevention agent. *Cited in*: V1·Ch18.[30]

Diet, lifestyle and dosing

DASH and **DASH-Sodium** (1997, 2001). *Question*: can a dietary pattern lower blood pressure? *Result*: the DASH diet lowered systolic pressure by about 11 mmHg in hypertensives, and combining it with sodium reduction lowered it further. *Why it matters*: the evidence base for dietary treatment. *Cited in*: Chapters 12, 22, and the dedicated elevated-BP chapter.[3,23]

SSaSS (Salt Substitute and Stroke Study, 2021). *Question*: does replacing some sodium with potassium in household salt reduce events? *Design*: large RCT in rural China. *Result*: reduced stroke, major cardiovascular events and

death. *Why it matters*: hard-outcome evidence for potassium-based salt substitution. *Cited in*: V1·Ch12.[19]

TIME (2022) and the **HYGIA** controversy. *Question*: does dosing antihypertensives at bedtime rather than morning reduce events? *Result*: HYGIA claimed a 45% reduction, HR 0.55 (0.50–0.61), and carries a standing expression of concern; the rigorous TIME trial found **no difference** (HR 0.95, non-significant). *Why it matters*: the settled position that dosing time does not affect outcomes for most patients — and a case study in scepticism. *Cited in*: V1·Ch7.[17,38,39]

Obesity and metabolic

SELECT (2023) and **SURMOUNT** (2022 onward). *Question*: do the incretin weight-loss agents help cardiovascularly and lower blood pressure? *Result*: semaglutide (SELECT) reduced cardiovascular events in obese patients without diabetes; tirzepatide (SURMOUNT) produced large weight loss and lowered systolic pressure by roughly 7–11 mmHg. *Why it matters*: a new pharmacological route to blood-pressure reduction through weight loss. *Cited in*: Chapters 20, 21.[15,16]

KEY POINTS

1. **Every recommendation in this book rests on trial evidence**, and a reader who cannot interrogate that evidence is taking the recommendations on authority — which this book does not ask for.
2. **Randomisation is what separates a trial from an observation**, distributing unknown confounders as well as known ones.
3. **Blinding protects the outcome, not the allocation** — its absence matters most for subjective endpoints.
4. **Absolute risk reduction and number needed to treat translate a result into practice**; relative risk reduction alone can make a small benefit sound large.
5. **Treat subgroup findings as hypothesis-generating** unless pre-specified and adequately powered.
6. **A surrogate endpoint is a promise, not a result** — blood pressure lowered is not by itself an event prevented, though for hypertension the link is unusually well established.
7. **The landmark trials in Part B are presented in one common format**, so that reading them is itself practice in the method of Part A.

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VOLUME ONE · PART VI

Secondary hypertension

The correctable causes. Why each one raises the pressure, what it looks like at the bedside, which single test finds it, and what changes when you do.

Hypertension: A Phenotype-Based Approach

Volume 1 · Why Is This Patient Hypertensive?

Dr Ravikiran Jadhav

MBBS · AFIH · Occupational Health Physician

7 chapters

Part VI of six

CHAPTER 31 PART VI · SECONDARY HYPERTENSION

Renal parenchymal disease and polycystic kidney disease

The commonest secondary cause, and the one most often recorded as essential hypertension because nobody looked at the urine.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Five mechanisms, one direction** — how a scarred kidney raises arterial pressure, and why they compound rather than compete.
2. **The volume phenotype** — salt sensitivity, non-dipping, and resistance to any regimen that does not address sodium.
3. **Cause or consequence** — separating hypertension that damaged the kidney from kidney disease that raised the pressure.
4. **Polycystic kidney disease** — why the pressure rises years before the filtration falls.
5. **The three tests** that identify almost all of it, and what each one is actually telling you.
6. **What changes** — targets, the expected creatinine rise, diuretic choice as filtration falls, and the salt that makes the regimen possible.

31.1 Why the diseased kidney raises the pressure

Chapter 5 established the central fact of blood pressure regulation: the kidney sets the long-term operating pressure, because it alone can alter total body sodium without limit. Every other mechanism modulates. The kidney decides. It follows that any disease which damages renal parenchyma must raise arterial pressure, and the only question is by how much and through which route.

The answer is that it does so by five routes at once, and this is what makes renal parenchymal hypertension so difficult to control. A patient with primary aldosteronism has one dominant mechanism, and blocking it works. A patient with a scarred kidney has five, operating simultaneously, each partially compensating when another is blocked. That is the mechanistic explanation for a clinical observation every physician has made: these patients need three and four drugs, and still the pressure sits above target.

The single most useful sentence in this chapter

A patient with resistant hypertension who has never had a urinalysis and a creatinine has not been investigated for the commonest secondary cause.

TABLE 31.1 — THE FIVE MECHANISMS OF RENAL PARENCHYMAL HYPERTENSION

MECHANISM	WHAT IS PHYSICALLY HAPPENING	CLINICAL SIGNATURE
Sodium and volume retention	Nephron loss reduces the capacity to excrete a sodium load, so the pressure–natriuresis curve shifts rightward. A higher arterial pressure is now required to excrete the same daily sodium. The body defends volume at the cost of pressure.[11]	Salt sensitivity. Oedema. Pressure that falls markedly with a diuretic and with sodium restriction, and barely at all without them.
Renal afferent sympathetic signalling	Chemoreceptors and mechanoreceptors in the injured kidney send afferent traffic to central sympathetic nuclei, raising systemic sympathetic outflow. Plasma noradrenaline is higher in dialysis patients than in hypertensives matched for blood pressure and body mass — so the drive comes from the kidney, not from the pressure.[13]	Tachycardia, high pressure variability, and hypertension that persists after volume has been corrected.
RAAS activation despite volume expansion	The apparent paradox. Reduced renal blood flow and filtration trigger renin release irrespective of total body sodium, so angiotensin II and aldosterone remain inappropriately high in a patient who is already overfilled.[2]	A response to RAAS blockade greater than the volume state would predict — and the reason these agents remain first-line.
Endothelial dysfunction and ADMA	Asymmetric dimethylarginine, an endogenous competitive inhibitor of nitric oxide synthase, is cleared by the kidney. In uraemia it accumulates, nitric oxide availability falls, and the vasodilator arm of the system weakens.[29]	Stiff, poorly vasodilating vessels. Rising pulse pressure. A predictor of both cardiovascular events and further renal decline.
Glomerular hyperfiltration in the remnant nephrons	Surviving nephrons dilate the afferent arteriole and constrict the efferent, raising pressure inside each remaining glomerulus to maintain total filtration. It works, and it is destructive: intraglomerular hypertension drives glomerulosclerosis, which destroys more nephrons.[5]	The reason this disease accelerates. It is a feedback loop, and antihypertensive treatment is the only thing that interrupts it.

Read the table as one process rather than five. Nephron loss produces volume retention *and* afferent sympathetic signalling *and* inappropriate renin release; the resulting hypertension causes further glomerular injury, which causes further nephron loss. The clinical implication is that treating one arm produces a disappointing fall in pressure, and the counter-regulatory response described in Chapter 10 is unusually strong here.

31.2 The phenotype at the bedside

Renal parenchymal hypertension has a recognisable clinical signature, and it is one a physician can identify before any investigation returns. The pressure is **volume-dependent and salt-sensitive.** It **does not dip at night**, and in advanced disease it reverses — the nocturnal pressure exceeds the daytime pressure, because the kidney is using the night to excrete the sodium it could not excrete by day. That nocturnal rise is not incidental; it is pressure–natriuresis working, visible on an ambulatory trace.

The non-dipping pattern matters in its own right. In a cohort of 156 hypertensive patients followed for 7.3 years, cardiovascular event rates were 4.3 per 100 patient-years in the salt-sensitive against 2 per 100 patient-years in the salt-resistant, independent of the blood pressure itself. Salt sensitivity is not merely a mechanism; it is a prognosis.

31.3 Cause or consequence: the question that is often unanswerable

A patient presents with hypertension, a creatinine of 180 µmol/L and small echogenic kidneys. Did the hypertension destroy the kidneys, or did the kidneys raise the pressure? The honest answer is that this is frequently impossible to determine, and the literature says so plainly: once a patient reaches end-stage disease, deciding whether nephrosclerosis is the cause or the consequence of renal injury may be impossible.[16]

That is not a counsel of despair, because the distinction changes management less than it appears to. Both need the pressure controlled, the sodium restricted, the RAAS blocked if there is albuminuria, and the trajectory monitored. What the distinction changes is *whether you keep looking*. A presumptive diagnosis of hypertensive nephrosclerosis in a patient who has never had a urine microscopy, a renal ultrasound or an immunological screen is not a diagnosis; it is the absence of one, and it is how glomerulonephritis, reflux nephropathy and polycystic disease are missed for a decade.

What to ask and what to look for

Nocturia before oedema. Frothy urine. A family history of kidney disease or dialysis. Flank or back pain. Anaemia disproportionate to anything else. Previous pregnancies complicated by hypertension or proteinuria. Analgesic use over years. And in a young patient, ask directly about childhood urinary infections and reflux.

TABLE 31.2 — WHICH WAY ROUND IS IT?

POINTS TOWARDS KIDNEY DISEASE AS THE CAUSE	POINTS TOWARDS HYPERTENSION AS THE CAUSE
Proteinuria that preceded, or is disproportionate to, the pressure	Long-standing hypertension with late, modest proteinuria
Active urinary sediment — dysmorphic red cells, red-cell casts	Bland urinary sediment
Asymmetric kidneys, scarring, cysts, or obstruction on ultrasound	Symmetrically small, smooth kidneys with preserved cortical outline
Young onset, or hypertension appearing together with the renal impairment	Hypertension established for years before the creatinine moved
A syndromic or family history — deafness, haematuria, dialysis in relatives	Other target-organ damage of long-standing hypertension: LVH, retinopathy

31.4 Polycystic kidney disease: pressure before filtration

Autosomal dominant polycystic kidney disease deserves separate treatment because its hypertension behaves unlike the rest of this chapter. It appears **early** — hypertension is the most prevalent initial clinical finding, present in 50 to 70% of patients, and it typically arrives before any meaningful fall in glomerular filtration rate. A young adult with hypertension, a normal creatinine and a family history of kidney disease is the presentation that gets missed.[19]

The mechanism explains the timing. Expanding cysts compress the intrarenal vasculature and produce *focal* parenchymal ischaemia. The affected segments release renin even though total renal function is preserved. This is local, not global, ischaemia — which is why the RAAS is activated years before the filtration falls, and why these patients respond well to RAAS blockade.

The clinical trap

A normal creatinine does not exclude polycystic disease, and in a hypertensive patient under fifty with a family history it is the wrong test to reassure yourself with. The right test is an ultrasound.

TABLE 31.3 — ULTRASOUND CRITERIA FOR ADPKD IN A PATIENT WITH A FAMILY HISTORY

AGE	CYSTS REQUIRED FOR DIAGNOSIS	NOTE
15–39	At least 3 renal cysts in total, unilateral or bilateral[18]	A later refinement tightens the 30–39 band to at least 2 cysts in each kidney
40–59	At least 2 cysts in each kidney	—
60 and over	At least 4 cysts in each kidney	Simple cysts become common with age, so the threshold rises

These are the unified criteria and they apply to a patient with a known family history. In a patient without one, an ultrasound showing bilateral cysts and enlarged kidneys still warrants a nephrological opinion and consideration of genetic testing, since a substantial minority have no informative family history.

31.5 Which parenchymal disease? The two that matter most

"Renal parenchymal disease" is a category, not a diagnosis, and two of its members account for a large share of the hypertension it causes. Naming them changes what you look for and what you tell the patient.

Glomerulonephritis. IgA nephropathy is the commonest primary glomerulonephritis worldwide and its incidence is highest in Asia, which places it squarely in the readership of this book.[23] Focal segmental glomerulosclerosis commonly causes severe hypertension. The important physiological distinction is between the two syndromes: a *nephritic* presentation retains sodium primarily at the kidney and expands volume, while in *nephrotic* presentation the mechanism is disputed between an underfill model, in which low oncotic pressure drives RAAS activation, and an overfill model of primary tubular sodium avidity.[3] The clinical consequence is that nephritic hypertension responds to sodium restriction and diuresis, while nephrotic patients can be simultaneously oedematous and intravascularly depleted.[14,17,22]

The urine identifies it. Dysmorphic red cells are highly specific and poorly sensitive — at a threshold of 25% dysmorphic cells, one series reports a sensitivity of 20.4% against a specificity of 96.3%. That asymmetry is exactly how the test should be used: finding them is close to diagnostic of glomerular bleeding, and not finding them excludes very little. Red-cell casts carry the

same weight. Biopsy follows when the result would change immunosuppression, and blood pressure targets and RAAS blockade in proteinuric glomerular disease follow the KDIGO guidance already given.[26]

Reflux nephropathy. Vesicoureteric reflux in childhood scars the kidney, and the scars raise the pressure decades later — often in a young adult with no recollection of the infections that caused them.[25] Hypertension is reported in 10 to 30% of patients with reflux nephropathy, and the proportion climbs with age, from around 10% in childhood to 18–20% and then 30–40% in adult series. It is among the commonest causes of hypertension in young adults in many published series, and it is the specific reason to ask a hypertensive twenty-five-year-old about childhood urinary infections. Ultrasound shows the scarring; DMSA scintigraphy defines it.[24] The finding also changes pregnancy counselling, which matters in the population most affected.[27,28]

A discrepancy the reader should know about

KDIGO 2012 and KDIGO 2021 give different blood pressure targets for proteinuric kidney disease — 130/80 mmHg and a systolic below 120 mmHg by standardised measurement respectively. The later figure rests on SPRINT-style unattended readings, and the two are less far apart in practice than they look on paper.[7]

31.6 The three tests

Almost all renal parenchymal disease in a hypertensive population is identified by three inexpensive investigations. There is no justification for omitting them in any hypertensive patient, and no excuse for omitting them in a resistant one.

TABLE 31.4 — WHAT EACH TEST IS ACTUALLY TELLING YOU

TEST	WHAT IT SHOWS	WHAT IT DOES NOT SHOW
Urinalysis with microscopy	Glomerular disease. Dysmorphic red cells and red-cell casts point to glomerulonephritis; white cells and casts to interstitial disease. This is the test that distinguishes a kidney under immunological attack from one that is simply scarred.[15]	Nothing about function. A bland sediment does not exclude advanced disease.
Urine albumin–creatinine ratio	Both a marker of glomerular injury and, independently, of cardiovascular risk. KDIGO categorises it as A1 (below 30 mg/g), A2 (30–299 mg/g) and A3 (300 mg/g or above); nephrotic range is typically above 2220 mg/g.[10]	Whether the albuminuria is the cause or the consequence of the pressure.
Renal ultrasound	Size, symmetry, cortical thickness, echogenicity, cysts, stones, obstruction. Asymmetry beyond roughly 1.5 cm is the finding that should turn your attention to the renal arteries (Chapter 32).	Reliable detection of early parenchymal disease. Radiologists' visual reading of echogenicity performs poorly — accuracy of 42.5–46.9% in one series — so a report of "normal echogenicity" is weak reassurance.[30]

31.7 What it changes

Identifying renal parenchymal disease changes the target, the drug, the diuretic and the diet, and it changes what you tell the patient about the next twenty years. It is the difference between treating a number and treating a trajectory.

TABLE 31.5 — MANAGEMENT CONSEQUENCES

DECISION	WHAT CHANGES	GRADE OR EVIDENCE
Blood pressure target	KDIGO 2021 suggests a systolic target below 120 mmHg by *standardised* office measurement, when tolerated. The measurement method is not a detail: the target was derived from trials using unattended automated readings, and applying it to a hurried manual reading will over-treat (Chapter 8).[4,8]	2B; excludes transplant recipients and children
RAAS blockade	Indicated where there is albuminuria. Expect the creatinine to rise: a rise of up to 30% within four weeks is an accepted haemodynamic effect and is not a reason to stop. Re-check creatinine and potassium two to four weeks after starting or increasing the dose.	KDIGO
Dietary sodium	Below 2 g of sodium daily — under 90 mmol, under 5 g of salt. This is not lifestyle advice appended to the prescription. In a volume-dependent hypertension it is what makes the regimen work at all.	2C
Diuretic choice	The old rule to abandon thiazides below an eGFR of 30 is being revised. In the CLICK trial, chlorthalidone in stage 4 disease (eGFR 15 to under 30) lowered 24-hour ambulatory systolic pressure by 11.0 mmHg against 0.5 mmHg on placebo, and reduced albuminuria substantially — at the cost of more hypokalaemia, hyperuricaemia and reversible creatinine rise.[1]	CLICK, 160 patients
In polycystic disease	KDIGO 2025 sets lower targets than general CKD: at or below 110/75 mmHg by home monitoring for ages 18–49 in stages G1–G2, and a mean systolic below 120 mmHg by standardised office measurement from age 50. Tolvaptan is for those with an eGFR of at least 25 who are judged at risk of rapid progression.[9]	1D and 2C; tolvaptan 1B
SGLT2 inhibitor	KDIGO 2024 recommends one at an eGFR of 20 or above with an ACR of 200 mg/g or more, and suggests one at an eGFR of 20 to 45 with lower albuminuria — with or without diabetes. Expect an early, reversible fall in eGFR on starting; it is not injury and not a reason to stop. Not established in polycystic kidney disease or where the kidney disease is being treated with immunosuppression — the trials excluded both.[31]	1A at ACR ≥200 mg/g; 2B at eGFR 20–45 with lower albuminuria

Two trials define the limits of what pressure control achieves in polycystic disease, and both are worth knowing because they temper expectations. In HALT-PKD Study A, 558 patients with preserved filtration were randomised to a standard target of 120/70–130/80 mmHg or a lower target of 95/60–110/75 mmHg. The lower target produced a smaller annual increase in total kidney volume — 5.6% against 6.6% — but no difference in the rate of filtration decline.[20] In Study B, in more advanced disease, dual RAAS blockade offered nothing over monotherapy, consistent with everything else this book says about blocking one pathway twice.[20]

The Indian context

Pooled prevalence of chronic kidney disease in the South Asian general population is 14% — one adult in seven — rising to 27% among people who already have hypertension. That is more than one hypertensive patient in four. It is the single strongest argument for making urinalysis, albumin–creatinine ratio and creatinine routine rather than selective.[21]

KEY POINTS

1. **Renal parenchymal disease is the commonest secondary cause of hypertension**, and the commonest to be recorded as essential because the urine was never examined.
2. **Five mechanisms operate at once** — sodium retention, renal afferent sympathetic signalling, inappropriate RAAS activation, ADMA-driven endothelial dysfunction and glomerular hyperfiltration. That is why these patients need several drugs.
3. **The phenotype is volume-dependent and salt-sensitive**, with a non-dipping or reverse-dipping nocturnal pattern that itself carries excess cardiovascular risk.
4. **Cause and consequence are often inseparable** once disease is advanced — but a presumptive diagnosis of hypertensive nephrosclerosis without a urinalysis, an ACR and an ultrasound is not a diagnosis.
5. **In polycystic disease the pressure rises before the filtration falls**, because cysts compress vessels and produce focal ischaemia. A normal creatinine is not reassurance; an ultrasound is the test.[12]
6. **Sodium below 2 g daily is part of the prescription**, not advice added to it, and thiazide-like diuretics remain effective further down the eGFR range than was once taught.[6]
7. **A creatinine rise of up to 30% within four weeks of starting RAAS blockade is expected** and is not a reason to stop the drug — but it is a reason to recheck potassium.

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CHAPTER 32 PART VI · SECONDARY HYPERTENSION

Renovascular hypertension

Three diseases that produce the same picture on an angiogram and are managed in three different ways — atherosclerosis, fibromuscular dysplasia, and the one this book cannot omit in India.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **The Goldblatt models** — and which human situation each of them actually describes.
2. **Three phases** — why renin is high early, normal later, and the pressure stays up either way.
3. **The bilateral trap** — why an ACE inhibitor rescues one patient and puts another into acute kidney injury.
4. **Three diseases, one lesion** — atherosclerotic stenosis, fibromuscular dysplasia and Takayasu arteritis, and why the treatment differs completely.
5. **What imaging can and cannot tell you**, including the gap between a lesion and a cause.
6. **Why revascularisation fell out of favour** after ASTRAL and CORAL — and the three patients for whom it did not.

32.1 How a narrowed renal artery raises the pressure

Reduce the perfusion pressure reaching one kidney and it does the only thing it can do: it concludes that the whole circulation is underfilled and acts accordingly. Renin is released, angiotensin II is generated, aldosterone follows, and arterial pressure rises until perfusion of that kidney is restored. The kidney has no way of knowing that the problem is a plaque at its own ostium rather than a haemorrhage somewhere in the body. The pressure rise is not a malfunction. It is the correct response to a false signal.

The threshold matters clinically. Autoregulation compensates for modest narrowing, and the lesion becomes haemodynamically significant only once renal perfusion pressure falls below roughly 70 to 85 mmHg — corresponding to about 70 to 80% luminal occlusion.[12] Below that degree of narrowing the pressure gradient is not transmitted and renin is not stimulated. This is why an incidentally reported “40% stenosis” explains nothing, and why finding a lesion is not the same as finding the cause.

Lesion or cause?

This is the central interpretive problem of the chapter. Atherosclerotic renal artery narrowing is common in elderly hypertensives, and most of it is not causing the hypertension. The imaging tells you a lesion is present. It does not tell you the pressure would fall if you fixed it.

TABLE 32.1 — THE GOLDBLATT MODELS AND WHAT THEY MEAN IN A REAL PATIENT

MODEL	THE HUMAN SITUATION	WHAT HAPPENS
Two-kidney, one-clip	Unilateral stenosis with a **normal contralateral kidney**	The stenotic kidney is ischaemic and hypersecretes renin. The normal kidney still senses the raised systemic pressure and excretes sodium through pressure-natriuresis. The result is renin-dependent hypertension without much volume expansion — and it responds well to RAAS blockade.[11]
One-kidney, one-clip	**Bilateral** stenosis, or stenosis in a single functioning kidney	There is no unaffected kidney to excrete the retained sodium. Volume expands, and the expansion suppresses renin back towards normal. The hypertension becomes volume-dependent, plasma renin is unhelpfully normal, and RAAS blockade now removes the efferent tone the filtration depends on.

32.2 Three phases, and why the renin level misleads

Renovascular hypertension evolves. In the first phase the rise in pressure is a direct consequence of hyperreninaemia, and plasma renin is high. In the second phase — particularly where there is no healthy contralateral kidney — sodium is retained, volume expands, renin falls back towards normal, and the hypertension is now predominantly volume-driven. In the third phase, structural change in the systemic resistance vessels and in the contralateral kidney sustains the pressure even if the stenosis is relieved.[13]

Two conclusions follow, and both are practical. First, **a normal plasma renin does not exclude renovascular disease**; it may simply mean the patient is no longer in phase one. Second, the longer the stenosis has been present, the less likely that fixing it will cure the hypertension — which is a large part of why the revascularisation trials disappointed.

That is the single most useful piece of renovascular physiology a general physician can carry. A patient whose creatinine jumps disproportionately within days of starting an ACE inhibitor or an ARB is telling you something about their renal arteries. The European renovascular guidance sets its threshold on eGFR — a fall of more than 30% demands attention — while KDIGO sets the parenchymal threshold in Chapter 31 on creatinine, a rise of

more than 30% within four weeks. These are not the same number: a 30% creatinine rise is about a 23% eGFR fall. Use whichever measure your laboratory reports, and do not convert one threshold into the other.[12]

The ACE inhibitor trap

In an ischaemic kidney, glomerular filtration is maintained by angiotensin II constricting the efferent arteriole. Remove angiotensin II and the efferent tone goes with it: filtration pressure collapses and the creatinine rises acutely. With one healthy kidney this is invisible. With bilateral disease, or a single functioning kidney, it is acute kidney injury — and it is a diagnostic clue as much as an adverse event.

32.3 Three diseases, one angiographic picture

A narrowed renal artery is a finding, not a diagnosis. Three quite different diseases produce it, they occur in different people, and they are treated in ways that have almost nothing in common. Getting this wrong means immunosuppressing a plaque or stenting an inflamed vessel.

TABLE 32.2 — TELLING THE THREE APART

	ATHEROSCLEROTIC	FIBROMUSCULAR DYSPLASIA	TAKAYASU ARTERITIS
Who	Older, vascular risk factors, disease elsewhere in the arterial tree	Women, strongly — reported ratios from 3:1 to 9:1 — median age around 48; often no cardiovascular risk factors	Predominantly women; onset from the second decade onward. Asian incidence around 2.69 per million per year, roughly a hundredfold that of Europe and North America
Where in the vessel	**Ostial and proximal** — it is aortic plaque encroaching on the renal origin	**Mid and distal**, the classic "string of beads". Medial fibroplasia accounts for 60–70%[18]	**Ostial** again, but from transmural inflammation of the aorta and its branch origins, not plaque
What it is	Atheroma	Idiopathic, segmental, non-atherosclerotic and non-inflammatory disease of arterial wall muscle[5]	Granulomatous, T-cell driven panarteritis with transmural fibrous thickening[20]
Other beds	Coronary, carotid, peripheral	Renal in about 58–75%, craniocervical in about 32%; multivessel disease in roughly half	Aorta, subclavian, carotid, coronary ostia. Renal involvement reported across a wide range, 28–75%[16]
Treatment	Medical therapy for almost all; revascularisation for a defined minority	Angioplasty, usually without a stent — potentially curative	**Immunosuppression first.** Revascularisation deferred to quiescent disease wherever possible[1]

32.4 Takayasu arteritis: the one this book cannot omit

Takayasu arteritis belongs in an India-focused hypertension text in a way it does not belong in an American one. Incidence across Asia is on the order of a hundred times that reported in Europe and North America, and India is named among the highest-burden regions alongside Japan, Southeast Asia and Mexico. More to the point for this chapter: in the Indian experience **hypertension is reported as the predominant presenting manifestation**, driven by renal artery and aortic involvement — whereas in other endemic regions the disease more often announces itself in other ways.[4,6]

It also breaks the instrument this whole book depends on. When the subclavian or axillary artery is stenosed, the brachial pressure is falsely low or unobtainable, and hypertension in Takayasu is described as frequently unrecognised for exactly this reason.[9] A patient can have severe central hypertension and a normal reading in the arm you happened to use.

Classification is by the 1990 ACR criteria — at least three of six: onset at or under 40, limb claudication, decreased brachial pulse, an inter-arm systolic difference above 10 mmHg, a subclavian or aortic bruit, and characteristic arteriographic narrowing — or by the 2022 ACR/EULAR criteria, which require age 60 or under at diagnosis plus imaging evidence of large-vessel vasculitis, then a weighted score. Two figures should be quoted together and rarely are: the 2022 criteria performed at 93.8% sensitivity and 99.2% specificity in the derivation cohort, but an independent multicentre validation at the same threshold found specificity of only **63.5%.** Classification criteria are built to define trial populations, not to diagnose the patient in front of you.[16,22]

Inflammatory markers are equally unreliable as a guide to activity. In one analysis the ESR had 72% sensitivity and 56% specificity; disease can be active with a normal CRP and a normal ESR. Serial imaging with clinical assessment, not a monthly inflammatory marker, is what follows these patients.[14]

Four pulses, both arms

In a young patient with hypertension, or with hypertension that cannot be measured consistently, palpate all four limbs and take the pressure in both arms. An asymmetry, an absent pulse or a bruit over the carotid, subclavian or abdominal aorta is worth more than any blood test at this point.

32.5 When to look, and with what

The clinical triggers for imaging are agreed across the guidelines: hypertension beginning before 30 or after 55; accelerated, resistant or malignant hypertension; an unexplained rise in creatinine, particularly after starting a RAAS blocker; asymmetric kidney size; recurrent flash pulmonary oedema; and an abdominal or flank bruit.[7,12]

On the bruit, this book will not give a number. A sensitivity and specificity for the abdominal bruit is widely quoted in teaching and could not be traced to a source that states it; a health-technology assessment reviewing renovascular evaluation contains no such data, and the best available statement is the qualitative one — a bruit is suggestive but not specific. Listen for it, act on it, and do not let its absence reassure you.

TABLE 32.3 — IMAGING, AND THE HONEST STATE OF ITS ACCURACY

TEST	REPORTED PERFORMANCE	COMMENT
Duplex ultrasound	Two source sets diverge: a Canadian health-technology assessment reports a positive predictive value of 0.943 in one study; a StatPearls chapter gives sensitivity 88–96% and specificity around 89%.[8]	First-line in most settings and recommended as first-line screening for fibromuscular dysplasia. Heavily operator-dependent, which is the likeliest source of the divergence above.
CT angiography	High sensitivity in most series; the reference standard remains catheter angiography.[17]	Best anatomical detail short of catheterisation. Contrast load is the limitation in exactly the patients most likely to need it.
MR angiography	Comparable to CTA in most series.	Avoids iodinated contrast; tends to overestimate stenosis severity.
Captopril renal scintigraphy	Positive predictive value 0.58–0.76 and negative predictive value 0.29–0.75 across studies in the same assessment.	Those figures are the reason it has largely fallen out of use.
In Takayasu	CT angiography is the standard for initial staging of disease distribution, showing wall thickening as well as luminal narrowing.	Wall thickening is the finding that distinguishes arteritis from atheroma, and a luminal-only study can miss it.

32.6 Two rarities worth recognising

The renin-secreting tumour. A juxtaglomerular cell tumour — a reninoma — is the purest renin-dependent hypertension there is, and its biochemistry is unmistakable once you know to look for it.[15] Severe hypertension with hypokalaemia in more than 80% of cases, a high aldosterone, and — the decisive finding — a renin that is **also high**, typically more than ten times the upper limit of normal.[15] Primary aldosteronism gives a high aldosterone with a *suppressed* renin. Here the renin is driving everything, and its failure to suppress is what separates the two. It is a tumour of young people, it is found on CT or MRI with renal vein renin sampling to lateralise, and it is curable by surgical removal.[15]

Vasculitis that is not Takayasu. Polyarteritis nodosa is a necrotising arteritis of medium vessels that involves the renal arteries and produces the characteristic microaneurysms seen on angiography; hypertension is a recognised feature, and there is a well-established association with hepatitis B.[21] It is distinguished from Takayasu by the calibre of vessel involved — medium rather than large — and by the systemic pattern of neuropathy, skin and gut involvement. Giant cell arteritis is the other large-vessel arteritis, and the separation from Takayasu is largely one of age and distribution: it is a disease of patients over fifty affecting the cranial and extracranial branches, where Takayasu affects younger patients and the aortic arch.[10] Renovascular hypertension is not its typical presentation. In all of them the treatment principle is the same as in Chapter 32's earlier section: immunosuppression treats the disease, and revascularisation is a decision about the plumbing that comes afterwards.

The one-line rule

High aldosterone with low renin: think adrenal. High aldosterone with high renin: think renal artery — or, rarely and curably, a tumour making the renin itself.

32.7 What it changes

For twenty years the logic was irresistible: a narrowed artery causes the hypertension, so open the artery. Two large trials tested it and found almost nothing. ASTRAL randomised 806 patients across 57 centres; CORAL

randomised 947 with a median follow-up of 43 months and concluded plainly that renal artery stenting does not improve renal or cardiac outcomes in atherosclerotic disease.[2,3]

Both trials carry a real limitation that should be stated alongside the result: clinicians were required to exclude patients they believed would clearly benefit from revascularisation. The trials therefore tested stenting in the patients about whom there was doubt, which is a fair test of routine practice and a poor test of the extreme case. A 2023 European clinical-practice document accepts the trials and still names three phenotypes in whom revascularisation remains on the table: **resistant hypertension**, **ischaemic nephropathy with rapidly declining function**, and **recurrent flash pulmonary oedema.**[12]

Fibromuscular dysplasia is the opposite story, and the one worth not missing, because it is the closest thing in adult hypertension to a cure. Angioplasty — usually without a stent — has technical success reported up to 100%. Reported cure rates, however, should be quoted with care: figures of 60–80% appear widely, while an adjusted analysis gives 35.8%. The honest statement is that a substantial proportion are cured and most of the rest improve, and that the discrepancy between those figures is unresolved in the literature.

Takayasu is treated as the inflammatory disease it is. The 2021 guidance from the American College of Rheumatology and the Vasculitis Foundation recommends a non-glucocorticoid immunosuppressive agent together with glucocorticoids rather than glucocorticoids alone.[1] Where there is worsening limb or organ ischaemia, intervention is preferably deferred until disease is quiescent — and the reason is visible in the outcomes: one series found 78% restenosis after angioplasty over a mean follow-up. Stenting an actively inflamed vessel buys a short reprieve.

The rule that ties the chapter together

Unilateral disease with a healthy other kidney: block the RAAS, and watch the creatinine. Bilateral disease or a single kidney: block the RAAS only with deliberate monitoring, and treat a fall in eGFR beyond 30% as a signal, not a side effect.

KEY POINTS

1. **A stenosis becomes haemodynamically significant only below about 70–85 mmHg of renal perfusion pressure**, around 70–80% occlusion. A lesser lesion is a finding, not a cause.[19]
2. **The two Goldblatt models describe two different patients.** Unilateral disease with a healthy contralateral kidney is renin-dependent and responds to RAAS blockade; bilateral disease is volume-dependent, and RAAS blockade removes the efferent tone filtration depends on.
3. **A normal plasma renin does not exclude it** — renin falls as the disease moves from its renin-dependent phase to its volume-dependent one.
4. **An abrupt creatinine rise after starting an ACE inhibitor or ARB is a diagnostic clue**, not merely an adverse effect.
5. **Three diseases produce the same angiogram.** Atherosclerotic disease is ostial and medical; fibromuscular dysplasia is mid-vessel and potentially curable by angioplasty; Takayasu is inflammatory and treated with immunosuppression first.
6. **In India, Takayasu presents predominantly as hypertension** — and a stenosed subclavian artery can make the arm pressure falsely normal. Take the pressure in both arms and palpate all four limbs.
7. **ASTRAL and CORAL ended routine stenting**, but three phenotypes remain candidates: resistant hypertension, rapidly declining function, and recurrent flash pulmonary oedema.[12]

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CHAPTER 33 PART VI · SECONDARY HYPERTENSION

Primary aldosteronism

The commonest correctable cause, missed for forty years because the textbooks taught that it was rare and that it made you hypokalaemic. Both were wrong.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **What aldosterone actually does** — sodium retention through the mineralocorticoid receptor, and the injury it causes independently of the pressure.
2. **Why escape does not cure it** — the kidney stops retaining sodium and the hypertension continues.
3. **Why the potassium is usually normal**, and what that has cost patients.
4. **The aldosterone–renin ratio** — the units problem, the drugs that must stop, and the posture that matters.
5. **Confirming it**, and when confirmation can be skipped altogether.
6. **CT against adrenal vein sampling**, the discordance rate, and why imaging alone misdirects surgery.

33.1 What aldosterone does, and what it damages

Aldosterone binds the mineralocorticoid receptor in the principal cells of the distal nephron and collecting duct. The receptor drives insertion and activation of the epithelial sodium channel, ENaC, on the luminal membrane. Sodium is reabsorbed, potassium and hydrogen ion are secreted in exchange, water follows the sodium, and extracellular volume expands. That much is standard physiology and it explains the hypertension, the hypokalaemia and the metabolic alkalosis of the classic case.[12]

It does not explain why these patients do so much worse than their blood pressure predicts. Aldosterone is not only a sodium-retaining hormone. Mineralocorticoid receptors are present in the heart, the vasculature and the kidney, and their chronic activation drives inflammation and fibrosis independently of the arterial pressure. Two patients with identical readings, one with primary aldosteronism and one without, do not carry identical risk.

TABLE 33.1 — CARDIOVASCULAR RISK IN PRIMARY ALDOSTERONISM AGAINST ESSENTIAL HYPERTENSION

OUTCOME	ODDS RATIO
Stroke	2.58
Coronary artery disease	1.77
Atrial fibrillation	3.52
Heart failure	2.05

33.2 Aldosterone escape, and why the pressure stays up

Give a person continuous aldosterone and they do not swell indefinitely. After a few days of sodium retention and a gain of two or three litres, the kidney escapes: natriuretic peptides rise, pressure–natriuresis takes over, and sodium excretion returns to match intake. Volume stabilises. The oedema that theory predicts does not appear, and its absence is one reason the diagnosis is missed.

But the hypertension does not escape. Once volume has expanded and the pressure has risen, the mineralocorticoid receptor continues to act on the vessel wall and the myocardium, sympathetic activation is sustained, and vascular remodelling raises resistance structurally. The patient is now hypertensive for reasons that have moved beyond sodium. This is why a diuretic alone disappoints, and why the specific treatment is blockade of the receptor rather than removal of the fluid.[2]

Why this changes the consultation

This is the argument for finding it even in a patient whose pressure is already controlled on three drugs. Control of the number does not undo the receptor activation. Blocking the receptor, or removing the source, does.

33.3 The two teachings to discard

Generations were taught that primary aldosteronism is rare and that it presents with hypokalaemia. The first made physicians not look. The second made them stop looking when the potassium came back normal.

Hypokalaemia is present in only about 9 to 37% of confirmed cases. The great majority of patients with primary aldosteronism have a normal serum potassium at the time of testing. A normal potassium is not a negative screening test; it is not a screening test at all.

33.4 The aldosterone-to-renin ratio, and how to not get it wrong

The screening test is the ratio of plasma aldosterone concentration to plasma renin. It is a ratio because the diagnosis is not a high aldosterone in isolation — it is aldosterone that is inappropriately high *for the renin*, which is to say autonomous of the system that should be regulating it. A patient with secondary hyperaldosteronism from renal artery stenosis has a high aldosterone and a high renin. The ratio, not the aldosterone, separates them.

Three technical points defeat this test more often than the biology does.

A raised ratio is a screening result, not a diagnosis, and normally requires confirmation. There is one exception worth knowing: where aldosterone is markedly elevated with spontaneous hypokalaemia and an undetectable renin, confirmatory testing adds nothing and can be omitted.[4]

Who to screen

Resistant hypertension. Hypertension with spontaneous or diuretic-induced hypokalaemia. Hypertension with an adrenal incidentaloma. Hypertension with obstructive sleep apnoea. Hypertension with a family history of early hypertension or stroke. Hypertension with atrial fibrillation unexplained by structural disease. And, in the direction current guidance has moved, hypertension itself.[5]

TABLE 33.2 — THE THREE WAYS AN ALDOSTERONE-RENIN RATIO GOES WRONG

PROBLEM	WHAT HAPPENS	WHAT TO DO
Units	The cut-off depends entirely on whether aldosterone is reported in ng/dL or pmol/L and whether renin is a plasma renin activity or a direct renin concentration. A ratio quoted without units is meaningless. As a working figure, current guidance takes a ratio above **20** where aldosterone is in ng/dL and renin is a plasma renin activity in ng/mL/h, or above **70** where aldosterone is in pmol/L and renin is a direct concentration in mU/L — about a quarter lower where aldosterone is measured by mass spectrometry.[1,4]	Use your own laboratory's cut-off, and know which assay it runs.
Interfering drugs	Mineralocorticoid receptor antagonists, amiloride and potassium-wasting diuretics interfere most; beta-blockers, central agents, ACE inhibitors, ARBs, renin inhibitors and dihydropyridine calcium blockers all shift the ratio in one direction or the other.[4]	Send the first ratio on the patient's existing drugs where withdrawal is unsafe or impractical — the 2025 guideline allows a minimal-withdrawal or no-withdrawal strategy — and read the result against them. If the ratio is negative and suspicion persists, withdraw before repeating: **four weeks** for spironolactone, eplerenone, amiloride, triamterene, potassium-wasting diuretics and liquorice; **two weeks** for beta-blockers, clonidine and methyldopa, NSAIDs, ACE inhibitors, ARBs, renin inhibitors and dihydropyridine calcium blockers. Cover the gap with slow-release verapamil, hydralazine, or prazosin, doxazosin or terazosin.[1,4]
Posture and timing	Aldosterone and renin both vary with posture, time of day and sodium status. A sample drawn at the end of a clinic on a hypokalaemic patient is not interpretable.	Sample mid-morning, seated for five to fifteen minutes, after the patient has been up for two hours. Do not let them restrict salt in the days before — a low-sodium diet raises renin and hides the diagnosis. Release the tourniquet and wait five seconds before drawing. Correct the potassium where you can, but do not hold the first test for it: if the screen is negative in a hypokalaemic patient, correct the potassium and repeat.[1]

33.5 Confirmation, and then the harder question

Confirmation demonstrates that aldosterone fails to suppress when it should. The saline infusion test and the captopril challenge are the two in common use, and a head-to-head comparison gives the saline infusion test a sensitivity of 90.4% and specificity of 95.9%, against 87.0% and 91.8% for the captopril challenge. Pooled data put the two level: 84% and 87% for the saline infusion test, 87% and 85% for the captopril challenge. The ranking therefore rests on a single centre's study, and the difference that matters is elsewhere — the captopril test is safer in a patient in whom a two-litre saline load is unwise, which is a substantial fraction of this population.[6,9]

Then comes the question that decides the operation: is this a unilateral adenoma, which surgery can cure, or bilateral hyperplasia, which it cannot? **Do not answer it with a CT scan.**[7] Adrenal CT for detecting an aldosterone-producing adenoma has a pooled sensitivity and specificity of roughly 68% and 57%, and comparison of CT against adrenal vein sampling shows discordance in **22 to 28%** of patients, depending on the lateralisation threshold applied.[3]

That means about one patient in four would have the wrong adrenal removed, or would be denied a curative operation, if imaging alone directed the decision. Small non-functioning adenomas are common; functioning micro-adenomas are invisible.

33.6 What it changes

A unilateral adenoma in a patient fit for surgery is one of the few genuinely curable causes of hypertension, with cure reported in about half of operated patients and improvement in most of the remainder. Bilateral disease is treated medically with a mineralocorticoid receptor antagonist. A comparison of the two strategies found broadly similar blood pressure and cardiovascular outcomes — but adrenalectomy achieved them on fewer drugs, which over decades is not a small thing.[10]

Medical treatment means **spironolactone, started at 12.5 to 25 mg daily** — 50 mg in severe disease — and titrated every eight to twelve weeks in 25 to 50 mg steps. The target is not only the pressure. The 2025 guideline asks you to raise the dose until **renin is no longer suppressed**, which most patients reach at 50 to 100 mg a day or the equivalent, because a normal pressure on a dose that leaves renin flat leaves the receptor still activated — and it is the receptor that damages the heart and kidney. Where the pressure is controlled but renin is still suppressed, increase the antagonist and reduce another agent, not the other way round. Check electrolytes, renal function and renin within two to three months of starting, and more often where there was severe hypokalaemia or renal impairment[1]; the spironolactone label separately asks for a serum potassium within a week of starting and of every dose change, and regularly thereafter.

The deeper change is in what you are treating. Once primary aldosteronism is identified, the mineralocorticoid receptor is no longer one option among several equivalent antihypertensives; it is the mechanism. That is the whole argument of this book applied to the one place where it is uncontroversial.

Where genetics has arrived

Somatic mutations in KCNJ5 and other channel and pump genes are found in a substantial proportion of aldosterone-producing adenomas — 59.5% in one Taiwanese cohort. This is not yet a clinical test, but it is why an adenoma behaves autonomously at all.[11]

KEY POINTS

1. **Aldosterone raises pressure through ENaC-mediated sodium retention**, and injures heart, vessel and kidney through mineralocorticoid receptors *independently of the pressure* — stroke OR 2.58, atrial fibrillation OR 3.52 against matched essential hypertension.[1]
2. **Aldosterone escape stops the volume expansion but not the hypertension.** The absence of oedema is a reason the diagnosis is missed, not a reason to exclude it.
3. **Only about 9 to 37% are hypokalaemic.** A normal potassium excludes nothing.[8]
4. **The aldosterone–renin ratio fails on technique more often than on biology** — units, interfering drugs, posture and an uncorrected potassium.
5. **The two confirmatory tests perform alike.** The saline infusion test discriminated better head-to-head (90.4% sensitivity, 95.9% specificity), but pooled data put it level with the captopril challenge — which is safer where a saline load is unwise.[6,9]
6. **CT and adrenal vein sampling disagree in 22 to 28% of patients.** Imaging alone must not choose which adrenal to remove.[3]
7. **Finding it matters even when the pressure is controlled**, because control of the number does not undo receptor-mediated fibrosis.

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CHAPTER 34 PART VI · SECONDARY HYPERTENSION

Phaeochromocytoma and paraganglioma

Rare, lethal if unrecognised, curable if found — and routinely mistaken for panic disorder because the paroxysm is the part everyone remembers and half the patients do not have it.[5]

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Which catecholamine, which picture** — why some of these tumours give paroxysms and others give steady hypertension.
2. **Why the patient is hypertensive and orthostatic at once**, which sounds contradictory and is not.
3. **The triad** — what it is actually worth as a diagnostic test.
4. **Metanephrines, not catecholamines**, and why the difference is decisive.
5. **The false positives** — the drugs and conditions that will send you looking for a tumour that is not there.
6. **Alpha before beta** — the safety rule of this chapter, and the physiology that makes it non-negotiable.

34.1 What the tumour secretes decides what you see

These are tumours of chromaffin tissue — in the adrenal medulla, where they are called phaeochromocytomas, and in extra-adrenal sympathetic and parasympathetic ganglia, where they are called paragangliomas.[1] They secrete catecholamines, and the clinical picture follows from *which* catecholamine and *how* it is released.

A tumour secreting predominantly **noradrenaline** releases it more or less continuously, acting mainly on alpha-1 receptors, and produces **sustained** hypertension. A tumour secreting predominantly **adrenaline** tends to release in bursts, with beta effects prominent, and produces the **paroxysm** — the episode of pounding headache, palpitations and drenching sweat that the textbooks describe. Roughly half of adult patients have sustained rather than episodic hypertension. The paroxysm is the memorable presentation, not the usual one.

34.2 What the classic triad is worth

Headache, palpitations and sweating together is the classic triad, and it does carry weight: a systematic review gives it a positive likelihood ratio of 6.3 and a negative likelihood ratio of 0.14. In plain terms, its presence raises the probability substantially and its absence lowers it substantially — which is more than most clinical signs achieve.[4]

The individual symptoms are much weaker. Pooled sensitivities are headache 60.4%, palpitations 59.3% and sweating 52.4%. Any one alone is close to useless. It is the combination that means something, and the combination in a patient with hypertension that is labile, drug-resistant, or provoked by anaesthesia, surgery, micturition or certain drugs.

About **30 to 40%** of these tumours are hereditary — von Hippel–Lindau, multiple endocrine neoplasia type 2, neurofibromatosis type 1 and the succinate dehydrogenase mutations — which is why current guidance recommends offering genetic testing to *all* patients, not only those with a family history.[2] About one in ten now presents as an adrenal incidentaloma found on a scan done for something else.

The apparent contradiction

Chronic catecholamine excess contracts the plasma volume and downregulates adrenoreceptors. So the patient is hypertensive when supine and drops when they stand. A hypertensive patient with unexplained postural symptoms — before any drug has been given — is a patient to think about.

The commonest misdiagnosis

Panic disorder. The episodes are sudden, terrifying, accompanied by palpitations and sweating, and resolve spontaneously. The distinguishing feature is that the pressure rises during them — which nobody measures during a panic attack.

34.3 Why metanephrines and not catecholamines

Catecholamines are secreted episodically and cleared in minutes. Measure them between paroxysms and they are normal. Metanephrines are different: they are produced *continuously within the tumour itself* by catechol-O-methyltransferase, independently of secretion. A tumour that has not released anything for a week is still making metanephrines. That is the whole reason this is the test.

TABLE 34.1 — WHICH METANEPHRINE TEST

TEST	SENSITIVITY	SPECIFICITY	NOTES
Plasma free metanephrines	97%[8]	85%[8]	Plasma buys sensitivity, so it is the test where the diagnosis is likely: a known syndrome, a family history, an adrenal mass. Requires supine sampling through an indwelling cannula after rest — the commonest reason for a false positive is a patient sampled sitting, immediately after venepuncture.
24-hour urinary fractionated metanephrines	90%[8]	98%[8]	Urine buys specificity, so it is the test in an ordinary clinic, where the disease is rare and a false positive costs a scan. Does not need the sampling conditions, but depends on a complete collection. Choose by pretest probability, not by habit (V3·Ch7).

Interpretation turns on magnitude. A mild elevation is common and usually not a tumour; an elevation beyond about **three times the upper limit of normal is rarely a false positive**. Between those, repeat under proper conditions after removing the interfering agents below.

TABLE 34.2 — WHAT CAUSES A FALSE POSITIVE

CATEGORY	EXAMPLES
Drugs	Tricyclic antidepressants, monoamine oxidase inhibitors, labetalol and other beta-blockers, sympathomimetics including decongestants, levodopa, sulfasalazine, methyldopa, phenoxybenzamine — which matters because it is the drug you may have started yourself — and paracetamol where the assay uses electrochemical detection[1,6]
Physiological stress	Acute illness, pain, surgery, sleep apnoea, and the sampling itself if the patient is upright or has just been cannulated
Withdrawal states	Alcohol and clonidine withdrawal

Only after biochemical confirmation does imaging follow. CT of the abdomen and pelvis is first line. MRI is preferred in children, pregnancy, and where a paraganglioma of the skull base or neck is suspected.[7] Functional imaging — MIBG, DOTATATE or FDG-PET — is for metastatic disease, multifocal disease, and tumours the anatomical imaging cannot find. Imaging first, in a patient with normal metanephrines, finds incidentalomas and creates problems.

34.4 Alpha before beta

This is the most important safety rule in this book, and its physiology is simple enough to hold permanently. Circulating catecholamines act on alpha-1 receptors, which constrict, and on beta-2 receptors, which dilate. The two partly oppose each other. Block beta first and the vasodilating arm is removed while the constricting arm continues unopposed: systemic vascular resistance rises abruptly, and the blood pressure can go dangerously higher in a patient who was already hypertensive.

So alpha blockade is established first, with volume repletion — these patients are volume-contracted and will drop when the alpha tone is removed — and a beta-blocker is added afterwards only if tachycardia requires it.[1] Definitive treatment is surgical excision, and the perioperative period is the hazardous part, because handling the tumour releases a catecholamine surge into a circulation whose reflexes have adapted to chronic excess.

The rule is worthless without the regimen, so here it is. The 2014 Endocrine Society guideline requires preoperative blockade for every patient with a hormonally functional tumour, with an alpha-blocker as the first choice, for 7 to 14 days.[1]

Where the same rule appears again

Chapter 30 applies this reasoning to cocaine and other sympathomimetics — and, honestly, reports that the evidence there is weaker than the teaching suggests. In phaeochromocytoma the rule is not in doubt.

TABLE 34.3 — PREOPERATIVE PREPARATION

STEP	WHAT IS DONE
Alpha blockade	**Phenoxybenzamine, or a selective alpha-1 blocker such as doxazosin**, started **7 to 14 days before surgery** and titrated until the blood pressure and heart rate have normalised. That is the time the guideline gives for the pressure, the heart rate and the plasma volume to come right — not a day or two.[1]
Sodium and volume	A **high-sodium diet and liberal fluid intake** alongside the alpha-blocker. These patients are volume-contracted, the blockade unmasks it, and the purpose is to prevent the severe hypotension that follows removal of the tumour.[1]
Beta-blocker	**Only after alpha blockade is established, and only for tachycardia.** Never first, and never alone.
After excision	**Blood pressure, heart rate and blood glucose** are monitored in the immediate postoperative period and the other drugs adjusted, because hypotension and hypoglycaemia follow the loss of catecholamine drive.[1]

The absolute is easy to state. No patient goes to theatre on days of blockade rather than one to two weeks of it, and the physician who refers is responsible for seeing that the alpha-blocker and the salt were started in time.

KEY POINTS

1. **Noradrenaline-secreting tumours give sustained hypertension; adrenaline-secreting tumours give paroxysms.** About half of adults have sustained hypertension, so the absence of paroxysms means little.[3]
2. **Hypertension with orthostatic symptoms before any drug** is a characteristic combination, explained by volume contraction and receptor downregulation.[4]
3. **The full triad carries a positive likelihood ratio of 6.3 and a negative of 0.14**; the individual symptoms, at 52–60% sensitivity each, carry very little.
4. **Measure metanephrines, not catecholamines** — they are produced continuously inside the tumour, so they do not depend on catching a paroxysm.
5. **Plasma free metanephrines are 97% sensitive but only 85% specific**; the urinary assay is 90% sensitive and 98% specific, so choose by pretest probability. Plasma demands supine sampling through an indwelling cannula; a seated sample is the commonest avoidable false positive.[1,8]
6. **An elevation beyond three times the upper limit of normal is rarely false**; smaller rises need the drug list reviewed and the test repeated properly.
7. **Alpha blockade before beta blockade, always**, with volume repletion — and offer genetic testing to every patient, since 30 to 40% are hereditary.

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CHAPTER 35 PART VI · SECONDARY HYPERTENSION

Cushing's syndrome and glucocorticoid excess

The endogenous form is rare and hard to find. The exogenous form is common, is sitting in the drug history, and is the one most often missed.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why cortisol reaches the mineralocorticoid receptor** — and why blocking that receptor does not fix the hypertension.
2. **The other mechanisms**, because the answer is multifactorial and the single-mechanism version taught for years is wrong.
3. **Prescribed steroids** — the dose above which risk begins, and which steroid carries mineralocorticoid activity.
4. **Which physical signs discriminate**, and which are simply common in the population you are screening.
5. **Three first-line tests**, their performance, and the states that mimic the disease.
6. **Why hypertension persists after cure** in most patients.

35.1 How cortisol raises the pressure

The mineralocorticoid receptor cannot tell cortisol from aldosterone. They bind it with similar affinity, and cortisol circulates at concentrations more than a hundred times higher. What normally prevents chaos is an enzyme: 11-beta-hydroxysteroid dehydrogenase type 2, sitting in the mineralocorticoid target tissues, converting cortisol to cortisone, which the receptor does not bind. The enzyme is the gatekeeper, and aldosterone gets through only because it is not a substrate.[17]

In cortisol excess the gatekeeper is overwhelmed. Cortisol saturates the enzyme, reaches the mineralocorticoid receptor in the distal nephron, and produces sodium retention, volume expansion and potassium loss — the same final pathway as Chapter 33, reached from a different direction. That is the mechanism every textbook gives, and it is real.

It is also not the whole answer, and the book should say so. A review of glucocorticoid-induced hypertension states plainly that the mechanism *remains unknown* and that multiple factors are involved. Cortisol also enhances vascular reactivity to catecholamines and angiotensin II, upregulates the angiotensin type 1 receptor, suppresses vasodilator systems including prostacyclin and nitric oxide, potentiates central angiotensin II effects, and worsens insulin resistance and sleep apnoea.[6] The most telling evidence against a purely mineralocorticoid account is pharmacological: **spironolactone does not reliably block glucocorticoid-induced hypertension**, which it should if the mineralocorticoid receptor were the whole story.

35.2 The common form: prescribed steroids

Endogenous Cushing's syndrome has an incidence of roughly 1.2 to 2.4 per million per year. Exogenous glucocorticoid exposure is ordinary. In a hypertension clinic the drug history will find far more glucocorticoid-induced hypertension than the adrenal will.[15]

The relationship is dose-dependent, and there appears to be a floor: no excess hypertension risk has been demonstrated below about 7.5 mg of prednisolone-equivalent daily. Above that, a large cohort of people with chronic inflammatory disease found the risk of incident hypertension rising with cumulative prednisolone-equivalent dose — hazard ratios of 1.14, 1.20 and 1.30 across increasing bands. Those are relative increases of 14, 20 and 30%, not the proportion of patients affected. New-onset hypertension appeared in about 9% by three months on high-dose therapy.[11,16]

What this changes at the bedside

Do not expect a mineralocorticoid receptor antagonist to control steroid-induced hypertension the way it controls primary aldosteronism. Reducing the steroid is the treatment; everything else is holding the line.

TABLE 35.1 — RELATIVE MINERALOCORTICOID POTENCY OF THE COMMON GLUCOCORTICOIDS

AGENT	RELATIVE MINERALOCORTICOID ACTIVITY
Hydrocortisone	1
Prednisolone	0.8
Methylprednisolone	0.5
Dexamethasone	0
Fludrocortisone	150

The table is practical. A patient needing long-term steroid whose blood pressure is the problem may do better on dexamethasone, which has no mineralocorticoid activity at all — though it has other drawbacks. And a patient on fludrocortisone is receiving a drug with 150 times the mineralocorticoid potency of hydrocortisone, which is the point of the drug and also the explanation for their pressure.[18]

35.3 Which signs actually discriminate

This is the diagnostic problem in one sentence: the features that make you think of Cushing's — central obesity, hypertension, diabetes — are the features of the population you are screening. One study found obesity was actually *more* common in the patients in whom Cushing's was excluded than in those in whom it was confirmed.

TABLE 35.2 — DISCRIMINATING AND NON-DISCRIMINATING FEATURES

THESE DISCRIMINATE	THESE DO NOT
Easy bruising	Central obesity or weight gain
Proximal myopathy — difficulty rising from a chair unaided	Hypertension
Wide violaceous striae	Type 2 diabetes
Facial plethora	Depression, fatigue, poor sleep
Unexplained osteoporotic fracture in a young adult	Menstrual irregularity

Multiple discriminating features together carry real weight — an odds ratio of 18.0 in one series. One of them alone does not. And there is a group in whom the pretest probability is much higher than the general hypertensive population: the CATALYST study found hypercortisolism in **24%** of patients with difficult-to-control type 2 diabetes, rising to about a third of those on three or more antihypertensives. That figure is high enough to be surprising, and a separate study in a different poorly-controlled diabetic population found none — so it should be read as a signal to look harder in that group rather than as a settled prevalence.[1,3]

35.4 The three first-line tests, and the states that mimic

One abnormal test is not a diagnosis. Two different tests must be concordantly abnormal before you go looking for the cause, because in the obese, diabetic, depressed or alcohol-exposed patient a single positive is more likely to be a pseudo-Cushing state than a tumour. Each row below carries its own cut-off; the rule governs all three.[13]

TABLE 35.3 — SCREENING FOR ENDOGENOUS CORTISOL EXCESS

TEST	PERFORMANCE	WHAT DEFEATS IT
Overnight 1 mg dexamethasone suppression — failure to suppress below 1.8 µg/dL (50 nmol/L) on the Endocrine Society threshold; the older 5 µg/dL cut-off misses about one case in seven[13]	Sensitivity above 95%, specificity about 80%	Anything inducing CYP3A4 accelerates dexamethasone clearance — anticonvulsants, rifampicin. Oral oestrogen raises cortisol-binding globulin and produces a false-positive test in about half of women taking the combined pill. Withdraw oestrogen-containing drugs six weeks before testing or retesting where that is possible — and where it is not, use late-night salivary cortisol or a 24-hour urine free cortisol instead, since both measure free cortisol and neither depends on the binding globulin.[13]
Late-night salivary cortisol — above 145 ng/dL (4 nmol/L), on two collections[13]	92–100% sensitivity, 93–100% specificity	Shift work and irregular sleep destroy the assumption of a nocturnal nadir.
24-hour urinary free cortisol — above the assay's reference range, on at least two collections[13]	Sensitivity about 89% in the paediatric data cited	Incomplete collection. High fluid intake. Insensitive to mild disease.

Two further points decide whether the work-up succeeds. First, **cyclical Cushing's** — reported in 14 to 18% of cases — means a single normal test does not exclude the disease in a patient whose story is convincing; repeat testing during a symptomatic phase is what finds it.[8] Second, the **pseudo-Cushing states**: alcohol excess, severe depression, obesity and poorly controlled diabetes all raise cortisol and can produce a positive screen without the disease. The dexamethasone–CRH test, midnight serum cortisol and the desmopressin test exist to separate them.[4]

Once cortisol excess is established, ACTH separates the two branches: a level below about 5 pg/mL indicates an ACTH-independent adrenal source, above about 20 pg/mL an ACTH-dependent one.[9] Between those two figures the result is indeterminate, which is common. Repeat it, and if it stays in between, a CRH stimulation test separates the branches — do not choose an imaging target on an equivocal ACTH. Localising the ACTH source is a specialist step, and

inferior petrosal sinus sampling is the reference; with CRH stimulation it performs at 91.3% sensitivity and 92.9% specificity, rising to 96.0% and 100% when a prolactin ratio is added.[5]

35.5 What it changes, and the disappointment to expect

Treatment is directed at the cause — surgical, medical or radiotherapeutic — and cure of the cortisol excess is the objective.[14] But the hypertension does not reliably follow. In one series hypertension resolved in only **36%** of patients after remission. Older age at treatment predicted persistence, and so, counterintuitively, did a *lower* baseline urinary free cortisol — almost certainly because milder biochemistry means longer undiagnosed disease, and longer disease means vascular remodelling that no longer reverses.[19]

That is the argument for looking early rather than thoroughly. Cardiovascular mortality in Cushing's runs at about four times that of the background population — standardised mortality ratios of 3.7 in the Danish series and 3.8 in the Spanish — and remains elevated after cure.[7] And a patient whose steroid is withdrawn after prolonged exposure faces adrenal insufficiency — a median of 37% on glucocorticoids of any kind, 48.7% on oral ones — and needs a planned taper; the pressure problem is replaced by a different one. The figure of 99% sometimes quoted here belongs to endogenous disease, not to prescribed steroids.[12]

The incidentaloma question

Adrenal incidentalomas are found in 15 to 30% of abdominal scans, and mild autonomous cortisol secretion in a proportion of them is associated with hypertension. This is now a recognised entity rather than a curiosity, and a hypertensive patient with an adrenal incidentaloma warrants assessment for both cortisol and aldosterone excess.[10]

KEY POINTS

1. **Cortisol saturates 11-beta-HSD2 and reaches the mineralocorticoid receptor** — but the mechanism is multifactorial, and spironolactone does not reliably block glucocorticoid-induced hypertension.[2]
2. **Prescribed steroids cause far more of this than adrenal disease does.** Risk begins above about 7.5 mg prednisolone-equivalent daily and rises with cumulative dose.
3. **Dexamethasone has no mineralocorticoid activity; fludrocortisone has 150 times that of hydrocortisone.** The choice of steroid is a blood pressure decision.
4. **Obesity, hypertension and diabetes do not discriminate.** Easy bruising, proximal myopathy, violaceous striae and facial plethora do — and together carry an odds ratio of 18.[12]
5. **Late-night salivary cortisol is the most specific screen** (92–100% and 93–100%); the 1 mg dexamethasone test is more sensitive but only about 80% specific.
6. **One normal test does not exclude it** — cyclical disease occurs in 14 to 18%, and pseudo-Cushing states produce false positives.
7. **Hypertension resolves after cure in only about a third**, and persistence is predicted by longer undiagnosed disease. Look early.

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CHAPTER 36 PART VI · SECONDARY HYPERTENSION

Thyroid, parathyroid and acromegaly

Three endocrine causes that raise the pressure by three different routes — and the only chapter in this book where treating the cause reliably does less than you expect.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Both thyroid directions** — systolic hypertension in thyrotoxicosis, diastolic hypertension in hypothyroidism, and the haemodynamics behind each.
2. **What replacement actually achieves**, in millimetres of mercury.
3. **Subclinical disease** — where the evidence is genuinely mixed, reported as mixed.
4. **Hyperparathyroidism** — a real association, and an honest account of what parathyroidectomy does to the pressure.
5. **Acromegaly** — sodium retention through ENaC, and the sleep apnoea that comes with it.
6. **When to order TSH, calcium and IGF-1** — and the guideline position that these are not routine.

36.1 Thyroid disease raises the pressure in both directions

Thyroid hormone acts on the heart and the vasculature in opposite ways depending on whether there is too much or too little, and the resulting hypertension has a different signature in each case. This is one of the neatest illustrations in the book of why the two numbers in a blood pressure carry different information.

TABLE 36.1 — THE TWO THYROID HAEMODYNAMICS

	HYPERTHYROIDISM	HYPOTHYROIDISM
Cardiac output	Increased — by up to 300% in the extreme	Reduced
Systemic vascular resistance	Reduced	**Increased**
Pulse pressure	Wide	Narrow
Which number rises	**Systolic**	**Diastolic** — diastolic hypertension in about 30% of overt cases
Rhythm	Atrial fibrillation	Bradycardia
Vessel wall	—	Increased arterial stiffness, reversible with replacement

So a patient with isolated systolic hypertension, a wide pulse pressure and atrial fibrillation has a thyroid explanation worth excluding — especially if they are younger than the arterial stiffening of Chapter 17 would predict. And a patient with diastolic hypertension, bradycardia, fatigue and dry skin has the opposite one.[3,4,14]

Replacement helps, and it is worth knowing by how much so that expectations are calibrated. The pooled figures are for **subclinical** hypothyroidism: levothyroxine lowered systolic pressure by about **2.48 mmHg** across ten randomised trials in 1,637 patients — the diastolic fall of 0.85 mmHg was not significant — and by 4.80/2.74 mmHg across nineteen prospective follow-up studies.[10] Real, and modest. Correcting the thyroid is not a substitute for treating the hypertension.

One drug deserves separate mention because it is prescribed for the arrhythmia the thyroid caused. Amiodarone induces thyroid dysfunction in two distinct forms: type 1, iodine-induced excess synthesis in a gland with pre-existing pathology, and type 2, a destructive thyroiditis releasing preformed hormone. They are separated on thyroid blood flow imaging and treated differently — thionamides for the first, glucocorticoids for the second. In thyroid storm, systolic hypertension is an early feature and hypotension a late and ominous one.[5,13]

Subclinical disease: report the mixture

A meta-analysis found subclinical hypothyroidism associated with a small but statistically significant pressure difference — systolic +1.89 and diastolic +0.75 mmHg — while subclinical hyperthyroidism showed no significant association. These are population effects of a size that changes nothing in an individual patient.[6,10]

36.2 Primary hyperparathyroidism, and an honest answer

Hypertension is common in primary hyperparathyroidism — reported in 40 to 60%, and up to 63% in some series. Several mechanisms have been proposed: direct vascular effects of parathyroid hormone, RAAS activation, endothelin and oxidative stress, and the vascular consequences of chronic hypercalcaemia. The association is not in doubt.[8]

What is in doubt is whether removing the parathyroid does anything about it, and this book will not overstate the case. The best available systematic review finds that arterial stiffness improves after parathyroidectomy, but the effect on blood pressure itself is **not statistically significant once an outlier study is removed**. Individual studies point both ways.

Vitamin D is adjacent and asked about constantly. The evidence there is mixed in the same way: a large cohort found no significant association with blood pressure after adjustment, while a pooled meta-analysis did find one. It is not established as a treatment for hypertension.[12]

What to tell the patient

Parathyroidectomy is indicated on its own merits — bone, stones, symptoms, calcium. It should not be offered as a treatment for the hypertension, because the evidence does not support that promise.

36.3 Acromegaly

Growth hormone and IGF-1 produce hypertension mainly through **sodium retention**. Growth hormone acts on the epithelial sodium channel in the distal nephron — the same channel as aldosterone and cortisol reach it through, arrived at by a third route — and the result is plasma volume expansion. Two other contributors matter: an acromegalic cardiomyopathy that progresses through hyperkinetic, hypertrophic and eventually failing stages, with heart failure in 3 to 4%; and obstructive sleep apnoea, present in 40 to 80% of patients in one source and 69% in the guideline, driven by soft-tissue overgrowth in the upper airway.[7]

Reported prevalence of hypertension in acromegaly varies widely between sources — 22% in one, 33 to 46% in another — and the book records the range rather than choosing. What is consistent is that the diagnosis is typically made

years after the disease began, because acral and facial change is slow enough that neither patient nor physician notices it. Looking at an old photograph is a better diagnostic test than looking at the patient.[1]

IGF-1 is the first-line test, and the guideline explicitly recommends measuring it in a hypertensive patient who has other features suggesting acromegaly. What happens to the pressure after successful treatment is unsettled: two outcome studies point in directly opposite directions, and this book reports that rather than picking the encouraging one.[9,11]

36.4 When to order these tests

The guideline position is unambiguous and worth stating plainly, because it runs against a common instinct to add these to every panel: TSH, calcium and IGF-1 are **not** routine tests in the assessment of hypertension. They are suspicion-triggered.[15]

That restraint is itself a clinical principle. A test ordered without a reason produces results without a meaning, and in a population where mild abnormalities are common, the borderline TSH generates more consultations than it resolves.

TABLE 36.2 — WHAT TRIGGERS EACH TEST

TEST	ORDER IT WHEN
TSH	Isolated systolic hypertension with wide pulse pressure in a younger patient, atrial fibrillation, weight change, tremor, heat or cold intolerance, bradycardia with diastolic hypertension — or the patient is on amiodarone or lithium
Serum calcium	Hypercalcaemia found incidentally, renal stones, osteoporosis or fragility fracture, unexplained fatigue or constipation. Always interpret with a parathyroid hormone level drawn at the same time
IGF-1	Acral enlargement, coarsening facial features, new dental spacing, ring or shoe size increasing in adulthood, carpal tunnel syndrome, or sleep apnoea with these features

KEY POINTS

1. **Hyperthyroidism raises the systolic pressure** through high cardiac output and low resistance; **hypothyroidism raises the diastolic** through increased systemic vascular resistance, present in about 30% of overt cases.[3]
2. **Levothyroxine lowers systolic pressure by about 2.5 mmHg** in randomised trials — real, modest, and not a substitute for antihypertensive treatment.
3. **Subclinical hypothyroidism shows a small significant association** (+1.89/+0.75 mmHg); subclinical hyperthyroidism shows none.
4. **Hypertension occurs in 40 to 63% of primary hyperparathyroidism** — but parathyroidectomy does not significantly lower blood pressure once an outlier study is removed. Do not offer it as a cure for the pressure.[2]
5. **Acromegaly raises pressure through ENaC-mediated sodium retention**, with cardiomyopathy and sleep apnoea in 40 to 80% contributing.
6. **An old photograph beats an examination** for suspecting acromegaly, because the change is too slow to notice.
7. **TSH, calcium and IGF-1 are not routine tests in hypertension.** Order them when something specific points there.

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CHAPTER 37 PART VI · SECONDARY HYPERTENSION

Coarctation of the aorta, and how to search for a secondary cause

One cause you find by touching the patient, one you find by not being reassured after the repair — and the strategy that decides when to look at all.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **Why a coarctation raises the pressure** — and why the mechanical explanation alone is not enough.
2. **Why the pressure stays up after repair** in roughly half of patients, decades later.
3. **Four limbs, one examination** — the physical findings, and the gradient that counts.
4. **How common secondary hypertension really is**, and how age transforms that number.
5. **Which findings raise the probability most**, and which cause to think of first.
6. **The screening argument** — including the case against it, stated fairly.

37.1 Coarctation: more than a narrowing

The mechanical account is the obvious one: a narrowing of the aorta, usually just distal to the left subclavian origin, raises the pressure proximal to it and lowers it distally. It is correct and it is incomplete, because it does not explain the two things that matter most about this condition.

It does not explain why the hypertension is not confined to the upper body in the way pure mechanics would predict — reduced renal perfusion beyond the narrowing activates the renin–angiotensin system, which raises pressure everywhere. And it does not explain why the pressure remains high after the obstruction is gone.[6] Three further mechanisms are implicated: **abnormal aortic compliance**, with reduced distensibility of the pre-stenotic aorta; **baroreceptor dysfunction**, since the baroreceptors sit in a vessel wall whose mechanics have been abnormal since fetal life; and a hypothesis with the memorable name of the **"selfish brain"** — vertebral artery hypoplasia and an incomplete circle of Willis producing brainstem hypoperfusion and a compensatory sympathetic drive, associated with an odds ratio of 2.5 for hypertension and 3.3 for uncontrolled hypertension.[12,16]

37.2 Finding it with your hands

Coarctation is one of the few causes of hypertension that a complete physical examination reliably finds and an incomplete one reliably misses. The findings are unglamorous and they are free.

The number that should change practice

Pooled prevalence of hypertension after coarctation repair is **47.3%**, and rises to 57.8% when ambulatory monitoring is used rather than clinic readings. A repaired coarctation is a lifelong hypertension diagnosis, not a cured one.[14]

TABLE 37.1 — THE EXAMINATION

FINDING	WHAT IT MEANS
Radio-femoral delay	The femoral pulse arrives after the radial because the wave has travelled through collaterals. Palpate them simultaneously, not in sequence.[8]
Upper-limb pressure exceeding lower limb	A gradient greater than **20 mmHg** is the cited threshold for significance. Measure all four limbs, simultaneously where possible.[5]
Interscapular murmur or bruit	Flow across the narrowing and through collaterals.
Bicuspid aortic valve	Present in 45 to 75% overall — about two-thirds of infant presentations and around 30% of those presenting in childhood.
Rib notching on chest radiograph	Inferior borders of ribs three to eight, bilateral, from dilated intercostal collaterals. A late sign, and an easy one to miss on a film taken for another reason.

Infants present with heart failure. Adults and older children present through hypertension found incidentally — which means the diagnosis rests entirely on whether someone examined the femoral pulses of a hypertensive young adult. Echocardiography confirms and quantifies, and CT or MR angiography defines the anatomy for intervention.[9,10]

After repair, surveillance is lifelong. Recoarctation occurs in 10 to 20%, aneurysm is a recognised late complication, ambulatory monitoring frequently reveals masked hypertension and non-dipping that clinic readings miss, and exercise-induced hypertension appears in up to a third of repaired patients who are normotensive at rest — an early marker worth knowing about.[10,18]

37.3 How often is it worth looking?

Secondary hypertension accounts for roughly **5 to 10%** of unselected hypertensive adults, and current European guidance considers that figure likely to be an underestimate as screening improves. Taken alone, 5 to 10% argues for restraint. But the figure is not a constant — it is a strong function of age, and of how the hypertension is behaving.[1,2]

TABLE 37.2 — THE PROBABILITY OF A SECONDARY CAUSE, BY POPULATION

POPULATION	SECONDARY
Unselected hypertensive adults	5–10%
Confirmed hypertensives aged 18–40	29.6%
Hypertensives aged 16–30 (Finnish cohort, n = 243)	40.3%
Children newly diagnosed at school or in primary care (26-study meta-analysis, n = 2,575)[19]	3.7%[19]
Children newly diagnosed in a paediatric referral clinic — the older figures of 70–85% describe historical tertiary nephrology series and that denominator only	20.1%[19]

In that Finnish cohort, renal disease accounted for about **four-fifths** of the secondary cases, with sleep apnoea second. That is the single most useful fact for directing a search in a young hypertensive: start with the kidney. A urinalysis, an albumin–creatinine ratio, a creatinine and a renal ultrasound will find most of what there is to find.[11]

Within confirmed secondary cases, one 2024 young-adult study distributes them as primary aldosteronism 54.8%, renovascular disease 18.4%, primary kidney disease 12.9%, drug-induced 6.0%, and phaeochromocytoma or paraganglioma 5.9%. A British young-onset guideline instead puts aldosteronism, renal artery stenosis and renal parenchymal disease together at up to about 10% of all young hypertensives, with coarctation, phaeochromocytoma, Cushing's and thyroid disease each at 1% or below. The two are not contradictory — they have different denominators — and any ranking should be read as a statement about the population it came from.[2,17]

37.4 What should make you look

TABLE 37.3 — FINDINGS THAT RAISE THE PROBABILITY OF A SECONDARY CAUSE

FINDING	THINK FIRST OF
Onset before 30, or after 55	Renal parenchymal disease and renovascular disease; coarctation in the young[2]
Resistant hypertension — uncontrolled on three drugs including a diuretic	Primary aldosteronism, sleep apnoea, renal parenchymal disease, non-adherence
Spontaneous or diuretic-induced hypokalaemia	Primary aldosteronism; and if renin is *also* high, a renin-secreting tumour
Abrupt onset, or an established hypertensive who accelerates	Renovascular disease; phaeochromocytoma
Creatinine rising after a RAAS blocker is started	Bilateral renal artery stenosis, or stenosis in a single functioning kidney
Target-organ damage out of proportion to the pressure or its duration	Primary aldosteronism
Recurrent flash pulmonary oedema	Bilateral renovascular disease — Pickering syndrome
Labile pressure with paroxysmal symptoms	Phaeochromocytoma
Absent or asymmetric pulses, inter-arm difference	Coarctation; Takayasu arteritis
A pressure that rose when a drug was started	Drug-induced — and the patient may not consider it a drug

37.5 The screening argument, both sides

Whether to screen every hypertensive for primary aldosteronism is the live controversy in this field, and the book should give both cases rather than assert one.[13]

The case for. It is the commonest correctable cause. It is specifically treatable, by a targeted drug or by an operation that can cure. It carries excess cardiovascular risk beyond its blood pressure. It is missed for decades because clinicians wait for hypokalaemia that most patients never develop. And selective screening has under-performed: the number of patients diagnosed remains far below the number the prevalence studies predict.[7]

The case against. The screening test is technically fragile and generates false positives that lead to invasive confirmation. Confirmatory testing and adrenal vein sampling are expensive, are available in few centres, and adrenal vein sampling is operator-dependent. Many patients found by universal screening have mild disease of uncertain significance. And in a health system where a large share of hypertensives are not treated at all, spending on case-finding rather than on treatment and adherence may not be where the next life is saved.

Where this book lands

Both cases are strong, and the balance depends on the health system. In a setting where the cascade of care loses most patients before control — which is the Indian situation described in Chapter 9 — the argument for spending first on treatment and adherence is real. The compromise this book recommends is to screen the groups in which yield is high: the young, the resistant, the hypokalaemic, and the patient with an adrenal incidentaloma.[3]

KEY POINTS

1. **Coarctation is not only a narrowing.** RAAS activation, abnormal aortic compliance, baroreceptor dysfunction and possibly brainstem hypoperfusion all contribute.[16]
2. **Hypertension persists after repair in 47.3% of patients**, rising to 57.8% on ambulatory monitoring. A repaired coarctation needs lifelong follow-up.[15]
3. **An upper-to-lower limb gradient above 20 mmHg is the threshold that matters** — and radio-femoral delay is found only if the pulses are palpated together.
4. **Secondary hypertension is 5 to 10% overall but 29.6% at ages 18–40 and 40.3% at 16–30.** Age is the strongest modifier of pretest probability.[4]
5. **In young secondary hypertension, renal disease is about four-fifths of it.** Start with the kidney.
6. **Published rankings of secondary causes disagree because their denominators differ.** Read every ranking as a statement about its population.
7. **Universal aldosteronism screening has a real case on both sides**; in a system losing most patients before control, screening the high-yield groups is the defensible compromise.

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APPENDIX A VOLUME ONE · APPENDICES

Secondary hypertension screening algorithm

When to suspect a secondary cause, and the first-line screen for each.

Secondary hypertension should be actively investigated when clinical features raise suspicion, rather than screened for indiscriminately — with the important modern exception of primary aldosteronism, for which universal screening of all confirmed hypertensives is now recommended (2024 ESC, 2025 Endocrine Society, 2025 AHA/ACC; Chapters 13 and 26).

TABLE A.1 — WHEN TO SUSPECT A SECONDARY CAUSE

TRIGGER	MOST LIKELY SECONDARY CAUSES TO CONSIDER
Onset before age 30, or severe hypertension before 40	Fibromuscular dysplasia, primary aldosteronism, phaeochromocytoma, coarctation, monogenic syndromes
Resistant hypertension (≥3 drugs including a diuretic)	Primary aldosteronism, obstructive sleep apnoea, renovascular disease, CKD
Spontaneous or diuretic-induced hypokalaemia	Primary aldosteronism; liquorice/mulethi (apparent mineralocorticoid excess); Cushing's
Paroxysmal hypertension with headache, palpitations, sweating	Phaeochromocytoma / paraganglioma
Abdominal bruit; >30% creatinine rise on ACEi/ARB	Renovascular hypertension (bilateral if the rise is marked)
Snoring, daytime sleepiness, non-dipping on ABPM	Obstructive sleep apnoea
Cushingoid features; central obesity + glucose intolerance	Cushing's syndrome
Radio-femoral delay; arm–leg BP difference	Coarctation of the aorta
Elevated creatinine, proteinuria, abnormal urinalysis	Chronic kidney disease (parenchymal)

TABLE A.2 — FIRST-LINE SCREENING TEST BY CAUSE

SUSPECTED CAUSE	FIRST-LINE SCREENING TEST	CONFIRMATORY / NEXT STEP
Primary aldosteronism	Aldosterone-to-renin ratio (ARR) — now considered in *all* confirmed hypertensives	Saline or fludrocortisone suppression; adrenal CT; adrenal vein sampling
Phaeochromocytoma	Plasma free or 24-hr urinary fractionated metanephrines	CT/MRI; MIBG or PET; genetic testing
Cushing's syndrome	Overnight dexamethasone suppression, late-night salivary cortisol, or 24-hr urinary free cortisol	ACTH; source-localisation tests
Renovascular disease	Renal Doppler ultrasound	CT or MR angiography; catheter angiography for FMD if intending to treat
Obstructive sleep apnoea	STOP-BANG; overnight oximetry	Polysomnography (apnoea-hypopnoea index)
Thyroid disease	Thyroid function tests (part of baseline work-up)	As indicated by the abnormality
Chronic kidney disease	Creatinine/eGFR, urinalysis, albumin-creatinine ratio	Renal ultrasound; nephrology referral
Coarctation of the aorta	Four-limb BP; echocardiography	CT or MR aortography

APPENDIX B

VOLUME ONE · APPENDICES

Drug-induced hypertension: master table

Agents that raise blood pressure, their mechanism, and management (V1·Ch27–30).

Systematic review of a patient's medications, over-the-counter products, supplements and traditional remedies for these agents is an essential step in assessment, particularly of resistant hypertension or lost control.

TABLE B.1 — AGENTS THAT RAISE BLOOD PRESSURE

AGENT / CLASS	MECHANISM	MANAGEMENT
NSAIDs and COX-2 inhibitors	Inhibit renal prostaglandins → Na^+/water retention, reduced renal blood flow, vasoconstriction	Avoid in hypertension, CKD, and the triple-whammy combination; prefer paracetamol; use a CCB if an NSAID is unavoidable
Paracetamol (regular, full-dose)	Raises BP ~5 mmHg systolic (PATH-BP), similar to NSAIDs	Lowest effective dose, shortest duration; monitor BP with regular use
Combined oral contraceptives	Oestrogen raises hepatic angiotensinogen → RAAS activation	Switch to progestogen-only or non-hormonal method; usually reversible in months
Oral oestrogen HRT	First-pass hepatic angiotensinogen production	Switch to transdermal oestrogen (bypasses first-pass metabolism)
Anabolic androgenic steroids	Na^+/fluid retention, raised red-cell mass/viscosity, adverse lipids	Cessation; usually improves; manage cardiovascular harm
Corticosteroids	Mineralocorticoid Na^+-retaining effect (agent-dependent)	Minimise dose/duration; low-sodium diet; diuretic
Calcineurin inhibitors (ciclosporin, tacrolimus)	Renal/systemic vasoconstriction (↑endothelin, ↓NO), SNS activation, Na^+ retention	CCB preferred (amlodipine); mind the diltiazem/verapamil–CNI level interaction
VEGF inhibitors (bevacizumab, sunitinib, sorafenib, pazopanib)	Impaired endothelial NO, vasoconstriction, microvascular rarefaction	Prompt RAAS blocker or CCB; resolves after cancer therapy ends
Erythropoiesis-stimulating agents	Raised red-cell mass/viscosity, vasoconstriction, reversal of anaemic vasodilation	Gradual Hb correction, conservative target; treat BP and volume
Sympathomimetic decongestants (pseudoephedrine, phenylephrine)	Alpha-adrenergic vasoconstriction	Avoid in hypertension; saline sprays; read combination-product labels
Cocaine, amphetamines, MDMA	Intense sympathetic activation (reuptake block or release of NA/dopamine)	Benzodiazepine first; nitrate, labetalol or phentolamine for the pressure. **Unopposed beta-blockade is not the first drug** — traditionally avoided for fear of unopposed alpha stimulation, a risk outcome data have not consistently confirmed; hold it until the alpha-mediated hypertension is controlled
Liquorice / mulethi (glycyrrhizin)	Inhibits 11-β-HSD2 → cortisol activates the mineralocorticoid receptor (apparent mineralocorticoid excess)	Stop the preparation — reversible, but over weeks to months; suspect with low K^+ and suppressed renin AND aldosterone
Other herbals (ephedra, bitter orange, yohimbe, ginseng, guarana)	Sympathomimetic or caffeine-related pressor effects	Identify by explicit enquiry; discontinue
St John's wort	Induces drug metabolism (CYP), lowering antihypertensive drug levels	Review interactions; adjust or avoid

APPENDIX C VOLUME ONE · APPENDICES

Blood pressure reference and classification

Classification thresholds side by side, out-of-office thresholds, and the Indian context (V1·Ch8 and Ch9).

An individual's classification must be based on properly measured, repeated readings, confirmed with out-of-office measurement where appropriate, not on a single reading.

TABLE C.1 — CLASSIFICATION THRESHOLDS COMPARED

CATEGORY	ACC/AHA 2017	ESC 2024	ESH 2023
Normal / Optimal	<120/80	<120/70 (non-elevated)	<120/80 (optimal)
Elevated BP	120–129/<80	**120–139/70–89 ("Elevated BP")**	120–129/80–84 (normal)
High-normal	—	(within Elevated BP)	130–139/85–89
Stage 1 / Grade 1 HTN	130–139/80–89	140–159/90–99	140–159/90–99
Stage 2 / Grade 2 HTN	≥140/90	160–179/100–109	160–179/100–109
Grade 3 HTN	—	≥180/110	≥180/110
Definition of hypertension	≥130/80	≥140/90	≥140/90

TABLE C.2 — TREATMENT TARGETS

GUIDELINE / SETTING	DEFAULT SYSTOLIC TARGET
ESC 2024 (most treated adults)	120–129 mmHg (ALARA for ≥85y, frail, orthostatic)
ACC/AHA	<130 mmHg
KDIGO 2021 (non-dialysis CKD)	<120 mmHg (standardised measurement)
Diabetes (most guidelines)	<130/80
Kidney transplant	<130/80
Very elderly / frail	ESC 2024: the same 120–129 where tolerated; relaxed to as low as reasonably achievable from age 85, with moderate-to-severe frailty, or with symptomatic orthostatic hypotension. Record the diastolic and examine the patient if it falls low; it is not a stop-line that overrides systolic control (V3 Ch13)

TABLE C.3 — OUT-OF-OFFICE DIAGNOSTIC THRESHOLDS

MEASUREMENT	HYPERTENSION THRESHOLD
Office / clinic BP	≥140/90
Home BP monitoring (average)	≥135/85
Ambulatory — daytime average	≥135/85
Ambulatory — night-time average	≥120/70
Ambulatory — 24-hour average	≥130/80

The **≥140/90 threshold** is the point of broad international agreement for diagnosing hypertension (ESC 2024, ESH 2023, ISH 2020, Indian Society of Hypertension); ACC/AHA 2017 sets it at ≥130/80. Risk is continuous from ~115/75 (61-study meta-analysis).

APPENDIX D — VOLUME ONE · APPENDICES

Monogenic hypertension syndromes

The inherited syndromes of hypertension (V1·Ch11).

These syndromes are individually rare but collectively important: specifically treatable when identified, illuminating pathways that also operate in common essential hypertension, and to be considered in the young patient with severe hypertension, spontaneous hypokalaemia, or a strong family history. **Every one increases sodium reabsorption in the distal nephron** — reinforcing Guyton's principle that the kidney is the final common pathway of sustained hypertension.

TABLE D.1 — THE MONOGENIC HYPERTENSION SYNDROMES

SYNDROME	GENETIC DEFECT / MECHANISM	BIOCHEMISTRY	SPECIFIC TREATMENT
Liddle syndrome	Gain-of-function in ENaC (SCNN1B/SCNN1G); constitutively active Na^+ channel	Low K^+, metabolic alkalosis, **LOW renin, LOW aldosterone**	**Amiloride or triamterene** (ENaC blockers). NOT spironolactone
Gordon syndrome (PHA type II)	WNK1/WNK4/KLHL3/CUL3; increased NCC activity	**HIGH K^+** (distinctive), metabolic acidosis	**Low-dose thiazide** (NCC blockade) — very effective
Glucocorticoid-remediable aldosteronism (GRA)	CYP11B1/CYP11B2 chimeric gene; aldosterone under ACTH control	Low K^+, family history, early stroke	**Dexamethasone** (suppresses ACTH) or a mineralocorticoid antagonist
Apparent mineralocorticoid excess (AME)	Loss of function of 11–β-HSD2; cortisol activates the MR	Low K^+, LOW renin, LOW aldosterone	Spironolactone/eplerenone; **acquired form from liquorice/mulethi → stop the source**
Congenital adrenal hyperplasia (11–β-hydroxylase deficiency)	CYP11B1 deficiency; excess 11–deoxycorticosterone	Virilisation, elevated 11–deoxycortisol, low cortisol	Glucocorticoid replacement (suppresses ACTH-driven excess steroid)
Familial phaeochromocytoma–paraganglioma	VHL, RET (MEN2), NF1, SDHB/C/D mutations	Elevated metanephrines; episodic catecholamine excess	**Alpha-blockade first**, then surgical excision; lifelong surveillance

CHAPTER E VOLUME ONE · APPENDIX

Causes of hypertension: master table

Every cause this volume discusses, in one place — what is physically wrong, what makes you suspect it, and the single test that settles it.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

1. **How the two categories actually divide** — and why "essential" names a group of mechanisms rather than an absence of one.
2. **How common secondary hypertension really is**, and how that figure changes with age, resistance and severity.
3. **The rank order** — which secondary causes account for most of the yield, and which are vanishingly rare.
4. **One row per cause**: mechanism, clinical clue, first test, and the chapter that treats it properly.

E.1 What the two categories mean

"Essential" hypertension is not hypertension without a cause. It is hypertension whose cause is distributed across several interacting systems — the mosaic of Chapter 10 — rather than concentrated in one correctable lesion. The distinction from secondary hypertension is therefore practical rather than philosophical: in secondary hypertension there is a single dominant abnormality that can be removed, blocked or cured, and removing it changes the pressure.

That is why the search matters even though the yield is modest. Secondary hypertension accounts for roughly **5 to 10%** of unselected hypertensive adults — a figure the 2024 European guidance itself flags as probably an underestimate with modern screening.[2] But the proportion is not fixed. It rises steeply in the young: one study of confirmed hypertensives aged 18 to 40 found 29.6% secondary, and a Finnish cohort aged 16 to 30 found 40.3%, of which renal disease accounted for about four-fifths.[2,9] In prepubertal children the older tertiary series give 70 to 85% secondary; the 2022 pooled figures are 3.7% for children found at school or in primary care and 20.1% in referral clinics, and the denominator decides which applies (Ch 37).[8]

Where the yield is

Age is the strongest single modifier of pretest probability. A 62-year-old with grade 1 hypertension and a normal potassium warrants the basic panel. A 24-year-old with the same reading warrants a search.[7]

TABLE E.1 — HOW THE PROBABILITY OF A SECONDARY CAUSE SHIFTS

POPULATION	PROPORTION SECONDARY	SOURCE POPULATION
Unselected hypertensive adults	5–10%	General adult hypertensive population
Confirmed hypertensives aged 18–40	29.6%	Young-adult study cited in current review
Hypertensives aged 16–30	40.3%	Finnish cohort, n = 243; renal disease was about 79% of the secondary cases
Prepubertal children	3.7% to 20.1%; 70–85% in older tertiary series	Lower figure at school or primary-care screening, higher in referral clinics; the 70–85% describes historical tertiary nephrology series only (Ch 37)
Resistant hypertension	Not established as a single figure	Cause-specific instead: obstructive sleep apnoea present in 60–80%, primary aldosteronism in up to 20%

The rank order within secondary hypertension depends heavily on the population sampled, and the sources disagree in ways worth seeing rather than smoothing over. A British young-onset guideline puts primary aldosteronism, renal artery stenosis and renal parenchymal disease together at up to about 10%, with coarctation, phaeochromocytoma, Cushing's and thyroid disease each at 1% or below. A 2024 young-adult study, counting only within confirmed secondary cases, gives primary aldosteronism 54.8%, renovascular disease 18.4%, primary kidney disease 12.9%, drug-induced 6.0% and phaeochromocytoma or paraganglioma 5.9%. A general review ranks renovascular disease, renal parenchymal disease, primary aldosteronism and sleep apnoea as the leading four overall, with atherosclerotic renal artery stenosis, renal failure and hypothyroidism predominating in the elderly.[2,3]

E.2 The master table

The table that follows is the chapter map of this volume. It is arranged so that the causes accounting for most of the yield come first. The mechanism column answers the question this book is built on — what is physically wrong that raises the pressure — and the test column names the single first investigation, not the full work-up.

TABLE E.2 — ESSENTIAL HYPERTENSION: THE MECHANISMS BEHIND THE DIAGNOSIS OF EXCLUSION

MECHANISM	WHAT RAISES THE PRESSURE	CLINICAL SIGNATURE	CHAPTER
Sympathetic overactivity	Raised central sympathetic outflow: cardiac output up, renin released, renal sodium retention, vasoconstriction	Younger, lean or not, resting tachycardia, high pressure variability, morning-dominant pattern	4, 14
Volume and salt sensitivity	Rightward-shifted pressure–natriuresis: a higher pressure is needed to excrete the same sodium load	Salt-sensitive, non-dipping, responds to diuretic and to sodium restriction	5, 12, 22
RAAS dysregulation	Inappropriate renin or aldosterone for the volume state, including low-renin hypertension	Response to RAAS blockade out of proportion; the low-renin patient who responds to a diuretic	3, 13
Arterial stiffening	Loss of Windkessel function: systolic pressure rises, diastolic falls, pulse pressure widens	Isolated systolic hypertension, wide pulse pressure, raised pulse wave velocity	1, 15, 17
Endothelial dysfunction	Reduced nitric oxide availability, raised endothelin, oxidative stress	Often silent; inferred rather than measured	6

TABLE E.3 — SECONDARY HYPERTENSION: MECHANISM, CLUE AND FIRST TEST

CAUSE	WHAT IS PHYSICALLY WRONG	WHAT MAKES YOU SUSPECT IT	FIRST TEST	CH
Renal parenchymal disease	Nephron loss shifts pressure–natriuresis rightward; renal afferent sympathetic drive; RAAS activation despite volume expansion; ADMA accumulation; glomerular hyperfiltration	Nocturia, oedema, anaemia, family history; non-dipping; resistant to any regimen that ignores sodium	Urinalysis, urine albumin–creatinine ratio, creatinine, renal ultrasound	31
Obstructive sleep apnoea	Intermittent hypoxia sensitises the carotid body; sustained sympathetic outflow persists into the day; intrathoracic pressure swings; aldosterone and fluid shift	Snoring, witnessed apnoea, daytime sleepiness, obesity, resistant hypertension, non-dipping	STOP-BANG, then sleep study	24
Primary aldosteronism	Autonomous aldosterone drives mineralocorticoid receptor activation, ENaC-mediated sodium retention, and direct vascular and cardiac injury independent of pressure	Resistant hypertension; hypokalaemia when present, but only a minority are hypokalaemic; target-organ damage out of proportion[4]	Aldosterone-to-renin ratio	13, 33
Renovascular disease	Reduced renal perfusion pressure triggers renin release; later, sodium retention and volume expansion sustain it	Onset before 30 or after 55; abrupt or accelerating; flash pulmonary oedema; asymmetric kidneys; creatinine rise on a RAAS blocker	Duplex ultrasound, then CT or MR angiography	32
Drug-induced	Depends on the agent: prostaglandin inhibition and sodium retention, mineralocorticoid effect, sympathomimetic drive, VEGF pathway inhibition	A pressure that rose when something was started — including things the patient does not consider medicines	A full drug and supplement history	27–30, App B
Occupational exposure	Lead: chronic tubulointerstitial nephropathy with a weak direct pressure effect. Cadmium: proximal tubular injury. Carbon disulphide: accelerated atherosclerosis	Suspect it from the job, not the presentation — battery manufacture and recycling, smelting, informal recycling, viscose rayon. Young, male, resistant, with an unexplained creatinine	An occupational history first, then blood lead or urinary cadmium as the exposure indicates	25

CAUSE	WHAT IS PHYSICALLY WRONG	WHAT MAKES YOU SUSPECT IT	FIRST TEST	CH
Phaeochromocytoma	Catecholamine secretion; noradrenaline-predominant tumours give sustained hypertension, adrenaline-predominant give paroxysms; volume contraction explains the coexisting orthostatic drop	Paroxysms of headache, palpitations and sweating; labile pressure; misdiagnosed as panic disorder	Plasma free or 24-hour urinary fractionated metanephrines	34
Thyroid disease	Hyperthyroidism: high output, low resistance, wide pulse pressure. Hypothyroidism: raised systemic vascular resistance and arterial stiffness	Systolic hypertension with atrial fibrillation, or diastolic hypertension with bradycardia and fatigue	TSH	26, 36
Cushing's syndrome	Cortisol saturates 11-beta-HSD2 and reaches the mineralocorticoid receptor — but the mechanism is multifactorial, also involving vascular reactivity, RAAS and insulin resistance	Easy bruising, proximal myopathy, violaceous striae, facial plethora — not obesity and diabetes alone	Overnight 1 mg dexamethasone suppression, late-night salivary cortisol, or 24-hour urinary free cortisol	35
Coarctation of the aorta	Mechanical obstruction, plus reduced renal perfusion with RAAS activation, and abnormal arch compliance affecting baroreceptor function	Radio-femoral delay; upper-limb pressure exceeding lower limb by more than 20 mmHg; interscapular bruit[5]	Four-limb blood pressure, then echocardiography	37
Takayasu arteritis	Granulomatous panarteritis narrowing the aorta and its branch origins, including the renal ostia	Absent or asymmetric pulses; inter-arm difference; bruits; young woman; a pressure that cannot be measured consistently	Both-arm and four-limb pressure, then CT angiography	32
Primary hyperparathyroidism	Association established; mechanisms proposed but not settled	Hypercalcaemia found incidentally	Serum calcium with PTH	36
Acromegaly	Growth hormone and IGF-1 drive ENaC-mediated sodium retention and plasma volume expansion; cardiomyopathy and sleep apnoea contribute	Acral and facial change, often present for years before diagnosis	IGF-1	36
Monogenic syndromes	Single-gene defects in renal sodium handling — Liddle, apparent mineralocorticoid excess, Gordon syndrome, glucocorticoid-remediable aldosteronism	Young onset, strong family history, suppressed renin, characteristic potassium abnormality	Renin and aldosterone, then genetic testing	11, App D

KEY POINTS

1. **Essential hypertension is not hypertension without a cause** — it is hypertension whose causes are distributed across interacting systems rather than concentrated in one correctable lesion.
2. **Roughly 5 to 10% of unselected hypertensive adults have a secondary cause**, and current European guidance considers that an underestimate.[1]
3. **Age transforms the probability**: 29.6% in confirmed hypertensives aged 18–40 and 40.3% in a cohort aged 16–30 — both referred series; an unselected young cohort gives about 2% (Ch 16) — and in prepubertal children 3.7% at screening against 20.1% in referral clinics, with the older 70–85% belonging to tertiary series only.
4. **Renal disease dominates the young secondary cases** — about four-fifths of them in the Finnish cohort.[6]
5. **The rank order depends on the population sampled**, and published rankings disagree. Read any single ranking as a statement about its denominator.
6. **Four causes account for most of the yield** in adults: renal parenchymal disease, sleep apnoea, primary aldosteronism and renovascular disease. Coarctation, phaeochromocytoma, Cushing's and thyroid disease each sit at or below 1%.
7. **Every row in Table E.3 has a first test that is cheap**. The barrier to finding secondary hypertension is not cost; it is remembering to look.

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