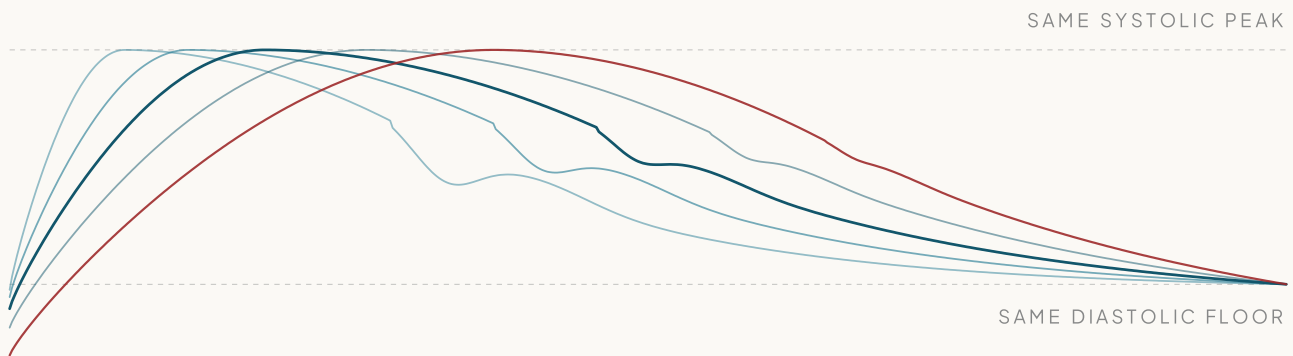

Hypertension

A Phenotype-Based Approach



VOLUME TWO

Choosing and Combining the Drugs

Dr Ravikiran Jadhav

MBBS · AFIH · OCCUPATIONAL HEALTH PHYSICIAN

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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.

VOL	TITLE	FOCUS	EXTENT
V1	Understanding Hypertension	Foundations · aetiology · special populations · contributing factors · drug-induced hypertension	Ch 1–37 + assessment + 2 supplementary + 5 appendices
V2	Choosing and Combining the Drugs	Eleven classes · which class, which molecule, which combination · grading trials · deviating from a guideline	3 opening + Ch 1–15 + 6 appendices
V3	Clinical Practice	Examination · investigations · treatment · OPD practice · crises · cases	Ch 1–36 + 30 cases + 6 appendices

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

V1 · Assess **Assessing the Patient: Reading the Phenotype**

- Measuring the pressure before interpreting it; the history and examination organised by what each finding means
- Hypertension-mediated organ damage as evidence of mechanism, not only prognosis; risk scores and why European calibration misleads in India

PART I — FOUNDATIONS OF BLOOD PRESSURE

V1 · Ch1 **Blood Pressure Physics and Haemodynamics**

- $MAP = CO \times SVR$ — the fundamental haemodynamic equation
- Mean arterial pressure: calculation and clinical significance
- Cardiac output: heart rate, stroke volume, preload, contractility, afterload
- Systemic vascular resistance: Poiseuille's Law and the fourth-power rule
- Systolic, diastolic, pulse pressure, MAP — what each number tells you
- Laplace's Law: why arterioles rupture before large vessels
- Arterial compliance, pulse wave velocity, and wave reflection
- The autoregulatory curve and its rightward shift in chronic hypertension

V1 · Ch2 **Baroreceptors, Chemoreceptors, and Central Regulation**

- Baroreceptor reflex arc: sensors, afferent, NTS integration, efferent limb
- Carotid sinus and aortic arch baroreceptors: anatomy and firing characteristics
- Orthostatic response: how BP is maintained on standing
- Baroreceptor resetting in chronic hypertension: the self-perpetuating set point
- Nucleus tractus solitarius: central cardiovascular integration hub
- Rostral ventrolateral medulla: the sympathetic vasomotor centre
- Peripheral chemoreceptors: hypoxia, hypercapnia, and BP; the OSA link
- Orthostatic hypotension in clinical practice: causes and management

V1 · Ch3 **The Renin–Angiotensin–Aldosterone System (RAAS)**

- Complete cascade: angiotensinogen → renin → Ang I → ACE → Ang II → aldosterone
- Juxtaglomerular apparatus: anatomy and the three stimuli for renin secretion
- Angiotensin II beyond vasoconstriction: fibrosis, LVH, renal damage, ROS
- AT_1 receptor signalling: Gq/G11, MAPK, NF- κ B pathways
- AT_2 receptor: counter-regulatory vasodilation and anti-proliferation
- Aldosterone: genomic Na^+ retention, K^+ loss, and non-genomic vascular fibrosis
- Counter-regulatory arm: ACE2 — angiotensin(1–7) — Mas receptor axis
- Local tissue RAAS: cardiac, renal, brain, and vascular systems
- Key trials: HOPE, LIFE, ONTARGET

V1 • Ch4	The Sympathetic Nervous System in BP Regulation – Three pathways: cardiac stimulation, arteriolar constriction, renal Na⁺ retention – Adrenergic receptor subtypes: alpha-1, alpha-2, beta-1, beta-2, beta-3, dopamine D1 – Renal sympathetic nerves: afferent signalling and efferent Na⁺/renin effects – Afferent renal nerve–CNS axis: how CKD perpetuates central sympathetic tone – MSNA studies and noradrenaline spillover: direct human evidence – SNS overactivation in obesity, OSA, CKD, and heart failure – Renal denervation: rationale, SYMPLICITY, SPYRAL trial results
V1 • Ch5	Renal Pressure–Natriuresis: Guyton's Infinite Gain Theory – Guyton's infinite gain: the kidney as the ultimate BP arbiter – Pressure–natriuresis curve: normal against hypertensive kidney; the rightward shift – RAAS mechanism, renal sympathetic mechanism, and reduced nephron number – Brenner hypothesis: autopsy, donor, preterm, and low birth weight evidence – Renal immune infiltration: Th17, macrophages, Tregs — the salt-immune pathway – Why diuretics always work regardless of hypertension subtype
V1 • Ch6	The Endothelium: Nitric Oxide, Prostacyclin, and Endothelin-1 – eNOS pathway: stimulus, synthesis, NO action on VSMC via cGMP – Non-vasodilatory functions of NO: anti-platelet, anti-adhesion, anti-proliferative – How hypertension destroys NO: NADPH oxidase, ROS, eNOS uncoupling, ADMA – Prostacyclin against thromboxane A₂: the vascular balance – NSAIDs and BP: PGE₂, PGI₂, COX-1 against COX-2 — the mechanism of NSAID hypertension – Endothelin-1: synthesis, ET-A against ET-B receptors, clinical significance – Flow-mediated dilation: measurement, prognostic value, reversibility
V1 • Ch7	Circadian Rhythm of Blood Pressure – Normal 24-hour BP pattern: pre-dawn nadir, morning surge, nocturnal dip – Dipping classification: normal, non-dipper, extreme dipper, reverse dipper – Morning BP surge: six converging mechanisms; why cardiac events cluster at dawn – Non-dipping causes: diabetic autonomic neuropathy, OSA, CKD, aldosteronism, obesity – ABPM: white coat, masked, nocturnal hypertension — what clinic BP cannot reveal – Chronopharmacology: the HYGIA trial, the TIME trial, bedtime dosing evidence
V1 • Ch8	Classification and Definitions of Hypertension – JNC 8 (2014), ACC/AHA 2017, ESC/ESH 2023: thresholds compared – SPRINT controversy: attended against unattended BP and the 130/80 debate – White coat and masked hypertension: definitions, risks, management – Isolated systolic, isolated diastolic, and combined hypertension – Hypertensive urgency, emergency, accelerated, and malignant — key distinctions – Primary against secondary hypertension: prevalence and diagnostic clues
V1 • Ch9	Epidemiology: Global and India – Global prevalence: 1.28 billion adults, WHO 2021; deaths and DALYs (GBD 2019) – India: NFHS-5 and ICMR-INDIAB — 200–220 million adults with hypertension – India's cascade: only about 15 per 100 hypertensives adequately controlled – Urban against rural, north against south India: regional patterns and drivers – Rising young adult hypertension in India: obesity, processed food, stress, sleep deprivation – India Hypertension Control Initiative (IHCI)

V1 • Ch10

The Mosaic Theory of Essential Hypertension

- Page's Mosaic Theory (1949) and its modern eight-mechanism validation
- Haemodynamic transition: high-CO young hypertension → high-SVR established hypertension
- Vascular remodelling: inward eutrophic, hypertrophic, rarefaction, atherosclerosis
- Epigenetics: DNA methylation, histone modification, microRNAs
- Fetal programming and the Barker hypothesis: the 1,000-day window
- Why monotherapy has a ceiling and combination therapy is mechanistically superior

PART II — AETIOLOGY OF ESSENTIAL HYPERTENSION

V1 • Ch11

Genetics of Hypertension

- Heritability of BP: 30–50% from twin and family studies
- Monogenic syndromes: Liddle, Gordon, GRA, AME, CAH, pheochromocytoma-PGL
- Polygenic GWAS findings: ACE I/D, AGT M235T, AT1R A1166C polymorphisms
- Pharmacogenomics: why the same drug has different effects in different patients

V1 • Ch12

Salt Sensitivity: The Renal-Genetic Axis

- Definition, prevalence, mechanisms: renal, immune, endocrine, genetic
- Salt sensitivity, race, and age: clinical and drug-selection implications

V1 • Ch13

RAAS Dysregulation in Essential Hypertension

- High-renin against low-renin phenotypes: clinical patterns and drug choice
- ARR in primary aldosteronism: prevalence 5–10% of resistant hypertension
- Laragh's renin-profiling approach to drug selection

V1 • Ch14

Sympathetic Overactivation in Essential Hypertension

- Neurogenic hypertension evidence: MSNA, noradrenaline spillover, HRV, baroreflex sensitivity
- Psychological factors and central sensitisation of the RVLM set point
- SNS and metabolic syndrome: the common sympathetic thread

V1 • Ch15

Vascular Biology of Essential Hypertension

- Functional vasoconstriction → structural vascular remodelling: the two phases
- Media-to-lumen ratio shift, collagen and elastin deposition, microvascular rarefaction
- Aortic stiffness and pulse wave velocity as biomarkers

PART III — HYPERTENSION IN SPECIAL POPULATIONS

V1 • Ch16

Hypertension in Young Adults (Age under 40)

- Epidemiology, secondary causes to exclude, dominant mechanisms
- Drug selection: beta-blockers, ACEi/ARBs; fertility and pregnancy planning

V1 • Ch16A

Hypertension in Children and Adolescents

- Why the reference is a percentile for age, sex and height — and what changes at thirteen
- About half is secondary, and the yield falls with age; the femoral pulses; when to refer
- Indian adolescent prevalence, and why the study estimates range from 2% to 20.5%

V1 • Ch17

Hypertension in the Elderly

- ISH mechanisms; systolic targets; J-curve and frailty considerations
- HYVET trial; orthostatic hypotension; fall risk; pseudohypertension

V1 • Ch18

Hypertension in Pregnancy

- Classification: chronic hypertension, gestational hypertension, pre-eclampsia, eclampsia, HELLP
- Safe drugs: methyl dopa, labetalol, nifedipine MR; contraindicated: ACEi, ARBs
- Pre-eclampsia: aspirin and calcium prevention; MgSO₄ protocol; delivery timing
- Postpartum: breastfeeding-safe drugs; long-term cardiovascular risk marker

V1 · Ch19 Hypertension in Chronic Kidney Disease

- Bidirectional hypertension–CKD relationship; BP targets: KDIGO 2021, ESC 2023
- RAAS blockade, expected GFR dip; dialysis and transplant hypertension

V1 · Ch20 Hypertension in Diabetes Mellitus

- Prevalence 70–80% of type 2 diabetes; targets; ACEi/ARBs mandatory with albuminuria
- SGLT2 inhibitors, GLP-1 agonists, indapamide against HCTZ; beta-blockers in diabetes

V1 · Ch21 Hypertension in Obesity

- Mechanisms: adipose RAAS, leptin, insulin resistance, OSA, renal compression
- Weight loss and BP; SGLT2 inhibitors; bariatric surgery outcomes

PART IV — CONTRIBUTING FACTORS TO HYPERTENSION**V1 · Ch22 Dietary Sodium and the Salt–Hypertension Link**

- Evidence: Intersalt, DASH–Sodium, PURE; the Na⁺–Th17 immune pathway
- Hidden salt in the Indian diet; DASH diet; potassium as the counter; salt substitutes

V1 · Ch23 Alcohol, Smoking, and Caffeine

- Alcohol dose–response; mechanisms; withdrawal hypertension; counselling scripts
- Smoking: endothelial damage against transient pressor effect; energy drinks in young adults

V1 · Ch24 Obstructive Sleep Apnoea and Hypertension

- OSA in 30–40% of resistant hypertension; intermittent hypoxia → carotid body → SNS
- STOP–BANG screening; CPAP and BP reduction; aldosterone antagonists if CPAP refused

V1 · Ch25 Psychological Stress and Occupational Hypertension

- Chronic stress: HPA dysregulation, RVL set point elevation
- Job strain model; effort–reward imbalance; India IT sector and shift worker data
- Mindfulness, yoga and BP; the AFIH physician's role in workplace BP management

V1 · Ch26 Endocrine Causes of Hypertension

- Primary hyperaldosteronism: subtypes, ARR, adrenal CT, AVS, treatment
- Pheochromocytoma: biochemical diagnosis, imaging, alpha-first pre-operative management
- Cushing's syndrome, thyroid disorders, hyperparathyroidism, acromegaly
- Renovascular hypertension: atherosclerotic against fibromuscular dysplasia; ASTRAL and CORAL trial context

PART V — DRUG-INDUCED HYPERTENSION**V1 · Ch27 NSAIDs, COX–2 Inhibitors, and Analgesics**

- Mechanism: renal PGE₂ and systemic PGI₂ inhibition; COX-2 selectivity worsens BP
- Triple whammy: ACEi + diuretic + NSAID = acute kidney injury; paracetamol re-examined

V1 · Ch28 Hormonal Agents

- Oral contraceptives: oestrogen → angiotensinogen ↑ → RAAS; risk factors; progestogen-only as alternative
- HRT oral against transdermal; anabolic steroids; corticosteroids: managing steroid hypertension

V1 · Ch29 Immunosuppressants and Oncology Drugs

- Cyclosporine and tacrolimus: hypertension in 70–100% of transplant recipients; CCB preferred
- VEGF inhibitors: rapid severe hypertension; erythropoiesis-stimulating agents: viscosity and vasoconstriction

V1 · Ch30 Sympathomimetics, Stimulants, Recreational Drugs, and Herbal Agents

- Decongestants, cocaine (a beta-blocker is not the first drug), amphetamines, MDMA
- Herbal agents in India: liquorice (mulethi) — 11β-HSD2 inhibition → severe hypertension
- Ginseng, guarana, bitter orange, yohimbe, St John's Wort; energy drinks

PART VI — SECONDARY HYPERTENSION**V1 • Ch31 Renal Parenchymal Disease and Polycystic Kidney Disease**

- Five mechanisms: sodium retention, renal afferent sympathetic drive, RAAS activation despite volume expansion, ADMA, glomerular hyperfiltration
- Cause or consequence; the Pei ultrasound criteria; KDIGO targets and the expected creatinine rise

V1 • Ch32 Renovascular Hypertension

- The Goldblatt models, the three phases, and the ACE-inhibitor creatinine rise as a diagnostic clue
- Atherosclerotic disease, fibromuscular dysplasia and Takayasu arteritis — one angiogram, three treatments

V1 • Ch33 Primary Aldosteronism

- Mineralocorticoid receptor activation, aldosterone escape, and injury independent of the pressure
- The aldosterone–renin ratio and its three technical traps; CT against adrenal vein sampling, and the 22–28% discordance

V1 • Ch34 Pheochromocytoma and Paraganglioma

- Noradrenaline gives sustained hypertension, adrenaline gives paroxysms; hypertension with orthostasis explained
- Metanephrines rather than catecholamines; the false-positive list; alpha blockade before beta

V1 • Ch35 Cushing's Syndrome and Glucocorticoid Excess

- 11- β -HSD2 saturation — and why the mechanism is multifactorial, not purely mineralocorticoid
- Prescribed steroids: the dose threshold, relative mineralocorticoid potency, and which signs discriminate

V1 • Ch36 Thyroid, Parathyroid and Acromegaly

- Systolic hypertension in thyrotoxicosis, diastolic in hypothyroidism; what replacement achieves in mmHg
- Hyperparathyroidism and the honest answer on parathyroidectomy; acromegaly and ENaC-mediated sodium retention

V1 • Ch37 Coarctation of the Aorta, and the Search for a Cause

- Why the pressure stays up after repair in 47% of patients; the four-limb examination
- How common secondary hypertension really is by age, and the screening argument on both sides

SUPPLEMENTARY CHAPTERS — VOLUME 1**V1 • S1 Elevated Blood Pressure**

- The 120–129/<80 band: what it is, what it predicts, and what reverses it
- Lifestyle effect sizes, and what to actually tell the patient

V1 • S2 Understanding Clinical Trials and Research Papers

- Reading a trial: design, endpoints, effect size, and what a result does and does not establish
- The landmark hypertension trials, one by one, and what each one changed

APPENDICES — VOLUME 1

V1 • App A	Secondary Hypertension Screening Algorithm
V1 • App B	Drug-Induced Hypertension Master Table – All agents, mechanism, BP rise, management
V1 • App C	Normal BP Reference Values by Age and Sex – Indian population, NFHS-5
V1 • App D	Monogenic Hypertension Syndromes: Complete Reference Table
V1 • App E	Causes of Hypertension: Master Table – Every cause in one place — mechanism, clinical clue, first test, chapter

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

OPENING — HOW THE DECISIONS ARE MADE

- V2·0p 1 Where the Drug Acts**
 – The eight sites, the two walks, and what a specialist, a superspecialist and a first-contact physician each think before the first drug
-
- V2·0p 2 What the Trials Decided**
 – Grading a trial on two axes — the margin of victory (A to E) and the conduct (sound, qualified, weak) — and the five biases, drawn where each enters a trial
-
- V2·0p 3 How the Guideline Was Made**
 – Class and level of evidence, how a committee turns a trial into a recommendation, and where it deliberately leaves you the choice
-

PART I — THE CASCADE

- V2·Ch 1 ACE Inhibitors**
 – One enzyme, two substrates · the cough as a class effect · molecule choice · the potassium and creatinine visit that gets missed
-
- V2·Ch 2 Angiotensin Receptor Blockers**
 – What the class does and does not buy over an ACE inhibitor · why never both
-
- V2·Ch 3 Direct Renin Inhibitors**
 – A chapter kept for the reasoning, not the prescription: upstream is not better
-

PART II — THE CHANNEL

- V2·Ch 4 Calcium Channel Blockers**
 – One channel, two tissues · dihydropyridine against verapamil and diltiazem · ankle oedema is a pressure gradient, not fluid
-

PART III — THE NEPHRON

- V2·Ch 5 Thiazide and Thiazide-like Diuretics**
 – The four diuretic sites and the sodium each handles · why a thiazide fails as filtration falls
-
- V2·Ch 6 Loop Diuretics**
 – Congestion, not pressure · the class with no outcome trial in hypertension
-
- V2·Ch 7 Aldosterone — the Receptor, the Channel, and the Enzyme**
 – The fourth drug in resistant hypertension · spironolactone, eplerenone, finerenone, amiloride
-

PART IV — THE SYMPATHETIC LIMB

- V2·Ch 8 Beta-Blockers**
 – One limb, four interruptions · the target map: every adverse effect derived from where the receptor sits
-

V2·Ch 9 **Alpha-1 Adrenoceptor Blockers**
– A demoted class, and the man in whom it treats two problems at once

V2·Ch 10 **Central Sympatholytics**
– Methyldopa in pregnancy · clonidine, and why it is never stopped abruptly

V2·Ch 11 **Direct Vasodilators and the Intravenous Agents**
– Never given alone · the intravenous agents by situation

PART V — CHOOSING BETWEEN THEM

V2·Ch 12 **Head to Head**
– The nine direct class comparisons · the four situations where the choice changes outcomes, and what decides when it does not

V2·Ch 13 **The Patient Who Has Something Else**
– The four ways a second diagnosis changes the answer · what to do when two comorbidities disagree

V2·Ch 14 **When in the Day**
– What three trials settled about bedtime dosing · the six reasons an hour is ever chosen

V2·Ch 15 **Reading a Prescription Backwards**
– Decoding what a prescription tells you about the patient — built forwards from the guidelines, then inverted

APPENDICES — VOLUME 2

V2·App A **Oral dosing, by class**

V2·App B **Intravenous agents**

V2·App C **Thresholds, monitoring and pregnancy**

V2·App D **Trial atlas — twenty-four trials with both grades**

V2·App E **Appraisal checklist and deviation worksheet**

V2·App F **References**

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

V3 · Ch1 Taking the History: The Decision–Altering Questions

Only the questions whose answer sends you down a different path.

- Duration and severity — and what “since when” is actually worth
- The branch points: paroxysms, snoring, cramps, flushing, weight change
- Every drug that raises pressure — prescribed, bought, and taken quietly
- Occupation, shift and exposure — the history a physician rarely takes
- What the patient has already been told, and by whom

V3 · Ch2 Measuring the Pressure: Getting It Right

The commonest error in hypertension is not a wrong drug. It is a wrong number, treated confidently.

- Cuff, device and position — the errors ranked by how often they occur
- Both arms, and what a difference above 10 mmHg obliges
- Home monitoring: the seven-day protocol and how to read it
- Ambulatory monitoring: indications, thresholds, dipping pattern

V3 · Ch3 The Examination: Every Finding and What It Changes

Each finding paired with the decision it forces, not with its name.

- Pulse, four-limb pressures, the asymmetry algorithm
- Precordium: heaving apex, displaced apex, the fourth sound
- Bruits, oedema, and distinguishing volume from calcium-blocker swelling
- The ankle–brachial index, and why above 1.4 is not reassurance

V3 · Ch4 The Negative Examination: What an Absent Finding Rules Out NEW

Every text tells you what a finding means. Almost none tell you what its absence excludes, and with what confidence — yet that is the judgement made on every normal examination.

- Likelihood ratios for absent findings, stated rather than implied
- No radio–femoral delay: how far that lowers coarctation, and how far it does not
- No bruit does not exclude renovascular disease — the number behind that sentence
- A normal fundus in a pressure of 210: what it does and does not permit
- The findings whose absence is genuinely reassuring, and the ones that are not
- How to write “normal examination” so it means something

V3 · Ch5 Fundoscopy: The Only Place You See the Arterioles

A skill most physicians lose within five years of qualifying, in the one organ where these vessels can be seen directly.

- Getting a view: the technique, and the phone–camera alternative
- Keith–Wagener–Barker grades 1 to 4 and the decision at each
- Grade 3: admit. Grade 4: this is malignant hypertension
- Hypertensive against diabetic retinopathy in the same fundus

V3 · Ch6 First–Line Investigations: What Every New Hypertensive Needs

A defined baseline with a stated reason for each test — and an explicit list of what not to order.

- The baseline panel, and what each item is for
- Cost-tiered ordering for the Indian OPD
- The tests not to order, and the harm of ordering them

V3 • Ch7

Second and Third Line: What Each Result Triggers

A decision table. Every first-line abnormality has one next step.

- Low potassium → the aldosterone–renin ratio, read against the drugs distorting it
- Voltage criteria → echocardiogram; asymmetric kidneys → imaging
- Adrenal vein sampling, MIBG, genetic panels: who actually needs them
- When to stop investigating

PART TWO — READING WHAT COMES BACK 4 chapters

V3 • Ch8

The ECG in Hypertension

Read for what changes management, not for completeness.

- Sokolow–Lyon and Cornell: the calculation done on the page
- Strain, and why it is not the same as voltage
- Atrial fibrillation found incidentally: the immediate obligations

V3 • Ch9

The Echocardiogram Report, Line by Line

The report your patient brings back, read in the order it is printed.

- Mass index and relative wall thickness: the four geometries
- E/A, E/e', LAVI — diastolic function without the jargon
- When the echo changes the target rather than the tablet

V3 • Ch10

Urine, ACR and the Renal Ultrasound Report

The kidney is both cause and casualty. These reports tell you which.

- Dipstick, ACR and microscopy: a decision for each finding
- Size, echogenicity, asymmetry, resistive index
- Hypertensive nephrosclerosis against a primary renal disease

V3 • Ch11

When the Reports Disagree with the Patient

Normal tests in a patient who is clearly unwell, and abnormal ones in a patient who is not.

- The incidental adrenal nodule
- The borderline aldosterone–renin ratio
- Repeating a test, and when repeating it is the wrong move

PART THREE — STARTING AND RUNNING TREATMENT 6 chapters

V3 • Ch12

When to Start

The threshold argument, resolved for a working OPD rather than for a committee.

- 140/90 against 130/80: what actually turns on the difference
- Risk-stratified starting, and why European calibration misleads in India
- The lifestyle trial: how long, what counts, what failure looks like

V3 • Ch13

Targets, and the J–Curve Honestly

What the evidence supports, what it does not, and where the honest answer is that nobody knows.

- The diastolic floor: what CLARIFY and ONTARGET actually showed
- Targets by condition, in one table
- Unattended against attended measurement, and why SPRINT is not 120

V3 • Ch14

Time to Benefit: How Long Must This Patient Live? NEW

The question that decides how hard to treat an eighty-year-old, and which no hypertension text asks out loud. A drug that pays off in two and a half years is a different proposition in a patient with eighteen months.

- Time-to-benefit as a number, not a feeling
- The frail patient: when starting a drug is the wrong act of care
- Deprescribing on the same logic that started the drug
- What to say to a family who want everything done

V3 • Ch15	Starting: One Drug or Two The first prescription, and the case for not making it a single drug. – Two from day one above stage 2, and the evidence for it – Compelling indications: condition → obligatory class – Fixed-dose combinations: the adherence case and the dosing cost
V3 • Ch16	Escalation, Titration and Follow-Up What most books leave out: what happens between visit one and control. – Add a class before doubling a dose — and the size of that difference – The follow-up interval, and why four weeks is usually wrong – Recognising that you have reached the ceiling – When to refer, stated as a rule rather than a feeling
V3 • Ch17	Distributing the Dose The decision guidelines do not describe and specialists make without discussing: the same two molecules, split three different ways. – Telmisartan 40 + amlodipine 5, against 20 + 10, against 80 alone – Where on its dose–response curve each drug actually sits – The dose at which a drug stops buying pressure and starts buying side effects – What decides the split: the phenotype, the comorbidity, the tolerability
V3 • Ch18	Writing the Prescription a Cardiologist Would Write Volume 2 taught you to read a specialist's prescription backwards. This is the other direction. – Every line of a specialist prescription, and why it is there – The reasoning that is never written down – Writing at that level without the specialist in the room
V3 • Ch19	Resistant Hypertension in the OPD The clinic-side approach; the drug reasoning is settled in Volume 2. – Pseudo-resistance first: measurement, adherence, dose, interaction – The secondary-cause sweep, in order of yield – Sleep apnoea before the fourth drug
PART FOUR — THE PATIENT WHO HAS SOMETHING ELSE 4 chapters	
V3 • Ch20	Diabetes and Chronic Kidney Disease Taken together because in practice they arrive together. – Targets, and the albuminuria that changes them – Living with the creatinine rise after blockade – SGLT2 inhibitors and finerenone in the clinic – Potassium: the monitoring that actually prevents harm
V3 • Ch21	Heart Failure, Post-Infarct and Atrial Fibrillation Where the blood pressure is no longer the thing being treated. – HFrEF: the four pillars, and where pressure limits them – HFpEF: the honest position – After infarction: what is obligatory, and for how long – Pressure before anticoagulation
V3 • Ch22	Stroke and Transient Ischaemic Attack The one setting where lowering pressure quickly does the harm. – Permissive hypertension, and its limits – Thrombolysis and the ceiling it imposes – Secondary prevention: what PROGRESS did and did not show – When to start after the event

V3 • Ch23

Pregnancy, Delivery and the Years After

Including the part usually omitted: what the pregnancy predicted.

- Safe, unsafe, and what to stop before conception
- Treating mild chronic hypertension: what CHAP settled
- Pre-eclampsia and eclampsia: the protocol
- A hypertensive pregnancy as a lifelong marker

PART FIVE — CRISES 4 chapters · every protocol opens with its failure mode

V3 • Ch24

Urgency: What To Do, and What Never To Do

The commonest hypertensive presentation, mismanaged in both directions.

- **How this goes wrong:** sublingual nifedipine, and the stroke it causes
- Urgency against emergency: the distinction is organ damage, not the number
- Oral options, the pace, and discharge with a written plan

V3 • Ch25

Emergency: Principles and the Reduction Rule

Why the ceiling on how fast you may lower a pressure is a statement about the brain.

- **How this goes wrong:** normalising the pressure in the first hour
- No more than 25% in the first hour — where the rule comes from
- The autoregulatory curve as the reason (V1 • Ch1)
- The exceptions: dissection, ischaemic stroke, pre-eclampsia

V3 • Ch26

Emergency: Organ-Specific Protocols

One protocol per presentation, written to be followed at three in the morning.

- **How this goes wrong:** beta before alpha in pheochromocytoma
- Encephalopathy; dissection; pulmonary oedema; acute coronary syndrome
- Ischaemic and haemorrhagic stroke; eclampsia; sympathomimetic crisis

V3 • Ch27

The Intravenous Agents

Dose, rate, dilution, monitoring and the failure mode of each.

- **How this goes wrong:** nitroprusside without a ceiling or a monitor
- Labetalol, esmolol, nicardipine, clevidipine, glyceryl trinitrate
- The selection matrix: presentation → agent → dose → what to watch
- What is actually available in an Indian district hospital

PART SIX — THE REAL OPD 9 chapters · the volume's own material

V3 • Ch28

Taking Over a Patient from Another Doctor **NEW**

The commonest consultation in Indian practice, and the one no textbook describes.

- Understand what was done before you change it
- The structured takeover: drugs, trend, tests, effects, and why they left
- Controlled once and escaped since — the five reasons
- Controlled but unhappy: the class-by-class switch
- The well-controlled patient: when to change nothing at all

V3 • Ch29

The Referral, Both Directions **NEW**

A referral is a question with a colleague attached. Sometimes the question is the wrong one, and saying so is part of the job.

- Reading a referral letter for what it does not say
- When the referral question is wrong — answering it and the real one
- Referring well: what the specialist needs and what wastes the visit
- The patient sent back “for ongoing management”: what that actually delegates
- Disagreeing with a consultant, in writing, without a fight

V3 • Ch30

The Non-Adherent Patient

Adherence is not a character trait. It is a set of causes, most of them addressable.

- Why Indian patients stop, in their own words
- The on-off pattern and its dangers: clonidine and beta-blocker rebound
- Measuring adherence without accusing anybody
- Scripts that work in a six-minute consultation

V3 • Ch31

The Neglected Hypertensive

Ten years untreated, arriving with a complication. Not the same as a new diagnosis.

- Do not normalise the pressure on day one, and why
- Two drugs from the start above 160 systolic; start low, go slow
- Managing damage already done
- What to promise and what not to

V3 • Ch32

Seasonal and Situational Variation

The calendar is a clinical variable in India.

- The winter rise and the summer fall: adjusting on purpose
- Festivals, weddings and the salt load nobody records
- Travel, altitude and pilgrimage; heat and night shift

V3 • Ch33

Hypertension at Work: Screening, Fitness and Return

Volume 1 explains the mechanisms; this is the regulatory and fitness practice.

- Fitness criteria by job: drivers, heights, confined space, process plant
- The Indian regulatory framework, stated plainly
- Return to work after an emergency or a stroke
- Writing a fitness certificate you can defend

V3 • Ch34

Cost per Millimetre: What the Patient Can Actually Buy NEW

A prescription that cannot be afforded is not a treatment. Costed per mmHg per month, which nobody publishes and every Indian physician needs.

- What the common regimens cost per month, and per mmHg gained
- Generic substitution: where it is safe and where it is not
- Government supply, Jan Aushadhi and the public programme
- The patient rationing tablets who has not told you

V3 • Ch35

Common Mistakes

Ordered by how often they occur, not by how serious they sound.

- One reading, wrong cuff, white coat, masked
- Treating too hard in the elderly
- Adding a drug before checking adherence
- Asthma, bilateral stenosis, dual blockade
- Grade 4 retinopathy sent home

V3 • Ch36

Sick-Day Rules and the Written Action Plan

What the patient does when you are not there, which is almost always.

- What to hold, what to continue, when to restart
- The missed dose, and the one drug where doubling is dangerous
- Home thresholds: when to call, when to come in
- The plan on one side of paper

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	Snore, 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

VOLUME TWO

Choosing and Combining the Drugs

Where the drug acts · what the trials decided · how the guideline was made · and the eleven classes

3 OPENING CHAPTERS · 16 OF 11 CLASS CHAPTERS WRITTEN · 6 APPENDICES PLANNED · 190 PAGES IN THIS DRAFT

Volume 1 asked why this patient is hypertensive. This volume asks why this drug. The three opening chapters come before the classes because they carry the reasoning the classes depend on: where a drug acts, what the trials decided, and how much room the guideline actually leaves you.

PART ONE — THE BASICS: HOW A DRUG GETS CHOSEN

Opening 1	Where the Drug Acts	1
	<i>Volume 1 asked why this patient is hypertensive. This volume asks why this drug — and the honest answer is that you are not choosing a molecule. You are choosing a place to interrupt, in a patient who has to live with the choice.</i>	
	– 0.1 What you are actually choosing	
	– 0.2 How a consultant actually chooses	
	– 0.3 Before the first drug — what has already been settled	
	– 0.4 Three readers, one patient	
	– 0.5 How the guideline was set, and where it leaves you the choice	
	– 0.6 The map	
	– 0.7 The first walk — down the nephron	
	– 0.8 The second walk — along the cascade	
	– 0.9 Where the two walks meet	
	– 0.10 Which patient, which class	
	– 0.11 Twenty-four hour cover — the question nobody asks	
	– 0.12 One drug, or two?	
	– 0.13 It is not controlled — the specialist's sequence	
	– 0.14 Still not controlled — the superspecialist's question	
	– 0.15 How each chapter is built	
Opening 2	What the Trials Decided	17
	<i>A thiazide is first-line because of what happened to 33,357 people, not because of what happens at the sodium-chloride cotransporter. This chapter puts the evidence where it belongs — in front of the mechanism, not behind it.</i>	
	– T.1 Why this chapter exists	
	– T.2 What a trial can decide, and what it cannot	
	– T.3 Reading a trial before you believe it	
	– T.4 How a trial can be wrong when the number is right	
	– T.5 The trials that set the first line	
	– T.6 The trials that chose the second drug	
	– T.7 The trials that ended a practice	
	– T.8 How decisive was it? — the margin behind each recommendation	
	– T.9 The same pressure, different outcomes	
	– T.10 What you are protecting, not what you are lowering	
	– T.11 Where the trials run out	
	– T.12 Every class, its trial, its verdict	

Opening 3	How the Guideline Was Made	33
	<i>Most doctors know what the guideline says. Far fewer know who wrote it, from what evidence, how strong that evidence was, and where the committee itself expected you to use your judgement. This chapter is about the difference.</i>	
	– G.1 What a guideline is, and what it is not – G.2 Reading a recommendation – G.3 Why respectable guidelines disagree – G.4 Which guidance for an Indian patient – G.5 What a committee does when the trials are silent – G.6 Is there a trial for my patient? – G.7 The skill is not about hypertension – G.8 When you may depart from the guideline	
PART TWO — THE DRUGS, CLASS BY CLASS		
Every chapter here runs the same nine-part shape — why act at this site, where the class ranks, the ledger, when it is wrong, what to do when an adverse effect happens, the molecules compared, combinations, and a rapid reference. That shape is set out once in 0.15 and is not repeated below. What is listed for each chapter is the molecules it covers and the sections that belong to it alone.		
PART I — THE RENIN-ANGIOTENSIN CASCADE		
Chapter 1	ACE Inhibitors	42
	<i>The enzyme does two jobs. You cannot block one without blocking the other — and almost everything about this class, good and bad, follows from that single fact.</i>	
	DRUGS Ramipril · Enalapril · Lisinopril · Perindopril · Captopril · Fosinopril · Trandolapril	
	– 1.1 – 1.4 Why here, and not the nephron – 1.7 What to check, and when – 1.9 The adverse effects, in detail – 1.11 Interactions, and what to do about them – 1.12 Special populations – 1.15 The seven molecules	
Chapter 2	Angiotensin Receptor Blockers	60
	<i>The same cascade, blocked one step later. That single step removes the cough — and takes something else with it.</i>	
	DRUGS Losartan · Valsartan · Telmisartan · Olmesartan · Irbesartan · Candesartan · Azilsartan · Sacubitril/valsartan	
	– 2.1 – 2.4 The enzyme or the receptor — an honest disagreement – 2.8 One step beyond the receptor — sacubitril/valsartan – 2.11 Why not one ARB for every patient – 2.12 Pairing durations — and when once daily is not enough – 2.13 Which ARB when the partner is amlodipine	
Chapter 3	Direct Renin Inhibitors	69
	<i>The most upstream target on the cascade, and the least useful drug in this book. That is not a contradiction — it is the chapter's entire lesson.</i>	
	DRUGS Aliskiren	
	– 3.3 What happened — ALTITUDE – 3.5 The lesson that outlives the drug – 3.6 The molecule	

PART II — THE CALCIUM CHANNEL

- Chapter 4 Calcium Channel Blockers** 73
- One channel, three drugs that behave nothing alike — and the commonest side effect in the chapter is the one most often treated wrongly.*
-
- DRUGS** Amlodipine · Nifedipine · Felodipine · Lercanidipine · Lacidipine · Cilnidipine · Verapamil · Diltiazem
- 4.2 Three drugs, one channel — and an honest caveat
 - 4.8 Interactions, and what to check
 - 4.9 The generations of dihydropyridine
 - 4.10 Cilnidipine — does a second channel earn its place?
-

PART III — THE NEPHRON

- Chapter 5 Thiazide and Thiazide-like Diuretics** 85
- The oldest class in the book, the cheapest, and the one with the most evidence behind it — and two recent trials have quietly overturned two things every clinician was taught about it.*
-
- DRUGS** Chlorthalidone · Hydrochlorothiazide · Indapamide · Metolazone
- 5.3 Thiazide, or thiazide-like?
 - 5.4 The chlorthalidone question — and the trial that answered it
 - 5.5 Below an eGFR of 30 — a rule that has expired
 - 5.14 Evidence annexe
-
- Chapter 6 Loop Diuretics** 99
- The most powerful natriuretic in the book, and the one with the least evidence for treating blood pressure. Both facts matter, and the second is the one usually left out.*
-
- DRUGS** Furosemide · Torsemide · Bumetanide · Ethacrynic acid
- 6.3 Furosemide, torsemide, bumetanide
-
- Chapter 7 Aldosterone — the Receptor, the Channel, and the Enzyme** 105
- One hormone, three places to interrupt it, and the newest of the three was approved while this volume was being written. A book organised by drug class cannot say what is new about it. A book organised by site can.*
-
- DRUGS** Spironolactone · Eplerenone · Finerenone · Amiloride · Triamterene · Baxdrostat
- 7.3 Three sites, one hormone
 - 7.4 Why spironolactone is the fourth drug
 - 7.5 Baxdrostat — the newest site in this book
-

PART IV — THE SYMPATHETIC LIMB

- Chapter 8 Beta-Blockers** 115
- Demoted from first line by two trials in which the drug that lost was the same drug both times — and never retested in the members of the class that behave least like it. The demotion was right. The reasoning behind it reaches further than the evidence does.*
-
- DRUGS** Bisoprolol · Metoprolol succinate · Carvedilol · Nebivolol · Atenolol · Propranolol · Labetalol · Esmolol
- 8.2 The classification that matters at the bedside
 - 8.3 Why atenolol lost, twice
 - 8.6 The asthma question, answered properly
-

PART V — THE SYMPATHETIC LIMB, CONTINUED

- Chapter 9 Alpha-1 Adrenoceptor Blockers** 126
- The only class in this volume whose trial arm was stopped early because the drug was causing harm — and which survives anyway, for a reason that has nothing to do with blood pressure.*
-
- DRUGS** Doxazosin · Prazosin · Terazosin · Tamsulosin · Alfuzosin · Silodosin
- 9.2 What happened to the doxazosin arm
-
- Chapter 10 Central Sympatholytics** 131
- The oldest drugs in this volume, and the ones with the least modern evidence — kept by two situations nothing has replaced them in, and dangerous mainly through the way they are stopped.*
-
- DRUGS** Methyldopa · Clonidine · Moxonidine · Rilmenidine
- 10.2 Where these agents rank, and on what
 - 10.3 Methyldopa — and the two tests it obliges
 - 10.4 Clonidine rebound
-

PART VI — DIRECT VASODILATION, AND THE IV AGENTS

- Chapter 11 Direct Vasodilators and the Intravenous Agents** 136
- Drugs that dilate an arteriole without asking a receptor's permission — which is why none of them is given alone, and why the last table in this volume is a selection matrix rather than a protocol.*
-
- DRUGS** Hydralazine · Minoxidil · Sodium nitroprusside · Nitroglycerin · Nicardipine · Clevidipine · Phentolamine · Enalaprilat · Fenoldopam
- 11.2 Hydralazine
 - 11.3 Minoxidil
 - 11.4 Choosing an intravenous agent
 - 11.5 Where these agents rank, and on what
-

PART VII — COMPARISON

- Chapter 12 Head to Head** 143
- Eleven chapters have argued one class at a time. This one puts the direct comparisons side by side and answers the question underneath all of them: when two classes are both allowed, does the choice actually matter?*
- 12.1 What has actually been compared
 - 12.2 The four situations where the choice changes outcomes
 - 12.3 Where the choice does not matter — and what decides instead
 - 12.4 The comparisons nobody has run
-
- A–E The Patient Who Has Something Else** 149
- Chapter 12 found that class choice rarely changes outcomes on its own. The exception is the common case: most hypertensive patients carry a second diagnosis, and it is usually the second diagnosis that decides the drug.*
- 13.1 Why the second diagnosis usually decides
 - 13.2 The four mechanisms, and there are only four
 - 13.3 When one drug does two jobs
 - 13.4 When the comorbidity forbids
 - 13.5 When the drug stops behaving as expected
 - 13.6 The precaution that actually gets missed
 - 13.7 When two diagnoses disagree
 - 13.8 The conflicts with no clean answer
-

Chapter 14 When in the Day 158

The guideline names the drug, the dose and the target, and says almost nothing about the hour. That silence is a real clinical space — and it is settled by sleep, tolerability and adherence, not by chronotherapy.

- 13.1 The question the guideline does not answer
- 13.2 What the trials decided about bedtime dosing
- 13.3 Why the hour still matters
- 13.4 The six reasons an hour is ever chosen
- 13.5 Protecting sleep — the diuretic rule
- 13.6 When another drug owns the hour
- 13.7 Splitting a dose — reasoning, or habit in costume?
- 13.8 The high morning reading
- 13.9 The scenarios, resolved
- 13.10 What to write on the prescription

Chapter 15 Reading a Prescription Backwards 167

Twelve chapters have gone from the patient to the drug. A general physician in India usually meets the problem in the other direction — a patient arrives holding somebody else's prescription, with no letter and no echo report. This chapter runs the volume in reverse.

- 15.1 The direction a physician actually works in
- 15.2 The method — build it forwards, then invert it
- 15.3 The prior — what is actually common in India
- 15.4 The forward map — condition to regimen
- 15.5 What each modifier changes
- 15.6 The inversion — the codebook
- 15.7 Loud drugs and silent drugs
- 15.8 Within the class — which molecule, and why that one
- 15.9 The narrowing law
- 15.10 Read the non-antihypertensives first
- 15.11 Absence is information
- 15.12 Dose, timing and packaging
- 15.13 A published Indian series, read backwards
- 15.14 What a prescription cannot tell you
- 15.15 The confounders that break the method
- 15.16 When the prescription does not fit
- 15.17 The rule this chapter ends on
- 15.18 The short list that needs no deliberation

APPENDICES — WHAT YOU LOOK UP

Appendices Appendices 184

Everything in this volume that is consulted rather than read. Nothing here argues; the chapters do that. If you want a dose, a threshold, a trial's numbers or a checklist, it is on one of these pages.

- A Oral dosing, by class
- B Intravenous agents
- C Thresholds, monitoring and pregnancy
- D Trial atlas
- E Appraisal checklist and deviation worksheet

FINDING A DRUG

Every molecule discussed in this volume, with its chapter and the page that chapter starts on.

Alfuzosin	9 · 126	Amiloride	7 · 105	Atenolol	8 · 115
Aliskiren	3 · 69	Amlodipine	4 · 73	Azilsartan	2 · 60

Baxdrostat	7 · 105	Fosinopril	1 · 42	Olmesartan	2 · 60
Bisoprolol	8 · 115	Furosemide	6 · 99	Perindopril	1 · 42
Bumetanide	6 · 99	Hydralazine	11 · 136	Phentolamine	11 · 136
Candesartan	2 · 60	Hydrochlorothiazide	5 · 85	Prazosin	9 · 126
Captopril	1 · 42	Indapamide	5 · 85	Propranolol	8 · 115
Carvedilol	8 · 115	Irbesartan	2 · 60	Ramipril	1 · 42
Chlorthalidone	5 · 85	Labetalol	8 · 115	Rilmenidine	10 · 131
Cilnidipine	4 · 73	Lacidipine	4 · 73	Sacubitril/valsartan	2 · 60
Clevidipine	11 · 136	Lercanidipine	4 · 73	Silodosin	9 · 126
Clonidine	10 · 131	Lisinopril	1 · 42	Sodium nitroprusside	11 · 136
Diltiazem	4 · 73	Losartan	2 · 60	Spironolactone	7 · 105
Doxazosin	9 · 126	Methyldopa	10 · 131	Tamsulosin	9 · 126
Enalapril	1 · 42	Metolazone	5 · 85	Telmisartan	2 · 60
Enalaprilat	11 · 136	Metoprolol succinate	8 · 115	Terazosin	9 · 126
Eplerenone	7 · 105	Minoxidil	11 · 136	Torsemide	6 · 99
Esmolol	8 · 115	Moxonidine	10 · 131	Trandolapril	1 · 42
Ethacrynic acid	6 · 99	Nebivolol	8 · 115	Triamterene	7 · 105
Felodipine	4 · 73	Nicardipine	11 · 136	Valsartan	2 · 60
Fenoldopam	11 · 136	Nifedipine	4 · 73	Verapamil	4 · 73
Finerenone	7 · 105	Nitroglycerin	11 · 136		

STILL TO BE WRITTEN — THIS VOLUME

V2 · App

Appendices

- A Indian brands, generic names, strengths and approximate price
- B Fixed-dose combinations available in India
- C Dose adjustment by renal function
- D Pregnancy safety classification
- E Trough-to-peak ratios and duration of action
- F Drug interaction master table

Where the Drug Acts

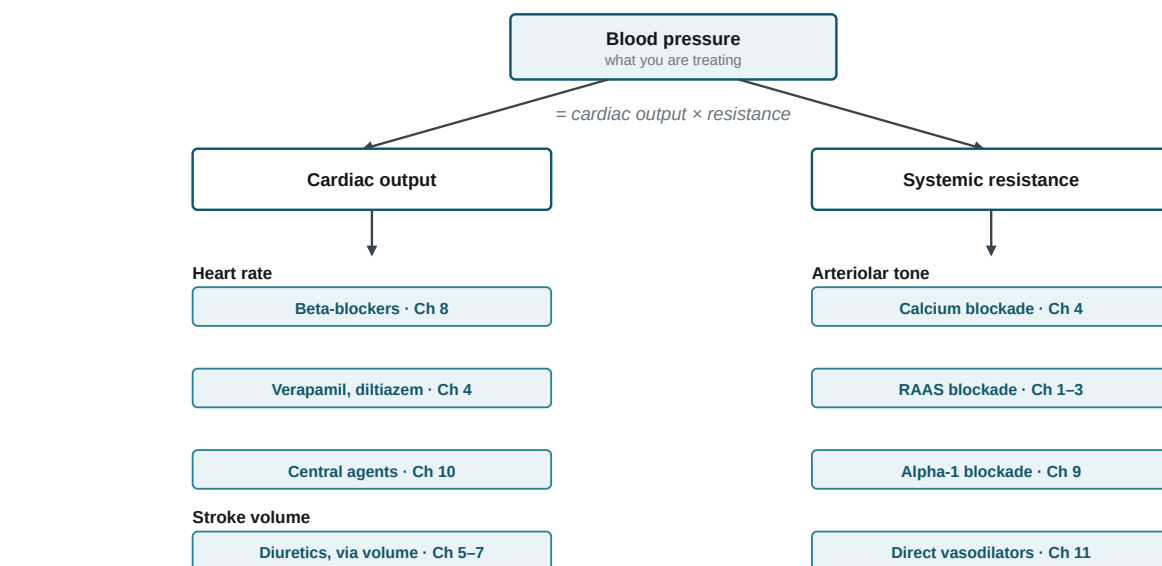
Volume 1 asked why this patient is hypertensive. This volume asks why this drug — and the honest answer is that you are not choosing a molecule. You are choosing a place to interrupt, in a patient who has to live with the choice.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 The four questions settled before the first drug, and the four filters that then choose it.
- 2 How a first-contact physician, a specialist and a hypertension clinic think about the same patient — and where each one goes wrong.
- 3 Why the guideline says what it says — and where it deliberately leaves you the choice.
- 4 The eight sites, and the two walks that make them memorable.
- 5 Which patient gets which class, and what makes a class the wrong one.
- 6 Whether the regimen covers twenty-four hours — and whether to start with one drug or two.
- 7 The five questions to ask before a fourth tablet, and the site audit to run before a fifth.

0.1 What you are actually choosing

FIGURE 0.1 — THE TWO TERMS EVERY ANTIHYPERTENSIVE ACTS ON



Two terms, eleven classes, and no third option.

Every antihypertensive ever made lowers one of these two numbers. Choosing a drug is choosing which one, and in which organ.

This is the map the rest of the volume fills in. When a second drug is needed, the useful question is not which drug but *which column has not been touched* — and within a column, which organ. That single habit is most of what separates a considered prescription from an anxious one.

Volume 1 closed with Page's mosaic: hypertension is not one disease but several mechanisms running at once, in proportions that differ between patients. That has a pharmacological consequence which is rarely written down.

Every antihypertensive class presses on exactly one tile of that mosaic. A diuretic acts on sodium handling in the nephron. An ARB acts on a receptor. A calcium channel blocker acts on the vascular smooth muscle cell. A beta-blocker acts on the sympathetic limb. Writing a prescription is choosing which mechanism to interrupt in a patient whose mosaic has a particular shape.

It should also be easier to remember than most pharmacology. Reading class by class does not stick: each class arrives as a fresh list — mechanism, agents, side effects, trials — with nothing to hang it on, so by the fourth class the first has gone. Most clinicians blame themselves. The fault is the organisation.

0.2 How a consultant actually chooses

Watch an experienced physician write an antihypertensive and it looks like recall. It is not. Four questions are being asked in a fixed order, and the order matters more than the answers — because the first question that returns an answer usually ends the decision.

A site is a place

You can walk down a nephron. You can follow a cascade from one end to the other. Drugs hang off those journeys in order, and a reader who can draw the journey cannot lose the drugs.

TABLE 0.1 — THE FOUR FILTERS, IN THE ORDER THEY ARE APPLIED

	THE QUESTION	WHAT IT SETTLES	FOUR EXAMPLES
1	Is there a compelling indication? A second disease that names a class on outcome grounds.	If yes, the decision is over, and the reason has nothing to do with the blood pressure. The authority is an outcome trial, not a mechanism.	— Heart failure with reduced ejection fraction → ACE inhibitor or sacubitril/valsartan, beta-blocker, MRA and SGLT2 inhibitor³⁰. RALES: mortality 35% against 46%²⁵. — Type 2 diabetes with nephropathy → a RAAS blocker. RENAAL: end-stage renal disease 19.6% against 25.5%²⁴. — Left ventricular hypertrophy → an ARB rather than atenolol. LIFE³. — Atrial fibrillation needing rate control → a beta-blocker, or verapamil or diltiazem.
2	Which mechanism is running? The phenotype.	Reached only when the first question is silent — which in uncomplicated hypertension is most of the time. This is Volume 1 arriving at the prescription.	— Young, lean, high-renin → the cascade: an ACE inhibitor or ARB. — Elderly, wide pulse pressure, stiff arteries → the channel or the nephron. SHEP²¹. — Obese, salt-loaded, low-renin → a thiazide-type diuretic; RAAS blockade alone will disappoint. — Non-dipper on ambulatory monitoring → look for the cause first (apnoea, kidney disease, aldosteronism); a change of dosing hour is worth a trial but does not change outcomes (Chapter 14).
3	What must I avoid in this patient?	A veto, not a preference. This filter can override both of the ones above, and it is the only one of the four that is absolute.	— Pregnancy, or planning it → no ACE inhibitor, ARB or renin inhibitor, at any dose. — Gout, or already on a urate-raising drug → not a thiazide or a loop; among ARBs, losartan¹³. — Asthma → not a non-selective beta-blocker. — Bilateral renal artery stenosis → nothing acting on the cascade. — Potassium already 5.4 → not an MRA, whatever the guideline says about the fourth drug.
4	Will this cover the day, and will they take it?	Duration, dose frequency, tablet burden, cost, and what happens when a dose is missed. The filter most often skipped, and the commonest reason a correct prescription fails.	— Two short-acting drugs, both in the morning → controlled in clinic, uncovered at dawn. — Captopril three times a day → ruled out for maintenance by its schedule, not its efficacy. — A single-pill combination the patient can afford → usually beats a theoretically better two-tablet regimen. — A drug the patient pays for monthly → ask the price before writing it, not after they stop.

The order is the teaching point. A junior clinician tends to start at question two, because mechanism is what was taught most recently and it feels like the clever answer. A consultant starts at question one, and most of the time never reaches question two at all — because the patient's second disease has already decided the class.

0.3 Before the first drug — what has already been settled

The four filters decide *which* drug. They are reached only after four other questions have been answered, and a prescription written before those answers exist is a guess wearing the clothes of a decision. Watching a consultant, this is

the part that is invisible: it happens in the thirty seconds before the pen moves, and none of it is about pharmacology.

And the filter nobody applies

Question four. A drug with a twelve-hour half-life given once daily is a treated clinic reading and an untreated dawn. Section 0.11.

TABLE 0.2 — THE FOUR QUESTIONS THAT COME BEFORE THE FOUR FILTERS

	THE QUESTION	WHY IT COMES FIRST	WHAT IT CHANGES
1	Is the number real?	A reading taken over clothing, on an unrested patient, with a cuff too small, in one arm only, is not a diagnosis. Neither is a single office reading in a patient who is anxious in clinics.	Out-of-office confirmation before committing anyone to lifelong treatment. Among patients already labelled resistant, 37.5% had 24-hour pressures below 130/80 ¹⁵ — more than a third of the hardest cases were a measurement problem.
2	Is something already raising it?	The cheapest antihypertensive is the drug you stop. Adding a drug to counteract another drug is a regimen that grows and never improves.	A full drug history including what was never prescribed: analgesics, decongestants, oral contraceptives, steroids, ciclosporin, erythropoietin, alcohol, liquorice, energy drinks, herbal preparations. VI-Part V.
3	What is the total risk, not the pressure?	The benefit of treatment scales with baseline risk, not with the height of the reading. Two patients at 152/94 can deserve quite different urgency.	HOPE gave a quarter fewer events on a systolic difference of 3.3 mmHg ² . In a high-risk patient you are not treating the number, and the class you choose should reflect that.
4	What is the target, and when am I seeing them again?	A drug started without a target and a date is a drug nobody will ever escalate or stop. This is where most treatment inertia is created.	SPRINT, in 9,361 high-risk patients, found 5.2% against 6.8% events and 3.3% against 4.5% deaths for a systolic target under 120 ¹⁷ — with more acute kidney injury (4.1% against 2.5%) and more hypotension. The target is a judgement, and how the pressure was measured changes it (VI-Ch8).

What follows from all four is a habit worth naming: **the prescription is the plan, not the tablet**. An experienced clinician decides, before the patient leaves, what the target is, when they will be seen, what will be checked at that visit, and what the second drug will be if the first is not enough. The junior version of the same consultation produces a drug and a vague instruction to return.

0.4 Three readers, one patient

This volume is written for a general physician, a specialist and a postgraduate at the same time, and it is worth being explicit about how their thinking differs — because it is not that one knows more drugs. Each level asks a question the level before it did not need to ask, and the reason is the population in front of them. General practice sees mostly uncomplicated hypertension, where the algorithm is correct and speed is the virtue. A specialist sees the patients the algorithm did not fix. A hypertension clinic sees the patients the specialist did not fix — a population in which the base rates have changed so far that the diagnosis is more often wrong than the drug.

The sentence that prevents a stopped drug

Tell the patient what to expect before it happens. A creatinine that rises a little is the ACE inhibitor working; ankles that swell on amlodipine are not heart failure. A patient who was not warned stops the drug and tells the next doctor they are allergic to it.

TABLE 0.3 — THE SAME PATIENT, THREE WAYS OF THINKING

	THE QUESTION IN THEIR HEAD	WHAT THEY ACTUALLY MEASURE	THE MOVE	WHAT GOES WRONG AT THIS LEVEL
First contact	“Which class does the guideline name for this patient?”	Office pressure, basic bloods, urine, ECG.	Start the guideline-named class at a sensible dose. Review in four weeks.	Treating a reading that was never confirmed; raising the dose when the problem was that the tablets were not taken.
Specialist	“Is this pressure real — and is it still the same problem I was told about?”	Out-of-office pressure, albumin-to-creatinine ratio, a drug history including what was bought over the counter, and adherence.	Subtract before adding. Repair the regimen before extending it: right diuretic, right dose, right timing.	Sending everyone for a secondary workup; or the opposite, accepting three drugs as maximal when one site was never blocked.
Superspecialist	“Which mechanism is still unblocked — and can I measure it rather than guess it?”	24-hour urinary sodium, renin and aldosterone, ambulatory monitoring, and where necessary drug levels.	Complete the blockade at the site that is missing; screen for the secondary cause the base rate now justifies.	Over-investigating; trusting a phenotype test that has never been shown to improve outcomes; pushing a frail patient below a pressure that was protecting them.

Put in one line: **the first asks which drug, the second asks whether the question was right, and the third treats the failure as a diagnostic finding rather than a therapeutic one.** That last shift is the whole of the difference. When a hypertension clinic receives a patient uncontrolled on four drugs, the working assumption is not that a fifth drug is needed. It is that something has been measured wrongly, taken irregularly, undone by something else, or missed entirely — and the drugs are examined last.

0.5 How the guideline was set, and where it leaves you the choice

This volume keeps saying that the guideline chooses the class and mechanism explains why. That is worth unpacking once, here, because it determines how everything after it should be read.

A guideline committee does not reason from physiology. It asks a narrower question: *in a randomised trial with a hard endpoint, did this class reduce death, stroke, infarction or renal failure more than the comparator?* Where the answer is yes, the class is named first-line for that population. Where trials showed classes to be equivalent, the guideline names several and stops — not from indecision, but because the evidence genuinely does not distinguish them.

So mechanism is not a rival authority. It is the explanation of an authority that already exists, and the decision procedure for the space that authority deliberately leaves open. A clinician who understands *why* beta-blockers lost first-line status follows that guidance more reliably than one who was simply told, because they now agree with it.

Why this matters to a reader who is none of these

The three questions are sequential, not ranked. Any clinician can ask all three, and most of the available benefit is in asking the second before reaching for the third. Sections 0.13 and 0.14 are those two questions written out as procedures.

TABLE 0.4 — WHAT THAT MEANS FOR A READER OF THIS BOOK

WHERE THE GUIDELINE IS	WHAT IT MEANS	FOUR EXAMPLES	WHAT THIS BOOK ADDS
It names one class	A trial showed an outcome advantage in this population. The committee has already done work you cannot repeat in clinic.	— HFrEF: ACE inhibitor, beta-blocker, MRA^{25,26}. — Diabetic nephropathy with albuminuria: a RAAS blocker²⁴. — Diabetic CKD still progressing on a RAAS blocker: finerenone²⁷. — Pregnancy: methyldopa, labetalol or nifedipine, and nothing on the cascade.	The mechanism — so you understand the recommendation rather than memorising it, and recognise the patient it was written for.
It names several	Trials found them equivalent on the hard endpoint. The choice is genuinely open, and the guideline says so deliberately.	— Uncomplicated hypertension: ACE inhibitor, ARB, calcium channel blocker or thiazide-type diuretic. ALLHAT found no primary-outcome difference across three of them in 33,357 patients²². — Which of two first-line classes for a 58-year-old with nothing else. — Whether the second drug goes on at half dose or the first goes to full dose. — ACE inhibitor or ARB when both are permitted.	This is where mechanism, phenotype, tolerability and cost legitimately decide. Most of this volume lives here.
It is silent	No adequate trial. Common in exactly the questions clinicians actually ask, because those questions are too granular to have been randomised.	— Which ARB, of the seven. — Whether to give the dose at night. — Which molecule within a class for a patient with cirrhosis. — What to do at the fifth drug, or when spironolactone is contraindicated.	Physiological reasoning, labelled as such, and never dressed up as trial evidence.

0.6 The map

Eight sites account for every drug in this volume. Each chapter that follows is one row of this table, opened out.

The rule, stated once and repeated in every chapter

The guideline chooses the class wherever it has spoken. Mechanism chooses among the options it leaves open. Nothing in this volume is a reason to delay a guideline-directed drug in a patient who needs one.

TABLE 0.5 — SITE OF ACTION, AND THE MECHANISM IT INTERRUPTS

SITE	WHAT IS HAPPENING THERE	CLASS	PHENOTYPE IT SUITS	WHAT ACTING HERE COSTS
Distal nephron — NCC, NKCC2, ENaC	Sodium reabsorption sets total body sodium, and the kidney sets long-term pressure (V1-Ch5)	Thiazides, loops, ENaC blockers	Volume-dependent, salt-sensitive, low-renin, non-dipping	Potassium, urate, glucose. A reflex rise in renin that partly undoes the work
Mineralocorticoid receptor	Aldosterone-driven sodium retention, and separately vascular and myocardial fibrosis	Spironolactone, eplerenone, finerenone	Resistant hypertension, aldosteronism, proteinuric CKD	Potassium — the reason this sits fourth rather than first
ACE — the enzyme	Angiotensin II synthesis, and bradykinin degradation. Two jobs; you interrupt both	ACE inhibitors	High-renin, young, proteinuric, diabetic, post-MI, HFrEF	Cough and angioedema ¹¹ — and possibly, on the same mechanism, part of the benefit ⁶

SITE	WHAT IS HAPPENING THERE	CLASS	PHENOTYPE IT SUITS	WHAT ACTING HERE COSTS
AT₁ receptor	The same signal blocked one step later, leaving bradykinin untouched	ARBs	The same phenotypes, where the enzyme approach is not tolerated	No cough ¹³ — and, on meta-analysis, no demonstrated all-cause mortality benefit either ⁶
L-type calcium channel	Arteriolar tone — the SVR term of $MAP = CO \times SVR$ (V1:Ch1)	Dihydropyridine CCBs	Elderly, isolated systolic, low-renin, stiff arteries, salt-loaded	Ankle oedema from pre-capillary dilation ⁹ — mechanical, not fluid overload, and it does not answer to a diuretic. Rates differ by molecule: nifedipine RR 6.03, amlodipine 3.34, lercanidipine 1.27 ⁸
β₁ receptor — SA node and myocardium	Rate, contractility and renin release — the CO term, and the sympathetic limb of V1:Ch4	Beta-blockers	Neurogenic, high-output, post-MI, HFrEF, atrial fibrillation	Metabolic cost, and a shortfall in central aortic pressure relative to the cuff
α₁ receptor — vascular smooth muscle	Sympathetic vasoconstriction at the effector end	Doxazosin, prazosin, terazosin	Resistant hypertension, coexisting prostatic symptoms	First-dose hypotension, and an outcome signal that demoted the class
Central α₂ and I₁ — brainstem	Sympathetic outflow at its origin, upstream of every peripheral effect	Methyldopa, clonidine, moxonidine	Resistant, pregnancy, where peripheral blockade has failed	Sedation, and rebound on withdrawal

0.7 The first walk — down the nephron

Filtrate leaves the glomerulus and travels a fixed route. Four drug classes intervene along it, in order, each defined by the transporter it blocks.

One anatomical journey, taught in every physiology course, carrying four drug classes in sequence. A reader who can draw the nephron cannot forget where a thiazide acts. A reader who has only memorised that thiazides are first-line has nothing to recover the fact from once it fades.

The right-hand column is worth reading across as well as down, because it is not uniform. Two of these four stations have hard outcome trials in hypertension and two do not, and the two that do are the two the guidelines name first. That is not a coincidence, and it is the point of the chapter that follows this one.

TABLE 0.6 — ONE JOURNEY, FOUR CLASSES — AND THE TRIAL BEHIND EACH

SEGMENT AND TRANSPORTER	CLASS	THE PHENOTYPE IT SUITS, AND WHY	THE TRIAL THAT PUT IT THERE
Thick ascending limb — NKCC2, the sodium–potassium–two–chloride cotransporter	Loop diuretics	Volume overload where filtration is failing: CKD below roughly 30 mL/min, and heart failure. This segment reabsorbs about a quarter of the filtered sodium, so the natriuresis is large and holds up as the GFR falls. A thiazide-type agent is weaker there but not inert — chlorthalidone still cut twenty-four-hour systolic pressure by 11 mmHg against placebo in stage 4 disease ²⁸ . The loop is the drug for volume; the thiazide is not struck off for pressure.	No outcome trial in hypertension. Loop diuretics are in this book on the strength of heart failure and CKD practice, not because a randomised trial showed they prevent cardiovascular events in hypertensive patients. The book says so rather than borrowing the thiazides' evidence.
Distal convoluted tubule — NCC, the sodium–chloride cotransporter	Thiazides and thiazide-like agents	Salt-sensitive, low-renin, elderly, isolated systolic. A smaller and more sustained natriuresis than a loop, and over time a fall in vascular resistance that suits a stiff arterial tree better than a brisk diuresis does.	SHEP: 4,736 patients, mean age 72, isolated systolic hypertension 160–219/<90. Chlorthalidone-based treatment cut five-year stroke from 8.2 to 5.2 per 100, RR 0.64 ²¹ . HYVET , in 3,845 patients aged 80 or over: indapamide with perindopril as needed, heart failure HR 0.36 and all-cause mortality HR 0.79 ²³ . ALLHAT: chlorthalidone matched amlodipine and lisinopril on the primary outcome in 33,357 patients and beat both on heart failure ²² .
Collecting duct — the channel — ENaC, the epithelial sodium channel	Amiloride, triamterene	Low-renin hypertension, hypokalaemia on a thiazide, and Liddle syndrome, where the channel itself is the disease. The final sodium adjustment, and the point at which potassium stops being lost and starts being retained.	No dedicated outcome trial in hypertension. These agents are prescribed for the potassium and for the mechanism, and in Liddle syndrome for the diagnosis. That is a legitimate reason to use a drug; it is not the same kind of reason as SHEP.
Collecting duct — the receptor above it — the mineralocorticoid receptor, which opens ENaC	Spironolactone, eplerenone, finerenone	Resistant hypertension, primary and secondary aldosteronism, proteinuric diabetic kidney disease. One step upstream of the channel, so the effect is broader — and the potassium risk larger — than blocking ENaC directly.	PATHWAY-2 made spironolactone the fourth drug: home systolic 8.70 mmHg below placebo, and below doxazosin and bisoprolol too ¹⁶ . RALES in severe HFrEF: mortality 35% against 46% ²⁵ . EMPHASIS-HF in NYHA II: 18.3% against 25.9% ²⁶ . FIDELIO-DKD: renal composite 17.8% against 21.1% ²⁷ .

0.8 The second walk — along the cascade

The renin–angiotensin–aldosterone system of V1·Ch3 is a production line, and drugs interrupt it at four successive stations.

Read the two tables side by side and a pattern appears that neither shows alone. The classes with the strongest evidence are not the ones with the most elegant mechanism — the direct renin inhibitor has the most elegant mechanism in this book and no place in practice, while chlorthalidone, whose mechanism was worked out long after it was in use, is still first-line. **Mechanism explains why a class works. It does not decide whether it is used.** That decision was made by trials, and the next chapter is about them.

TABLE 0.7 — ONE CASCADE, FOUR CLASSES — AND THE TRIAL BEHIND EACH

STATION	CLASS	THE PHENOTYPE IT SUITS, AND WHY	THE TRIAL THAT PUT IT THERE
Renin acts on angiotensinogen	Direct renin inhibitors	On paper the ideal patient is anyone with a running cascade, because this is the first and rate-limiting step. In practice there is no population in which the class wins.	ALTITUDE is the reason, and it is a negative reason: added to an ACE inhibitor or ARB in diabetic patients it produced more hyperkalaemia and more hypotension and no benefit, and was stopped early ⁷ . A class can be removed from practice by a trial as decisively as it is placed by one. Chapter 3.
ACE converts angiotensin I to II	ACE inhibitors	High-renin, young, proteinuric, diabetic, post-infarct, HFrEF. The enzyme also degrades bradykinin, so this station has a second consequence no other has — the cough, and possibly part of the benefit.	HOPE : 9,297 patients at high cardiovascular risk, a quarter fewer events on a systolic difference of 3.3 mmHg ² — the trial that turned this class from a blood pressure drug into a risk-reduction drug. Van Vark , pooling 158,998 patients, found an all-cause mortality reduction for ACE inhibitors that ARBs did not show ⁶ . Chapter 1.
Angiotensin II acts at AT ₁	ARBs	The same phenotypes, in a patient the enzyme approach cannot tolerate — and left ventricular hypertrophy specifically, where the evidence is the ARBs' own rather than borrowed.	LIFE : 9,222 hypertensives with ECG left ventricular hypertrophy, losartan against atenolol at 144.1/81.3 versus 145.4/80.9 mmHg — effectively the same pressure — with the composite at 11% against 13% and stroke at 5% against 7% ³ . RENAAL in type 2 diabetic nephropathy: end-stage renal disease 19.6% against 25.5% ²⁴ . And ONTARGET , which showed what this station cannot do: added to an ACE inhibitor it gained nothing and cost renal function ^{4,5} . Chapter 2.
Aldosterone acts at the mineralocorticoid receptor	Spironolactone, eplerenone, finerenone	Resistant hypertension, aldosteronism, proteinuric CKD. The last station on the cascade — and the same receptor the nephron walk arrived at from the other direction.	The same four trials as the nephron walk, reached by a different route: PATHWAY-2 ¹⁶ , RALES ²⁵ , EMPHASIS-HF ²⁶ , FIDELIO-DKD ²⁷ . Chapter 7.

0.9 Where the two walks meet

The mineralocorticoid receptor is the last stop on the cascade and the fourth stop down the nephron. That is not a curiosity. It is the reason a diuretic and a RAAS blocker work so well together, and the reason spironolactone belongs in a conversation about volume as much as one about aldosterone.

It also gives the most useful combination rule in the book. Block the cascade and the kidney, sensing less angiotensin II, releases more renin. Give a diuretic and volume falls, which also raises renin. Each drug moves the patient toward the state in which the other works best. **The reflex a drug provokes is the argument for its partner.**

0.10 Which patient, which class

The table this volume exists to make usable. Read a row and the class is decided; the chapter tells you which molecule and what to watch.

And the converse

A drug given into a system already suppressed does nothing much. RAAS blockade in a low-renin, salt-loaded patient is the commonest example, and it is usually mistaken for treatment failure rather than recognised as a site chosen wrongly.

TABLE 0.8 — THE CLINICAL SITUATION DECIDES THE CLASS

THE PATIENT	FIRST	SECOND	AVOID, OR USE ONLY WITH CARE
Uncomplicated, young, lean, high-renin	ACE inhibitor	ARB	— nothing to avoid. Expect a diuretic to give a smaller fall than a cascade drug in a high-renin patient and prefer the cascade drug for that reason where cost and tolerability allow. That is a preference, not an avoidance: ALLHAT found the classes equivalent on the primary endpoint ²² .
Uncomplicated, older, obese, salt-loaded, low-renin	Calcium channel blocker, or thiazide-type diuretic	The other of those two	— nothing is contraindicated. Expect a smaller fall from RAAS blockade alone in a suppressed cascade, and pair it early with a calcium channel blocker or a thiazide-type diuretic rather than substituting for it; never withhold it where diabetes, albuminuria, heart failure or prior infarction indicate it.
Isolated systolic hypertension in the elderly	Calcium channel blocker	Thiazide-type diuretic	Beta-blocker as first line
Diabetic kidney disease, or any proteinuric CKD	ACE inhibitor ⁶	ARB	A calcium channel blocker alone — it lowers the pressure without touching the glomerulus
Heart failure with reduced ejection fraction	All four pillars: an ACE inhibitor — replaced by sacubitril/valsartan in the patient who stays symptomatic — a beta-blocker, a mineralocorticoid antagonist and an SGLT2 inhibitor, each Class I ³⁰	A loop diuretic for congestion. The pressure is a constraint on uptitration, not the target — V3-Ch21	Non-dihydropyridine calcium channel blockers — avoid entirely: verapamil is contraindicated in severe left ventricular dysfunction, diltiazem carries a warning rather than a contraindication ¹²²⁹
Heart failure with preserved ejection fraction	An SGLT2 inhibitor, plus the ordinary antihypertensive regimen to the ordinary target ³⁰	A loop diuretic titrated to congestion	Assuming a lower pressure target exists here — none does. V3-Ch21, Case 14
After stroke or transient ischaemic attack	An ACE inhibitor with a thiazide-type diuretic — the PROGRESS regimen; started before discharge, not weeks after	Any first-line class, to a systolic of 120–129 if tolerated	Leaving the patient untreated because “permissive” was written in the acute notes. V3-Ch22, Case 19
After myocardial infarction	ACE inhibitor and beta-blocker	ARB if cough	—
Left ventricular hypertrophy	ARB ³	ACE inhibitor	Atenolol specifically — LIFE ³

THE PATIENT	FIRST	SECOND	AVOID, OR USE ONLY WITH CARE
Atrial fibrillation needing rate control	Beta-blocker, or verapamil/diltiazem	—	Beta-blocker with verapamil or diltiazem — two drugs on one node
Angina with hypertension	Beta-blocker, or calcium channel blocker	—	—
Gout, or on a urate-raising diuretic	Calcium channel blocker; losartan among ARBs ¹³	ACE inhibitor	Thiazides and loops — both raise urate
Asthma or significant airways disease	Calcium channel blocker, ARB, diuretic	—	Non-selective beta-blockers
Pregnancy, or planning it	Methyldopa, labetalol, nifedipine	—	ACE inhibitors, ARBs, renin inhibitors — all absolutely
Benign prostatic symptoms with hypertension	Alpha-blocker as add-on	—	Alpha-blocker as sole first-line agent
Resistant on three drugs including a diuretic	Spironolactone as fourth	—	A fourth drug at a site already blocked
Bilateral renal artery stenosis	Calcium channel blocker	—	Anything acting on the cascade — V1·Ch32

0.11 Twenty-four hour cover — the question nobody asks

Blood pressure is not a number. It is a curve with a trough, and the dangerous part of that curve is the last few hours before the next dose — the early morning, where the sympathetic surge of V1·Ch7 meets the lowest drug level of the day. A regimen that controls the clinic reading and loses the dawn has treated the measurement rather than the patient.

Two properties decide whether a drug holds that trough. The obvious one is half-life. The less obvious one is how the drug leaves its receptor: a competitive antagonist can be displaced when its ligand rises, an insurmountable one cannot, so the block outlasts the plasma level.¹⁰

How to use this table

Find the row, take the class, then go to that chapter for the molecule. If two rows apply and they disagree, the one naming an absolute contraindication wins — filter three overrides filters one and two.

How to tell without ambulatory monitoring

Ask when they take the tablet, then measure at the *end* of the dosing interval rather than at its peak — a morning reading before the morning dose. If that is much worse than a clinic reading taken two hours after a dose, the problem is duration, not dose.

TABLE 0.9 — THE PAIRING RULES THAT FOLLOW

THE COMBINATION	WHAT HAPPENS	WHAT TO DO
Long-acting plus long-acting	Cover holds through the trough from both directions.	Once daily, both. The safe default.
Long-acting plus short-acting	The long agent carries the trough while the short one fades.	Once daily is defensible — give the short-acting agent at night if the pressure is morning-dominant.
Short-acting plus short-acting	Both troughs fall together, and the patient is least protected exactly when risk is highest.	Twice-daily dosing, or change one molecule. This is the regimen that looks controlled in clinic and is not.
Morning dosing with a morning-dominant profile	The peak arrives after the surge it was meant to cover.	Move a dose to the evening before adding a third drug — it costs nothing, it is safe, and it sometimes improves a morning reading. It does not change outcomes (Chapter 14), so treat it as a trial of timing, review it against home readings, and if the pressure is still above target the answer is a second site, not a different hour.

This is also the honest argument for the fixed-dose combinations that dominate Indian prescribing. One tablet improves adherence, which is the largest single determinant of control. But a combination is only as good as its shorter component: a once-daily pill containing a short-acting agent inherits that agent's trough.

0.12 One drug, or two?

The reflex is to start one drug, titrate it, and add a second when the first fails. That is defensible and it is often wrong, for a reason that is mechanical rather than clinical.

Doubling the dose of one drug buys much less than adding a second at a different site. A single agent blocks one mechanism; once that mechanism is blocked, more of the same drug has little left to do, while its dose-related adverse effects go on rising. Two drugs at half doses block two mechanisms and carry less of each drug's cost.

TABLE 0.10 — WHEN TO START WITH TWO

START WITH ONE WHEN	START WITH TWO WHEN
The pressure is close to target — within about 20/10 mmHg.	The pressure is far from target. One drug will not get there, and you will spend three months finding out.
The patient is frail, elderly, or volume-depleted, and first-dose hypotension is the risk.	Cardiovascular risk is high and time to control matters.
A compelling indication names one class and you need to know that drug is tolerated.	A single-pill combination is available, affordable, and improves the chance the patient keeps taking it.
Renal function is unstable and you want to attribute any change to one agent.	Previous monotherapy has already failed at a full dose.

Which two is not a matter of taste. ACCOMPLISH randomised 11,506 high-risk patients to an ACE inhibitor with amlodipine or the same ACE inhibitor with hydrochlorothiazide: events 9.6% against 11.8%, hazard ratio 0.80 (95% CI 0.72–0.90), at 131.6/73.3 against 132.5/74.4 mmHg.¹ Under a millimetre apart, a fifth fewer events.

0.13 It is not controlled — the specialist’s sequence

The patient returns, the pressure is still high, and the reflex is to add a drug. That reflex is wrong often enough to be worth resisting on principle. Five questions come first, in this order, because each is cheaper and more likely to be the answer than the one after it. None of them is about pharmacology, and four of the five cost nothing.

One rule that is absolute, and one that is nearly so

Never two drugs at the same station of one cascade — ONTARGET found no benefit and a third more renal impairment^{4,5}, and ALTITUDE found harm⁷. And do not put a non-dihydropyridine calcium blocker with a beta-blocker for blood pressure: two drugs on one node, additive on rate, conduction and contractility²⁹. Where a cardiologist wants the pair for rate control, that is a decision taken with a normal ejection fraction, a clean conduction system and close monitoring — not one to copy onto a hypertension sheet.

Where the specialist differs

Not in knowing more drugs. In doubting the input — the reading, the history, the assumption that the prescription describes what the patient swallows.

TABLE 0.11 — FIVE QUESTIONS BEFORE A FOURTH TABLET

	ASK THIS	BECAUSE	AND THEN
1	Is the measurement right?	Cuff too small, arm unsupported, no rest, talking, one arm only, or simply this clinic. Of patients already carrying the label of resistant hypertension, 37.5% had 24-hour ambulatory pressures below 130/80 ¹⁵ .	Home readings over a week, or ambulatory monitoring. Do this before the fourth drug, not after it.
2	Are they taking it?	In a specialist clinic screening urine by mass spectrometry, 25% of 208 patients were partly or wholly non-adherent — and among those referred specifically for inadequate control it was 37.9% ¹⁴ . Nobody in that study looked non-adherent.	Ask without accusing. Then simplify: once daily, single-pill combination, cheapest equivalent, one pharmacy.
3	Is something undoing it?	A regular NSAID, a decongestant, an oral contraceptive, a steroid, alcohol, liquorice, or salt at a level no diuretic can match. In Indian practice the over-the-counter combination analgesic is the commonest and the least often volunteered.	Subtract before you add. This is a free intervention and it is skipped in most consultations.
4	Is the regimen right, or merely large?	Three drugs acting at one site is one drug. Is there a diuretic in it at all — and is it the right one at an adequate dose? Does the combination hold the last four hours before the next dose (0.11)?	Repair the regimen before extending it. A missing or under-dosed diuretic is the commonest structural fault.

	ASK THIS	BECAUSE	AND THEN
5	Only now, what do I add?	And this is not free choice. PATHWAY-2 rotated 335 patients with resistant hypertension through spironolactone, doxazosin, bisoprolol and placebo: home systolic fell 8.70 mmHg further than on placebo, 4.03 further than on doxazosin and 4.48 further than on bisoprolol ¹⁶ .	Spironolactone as the fourth drug, unless potassium or renal function forbids it. Chapter 7.

One definition is worth holding to, because it is routinely misapplied. **Resistant hypertension means uncontrolled on three drugs at adequate doses, one of which is a diuretic.** A patient on three drugs with no diuretic does not have resistant hypertension. They have an incomplete regimen, and the treatment is the missing drug rather than an investigation. Question two above deserves a note of its own, because it is the one clinicians ask badly.

0.14 Still not controlled — the superspecialist’s question

The sequence above has been worked through, the readings are real, the tablets are being taken, nothing obvious is undoing them, and the pressure is still high. At this point the question changes character. It stops being *what do I add* and becomes *what have I got wrong* — and it is answered in three moves, each of which is the same site question this volume is built around.

The first move is an audit of sites, not of drugs. Count the mechanisms blocked, not the tablets swallowed. A patient on five drugs covering three sites is under-treated; a patient on four drugs covering four sites is fully treated and needs a diagnosis rather than a fifth tablet. That distinction cannot be made by reading the number of drugs off a prescription, which is why it is so often missed.

Asking about adherence

Not “are you taking your tablets?” — which has one socially acceptable answer. Try: “most people miss doses; how many did you miss last week?”, then ask what the tablets are for. A patient who cannot say why they take a drug will not take it for thirty years.

TABLE 0.12 — THE COMPLETENESS AUDIT — IS EACH SITE ACTUALLY BLOCKED?

SITE	BLOCKED BY	WHAT COUNTS AS BLOCKED	WHAT DOES NOT COUNT
The cascade	ACE inhibitor or ARB	A full dose of one of them.	Both together — no added benefit and more renal impairment ^{4,5} . Two drugs, one site.
The channel	A dihydropyridine calcium channel blocker	A long-acting agent at a dose that was actually titrated.	A non-dihydropyridine given for rate control. Different job.
The nephron	A thiazide-type diuretic, or a loop if eGFR is low	The right diuretic, at an adequate dose, for the patient’s renal function.	A token dose of hydrochlorothiazide left unchanged for years — the commonest structural fault in a resistant regimen.
The mineralocorticoid receptor	Spironolactone, or eplerenone if intolerant	Added as the fourth agent, with potassium monitored ¹⁶ .	A potassium-sparing diuretic used only to protect potassium. Same corner of the nephron, different intention.
The sympathetic limb	Beta-blocker, alpha-blocker, or a central agent	Reached only after the four above — and the point at which refractory hypertension becomes the question.	Adding it early because it was the drug the last clinic had not tried.

The second move is to measure the mechanism instead of inferring it. Everything in Volume 1 pointed at phenotype from the history and the examination. A hypertension clinic can go further, and two measurements do

most of the work.

TABLE 0.13 — TWO MEASUREMENTS THAT CHANGE THE PLAN

	WHAT IT TELLS YOU, AND WHAT IT DOES NOT
24-hour urinary sodium	The single most informative test in a resistant patient, because it converts a suspicion about diet into a number the patient cannot argue with. In fifteen patients with treatment-resistant hypertension, sodium excretion fell from 186 to 91 mmol per 24 hours on a restricted diet and 24-hour systolic pressure fell by 10 mmHg ¹⁸ . A small study, and the direction is not in doubt. A high sodium excretion means the diet is undoing the diuretic, and no drug added at that point is being given a fair trial.
Renin and aldosterone	How a superspecialist decides between the cascade and the volume site: a suppressed renin in a patient on a RAAS blocker says the drug is being given where there is no signal to block. It also raises the aldosterone-to-renin ratio and the question of primary aldosteronism (VI-Ch13, VI-Ch33). The honest caveat: renin-guided prescribing has not been shown to improve hard outcomes , and the trials that would settle it have not been done ¹⁹ . It is a way of thinking, not a validated protocol, and this book prints it as such.

The third move is to recognise when it has become a different disease. Beyond resistant hypertension lies a smaller group defined by failure at five drugs rather than three — refractory hypertension: uncontrolled despite five agents of different classes including a long-acting thiazide and a mineralocorticoid receptor antagonist. It is rare. In a national survey, 0.8% of people taking antihypertensives met that definition²⁰.

It is worth a paragraph here because of the mechanism, which lands exactly where this volume’s architecture predicts. Resistant hypertension behaves like a volume problem — aldosterone and sodium — which is why a mineralocorticoid antagonist is the drug that answers it. Refractory hypertension appears instead to be driven by sympathetic overactivity: 24-hour urinary normetanephrine was higher in refractory than in controlled resistant patients, 464.4 against 309.8 µg²⁰. **Adding a sixth volume-directed drug to a refractory patient is another drug at a site already blocked.** The remaining options are at the sympathetic site, and Chapters 8 to 10 are where they are.

Every one of these three moves is the same question the rest of this volume asks, applied to a harder patient: *which site, and is it actually blocked?* The difference at this level is only that the answer is measured rather than assumed, and that failure is read as information rather than as a reason to prescribe again.

0.15 How each chapter is built

Every chapter runs the same sequence, so that by the third you know where to find what you need.

TABLE 0.14 — THE SHAPE OF EVERY CHAPTER

	WHAT IT DOES
Why act here	The site, what is happening at it, and what interrupting it does — grounded in the Volume 1 chapter that established the physiology.
Where this class ranks	First, second or contraindicated, population by population, with the reason.
Why here and not there	The comparison between sites, and the phenotype that decides it.
The ledger, and the counterfactual	What you want, what comes with it, the verdict — and where the class would sit if the costs were absent.

Stopping is also a move

In a frail patient, or one whose diastolic is already low, or one whose last drug produced falls, the honest answer is a higher accepted target. SPRINT bought its benefit with more acute kidney injury and more hypotension¹⁷.

	WHAT IT DOES
When acting here is wrong	Contraindications as situations, each with the site that replaces it.
What to check, and when	Monitoring, with the thresholds that change what you do.
The adverse effects, and what to do when they happen	Each effect mapped to a decision, not just named.
Interactions, and special populations	Mechanism, effect and management — not a list of names.
The molecules, compared, then individually	Comparative tables first, then a profile for each: why it exists, when to reach for it, what stops you.
Combinations	What to add, what never to add, and why.
Quick reference and clinical pearls	One page for the point of writing, and the points that change practice.

Individual drug detail comes last on purpose. A doctor does not need a book to find the dose of ramipril; what is genuinely hard is the decision in front of it. Every dose printed here was read out of a named label, and where a source is silent the book says so — because a blank space in a drug table reads as reassurance.

KEY POINTS

- Every antihypertensive class presses on one tile of Page’s mosaic. Writing a prescription is choosing which mechanism to interrupt.
- Four filters, in order: a compelling indication, then the phenotype, then what must be avoided, then whether it covers the day and will be taken. The first that answers ends the decision.
- The guideline names a class where a trial showed an outcome advantage, and names several where trials found them equivalent. Mechanism decides in the space it deliberately leaves open.
- The nephron is one walk carrying four classes; the cascade is another carrying four more. They meet at the mineralocorticoid receptor.
- The reflex a drug provokes is the argument for its partner — which is why diuretics and RAAS blockers are complementary rather than merely additive.
- A regimen of two short-acting drugs looks controlled in clinic and loses the dawn. Measure before the morning dose, not after it.
- Two drugs at half dose beat one at double, and ACCOMPLISH says which two: a calcium channel blocker rather than a thiazide, a fifth fewer events at the same pressure.
- Before the first drug: confirm the number, subtract what is raising it, weigh the total risk rather than the reading, and set a target with a review date. The prescription is the plan, not the tablet.
- The three levels of thinking differ in the question, not the drug list. Which drug; then whether the question was right; then what the failure is telling you.
- When it is not controlled, five questions come before a fourth tablet: measurement, adherence, what is undoing it, whether the regimen is right rather than merely large — and only then what to add, which is spironolactone.
- Count sites blocked, not tablets taken. Five drugs covering three sites is under-treatment; four drugs covering four sites is a diagnosis waiting to be made.
- Resistant hypertension behaves like a volume problem, which is why an MRA answers it. Refractory hypertension — uncontrolled on five including an MRA — carries the marks of sympathetic overactivity, and the remaining options are at that site.

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What the Trials Decided

A thiazide is first-line because of what happened to 33,357 people, not because of what happens at the sodium–chloride cotransporter. This chapter puts the evidence where it belongs — in front of the mechanism, not behind it.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 Why a trial, and not a mechanism, is the reason any class sits where it sits.
- 2 What a randomised trial can decide, and the four questions it cannot answer.
- 3 How to read a trial before believing it: the comparator, the population, the endpoint, and the difference between relative and absolute.
- 4 The trials that set the first line, chose the second drug, and ended three practices.
- 5 Why two regimens can produce the same cuff reading and different outcomes — and what that means for drug choice.
- 6 Which organ you are protecting, rather than which number you are lowering.
- 7 Where the evidence runs out, and what this book does at that point.

T.1 Why this chapter exists

The previous chapter is a map of mechanisms, and it would be easy to close it believing that mechanism is how drugs get chosen. It is not, and a book that left that impression would be teaching something false.

Here is the actual chain. A trial randomises thousands of patients and counts strokes, infarctions, admissions and deaths. A committee reads the trials and writes a guideline. A clinician reads the guideline — or absorbs it from colleagues, from a course, from the way things are done — and writes a prescription. **Mechanism enters that chain nowhere.** It is how we explain the result afterwards, and it is indispensable for that, but no thiazide became first-line because someone understood the sodium–chloride cotransporter.

Getting that order backwards is the commonest intellectual error in clinical pharmacology, and most textbooks teach it backwards by arranging themselves around mechanism and mentioning the trials at the end of the chapter. This volume does the reverse.

This matters most to a reader in general practice, because it changes what a specialist's recommendation means. When a cardiologist puts a patient on chlorthalidone rather than the hydrochlorothiazide that was working perfectly well, the reason is not a superior grasp of distal tubular physiology. It is ALLHAT³. When a nephrologist insists on a RAAS blocker in a diabetic patient whose pressure is already controlled, the reason is RENAAL¹⁴, not a view about glomerular haemodynamics. The specialist is not being clever. They are quoting a trial, and the trial is quotable by anybody.

The chain, in the order it runs

Trial → guideline → prescription.
Mechanism explains the trial afterwards and fills the gaps it left. It never authorises a drug on its own.

So this chapter is the one that makes the rest of the volume usable by a reader who is not a specialist. Every chapter after it says where a class ranks. This chapter says who decided, on what evidence, in which patients, and how confident anyone is entitled to be.

T.2 What a trial can decide, and what it cannot

A randomised controlled trial is a machine for answering one narrow question well. Understanding how narrow is what separates a reader who uses trials from one who is impressed by them.

The last row on the right is not a small caveat. The patient in front of an Indian physician — younger at onset, more centrally obese, more often diabetic, on a higher salt intake, and paying for the tablets — is not the patient in ALLHAT or ASCOT. That does not make the trials inapplicable. It makes them the best available evidence about a related population, which is a different and more honest claim.

TABLE T.1 — THE REACH OF A TRIAL

A TRIAL CAN SETTLE	A TRIAL CANNOT SETTLE
Whether <i>this class</i> , against <i>that comparator</i> , in <i>this population</i> , changed <i>this endpoint</i> . All four qualifiers are load-bearing.	Which molecule inside the class to use. Almost no trial randomised ramipril against perindopril, so almost nothing is known about that question at the level of hard outcomes.
Whether an effect is large enough to be worth its harms, when the harms were counted in the same study.	What time of day to give the dose, what to do when the fourth drug fails, or how to manage a patient the trial would have excluded.
Whether a plausible idea is wrong. This is the use most often forgotten, and three of the most important trials in this book are negative ones.	Whether the result transfers to a population that was not enrolled — which for most of these trials means South Asian patients, who were a small minority or absent.
Whether two regimens differ when the blood pressure they achieve is the same. That comparison is where the interesting findings are.	Anything about a patient with several conditions at once, since trials enrol the opposite of that patient by design.

T.3 Reading a trial before you believe it

Four questions, asked in this order, will correctly deflate most trial claims a reader will meet — including several in this book.

And the question behind all four

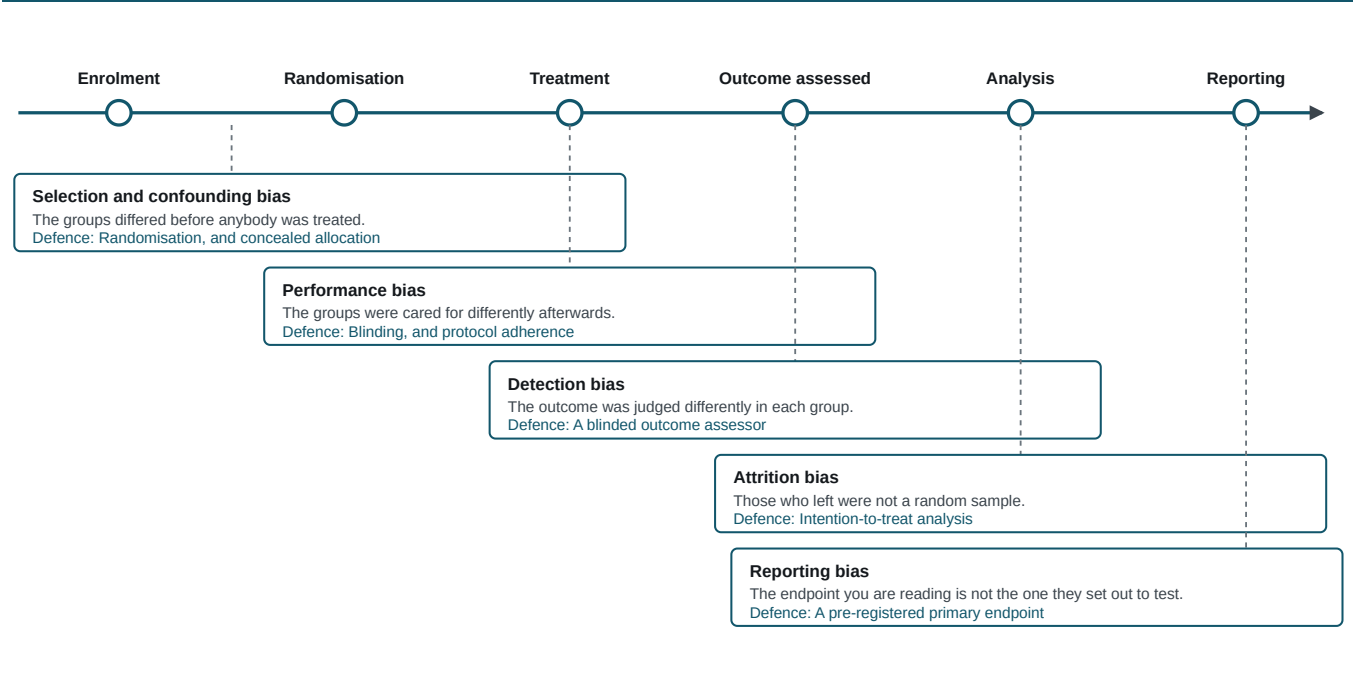
Would this trial have enrolled the patient in front of me? If the honest answer is no, the recommendation is being extended rather than applied — which is often reasonable, and should be done knowingly.

TABLE T.2 — FOUR QUESTIONS TO ASK OF ANY ANTIHYPERTENSIVE TRIAL

	ASK	WHY IT CHANGES THE ANSWER	A WORKED EXAMPLE FROM THIS VOLUME
1	What was the comparator?	A drug that beats placebo has shown one thing; a drug that beats another active drug has shown something far more useful. And a drug that beats a weak active comparator has shown less than it appears to.	LIFE is usually quoted as evidence for ARBs. It is more precisely evidence against atenolol , which was the comparator ⁵ . ASCOT has the same shape: amlodipine-based against atenolol-based ⁶ . Two large trials in which the loser was the same drug.
2	Who was enrolled?	The population is the boundary of the claim. Age, baseline risk, renal function and ethnicity all move the result, and the entry criteria are usually more restrictive than the way the trial is later quoted.	SHEP enrolled only isolated systolic hypertension, 160–219 systolic with diastolic under 90, mean age 72 ¹ . It says nothing about a 45-year-old with 150/100, and it should not be quoted as though it did.
3	What was the endpoint — and was it the primary one?	A primary endpoint was declared in advance. A secondary endpoint is a finding, and a subgroup is a hypothesis. All three get reported in the same font.	ALLHAT's primary endpoint — fatal coronary disease or non-fatal infarction — showed <i>no difference</i> at 11.5%, 11.3% and 11.4%. The famous result, chlorthalidone's advantage on heart failure, is a secondary endpoint ³ . It is still believable, and it is still secondary.
4	Relative or absolute?	A relative risk reduction sounds the same whether the event rate was 40% or 0.4%. The absolute difference, and the number needed to treat, is what a patient actually receives.	SPRINT's intensive arm gave a 25% relative reduction, which over a median 3.26 years is 5.2% against 6.8% — 63 patients treated for 3.3 years for one to avoid a major cardiovascular event or death, against one in 63 over the same period with an episode of acute kidney injury, most of which resolved. Both numbers are true, they are not the same kind of event, and they read very differently ¹⁹ . Both numbers are true and they read very differently.

T.4 How a trial can be wrong when the number is right

FIGURE T.1 — THE FIVE BIASES, DRAWN WHERE EACH ONE ENTERS THE TRIAL



Five doors, five locks, and a paper can be walked in about a minute. Ask at each one whether the lock was fitted. A trial with all five is *sound*; one defect the result can survive makes it *qualified*; two, or one that goes to the heart of the comparison, makes it *weak* — and a weak trial cannot carry a strong recommendation however large its number.

Everything in the last section was about how strong a result is. This one is about whether it is *trustworthy*, and the two are independent. A trial can produce a large difference on a primary endpoint and still be unreliable, because the difference was manufactured by the way the study was run rather than by the drug. **Effect size answers “how much”. Conduct answers “is it real”. A reader who checks only the first has done half the appraisal.**

Five things can go wrong, and they have names because each has a specific defence. The definitions below are the ones used by the agency that reviews trials for the American healthcare system, and the mitigations are the things you are checking a paper for.

TABLE T.3 — FIVE WAYS A TRIAL GOES WRONG, AND THE DEFENCE AGAINST EACH

WHAT GOES WRONG	WHAT IT MEANS	WHAT SHOULD HAVE PREVENTED IT	WHAT TO LOOK FOR IN THE PAPER
Selection bias, and confounding	“Systematic differences between baseline characteristics of the groups that are compared as a result of non-random enrolment” ²² — the two groups differed before anybody was treated.	Randomisation, and allocation concealment : the person enrolling must not be able to predict which arm the next patient gets ²² .	A baseline characteristics table that looks balanced. And the word <i>concealed</i> , not just <i>randomised</i> — they are different claims.
Performance bias	“Systematic differences in the care provided to participants” — contamination of the control group, unequal co-interventions, or inadequate blinding of patients and clinicians ²² .	Blinding of participants and clinicians, and protocol adherence ²² .	Whether the trial was blinded at all. An open-label trial of a drug with visible effects — a diuretic, a beta-blocker that slows the pulse — is not really blinded even when it says so.
Detection bias	“Systematic differences in outcomes assessment”: inconsistent definitions, shifting thresholds, or an unblinded assessor deciding whether an event happened ²² .	Blinding of the outcome assessor, and of the data analyst ²² .	Soft endpoints are where this bites. Death is hard to misclassify; “hospitalisation for heart failure” is a judgement someone made.
Attrition bias	“Systematic differences in the loss of participants from the study” ²² . Patients who drop out are not a random sample of those enrolled — they are often the ones the drug suited least.	Intention-to-treat analysis : everyone is counted in the arm they were randomised to, whatever they actually took ²² .	How many were lost, and whether the analysis was intention-to-treat or per-protocol. A per-protocol result flatters the drug.
Reporting bias	“Systematic differences between reported and unreported findings”, including selective reporting of outcomes ²² .	Reporting every pre-specified outcome ²² .	Whether the endpoint being celebrated is the one the trial was registered to test. A result promoted from secondary to headline is a warning.

And a sixth, which this book has to confess to. Several trials in this volume were stopped early — ALTITUDE²⁷, the ALLHAT doxazosin arm, MERIT-HF²⁶ — and the previous section treated that as a mark of how decisive they were. It is also a source of bias in the opposite direction. Trials stopped early for benefit overestimate the treatment effect, and the overestimation is worst when few outcome events had accumulated, particularly fewer than two hundred²³. One review found trials stopped for benefit had a median of 66 events at the point of stopping, with the smallest event counts producing the largest apparent effects²³.

So “stopped early” carries two meanings at once and a reader has to hold both. Stopped early for *harm* is close to unimpeachable — a safety board does not halt a trial on a small signal, and the direction of any bias makes the drug

look better, not worse. Stopped early for benefit is a different animal: the finding is probably real and the number is probably too big. **ALTITUDE and the doxazosin arm are the first kind. MERIT-HF²⁶ is the second, and its 34% reduction should be read as an upper bound rather than an estimate²⁸.**

TABLE T.4 — THE CONDUCT GRADE, ALONGSIDE THE EFFECT GRADE

CONDUCT GRADE	WHAT IT MEANS	HOW IT CHANGES THE EFFECT GRADE
Sound	Randomised with concealed allocation, blinded where blinding was possible, analysed by intention to treat, pre-specified primary endpoint reported, ran to completion.	No change. The effect grade stands.
Qualified	One defect that the result can survive — open-label with a hard endpoint, moderate attrition, or stopped early for benefit.	Down one. A Grade A finding in a trial stopped early for benefit is a Grade B recommendation, and the effect size is an upper bound.
Weak	Two or more defects, or one that goes to the heart of the comparison — a non-randomised comparison, a composite driven by its softest component, a promoted secondary endpoint.	Down two, or out. PROGRESS's combination-versus-monotherapy comparison sits here, and the section above shows why.

T.5 The trials that set the first line

Eight trials did most of the work of deciding which classes a clinician reaches for first. Read in date order they are a coherent argument, and each one is easier to remember as a site comparison than as a list of drug names — which is why the map came first.

The two questions, in order
How big, and on what endpoint? Then: how was it run? A large effect from a badly run trial and a small effect from a well-run one are both weak evidence, and they are weak for entirely different reasons — which is why the book grades them on two axes rather than one.

TABLE T.5 — THE TRIALS THAT MOVED A CLASS, AND WHAT THEY MOVED IT TO

TRIAL	WHO WAS IN IT	WHAT WAS COMPARED	WHAT CHANGED IN PRACTICE
SHEP 1991	4,736 patients, mean age 72, isolated systolic hypertension	Chlorthalidone-based treatment against placebo	Five-year stroke fell from 8.2 to 5.2 per 100, RR 0.64 ¹ . Before it, isolated systolic hypertension in an elderly patient was often watched rather than treated. This is the trial that made it a disease.
RALES 1999	1,663 patients with severe HFrEF	Spironolactone 25 mg against placebo, on top of standard therapy	Mortality 35% against 46% ¹⁵ . It re-established the mineralocorticoid receptor as a target after decades in which spironolactone was a niche diuretic, and it is why an MRA is now standard in heart failure.
HOPE 2000	9,297 patients at high cardiovascular risk	Ramipril 10 mg against placebo	A quarter fewer events on a systolic difference of 3.3 mmHg ² . It moved ACE inhibitors out of the category of blood pressure drugs and into the category of risk-reduction drugs — a change in how the class is thought about, not just where it ranks.
PROGRESS 2001	6,105 patients with prior stroke or TIA	Perindopril, with or without indapamide, against placebo	Recurrent stroke fell 43% on the combination but only 5% on perindopril alone ¹⁸ . Two lessons in one trial: treat blood pressure after stroke, and the size of the reduction is what bought the outcome — the combination stratum was not randomised, so it does not show that the combination beats a titrated single drug (T.9).

TRIAL	WHO WAS IN IT	WHAT WAS COMPARED	WHAT CHANGED IN PRACTICE
ALLHAT 2002	33,357 patients aged 55 or over with one other risk factor	Chlorthalidone against amlodipine against lisinopril	No difference on the primary endpoint. Chlorthalidone did better on heart failure than amlodipine (RR 1.38 against it) and lisinopril (RR 1.19) ³ . The largest trial in the field kept thiazide-type diuretics first-line and made “any of these” a defensible answer for everything else.
LIFE 2002	9,222 hypertensives with ECG left ventricular hypertrophy	Losartan-based against atenolol-based	At 144.1/81.3 against 145.4/80.9 mmHg — the same pressure — the composite was 11% against 13% and stroke 5% against 7% ⁵ . It gave ARBs the left ventricular hypertrophy indication and began the demotion of atenolol.
ASCOT-BPLA 2005	19,257 hypertensives with additional risk factors	Amlodipine adding perindopril against atenolol adding bendroflumethiazide	Stroke 3% against 4%, cardiovascular events 14% against 17%, new diabetes 6% against 8% ⁶ . This is the trial that ended beta-blockers as routine first-line therapy in uncomplicated hypertension.
HYVET 2008	3,845 patients aged 80 or over	Indapamide SR, with perindopril as required, against placebo	Heart failure HR 0.36 and all-cause mortality HR 0.79 ¹³ — secondary endpoints; the primary endpoint, stroke, missed conventional significance at $p = 0.055$. It settled a question that had been genuinely open: whether treating hypertension above the age of 80 does more good than harm. It does, and every guideline agrees.

Notice what the middle column contains. ALLHAT randomised the nephron against the channel against the cascade. ASCOT randomised the channel-and-cascade against the sympathetic-and-nephron. LIFE randomised the cascade against the sympathetic limb. **Every one of these trials is a comparison between sites**, and read that way the eight of them are a single experiment about where to interrupt — which is the argument the previous chapter makes on physiological grounds and this one confirms on empirical ones.

T.6 The trials that chose the second drug

Most patients need two drugs, and for a long time the second was chosen by habit. Two trials made it a decision with an answer.

TABLE T.6 — WHICH SECOND DRUG, AND ON WHAT EVIDENCE

	THE TRIAL, AND WHAT IT SETTLED
ACCOMPLISH	11,506 high-risk hypertensives randomised to an ACE inhibitor with amlodipine, or the same ACE inhibitor with hydrochlorothiazide. Events 9.6% against 11.8%, hazard ratio 0.80, at 131.6/73.3 against 132.5/74.4 mmHg ⁸ . Under one millimetre of mercury apart, a fifth fewer events. The pressure was not what differed; the site of the second drug was. Cascade plus channel beat cascade plus nephron.
PROGRESS	The same lesson from the other direction. Perindopril alone reduced recurrent stroke by 5% and did not reach significance; perindopril with indapamide reduced it by 43% ¹⁸ . Both figures are against placebo. The two strata were not randomly assigned and the combination stratum achieved two and a half times more blood-pressure reduction, so this is a reason to think about combination therapy, not evidence that it beats a well-titrated single drug — see T.9.
And the pairing rule they support	Blocking the cascade raises renin, and a diuretic raises it further; each drug moves the patient into the state where the other works best. The mechanism is in the previous chapter. These two trials are the reason to believe it matters.

T.7 The trials that ended a practice

A negative trial is not a failed trial. Three of them removed widely used practices from the field, and between them they have prevented more harm than most positive results have prevented events.

And a fourth, slower demotion, which no single trial delivered but two of them together did. Atenolol was the comparator that lost in LIFE⁵ and lost again in ASCOT⁶, in both cases while achieving essentially the same brachial pressure as the winner. Beta-blockers as a class did not fall out of first-line use because a trial condemned the class. They fell because atenolol kept losing, and the guidelines drew a broader conclusion than the trials strictly supported. **Whether that broader conclusion was fair to the newer vasodilating beta-blockers is a live question**, and Chapter 8 takes it up.

What ACCOMPLISH did not test

Hydrochlorothiazide, not chlorthalidone. Whether the result would survive against the diuretic ALLHAT actually validated is unknown, and anybody who tells you otherwise is arguing from mechanism.

TABLE T.7 — THREE PRACTICES THAT A TRIAL STOPPED

THE PRACTICE	THE TRIAL	WHAT IT FOUND	WHAT IT MEANS NOW
Blocking the cascade at two points at once — an ACE inhibitor together with an ARB, on the reasoning that more complete blockade must be better	ONTARGET	No added benefit over either drug alone, and about a third more renal impairment; a number needed to harm of 30 ^{9,10} .	Do not combine them for blood pressure. This is one of the few near-absolute combination rules in hypertension, and it holds because of a trial rather than a theory. The regulators stop short of a ban: the licensed exception is candesartan or valsartan added to an ACE inhibitor in heart failure, under specialist supervision with close monitoring ²⁵ .
Adding a renin inhibitor to existing RAAS blockade in diabetic patients — the same reasoning, applied one station further upstream	ALTITUDE	Stopped early. More hyperkalaemia, more hypotension, no benefit ¹¹ .	The direct renin inhibitors have essentially no role. The reasoning that produced them was elegant and it was wrong, twice.
Alpha-blockers as first-line therapy, which was common practice and looked reasonable	ALLHAT's doxazosin arm	Discontinued early after interim analysis: in 24,335 patients, doxazosin against chlorthalidone doubled heart failure, RR 2.04 ⁴ , with no difference on the primary endpoint.	Alpha-blockers survive as add-on agents, particularly where prostatic symptoms coexist. They are not a first choice. Chapter 9.

T.8 How decisive was it? — the margin behind each recommendation

A guideline sentence reads exactly the same whether the trial behind it was a rout or a photo finish. “A thiazide-type diuretic, calcium channel blocker, ACE inhibitor or ARB may be used as initial therapy” and “an ACE inhibitor and an ARB should not be combined” arrive in the same typeface, in the same tone, from the same committee. One of them rests on a dead heat between three drugs in 33,357 patients. The other rests on a trial that found harm. **Knowing which is which is the difference between following a guideline and understanding it**, and it decides how much room a clinician has to think.

Five things make a result decisive, and they can be checked on any trial in a minute: was the finding on the *primary* endpoint; was the comparison *randomised*; how large was the *absolute* difference; did *more than one* study find it; and does anything good *disagree*. Together they sort the recommendations in this volume onto a five-point scale, which the rest of this chapter and every chapter after it uses.

TABLE T.8 — A FIVE-POINT SCALE FOR HOW MUCH A RECOMMENDATION IS WORTH

	WHAT IT MEANS, AND WHAT YOU MAY DO WITH IT
Grade A Settled	Primary endpoint, randomised comparison, large absolute difference — or a harm signal, which is one-sided and needs no margin at all. Replicated, or halted early for safety. No latitude. Follow it.
Grade B Strong default	Primary endpoint met, randomised, moderate absolute difference, but resting on a single trial or a single population. Latitude only for a reason specific to this patient — intolerance, contraindication, cost.
Grade C Weak default	A secondary endpoint, or a small absolute difference, or a caveat about the comparator or the population that the recommendation does not carry with it. Genuine latitude. Choose either, and be able to say why.
Grade D Dead heat	The trial was done, and found no difference on its primary endpoint. Full latitude, granted by the evidence itself. Decide on phenotype, tolerability, cost and adherence, which is exactly what the rest of this volume is for.
Grade E Not a trial finding	A convention, an extrapolation, or an inference from which drug happened to be studied. Often sensible. Reason from mechanism, and know that is what you are doing.

One point about Grade C is worth separating out, because the two ways of being weak are frequently confused. **A finding can be weak in its position in the hierarchy without being weak in its precision.** ALLHAT's heart-failure result — relative risk 1.38 for amlodipine against chlorthalidone, with a confidence interval of 1.24 to 1.52, in 33,357 patients³ — is statistically about as solid as a number gets. It is Grade C because it is a secondary endpoint in a trial whose primary endpoint showed nothing, not because the estimate is shaky. A different Grade C finding may be weak in the opposite way: a primary endpoint with wide confidence intervals in three hundred patients. Both deserve latitude, and for opposite reasons.

TABLE T.9 — THE MARGIN BEHIND EACH RECOMMENDATION, AND THE LATITUDE IT LEAVES

THE RECOMMENDATION	WHAT THE EVIDENCE ACTUALLY SHOWED	GRADE	YOUR LATITUDE
Do not combine an ACE inhibitor with an ARB	No added benefit over either alone, and about a third more renal impairment; number needed to harm 30 ^{9,10} .	A — a harm signal, which is one-sided and needs no margin.	Almost none, and none at all in hypertension. The single licensed exception is an ARB added to an ACE inhibitor in heart failure, under specialist supervision ²⁵ .
Never add a renin inhibitor to RAAS blockade in diabetes	Stopped early for hyperkalaemia and hypotension with no benefit ¹¹ .	A — halted by its own safety board.	None.
An MRA in heart failure with reduced ejection fraction	Mortality 35% against 46% ¹⁵ — an eleven-point absolute difference — and the class benefit extended to milder disease, where eplerenone reduced cardiovascular death or heart-failure admission from 25.9% to 18.3% ¹⁶ .	A — among the largest absolute effects in this book, and replicated.	None on whether. Only on which agent, and on the potassium.
Spirolactone as the fourth drug in resistant hypertension	Beat placebo, doxazosin and bisoprolol, all at $P < 0.0001$, in a randomised crossover ¹² .	A — decisive against every comparator tested.	Only where potassium or renal function forbids it.
Treat isolated systolic hypertension in the elderly	Five-year stroke 5.2 against 8.2 per 100, RR 0.64 ¹ .	A — and it overturned a practice of leaving these patients alone.	None on whether to treat.

THE RECOMMENDATION	WHAT THE EVIDENCE ACTUALLY SHOWED	GRADE	YOUR LATITUDE
Treat hypertension above the age of 80	All-cause mortality HR 0.79, heart failure HR 0.36 ¹³ — both secondary endpoints; the primary endpoint, stroke, fell about 30% at $p = 0.055$ and missed conventional significance.	B — on a question that was genuinely open before it, but carried by secondary endpoints in a trial stopped early for benefit.	On the target and the pace. Not on whether.
A RAAS blocker in diabetic nephropathy	End-stage renal disease 19.6% against 25.5%, doubling of creatinine 21.6% against 26.0% ¹⁴ .	B — primary composite met, one trial, moderate margin.	Which one — ACE inhibitor or ARB. Not whether.
A calcium channel blocker rather than a thiazide as the second drug	Events 9.6% against 11.8%, hazard ratio 0.80 ⁸ .	B/C — primary endpoint met, but the comparator was hydrochlorothiazide, not the chlorthalidone that ALLHAT validated.	Real. If your diuretic is chlorthalidone, this trial did not test your question.
Combination therapy rather than one drug after stroke	Recurrent stroke fell 43% in the combination stratum and 5% on perindopril alone ¹⁸ — a difference that looks enormous. But the two strata were not randomly assigned: the treating physician decided before randomisation who would receive the diuretic, and each stratum was then randomised only against placebo. The combination also lowered pressure 12.3/5.0 against 4.9/2.8 mmHg.	C — the 43% is a real randomised result <i>against placebo</i> . The comparison with 5% is between two non-randomised groups getting different amounts of blood pressure reduction.	Treat blood pressure after stroke: no latitude. Believe that the combination is intrinsically better than a well-titrated single drug: not established here.
Beta-blockers are not first-line in uncomplicated hypertension	Atenolol lost in LIFE and again in ASCOT, both times at essentially matched brachial pressure ^{5,6} .	C — clear against atenolol; the extension to the whole class was never tested.	Real, particularly for the vasodilating agents. Chapter 8.
An ACE inhibitor rather than an ARB	A meta-analysis of 158,998 patients found an all-cause mortality reduction for ACE inhibitors that ARBs did not show ²⁰ . ONTARGET found telmisartan and ramipril equivalent ⁹ .	C — genuinely disputed. Two good analyses, different answers.	Full. In practice the cough decides it, and that is a defensible way to decide it.
Which class to start in uncomplicated hypertension	Primary endpoint 11.5%, 11.3% and 11.4% for chlorthalidone, amlodipine and lisinopril ³ . A dead heat. Heart failure was commoner on amlodipine, RR 1.38 (95% CI 1.24–1.52), and on lisinopril, RR 1.19 (1.07–1.31) — a secondary endpoint, precisely estimated.	D on which class, C on the heart-failure advantage.	Full. This is where phenotype, tolerability and cost legitimately decide, and most of this volume lives in this row.
Chlorthalidone rather than hydrochlorothiazide	For years this was an inference rather than a finding: chlorthalidone was preferred because it was the molecule ALLHAT and SHEP happened to study ^{3,1} . It has since been tested. The Diuretic Comparison Project randomised 13,523 patients and found major cardiovascular events in 10.4% against 10.0%, hazard ratio 1.04 — with more hypokalaemia on chlorthalidone, 6.0% against 4.4% ²¹ .	D — a dead heat, where the field expected a win. It was Grade E until 2022.	Full. Do not switch a controlled patient. Chapter 5.

The PROGRESS row is the one to study, because it is the trap this whole chapter exists to teach. Forty-three per cent against five per cent is the largest-looking contrast in this book, and a reader who quotes it as evidence that two drugs beat one has been fooled by a table. The 43% is real and it is randomised

— against placebo. The comparison with the 5% is between two groups a doctor sorted by hand, one of which got two and a half times more blood pressure reduction¹⁸. **The conclusion “treat blood pressure after stroke” is Grade A. The conclusion “the combination is intrinsically superior” is not established by this trial at all, however large the two numbers look side by side.**

Read the third column downwards and the volume splits in two. The top half is a set of instructions with no room in them: a clinician who departs from those rows is not exercising judgement, because there is no judgement left to exercise — a trial already answered the question, often by finding harm. The bottom half is a set of *defaults*, some of which rest on a single trial, one of which rests on a comparison that came out level, and one of which is not a trial finding at all. **In the bottom half a thoughtful clinician may choose the other option, and should be able to say why.**

One row in that table moved while this volume was being written, which is the best argument for the whole exercise. The chlorthalidone preference was Grade E — an inference from which drug the evidence happened to be about — until somebody randomised 13,523 patients and found no difference²¹. A reader who had graded it honestly would have been unsurprised. A reader who had been repeating it as though it were established would have been wrong for twenty years. This is also the honest answer to a question every reader has asked themselves at some point: how much does it matter if I prescribe the second-named drug rather than the first? For the top rows the answer is that it matters a great deal, and the trial will tell you exactly how. For the bottom rows the answer is that the difference between the two drugs is smaller than the difference between a patient who takes the tablets and one who does not — which puts the fourth filter of the previous chapter, adherence, back at the centre of the decision.

One boundary has to be drawn around all of this, and it is not a clinical one. Everything above concerns the space in which a clinician is entitled to exercise judgement. Where a treatment protocol is *mandatory* rather than advisory — a national or state programme protocol, an institutional formulary, a scheme or insurer’s approved list, a departmental standing order — the grade of the underlying evidence is beside the point. A Grade D dead heat does not authorise departing from a protocol you are required to follow; it only tells you why the protocol could reasonably have gone either way. If a mandated protocol seems wrong, the route is to say so through whatever mechanism reviews it, and to document the individual patient’s clinical reason where an exception is permitted — not to quietly substitute.

Within that boundary, though, the scale does exactly what a thoughtful clinician needs. Where the guideline is advisory and the grade is C, D or E, you are weighing two considerations that the evidence itself declined to separate — and if one of them clearly outweighs the other in the patient in front of you, choosing on that basis is not a deviation from evidence-based practice. It is evidence-based practice, correctly understood.

T.9 The same pressure, different outcomes

Everything so far has treated blood pressure as the quantity being reduced. The most important thing the trials collectively show is that it is not. Two regimens can produce the same cuff reading and different numbers of strokes, and once that is accepted the whole basis of drug selection changes: **the number is a proxy, and the drug is chosen for the damage it prevents rather than for the millimetres it removes.**

Three trials make the point, and the third makes it unanswerable. CAFE is the mechanistic explanation of ASCOT’s clinical result, and it is the single best argument in this book for reading past the cuff. A beta-blocker slows the heart, which shifts the timing of the reflected pressure wave so that it arrives during systole and augments central pressure — a physiological cost invisible to the brachial reading. The physics is in VI-Ch1. The trial is what makes it matter.

Three questions, no table needed

Was it the primary endpoint? Was the comparison actually randomised? How big was the absolute difference, and does anything good disagree? A primary randomised endpoint with a large difference and no contradiction means follow it. Anything else means you are choosing a default — unless a protocol you are bound by has already chosen for you.

TABLE T.10 — SAME PRESSURE, DIFFERENT RESULT

	WHAT WAS ACHIEVED, AND WHAT DIFFERED
LIFE	144.1/81.3 against 145.4/80.9 mmHg — a difference of about one millimetre. Stroke 5% against 7%, a 25% relative reduction, and new-onset diabetes 6% against 8% ⁵ . The pressures were the same. The strokes were not.
ACCOMPLISH	131.6/73.3 against 132.5/74.4 mmHg. Events 9.6% against 11.8% ⁸ . Under a millimetre apart, a fifth fewer events, and the only difference was which site the second drug acted on.
CAFE	2,073 patients from ASCOT. Brachial systolic pressure was <i>identical</i> — 133.2 against 133.9 mmHg. Central aortic systolic pressure was not: 121.2 against 125.5 mmHg, and central pulse pressure 43.4 against 46.4 ⁷ . The cuff on the arm and the pressure at the aortic root are different quantities, and drugs move them differently. The heart, the brain and the kidney experience the central pressure, and the clinician measures the peripheral one.

T.10 What you are protecting, not what you are lowering

This is the filter that most clearly separates a specialist’s prescription from a competent first-contact one, and it was missing from the four filters of the previous chapter for a reason: it cannot be applied without the trials in this one. The question is not *will this drug lower the pressure*. Every drug in this book lowers the pressure. The question is **which of this patient’s organs is being damaged, and does this class have evidence of protecting that organ?**

How to use this without over-claiming

It does not mean the cuff is useless; it means two drugs achieving the same cuff reading are not interchangeable. Where a guideline names several classes and the trials distinguish them on outcome, choose on the outcome rather than on which lowers the number fastest.

TABLE T.11 — THE ORGAN, THE EVIDENCE, AND THE CLASS IT NAMES

WHAT YOU ARE PROTECTING	WHY IT IS A TARGET IN ITS OWN RIGHT	THE EVIDENCE, AND THE CLASS IT NAMES
The left ventricle — hypertrophy and its regression	Left ventricular hypertrophy is not a passive marker of past pressure. It carries risk of its own, and reversing it appears to remove some of that risk.	A meta-analysis of 2,449 hypertensive patients found an adjusted hazard ratio of 0.54 for total cardiovascular events in those whose hypertrophy regressed compared with those in whom it persisted or developed ²⁴ . LIFE is the trial that attached a class to this: an ARB, in a population selected for ECG hypertrophy ⁵ . <i>The meta-analysis reports the association; it does not establish that regression is what caused the benefit.</i>

WHAT YOU ARE PROTECTING	WHY IT IS A TARGET IN ITS OWN RIGHT	THE EVIDENCE, AND THE CLASS IT NAMES
The kidney — albuminuria and the rate of GFR loss	A patient can be at target and still be losing nephrons. Proteinuria is both the marker and part of the mechanism of that loss.	RENAAL, in type 2 diabetic nephropathy: doubling of creatinine 21.6% against 26.0%, end-stage renal disease 19.6% against 25.5% ¹⁴ — an ARB. FIDELIO-DKD, in patients already on maximal RAAS blockade: renal composite 17.8% against 21.1% ¹⁷ — finerenone, a second site added to a blocked one.
The heart as a pump — preventing incident heart failure	Heart failure is the hypertensive complication that most reliably follows uncontrolled pressure, and the one on which the classes differ most.	ALLHAT: heart failure was commoner on amlodipine (RR 1.38) and on lisinopril (RR 1.19) than on chlorthalidone ³ . HYVET, in the over-80s: HR 0.36 for heart failure on indapamide-based treatment ¹³ . Where preventing heart failure is the priority, the nephron is the site with the evidence.
The brain — first and recurrent stroke	Stroke is the outcome most sensitive to blood pressure in absolute terms, and the dominant hypertensive complication in Indian practice.	SHEP in isolated systolic hypertension: RR 0.64 ¹ . PROGRESS after stroke or TIA: 43% on perindopril with indapamide, and only 5% on perindopril alone ¹⁸ . LIFE: fewer strokes at the same pressure ⁵ .
The metabolism — not causing the next disease	A drug that controls pressure and produces diabetes has moved the problem rather than solved it. In a population with India's diabetes prevalence this is not a footnote.	ASCOT: new-onset diabetes 6% against 8%, HR 0.70, for amlodipine-based against atenolol-based treatment ⁶ . LIFE: 6% against 8%, HR 0.75, for losartan against atenolol ⁵ . The same finding twice, with the same losing comparator.
The arterial tree — central pressure and wave reflection	What the aortic root sees, which is what the heart is loaded by and what the brain's small vessels are exposed to.	CAFE: identical brachial pressure, central systolic 121.2 against 125.5 mmHg ⁷ . No routine measurement exists in ordinary practice, so this operates as a reason to prefer a class rather than a target to titrate to.

Used honestly, this table changes prescriptions. A 60-year-old with hypertension and echocardiographic hypertrophy and a 60-year-old with hypertension and albuminuria may reach the same target on the same number of tablets, and should not necessarily be on the same tablets. That is what a superspecialist is doing when the choice looks arbitrary from outside. But the table has a ceiling worth marking: several of these findings are secondary endpoints, one is a meta-analysis of observational follow-up, and all of them come from populations that were not Indian. **They are reasons to prefer a class where the guideline leaves the choice open, and never reasons to override a guideline that has already spoken.**

T.11 Where the trials run out

A book that quotes trials well must also be clear about where it stops quoting them, because the questions a working clinician asks most often are precisely the ones nobody randomised.

TABLE T.12 — THE QUESTIONS WITH NO TRIAL BEHIND THEM

	WHAT EXISTS INSTEAD, AND WHAT THIS BOOK DOES
Which molecule within a class?	Head-to-head outcome trials between molecules of the same class are almost non-existent. What exists is pharmacokinetics, tolerability data and the occasional blood-pressure comparison. This book uses those, labels them as what they are, and does not present a half-life as though it were an endpoint.
What time of day to give the dose?	Chronotherapy trials exist and disagree with each other. The reasoning in this volume rests on duration of action and the morning surge, which is physiology, and it is presented as physiology.
What to do at the fifth drug?	Beyond spironolactone the evidence thins sharply, and beyond that there is essentially expert practice. The opening chapter's completeness audit is a reasoning procedure, not a trial result.

	WHAT EXISTS INSTEAD, AND WHAT THIS BOOK DOES
Which drug for an Indian patient specifically?	Very little. Almost every trial in this chapter enrolled predominantly European or North American populations. The commonest honest answer in this book is that the trial is the best available evidence about a related population — and where an Indian study exists, it is named as such.
Which fixed-dose combination?	The combinations that dominate Indian prescribing were largely not the combinations that were trialled. ACCOMPLISH tested a specific pair at specific doses; a marketed single pill resembling it is not the same intervention, and the book does not pretend otherwise.

This is the space the previous chapter was written for. Where a trial has spoken, quote the trial. Where it has not, reason from the site — carefully, explicitly, and with the label attached. **The failure mode this book tries hardest to avoid is a physiological argument presented in the voice of an endpoint.**

T.12 Every class, its trial, its verdict

One page. For each class: the trial a reader should be able to name, what it showed, and where the class consequently sits. The chapter given is where the full argument lives.

TABLE T.13 — THE EVIDENCE BEHIND EACH CHAPTER OF THIS VOLUME

CLASS	CHAPTER	NAME THIS TRIAL	AND IT SHOWED
ACE inhibitors	1	HOPE	A quarter fewer events on a 3.3 mmHg difference in 9,297 high-risk patients ² . Supported by a mortality signal on meta-analysis that the ARBs did not show ²⁰ .
ARBs	2	LIFE	Fewer strokes than atenolol at the same pressure, in patients with left ventricular hypertrophy ⁵ . RENAAL adds the renal indication ¹⁴ .
Direct renin inhibitors	3	ALTITUDE	Harm, and early termination ¹¹ . The class is in this book as a lesson, not as an option.
Calcium channel blockers	4	ASCOT-BPLA	Amlodipine-based treatment beat atenolol-based on stroke, events and new diabetes ⁶ . ACCOMPLISH makes it the preferred second drug ⁸ .
Thiazide and thiazide-like diuretics	5	ALLHAT	Equal on the primary endpoint, better on heart failure, in 33,357 patients ³ . SHEP and HYVET add the elderly and the very elderly ^{1,13} .
Loop diuretics	6	—	No outcome trial in hypertension. The class is used on heart failure and CKD grounds, and this book says so rather than implying evidence it does not have.
Mineralocorticoid antagonists	7	PATHWAY-2	The best fourth drug in resistant hypertension ¹² . RALES and EMPHASIS-HF carry the heart failure indication ^{15,16} ; FIDELIO-DKD the renal one ¹⁷ .
Beta-blockers	8	LIFE and ASCOT	Lost to an ARB and to a calcium channel blocker at matched pressure ^{5,6} — both times as atenolol. Retained where a compelling indication names them.
Alpha-blockers	9	The ALLHAT doxazosin arm	Stopped early: heart failure RR 2.04 against chlorthalidone ⁴ . An add-on, not a first choice.
Central agents	10	—	No modern outcome trial. Methyl dopa's place in pregnancy rests on long safety experience rather than on an endpoint trial, which is a legitimate but different kind of evidence.

CLASS	CHAPTER	NAME THIS TRIAL	AND IT SHOWED
Direct vasodilators and IV agents	11	—	Largely no randomised outcome evidence. These drugs are used for speed and control in situations where a placebo arm would be unethical. Volume 3 covers the settings.

Three of the eleven rows have no trial. That is not a gap in this book; it is the state of the field, and a reader who knows which three they are will prescribe more carefully than one who assumes all eleven rest on the same footing.

KEY POINTS

- 1 The chain runs trial → guideline → prescription. Mechanism explains the result afterwards and fills the gaps; it never authorises a drug on its own.
- 2 A trial settles one class, against one comparator, in one population, on one endpoint. All four qualifiers limit the claim, and the fourth is the one most often dropped when the result is quoted.
- 3 Ask of any trial: what was the comparator, who was enrolled, was the endpoint primary, and is the number relative or absolute.
- 4 ALLHAT randomised the nephron against the channel against the cascade; ASCOT and LIFE randomised sites too. Read that way the major trials are one long experiment about where to interrupt.
- 5 ALLHAT's primary endpoint showed no difference between three classes. Its famous heart-failure advantage for chlorthalidone is a secondary endpoint — believable, and still secondary.
- 6 ACCOMPLISH chose the second drug: a calcium channel blocker rather than a thiazide alongside an ACE inhibitor, a fifth fewer events at under a millimetre of difference.
- 7 Three negative trials removed three practices: ONTARGET ended dual RAAS blockade, ALTITUDE ended the renin inhibitors, and ALLHAT's doxazosin arm ended alpha-blockers as first-line.
- 8 Beta-blockers were demoted because atenolol lost twice, in LIFE and ASCOT, at the same brachial pressure. Whether that verdict is fair to the vasodilating beta-blockers is still open.
- 9 CAFE found identical brachial pressures and a 4.3 mmHg difference in central aortic systolic pressure. The cuff and the aortic root are different quantities.
- 10 Choose the drug for the organ you are protecting, not the number you are lowering — ventricle, kidney, brain, pump, metabolism. That filter needs the trials, which is why it is in this chapter and not the last one.
- 11 Three of the eleven classes in this volume have no outcome trial in hypertension at all — loop diuretics, the central agents, and the direct vasodilators and intravenous agents. Knowing which three is part of prescribing them honestly.

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How the Guideline Was Made

Most doctors know *what* the guideline says. Far fewer know *who* wrote it, *from what* evidence, *how strong* that evidence was, and *where* the committee itself expected you to use your judgement. This chapter is about the difference.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 What a guideline is, what it is not, and who is in the room when it is written.
- 2 How to read a recommendation: what class of recommendation and level of evidence actually mean.
- 3 Why three respectable guidelines disagree about the same patient, and what the disagreement is really about.
- 4 Which guidance an Indian physician should follow, and what the India Hypertension Control Initiative protocol shows.
- 5 What a committee does when the trials are silent — and how to tell when that has happened.
- 6 A procedure for answering: is there a trial for the patient in front of me?
- 7 Where a guideline may legitimately be departed from, and how to record that you did.
- 8 Why this skill transfers to every other disease you treat — and what has been measured about how many physicians have it.

G.1 What a guideline is, and what it is not

A guideline is a committee's summary of a literature, written for a population, at a moment in time. Every word of that sentence limits it. A **committee** means people with reputations, specialties and disagreements. A **summary** means compression, and compression loses the margins that the previous chapter spent so long recovering. A **population** means the one the committee had evidence about, which is rarely the one in front of an Indian physician. **At a moment in time** means it was already partly out of date when it was printed.

None of that is a criticism. A guideline is the most useful document in clinical medicine, because it does work no individual clinician can do: it reads several hundred trials properly, argues about them, and returns a defensible default. The error is not in trusting it. The error is in treating it as though it were a single kind of statement, when in fact it contains at least three kinds — things a trial proved, things a trial suggested, and things the committee decided because a doctor somewhere has to do something and no trial exists.

A clinician who cannot tell those three apart is following the guideline. A clinician who can tell them apart is using it, and the difference shows up in exactly the situations where the guideline does not fit — which, in a busy Indian outpatient department, is most of them.

G.2 Reading a recommendation

Every major guideline attaches two labels to each recommendation, and most readers skip both. They are the compressed form of everything the previous chapter took twelve pages to say, and once you can read them you can see the margin behind a recommendation without going to the trial.

The class of recommendation says how strongly the committee believes you should do it. **The level of evidence** says what the belief rests on. They are independent: a Class I recommendation on Level C evidence is a committee saying “do this” on the strength of its own opinion, which happens more often than most readers assume.

TABLE G.1 — THE TWO LABELS, AND WHAT EACH IS ACTUALLY CLAIMING

LABEL	THE STANDARD WORDING	WHAT IT MEANS WHEN YOU ARE PRESCRIBING
Class I	“Conditions for which there is evidence for and/or general agreement that a procedure or treatment is beneficial, useful, and effective” ⁴	Do it. Departing from this needs a specific reason in this patient, and the reason should be recordable.
Class IIa	“Weight of evidence/opinion is in favour of usefulness/efficacy” ⁴	Reasonable to do. This is where two competent clinicians may differ without either being wrong.
Class IIb	“Usefulness/efficacy is less well established by evidence/opinion” ⁴	May be considered. Read this as the committee telling you it is genuinely unsure.
Class III	“Evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful” ⁴	Do not. The dual-blockade rule from ONTARGET ⁸ lives here, and rules in this class are the ones with no latitude at all.
Level A	“Data derived from multiple randomized clinical trials or meta-analyses” ⁴	The strongest footing available. More than one trial found it.
Level B	“Data derived from a single randomized trial or nonrandomized studies” ⁴	One trial. Ask the four questions of the previous chapter before treating it as settled.
Level C	“Only consensus opinion of experts, case studies, or standard-of-care” ⁴	Expert opinion. Often sensible, occasionally wrong, and not evidence. A great deal of what clinicians believe is guideline-mandated sits here.

The pairing is what carries the information. **Class I Level A** is an instruction: several trials, strong agreement, no room. **Class IIa Level B** is a default: one trial, a committee leaning one way, and a legitimate alternative. **Class IIb Level C** is a suggestion in the costume of a recommendation, and a clinician who deviates from it is not deviating from evidence. Newer versions of the scheme subdivide these labels further, but the three-way distinction is the one that changes what you do.

G.3 Why respectable guidelines disagree

A reader who has followed the argument this far will already suspect the answer: they disagree because compressing the same evidence into a single instruction requires judgements the evidence does not make. Four major guidelines are current — the American document was revised in 2025, and the European Society of Cardiology issued its own in 2024 alongside the European Society of Hypertension’s of 2023 — and the differences between them are informative rather than embarrassing. The American row below describes the 2017 document, whose structure the 2025 revision keeps; where the 2025 numbers differ, Volume 1 and Volume 3 carry them.

What this chapter is not

It is not a summary of any guideline. Guidelines change and this book would date. It is a set of tools for reading whichever guideline is current when you read this.

The habit worth forming

When a colleague quotes a guideline at you, ask which class and which level. It is not a hostile question. Half the time the answer is that neither of you knows, and looking it up takes a minute and settles the argument.

TABLE G.2 — FOUR GUIDELINES, FOUR JOBS

GUIDELINE	WHAT IT IS OPTIMISING FOR	WHERE THAT LEADS IT
ACC/AHA (United States) ¹	Preventing events across a well-resourced population in which risk scoring, ambulatory monitoring and follow-up are all available.	A lower diagnostic threshold and lower targets, which reclassifies a large number of people as hypertensive and treats risk aggressively. Defensible where the system can carry the follow-up.
ESH (Europe) ²	The same events in a population with universal health systems and a longer tradition of ambulatory monitoring, with more caution about labelling.	Thresholds and targets that are close to but not identical with the American ones, and more explicit treatment of the elderly, of out-of-office measurement, and of where the evidence is weak.
ESC (Europe, 2024) ¹²	Treating measured risk rather than a diagnostic label, in a population where standardised measurement and follow-up are available.	A new category of elevated blood pressure at 120–139/70–89, a treated systolic target of 120–129 where tolerated, and an explicit carve-out for age 85 and over, frailty and orthostatic symptoms. The most ambitious targets of the four, the most recent, and the one most likely to be quoted at you.
ISH (global) ³	Being usable everywhere, including where there is no ambulatory monitor, no risk calculator and a limited drug list.	An explicitly two-tier structure: an <i>essential</i> standard for constrained settings and an <i>optimal</i> standard where resources allow. For much of Indian practice this is the most honest of the three.

The differences between them are rarely about the trials. They are about thresholds, about how much of a population to label, about how much follow-up the system can deliver, and about how much certainty is required before writing “should” rather than “may”. **Where two guidelines disagree, the underlying trial is usually the same trial**, and the disagreement is about how far to extend it.

This has a practical consequence that matters more than the theory. When a patient arrives having been told by another doctor that their target is different, the second doctor is usually not wrong — they are following a different guideline, or the same guideline read with a different appetite for risk. The useful response is to find out which, and then to have the conversation about this patient rather than about the literature.

G.4 Which guidance for an Indian patient

The honest starting point is that none of the three guidelines above was written about the patient in an Indian outpatient department, and their trials did not enrol many. That is not a reason to ignore them. It is a reason to know what has been shown here.

The **India Hypertension Control Initiative** is the most useful thing to know, because it is a programme rather than an opinion, and because it reports numbers. It replaced clinical freedom with a drug- and dose-specific standard treatment protocol in public facilities, and measured what happened. In Punjab and Maharashtra in 2022, among 159,292 patients, 70% and 76% respectively were controlled at the first step of the protocol, rising to 75% and 81% by the second⁵.

TABLE G.3 — THE IHCI STANDARD TREATMENT PROTOCOL, AS REPORTED

STEP	PUNJAB	MAHARASHTRA
1	Amlodipine 5 mg	Amlodipine 5 mg
2	Amlodipine 10 mg	Add telmisartan 40 mg
3	Add telmisartan 40 mg	Telmisartan 80 mg
4	Telmisartan 80 mg	Amlodipine to 10 mg
Then	Add chlorthalidone	Add chlorthalidone

Two things about that protocol deserve a reader’s attention, and they pull in opposite directions.

The first is that the drugs were chosen on **cost and availability**⁵, not on a claim of superiority — and that this is a perfectly respectable basis, because ALLHAT established that the major first-line classes do not differ on the primary endpoint⁶. Choosing the cheapest available member of a set the evidence says is equivalent is not a compromise. It is the correct reading of the evidence. A physician who insists on a costlier agent inside the same class, in a patient with no compelling indication, is departing from the evidence rather than upholding it.

The second is that two neighbouring states, running the same programme against the same evidence, put the drugs in a different order — Punjab titrating amlodipine to full dose before adding telmisartan, Maharashtra adding the second drug earlier. Both achieved control in around three quarters of patients. **That is what a genuinely open choice looks like when two committees make it independently**, and it is the ALLHAT dead heat expressed as an administrative decision.

G.5 What a committee does when the trials are silent

This is the part of guideline-writing that is invisible in the finished document, and it is where a careful reader gains the most. A committee cannot leave a common clinical question unanswered simply because nobody randomised it — a doctor will face that question tomorrow morning. So it answers, and the answer is labelled Level C, and it then circulates in exactly the same voice as everything else.

What this does not settle
 The IHCI reports blood pressure control, not cardiovascular events. It is strong evidence that a simple protocol delivers control at scale in Indian public facilities. It is not evidence that this protocol prevents more strokes than another, and it does not claim to be.

TABLE G.4 — FOUR RECOMMENDATIONS, AND WHAT IS ACTUALLY BEHIND THEM

	WHAT IT RESTS ON
“Start two drugs when pressure is more than 20/10 above target”	A sensible arithmetic argument — one drug will not close that gap — supported by the general observation that combination therapy outperforms dose escalation. Not a randomised comparison of the two strategies at that specific threshold. The number 20/10 is a convention.
“Spironolactone is the preferred fourth drug”	A genuine trial, and an unusually clean one ¹¹ . This is what a single clean randomised trial looks like — Level B on the scale in G.1, and stronger than most Level B recommendations because the comparators were active and the endpoint was blood pressure, not an outcome. It is worth contrasting with the row above.
“Review in four weeks after starting or changing”	Pharmacology — most agents are near steady state by then — plus practical sense. The interval is a convention, not a trial result, and it can be moved for a specific patient without any breach of evidence.
“Aim below 130/80 in most adults”	SPRINT, extended ⁷ . The trial used a specific measurement method and enrolled a specific high-risk, non-diabetic population, and the recommendation reaches further than the trial does. The extension may well be right; it is still an extension, and the difference matters most in the frail patient. Volume 3.

The lesson is not to distrust guidelines. It is that **a recommendation’s confidence and its evidence are two separate things**, and only one of them is printed in bold. When a recommendation does not fit the patient in front of you, the first question is which of these four kinds it is — because departing from the first and third rows costs nothing, and departing from the second is a decision you should be able to defend.

G.6 Is there a trial for my patient?

This is the question the whole of Opening 2 was written to make askable, and it deserves a procedure rather than a sentiment. It takes a few minutes, it can be done on a phone between patients, and it is the single habit that most reliably separates a doctor who is keeping up from one who stopped reading a decade ago.

TABLE G.5 — A PROCEDURE, IN FIVE STEPS

	WHAT TO DO
1	Name the population precisely. Not “hypertension” but “type 2 diabetes with albuminuria”, “isolated systolic hypertension over 80”, “uncontrolled on three drugs including a diuretic”. The precision of the question determines whether an answer exists, and most searches fail here rather than at the search box.
2	Name the comparison you actually face. Not “does this drug work” but “this drug against that one, in this patient”. A trial answers comparisons, so a question phrased as a comparison is the one a trial can answer.
3	Look for the trial before the review. A trial name, its population and its primary endpoint will tell you more in two minutes than a review will in twenty — and the chapter you are reading in this volume names the trial for each class. Start there.
4	Apply the four questions. Comparator, population, primary or secondary endpoint, absolute or relative. If the trial fails on population — and for an Indian patient it often will — you are extending rather than applying, which is usually reasonable and should be conscious.
5	Decide what the absence of a trial means. Sometimes it means nobody has asked. Sometimes it means the question was asked and the answer was negative and quietly buried. And sometimes it means the question is too granular ever to be randomised — which molecule, what time of day — in which case reason from the site, and know that you are doing so.

The reason to build this habit is not scholarship. It is that a doctor who can find the trial can also tell when a colleague, a representative, or a very confident piece of software is quoting one that does not say what they claim.

That is a defensive skill as much as an academic one, and it is becoming more useful, not less.

G.7 The skill is not about hypertension

Nothing in the last two chapters is specific to blood pressure. The grade scale, the four questions, the distinction between a primary and a secondary endpoint, the difference between a randomised comparison and two groups a clinician sorted by hand — all of it applies unchanged to the statin argument, to the glycaemic target argument, to subclinical thyroid disease, to when to start dialysis, to anticoagulation in atrial fibrillation. A physician who acquires the habit here will use it everywhere, and that is a larger prize than better hypertension prescribing.

It is fair to ask whether this is already standard equipment among specialist physicians — whether a chapter like this is teaching what postgraduate training already teaches. The measured answer is uncomfortable, and it is better stated with numbers than with an opinion.

TABLE G.6 — WHAT HAS BEEN MEASURED ABOUT APPRAISAL SKILL

	WHAT WAS FOUND
Internal medicine residents	277 residents across 11 programmes scored a mean of 41.4% correct on a test of biostatistics and interpretation of research results. Fellows and general medicine faculty with research training scored 71.5% ⁹ .
Family physicians in practice	Of 286 respondents to a survey of Ontario family physicians, just over half could satisfactorily answer questions on critical appraisal of methods and interpretation of results. The ability to calculate a number needed to treat, or sensitivity and specificity, was in the range of 47–57% even when the numbers required were supplied ¹⁰ .

Two cautions before anyone draws a conclusion from those figures. They are North American, from surveys with modest response rates, and the older of them is now some years old — postgraduate curricula have changed since. And a mean score on a written test is not the same thing as clinical competence: a physician who cannot compute a number needed to treat on paper may still prescribe extremely well, because good practice draws on pattern recognition and experience that a statistics question does not measure.

What the numbers do support is narrower and still worth saying. **Appraisal skill is not evenly distributed, and it does not arrive automatically with a postgraduate degree.** The gap between residents at 41% and research-trained faculty at 71% is a gap produced by training in appraisal specifically, not by seniority or by clinical exposure. That is encouraging rather than discouraging: it means the skill is teachable, and that a reader who works through the grade scale in Opening 2 is acquiring something that a substantial number of practising physicians were never explicitly taught.

G.8 When you may depart from the guideline

This section could be misread, so it is written carefully. Nothing in this volume is a licence to prescribe against a guideline because a mechanism seemed more interesting. The commonest cause of poor hypertension control is

And the honest limit
For a great many questions the answer will be that no trial exists for this patient. That is not a failure of the search. It is the state of the field, and Opening 2 ends with a table of exactly where it applies.

not excessive deference to guidelines; it is not following them at all. But there are situations in which departing is correct, and a clinician who cannot name them will either never depart, or depart for bad reasons.

What to do with this

Take one recommendation you follow without thinking — in any disease — and find the trial behind it. Ask the four questions. Most of the time it will hold. Occasionally it will turn out to be a convention, an extrapolation, or a secondary endpoint, and you will have learned something you cannot unlearn.

TABLE G.7 — DEPARTING FROM A GUIDELINE: WHEN IT IS REASONING, AND WHEN IT IS DRIFT

THIS IS LEGITIMATE	THIS IS NOT
The recommendation is Class IIa or IIb, or the trial behind it was close — the ALLHAT dead heat being the clearest case ⁶ . You are choosing between defaults, which is what the committee expected.	The recommendation is Class III, or the trial found harm. There is no reasoning to be done in the dual-blockade row ⁸ ; there is only compliance.
The patient falls outside the trial population in a way that matters — far older, far frailer, a much lower GFR, pregnant. Extension is a judgement and it can go either way.	The patient falls outside the trial population in a way that does not matter, and the departure is really about habit, familiarity, or what was sampled last month.
The recommended drug is unaffordable or unavailable, and a same-class alternative exists. The IHC1 protocol chose on exactly these grounds ⁵ .	The recommended drug is cheap and available, and the alternative is neither — without a clinical reason that can be stated.
An adverse effect, a contraindication or an interaction makes the recommended class wrong for this person. Filter three of Opening 1 overrides everything above it.	The first drug was not given long enough, at an adequate dose, or was not being taken — and the departure is really a diagnosis of failure that was never made.
The evidence has moved and the guideline has not caught up. This is real, and it is why the level of evidence and the publication date are both worth checking.	A single trial, a conference abstract or a confident summary has moved and nothing else has. One study rarely overturns a guideline, and the ones that do are unmistakable.

And one practical habit that costs nothing: **when you depart, write down why**. One line in the record naming the reason — intolerance, cost, pregnancy, a specific comorbidity — converts a departure from something that looks like an oversight into something that is visibly a decision. It protects the patient, because the next doctor will not simply switch them back. It protects you. And it is the clearest possible evidence that you knew what the guideline said.

The rule this volume runs on, restated

The guideline chooses the class wherever it has spoken clearly. Mechanism chooses among the options it leaves open, and reasons carefully where it is silent. Nothing here is a reason to delay a guideline-directed drug in a patient who needs one.

KEY POINTS

- 1 A guideline is a committee's compressed summary of a literature, written for a population, at a moment in time. Every part of that sentence limits what it can tell you about your patient.
- 2 It contains three kinds of statement in one typeface: what a trial proved, what a trial suggested, and what the committee decided because no trial exists.
- 3 Class of recommendation says how strongly to act; level of evidence says what that rests on. They are independent, and Class I on Level C evidence is a committee stating its own opinion firmly.
- 4 Level C means expert consensus. A good deal of what clinicians believe is mandated by evidence sits here.
- 5 Guidelines disagree about thresholds, labelling and how much follow-up the system can deliver — rarely about the trials, which are usually the same trials.
- 6 The ISH guideline's essential-versus-optimal structure is the most honest fit for much of Indian practice, because it was written for settings with a limited drug list.
- 7 The India Hypertension Control Initiative controlled 70–76% of patients at the first protocol step across 159,292 people, using drugs chosen for cost and availability — which is the correct reading of ALLHAT, not a compromise on it.
- 8 Two Indian states ran the same evidence and ordered the drugs differently, and both worked. That is what a genuinely open choice looks like.
- 9 Ask of any patient: is there a trial for this population, and this comparison? Name the population precisely, find the trial before the review, and apply the four questions.
- 10 Departing from a Class IIa or IIb recommendation is what the committee expected. Departing from a Class III recommendation is not reasoning.
- 11 When you depart, write one line saying why. It turns an apparent oversight into a visible decision, and stops the next doctor reversing it blindly.

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CHAPTER
1

PART I · THE RENIN-ANGIOTENSIN CASCADE

ACE Inhibitors

The enzyme does two jobs. You cannot block one without blocking the other — and almost everything about this class, good and bad, follows from that single fact.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

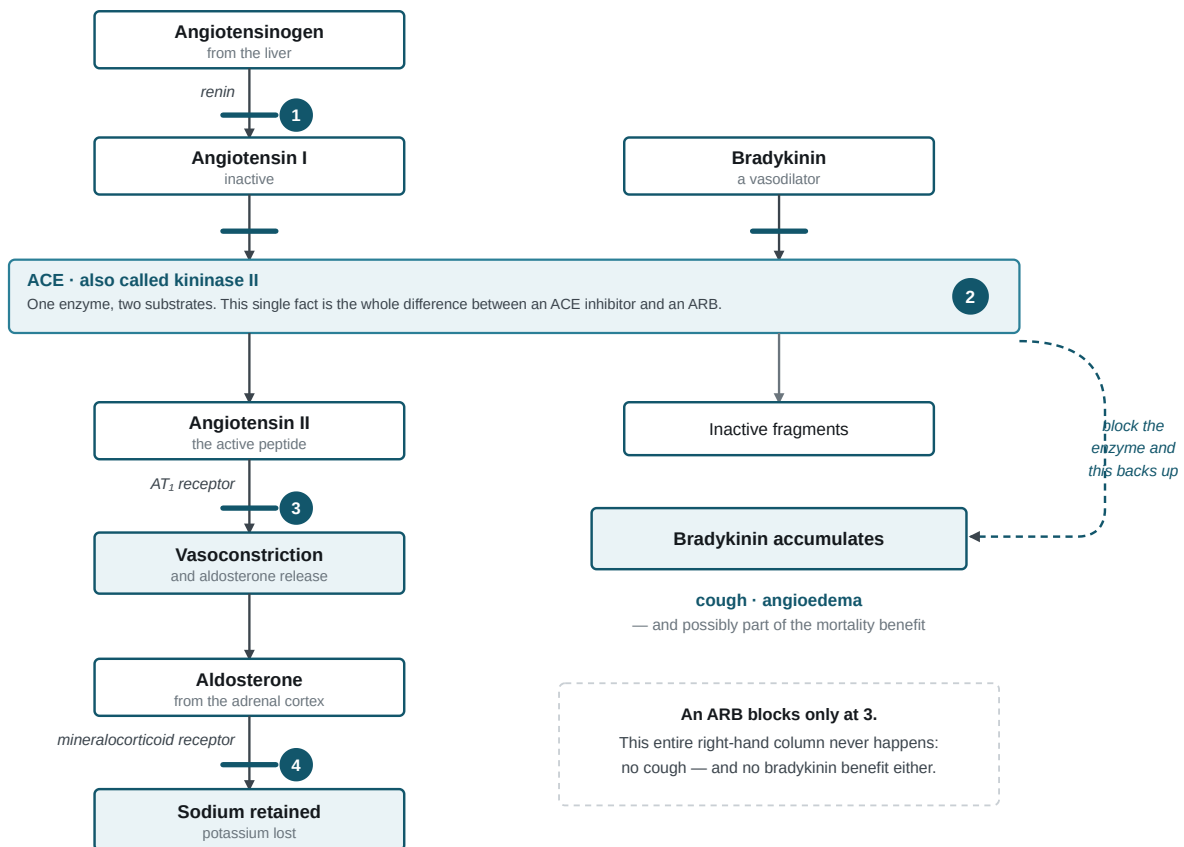
- Why the enzyme is worth acting on, and where this class ranks in each population.
 - Why act here rather than on the nephron — and the phenotype that decides.
 - The ledger: what you get, what comes with it, and why the guideline places it where it does.
 - The counterfactual — and why the drug that answers it already exists.
 - Which molecule, what to check, what to combine, and what never to combine.

1.1

AT THE POINT OF PRESCRIBING		LAYER 1 · 60 SECONDS
USE WHEN	Proteinuric CKD or diabetic nephropathy · heart failure with reduced ejection fraction · after myocardial infarction · high cardiovascular risk · young, lean, high-renin	
DO NOT USE	Pregnancy, or planning it · previous angioedema on any ACE inhibitor · bilateral renal artery stenosis · potassium already high	
WHICH MOLECULE	Ramipril for cardiovascular risk. Enalapril if cough on another. Fosinopril if renal function is uncertain — no dose adjustment at any eGFR. Lisinopril or captopril in liver disease: both are active as given.	
STARTING DOSE	Low, at bedtime. Lower again in the elderly and in anyone already on a diuretic.	
FIRST CHECK	Potassium and creatinine at one to two weeks , and after every dose increase — earlier than the two to four weeks KDIGO states ²¹ , and deliberately so in a patient on a diuretic or below an eGFR of 30. This is the visit that gets missed.	
EXPECT	A creatinine rise. Up to 30% within four weeks, then stable, is a reason to continue and watch — not a reason to stop, and not reassurance either ²¹ . Work through the correctable causes first (V3-Case 12). A <i>disproportionate</i> rise within days means image the renal arteries.	
IF THEY COUGH	Switch to an ARB. Not to another ACE inhibitor — the cough is a class effect.	
NEVER WITH	An ARB · aliskiren in diabetes · within 36 hours of sacubitril/valsartan · an NSAID plus a diuretic together	

1.2 Why act here

FIGURE 1.1 — THE CASCADE, ITS FOUR BLOCKING POINTS, AND THE SECOND SUBSTRATE

**1 Renin****Aliskiren — Chapter 3**

The rate-limiting step, and the most upstream target available. It was the strongest theoretical case in this volume and it failed in patients.

2 ACE, also called kininase II**ACE inhibitors — Chapter 1**

Blocks the making of angiotensin II and the breakdown of bradykinin. You cannot have one without the other.

3 The AT₁ receptor**ARBs — Chapter 2**

Blocks the ligand at its receptor and leaves bradykinin alone. That is the entire clinical difference between the two classes.

4 The mineralocorticoid receptor**Spironolactone, eplerenone — Chapter 7**

The last station, and the one that settles sodium and potassium. This is why it is the fourth drug in resistant hypertension.

Read down one column, and the reason a second RAAS drug is never the answer becomes obvious. Blocking twice on one line does not double the effect: the cascade exists to defend arterial pressure and it routes around an interruption. That is why an ACE inhibitor with an ARB fails, why aliskiren added to either caused harm, and why the next drug always belongs at a *different* site — the channel, the nephron, or the sympathetic limb.

Angiotensin-converting enzyme sits in the middle of the cascade of V1·Ch3. Renin cuts angiotensinogen to angiotensin I, which is inert. ACE converts it to angiotensin II, which is not. Acting at the enzyme means acting where an inactive precursor becomes the most powerful pressor peptide the body makes. Blocking it does five things, and clinicians tend to remember only the first.

TABLE 1.1 — WHAT BLOCKING THE ENZYME ACTUALLY DOES

AT THE ENZYME	IN THE BODY	WHAT IT GIVES YOU CLINICALLY
Less angiotensin II	Arterioles dilate	Resistance falls. The blood pressure effect.
Less angiotensin II	Aldosterone release drops	Sodium retained less avidly; potassium retained more.
Less angiotensin II	The glomerular <i>efferent</i> arteriole relaxes	Pressure inside the glomerulus falls. This is why proteinuria improves — the class protects kidneys rather than merely lowering the pressure that damages them.
Less angiotensin II	Trophic signalling recedes	Less cardiac and vascular fibrosis, less hypertrophy. The remodelling slows.
Bradykinin is no longer degraded	It accumulates ²	Extra vasodilation through nitric oxide and prostacyclin — and the cough, and the angioedema.

That last row is the whole chapter. One enzyme, two substrates: every advantage and every disadvantage of this class follows from the fact that you cannot block one without blocking the other.

1.3 Where this class ranks, and why

Every class lowers blood pressure. What earns a class first place is what it does beyond the number, and here the evidence is unusually direct. Across 20 randomised trials in 158,998 hypertensive patients followed a mean of 4.3 years, ACE inhibitors reduced all-cause mortality by 10% — HR 0.90 (95% CI 0.84–0.97, $p = 0.004$).³

One trial shows this most clearly. HOPE randomised 9,297 patients aged 55 and over with vascular disease or diabetes plus a risk factor — and specifically excluded heart failure — to ramipril 10 mg or placebo.

The composite of myocardial infarction, stroke or cardiovascular death occurred in 14.0% against 17.8%: HR 0.78 (95% CI 0.70–0.86, $p < 0.001$), number needed to treat 27.⁵

Where a class sits is not a fixed property of the drug. It is a property of the drug meeting a population, and the question is always the same: is the mechanism it interrupts the one that is running?

What this means at the bedside

You are not choosing a drug that lowers pressure. You are choosing to interrupt a cascade — and getting the kidney, the myocardium and the vessel wall along with the number.

3.3 mmHg systolic difference

The average separation between the arms — for a quarter fewer events. The trial's authors concluded the benefit came from RAAS inhibition in addition to pressure reduction, not from the pressure alone.⁵

TABLE 1.2 — WHERE THIS CLASS RANKS, AND WHY

POPULATION	RANK	THE REASON
Diabetic kidney disease, or any proteinuric CKD	First	The efferent arteriole is where proteinuria is generated, and this is the only site that relaxes it. A drug acting elsewhere lowers systemic pressure and leaves the glomerulus doing the same damage more slowly.
Heart failure with reduced ejection fraction; after myocardial infarction	First	The trophic effects of angiotensin II — fibrosis, remodelling, hypertrophy — are the disease process, not a side issue.
High cardiovascular risk with only modest hypertension	First	HOPE ⁵ — a quarter fewer events on 3.3 mmHg. The pressure is not what you are treating.
Young, lean, high-renin, uncomplicated hypertension	First	The renin-angiotensin system is the mechanism that is running. Block a system that is active and it responds.
Older, obese, salt-loaded, low-renin, non-dipping	Second or third	Not because the drug is weak, but because the system is already suppressed. The nephron or the calcium channel comes first here; add this afterwards, once the diuretic has raised renin and created the conditions this drug needs.
Isolated systolic hypertension in the elderly	Second	The problem is arterial stiffness, not a running cascade.
Pregnancy, or a woman who may conceive	Contraindicated	Fetal toxicity. Not a ranking — an exclusion.
Bilateral renal artery stenosis, or a single functioning kidney	Avoid	Efferent tone is holding filtration up. Removing it removes the filtration. The 2023 ERBP/ESH renovascular document says the class should generally be avoided here and the patient evaluated directly for revascularisation; an eGFR fall of more than 30% on either drug is itself a trigger for that evaluation ²² . VI·Ch32.

1.4 Why here, and not the nephron

A diuretic will also lower this patient's pressure. The two are not interchangeable, and the difference is not potency — it is which mechanism you interrupt.

The rule that governs this chapter

The guideline chooses the class wherever it has spoken. What follows explains *why* it says what it says, and decides among the options it leaves open. Nothing here is a reason to delay a first-line drug in a patient who needs one.

TABLE 1.3 — SIGNAL OR VOLUME — THE TWO SITES COMPARED

	THE CASCADE	THE NEPHRON
What is interrupted	A signal . Angiotensin II stops being made.	A volume . Sodium is not reabsorbed.
What stops with it	Constriction, aldosterone, efferent tone, fibrosis — all at once.	Total body sodium falls. Nothing else is affected.
At the glomerulus	Efferent tone relaxes, intraglomerular pressure falls, proteinuria falls with it.	Systemic pressure falls; the glomerulus is left alone.
When it fails	In a low-renin patient there is no signal to block. Switching off a system that is already off.	Rarely fails on mechanism — volume is always removable.
The arm it acts on	The one that adapts.	The one Guyton showed decisive for long-term pressure — VI·Ch5.

TABLE 1.4 — WHICH SITE, AND WHAT TELLS YOU

	ACT ON THE CASCADE, OR ON THE NEPHRON
High renin, young, lean, proteinuric, diabetic kidney	The cascade. This is a signalling problem and the signal is running.
Low renin, elderly, obese, salt-loaded, non-dipping, oedematous	The nephron. Blocking a suppressed system will disappoint, and the answer is not a higher dose.
Neither obvious, or both present	Both — and see 1.9b. The reflex each drug provokes is the argument for the other.

This is the comparison the standard references leave to the reader, and it is the one actually being made at the first prescription. Nobody is choosing between ramipril and enalapril. They are choosing between the cascade and the nephron.

1.5 The ledger — and the counterfactual that already exists

Every class in this volume is judged on the same reckoning: what you want from it, what comes with it, and the verdict that follows.

TABLE 1.5 — THE ACE INHIBITOR LEDGER

WHAT YOU WANT FROM IT	WHAT COMES WITH IT
Arteriolar dilation, and less aldosterone.	Dry cough. RR 2.66 (95% CI 2.20–3.20), NNH about 28. ⁴
A fall in intraglomerular pressure — proteinuria reduced, not merely tolerated.	Cough is worse in Asian series: 24.1% in Malaysia, ¹⁰ 44% in Hong Kong. ⁹
Regression of cardiac and vascular fibrosis.	Angioedema. Mechanism certain ² ; across 378 trials RR 1.32 (95% CI 0.90–1.95, $p = 0.160$). ⁴
All-cause mortality down 10% across 158,998 patients. ³	Hyperkalaemia. RR 1.24 (95% CI 1.01–1.52), NNH about 111. ⁴
A quarter fewer events on 3.3 mmHg in HOPE. ⁵	Fetal toxicity — boxed on every label in the class. ^{12,19}
Bradykinin adds nitric-oxide and prostacyclin vasodilation the ARBs do not get.	A creatinine rise that has to be interpreted rather than ignored.

The verdict. First line, and first among the drugs acting on this cascade wherever a second indication exists and the patient tolerates it.

Now the counterfactual. Suppose you could keep everything in the left column and remove the cough and the angioedema. That drug would be the unambiguous choice for this cascade.

That drug exists. It is the ARB — it blocks the receptor one step downstream, leaves bradykinin alone, and does not cough.

And here is the finding that makes this chapter worth reading. In the same meta-analysis the mortality benefit was not a property of RAAS blockade. ARBs did not reduce all-cause mortality: HR 0.99 (95% CI 0.94–1.04, $p = 0.683$), and the difference between the two classes was itself significant at $p = 0.036$.³

The authors attribute that difference to the bradykinin arm — the very mechanism that causes the cough.

One honest caution. This was a meta-analysis across separate trials, not a randomisation of one class against the other. ONTARGET comes closer and disagrees; that argument is set out in Chapter 2.⁷

1.6 When acting here is wrong

Read this twice

The cost and the benefit may come from the same mechanism. Remove the bradykinin accumulation and you remove the cough — and, on this evidence, possibly the mortality advantage with it. That is why both classes still exist.

TABLE 1.6 — FOUR SITUATIONS, AND WHAT REPLACES THIS SITE

SITUATION	WHY THE SITE FAILS HERE	WHERE TO ACT INSTEAD
Pregnancy, or a woman who may become pregnant	Fetal toxicity, boxed on every label. ^{12,19,18} The fetal kidney depends on angiotensin II to develop.	Methyldopa, labetalol or nifedipine. Switch when pregnancy becomes a plan, not a fact — V1·Ch18.
Angioedema on any ACE inhibitor	Bradykinin-mediated and recurrent. Contraindicated on every label. ^{12,19,14}	The receptor, one step downstream — an ARB. Angioedema is reported on ARBs, far less often.
Bilateral renal artery stenosis, or a single functioning kidney	Efferent tone holds filtration up. Remove it and filtration falls. The disproportionate creatinine rise on starting is diagnostic — V1·Ch32.	Stop, image the arteries, and use a site that does not depend on that arteriole. The 2023 ERBP/ESH renovascular document says generally avoid the class here and evaluate for revascularisation; an eGFR fall of more than 30% is itself a trigger for that evaluation ²² .
A potassium that will not stay down	Less aldosterone, less potassium excretion. RR 1.24 across trials ⁴ — modest in a population, decisive in this patient.	The calcium channel, or the nephron with a thiazide-type agent. And find what is raising the potassium.

On managing angioedema this book prints no protocol. The class reference states the primary treatment is stopping the drug.²

For acquired angioedema more broadly, one source records that adrenaline, corticosteroid and antihistamine regimens have little effect and are not recommended, and that C1-esterase inhibitor, icatibant and ecallantide are among the effective options.¹¹ That is a statement about acquired angioedema as a category, not about ACE-inhibitor angioedema specifically, and no trial evidence in this indication was located for this edition. Airway first; the drug stops and never restarts.

Two combination rules sit in the contraindications section of the label itself and are not matters of judgement: never with aliskiren in a patient with diabetes, and never within 36 hours of switching to or from sacubitril/valsartan.^{12,19} A third — never with an ARB — is as firm in practice, but it is worth knowing where it comes from: the label carries dual RAAS blockade as a drug-interaction warning rather than a contraindication, and the reason to treat it as absolute is ONTARGET.^{12,19}

A fifth situation is not a contraindication but a predictable disappointment, and it looks like treatment failure. In the low-renin, volume-dependent phenotype of V1·Ch12 and V1·Ch13 — older, obese, salt-loaded — this class underperforms as monotherapy. Add a second site; do not raise the dose.

1.7 What to check, and when

Every source in this chapter agrees about monitoring, and it is the step most often skipped. The drug is safe; not checking is what causes harm.

TABLE 1.7 — THE MONITORING THAT IS NOT OPTIONAL

	WHAT TO DO, AND WHAT THE RESULT MEANS
Before starting	Renal function and potassium. ² You are about to remove the efferent tone holding up filtration in an unknown proportion of these patients.
One to two weeks after starting, and after every dose increase	Creatinine and potassium again. ¹³ KDIGO says two to four weeks ²¹ ; the earlier check is this book’s convention, chosen for the patient on a diuretic or below an eGFR of 30, and V3·Ch20 explains why every interval here is convention rather than evidence. This is where hyperkalaemia and acute kidney injury are caught, and it is the visit that gets missed.
Interpreting the creatinine rise	A rise is expected — efferent tone has been released — but it is not reassurance. Up to 30% within four weeks, then stable, is a reason to continue and watch more closely ²¹ ; an NSAID, a diuretic increase and volume depletion are excluded first — V3·Case 12. The threshold at which it stops being acceptable is in V1·Ch19. A disproportionate rise points at the renal arteries — V1·Ch32.
Potassium	If it will not stay below 5.5 mmol/L, review every other drug raising it before abandoning the class — potassium-sparing diuretics, trimethoprim, NSAIDs, and supplements the patient may not consider medicines.
Full blood count	Periodically where there is collagen vascular disease or chronic kidney disease. ¹³ For captopril in impaired renal function, before starting and then at about two-week intervals for three months, and periodically thereafter — the label sets this by renal function and by collagen vascular disease, not by a daily dose. ²⁰
At every visit thereafter	Ask about cough. Patients rarely volunteer it, blame the weather, and get antibiotics for a pharmacological symptom.

TABLE 1.8 — THREE POINTS THAT CHANGE TOLERABILITY, NOT EFFICACY

	WHY
Give the first dose at bedtime	Blunts first-dose hypotension in a volume-depleted patient — and most of them are, if they are already on a diuretic.
Start reduced in the elderly, and in anyone on a diuretic	The same two groups in whom the first dose does most harm.
Withhold around contrast procedures and major surgery — and write the restart date at the same time	A fall in perfusion pressure meeting a kidney that has lost its efferent compensation is how the avoidable injuries happen. The judgement is sharpest in the volume-depleted or haemodynamically marginal patient. A drug stopped without a restart date is usually a drug stopped for good — V3·Case 12.

1.8 The target map — where else this reaches

Every adverse effect in this chapter comes from one fact, and a reader who holds it can derive the list instead of memorising it. **Angiotensin-converting enzyme has two substrates.** It makes angiotensin II, which is what you are trying to stop. It also destroys bradykinin, which you are not trying to do and cannot avoid. Block the enzyme and bradykinin accumulates wherever it is produced.

The triple whammy
An ACE inhibitor with an NSAID and a diuretic is the commonest avoidable acute kidney injury in general practice. Each is reasonable alone; together they remove efferent tone, prostaglandin-dependent afferent dilation, and volume — three arms of glomerular perfusion at once. Ask about over-the-counter painkillers at every review. Patients do not report them because they do not consider them drugs.

TABLE 1.9 — FROM ONE ENZYME WITH TWO JOBS TO EVERY EFFECT IN THE CHAPTER

WHERE THE CONSEQUENCE LANDS	WHAT HAPPENS THERE	WHAT THE PATIENT REPORTS
Airway sensory nerves	Bradykinin and substance P accumulate in the bronchial mucosa and sensitise the cough reflex. This is a <i>receptor-independent</i> consequence — nothing to do with angiotensin.	Dry cough , which is why it is a class effect and why switching to another ACE inhibitor fails. Switch downstream, to an ARB.
Deep dermal and submucosal tissue	The same peptide, at a site where accumulation produces vasodilatation and plasma extravasation rather than irritation.	Angioedema — and the reason it is a lifetime contraindication to the whole class rather than a dose problem.
The efferent arteriole	Angiotensin II constricts it, and that constriction is what maintains filtration pressure. Remove it and the glomerulus filters at a lower pressure.	A creatinine rise . Expected, and evidence the drug is acting where intended. It becomes a warning only when disproportionate — which means the kidney was depending on that constriction.
The adrenal zona glomerulosa	Less angiotensin II means less aldosterone, and aldosterone is what drives potassium out in the collecting duct.	Hyperkalaemia . Predictable, additive with every other potassium-raising drug, and the reason the potassium check is not optional.
The fetal kidney	Fetal renal development requires an intact renin-angiotensin system. This is on-target action in a patient who cannot be asked.	Fetal toxicity . Absolute contraindication, and the reason to stop at the point pregnancy becomes a plan rather than a fact.
Taste, and the marrow	Sulfhydryl-group effects specific to captopril rather than consequences of enzyme inhibition — the one row here that is genuinely off-target.	Taste disturbance, neutropenia . Molecule-specific, which is why captopril alone carries a blood-count requirement.

Read the first two rows together and the chapter’s central decision falls out. Cough and angioedema are the *same molecule* at two sites. That is why no dose reduction helps, why no other ACE inhibitor helps, and why the ARB — which blocks one step downstream and leaves bradykinin alone — is the answer to both. It is also why the ARB gave up whatever part of the mortality benefit bradykinin was contributing.

1.9 The adverse effects, in detail

Four matter across the class and each has a number. Three more belong to single molecules.

What the map predicts that the list does not

A patient on an ACE inhibitor who develops a persistent tickling cough three months in does not need a chest radiograph first. And a patient with hereditary angioedema should never be given one at all — the map says why without anyone having to have written the warning down.

TABLE 1.10 — CLASS ADVERSE EFFECTS, WITH THE FIGURES

EFFECT	FREQUENCY OR RISK	WHAT IT MEANS FOR THE PRESCRIPTION
Dry cough	RR 2.66 against placebo (95% CI 2.20–3.20), NNH about 28 ⁴ . Asian series higher: 24.1% Malaysia, ¹⁰ 44% Hong Kong ⁹	Mechanistic, not idiosyncratic. Switch across to an ARB, not sideways within the class. Within the class the range runs RR 4.19 (perindopril) to 1.23 (enalapril) ⁴
Angioedema	Across 378 trials RR 1.32 (95% CI 0.90–1.95, $p = 0.160$) — not statistically significant ⁴ . Fosinopril series 0.1–0.7% ¹⁷	Rare, serious, and less well demonstrated by randomised evidence than the teaching implies. A lifetime contraindication to the whole class once it happens.
Hyperkalaemia	RR 1.24 (95% CI 1.01–1.52), NNH about 111 ⁴ . For ramipril, 1–10% of patients ¹³	Modest across a population, decisive in the patient at 5.5. Review every other potassium-raising drug before abandoning the class.
Creatinine rise	1–2% of patients on ramipril ¹³	Expected, and not reassurance: below 30% and stable, continue and watch ²¹ , and exclude the correctable causes first — V3·Case 12. The threshold that ends it is in V1·Ch19; a disproportionate rise means image the arteries.

TABLE 1.11 — EFFECTS THAT BELONG TO ONE MOLECULE

MOLECULE	EFFECT	FREQUENCY
Captopril	Rash with pruritus ¹⁶	4–7%
Captopril	Taste disturbance — the sulphhydryl group ¹⁶	2–4%
Captopril	Neutropenia or agranulocytosis ¹⁶	under 1% with normal renal function; 3.7% with renal impairment and collagen-vascular disease
Captopril	Proteinuria ¹⁶	1%
Enalapril	Cholestatic jaundice ¹⁴	<i>frequency not stated</i>
Fosinopril	Raised liver enzymes ¹⁷	under 2%

1.10 It happened — now what?

An adverse effect is not a fact to look up. It is a decision point, and the right move follows from the mechanism.

The one that ends the class

Angioedema. Everything else is managed, dose-adjusted or monitored. This one is a lifetime exclusion from every molecule in the chapter, and there is no rechallenge.

TABLE 1.12 — THE SIX THAT ACTUALLY HAPPEN, AND THE MOVE EACH CALLS FOR

WHAT HAPPENED	WHAT IT IS	THE MOVE
Dry cough	Bradykinin accumulation. A class effect, not a molecule failure ² .	Switch across to an ARB. Switching sideways to enalapril lowers the odds (RR 1.23 against 4.13) ⁴ without removing the mechanism, and costs two months to find out. The class reference says the same: try another class ² .
Angioedema	Bradykinin-mediated, and an airway emergency.	Airway first. The drug stops and never restarts, and the whole class is contraindicated for life. No rechallenge, no substitution within the class.
Creatinine rises	Expected haemodynamic effect of relaxing the efferent arteriole — but not reassurance, and not 'the drug working'. Below 30% and stable, continue and watch ²¹ .	Interpret it against the threshold in V1·Ch19. A disproportionate rise within days is bilateral renal artery stenosis until proven otherwise — V1·Ch32.

WHAT HAPPENED	WHAT IT IS	THE MOVE
Potassium climbs	Less aldosterone, less potassium excretion. RR 1.24 across trials ⁴ .	Review every other potassium-raising drug first — potassium-sparing diuretics, supplements, trimethoprim, NSAIDs, fluconazole ² . Abandon the class last, not first.
Dizzy on the first dose	First-dose hypotension, worst in the volume-depleted and the elderly.	Not a reason to stop. Give it at bedtime, halve the dose, and check whether the diuretic they are on is the real problem.
Metallic taste, or a rash	Captopril's sulphhydryl group. Dysgeusia 2–4%, rash with pruritus 4–7% ¹⁶ .	Molecule-specific, not class. Switch to any non-sulphydryl ACE inhibitor and it resolves.

1.11 Interactions, and what to do about them

Eight interactions are named in the class reference. Three change a decision; the rest change monitoring.

The distinction that matters most

Cough is a nuisance that costs you the drug. Angioedema is an emergency that costs the patient the class. They share a mechanism and nothing else, and conflating them leads either to stopping a good drug too early or to rechallenging a patient who must never be rechallenged.

TABLE 1.13 — INTERACTIONS THAT CHANGE A DECISION

WITH	WHAT HAPPENS	WHAT TO DO
NSAIDs, with a diuretic	The triple whammy. Efferent tone, prostaglandin-dependent afferent dilation and volume removed together.	Ask at every review. This is the commonest preventable acute kidney injury in general practice.
Lithium	Renal lithium clearance falls and toxicity follows ² .	Check a level early if the combination is unavoidable. Tremor, confusion and nausea are the signs.
Azathioprine	Bone marrow suppression — anaemia and leukopenia ² .	A full blood count, and a conversation with whoever prescribed the azathioprine.
Spinal anaesthesia with bupivacaine	Reports of severe hypotension and bradycardia ² .	The anaesthetist needs to know the patient is on this class. It is on the pre-operative list for a reason.

TABLE 1.14 — INTERACTIONS THAT CHANGE MONITORING

WITH	WHAT HAPPENS
Sulfonylureas	Increased risk of hypoglycaemia in a diabetic patient ² . Warn the patient at initiation, particularly if they are on insulin.
Potassium-sparing diuretics, potassium supplements	Additive hyperkalaemia. The commonest reason potassium will not settle.
Fluconazole	Raises hyperkalaemia risk ² .
Ketoconazole	Inhibits the hepatic enzymes that metabolise co-prescribed drugs, amplifying their effect ² .
Allopurinol	Raises the risk of hypersensitivity reactions ² . Warn the patient to seek care for any rash.
Magnesium supplements	Enhance the blood-pressure-lowering effect ² .

1.12 Special populations

Four groups change the prescription, and one of them changes which molecule rather than whether to prescribe at all.

Toxicity
 At therapeutic doses toxicity is rare, and most poisoning is mild and needs observation.² Severe cases need intravenous fluids and inotropic or vasopressor support; naloxone or angiotensin II have been used in refractory shock.² One molecule-specific point: **captopril is the only ACE inhibitor that crosses the blood–brain barrier**, and can cause confusion and lethargy.²

TABLE 1.15 — WHAT CHANGES, AND IN WHOM

POPULATION	WHAT CHANGES	WHICH MOLECULE
Pregnancy	Absolute exclusion. Boxed warning on every label ^{12,19,18} . Contraindicated throughout pregnancy, not only the second and third trimesters . Second- and third-trimester exposure causes the classical fetopathy; the first-trimester malformation risk is disputed : a relative risk of about 2.7 was reported against women taking no antihypertensive ² , but a cohort of 465,754 pregnancies found the same association in <i>untreated hypertensive</i> women, implicating the condition rather than the drug ¹ . The contraindication does not rest on that disputed signal — it rests on the second- and third-trimester fetopathy, which is not in doubt. Stop when pregnancy is planned, not when it is confirmed.	None. Methyl dopa, labetalol or nifedipine — and the switch is made when pregnancy becomes a plan. V1·Ch18.
Renal impairment	Dose thresholds differ molecule by molecule — see the dosing table. Perindopril is not recommended below CrCl 30 at all ¹⁸ .	Fosinopril : no adjustment at any degree, because the liver takes over ¹⁷ . The molecule that removes a decision.
Hepatic impairment	A prodrug needs hepatic activation, which is unreliable here. Fosinopril is the wrong choice in cirrhosis with ascites — the liver is doing half its clearance ¹⁷ .	Lisinopril or captopril , neither of which is a prodrug. Trandolapril if used: 0.5 mg daily ¹⁹ .
The elderly	First-dose hypotension is the risk, and most are on a diuretic already. Do not start the drug in a dehydrated patient² ; monitor creatinine and potassium regularly thereafter ² .	Perindopril specifically: start at 4 mg or less, and experience above 8 mg is limited ¹⁸ .
Breastfeeding	The class may be used cautiously ² . Avoid fosinopril specifically ¹⁷ .	Enalapril — it has the most published safety data in lactation ² .
Children	Used in paediatric hypertension ² . Dosing is outside the scope of this volume.	Captopril, lisinopril and enalapril are the molecules used ² .
On dialysis	The class is usable.	Captopril, enalapril, lisinopril and ramipril ² .

1.13 Four patients, one site question

Illustrative composites, each chosen because the same decision resolves differently.

TABLE 1.16 — THE SAME QUESTION, FOUR ANSWERS

THE PATIENT	THE SITE	WHY, AND WHY NOT THE ALTERNATIVE
52, type 2 diabetes nine years, BP 152/94, urine ACR 180 mg/g	The cascade, with an ACE inhibitor	Two problems, one drug: the pressure and the protein. The efferent arteriole is where proteinuria is generated; a diuretic would not touch it. The mortality evidence points the same way. ³
58, six weeks on ramipril, dry persistent cough, pressure controlled	Same site, one step downstream	An ARB. Switching to enalapril lowers the odds (RR 1.23 against 4.13) without removing the mechanism ⁴ — and you will spend two months finding that out.
34, planning pregnancy this year, BP 146/92 on enalapril	Neither — leave the cascade	Boxed warning for fetal toxicity. ^{12,19} Switch when the pregnancy becomes a plan. V1·Ch18.
71, creatinine 96 to 168 μ mol/L in twelve days after starting ramipril	Stop, and look at the arteries	The classic presentation of bilateral renal artery stenosis. The expected haemodynamic dip is smaller and settles — V1·Ch19, V1·Ch32.

1.14 The molecules, compared

Everything above is about the class. This section is where the seven molecules differ, set out as one comparison rather than seven monographs — because the choice between them is a smaller decision than the choice of site, and it reads better side by side. Where a source did not state a figure the cell says so; this book does not fill gaps by inference.

TABLE 1.17 — COMPARATIVE PHARMACOLOGY

DRUG	PRODRUG	ACTIVE FORM	PEAK	HALF-LIFE	ELIMINATION	PER DAY
Ramipril	Yes	Ramiprilat	~1 h	13–17 h effective; terminal >50 h	60% urine, 40% faeces	1
Enalapril	Yes	Enalaprilat	~1 h	<i>not stated</i>	~2/3 urine, rest in faeces via bile	1–2
Lisinopril	No	Lisinopril itself	6–8 h	<i>not given as a figure</i>	Excreted unchanged in urine	1
Perindopril	Yes	Perindoprilat	1 h parent, 3–7 h active	3–10 h bulk; terminal 30–120 h	<i>not stated</i>	1
Captopril	No	Captopril itself	~1 h	~2 h	Kidney is the major route	2–3
Fosinopril	Yes	Fosinoprilat	<i>not stated</i>	<i>not stated</i>	Liver and kidney both	1
Trandolapril	Yes	Trandolaprilat	<i>not stated</i>	22.5 h at steady state	<i>not stated</i>	1

TABLE 1.18 — HYPERTENSION DOSING, AND RENAL ADJUSTMENT

DRUG	START	USUAL RANGE	MAXIMUM	IN RENAL IMPAIRMENT
Ramipril	2.5 mg OD	2.5–20 mg daily	20 mg	CrCl <40: start 1.25 mg, ceiling 5 mg
Enalapril	5 mg OD	10–40 mg daily	40 mg	CrCl <30: start 2.5 mg
Lisinopril	10 mg OD	2.5–40 mg OD	40 mg	CrCl 10–30: halve the start. Below 10 and dialysis: 2.5 mg OD
Perindopril	4 mg OD	4–8 mg daily	16 mg	Not recommended below CrCl 30. Lesser impairment: 2 mg, max 8 mg
Captopril	25 mg BD–TDS	25–150 mg BD–TDS	450 mg	Reduce the start; <i>no threshold stated in source</i>
Fosinopril	10 mg OD	20–40 mg daily	80 mg	No adjustment at any degree, including end-stage

DRUG	START	USUAL RANGE	MAXIMUM	IN RENAL IMPAIRMENT
Trandolapril	1 mg OD	2–4 mg OD	little experience >8 mg	CrCl <30 or cirrhosis: 0.5 mg OD

TABLE 1.19 — WHICH MOLECULE, AND WHY

MOLECULE	CHOOSE IT WHEN	BECAUSE
Ramipril	Cardiovascular risk reduction is the goal	HOPE: events 14.0% against 17.8%, HR 0.78, NNT 27 — on 3.3 mmHg. ⁵
Fosinopril	Renal function is poor, falling, or unknown	The only one needing no adjustment at any degree of impairment: the liver takes over what the kidney stops clearing. ¹⁷
Trandolapril	Adherence is the problem, not the pressure	Effective half-life 22.5 hours — the longest here, and what once-daily cover rests on. ¹⁹
Lisinopril	Hepatic impairment, or predictability matters	No hepatic activation step to fail; excreted unchanged. ¹⁵ Slow on at 6–8 hours, slow off.
Enalapril	You must stay in the class after a cough	Lowest cough risk in the 378-trial analysis, RR 1.23 against ramipril's 4.13. ⁴ A last resort before an ARB, not a first move.
Captopril	Short-acting titration is genuinely wanted	Half-life about two hours. ¹⁶ Two or three doses daily, an hour before food — which rules it out for maintenance.
Perindopril	Cost and availability decide, as they often should	Nothing in the sourced data distinguishes it for a specific patient, and its cough risk is the highest in the class (RR 4.19). ⁴

1.15 The seven molecules

The comparative tables above carry the numbers. These carry what a table cannot: why each molecule exists, when to reach for it, and what stops you.

Ramipril

THE CARDIOVASCULAR-RISK AGENT — HOPE

CHOOSE IT WHEN

- Cardiovascular risk reduction is the goal, with or without heart failure⁵
- A high-risk patient whose pressure is only modestly raised
- Diabetic nephropathy or proteinuric CKD
- The default first ACE inhibitor where nothing else decides it

AVOID, OR USE WITH CAUTION

- Pregnancy — boxed warning for fetal toxicity¹²
- Previous angioedema on any ACE inhibitor¹²
- Within 36 hours of sacubitril/valsartan¹²
- With aliskiren in a patient with diabetes¹²
- High cough risk — RR 4.13, second only to perindopril⁴

DOSE 2.5 mg once daily; usual 2.5–20 mg daily as one dose or two divided; maximum 20 mg.¹² **CrCl below 40 mL/min:** start 1.25 mg, ceiling 5 mg — the label notes that a quarter of the usual dose produces full therapeutic ramiprilat levels.¹²

PEARL HOPE excluded heart failure and still found a quarter fewer events on a 3.3 mmHg difference.⁵ When you prescribe this for a high-risk patient you are not treating the number.

Enalapril

LOWEST COUGH RISK IN THE CLASS

CHOOSE IT WHEN

- A patient who has coughed on another ACE inhibitor and must stay in the class — RR 1.23 against ramipril's 4.¹³⁴
- Where cost and availability decide, which is often
- Any standard cascade indication

AVOID, OR USE WITH CAUTION

- Pregnancy¹⁴
- Previous ACE-inhibitor angioedema, or hereditary or idiopathic angioedema¹⁴
- Cholestatic jaundice is a recognised adverse effect of this molecule¹⁴

DOSE 10 mg once daily in a patient not on a diuretic; 5 mg if already on one; usual 10–40 mg daily, once or twice; maximum 40 mg.¹⁴ **CrCl below 30 mL/min:** start 2.5 mg daily and titrate gradually.¹⁴

PEARL A prodrug activated by hepatic carboxylesterase 1.¹⁴ Switching a cougher to this lowers the odds without removing the mechanism — it is a last move inside the class, not a first move.

Lisinopril

NOT A PRODRUG — NO HEPATIC ACTIVATION STEP

CHOOSE IT WHEN

- Hepatic impairment, where a prodrug's activation step is unreliable
- When predictable pharmacokinetics matter more than speed
- Any standard cascade indication

AVOID, OR USE WITH CAUTION

- Pregnancy¹⁵
- History of angioedema¹⁵
- Hyperkalaemia¹⁵
- Bilateral renal artery stenosis¹⁵
- Concurrent neprilysin inhibitor¹⁵

DOSE 10 mg once daily; usual 20–40 mg once daily. Doses to 80 mg have been used without further effect; 2.5 mg belongs to severe renal impairment and dialysis, not to the usual range.¹⁵ **Renal:** above CrCl 30 no adjustment; CrCl 10–30 halve the starting dose; below 10 and on dialysis, 2.5 mg once daily.¹⁵

PEARL Bioavailability is only 10–30% and the peak takes 6 to 8 hours.¹⁵ Slow on and slow off — which makes it predictable, and makes it the wrong choice when you need a response you can read this week.

Perindopril

HIGHEST COUGH RISK IN THE CLASS — RR 4.19

CHOOSE IT WHEN

- Cost and availability decide, as they often should
- A patient already established and tolerating it

AVOID, OR USE WITH CAUTION

- **Not recommended below CrCl 30 mL/min**¹⁸
- Pregnancy — boxed warning for fetal toxicity¹⁸
- Previous ACE-inhibitor angioedema, hereditary or idiopathic angioedema¹⁸
- With aliskiren in diabetes¹⁸
- Highest cough risk of the class, RR 4.19⁴
- In the elderly, start at 4 mg or less and titrate slowly; experience above 8 mg is limited¹⁸

DOSE 4 mg once daily; maintenance 4–8 mg as a single or divided dose; maximum 16 mg daily.¹⁸ **CrCl 30–60:** start 2 mg daily, maximum 8 mg. Below 30, not recommended.¹⁸

PEARL The pharmacokinetics are unusual — the active metabolite has a 3 to 10 hour bulk elimination but a terminal phase of 30 to 120 hours.¹⁸ Steady state takes longer to reach than the once-daily dosing suggests.

Captopril

SHORTEST HALF-LIFE — ABOUT TWO HOURS

CHOOSE IT WHEN

- Short-acting titration is genuinely wanted
- Hepatic impairment — active as given, no activation step

AVOID, OR USE WITH CAUTION

- Two or three doses daily, which rules it out for most maintenance
- Food reduces absorption — must be given an hour before meals¹⁶
- Rash with pruritus in 4–7%, taste disturbance in 2–4%¹⁶
- Neutropenia or agranulocytosis in under 1% with normal renal function — but about 1 in 500 with renal impairment, and 3.7% where renal impairment and a collagen-vascular disease coexist¹⁶
- Pregnancy, previous angioedema, aliskiren in diabetes¹⁶

DOSE 25 mg two or three times daily; usual 25–150 mg two or three times daily; maximum 450 mg daily. **An hour before food.**¹⁶ **Renal:** reduce the starting dose and titrate gradually — the source gives no creatinine-clearance threshold, and none is invented here.¹⁶

PEARL Above 150 mg daily, or in collagen vascular disease or renal impairment, check a full blood count with differential before starting, then every two weeks for three months.¹⁶

Fosinopril

DUAL ELIMINATION — NO RENAL DOSE ADJUSTMENT AT ANY EGFR

CHOOSE IT WHEN

- Renal function is poor, falling, or simply unknown
- Advanced chronic kidney disease, including end-stage
- A patient whose renal function you cannot easily recheck

AVOID, OR USE WITH CAUTION

- **Avoid in hepatic cirrhosis with ascites** — the liver is doing half the clearing¹⁷
- Pregnancy; avoid in breastfeeding¹⁷
- Previous ACE-inhibitor angioedema¹⁷
- Angioedema reported in 0.2–1.0%¹⁷

DOSE 10 mg once daily; usual 20–40 mg daily; maximum 80 mg.¹⁷ **Renal: no adjustment at any degree of impairment, including end-stage disease.** Renal clearance falls by about half and hepatobiliary elimination compensates, so total body clearance is maintained.¹⁷

PEARL The one property in this chapter that removes a decision rather than adding one. In a patient whose eGFR is moving, this is the molecule that does not need watching for dose.

Trandolapril

LONGEST HALF-LIFE — 22.5 HOURS AT STEADY STATE

CHOOSE IT WHEN

- Adherence is the problem rather than the pressure
- Genuine 24-hour cover from a single daily dose is the objective

AVOID, OR USE WITH CAUTION

- Pregnancy — boxed warning¹⁹
- Hereditary or idiopathic angioedema, or previous ACE-inhibitor angioedema¹⁹
- Combination with a neprilysin inhibitor such as sacubitril¹⁹
- With aliskiren in diabetes¹⁹
- Hepatic cirrhosis — start 0.5 mg daily¹⁹

DOSE 1 mg once daily in a patient not on a diuretic; most need 2–4 mg once daily; there is little clinical experience above 8 mg.¹⁹ **CrCl below 30, or hepatic cirrhosis:** start 0.5 mg daily.¹⁹

PEARL The US label states a higher 2 mg start in Black patients.¹⁹ That reflects the lower-renin response pattern of V1-Ch13, not a separate biology — and a clinician titrating to response arrives at the same place without it.

1.16 Combinations

The reflex a drug provokes is the argument for its partner. Block the cascade and the kidney releases more renin. Give a diuretic and volume falls, which also raises renin. Each drug moves the patient toward the state in which the other works best.

Which second site is settled by a trial rather than a preference. ACCOMPLISH randomised 11,506 high-risk hypertensive patients to benazepril with amlodipine or benazepril with hydrochlorothiazide. Events occurred in 9.6% against 11.8% — HR 0.80 (95% CI 0.72–0.90, $p < 0.001$) — at 131.6/73.3 against 132.5/74.4 mmHg.⁶ Under a millimetre apart, a fifth fewer events.

TABLE 1.20 — WHAT TO ADD, AND WHAT NEVER TO ADD

COMBINATION	VERDICT	THE REASON
+ Calcium channel blocker	Preferred	ACCOMPLISH. ⁶ And the cascade drug relaxes the venule, which fixes the ankle oedema the calcium channel blocker causes — Chapter 4. Each treats the other's problem.
+ Thiazide-type diuretic	Good	The diuretic raises renin, which is the state in which cascade blockade works best. Prefer chlorthalidone or indapamide to hydrochlorothiazide — Chapter 5.
+ Beta-blocker	In heart failure, both	Not a blood-pressure combination but a mortality one: different limbs, both foundational in HFrEF.
+ Mineralocorticoid antagonist	With care	Two drugs raising potassium at different stations of one cascade. Real benefit in heart failure and resistant hypertension — potassium at one week, four weeks, then regularly.
+ ARB	Never	Two drugs at one station. ONTARGET: no added benefit, a third more renal impairment, NNH 30. ^{7,8}
+ Aliskiren in diabetes	Never	Contraindicated on the label, ^{12,19} and ALTITUDE showed why — Chapter 3.
+ NSAID and a diuretic	The triple whammy	Not a treatment combination but the commonest avoidable acute kidney injury in practice.

1.17 Clinical pearls

Thirty-two points that change practice, for a reader who has one minute.

The fair criticism of ACCOMPLISH

The diuretic arm used hydrochlorothiazide rather than chlorthalidone, which gives worse 24-hour control.⁶ A reason to prefer chlorthalidone in Part III, not a reason to set the result aside.

- 1 ACE inhibitors block angiotensin II formation and bradykinin degradation. That dual action is the whole difference from the ARBs.
- 2 The cough is bradykinin-mediated and therefore a class effect, not a molecule failure. Switch to an ARB, not to another ACE inhibitor.
- 3 Within the class the cough range is real: perindopril RR 4.19, ramipril 4.13, enalapril 1.23.
- 4 Reported cough rates in Asian series run above the Western figure — 24.1% Malaysia, 44% Hong Kong. No Indian study was found for this edition.
- 5 Angioedema is a lifetime contraindication to every molecule in the class. There is no rechallenge and no substitution within the class.
- 6 Across 378 randomised trials the angioedema association did not reach significance. Rare event, short trials — weak evidence, not evidence of absence.
- 7 A creatinine rise after starting is expected, but it is not reassurance. Below 30% within four weeks and stable, continue and watch²¹; exclude the correctable causes first (V3-Case 12). The threshold that ends it is in VI-Ch19.
- 8 A disproportionate creatinine rise within days means image the renal arteries, not stop and forget.
- 9 Check potassium and creatinine at one to two weeks and after every dose increase. This is the visit that gets missed.
- 10 If potassium will not stay below 5.5, review every other drug raising it before abandoning the class.
- 11 Prodrugs need hepatic activation. In significant liver disease use lisinopril or captopril, which are active as given.
- 12 Fosinopril needs no dose adjustment at any degree of renal impairment, because hepatobiliary elimination compensates.
- 13 But avoid fosinopril in cirrhosis with ascites — you are relying on the organ that has failed.
- 14 Trandolapril has the longest effective half-life at 22.5 hours; it is the molecule for a patient whose problem is remembering.
- 15 Captopril must be given an hour before food, two or three times a day. That schedule, not its efficacy, rules it out for maintenance.
- 16 Captopril in impaired renal function needs a white cell and differential count before starting, then about every two weeks for three months, then periodically — a renal-function rule, not a dose rule.²⁰
- 17 Lisinopril peaks at 6 to 8 hours with 10–30% bioavailability. Predictable, and slow — not the drug when you need to read a response quickly.
- 18 Perindopril has a terminal elimination phase of 30 to 120 hours. Steady state takes longer than once-daily dosing suggests.
- 19 Perindopril is not recommended below a creatinine clearance of 30 mL/min at all.
- 20 Give the first dose at bedtime. Start reduced in the elderly and in anyone already taking a diuretic.
- 21 Withhold around contrast procedures and major surgery — and write the restart date at the same time. A drug stopped without one is usually stopped for good.
- 22 Never with an ARB: ONTARGET found no added benefit and a third more renal impairment, number needed to harm 30.
- 23 Never with aliskiren in a patient with diabetes, and never within 36 hours of sacubitril/valsartan in either direction.
- 24 ACE inhibitor plus NSAID plus diuretic is the commonest preventable acute kidney injury in general practice. Ask about over-the-counter painkillers at every review.
- 25 Add a calcium channel blocker rather than a thiazide when a second drug is needed: ACCOMPLISH, a fifth fewer events at the same pressure.
- 26 The cascade drug also relaxes the venule, which fixes the ankle oedema a calcium channel blocker causes. Each treats the other's problem.
- 27 A diuretic raises renin, which is the state in which cascade blockade works best. The reflex is the argument for the pairing.
- 28 In a low-renin, salt-loaded patient this class disappoints because there is no signal to block. That is a wrongly chosen site, not treatment failure.
- 29 HOPE excluded heart failure and still found a quarter fewer events on a 3.3 mmHg difference. In the high-risk patient you are not treating the number.
- 30 Stop at the point pregnancy becomes a plan, not the point it becomes a fact.
- 31 Ask about cough at every visit. Patients blame the weather and get antibiotics for a pharmacological symptom.
- 32 The mortality signal is the ACE inhibitors' own: ARBs did not show it, and the difference between classes was statistically significant.

KEY POINTS

- 1 One enzyme, two substrates. Angiotensin II falls, which is the intention; bradykinin rises, which is the cough, the angioedema, and possibly the mortality benefit as well.
- 2 HOPE: a quarter fewer events on a 3.3 mmHg systolic difference. The pressure is not what you are treating in the high-risk patient.
- 3 Act on the cascade when renin is running. Blocking a suppressed system is a wrongly chosen site, not a dosing problem.
- 4 The counterfactual drug — all the benefit, none of the cough — already exists. It is the ARB, and on this evidence it gave up the mortality advantage along with the cough.
- 5 Switch a coughing patient across to an ARB, not sideways within the class.
- 6 Fosinopril needs no renal adjustment; trandolapril has the longest half-life; captopril is ruled out for maintenance by its dosing, not its efficacy.
- 7 Potassium and creatinine at one to two weeks is not optional, and the triple whammy is the commonest avoidable harm in this chapter.

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CHAPTER 2

PART I · THE RENIN-ANGIOTENSIN CASCADE

Angiotensin Receptor Blockers

The same cascade, blocked one step later. That single step removes the cough — and takes something else with it.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 What changes when you block the receptor instead of the enzyme.
 - 2 Where this class ranks by population, and the one group where it leads outright.
 - 3 The enzyme or the receptor: two good studies that disagree.
 - 4 Which molecule — and the two that carry something the others do not.
 - 5 The combination that harms, and the trial that proved it.

2.1

AT THE POINT OF PRESCRIBING		LAYER 1 · 60 SECONDS
USE WHEN	Everything an ACE inhibitor is used for, in a patient who cannot tolerate one · left ventricular hypertrophy specifically · type 2 diabetic nephropathy	
DO NOT USE	Pregnancy, or planning it · bilateral renal artery stenosis · potassium already high	
WHICH MOLECULE	Telmisartan when the dawn hours matter — the longest cover in the class. Losartan if the patient has gout. Candesartan or olmesartan for the tightest receptor binding.	
STARTING DOSE	Standard — unless the patient is volume- or salt-depleted or already on a diuretic, when the labels ask you to correct the depletion first or halve the start: losartan 25 mg ^{13,14} . The difference from an ACE inhibitor is the cough, not the first dose.	
FIRST CHECK	Potassium and creatinine at one to two weeks, exactly as for an ACE inhibitor.	
EXPECT	No cough. That is the point of the class, and it is the only reliable difference.	
NEVER WITH	An ACE inhibitor — no benefit, a third more renal impairment · aliskiren in diabetes	

2.2 Why act here

Chapter 1 acted on the enzyme that makes angiotensin II. This chapter acts one station further along, on the receptor angiotensin II acts through. The peptide is still made. It simply cannot deliver its message at AT₁.

Two consequences follow, and they are the whole chapter. ACE is left alone, so bradykinin is degraded normally and does not accumulate — no accumulation, no cough. And angiotensin II is still circulating and free to act at AT₂, which is not a redundant receptor: binding there produces

vasodilation, largely through nitric oxide and locally generated bradykinin, and promotes renal sodium excretion.¹ Blocking AT₁ redirects the peptide toward its counter-regulatory arm.

2.3 Where this class ranks, and why

The indications are Chapter 1’s, because it is the same cascade. What decides between the two chapters is rarely the indication — it is tolerance, and one outcome trial.

LIFE compared losartan with atenolol in 9,222 hypertensive patients aged 55 to 80 with left ventricular hypertrophy over a mean 4.8 years. The composite of stroke, myocardial infarction and cardiovascular death occurred in 11% against 13% — HR 0.87 (95% CI 0.77–0.98, p = 0.02).² Two details matter more than the headline: achieved pressures were 144.1/81.3 and 145.4/80.9 mmHg, effectively identical, and the benefit was almost entirely stroke — 5% against 7%, HR 0.75 (95% CI 0.63–0.89, p = 0.001), with no significant difference in infarction or cardiovascular death.²

A cleaner block, not a stronger one

Everything downstream of AT₁ still stops — constriction, aldosterone, efferent tone, fibrosis. What changes is what happens to bradykinin, and to the angiotensin II that is still there.

The criticisms, which are fair

The population was 92% white, dropout and escalation differed between arms, and there was a non-significant excess of myocardial infarction on losartan despite greater regression of hypertrophy.² The stroke finding is robust; the whole picture is less tidy than the headline.

TABLE 2.1 — WHERE THIS CLASS RANKS, AND WHY

POPULATION	RANK	THE REASON
Hypertension with left ventricular hypertrophy	First	LIFE randomised exactly this population and found fewer strokes at all but the same blood pressure. ² The one population with a direct outcome trial for an ARB against a real comparator.
Any cascade indication in a patient who coughed on an ACE inhibitor	First	The cough is mechanistic. Another ACE inhibitor reproduces it; this station does not. ¹ A drug the patient takes beats a better drug they stop.
Diabetic kidney disease, proteinuric CKD, HFrEF, post-MI	First or second	Same indication as Chapter 1; the choice turns on the disagreement in 2.3. Either is defensible; the enzyme has the older claim.
Hypertension with gout, or on a urate-raising diuretic	First — losartan specifically	The only molecule in either chapter that lowers urate, through URAT1. ¹ A within-class choice that outranks the between-class one.
Older, obese, salt-loaded, low-renin	Second or third	Blocking a receptor for a signal that is not being sent achieves nothing that blocking its synthesis would not.
Pregnancy; bilateral renal artery stenosis	Contraindicated	Moving one station downstream changes neither. The fetal kidney and the efferent arteriole depend on the signal, not on where it was made. ¹

2.4 The enzyme or the receptor — an honest disagreement

Chapter 1 reported that across 158,998 hypertensive patients ACE inhibitors reduced all-cause mortality by 10% and ARBs did not (HR 0.99, 95% CI 0.94–1.04), the difference between classes being significant at $p = 0.036$.⁵ It also noted the caveat: a comparison across separate trials, not a randomisation of one class against the other.

ONTARGET is close to the trial that caveat asked for. It randomised 25,620 patients aged 55 and over with vascular disease or diabetes with end-organ damage to ramipril 10 mg, telmisartan 80 mg, or both, over a median 56 months. Telmisartan was *non-inferior*: 16.7% against 16.5% on the primary composite, relative risk 1.01 (95% CI 0.94–1.09).³

Two good studies, different directions, and the book will not pretend otherwise. They do not measure the same thing. ONTARGET is a within-trial randomisation — the stronger design — but its endpoint is a cardiovascular composite in a high-risk vascular population, many not primarily hypertensive. The meta-analysis measures all-cause mortality across hypertension trials, the harder endpoint to argue with, using the weaker design.

TABLE 2.2 — WHAT A CLINICIAN CAN TAKE FROM THE DISAGREEMENT

THE PATIENT	WHAT THE EVIDENCE SUPPORTS
High-risk vascular patient who cannot take an ACE inhibitor	Telmisartan is a genuine equivalent, not a compromise. ONTARGET randomised this exact population. ³
Hypertensive, second indication present, tolerating either	The meta-analytic signal on all-cause mortality favours the ACE inhibitor. ⁵ Start there.
Hypertensive with left ventricular hypertrophy	LIFE gives an ARB a direct stroke-reduction result against a real comparator. ²
Uncomplicated hypertension, no second indication	Nobody has run the trial that settles it. Cost, tolerance and once-daily dosing decide — that is the state of the evidence, not a failure of nerve.

2.5 The ledger — and why both classes still exist

TABLE 2.3 — THE ARB LEDGER

WHAT YOU WANT FROM IT	WHAT COMES WITH IT
Everything downstream of AT ₁ stops — constriction, aldosterone, efferent tone, fibrosis — exactly as with an ACE inhibitor.	No demonstrated all-cause mortality benefit in the 158,998-patient meta-analysis, where ACE inhibitors had one. ⁵ ONTARGET disagrees on a different endpoint. ³
No cough, because ACE is untouched and bradykinin is degraded normally. ¹ Where reported cough rates run to a quarter or more, that is an adherence argument as much as a comfort one.	Angioedema still occurs, though less often than with ACE inhibitors. ¹ A patient who had angioedema on an ACE inhibitor is not guaranteed safe here.
Angiotensin II remains free to act at AT ₂ , the counter-regulatory receptor — vasodilation and sodium excretion. ¹	Hyperkalaemia and a fall in filtration in the wrong kidney, exactly as with an ACE inhibitor. Same cascade, different station.
A direct stroke reduction against atenolol at the same blood pressure in patients with LVH. ²	Fetal toxicity. Contraindicated in pregnancy. ¹ The step downstream changes nothing about this.

The verdict. First line, and the drug of choice on this cascade wherever an ACE inhibitor cannot be tolerated.

The counterfactual, run in reverse. Chapter 1 asked what an ACE inhibitor would look like without the cough and answered: like an ARB, but possibly without the mortality signal. Ask it the other way and the same fact appears

from the other side. If the ARB carried the all-cause mortality benefit, the ACE inhibitor would have no advantage left and would be an obsolete drug with a cough. It is not obsolete. Neither class has made the other redundant, and that is the clearest available evidence that the bradykinin arm does something real.

2.6 When acting here is wrong

One label rule stands with the others: never co-administered with aliskiren in a patient with diabetes.¹

TABLE 2.4 — WHEN TO LEAVE THIS SITE

SITUATION	WHY	WHERE TO ACT INSTEAD
Pregnancy, or its possibility	Fetal toxicity; the class is contraindicated. ¹ Blocking the receptor spares the fetal kidney no more than blocking the enzyme.	Methyldopa, labetalol or nifedipine — switch when pregnancy becomes a plan. V1·Ch18.
Bilateral renal artery stenosis	The same efferent-tone dependency as Chapter 1; acute renal failure can follow. ¹	Stop, image the arteries, choose a site independent of that arteriole. V1·Ch32.
Persistent hyperkalaemia	Less aldosterone, less potassium excretion. The station changed; the consequence did not.	The calcium channel, or the nephron with a thiazide-type agent.
Already on an ACE inhibitor	Dual blockade of one cascade. In hypertension a prohibition rather than a caution — see 2.8.	Add a different site, not a second drug at the same one.

2.7 The molecules, compared

The molecules are more alike than the marketing suggests. Two carry something the others do not, and one carries a liability worth knowing. Doses are those stated in the class reference;¹ where a figure was not given, the cell says so.

TABLE 2.5 — HYPERTENSION DOSING ACROSS THE CLASS

DRUG	START	MAXIMUM	WHAT DISTINGUISHES IT
Losartan	50 mg OD	100 mg	Lowers urate by inhibiting URAT1 in the proximal tubule ¹¹ — uricosuric, and unique in the class. The molecule LIFE tested.
Telmisartan	40 mg OD	80 mg	The molecule ONTARGET tested head-to-head against ramipril, with non-inferiority in a high-risk vascular population. ³
Olmesartan	20 mg OD	40 mg	Sprue-like enteropathy — chronic diarrhoea, weight loss and villous atrophy that resolve on withdrawal and are repeatedly mistaken for coeliac disease.
Valsartan	80–160 mg OD	320 mg	The ARB component of sacubitril/valsartan. Otherwise unremarkable.
Irbesartan	150 mg OD	300 mg	No property in the sourced data distinguishes it for a specific patient.
Candesartan	16 mg OD	32 mg	No property in the sourced data distinguishes it for a specific patient.
Azilsartan	80 mg OD	80 mg	80 mg is the dose, not the target — there is no titration step and no 20 mg strength on the label. Start at 40 mg only where the patient is already on a high-dose diuretic. ⁹ The newest of the group; nothing else in the sourced data distinguishes it.

Chapter 1 gives the ACE inhibitors a renal column. The ARBs need one less often, and the asymmetry should not be read as meaning they need none: the liver is where two of the labels adjust, and the interactions are the same as for

the ACE inhibitors with one addition.

Say when it does not matter

Four of these seven differ in dose and trial portfolio rather than in kind. Choose on availability, cost and once-daily dosing, and do not pretend the pharmacology decides it.

TABLE 2.5A — RENAL AND HEPATIC ADJUSTMENT, AND THE INTERACTIONS THAT CHANGE A DECISION

	WHAT THE LABEL SAYS
Losartan	Start at 25 mg where intravascular depletion is possible, as on a diuretic, and at 25 mg in mild-to-moderate hepatic impairment ¹³ .
Telmisartan	No initial adjustment in renal impairment, including haemodialysis — a positive finding, and worth knowing ¹⁴ . In biliary obstruction or hepatic insufficiency, start low and titrate slowly ¹⁴ . Volume- or salt-depleted: correct it first, or start reduced under close supervision ¹⁴ .
The other five	Their renal and hepatic adjustments are not printed here; read the label before prescribing in liver disease.
Lithium	Serum lithium rises and toxicity has been reported with the ARBs — monitor the level ^{13,14} .
Digoxin, with telmisartan	Median rise in digoxin peak of 49% and in trough of 20% — monitor the level when starting or stopping ¹⁴ .
NSAIDs	Renal function may deteriorate and the antihypertensive effect is blunted ¹⁴ ; with a diuretic as well, it is the triple whammy of Chapter 1.
Potassium	Supplements, salt substitutes, trimethoprim and a mineralocorticoid antagonist add to the hyperkalaemia in Table 2.4. Review them before abandoning the class.

2.8 One step beyond the receptor — sacubitril/valsartan

A neprilysin inhibitor paired with an ARB. Neprilysin degrades natriuretic peptides; inhibit it and they persist, adding natriuresis and vasodilation to receptor blockade. The pairing is with an ARB rather than an ACE inhibitor for a specific reason — combining neprilysin inhibition with ACE inhibition raises bradykinin from both directions and produced unacceptable angioedema in earlier work.

PARADIGM-HF randomised 8,399 patients with heart failure and reduced ejection fraction, already on a stable ACE inhibitor or ARB, to sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily. The composite of cardiovascular death or heart-failure hospitalisation occurred in 21.8% against 26.5% — HR 0.80 (95% CI 0.73–0.87, $p < 0.001$), NNT 21 — and all-cause mortality fell from 19.8% to 17.0% (HR 0.84, 95% CI 0.76–0.93). Stopped early on a positive interim analysis.⁶

Symptomatic hypotension was commoner on the combination, 14.0% against 9.2% (NNH 21); cough was less frequent, 11.3% against 14.3%; angioedema did not differ.⁶

This is a heart failure drug, not a hypertension drug, and it sits here because of where it acts. The label rule from Chapter 1 governs the switch: never within 36 hours of an ACE inhibitor, in either direction.

2.9 Combinations — and the one that harms

The partners are Chapter 1’s: a calcium channel blocker or a thiazide-type diuretic, each of which raises renin and so creates the state in which cascade blockade works best.

Read the run-in before you generalise

Patients received enalapril for two weeks and then sacubitril/valsartan for four to six weeks before randomisation. Only those who tolerated both entered.⁶ That selects for tolerance and understates the real-world adverse-effect rate. The efficacy stands; the tolerability figures are the best case.

TABLE 2.6 — WHAT TO ADD, AND WHAT NEVER TO ADD

COMBINATION	VERDICT	THE REASON
+ Calcium channel blocker	Preferred	ACCOMPLISH tested the pairing with an ACE inhibitor and found a fifth fewer events than with a thiazide at the same pressure. ⁷ The cascade drug also relaxes the venule, which fixes the calcium channel blocker’s ankle oedema — Chapter 4.
+ Thiazide-type diuretic	Good	The diuretic raises renin, which is the state this class needs. Prefer chlorthalidone or indapamide — Chapter 5.
+ Mineralocorticoid antagonist	With care	Two potassium-raising drugs at different stations of one cascade. Real benefit in resistant hypertension; potassium at one week, four weeks, then regularly.
+ ACE inhibitor	Never for blood pressure	See below. The trial is unambiguous. The one licensed exception is elsewhere: candesartan or valsartan added to an ACE inhibitor in heart failure, under specialist supervision with close monitoring ¹² .
+ Aliskiren in diabetes	Never	Contraindicated on the label ¹ and ALTITUDE showed why — Chapter 3.
+ NSAID and a diuretic	The triple whammy	Three arms of glomerular perfusion removed at once. The commonest avoidable acute kidney injury in practice.

ONTARGET is why the dual-blockade rule is a prohibition rather than a caution. Its third arm gave both drugs. It was no better than ramipril alone on the primary composite — 16.3% against 16.5%, relative risk 0.99 (95% CI 0.92–1.07) — and worse on harm: renal impairment 13.5% against 10.2% (RR 1.33, 95% CI 1.22–1.44, number needed to harm 30), discontinuation for symptomatic hypotension 4.8% against 1.7% (RR 2.75), and more diarrhoea.^{3,4}

2.10 Four patients, one site question

The general lesson

Two drugs at one station on a cascade buy no additional benefit and cost real harm. Blocking harder is not blocking better. When one site is not enough, the answer is a second site.

TABLE 2.7 — THE SAME QUESTION, FOUR ANSWERS

THE PATIENT	THE MOVE	WHY
61, hypertension with LVH on echocardiography, BP 158/92	ARB	LIFE randomised this population and found fewer strokes at all but the same blood pressure. ² The hypertrophy is the reason, not the number.
54, hypertension and gout, on indapamide, urate 480 µmol/L	Losartan specifically	The only ARB that lowers urate, through URAT1. ^{1,11} One drug answering two problems, and it removes the argument against continuing the diuretic.
47, two years on olmesartan, six months of diarrhoea, 7 kg lost, coeliac serology negative	Exclude the other causes, then stop the olmesartan	Sprue-like enteropathy. ¹ It resolves on withdrawal and is missed for years, but the label's order is exclusion first and substitution second — 7 kg demands that malignancy and inflammatory bowel disease are accounted for before the drug is blamed. ¹⁰
68, vascular disease, controlled on ramipril, intractable cough	Telmisartan	The one molecule with head-to-head non-inferiority against ramipril in exactly this population. ³ An equivalent, not a downgrade.

2.11 Why not one ARB for every patient

A fair question, and one most prescribers answer by habit rather than by reason: if the class blocks one receptor, why does it matter which molecule does the blocking? Three real pharmacological differences separate them, and each decides something at the bedside.

That is why a thoughtful physician does not write the same ARB for every patient, and it is not brand loyalty. The molecule is chosen for the shape of the day the patient has to get through.

TABLE 2.8 — THREE DIFFERENCES THAT ARE NOT MARKETING

THE DIFFERENCE	WHAT IT MEANS	WHICH MOLECULES
How the drug leaves the receptor	A competitive antagonist can be displaced when angiotensin II rises. An insurmountable one cannot — it stays put, so the block holds through a surge and lasts longer than the plasma level alone would predict.	Insurmountable: candesartan, irbesartan. Competitive: losartan, valsartan, eprosartan. ⁸
How long it acts	Whether one daily dose still covers the patient in the sixth hour before the next one — which is the early morning, and when strokes and infarcts cluster.	Shorter: losartan, valsartan, eprosartan. Longer: candesartan, irbesartan. ⁸
Where it is activated	A prodrug converted in the liver is at the mercy of that liver. One converted during absorption is not.	Losartan is <i>partially</i> converted to EXP3174 in the liver. Candesartan cilexetil is converted <i>completely</i> during gastrointestinal absorption. ⁸
How tightly it binds	Higher affinity means a lower milligram dose does the same work — which matters for tablet burden, not for outcome.	Candesartan has the highest AT1 affinity of the class and requires the lowest dosage. ⁸

TABLE 2.9 — SO WHICH ONE, AND WHEN

THIS PATIENT	THIS MOLECULE	THE REASON
Morning-dominant pressure, or a large morning surge on ambulatory monitoring	A long-acting, insurmountable agent — candesartan or irbesartan	The block has to still be there twenty hours after the dose. A competitive antagonist can be displaced exactly when angiotensin II is rising. ⁸
Takes the tablet at unpredictable times, or misses doses	Long-acting	A long half-life forgives a late dose. A short-acting agent taken twelve hours late leaves the patient unprotected.
Hypertension with gout, or on a urate-raising diuretic	Losartan	The only one that lowers urate, through URAT1 ¹ . This reason outranks duration.
High-risk vascular disease, intolerant of an ACE inhibitor	Telmisartan	The molecule with head-to-head non-inferiority against ramipril in exactly that population ³ .
Hypertension with left ventricular hypertrophy	Losartan	The molecule LIFE actually tested, with a stroke reduction at the same blood pressure ² .
Significant liver disease	Not losartan	Its conversion to the active EXP3174 is partial and hepatic ⁸ . Candesartan is converted during absorption instead.
Chronic diarrhoea of unclear cause develops	Not olmesartan	Sprue-like enteropathy ¹ . Exclude the other causes first; where none is found, the label says to change the antihypertensive ¹⁰ .
Nothing in particular decides it	Whichever is available and affordable	Said plainly, because it is true more often than the rest of this table.

2.12 Pairing durations — and when once daily is not enough

A second drug is added for the pressure. What is rarely asked is whether the pair covers twenty-four hours, and that question has a mechanical answer.

Blood pressure is not a number; it is a curve with a trough. The dangerous part of that curve is the last few hours before the next dose — the early morning, when the sympathetic surge of V1-Ch7 meets the lowest drug level of the day. A regimen that controls the clinic reading and loses the dawn has treated the measurement rather than the patient.

TABLE 2.10 — THE PAIRING RULES THAT FOLLOW

THE COMBINATION	WHAT HAPPENS	WHAT TO DO
Long-acting plus long-acting	Cover holds through the trough from both directions. The safest default.	Once daily, both. Nothing further needed.
Long-acting plus short-acting	The long agent carries the trough while the short one is fading. Acceptable.	Once daily is defensible — but give the short-acting agent at night if the pressure is morning-dominant.
Short-acting plus short-acting	Both troughs fall together. The patient is least protected exactly when risk is highest.	Twice-daily dosing, or change one molecule. This is the combination that looks controlled in clinic and is not.
Either, in a patient taking the dose in the morning with a morning-dominant profile	The peak arrives after the surge it was meant to cover.	Move a dose to the evening before adding a third drug. It costs nothing and it is frequently the whole answer.

This is also the honest argument for the fixed-dose combinations that dominate Indian prescribing. One tablet improves adherence, which is the largest single determinant of control. But the combination is only as good as its shorter component, and a once-daily fixed-dose pill containing a short-acting agent inherits that agent's trough.

2.13 Which ARB when the partner is amlodipine

The commonest two-drug regimen in Indian practice, and it deserves a specific answer rather than a general one.

Amlodipine is the long-acting member of its class — that is the property it was designed around, and it is why it survived while short-acting nifedipine was abandoned for chronic use (Chapter 4). So the calcium channel side of this pair already carries the trough. That relaxes the constraint on the ARB, and it means the ARB can be chosen for something other than duration.

How to tell without an ABPM

Ask when they take the tablet, and take the pressure at the end of the dosing interval rather than at its peak — a morning reading before the morning dose. If that reading is much worse than the clinic reading taken two hours after a dose, the problem is duration, not dose.

TABLE 2.11 — CHOOSING THE ARB FOR AN AMLODIPINE-BASED REGIMEN

IF THE DECIDING PROBLEM IS	CHOOSE	WHY
Ankle oedema on the amlodipine	Any ARB — the class effect is what matters	The RAAS blocker relaxes the post-capillary venule and equalises the capillary gradient. This is a class property, not a molecular one, so pick on the other reasons.
Coexisting gout, or a diuretic also in the regimen	Losartan	Urate falls through URAT1 ^{1,11} — and a thiazide in the same regimen raises it.
A large morning surge despite good clinic readings	Candesartan or irbesartan	Insurmountable and longer acting ⁸ . Amlodipine covers the trough; now both components do.
Established vascular disease	Telmisartan	The head-to-head evidence in that population sits with this molecule ³ .
Left ventricular hypertrophy	Losartan	LIFE ² .

2.14 Clinical pearls

Ten points that change practice, for a reader who has one minute.

And the reverse question

If the calcium channel blocker is *not* amlodipine — if it is a shorter-acting dihydropyridine, or a divided-dose non-dihydropyridine — then the ARB must carry the trough, and the long-acting insurmountable agents become the right choice rather than an optional one.

- 1 Blocking the receptor leaves ACE alone, so bradykinin is degraded normally and there is no cough.
- 2 LIFE: losartan beat atenolol in hypertensives with LVH at all but the same blood pressure, and the benefit was almost entirely stroke.
- 3 The meta-analysis favours ACE inhibitors on all-cause mortality, each class against control rather than against the other; ONTARGET found telmisartan non-inferior on a cardiovascular composite. Different endpoints, different designs — both are printed here.
- 4 Neither class has made the other obsolete, which is the clearest evidence the bradykinin arm does something real.
- 5 Losartan lowers urate through URAT1¹¹ — the one within-class difference that decides a prescription on its own.
- 6 Olmesartan causes a sprue-like enteropathy mistaken for coeliac disease. In severe chronic diarrhoea with weight loss, exclude the other causes first, and change the antihypertensive if none is found.¹⁰
- 7 Never an ACE inhibitor and an ARB together for blood pressure: no benefit, a third more renal impairment, number needed to harm 30.
- 8 Angioedema on an ACE inhibitor does not guarantee safety here; it is reported on ARBs, far less often.
- 9 Pregnancy and bilateral renal artery stenosis rule out this class exactly as they rule out Chapter 1.
- 10 Sacubitril/valsartan is a heart failure drug. Never within 36 hours of an ACE inhibitor, in either direction.

KEY POINTS

- 1 Blocking the receptor leaves ACE alone, so bradykinin is degraded normally and there is no cough.
- 2 LIFE: losartan beat atenolol in hypertensives with LVH at all but the same blood pressure, and the benefit was almost entirely stroke.
- 3 The meta-analysis favours ACE inhibitors on all-cause mortality, each class against control rather than against the other; ONTARGET found telmisartan non-inferior on a cardiovascular composite. Different endpoints, different designs — both are printed here.
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- 7 Never an ACE inhibitor and an ARB together for blood pressure: no benefit, a third more renal impairment, number needed to harm 30.

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CHAPTER 3

PART I · THE RENIN-ANGIOTENSIN CASCADE

Direct Renin Inhibitors

The most upstream target on the cascade, and the least useful drug in this book. That is not a contradiction — it is the chapter’s entire lesson.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 Why renin looked like the ideal target, on paper.

2 What happened when the idea met two trials.

3 Why more complete blockade of a cascade is not better blockade.

4 The lesson that outlives the drug, and applies to every chapter after this one.

AT THE POINT OF PRESCRIBING		LAYER 1 · 60 SECONDS
USE WHEN	Essentially never. This chapter is here for the reasoning, not for the prescription.	
DO NOT USE	With an ACE inhibitor or ARB in a patient with diabetes — the combination was tested and it caused harm. In pregnancy , on a boxed warning for fetal toxicity: stop it as soon as pregnancy is detected ⁴	
THE MOLECULE	Aliskiren. Still licensed and still on some formularies ⁵ , but effectively abandoned in practice. If you find it on a prescription, check what else is blocking the cascade — with an ACE inhibitor or ARB in diabetes it is contraindicated ⁴ .	
WHAT TO CARRY AWAY	Asite’s position in a pathway does not predict its clinical value. Upstream is not better.	

3.1 Why act here — the argument that was almost right

Renin is the first step of the cascade and the rate-limiting one. It is also extraordinarily specific: angiotensinogen is its only substrate, so inhibiting renin does nothing else anywhere in the body. On paper that is close to an ideal drug target — the earliest point, the controlling point, and no off-target work.

Aliskiren blocks the conversion of angiotensinogen to angiotensin I,¹ upstream of the enzyme of Chapter 1 and of the receptor of Chapter 2. Everything downstream should fall away. The reasoning is clean, and it is the reasoning this whole volume uses.

It did not work. Understanding why is worth more than the drug ever was.

3.2 Where this class ranks

TABLE 3.1 — WHERE THIS CLASS RANKS, AND WHY

	THE REASON
Any population, as monotherapy	Last, and in practice not at all. Oral bioavailability is 2.0–2.5% ¹ — two per cent of the dose reaches the circulation. There is no outcome evidence placing it above the classes in Chapters 1 and 2, and after the hyperkalaemia and hypotension of ALTITUDE ¹ it has been abandoned in practice. It has not been withdrawn: active labels for aliskiren and Tekturna are still current ⁵ .
Added to an ACE inhibitor or ARB in diabetes	Contraindicated. Not a ranking. ALTITUDE is why, and it is in 3.4.
Pregnancy, or a woman who may become pregnant	Barred, on a boxed warning. The label requires the drug to be stopped as soon as pregnancy is detected: a drug acting directly on the renin–angiotensin system can injure and kill the developing fetus. ⁴
The reason this chapter exists at all	The contents page promised it, the molecule still appears on some formularies, and the reasoning behind its failure is the most useful thing in Part I.

3.3 What happened — ALTITUDE

ALTITUDE randomised 8,561 patients with type 2 diabetes and chronic kidney disease, cardiovascular disease or both. Every patient was already taking an ACE inhibitor or an ARB. Aliskiren, or placebo, was added on top.

It was stopped early. Major cardiovascular and renal events were not reduced — 18.3% against 17.1% for placebo, numerically worse — and the harms were clear: hyperkalaemia in 11.2% against 7.2%, and hypotension in 12.1% against 8.3%.²

Set that beside ONTARGET from the previous chapter, where adding an ARB to an ACE inhibitor produced no benefit on the primary composite and a third more renal impairment.³ Two large trials, two different second drugs, two different stations on the cascade, and the same answer.

3.4 The ledger, and the counterfactual

The pattern is the finding

Every attempt to block this cascade more completely has produced more harm without more benefit. That is now true at three combinations of stations. It should be treated as a property of the cascade rather than a property of any one drug.

TABLE 3.2 — THE DIRECT RENIN INHIBITOR LEDGER

WHAT YOU WANTED FROM IT	WHAT CAME WITH IT
The first step of the cascade, blocked directly, with perfect substrate specificity — the cleanest theoretical target in RAAS pharmacology.	Bioavailability of 2.0–2.5%. ¹ The elegance of the target could not survive the pharmacokinetics.
A 24-hour half-life supporting once-daily dosing. ¹	No outcome benefit to place it above two established classes, and harm when combined with either. ²
In principle, blockade unescapable by the reactive rise in renin that ACE inhibitors and ARBs both provoke.	Hyperkalaemia and hypotension sufficient to end its use in practice, though not its licence. ¹⁵

The verdict. Not a treatment option in current practice.

The counterfactual. Suppose bioavailability had been 60% rather than 2%, and suppose the harms had not appeared. Would this then be the RAAS drug of choice, being the most upstream? The honest answer is that we do not know, and ALTITUDE gives a reason to doubt it. The trial did not fail because too little drug arrived. It failed because *more complete blockade of this cascade was not the objective* — the objective was a clinical outcome, and the two came apart.

3.5 The lesson that outlives the drug

This volume argues that choosing a drug means choosing a site. Chapter 3 marks the limit of that idea, and the limit is important enough to state plainly: **a site’s position in a pathway does not predict its clinical value.** Upstream is not better. Nor is downstream. What matters is what happens to the patient when you interrupt there, and that is an empirical question every time.

Two reasons the cascade defeats the intuition. First, it is not a one-way pipe. Block renin and plasma renin concentration rises steeply as the feedback loop responds; block the enzyme and angiotensin II is still generated by alternative pathways; block the receptor and the ligand accumulates and finds AT₂. The system is built to resist being switched off, which is precisely what you would expect of a mechanism defending arterial pressure.

Second, completeness is the wrong target. A patient does not benefit from having no angiotensin II. They benefit from a lower pressure, a protected kidney and an unremodelled heart — and beyond a certain point the additional blockade buys none of those while costing potassium, filtration and blood pressure in the wrong direction.

3.6 The molecule

Aliskiren DIRECT RENIN INHIBITOR

MECHANISM	Inhibits renin itself, blocking the conversion of angiotensinogen to angiotensin I — the first and rate-limiting step of the cascade, upstream of every other RAAS drug.
PHARMACOKINETICS	Bioavailability 2.0–2.5%. Half-life averages 24 hours.
DOSE	Hypertension: 150 mg daily initially; maximum 300 mg daily.
RENAL IMPAIRMENT	No adjustment of the starting dose is required. Avoid the combination with an ACE inhibitor or an ARB where the creatinine clearance is below 60 mL/min. ⁴
PREGNANCY	Boxed warning for fetal toxicity. Stop the drug as soon as pregnancy is detected — a drug acting directly on the renin-angiotensin system can injure and kill the developing fetus. ⁴
CONTRAINDICATIONS	With an ACE inhibitor or an ARB in a patient with diabetes; known hypersensitivity to aliskiren; and children under two years. The boxed warning for fetal toxicity bars it in pregnancy as well. ⁴
ADVERSE EFFECTS	Diarrhoea in 2.3%. Cough, rash, headache and dizziness.

Carry this into every chapter that follows

When a second drug is needed, the answer is a second site, not a second drug at the site already blocked. That principle is derived here, from the one class that tested it to destruction.

3.7 Clinical pearls

Ten points that change practice, for a reader who has one minute.

- 1 Renin has one substrate and sits at the rate-limiting step. That is the strongest theoretical case any antihypertensive target has ever had, and it did not survive contact with patients.
- 2 Aliskiren lowers blood pressure. It was never shown to lower events. Those are different claims, and only the second one licenses a prescription.
- 3 Oral bioavailability of 2.0–2.5% means most of the dose never arrives. A drug can fail on pharmacokinetics long before its mechanism is tested.
- 4 Blocking renin raises plasma renin concentration steeply. The cascade is built to defend arterial pressure and it responds to being switched off.
- 5 ALTITUDE randomised 8,561 diabetic patients to aliskiren added to an ACE inhibitor or ARB. Hyperkalaemia 11.2% against 7.2%, hypotension 12.1% against 8.3%, benefit none. The trial was stopped early.
- 6 Aliskiren with an ACE inhibitor or an ARB in diabetes is contraindicated on the label, and the label carries a boxed warning for fetal toxicity. Stop it as soon as pregnancy is detected. Neither is a matter of judgement.⁴
- 7 ONTARGET found the same shape with a different pair of drugs: no added benefit, a third more renal impairment. Two trials, one lesson.
- 8 When one site is not enough, the answer is a second site. Adding a second drug at a site already blocked is the error both trials made.
- 9 A site's position in a pathway does not predict its clinical value. Upstream is not better, and neither is downstream — it is an empirical question every time.
- 10 The drug is still licensed but abandoned in practice. The chapter stays because the reasoning transfers to every class in this volume, and to classes outside it.

KEY POINTS

- 1 Renin is the first and rate-limiting step of the cascade and has one substrate. On paper it is the ideal target; in practice the class never worked.
- 2 Oral bioavailability of 2.0–2.5% is part of the answer, but not the whole of it.
- 3 ALTITUDE: added to an ACE inhibitor or ARB in 8,561 diabetic patients, aliskiren reduced nothing and increased hyperkalaemia (11.2% against 7.2%) and hypotension (12.1% against 8.3%). Stopped early.
- 4 Read alongside ONTARGET, the pattern is a property of the cascade, not of a drug: more complete blockade has repeatedly produced more harm and no more benefit.
- 5 A site's position in a pathway does not predict its clinical value. Upstream is not better.
- 6 When one site is not enough, add a second site — never a second drug at the same one.
- 7 Aliskiren is still licensed and still on some formularies, but it is in this book for the reasoning, not for the prescription. If it turns up on a prescription, check what else is blocking the cascade.

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CHAPTER 4

PART II · THE CALCIUM CHANNEL

Calcium Channel Blockers

One channel, three drugs that behave nothing alike — and the commonest side effect in the chapter is the one most often treated wrongly.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 Why one channel produces a vasodilator, a rate-control drug, and something in between.
- 2 Where this class ranks by population — and the four groups where it leads outright.
- 3 Ankle swelling on amlodipine: what it is, what it is not, and the four moves that follow.
- 4 What separates the generations of dihydropyridine, with the numbers.
- 5 Cilnidipine, and whether a second channel earns its place.

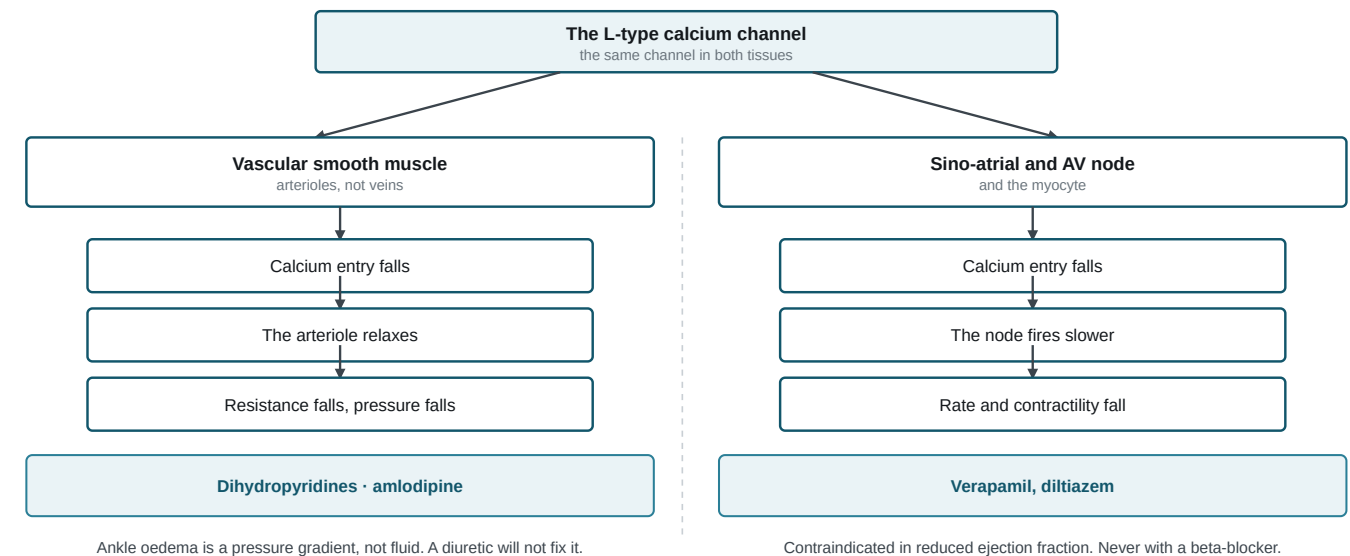
AT THE POINT OF PRESCRIBING

LAYER 1 · 60 SECONDS

USE WHEN	Isolated systolic hypertension · older patient · stiff arteries, wide pulse pressure · low-renin or salt-loaded · angina · as the second drug alongside a RAAS blocker
DO NOT USE	Verapamil in severe left ventricular dysfunction — contraindicated; diltiazem carries a warning there rather than a contraindication, and is avoided for the same reason · a non-dihydropyridine with a beta-blocker for blood pressure — additive on rate, conduction and contractility
WHICH MOLECULE	Amlodipine as default — longest half-life, most evidence. Lercanidipine if ankle oedema is the problem: relative risk 1.27 against amlodipine's 3.34. Verapamil or diltiazem only when rate control is the goal.
STARTING DOSE	Amlodipine 2.5–5 mg once daily. Oedema is dose-related; the lower dose plus a second drug beats the higher dose alone.
FIRST CHECK	Ankles at four weeks. Blood pressure at four weeks.
IF ANKLES SWELL	It is not fluid overload and a diuretic will not fix it. Halve the dose, or add a RAAS blocker, or switch to lercanidipine. In that order.
NEVER WITH	Verapamil plus a beta-blocker — two drugs on one node. Diltiazem with one only under monitoring

4.1 Why act here

FIGURE 4.1 — ONE CHANNEL, TWO TISSUES, AND WHERE EACH MOLECULE LANDS



Selectivity between tissues, not between channels. A dihydropyridine reaches the vessel and largely spares the node; verapamil and diltiazem do the reverse. Every clinical rule in this chapter follows from which column a molecule lands in — including the one that matters most, that you may put a dihydropyridine with a beta-blocker and should not put verapamil with one for blood pressure.

Vascular smooth muscle contracts when calcium enters through the L-type channel. Block the channel, less calcium enters, the cell relaxes, the arteriole dilates and resistance falls. This is the SVR term of $MAP = CO \times SVR$ from V1-Ch1, addressed directly rather than through a hormone or a nerve.

That directness is the class's defining property. Every other site in this book works by removing a signal — angiotensin II, aldosterone, noradrenaline. This one works on the effector, so it does not care whether renin is high or low, whether the patient is young or old, or whether the sympathetic system is driving anything. It lowers resistance in whoever takes it.

The same L-type channel sits in the myocardium and the conducting tissue, and this is where the class divides. Dihydropyridines have “*minimal direct effects on the myocardium and are primarily peripheral vasodilators*”, while the non-dihydropyridines “*exert inhibitory effects on the SA and AV nodes, thereby slowing cardiac conduction and contractility*”.¹ Same channel, two tissues, two drugs that behave nothing alike.

4.2 Three drugs, one channel — and an honest caveat

The clean account taught everywhere is that the three subclasses bind three distinct sites on the same α_1 subunit, and that each prefers a different channel state: dihydropyridines the inactivated state, verapamil the open and inactivated states, diltiazem somewhere between. From that, everything else is said to follow.

The molecular literature is less settled than the teaching. Transferring three channel segments confers sensitivity to all three drug classes, and the authors state that “it is currently not entirely clear which of the determinants ... form part of the drug binding pocket and which affect the drug-channel interaction in an indirect manner”.² On state preference they are equally careful: the drugs show

Hold on to this

The split is not a pharmacological curiosity. It is the reason one half of the class is a first-line antihypertensive and the other half is a rate-control drug that goes with a beta-blocker only for a clear reason and under close monitoring.

higher affinity for open or inactivated channels, but the evidence suggests they may accelerate transitions into the fast inactivated state rather than selectively bind it.²

And the clinical consequences are not in doubt either, whatever the molecular detail: dihydropyridines dilate vessels and leave the heart alone; verapamil and diltiazem slow the node. This book gives the clean account because it predicts behaviour correctly, and gives the caveat because the mechanism underneath it is less certain than a textbook diagram suggests.

What is not in doubt
Use-dependence. Verapamil's block accumulates during a train of depolarisations before the drug dissociates from resting channels² — so the faster the heart goes, the more blockade there is. The drug intensifies during the very tachyarrhythmia it is treating. That is a real property with a real clinical use.

TABLE 4.1 — THE THREE SUBCLASSES AT A GLANCE

PROPERTY	DIHYDROPYRIDINE (AMLODIPINE TYPE)	PHENYLALKYLAMINE (VERAPAMIL)	BENZOTHIAZEPINE (DILTIAZEM)
Vascular selectivity	Very high	Low to moderate	Moderate
SA node — rate	No direct effect; reflex rise possible	Slows significantly	Slows moderately
AV node — conduction	No effect	Prolongs the PR interval	Mild to moderate
Contractility	Negligible	Reduced significantly	Mildly reduced
Peripheral oedema	Common ⁴	Uncommon	Uncommon
Reflex tachycardia	With rapid-onset agents; not with amlodipine	No — rate usually falls	No — rate usually falls
Rate control in AF	No	Yes, first line	Yes, first line
Safe in HFrEF	Amlodipine and felodipine only	Contraindicated ¹	Warned against, not contraindicated — avoided for the same reason ¹²
With a beta-blocker	Safe	Avoid	Extreme caution

4.3 Where this class ranks, and why

Because it acts on the effector rather than on a signal, this class works where signal-blocking drugs disappoint. That is the whole of its ranking.

TABLE 4.2 — WHERE THIS CLASS RANKS, AND WHY

POPULATION	RANK	THE REASON
Elderly, isolated systolic hypertension, stiff arteries	First	The problem is the vessel wall, and this is the only class that acts on it directly. Nothing is being signalled that could be blocked instead.
Low-renin, salt-loaded, obese, non-dipping	First	RAAS blockade underperforms because the cascade is already suppressed — V1-Ch12. Channel blockade does not depend on renin being high.
Hypertension with gout, or on a urate-raising diuretic	First	Metabolically neutral: no effect on urate, glucose or potassium, and no monitoring bloods for the dihydropyridines ¹ .
Pregnancy	First-line option	Nifedipine is among the accepted agents. The cascade is closed entirely here, so the channel and the sympathetic sites are what remain. V1-Ch18.
Hypertension with angina, or with atrial fibrillation needing rate control	First — the other half of the class	Verapamil or diltiazem. Their effect on the AV node is the point, not a side effect.
Proteinuric kidney disease	Second	A dihydropyridine lowers systemic pressure without relaxing the efferent arteriole. Add it to a RAAS blocker; do not use it instead of one. Cilnidipine is the partial exception — 4.9.
Heart failure with reduced ejection fraction	Avoid the non-dihydropyridines entirely	Negative inotropy in a failing ventricle. Verapamil is contraindicated in severe left ventricular dysfunction; diltiazem carries a warning rather than a contraindication, and is avoided for the same reason ¹² . Amlodipine is the dihydropyridine with safety data here.

4.4 The ledger, and the counterfactual

The verdict. First line, and the most broadly applicable class in the volume.

The counterfactual. Remove the ankle oedema and this would be the default first drug in almost every hypertensive: it works in everyone, needs no blood tests, and has outcome data. The oedema is the entire reason it is not automatic. And unlike the beta-blocker's metabolic cost, this one is largely fixable — which is the next section.

TABLE 4.3 — THE CALCIUM CHANNEL BLOCKER LEDGER

WHAT YOU WANT FROM IT	WHAT COMES WITH IT
Direct arteriolar dilation that works irrespective of renin, age or sympathetic tone. The most dependable single agent in the book.	Peripheral oedema. Relative risk against placebo 3.34 for amlodipine and 6.03 for nifedipine ⁴ .
Metabolic neutrality — no effect on glucose, potassium or urate, and no monitoring bloods for the dihydropyridines ¹ .	Flushing, headache and ankle swelling appearing two to three weeks in ¹ — just as the patient has decided the drug suits them.
Fewer cardiovascular events than a thiazide when added to a cascade drug, at the same blood pressure ⁶ .	Constipation, bradycardia and negative inotropy — but only from the non-dihydropyridine half. ¹
An accepted option in pregnancy, where most of this book is closed.	CYP3A4 metabolism, so grapefruit and a long list of inhibitors raise levels ¹ .

4.5 The target map — where else this channel is

The L-type calcium channel is not a vascular channel. It is a channel found in vascular smooth muscle, cardiac muscle, the conducting system, gut smooth muscle and gingival fibroblasts — and a drug that blocks it reaches all of them in proportion to how much it is drawn to each tissue. **That tissue preference is the entire difference between amlodipine and verapamil, and it is what this map is for.**

TABLE 4.4 — ONE CHANNEL, FIVE TISSUES, AND WHAT BLOCKING EACH PRODUCES

WHERE THE CHANNEL IS	WHAT IT NORMALLY DOES THERE	WHAT BLOCKING IT PRODUCES
Arteriolar smooth muscle	Calcium entry sustains vascular tone. This is where the dihydropyridines act almost exclusively.	The intended effect: vasodilatation and a fall in resistance . And its immediate consequences — flushing, headache, and a reflex tachycardia the baroreflex produces because it can still detect the fall.
Pre-capillary arterioles, specifically	The arteriolar side dilates while the venular side does not, so capillary hydrostatic pressure rises.	Ankle oedema ³ . Mechanical, not fluid overload — which is why a diuretic does not touch it and a venodilating RAAS blocker does. Rates track vascular selectivity: nifedipine 6.03, amlodipine 3.34, lercanidipine 1.27 ⁴ .
Sinoatrial and atrioventricular node	Calcium entry drives the pacemaker current and nodal conduction. Verapamil and diltiazem bind here; dihydropyridines barely do.	Bradycardia and heart block for the non-dihydropyridines — useful when rate control is the goal, and the reason a beta-blocker on top is a combination to avoid for blood pressure: the suppression of the node is additive. Verapamil's label draws two lines: avoid it outright in severe left ventricular dysfunction — an ejection fraction below 30% or moderate-to-severe symptoms — and avoid it in any degree of ventricular dysfunction if a beta-blocker is already being given ¹² . With diltiazem the pair is described as usually well tolerated, but only under monitoring ¹² .
Myocardium	Calcium entry contributes to contractile force.	Negative inotropy , which is why verapamil is contraindicated in severe left ventricular dysfunction — the warnings that contraindication points to define it as an ejection fraction below 30% or moderate-to-severe symptoms of cardiac failure ¹² . Diltiazem carries no contraindication in chronic heart failure; it is contraindicated in acute myocardial infarction with pulmonary congestion on the admission film, and its warnings record heart failure worsening where ventricular function was already impaired ¹² . Neither restriction extends to heart failure with preserved ejection fraction, and the dihydropyridines carry neither ¹ .
Gut smooth muscle	Calcium entry maintains colonic tone and peristalsis.	Constipation — a verapamil effect in particular, and a common unspoken reason older patients stop it.
Gingival fibroblasts	Calcium signalling regulates fibroblast turnover in the gingiva.	Gum hypertrophy . Slow, painless, easily attributed to dental hygiene, and reversible on withdrawal. Worth asking about at annual review.

The map explains the chapter's central clinical instruction better than any warning could. **Ankle oedema is in the second row, not the first.** It is a consequence of dilating one side of the capillary bed and not the other — so the fix is either less dilatation (halve the dose), a more selective agent (lercanidipine), or dilatation of the other side too (add a RAAS blocker). A diuretic addresses none of those, which is why prescribing one is the commonest wrong answer in this chapter.

4.6 It happened — now what?

This is the section a drug app cannot give you. An adverse effect is a decision point, and the right move follows from the mechanism.

Ankle swelling on amlodipine. Be clear first what it is. Dihydropyridines dilate the pre-capillary arteriole far more than the post-capillary venule, so pressure inside the capillary rises and fluid is pushed into tissue. “Calcium channel blocker-related edema is not due to excess intravascular volume and therefore is not responsive to diuretics.”³ The patient is not overloaded. They have a pressure-gradient problem in one capillary bed.

And the distinction that matters most. Ankle oedema and angioedema are different events with opposite answers. Ankle oedema is bilateral, dependent, pitting, painless, worse by evening, and unaccompanied by breathlessness or a raised JVP — a mechanical consequence of the drug working. Angioedema is facial, lingual or laryngeal, and an airway emergency. If a patient on amlodipine and an ACE inhibitor develops angioedema, the ACE inhibitor is the cause: that class is contraindicated for life while the calcium channel blocker continues. Do not stop the wrong drug.

And the row that predicts a drug interaction
Every dihydropyridine is metabolised by CYP3A4¹. The map does not show that — metabolism is not a site of action. It is worth separating the two ideas: a target map predicts effects, a metabolic pathway predicts interactions, and confusing them produces confident nonsense.

The commonest mistake in this chapter
Adding a diuretic. It cannot work, because there is no excess volume to remove — and you will have added potassium loss, urate and glucose to a patient who had a mechanical problem.

TABLE 4.5 — ANKLE OEDEMA ON A DIHYDROPYRIDINE: THE FOUR MOVES, IN ORDER

MOVE	WHY IT WORKS	WHEN TO CHOOSE IT
1. Add an ACE inhibitor or ARB	Relaxes the post-capillary venule so pressure equalises across the capillary and the leak stops. Adding a RAAS blocker has been reported to reduce this oedema ³ .	Almost always first — the patient usually needs a second drug anyway, and this one treats the problem while lowering the pressure further.
2. Switch within the class	Third-generation agents dilate both sides more evenly ³ . Across 71 trials and 56,283 patients: lercanidipine RR 1.27 (95% CI 0.48–3.33, not significant) against amlodipine 3.34 and nifedipine 6.03 ⁴ .	When a cascade drug is already aboard, or cannot be. Amlodipine to lercanidipine is a real reduction, not a gesture — but check the renal function first: lercanidipine is contraindicated below a GFR of 30 mL/min ⁸ .
3. Reduce the dose	The effect is dose-related. Half doses of two drugs beat a full dose of one.	When the pressure is at target and there is room to trade.
4. Change site	If swelling persists on a third-generation agent with a RAAS blocker aboard, the channel is not the right site for this patient.	Last, not first. The class is too useful to abandon over a manageable effect.

TABLE 4.6 — THE OTHER FOUR, AND THE MOVE EACH CALLS FOR

	WHAT TO DO
Flushing and headache in the first fortnight	Usually settles. Warn the patient before starting, use a long-acting or slow-release preparation, and do not stop on day three. This is the most commonly abandoned effective drug in general practice.
Constipation on verapamil	Predictable and often intolerable. Switch to diltiazem, which does it less, or to a dihydropyridine if rate control was not the point.
Bradycardia or AV block on verapamil or diltiazem	Stop, and check what else the patient takes. A non-dihydropyridine with a beta-blocker is two drugs on one node.
Gingival hypertrophy	A real class effect, most reported with nifedipine. Switch molecule or change site; dental hygiene alone will not fix it.

4.7 When acting here is wrong

TABLE 4.7 — WHEN TO LEAVE THIS SITE

SITUATION	WHY	WHERE TO ACT INSTEAD
Heart failure with reduced ejection fraction — non-dihydropyridines	Negative inotropy in a ventricle that cannot afford it. Verapamil is contraindicated in severe left ventricular dysfunction; diltiazem carries a warning that heart failure worsens where ventricular function is already impaired, which is reason enough to stay off it here too ¹² .	The cascade and the beta-blocker, the classes with mortality data here.
Second- or third-degree AV block, sick sinus syndrome	Verapamil and diltiazem act on the node that is already failing. Contraindicated on both labels — unless a functioning ventricular pacemaker is in place, which is the exception both of them make ¹² .	A dihydropyridine, which does not touch conduction. With a pacemaker in place, either non-dihydropyridine is permitted.
Atrial flutter or fibrillation with an accessory pathway	Blocking the node hands the atrial rate to the pathway. Verapamil is contraindicated, and this is the one conduction setting in which these drugs kill ¹² .	Nothing from this class. This is an arrhythmia problem before it is a pressure problem.
GFR below 30 mL/min or dialysis — lercanidipine	Contraindicated on the United Kingdom label, along with severe hepatic impairment and untreated heart failure ⁸ . The molecule this chapter recommends for oedema is the one in it that advanced renal disease rules out.	Amlodipine, which carries no renal contraindication.
Already on a beta-blocker, considering verapamil	Two drugs depressing SA automaticity and AV conduction. Additive negative chronotropy and dromotropy.	A dihydropyridine, which combines with a beta-blocker safely. If a non-dihydropyridine is genuinely needed, diltiazem with close monitoring rather than verapamil.
Systolic blood pressure below 90 mmHg	Contraindicated for the non-dihydropyridines ¹ .	Correct the cause of the hypotension first.
Proteinuric kidney disease, as the only agent	It lowers systemic pressure without touching intraglomerular pressure.	The cascade first, this class second — not the other way round.

4.8 Interactions, and what to check

The whole class is metabolised by CYP3A4¹, which is where most of its interactions come from. The non-dihydropyridines add interactions of their own because they inhibit that enzyme rather than merely being cleared by it.

The combination to avoid, stated plainly

Verapamil with a beta-blocker. Both depress the sinoatrial node and atrioventricular conduction, and the combination risks complete heart block, severe bradycardia and asystole. If a patient on a beta-blocker needs rate control from this class, diltiazem with close monitoring is the safer choice.

TABLE 4.8 — INTERACTIONS THAT CHANGE A DECISION

WITH	WHAT HAPPENS	WHAT TO DO
Beta-blocker, with verapamil or diltiazem	Additive suppression of the SA and AV nodes.	Avoid with verapamil. Diltiazem only with monitoring.
CYP3A4 inhibitors — clarithromycin, ketoconazole, ritonavir	Levels of the calcium blocker rise ¹ .	Anticipate hypotension; reduce the dose or choose another antibiotic.
Grapefruit juice	A CYP3A inhibitor ¹ . The effect is minor with amlodipine and much larger with felodipine.	Worth asking about, and worth naming the fruit rather than saying “citrus”.

WITH	WHAT HAPPENS	WHAT TO DO
Statins	Amlodipine and the non-dihydropyridines raise levels of simvastatin and lovastatin through CYP3A4.	Simvastatin not above 20 mg with amlodipine , and not above 10 mg with verapamil or diltiazem ¹³ ; lovastatin not above 40 mg with verapamil ¹² . Atorvastatin and rosuvastatin avoid the question.
Digoxin, with verapamil or diltiazem	Serum digoxin rises by 50 to 75% in the first week of verapamil ¹² .	The label says reduce the digoxin dose when the verapamil starts ¹² ; check a level, and check one with diltiazem as well.
Rifampicin and other CYP3A4 inducers	The opposite problem, and the Indian one. Rifampicin markedly reduces oral verapamil bioavailability ¹² , and the whole class is cleared by the enzyme it induces ¹ .	A patient started on antitubercular treatment loses much of the effect. Expect the pressure to rise, and do not read it as non-adherence.
Ciclosporin, tacrolimus	Immunosuppressant levels rise.	Monitor levels. A transplant physician needs to know before the calcium blocker starts.

TABLE 4.9 — MONITORING — AND IT DIFFERS BY HALF OF THE CLASS

	WHAT TO CHECK
Dihydropyridines	Blood pressure and heart rate ¹ . No routine bloods — one of the reasons this class is easy to run in a busy clinic.
Verapamil or diltiazem	Liver function, blood pressure, heart rate and an ECG on starting ¹ . The ECG is for the PR interval, and it is not optional.
Every visit, either half	Look at the ankles. Ask whether the patient has stopped the drug because of them — many do without saying so.

4.9 The generations of dihydropyridine

The dihydropyridines were not developed in parallel. Each generation was an attempt to fix what the previous one did wrong, and knowing which problem was being solved tells you which agent to reach for.

TABLE 4.10 — WHAT EACH GENERATION WAS TRYING TO FIX

GENERATION	AGENTS	WHAT CHANGED	WHAT IT STILL COSTS
First	Nifedipine immediate-release	Proved the principle: block the vascular channel and the pressure falls.	Onset so rapid that the baroreflex fires — reflex tachycardia, and a short half-life needing three doses a day.
Second	Nifedipine SR and GITS, nicaidipine, felodipine	The same molecule, slowed down by formulation. Blunting the rate of rise blunts the reflex.	Still shorter-acting than a day, and oedema remains.
Third	Amlodipine, lercanidipine, lacidipine	Intrinsically slow onset and long duration by molecular design rather than by tablet engineering. Reflex tachycardia essentially disappears.	Oedema persists, at rates that differ between them: amlodipine RR 3.34, lercanidipine 1.27 ⁴ .
Third, plus a second channel	Cilnidipine	Adds N-type blockade on sympathetic nerve terminals to the L-type vascular block — 4.9.	Shorter plasma half-life than amlodipine; the evidence base is smaller.

4.10 Cilnidipine — does a second channel earn its place?

Cilnidipine blocks the N-type calcium channel as well as the L-type. N-type channels sit on sympathetic nerve terminals, including those supplying the kidney, so blocking them suppresses noradrenaline release rather than merely

dilating the vessel the noradrenaline would have constricted. It is widely available in India, and the question is whether the second channel does anything a reader should act on.

The best evidence located for this edition is TACTICAL: 35 hypertensive patients already taking a renin–angiotensin inhibitor, randomised to cilnidipine or amlodipine for six months. The urinary albumin–creatinine ratio fell significantly in the cilnidipine group and not in the amlodipine group, while “systolic and diastolic BPs were significantly reduced in both of the groups, without any significant difference between the groups”.⁵ The authors report the fall in proteinuria was not correlated with the change in systolic pressure, and attribute it to inhibition of noradrenaline secretion and to efferent arteriolar dilation.⁵

So the honest position: in a proteinuric hypertensive already on a RAAS blocker who needs a calcium channel blocker, cilnidipine is a defensible choice over amlodipine on this evidence, and its lack of reflex tachycardia is a second small argument. In everyone else, amlodipine has the larger evidence base and the longer half-life, and there is no reason to move.

4.11 The molecules, compared

Where a source did not state a figure, the cell says so. Indian brand names are given as examples of what is commonly dispensed, from the author’s knowledge of Indian availability, not as a directory and not as a ranking — and never as a substitute for checking the strength on the pack.

TABLE 4.11 — DOSING, FREQUENCY AND WHAT IS DISPENSED IN INDIA

DRUG	START	USUAL RANGE	MAX/DAY	FREQUENCY	EXAMPLES OF INDIAN BRANDS
Amlodipine	2.5–5 mg	5–10 mg	10 mg	Once daily	Amlong, Amlip, Stamlo, Amloz, Norvasc
Nifedipine GITS/XL	30 mg	30–60 mg	90 mg on the coat-core extended-release label; the osmotic GITS label allows titration to 120 mg ¹¹ . Indian once-daily products are not always the osmotic formulation — treat 90 mg as the ceiling unless the product is.	Once daily — not a twice-daily formulation	Adalat CR/GITS, Nicardia XL
Nifedipine retard (MR)	10–20 mg twice daily	20–40 mg twice daily	80 mg ¹¹	Twice daily — every 12 hours	Depin Retard, Nicardia Retard

Nifedipine immediate-release, and why it is not on this list as an option

It should not be used for routine hypertension. The rapid fall provokes reflex sympathetic activation and tachycardia, and sublingual administration for hypertensive urgency has been abandoned for the same reason. Where nifedipine is used chronically it is a slow-release or GITS preparation.

Read the sample size before you generalise

Thirty-five patients, open-label, six months, a surrogate endpoint. That is a signal worth knowing and acting on where proteinuria is the problem — it is not the basis for replacing amlodipine as a default. This book prints the size of the trial next to its result for exactly this reason.

DRUG	START	USUAL RANGE	MAX/DAY	FREQUENCY	EXAMPLES OF INDIAN BRANDS
<i>Nifedipine IR</i>	—	—	—	—	Not for routine hypertension — see 4.8
Felodipine	2.5–5 mg	5–10 mg	10 mg	Once daily	Plendil, Felodip
Lercanidipine	10 mg	10–20 mg	20 mg ⁸	Once daily, at least 15 minutes before food	Zanidip, Lercadip
Lacidipine	2 mg	4–6 mg	6 mg ⁹	Once daily, in the morning	Lacipil
Cilnidipine	5–10 mg	10–20 mg	20 mg ¹⁰	Once daily, after breakfast	Cilacar, Cilinova, Cilnidip
Verapamil SR	120–180 mg	240–480 mg	480 mg	OD to BD	Calaptin SR
Diltiazem CD	120–240 mg	120–540 mg	To 480 mg on the Cardizem CD label; Tiazac's label allows 540 mg ¹²	Once daily	Dilzem CD, Angizem CD

The retard tablet and the osmotic-release tablet are separated above because they are not interchangeable. The osmotic preparation releases over twenty-four hours and is given once a day; a twice- or three-times-daily instruction written against a 90 mg tablet delivers a multiple of the licensed maximum¹¹. Three of these molecules have no United States licence and their figures come from elsewhere: lercanidipine and lacidipine from the United Kingdom Summary of Product Characteristics^{8,9}, cilnidipine from the product information held by national regulators for Indian-manufactured tablets¹⁰. Each carries restrictions the amlodipine row does not. Lercanidipine is taken at least fifteen minutes before food, because exposure rises four-fold after a fatty meal, and it is contraindicated where the GFR is below 30 mL/min or the patient is on dialysis, in severe hepatic impairment, in untreated heart failure, in left ventricular outflow tract obstruction, in unstable angina or within a month of an infarction, and with ciclosporin, a strong CYP3A4 inhibitor or grapefruit⁸. The renal line is the one to hold on to: 4.6 sends the oedematous patient to lercanidipine, and the low-eGFR patient of Chapter 5 can be the same patient. Cilnidipine is taken after breakfast and is contraindicated in pregnancy or the possibility of it, in advanced aortic stenosis, and in hypersensitivity to a calcium channel antagonist — which matters, because 4.10 recommends it in proteinuric kidney disease, a population that includes women of childbearing age¹⁰. Lacidipine is contraindicated in aortic stenosis and within a month of an infarction, and its label asks for three to four weeks between dose steps — the reason it looks ineffective when titrated on a monthly clinic rhythm⁹. The diltiazem ceiling is 480 mg on the Cardizem CD label; Tiazac's label allows 540 mg, so read the ceiling off the brand actually dispensed¹².

4.12 Combinations

ACCOMPLISH randomised 11,506 high-risk hypertensive patients aged 55 and over to an ACE inhibitor with amlodipine or the same ACE inhibitor with hydrochlorothiazide. Events occurred in 9.6% against 11.8% — HR 0.80 (95% CI 0.72–0.90, $p < 0.001$) — at achieved pressures of 131.6/73.3 and 132.5/74.4 mmHg⁶. Under a millimetre apart, a fifth fewer events.

The pairing is mechanically sensible as well as empirically better: the cascade drug relaxes the venule, which reduces the oedema this class causes without abolishing it. In ACCOMPLISH itself, with an ACE inhibitor in both arms, peripheral oedema still affected 31.2% of the amlodipine group against 13.4% of the diuretic group⁶. One drug blunts the other's commonest side effect while both lower the pressure — and the patient should be told so, or the swelling arrives as a surprise.

Amlodipine's long half-life, and what it means in the clinic

Steady state takes days rather than hours, so efficacy should not be judged too early and a dose change should be given time before the next one. A missed dose does not produce the rebound a short-acting agent would, and when the drug is stopped the pressure returns over days rather than hours. That forgiveness is a genuine clinical property, and it is why amlodipine suits the patient whose problem is remembering.

TABLE 4.12 — WHAT TO ADD, AND WHAT NEVER TO ADD

COMBINATION	VERDICT	THE REASON
Dihydropyridine + ACE inhibitor or ARB	Preferred	ACCOMPLISH ⁶ , and the cascade drug treats the oedema.
Dihydropyridine + thiazide	Acceptable	Works, but ACCOMPLISH says the cascade partner is better. And a thiazide will not touch the oedema.
Dihydropyridine + beta-blocker	Safe	Complementary: the beta-blocker also blunts any reflex tachycardia.
Non-dihydropyridine + beta-blocker	Avoid	Two drugs on one node. Verapamil especially.
Dihydropyridine + non-dihydropyridine	No	Two drugs at one site, which is the general rule of Chapter 3.
Any CCB + a diuretic for the ankle oedema	Ineffective	There is no excess volume to remove ³ . The commonest wrong move in this chapter.

4.13 Four patients, one site question

TABLE 4.13 — THE SAME QUESTION, FOUR ANSWERS

THE PATIENT	THE MOVE	WHY
64, amlodipine 10 mg four months, BP 132/78, bilateral ankle swelling to mid-shin	Add an ACE inhibitor or ARB	Not a diuretic — there is no excess volume ³ . The RAAS blocker relaxes the venule, equalises the capillary gradient and lowers the pressure further. If it persists, lercanidipine next (RR 1.27 against 3.34) ⁴ .
58, hypertension and recurrent gout, urate 510 $\mu\text{mol/L}$, on indapamide	Swap the diuretic for a calcium channel blocker	Metabolically neutral, no urate effect ¹ . If a cascade drug is also needed, losartan — the one ARB that lowers urate ⁷ .
52, proteinuric CKD, urine ACR 320 mg/g, already on an ARB, needs a second drug	Cilnidipine rather than amlodipine	TACTICAL: albuminuria fell on cilnidipine and not on amlodipine at the same blood pressure ⁵ . Thirty-five patients, so a signal rather than a settled fact — but this is the patient it applies to.
70, hypertension with atrial fibrillation, rate 104, already on bisoprolol	Raise the bisoprolol first; then a dihydropyridine, not verapamil	A rate of 104 is uncontrolled, and the bisoprolol is doing two jobs — raise it before adding anything (V3-Case 17). Then amlodipine for the residual pressure. Not verapamil: two drugs on one node, and whether it is available at all depends on an ejection fraction nobody has yet measured.

4.14 Clinical pearls

Twenty points that change practice, for a reader who has one minute.

- 1 One channel, three drugs. Dihydropyridines dilate vessels; verapamil and diltiazem also slow the AV node. The split decides everything else.
- 2 This class acts on the effector, not on a signal, so it works irrespective of renin, age or sympathetic tone — the most dependable monotherapy and the least specific one.
- 3 Verapamil's block is use-dependent: the faster the heart, the more blockade. The drug intensifies during the tachyarrhythmia it is treating.
- 4 The molecular story of three distinct binding sites and three state preferences is less settled than the teaching suggests. The clinical consequences are not in doubt.
- 5 Ankle oedema is pre-capillary dilation, not fluid overload, and does not answer to a diuretic. Adding a RAAS blocker is the first move.
- 6 If switching within the class for oedema: lercanidipine RR 1.27, amlodipine 3.34, nifedipine 6.03, across 71 trials and 56,283 patients.
- 7 Ankle oedema and angioedema have opposite answers. On amlodipine plus an ACE inhibitor, angioedema means stop the ACE inhibitor.
- 8 First choice in isolated systolic hypertension, in low-renin salt-loaded patients, in gout, and among the options in pregnancy.
- 9 Second, not first, in proteinuric kidney disease — a dihydropyridine lowers systemic pressure without relaxing the efferent arteriole.
- 10 Cilnidipine blocks the N-type channel as well: albuminuria fell where amlodipine's did not, at the same blood pressure — in 35 patients. A signal, not a settled fact.
- 11 Amlodipine's long duration means steady state takes days. Do not judge efficacy too early, and give a dose change time before the next.
- 12 Nifedipine immediate-release has no place in chronic hypertension, and sublingual nifedipine has none in urgency.
- 13 Verapamil with a beta-blocker risks complete heart block. If a non-dihydropyridine is needed alongside one, diltiazem with monitoring.
- 14 Verapamil is contraindicated in severe left ventricular dysfunction; diltiazem carries a warning there rather than a contraindication, and is avoided for the same reason¹². Amlodipine is the dihydropyridine with safety data there.
- 15 Non-dihydropyridines need an ECG on starting, for the PR interval. Dihydropyridines need no routine bloods at all.
- 16 The whole class is cleared by CYP3A4. Grapefruit matters little with amlodipine and a great deal with felodipine.
- 17 Amlodipine and the non-dihydropyridines raise simvastatin levels. Cap it at 20 mg with amlodipine and 10 mg with verapamil or diltiazem, or change the statin.
- 18 ACCOMPLISH: paired with a cascade drug, this class gave a fifth fewer events than a thiazide at the same blood pressure — and the cascade drug blunts its oedema at the same time without abolishing it — 31.2% against 13.4% in that trial⁶.
- 19 Flushing and headache in the first fortnight usually settle. Warn the patient before starting, or lose the drug in week two.
- 20 Look at the ankles at every visit, and ask whether the patient has quietly stopped the tablet because of them. Many have.

KEY POINTS

- 1 One channel, three drugs. Dihydropyridines dilate vessels; verapamil and diltiazem also slow the AV node. The split decides everything else.
- 2 This class acts on the effector, not on a signal, so it works irrespective of renin, age or sympathetic tone — the most dependable monotherapy and the least specific one.
- 3 Verapamil's block is use-dependent: the faster the heart, the more blockade. The drug intensifies during the tachyarrhythmia it is treating.
- 4 The molecular story of three distinct binding sites and three state preferences is less settled than the teaching suggests. The clinical consequences are not in doubt.
- 5 Ankle oedema is pre-capillary dilation, not fluid overload, and does not answer to a diuretic. Adding a RAAS blocker is the first move.
- 6 If switching within the class for oedema: lercanidipine RR 1.27, amlodipine 3.34, nifedipine 6.03, across 71 trials and 56,283 patients.
- 7 Ankle oedema and angioedema have opposite answers. On amlodipine plus an ACE inhibitor, angioedema means stop the ACE inhibitor.

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CHAPTER 5

PART III · THE NEPHRON

Thiazide and Thiazide-like Diuretics

The oldest class in the book, the cheapest, and the one with the most evidence behind it — and two recent trials have quietly overturned two things every clinician was taught about it.

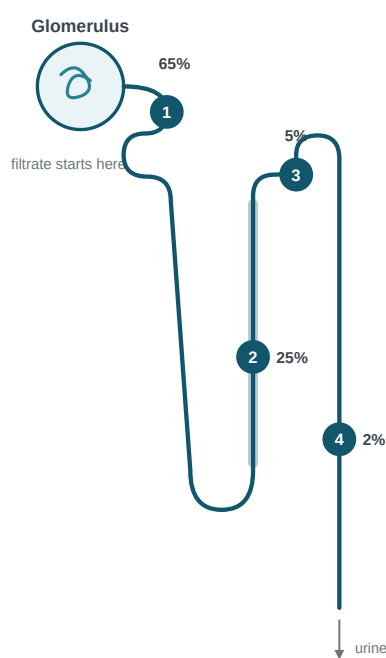
AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- Why blocking three to five per cent of sodium reabsorption lowers pressure for years — and why the mechanism is still unsettled after fifty years.
 - Where this class ranks by population, with the grade of the evidence behind each row.
 - What the Diuretic Comparison Project did to the chlorthalidone-versus-hydrochlorothiazide argument.
 - Why the rule that thiazides fail below an eGFR of 30 is no longer safe to teach.
 - The metabolic cost, what to do when each part of it happens, and which molecule carries least of it.

AT THE POINT OF PRESCRIBING		LAYER 1 · 60 SECONDS
USE WHEN	Isolated systolic hypertension in an older patient · age 80 or over · any uncomplicated hypertension · where preventing heart failure is the priority · salt-sensitive or low-renin	
DO NOT USE	Anuria · a documented reaction to a sulfonamide-derived drug — not a remembered reaction to a sulfonamide antibiotic · established gout	
WHICH MOLECULE	Chlorthalidone 12.5 mg if 24-hour cover matters or eGFR is low — and titrate it, as CLICK did, rather than leaving it at the starting dose. Indapamide 1.25 mg if diabetic, dyslipidaemic, over 80, or post-stroke. Hydrochlorothiazide 25 mg if already on it and controlled — do not switch.	
STARTING DOSE	The lower end. The metabolic cost is dose-dependent; most of the pressure benefit is not.	
FIRST CHECK	Sodium, potassium, urate, creatinine at 2 to 4 weeks . Potassium through the first three weeks; sodium falls at two to three.	
IF POTASSIUM FALLS	Halve the dose before stopping the drug. Then add or optimise a RAAS blocker.	
PAIR WITH	An ACE inhibitor or ARB. Each corrects what the other causes.	

5.1 Why act here

FIGURE 5.1 — THE FOUR DIURETIC SITES, AND THE SODIUM EACH ONE HANDLES



- 1 Proximal tubule** · carbonic anhydrase
Acetazolamide — not an antihypertensive · reabsorbs **65%** of filtered sodium
 Most sodium is recovered here, yet blocking it is a poor way to lower pressure: the segments downstream simply take up what escapes.
- 2 Thick ascending limb** · the NKCC2 co-transporter
Loop diuretics — Chapter 6 · reabsorbs **25%** of filtered sodium
 The largest block any diuretic can impose, which is why loops move fluid and why they keep working when filtration is poor.
- 3 Distal convoluted tubule** · the NCC co-transporter
Thiazides and thiazide-likes — Chapter 5 · reabsorbs **5%** of filtered sodium
 A small site, reached by secretion rather than filtration. That is the whole explanation for why a thiazide fails as the eGFR falls, and why it lowers pressure better than it moves fluid.
- 4 Collecting duct** · the epithelial sodium channel, under aldosterone
Spironolactone, eplerenone, amiloride — Chapter 7 · reabsorbs **2%** of filtered sodium
The potassium station. Sites 2 and 3 deliver extra sodium here, and it is exchanged for potassium — which is why loops and thiazides waste potassium and why a drug acting here corrects them.

Read the ladder, not the anatomy. Three facts the chapters otherwise have to assert are visible here at once: potency follows the sodium share, so the loop outranks the thiazide; a thiazide acts on a 5% site it must be secreted to reach, which is why its potency was thought to fail with filtration — a rule CLICK has since overturned for titrated chlorthalidone (5.5)²; and every drug acting above the collecting duct sends more sodium to the one station that trades it for potassium. *Sequential nephron blockade* — a loop with a thiazide, or either with an aldosterone antagonist — is simply this picture read as a strategy.

The distal convoluted tubule carries the sodium–chloride cotransporter, and blocking it reduces sodium reabsorption by three to five per cent of the filtered load¹. That is a small number, and it is worth pausing on: the segment upstream reabsorbs twenty-five per cent, so this class does not act where most of the sodium is. It acts where the last adjustable portion of it is, which turns out to be the difference between a drug for oedema and a drug for pressure.

Volume 1 explained why sodium sets long-term pressure at all, through Guyton’s pressure–natriuresis relationship (V1-Ch5). This class is that chapter made into a prescription: shift the renal set point a little, and the pressure the kidney defends falls with it.

What happens next is where the standard teaching becomes less secure than it sounds. The acute effect is straightforward — diuresis, a fall in plasma volume, a fall in cardiac output. But the pressure stays down for years, and the plasma volume does not stay down with it. In a review of fifty years of work on the question, the chronic reduction “appears dissociated from diuresis and decreased plasma volume”, with volume having “apparently returned to pre-TZD level despite continuous TZD for 1–12 months”³.

So something else sustains the effect, and the honest position is that nobody knows what. The same review concludes that the mechanism “remains unclear despite investigations over greater than five decades” and that “there is little consensus on the extrarenal target responsible”³. A direct vascular action is the leading candidate and it is not established.

5.2 Where this class ranks, and why

From this chapter onward every ranking table carries the grade defined in Opening 2. A row graded **A** is an instruction; a row graded **C** or **D** is a default you may reasonably depart from, with a reason. The grade is a property of the evidence, not of how strongly the recommendation is worded.

Why print an unsettled mechanism

Because the evidence that this class prevents strokes and heart failure is among the strongest in the book, and it does not depend on knowing why. A reader who believes the volume story completely will be puzzled when a patient's weight returns to baseline and the pressure stays controlled. Chapter 4 has the same shape: a textbook mechanism that is tidier than the literature.

TABLE 5.1 — WHERE THE THIAZIDE-TYPE DIURETICS RANK, AND ON WHAT

THE PATIENT	RANK	THE EVIDENCE, WITH NUMBERS	GRADE
Isolated systolic hypertension in an older patient	First	SHEP: 4,736 patients, mean age 72, entry systolic 160–219 with diastolic under 90. Chlorthalidone-based treatment cut five-year stroke from 8.2 to 5.2 per 100, RR 0.64 ⁵ .	A — primary endpoint, randomised, large absolute difference, and it changed practice.
Hypertension at 80 or over	First	HYVET: indapamide with perindopril as required in 3,845 patients. Heart failure HR 0.36, all-cause mortality HR 0.79 ⁶ .	A — on a question that was genuinely open beforehand.
Uncomplicated hypertension, any adult	First, jointly	ALLHAT: primary endpoint 11.5%, 11.3% and 11.4% for chlorthalidone, amlodipine and lisinopril in 33,357 patients ⁴ . No difference.	D — a dead heat. The class is first-line, and so are the other two.
Where preventing heart failure is the priority	First	ALLHAT again: heart failure was commoner on amlodipine, RR 1.38 (95% CI 1.24–1.52), and on lisinopril, RR 1.19 (1.07–1.31), than on chlorthalidone ⁴ .	C — a secondary endpoint, precisely estimated in a very large trial. Weak in position, not in precision.
Salt-sensitive, low-renin, or a high-salt diet	First	No trial randomised by renin or by urinary sodium. The argument is mechanistic: there is volume to remove and little angiotensin signal to block.	E — physiological reasoning, and the book says so.
As the second drug alongside a RAAS blocker	Second choice	ACCOMPLISH: an ACE inhibitor with amlodipine beat the same ACE inhibitor with hydrochlorothiazide, 9.6% against 11.8%, at under a millimetre of difference ¹⁰ .	B/C — one trial, and the diuretic tested was hydrochlorothiazide, not chlorthalidone.
After stroke or transient ischaemic attack	As part of a pair	PROGRESS: perindopril with indapamide reduced recurrence 43% against placebo; perindopril alone 5% ¹² . The two strata were not randomly assigned to each other (Opening 2, T.7).	A for treating the pressure; C for the claim that the combination is intrinsically better.
Advanced CKD, eGFR under 30	Now reasonable	CLICK: 160 patients with stage 4 disease, mean eGFR 23.2, already on 3.4 drugs. Chlorthalidone started at 12.5 mg and doubled four-weekly to as much as 50 mg — a mean of 23.1 mg by week twelve — cut 24-hour systolic by 11.0 mmHg against 0.5 on placebo ⁹ .	B — primary endpoint, randomised, large effect, but 160 patients and a surrogate outcome.
Gout, or a patient already on a urate-raising drug	Avoid	Hyperuricaemia is a recognised class effect ¹ ; the source gives no incidence figure.	E — a mechanism- and-label caution, not a trial.

THE PATIENT	RANK	THE EVIDENCE, WITH NUMBERS	GRADE
Anuria, or hypersensitivity to a sulfonamide-derived drug	Contraindicated	Both are stated contraindications ¹ . A remembered reaction to a sulfonamide <i>antibiotic</i> is a different claim — 5.7 ¹³ .	A in the sense that applies to contraindications: no latitude for either of them, and no extension of them to the antibiotic history.

Read the grade column and the class’s real position appears. Its first-line status in uncomplicated hypertension is a Grade D tie, which means a clinician who starts with amlodipine instead has not departed from the evidence. Its first-line status in the elderly with isolated systolic hypertension is Grade A, which means a clinician who avoids it there has. The same two words in a guideline, two entirely different obligations.

5.3 Thiazide, or thiazide-like?

The class splits on a point of chemistry that has no obvious clinical meaning: the thiazide-like agents — chlorthalidone, indapamide, metolazone — “lack the benzothiadiazine backbone”² of hydrochlorothiazide. They act at the same transporter. Everything that follows is pharmacokinetics, not pharmacology.

TABLE 5.2 — WHAT ACTUALLY SEPARATES THE FOUR MOLECULES

	HALF-LIFE	ELIMINATION	WHAT THAT BUYS, OR COSTS
Hydrochlorothiazide	5.6–14.8 hours ¹	Renal, 61% unchanged ¹	The shortest cover in the class. At 25 mg once daily the trough is real, which is the pharmacological case — not an outcome case — against it. Loses effect as filtration falls ¹ .
Chlorthalidone	About 40 hours ¹	Renal, unchanged; 75% protein bound ¹	Cover that survives a missed dose, and the molecule ALLHAT and SHEP actually studied ^{4,5} . More hypokalaemia (5.4). Retains effect below an eGFR of 30 ¹ .
Indapamide	About 14 hours ¹	Extensively metabolised; under 7% excreted unchanged; distributes into erythrocytes ¹	The least metabolic disturbance of the three — described as not interfering with lipid or glucose metabolism ² . The molecule in HYVET and in the PROGRESS combination ^{6,12} .
Metolazone	—	—	In practice reserved for combination with a loop diuretic in resistant oedema rather than used for hypertension. Chapter 6.

5.4 The chlorthalidone question — and the trial that answered it

Every reader has heard the argument, and this book made a version of it in Opening 2: chlorthalidone is preferred because chlorthalidone is the molecule that was studied. Longer half-life, more evidence, therefore the better drug. It is a good argument. It was also, until recently, untested — a Grade E inference rather than a finding.

The Diuretic Comparison Project tested it. In a pragmatic randomised trial inside the US Veterans Health Administration, 13,523 patients over 65 already taking hydrochlorothiazide were randomised either to continue it at

The claim this table deliberately does not make

That thiazide-like agents are better. One source describes them as “exceptional and better than thiazide-type diuretics”² — and the next section is a 13,523-patient randomised trial that tested exactly that and did not find it.

25 or 50 mg or to switch to chlorthalidone at 12.5 or 25 mg, and followed for a median of 2.4 years⁷.

TABLE 5.3 — THE DIURETIC COMPARISON PROJECT, IN FULL

	CHLORTHALIDONE	HYDROCHLOROTHIAZIDE	READING
Major adverse cardiovascular events	10.4%	10.0%	Hazard ratio 1.04, 95% CI 0.94–1.16 ⁷ . No difference , and the confidence interval is narrow enough to exclude a meaningful one.
Hypokalaemia	6.0%	4.4%	More on chlorthalidone ⁷ . The direction expected from a forty-hour half-life.
Potassium below 3.1 mmol/L	5.0%	3.6%	The same signal at a threshold that changes what you do ⁷ .
Allergic reactions	1.6%	0.3%	A five-fold difference on a small base ⁷ .
Kidney outcomes	—	—	A separate pre-planned analysis, reported later and counting differently, found chlorthalidone not superior for kidney outcomes either — with hypokalaemia again commoner, 8.9% against 6.9% in that analysis rather than the 6.0% against 4.4% of the row above ⁸ .

So the honest conclusion is **Grade D: a dead heat, with a safety cost on one side**. Chlorthalidone is not shown to be better; it is shown to cause more hypokalaemia. That is close to the reverse of what a great many clinicians were taught, and it corrects the inference this book itself printed two chapters ago as Grade E.

Three qualifications, because the trial has boundaries like any other. The population was 97% male, elderly, and already established on hydrochlorothiazide — patients who had already tolerated it, which quietly favours the drug they were staying on. It compared 25 mg of hydrochlorothiazide with 12.5 mg of chlorthalidone in most patients, which is a defensible equivalence and not the only possible one. And 2.4 years is a short follow-up for a hard endpoint.

What to do with it in clinic. If a patient is controlled and comfortable on hydrochlorothiazide, there is now randomised evidence that switching them buys nothing and costs some potassium. If you are starting a diuretic afresh, either is defensible — and the case for chlorthalidone shifts from “better outcomes” to “better twenty-four-hour cover”, which is a pharmacological argument and should be labelled as one.

5.5 Below an eGFR of 30 — a rule that has expired

The teaching is universal and it is in the reference works: thiazides stop working as filtration falls, so below an eGFR of about 30 you switch to a loop diuretic. Even the source this chapter leans on states that standard thiazides “lose effectiveness as renal function declines”¹.

CLICK randomised the question in the patients it actually matters for. 160 patients with stage 4 chronic kidney disease, mean eGFR 23.2 mL/min/1.73 m², already taking an average of 3.4 antihypertensive drugs and still uncontrolled, were started on chlorthalidone 12.5 mg daily or placebo and the dose was doubled every four weeks — to 25 mg, then to a maximum of 50 mg —

Why this section exists at all

Because it is a worked example of the whole book. A plausible mechanism, a confident consensus, a Grade E inference repeated until it sounded like evidence — and then somebody ran the trial. The reader who can spot the next one of these is the reader this volume is written for.

while home pressure stayed above target, reaching a mean of 23.1 mg by week twelve. Twenty-four-hour systolic pressure fell by 11.0 mmHg against 0.5 mmHg on placebo, and the urinary albumin-to-creatinine ratio fell by half⁹. The titration carried the harms with it: hypokalaemia, acute kidney injury, dizziness and hyperglycaemia were all commoner on chlorthalidone⁹.

An 11 mmHg fall in ambulatory systolic pressure, in patients already on three and a half drugs, at an eGFR of 23. That is a larger effect than most fourth drugs produce in patients with normal kidneys.

TABLE 5.4 — WHAT CLICK DOES AND DOES NOT LICENSE

IT SUPPORTS	IT DOES NOT SUPPORT
Chlorthalidone as an add-on in resistant hypertension with advanced CKD, where the previous answer was a loop diuretic or nothing.	Any claim about cardiovascular outcomes. The endpoint was blood pressure, over twelve weeks, in 160 patients.
Abandoning the flat rule that thiazides are useless below an eGFR of 30. That rule was never tested against a titrated thiazide-like agent in this population.	Extending the finding to hydrochlorothiazide, which was not studied and has the pharmacokinetics that generated the original rule.
Watching electrolytes closely when you do it — this is the population in which hypokalaemia and volume depletion are least forgiving.	Replacing a loop diuretic where the indication is oedema rather than pressure.

5.6 The ledger, and the counterfactual

Grade B, and why not A

Primary endpoint, randomised, large effect — but 160 patients and a surrogate outcome. Enough to change what you try in a difficult patient. Not enough to rewrite the first line of the chapter.

TABLE 5.5 — THE THIAZIDE LEDGER

	WHAT YOU GET, AND WHAT COMES WITH IT
What you want	Stroke prevention with the strongest evidence in the volume in the elderly ^{5,6} ; heart failure prevention better than a calcium channel blocker or an ACE inhibitor ⁴ ; once-daily dosing; and a cost that no other class can match, which in Indian practice is a clinical property and not an economic footnote.
What it costs	A metabolic bill: hypokalaemia, hyponatraemia, hyperuricaemia, hyperglycaemia, hyperlipidaemia, hypercalcaemia and metabolic alkalosis ¹ , all dose-dependent ² . None of these is rare, and all of them are found by a blood test rather than reported by the patient.
The verdict	First-line, and correctly so — but first-line in a joint tie rather than in a lead ⁴ , and first-line outright only where the trials were done: isolated systolic hypertension in the elderly, the very elderly, and preventing heart failure.
The counterfactual	Imagine the same natriuresis with no effect on potassium, urate or glucose. That drug would be first-line without qualification and the rest of Part III would be a short chapter. It does not exist — but indapamide is the closest, being reported not to interfere with lipid or glucose metabolism ² , and that is the strongest available argument for choosing it in a diabetic or dyslipidaemic patient.

5.7 The target map — where else this reaches

A list of adverse effects has to be memorised. A map of where a drug’s action reaches can be reasoned from, and it predicts effects the list has not got round to mentioning. This section is the map for the sodium–chloride cotransporter,

and every entry in the next section is derived from a row in it.

The transporter itself sits in one place — the distal convoluted tubule. But blocking it changes the composition of what arrives downstream, and changes the volume and hormonal state of the whole patient. **The adverse effects are not off-target actions of the drug. They are on-target consequences arriving somewhere the prescriber was not aiming.**

TABLE 5.6 — FROM ONE BLOCKED TRANSPORTER TO EVERY EFFECT IN THE CHAPTER

WHERE THE CONSEQUENCE LANDS	WHAT HAPPENS THERE	WHAT THE PATIENT OR THE LABORATORY REPORTS
The collecting duct	More sodium arrives distally than usual. Sodium is reabsorbed there in exchange for potassium, and the aldosterone system — already activated by the fall in volume — drives that exchange harder.	Hypokalaemia , the commonest effect and the one needing watching through the first three weeks ¹ . Also the metabolic alkalosis that travels with it ¹ .
Free water handling	The distal tubule is where dilute urine is generated. Block it and the capacity to excrete free water falls, while volume depletion simultaneously drives antidiuretic hormone.	Hyponatraemia , appearing within two to three weeks ¹ . This is why the classic patient is thin, older, female and on a low salt intake — least free-water reserve, most ADH drive.
The proximal tubule	Urate and thiazides compete for the same organic anion secretory pathway, and volume depletion increases proximal reabsorption of everything, urate included.	Hyperuricaemia, and gout ¹ . Two mechanisms pointing the same way, which is why the effect is reliable rather than idiosyncratic.
Calcium handling, opposite in direction	This is the one segment where calcium moves the other way: reduced intracellular sodium increases basolateral sodium-calcium exchange, so calcium is retained rather than lost.	Hypercalcaemia ¹ — and the reason thiazides are used off-label in recurrent calcium stones and in osteoporosis ¹ . The same mechanism, read as harm or as benefit depending on the patient.
The pancreatic beta cell	Potassium is required for insulin release. A cell chronically low in potassium releases less insulin.	Hyperglycaemia ¹ . Which is why this effect largely follows the hypokalaemia — and why correcting the potassium is the first move, not switching class.
Lipid metabolism	Not well characterised. The association is real and the mechanism is not established.	Hyperlipidaemia ¹ . The book prints the association and not an explanation , because it has not read one it could quote.
The sulfonamide moiety	A structural feature of the molecule rather than a consequence of the blockade — the only row in this table that is genuinely off-target.	Rash, urticaria, wheeze, anaphylaxis ¹ . And the reason a documented reaction to a sulfonamide-derived drug is a stated label contraindication rather than a caution — which a remembered reaction to a sulfonamide antibiotic is not, for the reason 5.7 gives ¹³ .
Pancreas, idiosyncratic	No derivation available. A rare reaction, not a predictable consequence.	Pancreatitis — rare, serious, and requiring immediate withdrawal ¹ . When a mechanism cannot be given, the book says so rather than inventing one.

Read the last two rows against the first six and the practical distinction appears. **A consequence of the mechanism is dose-dependent and manageable** — halve the dose, correct the potassium, wait. **A reaction to the molecule is not**: there is no dose of a sulfonamide that a sulfonamide-allergic patient tolerates, and no dose reduction for pancreatitis. That is why the chapter's response to hypokalaemia is to reduce, and its response to a rash is to stop.

5.8 It happened — now what?

The metabolic effects of this class are the commonest reason it is stopped, and most of the stopping is unnecessary. Each one has a move that is not withdrawal.

What this map is for

Two things. It converts a list into a derivation, so a reader who has forgotten the list can rebuild it. And it predicts: a reader who understands the calcium row can answer, without being told, why a thiazide is a reasonable choice in a hypertensive patient with recurrent calcium stones and a poor choice in one with hyperparathyroidism.

TABLE 5.7 — THE FIVE THAT ACTUALLY HAPPEN, AND WHAT TO DO

WHAT HAPPENED	WHAT IT IS	THE MOVE
Potassium falls	The commonest effect, needing monitoring through the first three weeks ¹ . Dose-dependent ² . Commoner on chlorthalidone than hydrochlorothiazide, 6.0% against 4.4% ⁷ .	Halve the dose before abandoning the drug — most of the pressure benefit sits at the lower end and most of the potassium loss at the upper. Then add or optimise a RAAS blocker, which raises potassium at a different site and is the pairing this volume keeps recommending for other reasons anyway. A potassium-sparing agent or an MRA is the next step (Chapter 7).
Sodium falls	Appears within two to three weeks of starting ¹ . Classically an older, thin, female patient, often with a low sodium intake.	Check at two to four weeks after starting, not only when the patient is confused. A sodium that is drifting is a reason to change class, not to reduce the dose — this effect is less forgiving than hypokalaemia and less easily corrected in the same patient.
Urate rises, or gout flares	Hyperuricaemia is a recognised class effect ¹ ; the source gives no frequency, so none is printed here.	If gout is established, this class is the wrong site — move to the channel. If urate is raised without gout, that alone is not a reason to stop. Among the alternatives, losartan is the ARB with a uricosuric effect (Chapter 2).
Glucose or lipids rise	Hyperglycaemia and hyperlipidaemia are class effects ¹ and dose-dependent ² .	Reduce the dose first. If it persists and the patient is diabetic or dyslipidaemic, indapamide is the molecule with the least of this ² . Do not accept a small glucose rise as a reason to abandon a class that prevents strokes in this population.
A rash, or worse, in a sulfonamide-allergic patient	Listed as a label contraindication — but the position that sulfonamide <i>antibiotics</i> and the non-antibiotic sulfonamides cross-react does not survive the one cohort large enough to test it. After a sulfonamide-antibiotic allergy the risk of reacting to a non-antibiotic sulfonamide was raised, adjusted odds ratio 2.8 (95% CI 2.1–3.7); but the risk of reacting to penicillin in the same patients was raised further still, 3.9 (3.5–4.3), which is the signature of a patient prone to drug allergy rather than of a shared antigen ¹³ . A remote antibiotic reaction is therefore not a reason to withhold a first-line drug. A documented reaction to a sulfonamide-derived drug is; reactions range from rash and urticaria to wheeze and anaphylaxis ¹ .	Do not rechallenge and do not substitute within the class. Note that allergic reactions were commoner on chlorthalidone in DCP, 1.6% against 0.3% ⁷ .

5.9 When acting here is wrong

And the one that is not on this list
 Pancreatitis. Rare, serious, and the instruction is to discontinue immediately if it is suspected¹. There is no dose reduction and no rechallenge for this one.

TABLE 5.8 — WHERE THE NEPHRON IS THE WRONG SITE

THE SITUATION	WHY	GO HERE INSTEAD
Anuria	A stated contraindication ¹ . A drug that works on filtrate needs filtrate.	A loop diuretic if there is any residual function; otherwise this is a dialysis question.
Hypersensitivity to a sulfonamide-derived drug	A stated contraindication ¹ . A remembered reaction to a sulfonamide <i>antibiotic</i> is not the same claim, and 5.7 says why ¹³ .	Any other class, where the reaction was to a sulfonamide-derived drug. The channel is the usual answer. A remote antibiotic reaction is not a reason to leave this site.
Established gout	Hyperuricaemia is a class effect ¹ .	The channel; or among cascade drugs, losartan.
A young, lean, high-renin patient	Not a contraindication — a mismatch. There is little volume to remove, the reflex rise in renin is proportionally larger, and the response disappoints. Grade E, as in 5.1: this is physiological reasoning, and no trial has randomised by renin or by urinary sodium.	The cascade. And note the converse: that same reflex is exactly why a diuretic is the right <i>partner</i> for a cascade blocker.

5.10 Combinations

This class is one half of the most reliable pairing in hypertension, and it is also the half that lost a head-to-head trial. Both statements are true and they are about different comparisons.

TABLE 5.9 — THE PAIRINGS, AND THEIR EVIDENCE

	WHAT IS KNOWN
With an ACE inhibitor or ARB	The mechanistic pairing this volume keeps returning to: the diuretic raises renin, which is the state in which cascade blockade works best, and the cascade blocker raises potassium, which is what the diuretic lowers. Each treats the other's problem. PROGRESS is the outcome evidence, with the caveat about its design in Opening 2 ¹² .
Against a calcium channel blocker, as the second drug	ACCOMPLISH: an ACE inhibitor with amlodipine beat the same ACE inhibitor with hydrochlorothiazide, 9.6% against 11.8%, at under a millimetre of pressure difference ¹⁰ . The diuretic lost. But the diuretic that lost was hydrochlorothiazide, and the one ALLHAT validated was chlorthalidone — a comparison nobody has run.
With an MRA	The standard fourth-drug regimen in resistant hypertension, and the combination in which potassium needs the most attention. Chapter 7.
With a loop diuretic	Sequential nephron blockade, used for resistant oedema rather than for pressure, and the usual reason metolazone appears on a prescription. Chapter 6.

5.11 The molecules, compared

TABLE 5.10 — DOSING AND SELECTION

MOLECULE	DOSE FOR HYPERTENSION	REACH FOR IT WHEN
Chlorthalidone	12.5–25 mg once daily ¹⁴	Twenty-four-hour cover matters, adherence is imperfect, or the eGFR is low ⁹ . Accept more hypokalaemia ⁷ and check potassium accordingly. The generic label starts at 25 mg and permits more; the trials this chapter rests on used 12.5 to 25 mg, and that is the range to prescribe. On the US label the smallest tablet is 25 mg, so 12.5 mg is half of one ¹⁴ ; lower strengths are marketed in some markets, and Volume 3, Chapter 17 prints the ladder as 6.25, 12.5 and 25 mg — check what is on the shelf before asking a patient to split a tablet. Thalitone is not substitutable milligram for milligram with other chlorthalidone products ¹⁴ .
Hydrochlorothiazide	12.5–25 mg once daily ¹⁴	The label starts at 12.5 mg and permits up to 50 mg, but the metabolic cost above 25 mg buys little further pressure ¹⁴ . The patient is already on it and controlled — there is now randomised evidence that switching gains nothing ⁷ . Also where it is the only fixed-dose combination available, which in Indian practice is often.
Indapamide	1.25–2.5 mg once daily, in the morning ¹⁴	The patient is diabetic or dyslipidaemic ² , is over 80 ⁶ , or is being treated after a stroke ¹² . The molecule with the most specific evidence and the least metabolic cost. The label allows 5 mg after two four-week steps, but above 2.5 mg the hypokalaemia grows and the pressure does not ¹⁴ .
Metolazone	2.5–5 mg once daily ¹	Rarely for hypertension. Its place is sequential blockade with a loop diuretic in resistant oedema. Chapter 6.

TABLE 5.10A — THE INTERACTIONS THAT CHANGE A DECISION

WITH	WHAT HAPPENS, AND WHAT TO DO
Lithium	Renal lithium clearance falls and toxicity follows. The label says a thiazide generally should not be given with lithium ¹⁴ . Where it is unavoidable, check a level within a week and warn about tremor, confusion and vomiting.
NSAIDs	Blunt the diuretic, natriuretic and antihypertensive effect ¹⁴ — and with a RAAS blocker complete the triple whammy of Chapter 1.
Digoxin	The thiazide's hypokalaemia and hypomagnesaemia are what make the digoxin toxic: the label says they sensitise or exaggerate the heart's response to it ¹⁴ . Check the potassium, not the digoxin level, first.
Sotalol and other QT-prolonging drugs	Hypokalaemia and hypomagnesaemia can provoke ventricular arrhythmias ¹⁴ . Correct the potassium before it matters.
Sulfonylureas and insulin	Hyperglycaemia; the antidiabetic dose may need adjusting ¹⁴ .

Indian brands are deliberately not printed in this edition. The author's own market knowledge covers the cascade and channel drugs and is printed in those chapters, labelled as author knowledge rather than as a sourced fact. For the diuretics that survey has not been done, and a list assembled from memory would be the kind of confident-looking, unverifiable content this book exists to avoid.

5.12 Four patients, one site question

Illustrative composites, each chosen because the site reasoning and the grade of the evidence point somewhere specific.

TABLE 5.11 — THE SAME QUESTION, FOUR ANSWERS

THE PATIENT	THE QUESTION	THE ANSWER, AND ITS GRADE
74, systolic 168, diastolic 78, otherwise well	Which class first?	A thiazide-type diuretic, and this is not a coin toss. SHEP studied exactly this patient ⁵ . Grade A . A calcium channel blocker is also defensible; leaving it untreated is not.
52, type 2 diabetes, HbA1c 8.1, needs a second drug	Which diuretic, if any?	Indapamide if a diuretic is chosen, for the metabolic profile ² . But ACCOMPLISH says a calcium channel blocker is the better second drug alongside the RAAS blocker this patient already needs ¹⁰ . Grade B/C — and the diuretic tested was hydrochlorothiazide.
68, eGFR 24, on four drugs, systolic 162	Is a thiazide-like agent pointless here?	No. CLICK is exactly this patient: chlorthalidone started at 12.5 mg and titrated to a mean of 23.1 mg cut 24-hour systolic by 11.0 mmHg ⁹ . Grade B . Check potassium and creatinine at one to two weeks without exception, and again after every dose increase.
61, controlled on hydrochlorothiazide 25 mg for six years	Should I switch to chlorthalidone?	No. DCP randomised 13,523 patients to that exact switch and found no difference in events with more hypokalaemia ⁷ . The exception is a prior myocardial infarction or stroke, where the trial's own subgroup favoured chlorthalidone ⁷ . Grade D — and here the dead heat is an argument for doing nothing, which is the cheapest intervention in the book.

5.13 Clinical pearls

Twenty-two points that change practice, for a reader who has one minute.

- 1 The site is the distal convoluted tubule and the target is the sodium–chloride cotransporter, worth three to five per cent of filtered sodium¹. Small, and enough.
- 2 The chronic mechanism is unknown. Plasma volume returns to baseline within one to twelve months while the pressure stays down³.
- 3 SHEP is the trial to be able to name: isolated systolic hypertension, mean age 72, stroke 5.2 against 8.2 per 100 over five years⁵.
- 4 HYVET settled treatment above 80: heart failure HR 0.36, all-cause mortality HR 0.79, on indapamide⁶.
- 5 ALLHAT's primary endpoint was a dead heat. Its heart-failure advantage for chlorthalidone — RR 1.38 against amlodipine, 1.19 against lisinopril — is a precisely estimated secondary endpoint⁴.
- 6 The Diuretic Comparison Project randomised 13,523 patients to chlorthalidone or hydrochlorothiazide: events 10.4% against 10.0%, HR 1.04⁷. No difference overall — though in the pre-specified subgroup with a prior myocardial infarction or stroke the result favoured chlorthalidone, 14.3% against 19.4%, HR 0.73 (0.57–0.94), which is a subgroup finding and should be read as one⁷.
- 7 The same trial found more hypokalaemia on chlorthalidone, 6.0% against 4.4%, and more severe hypokalaemia, 5.0% against 3.6%⁷.
- 8 So do not switch a controlled patient from hydrochlorothiazide to chlorthalidone. The evidence for that switch has been tested and it is negative — except in the prior-infarction and prior-stroke subgroup, where the same trial points the other way⁷.
- 9 The case for chlorthalidone survives as a pharmacokinetic one — a forty-hour half-life against 5.6 to 14.8 hours¹ — not as an outcome one.
- 10 CLICK: chlorthalidone started at 12.5 mg and titrated to a mean of 23.1 mg, at a mean eGFR of 23.2, cut 24-hour systolic pressure by 11.0 mmHg against 0.5 on placebo, and halved albuminuria⁹.
- 11 So the rule that thiazides fail below an eGFR of 30 is no longer safe to teach without qualification.
- 12 Indapamide is the molecule with the least metabolic disturbance, reported not to interfere with lipid or glucose metabolism².
- 13 Indapamide is also the molecule in HYVET and in the PROGRESS combination^{6,12} — the most specific evidence in the class.
- 14 Halve the dose before stopping for hypokalaemia. The metabolic cost is dose-dependent²; much of the pressure benefit is not.
- 15 Hyponatraemia appears at two to three weeks¹. Check then, not when the patient becomes confused.
- 16 A drifting sodium is a reason to change class. A raised urate without gout is not a reason to stop.
- 17 Sulfonamide allergy and anuria are the two stated contraindications¹. There is no substitution within the class for the first.
- 18 Pancreatitis is rare and there is no dose reduction for it — discontinue¹.
- 19 ACCOMPLISH beat this class as the second drug¹⁰ — but with hydrochlorothiazide, not the chlorthalidone ALLHAT validated. That trial has not been run.
- 20 A diuretic raises renin, and a cascade blocker raises potassium. Each drug treats the other's problem, which is why this pairing keeps appearing.
- 21 In a young, lean, high-renin patient this class disappoints. That is a wrongly chosen site, not treatment failure.
- 22 The cheapest class in the book, and in a patient paying monthly that is a clinical property rather than an economic one.

5.14 Evidence annexe

LAYER 3 · THE EVIDENCE ANNEXE — SKIP THIS AND LOSE NO PRESCRIBING DECISION

The body of this chapter states what to do. This annexe states how much the statements are worth, on the two axes set out in Opening 2: **the effect** — how large, on what endpoint — and **the conduct** — whether the trial was run in a way that makes the number believable. A GP can skip this page without losing a single prescribing decision. A specialist who disagrees with the chapter should start here.

TABLE 5.12 — THE FIVE TRIALS THIS CHAPTER RESTS ON, APPRAISED ON BOTH AXES

TRIAL	WHAT IT FOUND	EFFECT	CONDUCT, AND WHAT IT DOES TO THE GRADE
SHEP 1991	Chlorthalidone-based treatment against placebo in 4,736 patients with isolated systolic hypertension. Five-year stroke 5.2 against 8.2 per 100, RR 0.64 ⁵ .	A	Sound. Randomised, double-blind, placebo-controlled, with a hard primary endpoint that resists detection bias ¹¹ . The grade stands. The limit is the population, not the method: 160–219 systolic with diastolic under 90, mean age 72 — it says nothing about a 45-year-old.
HYVET 2008	Indapamide with perindopril as required in 3,845 patients aged 80 or over. Heart failure HR 0.36, all-cause mortality HR 0.79 ⁶ .	A	Qualified — stopped early for benefit. The finding is almost certainly real; the effect size should be read as an upper bound rather than an estimate, because trials halted for benefit overestimate, and worst when few events had accrued. Treat the direction as settled and the magnitude as generous.
ALLHAT 2002	Chlorthalidone against amlodipine against lisinopril in 33,357 patients. Primary endpoint 11.5%, 11.3%, 11.4%. Heart failure RR 1.38 for amlodipine and 1.19 for lisinopril, against chlorthalidone ⁴ .	D on class C on heart failure	Sound in design, qualified on the secondary endpoint. Very large, randomised, double-blind, with an active comparator rather than placebo — which is what makes the null primary result informative rather than uninformative. But “hospitalisation for heart failure” is an adjudicated soft endpoint, and soft endpoints are where detection bias lives ¹¹ . The finding is believable and it is not the endpoint the trial was built to answer.
DCP 2022	Chlorthalidone against hydrochlorothiazide in 13,523 veterans. Events 10.4% against 10.0%, HR 1.04; hypokalaemia 6.0% against 4.4% ⁷ .	D	Qualified — pragmatic and open-label. Its design is its strength and its weakness at once. Enrolling patients already established on hydrochlorothiazide gives a real-world population and quietly favours the drug they were tolerating, which is a selection problem at baseline ¹¹ . Open-label design does not threaten a hard cardiovascular endpoint much, and the null result is not the direction bias would push. The conclusion survives; the equivalence claim is for these patients, not for a treatment-naïve one.
CLICK 2021	Chlorthalidone, started at 12.5 mg and titrated four-weekly to a mean of 23.1 mg, against placebo in 160 patients with stage 4 CKD. 24-hour systolic –11.0 against –0.5 mmHg ⁹ .	B	Sound but small, and a surrogate endpoint. Randomised and placebo-controlled with an objective ambulatory measurement, which largely closes off detection bias. The limits are size and endpoint: 160 patients, twelve weeks, and blood pressure rather than events. Enough to change what you try in a difficult patient; not enough to claim outcomes.

The pattern across the five. The two Grade A rows are also the two with the cleanest conduct, which is reassuring and not automatic. The two most-quoted claims in the chapter each carry a qualification the guideline sentence does not: HYVET’s effect size is inflated by early stopping, and ALLHAT’s heart-failure advantage is a soft secondary endpoint in a trial whose primary endpoint was null. Neither qualification changes what to prescribe. Both change how hard you should argue for it.

TABLE 5.13 — DEVIATION LICENCE — WHO WAS LEFT OUT, AND WHAT THAT PERMITS

EXCLUDED OR UNREPRESENTED	WHICH TRIAL	WHAT YOU MAY REASONABLY DO
Adults under about 55	SHEP, HYVET, ALLHAT, DCP	Nothing here was tested in a 40-year-old. The class is not contraindicated, and it stays a first-line option at any adult age — the 2024 European guideline attaches no age qualifier to that Class I recommendation ¹⁵ . The trials simply are not about this patient, so the phenotype argument — low renin, salt-loaded — does more of the work than usual in choosing between the first-line classes. It does not license leaving one of them out.
Women, and non-White populations	DCP was 97% male	An equivalence result in an overwhelmingly male, elderly, American cohort is weaker evidence for a 58-year-old Indian woman. It remains the best available. It is not the same claim.
Treatment-naïve patients	DCP enrolled patients already on hydrochlorothiazide	The trial answers <i>should I switch?</i> — no. It does not answer <i>which should I start?</i> Starting chlorthalidone on pharmacokinetic grounds remains defensible and is not contradicted here.
eGFR under 30	Excluded from most; CLICK was built for them	This is the one row where the exclusion was repaired by a later trial. Before CLICK the rule was extrapolation; after it, a titrated trial of chlorthalidone — 12.5 mg raised every four weeks as home pressure requires — in an uncontrolled stage 4 patient is evidence-based.
Patients on the diuretic ALLHAT validated	ACCOMPLISH used hydrochlorothiazide	ACCOMPLISH says a calcium channel blocker is the better second drug. It compared against hydrochlorothiazide, not chlorthalidone ¹⁰ . If your diuretic is chlorthalidone, that comparison has not been run and you are entitled to say so.

That last row is the shape of a legitimate deviation, and it is worth naming as a template. A guideline says *prefer a calcium channel blocker as the second drug*. The trial behind it used a comparator you are not using. You are not disagreeing with the evidence; **you are observing that the evidence is about a different question, and reasoning from mechanism in the space it leaves**. Write the reason down and the deviation becomes a decision.

KEY POINTS

- 1 The target is the sodium–chloride cotransporter in the distal convoluted tubule, worth three to five per cent of filtered sodium. The chronic mechanism that keeps the pressure down is still unknown after fifty years.

2 The class is first-line twice over, but for different reasons: a Grade A instruction in isolated systolic hypertension and above 80, and a Grade D tie in everyone else.

3 ALLHAT's heart-failure advantage for chlorthalidone is weak in position and strong in precision. Those are different kinds of weakness and they license different things.

4 The Diuretic Comparison Project found chlorthalidone and hydrochlorothiazide equivalent on cardiovascular events in 13,523 patients, with more hypokalaemia on chlorthalidone. The preference most of us were taught is not supported by the trial that tested it.

5 CLICK showed chlorthalidone lowering 24-hour systolic pressure by 11 mmHg at a mean eGFR of 23. The rule about eGFR 30 needs qualifying.

6 Indapamide carries the least metabolic cost and the most population-specific evidence — the very elderly, and secondary stroke prevention.

7 Every metabolic effect in this chapter is dose-dependent. Halving the dose is the move that precedes stopping the drug.

8 This class pairs with a cascade blocker because each corrects what the other causes: renin and potassium, in opposite directions.

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CHAPTER 6

PART III · THE NEPHRON

Loop Diuretics

The most powerful natriuretic in the book, and the one with the least evidence for treating blood pressure. Both facts matter, and the second is the one usually left out.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 Why the largest natriuresis in the nephron is not the best antihypertensive.

2 The honest evidence position: no outcome trial in hypertension, and what the class is doing in this volume anyway.

3 The four situations where a loop diuretic is the right answer and a thiazide is not.

4 Whether torsemide's better pharmacokinetics translate into better outcomes — and what happened when that was tested.

AT THE POINT OF PRESCRIBING		LAYER 1 · 60 SECONDS
USE WHEN	Congestion, not pressure · heart failure · eGFR under about 30 · oedema from cirrhosis or nephrotic syndrome	
DO NOT USE	As a first-line antihypertensive. There is no outcome trial for this class in hypertension. Anuria, and hypersensitivity to the drug itself, on all three labels. Hepatic coma is a contraindication for bumetanide and for torsemide; severe electrolyte depletion for bumetanide alone. On furosemide both are warnings — there, correct the state first rather than withholding the drug ⁸ .	
WHICH MOLECULE	Furosemide by default. Torsemide when absorption is the identified problem — bioavailability about 80% against furosemide's 50 to 64%. Not as a general upgrade: mortality was identical in 2,859 patients.	
STARTING DOSE	The lowest that produces the diuresis you need. Adverse effects run greater than with thiazides, hyponatraemia excepted.	
FIRST CHECK	Weight, electrolytes including magnesium, creatinine.	
IF POTASSIUM WILL NOT CORRECT	Check magnesium. It is usually hypomagnesaemia underneath.	
CLASS-SPECIFIC HARM	Ototoxicity — worse with aminoglycosides, and irreversible most often with ethacrynic acid, though furosemide's label reports irreversible loss too ⁸ . No other diuretic does this.	

6.1 Why act here — and why it is not first-line

The thick ascending limb reabsorbs about a quarter of the filtered sodium², and loop diuretics block it by competing with chloride at the NKCC2 cotransporter on the apical membrane¹. That is five to eight times the fraction

a thiazide touches⁴, and it makes this the most powerful natriuretic available.

It should follow that this is the best antihypertensive in the nephron. It does not, and the reason is the most useful lesson in the chapter. **The size of a natriuresis is not what lowers pressure over years.** Chapter 5 established that the chronic thiazide effect is dissociated from plasma volume altogether, and that a small, sustained, evenly distributed effect is what the arterial tree responds to. A loop diuretic produces a large effect over a few hours and then stops: furosemide’s half-life is 1.5 to 2 hours¹. For most of the day the drug is absent and the kidney is compensating.

The label reflects this exactly. Loop diuretics are approved for hypertension, alone or with other agents, and are simultaneously described as “not used for first-line therapy”¹. That is not an inconsistency; it is a class whose licence is broader than its evidence.

6.2 Where this class ranks, and on what

This table looks different from the one in Chapter 5, and the difference is the point.

The comparison worth holding

A thiazide removes less sodium and lowers pressure better. In pharmacology, potency and clinical value are different quantities, and this is the clearest example of it in the volume.

TABLE 6.1 — WHERE THE LOOP DIURETICS RANK, AND THE GRADE BEHIND EACH ROW

THE PATIENT	RANK	THE EVIDENCE	GRADE
Uncomplicated hypertension	Not indicated	No outcome trial in hypertension exists for this class. Nothing here corresponds to ALLHAT or SHEP ⁷ . The label does not say so either: furosemide and torsemide are licensed for hypertension without qualification, and bumetanide is not licensed for it at all ⁸ .	E — and the absence is the finding. A reader should know that this class has never been shown to prevent a stroke.
Hypertension with heart failure	First, for the congestion	Standard practice, and the FDA indication is oedema in congestive heart failure ¹ . The drug is treating symptoms and volume, not the blood pressure as such.	E for the pressure. The heart failure indication is a different question with different evidence.
Hypertension with CKD, eGFR under 30	Traditionally first	“Loop diuretics are the primary agents used in CKD”, with higher starting doses recommended ³ . But CLICK showed chlorthalidone, started at 12.5 mg and titrated to a mean of 23.1 mg, cutting 24-hour systolic by 11.0 mmHg at a mean eGFR of 23.2 ⁶ , which the traditional teaching did not anticipate.	E for the loop, B for the thiazide-like alternative. The stronger evidence is now on the other side.
Hypertension with fluid overload from any cause	First	Cirrhosis with ascites, nephrotic syndrome, renal disease — all FDA-approved oedema indications ¹ .	E, and appropriately: nobody will randomise a congested patient to no diuretic.
Resistant oedema on a loop diuretic alone	Add a thiazide-like agent	Sequential nephron blockade — metolazone is the usual partner. The rationale is mechanistic: block two segments in series.	E — widely done, physiologically sound, no outcome trial.
Anuria, hepatic coma, severe electrolyte depletion, sulfonamide allergy	Contraindicated — but not all four, and not on every label	Anuria and hypersensitivity to the drug itself are contraindications on all three labels. Hepatic coma is a contraindication for bumetanide and for torsemide; severe electrolyte depletion for bumetanide alone. On furosemide’s label both sit under warnings — do not start until the underlying state is improved. Sulfonamide allergy is a contraindication on none of the three: furosemide and bumetanide carry it as a cross-sensitivity warning, and torsemide’s label does not raise it at all ⁸ .	A for anuria and for hypersensitivity to the drug, in the sense contraindications carry: no latitude. Less than that for the rest — and ethacrynic acid, which is not a sulfonamide, is there if the cross-sensitivity is taken seriously.

Five of the six rows are Grade E. That is unusual in this volume and it is stated plainly rather than disguised by writing the chapter at the same length as the others. This class earns its place through physiology, through licensing, and through the fact that in a congested patient no alternative exists — not through a randomised endpoint in hypertension. A reader who prescribes it should know which of those they are relying on.

6.3 Furosemide, torsemide, bumetanide

TABLE 6.2 — THE THREE MOLECULES

	BIOAVAILABILITY	HALF-LIFE	AVAILABLE FORMS
Furosemide	64% of an intravenous dose on the label ⁸ ; about 50% on average in the review literature ¹	1.5 to 2 hours, up to 2.6 with organ dysfunction ¹	Tablets 20, 40 and 80 mg; injection 10 mg/mL ¹
Torsemide	Closer to 80% ¹	The longest of the three at 3 to 4 hours, up to 5 to 6 with dysfunction ¹	Tablets 5, 10, 20 and 100 mg ⁸ . No intravenous presentation is currently marketed in the United States; where a torsemide injection is available it is supplied at 10 mg/mL ¹
Bumetanide	Closer to 80% ¹	About 1 hour, 1.3 to 1.6 with dysfunction ¹	Tablets 0.5, 1 and 2 mg; injection 0.25 mg/mL ¹

TABLE 6.2A — THE DOSES, AND THE SWITCH

	WHAT THE LABEL SAYS
Furosemide	Oedema: 20 to 80 mg as a single dose. Hypertension: 80 mg, usually as 40 mg twice daily ⁸ .
Torsemide	Heart failure: 10 or 20 mg once daily. Chronic renal failure: 20 mg once daily. Cirrhosis: 5 or 10 mg once daily. Hypertension: 5 mg once daily, to 10 mg after four to six weeks if needed. Titrate by doubling ⁹ .
Bumetanide	0.5 to 2 mg as a single daily dose; a further dose at four- to five-hour intervals if needed, to a maximum of 10 mg a day ⁹ .
The switch	Bumetanide's label puts 1 mg at about 40 mg of furosemide ⁹ . Torsemide's label states no equivalence; in practice the switch is made at about half the furosemide milligrams — furosemide 40 mg to torsemide 20 mg — which is where the torsemide label's own heart-failure start sits ⁹ . A switch made for absorption is a switch at equivalent dose, not at equivalent milligrams, and the first week after it is when the patient is weighed.

TABLE 6.2B — THE INTERACTIONS THAT CHANGE A DECISION

WITH	WHAT HAPPENS, AND WHAT TO DO
Lithium	All three labels say the same thing: renal lithium clearance falls and the risk of toxicity is high, so lithium generally should not be given with a diuretic ⁸⁹ . Where it is unavoidable, check a level within a week.
NSAIDs	The diuretic and antihypertensive effect is blunted ⁹ , and furosemide's label reports rises in urea, creatinine and potassium with weight gain when the two are combined ⁸ .
Aminoglycosides	The ototoxic potential of both drugs rises, most in impaired renal function ⁸⁹ . Review the drug list before the loop starts, not after the tinnitus.
Digoxin	Digitalis exaggerates the metabolic effects of hypokalaemia, especially on the myocardium ⁸ . Check the potassium and magnesium first.
Metolazone	Sequential nephron blockade is the combination that empties patients into hospital. Check electrolytes and creatinine within 48 hours of adding it, not at the next clinic, and weigh the patient daily for the first week.

Those numbers make an obvious argument. Furosemide's absorption is two thirds at best, and famously variable; torsemide's is consistent and its effect lasts twice as long. A patient whose oedema fluctuates unpredictably may be experiencing pharmacokinetics rather than disease. It is a good argument, it has been made for thirty years, and this book made a version of it in the notes that preceded this chapter.

TRANSFORM-HF tested it. 2,859 patients hospitalised with heart failure at 60 US centres were randomised at discharge to torsemide or furosemide. All-cause mortality was 26.1% against 26.2%, hazard ratio 1.02 (95% CI 0.89–1.18);

mortality or hospitalisation 47.3% against 49.3%⁵. The investigators concluded there was insufficient evidence to recommend torsemide over furosemide⁵.

What survives is narrower and still useful. Where absorption is the specific problem — gut oedema, an unpredictable response, a patient who does not respond to a dose that should work — the bioavailability difference is a reason to switch, because it addresses the mechanism that is failing. What does not survive is switching every patient on the expectation of better survival. That expectation has now been measured.

6.4 It happened — now what?

The second dead heat in two chapters

Chapter 5 has the same shape: a pharmacologically superior molecule, a confident consensus, and a large randomised trial finding no difference in outcomes. Chlorthalidone against hydrochlorothiazide, torsemide against furosemide. **Better pharmacokinetics is a hypothesis about outcomes, not a substitute for one** — and in the two cases where somebody has bothered to test it in this part of the book, the hypothesis lost.

TABLE 6.3 — WHAT HAPPENS ON A LOOP DIURETIC, AND WHAT FOLLOWS

WHAT HAPPENED	WHAT IT IS	THE MOVE
Potassium, sodium, chloride or magnesium fall	Hyponatraemia, hypokalaemia, hypochloraemia, hypomagnesaemia and metabolic alkalosis are all listed class effects ¹ , and adverse effects are described as higher with loop agents than with thiazides ³ .	Replace magnesium as well as potassium — hypokalaemia that will not correct is often hypomagnesaemia underneath. Reduce the dose or the frequency if the indication allows.
Creatinine rises and the patient is dry	Prerenal azotaemia and dehydration are listed effects ¹ ; profound diuresis with water and electrolyte depletion requires careful supervision ¹ .	Weigh the patient, and treat the number in the context of the weight. In hypertension this usually means the dose is too high; in decompensated heart failure it may be the price of decongestion.
Hearing changes, tinnitus	Ototoxicity is specific to this class and can occur with any of them, especially with concomitant aminoglycosides ¹ . Ethacrynic acid carries more of it and can cause permanent sensorineural loss ¹ . Baseline auditory testing is advised ³ .	Stop, and review the whole drug list for aminoglycosides. This is the one adverse effect in the nephron chapters that does not belong to any other class.
Urate rises, or gout flares	Hyperuricaemia and gout are listed ¹ — the same problem as the thiazides, at a different segment.	If gout is the issue and the indication is pressure rather than congestion, this is the wrong site entirely. If the indication is congestion, treat the gout.
Triglycerides or cholesterol rise	Hypertriglyceridaemia and hypercholesterolaemia are listed class effects ¹ .	Rarely a reason to stop a drug given for congestion. Worth knowing before attributing it to something else.

6.5 The ledger, and where this class belongs

TABLE 6.4 — THE LOOP DIURETIC LEDGER

	WHAT YOU GET, AND WHAT COMES WITH IT
What you want	The largest natriuresis available, working at a segment that handles a quarter of the filtered sodium ¹ , and an effect that survives a low GFR when a thiazide's was thought not to. Intravenous forms for when oral absorption cannot be relied on.
What it costs	A larger electrolyte bill than the thiazides ³ , ototoxicity that belongs to no other class ¹ , and a short duration that leaves most of the day uncovered.
The verdict	Not an antihypertensive of first resort, and this volume does not present it as one. Its place is congestion, advanced renal disease, and the patient in whom a thiazide has genuinely failed rather than been under-dosed.
The counterfactual	A loop diuretic with a twelve-hour duration and no ototoxicity would still probably not displace the thiazides, because the reason thiazides win is not their weakness of natriuresis but something in the chronic vascular effect that Chapter 5 admits nobody has identified ⁴ . That is an unusual position for a book to take, and it is the honest one.

6.6 Clinical pearls

Fifteen points that change practice, for a reader who has one minute.

- 1 The site is NKCC2 in the thick ascending limb, worth about 25% of filtered sodium¹ — five to eight times what a thiazide touches.
- 2 And it is still not the better antihypertensive. Size of natriuresis is not what lowers pressure over years.
- 3 **No outcome trial exists for this class in hypertension.** Nothing corresponds to ALLHAT or SHEP. Know that before you prescribe it for pressure.
- 4 Furosemide and torsemide are licensed for hypertension; bumetanide is not licensed for it at all⁸. What the furosemide label adds is that a patient a thiazide cannot control will probably not be controlled by furosemide alone — a licence broader than the evidence, and narrower than it first looks.
- 5 Furosemide bioavailability is 64% of the intravenous dose on the label and about 50% in the review literature^{1,8}; torsemide and bumetanide are closer to 80%¹.
- 6 Furosemide's half-life is 1.5 to 2 hours, torsemide's 3 to 4, bumetanide's about 1¹.
- 7 TRANSFORM-HF randomised 2,859 patients to torsemide or furosemide: mortality 26.1% against 26.2%, HR 1.02⁵. Better pharmacokinetics did not become better outcomes.
- 8 Switch to torsemide when absorption is the identified problem, not on the expectation of better survival — and at equivalent dose, not equivalent milligrams: furosemide 40 mg is about torsemide 20 mg, or bumetanide 1 mg⁹.
- 9 Ototoxicity belongs to this class alone and worsens with aminoglycosides. Irreversible loss is commonest with ethacrynic acid, but furosemide's own label reports tinnitus and hearing impairment that may be reversible or irreversible⁸.
- 10 Hypokalaemia that will not correct is often hypomagnesaemia underneath. Both are listed loop effects¹.
- 11 Adverse effects are described as greater with loop agents than with thiazides³, though no effect size is attached to the claim — and hyponatraemia runs the other way, being more a thiazide problem than a loop one.
- 12 CLICK put titrated chlorthalidone into stage 4 CKD with an 11 mmHg fall in 24-hour systolic⁶. The rule that only loops work at low GFR needs qualifying.
- 13 Metolazone with a loop diuretic is sequential nephron blockade for resistant oedema — physiologically sound, and without an outcome trial.
- 14 The contraindications common to all three are anuria and hypersensitivity to the drug. Hepatic coma is a contraindication for bumetanide and torsemide, severe electrolyte depletion for bumetanide alone, and both are warnings on furosemide; a reported sulfonamide allergy is a warning on every one of them⁸.
- 15 Weigh the patient. In hypertension a rising creatinine on a loop diuretic usually means the dose is too high.

KEY POINTS

- 1 This class blocks a quarter of filtered sodium and is still not a first-line antihypertensive. Potency and clinical value are different quantities.
- 2 There is no outcome trial for loop diuretics in hypertension. Five of the six rows in this chapter's ranking table are Grade E, and the chapter says so rather than writing around it.
- 3 Torsemide has better bioavailability and a longer half-life than furosemide. TRANSFORM-HF found no difference in mortality, 26.1% against 26.2%.
- 4 That is the second time in two chapters that a pharmacologically superior molecule failed to produce better outcomes when tested. Treat pharmacokinetic superiority as a hypothesis.
- 5 Switch to torsemide for a specific absorption problem, not as a general upgrade.
- 6 Ototoxicity is this class's own adverse effect and it is worse with aminoglycosides and with ethacrynic acid.
- 7 The place for a loop diuretic in hypertension is congestion, advanced renal disease, or genuine thiazide failure — and CLICK has narrowed the third of those.

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Aldosterone — the Receptor, the Channel, and the Enzyme

One hormone, three places to interrupt it, and the newest of the three was approved while this volume was being written. A book organised by drug class cannot say what is new about it. A book organised by site can.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 Where the two walks of the opening chapter meet, and why that makes this receptor unusual.
- 2 The distinction that explains the mortality evidence: acting only in the nephron, or wherever the receptor sits.
- 3 Why spironolactone is the fourth drug, and what PATHWAY-2 actually compared.
- 4 The three sites — receptor, channel and synthase — and what each buys and costs.
- 5 Baxdrostat: what was approved, on what evidence, and where it belongs in a regimen.
- 6 Hyperkalaemia and gynaecomastia mapped to decisions rather than to warnings.

AT THE POINT OF PRESCRIBING

LAYER 1 · 60 SECONDS

USE WHEN	Resistant hypertension, as the fourth drug · heart failure with reduced ejection fraction · primary aldosteronism · diabetic CKD progressing on maximal RAAS blockade
DO NOT USE	The label's contraindications are hyperkalaemia · Addison's disease · concomitant eplerenone · and, in practice, refractory hypertension, where this site has already failed. Do not start above a potassium of 5.0; at an eGFR of 30 to 50 reduce the starting dose rather than withhold; below 30 the risk usually outweighs the benefit, but that is a judgement and not a bar. The eGFR-under-30 and creatinine-above-2.5 figures are initiation thresholds and trial entry criteria — treating them as bars withholds a mortality drug (Table 7.1).
WHICH MOLECULE	Spironolactone as default. Eplerenone if gynaecomastia — but accept twice-daily dosing. Finerenone for diabetic CKD. Baxdrostat as an add-on where a receptor antagonist is not tolerated.
STARTING DOSE	Spironolactone 25 mg. Up to 100 mg daily in hypertension — the label's indication is essential, not resistant, hypertension, and PATHWAY-2 used 25–50 mg; up to 50 mg in heart failure.
FIRST CHECK	Potassium and creatinine at one to two weeks. Then again after any dose change.
IF POTASSIUM RISES	Review every other potassium-raising drug first — the RAAS blocker, the NSAID, the salt substitute, the co-trimoxazole. Then halve. Then stop.
WARN MEN	Gynaecomastia or breast pain in about one in ten. An unwarned patient stops the drug and does not say why.

7.1 Why act here

The mineralocorticoid receptor is the only site in this volume that both of the opening chapter's journeys reach. Walk down the nephron and it is the fourth station, sitting above the epithelial sodium channel and controlling it. Follow the renin–angiotensin cascade to its end and it is the last station, the point at which the whole cascade finally does something to sodium. That is not a curiosity of drawing. **It is why a drug acting here behaves like a diuretic and like a cascade blocker at the same time**, and why it belongs in a conversation about volume as much as one about aldosterone.

A second distinction organises everything that follows, and it is the one most often missed because drug classifications hide it. **Some drugs in this chapter act only where filtrate is; others act wherever the receptor is**. The mineralocorticoid receptor is expressed in the collecting duct, and also in the heart and the vessel wall. Spironolactone, eplerenone and finerenone block it everywhere it sits. Amiloride and triamterene block the sodium channel downstream of it, which exists only in the nephron.

That distinction is the cleanest available explanation of a fact readers often find puzzling: why spironolactone carries a mortality benefit in heart failure⁵ and a potassium-sparing diuretic does not. They are not weaker and stronger versions of the same drug. One is acting on the myocardium and the vessel wall; the other never leaves the kidney.

7.2 Where this class ranks, and on what

Renal, or extrarenal

It is worth carrying this phrase. When a reader meets a new agent in this area, the first question is not how potent it is. It is whether it acts only in the nephron, or everywhere the receptor is expressed — because that predicts which trials it can win.

TABLE 7.1 — WHERE THE ALDOSTERONE-DIRECTED DRUGS RANK

THE PATIENT	RANK	THE EVIDENCE, WITH NUMBERS	GRADE
Resistant hypertension, uncontrolled on three drugs including a diuretic	Fourth drug, first choice	PATHWAY-2: 335 patients, randomised crossover. Home systolic fell 8.70 mmHg further than on placebo, 4.03 further than on doxazosin and 4.48 further than on bisoprolol, all at $P < 0.0001^4$.	A — primary endpoint, randomised, and it beat every comparator tested rather than only placebo.
Heart failure with reduced ejection fraction, NYHA III–IV	Standard therapy	RALES: all-cause mortality 35% against 46%, RR 0.70 ⁵ . An eleven-point absolute difference.	A — among the largest absolute effects in this volume.
HFrEF with milder symptoms, NYHA II	Standard therapy	EMPHASIS-HF: cardiovascular death or heart failure hospitalisation 18.3% against 25.9%, HR 0.63; all-cause mortality 12.5% against 15.5% ⁶ .	A — replication in a different severity, on eplerenone rather than spironolactone.
Type 2 diabetes with CKD, already on maximal RAAS blockade	Add finerenone	FIDELIO-DKD: renal composite 17.8% against 21.1%, HR 0.82; cardiovascular composite 13.0% against 14.8%, HR 0.86 ⁷ .	B — primary endpoint met, one trial, moderate margin, and investigator-reported hyperkalaemia 18.3% against 9.0%.
Primary aldosteronism not suitable for surgery	First	An FDA-approved indication for spironolactone ¹ . The diagnosis is in VI·Ch13 and VI·Ch33.	E as a trial matter — nobody randomises a patient with a hormone-secreting adenoma to a drug that does not block that hormone.
Uncontrolled hypertension on existing therapy, as an add-on	Baxdrostat is now an option	BaxHTN: 794 patients randomised (the label's figure; 796 appears in the sponsor's announcement) to baxdrostat 2 mg, 1 mg or placebo for 12 weeks. Placebo-adjusted systolic reduction 9.8 mmHg at 2 mg and 8.7 mmHg at 1 mg ⁹ . Approved by the FDA in May 2026 ⁸ .	B — primary endpoint, randomised, large effect; one trial, twelve weeks, and no outcome data at all yet.
Hypokalaemia on a thiazide, or low-renin hypertension	Amiloride or triamterene	ENaC handles about 3% of the filtered sodium load ³ . No outcome trial in hypertension.	E — prescribed for the potassium and the mechanism.
Potassium above 5.0, or eGFR under 30	Initiation thresholds, not contraindications	The label contraindicates spironolactone in hyperkalaemia, Addison's disease and concomitant eplerenone ¹⁰ . The familiar numbers are not contraindications: a potassium at or below 5.0 and an eGFR above 50 are <i>dose-initiation</i> thresholds, an eGFR of 30 to 50 calls for a reduced dose, and creatinine above 2.5 was an entry criterion for RALES. Treating them as bars withholds a mortality drug. The figures themselves are a potassium above 5.0 mEq/L, an eGFR below 30, or creatinine above 2.5 mg/dL in men and 2.0 in women ¹ .	A for the label's three contraindications, in the sense contraindications carry; the numbers are dosing guidance ¹⁰ .

7.3 Three sites, one hormone

Until 2026 this chapter had two sites in it. It now has three, and the third is the first genuinely new site in antihypertensive pharmacology in many years — which is why it is worth setting the three out side by side before discussing any molecule.

TABLE 7.2 — THREE PLACES TO INTERRUPT ONE HORMONE

SITE	WHAT IS BLOCKED	DRUGS	WHAT IT BUYS, AND WHAT IT COSTS
The synthase upstream	Aldosterone synthase, the enzyme that makes the hormone. Less hormone is produced.	Baxdrostat	Blocks the hormone before it reaches any receptor, anywhere. The design question was always whether it would also suppress cortisol, since the synthetic pathways are adjacent; the reported answer is that it lowers aldosterone “without affecting cortisol levels” ⁹ . Costs: hyperkalaemia 10.2% at 2 mg ⁹ , and no outcome evidence yet.
The receptor midstream	The mineralocorticoid receptor itself, wherever it is expressed — collecting duct, myocardium, vessel wall.	Spirolactone, eplerenone, finerenone	The only site with mortality evidence ^{5,6} , and the extrarenal action is the likeliest reason. Costs: hyperkalaemia, and for spironolactone the androgen and progesterone effects it does not confine to the kidney.
The channel downstream	The epithelial sodium channel that aldosterone opens. About 3% of filtered sodium ³ .	Amiloride, triamterene	Renal only. Effective for sodium and potassium handling, useful in Liddle syndrome where the channel is the disease. Costs: hyperkalaemia — amiloride carries a boxed warning for it and must be avoided in renal dysfunction ³ . No mortality evidence, and on the reasoning above there is no obvious mechanism by which it would have any.

Read down the last column and a pattern appears that a class-based textbook cannot show. **Every one of these three interrupts the same hormone, and all three cause hyperkalaemia, because that is a property of the pathway rather than of any molecule.** But only the middle one has ever shown a mortality benefit, and the plausible reason is that only the middle one acts outside the kidney. The upstream agent removes the hormone altogether and might therefore be expected to behave like the middle one — but that is a prediction from mechanism, and the trials that would test it have not reported.

7.4 Why spironolactone is the fourth drug

The reason to admire PATHWAY-2 is not that spironolactone beat placebo. Almost any fourth antihypertensive would beat placebo. It is that the trial put three different sites against each other in the same patients, and the sites were not chosen at random.

What this book will not say

That baxdrostat is better than spironolactone. It is a first-in-class drug with twelve weeks of blood-pressure data and no outcome trial, against a comparator with an eleven-point absolute mortality difference in heart failure. Grade B against Grade A, and the newer drug is the one with more to prove.

TABLE 7.3 — WHAT PATHWAY-2 ACTUALLY TESTED

	AND WHAT EACH ARM REPRESENTED
Spironolactone	The mineralocorticoid receptor — the hypothesis that resistant hypertension is a sodium and aldosterone problem. Home systolic fell 8.70 mmHg further than on placebo ⁴ .
Doxazosin	The alpha-1 receptor — the hypothesis that it is a vasoconstriction problem. Spironolactone beat it by 4.03 mmHg ⁴ .
Bisoprolol	The beta-1 receptor — the hypothesis that it is a sympathetic problem. Spironolactone beat it by 4.48 mmHg ⁴ .
The conclusion	Not merely that spironolactone works, but that resistant hypertension behaves like a volume and aldosterone problem rather than a vasoconstrictor or sympathetic one — in the average patient. That is a statement about mechanism established by a randomised trial, which is rare and is why this trial carries more weight than its 335 patients would suggest.

It also sets up the exception. Opening 1 introduced refractory hypertension — uncontrolled despite five drugs including a diuretic and an MRA — and the evidence there points at sympathetic overactivity rather than volume. In other words, the patients in whom PATHWAY-2’s conclusion fails are precisely the ones defined by having failed the drug PATHWAY-2 recommends, and in those patients the bisoprolol arm’s logic becomes the relevant one. Chapters 8 to 10.

7.5 Baxdrostat — the newest site in this book

In May 2026 the FDA approved baxdrostat, marketed as Baxfendy, as the first aldosterone synthase inhibitor for hypertension^{8,9}. It is an add-on agent, indicated in combination with other antihypertensive drugs for adults whose pressure is not adequately controlled⁹.

It earns a section rather than a line because it is not another molecule at an existing site. **It is a new site.** Every previous attempt to interrupt aldosterone blocked the receptor or the channel; this one reduces the amount of hormone made. The obvious design hazard was cortisol: aldosterone synthase and 11-beta-hydroxylase are closely related, and an inhibitor that cannot tell them apart produces adrenal insufficiency. The reported result is that baxdrostat lowers aldosterone “without affecting cortisol levels” across the doses tested⁹.

TABLE 7.4 — BAXHTN, AND WHAT IT DOES AND DOES NOT ESTABLISH

	WHAT WAS FOUND	READING
Design	794 patients randomised (the label’s figure; 796 appears in the sponsor’s announcement) 1:1:1 to baxdrostat 2 mg, 1 mg or placebo, added to background antihypertensive therapy, over 12 weeks ⁹ .	A conventional add-on design. The comparator is placebo, not another fourth-line drug — so this trial does not tell you whether to use it instead of spironolactone.
Systolic reduction at 12 weeks	2 mg: 15.7 mmHg absolute, 9.8 mmHg placebo-adjusted. 1 mg: 14.5 mmHg absolute, 8.7 placebo-adjusted. Placebo: 5.8 mmHg ⁹ .	A large effect for an add-on agent. For scale, spironolactone’s advantage over placebo in PATHWAY-2 was 8.70 mmHg on home readings ⁴ — a different measurement in a different population, so the two numbers are not directly comparable.
Hyperkalaemia	6.6% at 1 mg and 10.2% at 2 mg ⁹ .	Substantial, and exactly what the mechanism predicts. This is not a drug that escapes the potassium problem by acting upstream.
Other adverse effects	Hypotension 2.1% and 3.6%; hyponatraemia 2.1% and 3.2%; dizziness and muscle spasms around 3% ⁹ .	Dose-related throughout.

	WHAT WAS FOUND	READING
Dosing	2 mg once daily; 1 mg once daily in patients at increased risk of hyperkalaemia or hyponatraemia ⁹ .	A rare example of a label that names the lower dose for a specific risk group rather than leaving it to judgement.
What is absent	No cardiovascular outcome data. No head- to- head comparison with an MRA. Twelve weeks.	Grade B. Enough to prescribe within the indication. Not enough to displace a drug with mortality evidence.

Where it belongs in a regimen, on today’s evidence. As an add-on in a patient uncontrolled on existing therapy — which is its indication. The specific place it is most obviously useful is the patient in whom the mineralocorticoid receptor is the right site but the receptor antagonist is not tolerated: gynaecomastia on spironolactone, or a patient in whom eplerenone’s twice-daily dosing and cost are the obstacle. That is reasoning from mechanism, not from a trial, and it is labelled accordingly.

7.6 The molecules, compared

A note on how this section will age

This is the newest material in the volume and it will date fastest. Outcome trials, comparisons against spironolactone, and the other agents in this area — endothelin antagonism and RNA-directed approaches — are all in motion. A reader consulting this chapter some years after publication should check what has reported since, and Opening 3 gives a procedure for doing exactly that.

The eplerenone trade a reader should make consciously

It removes gynaecomastia by being selective² and reintroduces a duration problem by having a three-to-six-hour half-life². One of those is visible to the patient and the other is not, which is why the second is the one that gets forgotten.

TABLE 7.5 — CHOOSING WITHIN THE CHAPTER

MOLECULE	DOSE	SELECTIVITY AND DURATION	REACH FOR IT WHEN
Spironolactone	Up to 50 mg daily in heart failure; up to 100 mg daily in hypertension — the label's indication is essential, not resistant, hypertension, and PATHWAY-2 used 25–50 mg ¹	Non-selective. Also binds androgen receptors ¹ , which is the whole of its tolerability problem.	The default. Resistant hypertension ⁴ , HFrEF ⁵ , primary aldosteronism, cirrhotic or nephrotic oedema, hypokalaemia ¹ .
Eplerenone	25 mg daily, to 50 mg after four weeks in heart failure ² ; 50 mg once daily in hypertension, with 50 mg twice daily reserved as the maximum for an inadequate response	Selective: 100– to 1000–fold lower affinity for glucocorticoid, progesterone and androgen receptors ² . Half-life 3–6 hours, so hypertension may need twice-daily dosing ² .	Gynaecomastia, breast tenderness, or menstrual irregularity on spironolactone. Post-infarction left ventricular dysfunction, which is its own indication ² . Weigh the twice-daily dosing against the adherence cost (Opening 1, 0.13). Not for hypertension in type 2 diabetes with microalbuminuria, nor alongside amiloride, triamterene or a potassium supplement — label contraindications, set out in Table 7.8 ¹² .
Finerenone	The label sets the dose by eGFR: 20 mg once daily at an eGFR of 60 or above; 10 mg once daily at 25 to under 60; not started below 25 ¹¹ . Do not start with a potassium above 5.0 ¹¹ . Potassium at four weeks after starting and four weeks after every dose change; withhold above 5.5, and consider restarting at 10 mg once it is 5.0 or below ¹¹ . Contraindicated with a strong CYP3A4 inhibitor — clarithromycin included — and in adrenal insufficiency ¹¹ .	Non-steroidal. A different molecular structure from the other two rather than a refinement of them.	Type 2 diabetes with CKD already on maximal RAAS blockade ⁷ . This is a renal indication with cardiovascular benefit attached, not a hypertension drug.
Amiloride, triamterene	—	Act at ENaC, downstream of the receptor and only in the nephron ³ . Amiloride carries a boxed warning for hyperkalaemia and must be avoided in renal dysfunction ³ .	Hypokalaemia on a thiazide, low-renin hypertension, Liddle syndrome. Not a substitute for an MRA where the evidence is for an MRA.

7.6b The target map — where else this receptor is

Section 7.1 introduced the distinction this chapter turns on — renal or extrarenal. The map makes it concrete, and adds the second distinction that decides tolerability: **whether the drug can tell the mineralocorticoid receptor apart from its relatives.**

TABLE 7.6 — ONE RECEPTOR, SEVERAL TISSUES, AND ONE MOLECULE THAT CANNOT TELL THEM APART

WHERE THE RECEPTOR IS	WHAT BLOCKING IT DOES THERE	WHICH DRUGS REACH IT
Collecting duct	Sodium reabsorption falls and potassium is retained. The intended effect, and the source of the hyperkalaemia that belongs to every drug in this chapter.	All of them. The ENaC blockers act one step further downstream, at the channel the receptor opens ³ .
Myocardium and vessel wall	Aldosterone drives fibrosis here, independently of sodium. Blocking it is the likeliest explanation of the mortality benefit.	Only the receptor antagonists. Spironolactone ⁵ , eplerenone ⁶ , finerenone ⁷ . Amiloride and triamterene never leave the kidney, and have no mortality evidence.
Androgen receptor	Not a mineralocorticoid site at all. Spironolactone binds it because its steroid structure resembles the natural ligand closely enough ¹ .	Spironolactone only. Gynaecomastia, breast pain, loss of libido, menstrual irregularity¹ — 10% against 1% on placebo in RALES ⁵ .
Progesterone and glucocorticoid receptors	Same problem, same cause: insufficient discrimination between related steroid receptors.	Spironolactone. Eplerenone has “100 to 1000-fold lower binding affinity” to these ² — which is the entire clinical case for it.
Aldosterone synthase, in the adrenal	Upstream of every receptor: less hormone is made at all. The adjacent enzyme makes cortisol, which is the design hazard.	Baxdrostat. Reported to lower aldosterone “without affecting cortisol levels” ⁹ . It still causes hyperkalaemia — 10.2% at 2 mg ⁹ — because that is a property of the pathway, not of the receptor.

Two conclusions the map hands you. **Gynaecomastia is a receptor-selectivity problem, not a dose problem** — so reducing the spironolactone dose and hoping is the wrong move, and switching to eplerenone is the right one, at the cost of twice-daily dosing². And **hyperkalaemia cannot be engineered away**: it appears in the first row, which every drug in the chapter reaches, including the one that works upstream of the receptor entirely.

7.7 It happened — now what?

TABLE 7.7 — THE THREE THAT ACTUALLY HAPPEN

WHAT HAPPENED	WHAT IT IS	THE MOVE
Potassium rises	The commonest electrolyte effect of spironolactone ¹ . For eplerenone the risk is roughly 1.5– to 2–fold, with a number needed to harm of 23 to 62 ² . For baxdrostat, 10.2% at the 2 mg dose ⁹ . It is a property of the pathway, not of a molecule.	Below 5.5: review every other drug raising potassium — the RAAS blocker, the NSAID, the potassium supplement, the salt substitute, and the trimethoprim in the co-trimoxazole somebody gave for a urinary infection last week ¹⁰ — before touching this one. Halve the dose. Above 5.5, or rising fast: stop, and recheck. The initiation threshold for spironolactone is a potassium at or below 5.0 with an eGFR above 50 ¹⁰ , not a contraindication; eplerenone <i>is</i> contraindicated above 5.5 ² .
Gynaecomastia, loss of libido, menstrual irregularity	Spironolactone binds androgen receptors ¹ ; in RALES gynaecomastia or breast pain occurred in 10% against 1% on placebo ⁵ . Reported at around 9% elsewhere ² .	Switch to eplerenone, which has 100– to 1000–fold lower affinity for those receptors ² — and accept twice-daily dosing in hypertension. Do not reduce the spironolactone dose and hope; this is a receptor effect, not a threshold one. Warn men before starting, because an unwarned patient stops the drug and does not say why.
Creatinine rises	Expected on starting, as with any drug that reduces glomerular filtration pressure or intravascular volume. Renal function decline needs routine monitoring ¹ .	Recheck at one to two weeks. Distinguish an expected settling rise from a progressive one. Remember what the familiar figures are: eGFR under 30 and creatinine over 2.5 mg/dL in men or 2.0 in women ¹ are initiation thresholds and RALES entry criteria, not label contraindications ¹⁰ . Below an eGFR of 50 the label reduces the starting dose; below 30 the decision is a judgement made with a potassium plan, not a bar.

7.8 When acting here is wrong

The drug interaction that catches people

Eplerenone is metabolised by CYP3A4, and potent inhibitors — protease inhibitors, azole antifungals, clarithromycin — can raise it to unsafe concentrations². A course of clarithromycin for a chest infection is the realistic version of this. For finerenone the same inhibitors are a contraindication rather than a caution¹¹. Two more on the spironolactone label: trimethoprim raises potassium, and in India it arrives as co-trimoxazole; and spironolactone reduces the renal clearance of lithium, so a patient on lithium needs a level¹⁰.

TABLE 7.8 — WHERE THIS SITE IS THE WRONG ONE

THE SITUATION	WHY	GO HERE INSTEAD
Potassium above 5.0, or eGFR below 30	Initiation thresholds for spironolactone rather than label contraindications — the label bars only hyperkalaemia, Addison's disease and concomitant eplerenone ¹⁰ ; eplerenone is contraindicated in every patient at a potassium above 5.5 at initiation, a creatinine clearance of 30 or below, or on a strong CYP3A inhibitor ¹² . For hypertension the label adds four more: type 2 diabetes with microalbuminuria, a creatinine above 2.0 mg/dL in men or 1.8 in women, a creatinine clearance below 50, and concomitant potassium supplements or potassium-sparing diuretics ¹² . The diabetic-microalbuminuria bar is the one most often crossed in practice.	The channel, or the sympathetic site. Chapters 4, 8 to 10. The channel is an alternative to eplerenone, not a companion — amiloride or triamterene alongside eplerenone in hypertension is a labelled contraindication ¹² .
Addison disease	A stated contraindication for spironolactone ¹⁰ ; adrenal insufficiency is the corresponding bar on the finerenone label ¹¹ . It is not on the eplerenone label, whose contraindications are set out in the row above ¹² .	Any other site.
On a potent CYP3A4 inhibitor	Contraindicated with eplerenone ² .	Spironolactone, or wait until the course is finished.
Refractory hypertension — already failing on five drugs including an MRA	Not a contraindication but a mismatch. By definition this site has been blocked and has not worked, and the evidence points elsewhere (Opening 1, 0.14).	The sympathetic limb. Adding a second aldosterone-directed drug is another drug at a site already blocked.

7.9 Clinical pearls

Twenty-two points that change practice, for a reader who has one minute.

- 1 This receptor is where both walks of the opening chapter meet — fourth station down the nephron, last station on the cascade.
- 2 **Renal or extrarenal** is the question to ask of any drug here. MRAs block the receptor wherever it sits; amiloride and triamterene never leave the kidney.
- 3 That distinction is the likeliest reason spironolactone has mortality evidence⁵ and a potassium-sparing diuretic does not.
- 4 PATHWAY-2 did not just beat placebo. It beat doxazosin by 4.03 mmHg and bisoprolol by 4.48⁴ — three sites in the same patients.
- 5 So resistant hypertension behaves like a volume and aldosterone problem, in the average patient. That is a mechanism established by randomisation, which is rare.
- 6 RALES: mortality 35% against 46%⁵. EMPHASIS-HF in milder disease: 18.3% against 25.9%⁶. Grade A both.
- 7 FIDELIO-DKD put finerenone on top of maximal RAAS blockade: renal composite 17.8% against 21.1%⁷. A second site added to a blocked one.
- 8 **Baxdrostat was approved in May 2026**, the first aldosterone synthase inhibitor — a new site, not a new molecule at an old one⁸.
- 9 BaxHTN: 796 patients, placebo-adjusted systolic 9.8 mmHg at 2 mg and 8.7 at 1 mg over twelve weeks⁹.
- 10 It lowers aldosterone without affecting cortisol⁹ — which was the design hazard, the two synthetic pathways being adjacent.
- 11 It does not escape hyperkalaemia: 10.2% at 2 mg⁹. Potassium is a property of the pathway, not of the molecule.
- 12 And it has no outcome data. Grade B against spironolactone's Grade A. The newer drug has more to prove, not less.
- 13 Spironolactone up to 100 mg daily in hypertension — the label's indication is essential, not resistant, hypertension, and PATHWAY-2 used 25–50 mg, up to 50 mg in heart failure¹.
- 14 Gynaecomastia or breast pain in 10% against 1% on placebo in RALES⁵. Warn men before starting.
- 15 Eplerenone has 100– to 1000-fold lower affinity for androgen, progesterone and glucocorticoid receptors² — which is why it does not do that.
- 16 But its half-life is 3 to 6 hours, so hypertension may need twice-daily dosing². A visible problem traded for an invisible one.
- 17 The label contraindicates spironolactone in hyperkalaemia, Addison's disease and concomitant eplerenone — and nothing else¹⁰. A potassium at or below 5.0 with an eGFR above 50 is the *initiation* threshold, and an eGFR of 30 to 50 calls for a reduced starting dose¹⁰. Treating those figures as bars withholds a mortality drug.
- 18 Eplerenone and potent CYP3A4 inhibitors — clarithromycin, azoles, protease inhibitors — are contraindicated together².
- 19 Before stopping this drug for hyperkalaemia, review every other drug raising potassium. It is usually not the only one.
- 20 Amiloride carries a boxed warning for hyperkalaemia and must be avoided in renal dysfunction³.
- 21 ENaC handles about 3% of filtered sodium³ — the final adjustment, and the point where potassium stops being lost.
- 22 In refractory hypertension this site has already been blocked and failed. A second drug here is a drug at a site already blocked.

KEY POINTS

- 1 The mineralocorticoid receptor is where the nephron walk and the cascade walk meet, which is why a drug acting here behaves like a diuretic and a cascade blocker at once.
- 2 Ask of every drug in this chapter whether it acts only in the nephron or wherever the receptor sits. That single distinction predicts which trials a drug can win.
- 3 PATHWAY-2 put three sites against each other and the receptor won, which makes resistant hypertension a volume and aldosterone problem in the average patient.
- 4 Spironolactone and eplerenone carry Grade A mortality evidence in heart failure; finerenone carries Grade B renal evidence on top of maximal RAAS blockade.
- 5 Baxdrostat, approved in May 2026, is the first aldosterone synthase inhibitor — a genuinely new site. Placebo-adjusted systolic 9.8 mmHg at 2 mg over twelve weeks.
- 6 It suppresses aldosterone without affecting cortisol, and it does not escape hyperkalaemia: 10.2% at the higher dose.
- 7 It has no outcome data and no comparison against an MRA. Grade B, and prescribed within its add-on indication rather than in place of a drug with mortality evidence.
- 8 Hyperkalaemia is a property of this pathway rather than of any molecule in it. Review the other potassium-raising drugs before abandoning this one.
- 9 Gynaecomastia is a receptor effect, not a dose effect. Switch to eplerenone rather than reducing the spironolactone, and accept twice-daily dosing.

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CHAPTER 8

PART IV · THE SYMPATHETIC LIMB

Beta-Blockers

Demoted from first line by two trials in which the drug that lost was the same drug both times — and never retested in the members of the class that behave least like it. The demotion was right. The reasoning behind it reaches further than the evidence does.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 What blocking the beta-1 receptor does to each term of $MAP = CO \times SVR$, and why that is the class's problem.
- 2 The three-way classification that actually matters at the bedside, and which drug sits where.
- 3 Why atenolol lost in LIFE and in ASCOT at the same brachial pressure — and what CAFE says was happening.
- 4 Where the class is still first choice, with the grade of the evidence behind each row.
- 5 The metabolic cost, the withdrawal problem, and the asthma question answered properly.

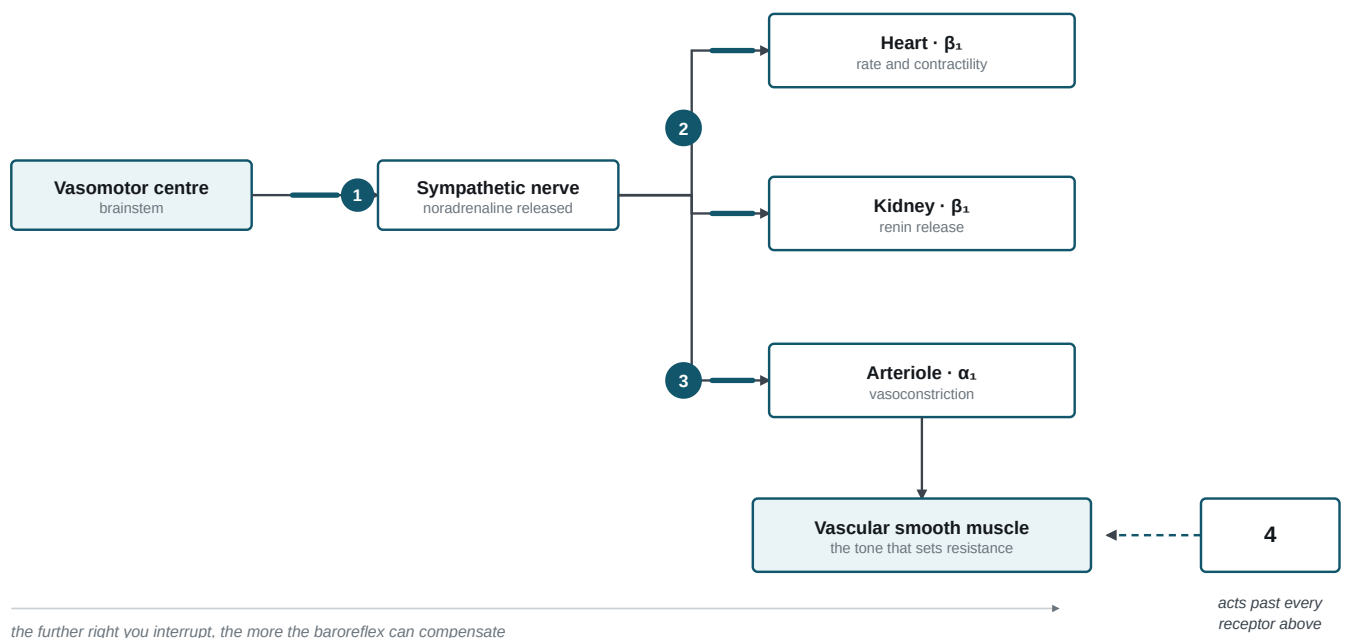
AT THE POINT OF PRESCRIBING

LAYER 1 · 60 SECONDS

USE WHEN	Heart failure with reduced ejection fraction · after myocardial infarction with a reduced ejection fraction — at a preserved ejection fraction it is no longer automatic (8.4) · rate control in atrial fibrillation · angina. Every strong indication for this class lies outside hypertension.
DO NOT USE	As first line in uncomplicated hypertension · in bronchospastic disease, unless the conditions in 8.6 are met — and never a non-selective agent there · severe bradycardia, high-grade block, cardiogenic shock, sick sinus syndrome without a pacemaker, decompensated heart failure · with verapamil or diltiazem
WHICH MOLECULE	Metoprolol succinate or bisoprolol in heart failure — note succinate, not tartrate. Carvedilol where vasodilation helps, but it is non-selective. Nebivolol in hypertension: it lowers resistance through nitric oxide. Not atenolol .
STARTING DOSE	Low, and titrate slowly. In heart failure, start lower still and go up over weeks.
FIRST CHECK	Heart rate and blood pressure. In heart failure, symptoms before numbers.
ASK ABOUT	Fatigue. Nightmares. Erectile dysfunction. None of these is volunteered, and each is a common silent reason for stopping.
NEVER	Stop abruptly for convenience . Taper over one to two weeks — rebound tachycardia, angina, infarction. Cardiogenic shock, symptomatic bradycardia or high-grade block is the exception.

8.1 Why act here

FIGURE 8.1 — ONE SYMPATHETIC LIMB, FOUR INTERRUPTIONS

**1 The brainstem, before the signal leaves****Central α_2 agonists — Chapter 10**

Methyldopa and clonidine turn the outflow down at its origin. Sedation is the price of acting inside the brain, and abrupt withdrawal is the danger.

2 The β_1 receptor, on heart and kidney**Beta-blockers — Chapter 8**

Two organs, one receptor: rate and contractility fall, and so does renin. Every strong indication for this class lies outside hypertension.

3 The α_1 receptor, on the arteriole**Alpha-1 blockers — Chapter 9**

The effector end. The baroreflex is intact here and answers back with tachycardia and sodium retention — the class's structural weakness.

4 The muscle itself, past every receptor**Direct vasodilators — Chapter 11**

Not an interruption of the limb at all. Which is why they provoke the fullest reflex response, and why they are never given alone.

The order along this line is the order of the next four chapters, and it explains their side effects before you read them. Interrupt in the brain and you get sedation. Interrupt at the receptor and you get whatever else that receptor does. Interrupt at the muscle and the body answers with tachycardia and salt retention — which is exactly why a direct vasodilator is prescribed with a beta-blocker and a diuretic, or not prescribed.

Blocking the beta-1 receptor does three things at once, and a reader who holds all three can predict most of this chapter. It slows the sinus node and weakens contraction, which lowers cardiac output. It suppresses renin release from the juxtaglomerular apparatus, which quietly makes this a cascade drug as well as a sympathetic one. And it removes catecholamine support from a circulation that was using it — reducing “cardiac chronotropic and inotropic effects... heart rate, blood pressure, and oxygen demand”¹.

Return to Volume 1's equation. Mean pressure is cardiac output times systemic vascular resistance, and **this class attacks the first term only**. Every other class in this volume attacks the second, or attacks volume, which feeds the first indirectly. That asymmetry is the whole of the class's clinical position.

It explains why beta-blockers suit the patient whose problem is output — young, neurogenic, tachycardic, post-infarction, in heart failure — and disappoint the patient whose problem is a stiff, high-resistance arterial tree, which is most older hypertensives. Worse, unopposed beta-1 blockade leaves alpha-mediated vasoconstriction untouched, so resistance may rise a little as output falls. The cuff records the net effect. Section 8.3 is about what the cuff does not record.

8.2 The classification that matters at the bedside

Textbooks classify this class several ways. Three distinctions change a prescription; the rest are for examinations.

The renin point is not a footnote

Suppressing renin is why beta-blockers work better in the young high-renin patient than the older low-renin one — the same phenotype logic that governs Chapters 1 and 2. A beta-blocker in a low-renin, salt-loaded patient is a wrongly chosen site twice over.

TABLE 8.1 — THREE DISTINCTIONS, AND WHAT EACH DECIDES

THE DISTINCTION	THE DRUGS	WHAT IT DECIDES
Non-selective	“Propranolol, carvedilol, sotalol, and labetalol” ¹	These block beta-2 as well, and beta-2 is what keeps a bronchus open. Non-selective agents “should not be used in patients with asthma” ¹ . This is the distinction that decides safety.
Beta-1 selective	“Atenolol, bisoprolol, metoprolol, and esmolol” ¹	In bronchospastic disease a cardio-selective agent may be used only where the patient does not respond to, or cannot tolerate, the alternatives — at the lowest possible dose, with a bronchodilator available or given alongside ¹⁰ . Selectivity is relative and dose-dependent, not absolute — see the nebivolol row.
Vasodilating	“Carvedilol, labetalol, and bucindolol”, through additional alpha-1 blockade ¹ ; nebivolol by a different route entirely	These agents lower resistance as well as output, which addresses the structural problem named in 8.1. Carvedilol is described as maintaining cardiac output by decreasing afterload ⁵ .
And the outlier	Nebivolol	It “stimulates NO synthase production from the endothelium via β-3 agonism, reducing systemic vascular resistance” ² — vasodilation through nitric oxide rather than alpha blockade. It has “the strongest β-receptor affinity of all β-blockers”, but that selectivity is lost “at higher doses and in patients who are slower metabolizers” ² .

8.3 Why atenolol lost, twice

Two large trials removed this class from routine first-line use, and in both the beta-blocker arm was built on atenolol.

The sentence to carry out of this table

“Beta-blocker” is not one drug. Propranolol and nebivolol share a receptor and almost nothing else, and the evidence that demoted the class was collected on neither of them.

TABLE 8.2 — THE TWO TRIALS THAT DEMOTED THE CLASS

	WHAT WAS COMPARED, AND WHAT WAS FOUND
LIFE, 2002	9,222 hypertensives with ECG left ventricular hypertrophy, losartan-based against atenolol-based. Achieved pressures 144.1/81.3 against 145.4/80.9 mmHg — effectively identical. Primary composite 11% against 13%, stroke 5% against 7%, new-onset diabetes 6% against 8% ⁴ .
ASCOT-BPLA, 2005	19,257 hypertensives, amlodipine adding perindopril against atenolol adding bendroflumethiazide. Stroke 3% against 4%, cardiovascular events 14% against 17%, new diabetes 6% against 8% ⁵ .
And the mechanism	CAFE, inside ASCOT, measured what the cuff could not. In 2,073 patients brachial systolic pressure was the same — 133.2 against 133.9 mmHg — while central aortic systolic pressure was 121.2 against 125.5 mmHg and central pulse pressure 43.4 against 46.4 ⁶ . The arm read the same number; the aortic root did not.

The physiology behind that gap is in V1·Ch1 and it is worth restating because it is the most satisfying explanation in this volume. A pressure wave travels down the aorta, reflects off the periphery and returns. In a young elastic artery it returns during diastole, where it usefully perfuses the coronaries. In a stiff artery it returns faster, arriving during systole and adding to the peak the heart must eject against. **Slowing the heart lengthens systole, so the reflected wave arrives while the ventricle is still ejecting.** A beta-blocker therefore raises central pressure relative to brachial, and the brachial cuff cannot see it.

That is a real finding and it is the strongest argument in the chapter. What it is not is a finding about the class. It is a finding about a drug that lowers heart rate without lowering resistance — which describes atenolol exactly, and describes carvedilol and nebivolol considerably less well. **No trial has compared a vasodilating beta-blocker against a calcium channel blocker on hard outcomes in hypertension**, so the extension of the verdict from atenolol to the class is an inference. It may well be right. It is not evidence, and this book will not print it as though it were.

8.4 Where this class ranks, and on what

TABLE 8.3 — WHERE THE BETA-BLOCKERS RANK

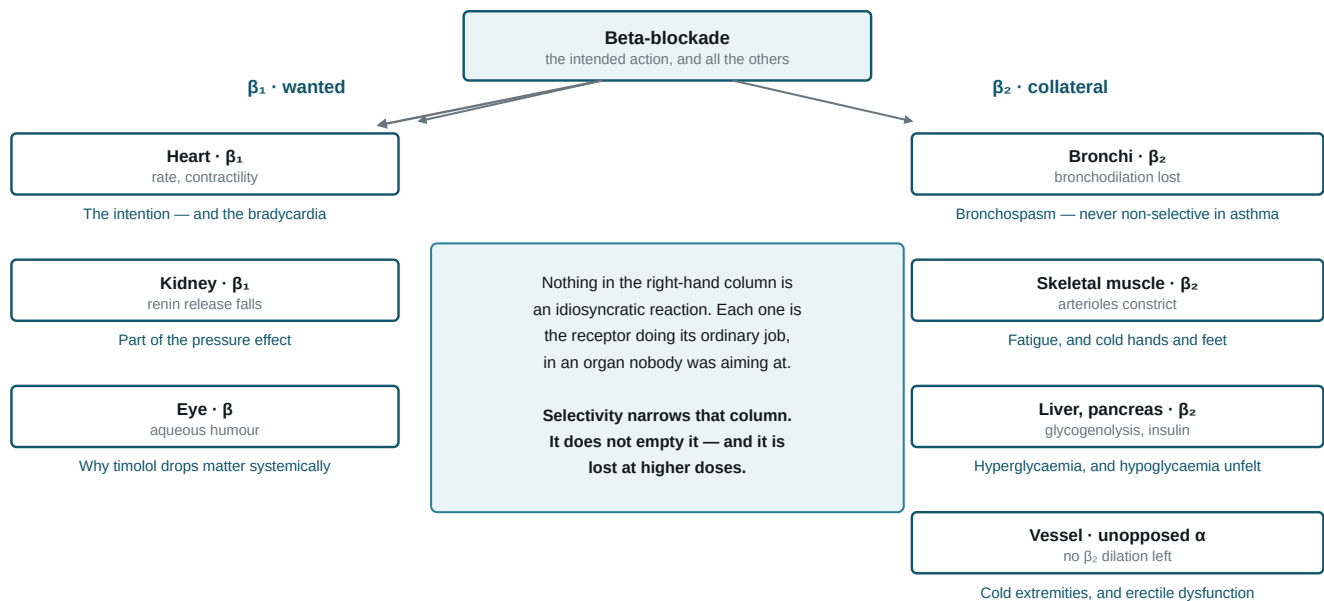
THE PATIENT	RANK	THE EVIDENCE	GRADE
Heart failure with reduced ejection fraction	First, with a RAAS blocker	MERIT-HF: 3,991 patients on metoprolol CR/XL against placebo, all-cause mortality 7.2% against 11% per patient-year — a 34% reduction, and the trial was stopped early ⁷ .	A — primary endpoint, large absolute effect, halted early for benefit.
After myocardial infarction, ejection fraction 40% or below	First, with a RAAS blocker	A standard FDA indication for the class ¹ ; carvedilol carries its own indication for left ventricular dysfunction after infarction ³ . The mortality evidence lives here, in the reduced ejection fraction.	B — long-established practice on trial evidence not reproduced here.
After myocardial infarction, ejection fraction above 40%	No longer automatic	Four randomised trials in two years — REDUCE-AMI, REBOOT, BETAMI-DANBLOCK and ABYSS — and they do not point the same way: two were null, one positive, and stopping an established beta-blocker was not non-inferior, with the harm concentrated in hypertensive patients. Starting one indefinitely is no longer clearly indicated at a preserved ejection fraction; stopping one that is established is a separate decision.	C — the trials are set out in Volume 3, Chapter 21 and Case 17.

THE PATIENT	RANK	THE EVIDENCE	GRADE
Atrial fibrillation needing rate control	First	A stated indication ¹ ; the class prolongs the atrial refractory period ¹ .	B — a rate-control indication, not a blood-pressure one.
Angina with hypertension	First or joint first	Coronary artery disease is a stated indication ¹ ; reducing rate reduces oxygen demand.	B.
Young, high-output, tachycardic, high-renin	Not first line — no guideline permits it here	Mechanistic only: this class attacks the output term and suppresses renin. No trial randomised by phenotype, and both current guidelines reserve the class for a compelling indication. A fast resting pulse is not one. Consider it after the guideline first-line classes, and only where a specific reason in this patient can be written down.	E — physiological reasoning, labelled as such. VI·Ch4 and VI·Ch14.
Uncomplicated hypertension in an older patient	Not first line	Atenolol lost to losartan ⁴ and to amlodipine ⁵ at matched brachial pressure, and CAFE showed a 4.3 mmHg gap in central systolic pressure ⁶ .	C — clear against atenolol; the extension to vasodilating agents was never tested.
Refractory hypertension — failing on five drugs including an MRA	Now the site to consider	24-hour urinary normetanephrine was higher in refractory than in controlled resistant patients, 464.4 against 309.8 µg ⁹ . And in PATHWAY-2 bisoprolol did lower pressure, just less than spironolactone ⁸ .	C — a mechanistic case supported by a biomarker difference, not by an outcome trial.
Asthma or significant airways disease	Non-selective contraindicated; cardio-selective only where no alternative will do, at the lowest effective dose	“Non-selective beta-blockers should not be used in patients with asthma” ¹ . The label starts further back: patients with bronchospastic disease should in general not receive a beta-blocker at all, and a beta-1 selective agent may be used where the alternatives have failed or are not tolerated, at the lowest possible dose, with a bronchodilator available or given concomitantly ¹⁰ .	A for the non-selective prohibition. See 8.6 for the four conditions attached to the exception.
Severe bradycardia, high-grade block, decompensated heart failure	Contraindicated	Stated contraindications ² — and the labels add three this row does not: cardiogenic shock, sick sinus syndrome without a pacemaker, and, for nebivolol, severe hepatic impairment ¹² . Metoprolol adds a systolic pressure below 100 mmHg ¹⁰ . Severe bradycardia is the labelled bar; lesser bradycardia and hypotension are the relative ones ¹ .	A.

Read the grades and the class's position is unusual in this volume: **its Grade A rows are all outside hypertension**. Heart failure, infarction, rate control — the class is indispensable there. In uncomplicated hypertension the strongest statement the evidence supports is Grade C, and it is a statement about atenolol.

8.4b The target map — where else these receptors are

FIGURE 8.2 — WHERE THE RECEPTORS ARE, AND THEREFORE WHAT THE ADVERSE EFFECTS MUST BE



This is the volume's method in one picture. The adverse effects of a class are not a list to be memorised; they are a map of where the receptor sits. Ask where else the target is, and the list writes itself — including the two nobody volunteers, fatigue and erectile dysfunction, which are the commonest silent reasons a patient stops the drug.

This is the class where a list of adverse effects is least useful and a map is most. The beta receptor is not a cardiac receptor that happens to appear elsewhere. It is a receptor found throughout the body, of which the cardiac population is one subset — and a drug that blocks it does so everywhere it reaches. **The side effects of this class are not off-target actions. They are the same action, arriving where nobody was aiming.**

TABLE 8.4 — ONE RECEPTOR FAMILY, SIX LOCATIONS, AND WHAT BLOCKING EACH PRODUCES

RECEPTOR AND LOCATION	WHAT IT NORMALLY DOES THERE	WHAT BLOCKING IT PRODUCES
β_1 — sinus node and myocardium	Raises rate and force of contraction under catecholamine drive.	The intended effect: lower rate, lower output, lower pressure and oxygen demand ¹ . And the dose-limiting one: bradycardia and hypotension ¹ .
β_1 — juxtaglomerular apparatus	Sympathetic drive releases renin here.	Renin falls. This is why the class behaves partly like a cascade blocker, and why it works better in a high-renin patient than a low-renin one.
β_2 — bronchial smooth muscle	Keeps the airway dilated. There is no beta-1 here worth speaking of.	Bronchospasm ¹ . This single row is the entire reason non-selective agents are prohibited in asthma, and the reason a cardio-selective agent is a conditional exception there rather than a free one ¹⁰ .
β_2 — skeletal muscle arterioles	Mediates the vasodilatation that lets working muscle receive more blood during exertion.	Fatigue and exercise intolerance . The commonest reason patients stop this class, and it is a vascular effect rather than a psychological one. Combined with a lower cardiac output, the muscle simply gets less.
β_2 — liver, pancreas, skeletal muscle	Drives glycogenolysis and modulates insulin release. It also produces the tachycardia and tremor of hypoglycaemia.	Hyperglycaemia and new-onset diabetes ¹ — 8% against 6% on atenolol in both LIFE and ASCOT ^{4,5} . And more dangerously, the warning signs of hypoglycaemia are removed ¹ while the hypoglycaemia itself is not.
α unopposed — peripheral arterioles	Alpha-mediated vasoconstriction normally runs against beta-2 vasodilatation. Block beta-2 and the alpha tone stands alone.	Cold hands and feet , and the reason patients with Raynaud phenomenon should avoid the class ¹ . Also part of why resistance does not fall as output does.
Central — lipophilic agents only	Propranolol and metoprolol cross the blood-brain barrier; atenolol largely does not.	Insomnia, vivid dreams, nightmares ¹ . Switch to a less lipophilic agent rather than out of the class.
Genital vascular smooth muscle and central pathways	Erection depends on arterial inflow and on autonomic balance. Both are altered by reduced cardiac output and by adrenergic blockade.	Erectile dysfunction ¹ . Nebivolol's is reported as less common than for conventional agents ² — which fits, because nebivolol is the one member that adds nitric-oxide vasodilatation rather than only removing beta support.

Two things follow from reading down that table that no list of side effects delivers. **First, the effects sort themselves into ones you can engineer around and ones you cannot.** Bronchospasm and cold extremities are beta-2 effects, so a cardio-selective agent reduces them. Nightmares are a lipophilicity effect, so a hydrophilic agent removes them. Erectile dysfunction is partly a vasodilatation problem, so the agent that vasodilates is the one to try. Bradycardia is beta-1 and therefore inseparable from the intended action — there is no molecule that fixes it.

Second, it explains why nebivolol is not simply a better beta-blocker. Every other member of the class works by subtraction: removing catecholamine support. Nebivolol subtracts at beta-1 and adds at the endothelium, stimulating nitric oxide synthase through beta-3 agonism². That is a different shape of drug, and it is why the row on cold extremities and the row on erectile dysfunction both behave differently for it — and why the trials that condemned atenolol say nothing about it.

8.5 It happened — now what?

The question this map answers before a patient asks it

“Why am I so tired on this tablet?” Not deconditioning, not age, not depression — beta-2 blockade in the arterioles of working muscle, on top of a deliberately reduced cardiac output. A physician who can say that keeps the patient on the drug when the drug is a Grade A indication, and changes it when it is not.

TABLE 8.5 — WHAT HAPPENS ON A BETA-BLOCKER, AND WHAT FOLLOWS

WHAT HAPPENED	WHAT IT IS	THE MOVE
Glucose rises, or a hypo is missed	The class “can induce hyperglycemia and mask the hemodynamic signs usually seen in a hypoglycemic patient, such as tachycardia” ¹ . New-onset diabetes was commoner on atenolol in both LIFE and ASCOT, 8% against 6% in each ^{4,5} .	In a diabetic on insulin or a sulfonylurea, the masking matters more than the glucose. Warn the patient that sweating may be the only warning left. If a beta-blocker is needed anyway — and after infarction or in heart failure it is — keep it and manage around it.
Fatigue, and exercise feels harder	Fatigue, dizziness, weight gain ¹ . The commonest reason patients stop the drug and the least often asked about.	Ask directly at review. Consider a vasodilating agent, or reconsider whether the indication is Grade A or Grade C — in a Grade C row this symptom is a sufficient reason to change class.
Nightmares, insomnia	“Insomnia, sleep changes, and nightmares”, particularly with agents crossing the blood-brain barrier ¹ .	Switch to a less lipophilic agent rather than abandoning the class. Patients rarely volunteer this, and attribute it to stress.
Wheeze	Bronchospasm occurs, and “asthmatic patients are at a higher risk” ¹ .	Stop a non-selective agent. In a patient who needs a beta-blocker for a Grade A indication and has airways disease, a cardio-selective agent may be used where nothing else is tolerated — at the lowest possible dose, with a bronchodilator available or given alongside ¹⁰ , and with the patient told what to watch for.
Erectile dysfunction	Sexual dysfunction is a recognised class effect ¹ ; carvedilol lists impotence ³ . Nebivolol’s is described as “less common than for conventional β-blockers” ² .	Ask, because the patient will not. It is a common silent reason for non-adherence, and there is a within-class option.
Cold hands, Raynaud	Patients with Raynaud phenomenon should avoid beta-blockers ¹ .	Change class. A vasodilating agent is a partial answer, not a licence.

8.6 The asthma question, answered properly

This deserves its own section because the usual teaching — never give a beta-blocker in airways disease — costs lives in the group who need one most. The label is more permissive than the folklore, and it is permissive on four conditions rather than none. Patients with bronchospastic disease “should in general, not receive beta-blockers”. A beta-1 selective agent “may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment”. Because “beta-1 selectivity is not absolute”, the lowest possible dose is used. And bronchodilators “should be readily available or administered concomitantly”¹⁰. Read together, that is not

permission to beta-block an asthmatic. It is a licence to take a measured risk when the indication is strong enough to be worth it — and somebody has to put the inhaler in the room.

The one that is dangerous

Never stop a beta-blocker abruptly for convenience. Receptor up-regulation during treatment means sudden withdrawal exposes an over-sensitised myocardium to circulating catecholamines — rebound tachycardia, hypertension, angina, and in a patient with coronary disease, infarction¹¹. Taper over one to two weeks, and more carefully still in ischaemic heart disease¹¹. One situation overrides the rule: cardiogenic shock, symptomatic bradycardia or high-grade block, where the drug comes out at once and the patient is watched while it does. Everywhere else — an admission, a patient who has run out of tablets, a well-meaning colleague stopping it because the pressure looks low — the taper applies.

TABLE 8.6 — AIRWAYS DISEASE AND THE BETA-BLOCKER DECISION

THE SITUATION	THE ANSWER
Asthma, and hypertension only	No beta-blocker. The indication is Grade C at best and there are four other classes. Do not spend a risk you do not need to take.
Asthma, and a Grade A indication — heart failure, recent infarction	A cardio-selective agent, on the label's four conditions: the alternatives have been tried and are not tolerated or do not work, the dose is the lowest possible because selectivity is not absolute, and a bronchodilator is available or given alongside ¹⁰ . Titrate slowly, and tell the patient exactly what to do if wheeze worsens. The mortality benefit in these indications is large ⁷ and the alternative is to forgo it.
COPD without a reversible component	Much less of a problem than asthma. The label's default still stands — in general a beta-blocker is not given in bronchospastic disease ¹⁰ — and so do its conditions, with the same reasoning: weigh the grade of the indication.
Any airways disease, non-selective agent	No. Propranolol, carvedilol, sotalol and labetalol all block beta-2 ¹ — and note that carvedilol, the drug most often wanted in heart failure, is on that list ³ .

8.7 The molecules, compared

The trap inside the answer

The vasodilating beta-blocker a clinician most wants to reach for in heart failure is carvedilol, and carvedilol is non-selective. The alpha-1 blockade that makes it attractive does not undo the beta-2 blockade that makes it unsafe in asthma.

TABLE 8.7 — CHOOSING WITHIN THE CLASS

MOLECULE	TYPE	DOSE	REACH FOR IT WHEN
Bisoprolol	Beta-1 selective ¹	—	A selective agent is wanted and once-daily dosing matters. The comparator arm in PATHWAY-2 ⁸ .
Metoprolol succinate	Beta-1 selective ¹ ; long-acting	Once daily ¹	Heart failure with reduced ejection fraction, where this formulation carries the trial evidence ⁷ . Note the succinate, not the tartrate.
Carvedilol	Non-selective with alpha-1 blockade ³	Hypertension: 6.25 mg twice daily, to 12.5 then 25 mg twice daily at intervals of seven to fourteen days, not exceeding 50 mg a day. Heart failure: 3.125 mg twice daily for two weeks, then doubled at intervals of at least two weeks ^{3,13}	Heart failure, and where vasodilation is wanted alongside rate control — it “maintains cardiac output by decreasing afterload” ³ . Not in asthma, and not in severe hepatic impairment ¹³ . Bioavailability is 25–35% ¹³ .
Nebivolol	Beta-1 selective with nitric-oxide vasodilation ²	5 mg once daily, titrated at two-week intervals; maximum 40 mg ² . Start at 2.5 mg where the creatinine clearance is below 30 mL/min or there is moderate hepatic impairment; severe hepatic impairment is a contraindication ¹²	Hypertension where a beta-blocker is wanted and resistance is the problem — the only agent that lowers it by releasing nitric oxide ² . Less erectile dysfunction than conventional agents ² . Remember selectivity is lost at higher doses ² .
Atenolol	Beta-1 selective ¹	50 mg once daily, to 100 mg; the label says more than 100 mg is unlikely to add anything ¹⁵ . Renally cleared: no significant accumulation until creatinine clearance falls below 35 mL/min, then a maximum of 50 mg daily at 15 to 35 and 25 mg daily below 15 ¹⁵	The molecule this chapter is about, and the one to avoid in uncomplicated hypertension ^{4,5} . Still widely and cheaply available in India, which is why the point needs making rather than assuming. It is the beta-blocker most often found on an old prescription and most often left unadjusted as the kidney declines.
Propranolol	Non-selective ¹ ; lipophilic	Often three or four times daily ¹	Essential tremor, migraine prophylaxis, thyrotoxicosis, portal hypertension ¹ . Rarely the right drug for chronic hypertension: dosing frequency and central effects both count against it.
Labetalol	Non-selective with alpha-1 blockade ¹	—	Pregnancy, and intravenous use in emergencies. Chapters 11 and Volume 3.
Esmolol	Beta-1 selective ¹ ; ultra-short	Intravenous only	When you want to be able to stop — aortic dissection, perioperative. Chapter 11.

MOLECULE	TYPE	DOSE	REACH FOR IT WHEN
Sotalol	Non-selective ¹ , and an antiarrhythmic before it is a beta-blocker	Not a hypertension drug; the interval is set by creatinine clearance, not the dose — every 12 hours above 60 mL/min, every 24 hours at 30 to 59, every 36 to 48 hours at 10 to 29 ¹⁴	Never for blood pressure. Its label is for life-threatening ventricular arrhythmia and atrial fibrillation, and carries a boxed warning for torsades de pointes: at a QT of 500 msec or more the dose is reduced, the interval lengthened, or the drug stopped ¹⁴ . Hypokalaemia and hypomagnesaemia are corrected before the first tablet, and a potassium below 4 mEq/L is a contraindication ¹⁴ . Found on a prescription alongside a thiazide, it is the potassium and the QT you check before anything else.

8.8 Clinical pearls

Twenty-four points that change practice, for a reader who has one minute.

- 1 This class attacks the cardiac output term of $MAP = CO \times SVR$ and leaves resistance alone. Every other class in the volume does the opposite.
- 2 It also suppresses renin¹, which makes it a cascade drug too — and explains why it suits the young high-renin patient and disappoints the old low-renin one.
- 3 Non-selective: propranolol, carvedilol, sotalol, labetalol. Beta-1 selective: atenolol, bisoprolol, metoprolol, esmolol¹.
- 4 “Beta-blocker” is not one drug. Propranolol and nebivolol share a receptor and little else.
- 5 Atenolol lost to losartan in LIFE and to amlodipine in ASCOT, both times at matched brachial pressure^{4,5}.
- 6 CAFE explains it: identical brachial systolic, 121.2 against 125.5 mmHg at the aortic root⁶. Slowing the heart lengthens systole, so the reflected wave arrives while the ventricle is still ejecting.
- 7 **That is a finding about atenolol.** No trial has tested a vasodilating beta-blocker against a calcium channel blocker on outcomes in hypertension. The class verdict is an inference.
- 8 Every Grade A row for this class is outside hypertension — heart failure, infarction, rate control. In uncomplicated hypertension the best the evidence supports is Grade C.
- 9 MERIT-HF: metoprolol CR/XL, mortality 7.2% against 11% per patient-year, a 34% reduction, stopped early⁷.
- 10 In heart failure use the formulation that was trialled: metoprolol *succinate*, not tartrate.
- 11 Carvedilol is non-selective³. The alpha-1 blockade that makes it attractive does not make it safe in asthma.
- 12 Nebivolol vasodilates through beta-3 agonism and nitric oxide, not alpha blockade² — the only agent in the class that does.
- 13 But nebivolol's selectivity is lost at higher doses and in slow metabolisers². Selectivity is a dose, not a property.
- 14 In airways disease a cardio-selective agent may be used where nothing else is tolerated, at the lowest possible dose, with a bronchodilator available¹⁰. The blanket prohibition is over-applied and costs patients a mortality benefit — but the licence is conditional.
- 15 But do not spend that risk for hypertension alone, where the indication is Grade C and four other classes exist.
- 16 **Never stop a beta-blocker abruptly for convenience** — rebound tachycardia, hypertension, angina, infarction. Taper over one to two weeks¹¹. Cardiogenic shock, symptomatic bradycardia and high-grade block are the exception: there it comes out at once.
- 17 The class masks hypoglycaemia by removing the tachycardia¹. In an insulin-treated diabetic that matters more than the glucose rise.
- 18 New-onset diabetes was 8% against 6% on atenolol in both LIFE and ASCOT^{4,5}. The same finding twice, with the same losing comparator.
- 19 Fatigue is the commonest reason patients stop this drug and the least often asked about.
- 20 Nightmares come from the lipophilic agents¹. Switch within the class rather than out of it.
- 21 Ask about erectile dysfunction. Nebivolol's is reported as less common², and the patient will not raise it.
- 22 A non-dihydropyridine calcium channel blocker with a beta-blocker is two drugs on one node. Not a combination for blood pressure; where a cardiologist wants it for rate control, that is a decision taken with close monitoring.
- 23 In refractory hypertension — five drugs including an MRA — this is the site the biomarker evidence points at⁹.
- 24 Atenolol remains cheap and widely dispensed in India. That is exactly why the LIFE and ASCOT point has to be made out loud.

KEY POINTS

- 1 Beta-blockers lower cardiac output and suppress renin, and leave systemic vascular resistance alone. That single asymmetry explains where the class wins and where it loses.
- 2 The class was demoted on two trials in which the losing drug was atenolol both times, at matched brachial pressure.
- 3 CAFE gives the mechanism: a 4.3 mmHg gap in central aortic systolic pressure that the cuff cannot see, because slowing the heart brings the reflected wave back into systole.
- 4 The extension from atenolol to the whole class has never been tested. It may be right; it is an inference, and the vasodilating agents are the untested part.
- 5 Every Grade A indication for this class lies outside hypertension: heart failure, post-infarction, rate control. There it is indispensable.
- 6 Carvedilol vasodilates by blocking alpha-1 and is non-selective; nebivolol vasodilates through beta-3 agonism and nitric oxide and is selective until the dose rises.
- 7 In asthma a cardio-selective agent is a conditional exception, not a permission: nothing else tolerated, lowest possible dose, bronchodilator to hand. Spend that risk on a Grade A indication, never on uncomplicated hypertension.
- 8 Never stop abruptly for convenience. Taper over one to two weeks, and say so on the prescription — cardiogenic shock, symptomatic bradycardia and high-grade block are the one exception.

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CHAPTER 9

PART V · THE SYMPATHETIC LIMB, CONTINUED

Alpha-1 Adrenoceptor Blockers

The only class in this volume whose trial arm was stopped early because the drug was causing harm — and which survives anyway, for a reason that has nothing to do with blood pressure.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 What blocking alpha-1 does, and why acting at the effector end is not the same as acting upstream.

2 What happened to the ALLHAT doxazosin arm, and what the finding does and does not mean.

3 Where the class is still the right answer, and the man in whom it treats two problems at once.

4 First-dose hypotension, and the eye complication a physician has to know about before a surgeon meets it.

AT THE POINT OF PRESCRIBING		LAYER 1 · 60 SECONDS
USE WHEN	The man has both hypertension and prostatic symptoms · resistant hypertension, fourth or fifth drug · phaeochromocytoma before surgery, and always before any beta-blocker	
DO NOT USE	As a first-line antihypertensive. In 24,335 patients doxazosin doubled heart failure against chlorthalidone and the trial arm was stopped early.	
WHICH MOLECULE	Doxazosin, prazosin, terazosin lower blood pressure. Tamsulosin, alfuzosin, silodosin are uroselective prostate drugs with minimal effect on pressure. Do not substitute one group for the other.	
STARTING DOSE	Lowest strength, given at bedtime — labelled for terazosin ⁴ , sensible for the rest. Not on a day the patient has started a diuretic or a nitrate.	
FIRST CHECK	Postural blood pressure. Falls risk, particularly in an older patient.	
TELL THE PATIENT	Tell your eye surgeon you take this. Floppy iris syndrome is on the label ⁵ and the surgical series put it at a third to four-fifths of users ¹ . It can be permanent.	

9.1 Why act here

Noradrenaline constricts a vessel by acting on the alpha-1 receptor of its smooth muscle. Block that receptor and the constriction fails: these drugs work by “blocking norepinephrine from activating the alpha-1 receptor, which lowers blood pressure”¹. This is the sympathetic limb interrupted at its far end, where the signal finally becomes tone — the mirror image of Chapter 10, which interrupts the same limb at its origin in the brainstem.

The same receptor sits on smooth muscle in the prostate and bladder neck, and blocking it there “induces smooth muscle relaxation in the prostate and bladder neck, facilitating urine flow”¹. One receptor, two organs, and the

reason this class has a future at all.

Acting at the effector end has a cost that acting upstream does not. The baroreflex is intact, senses the fall in resistance and responds with tachycardia and sodium retention — reflex tachycardia is a listed adverse effect¹. **The body can compensate for a blockade applied at the last step in a way it cannot for one applied at the first.** Section 9.2 is what that compensation looks like over four years.

9.2 What happened to the doxazosin arm

ALLHAT was a four-arm trial. Three arms ran to completion and are the backbone of Chapter 5. The fourth did not.

In 24,335 patients randomised to doxazosin 2–8 mg daily or chlorthalidone 12.5–25 mg daily, an interim analysis led to the alpha-blocker arm being discontinued early. There was **no significant difference on the primary outcome** of fatal coronary disease or non-fatal infarction — but congestive heart failure carried a relative risk of 2.04 (95% CI 1.79–2.32, $P<0.001$)².

Double the heart failure. That is a large effect, tightly estimated, in a very large sample, and it ended the use of alpha-blockers as first-line antihypertensives more or less overnight.

TABLE 9.1 — WHAT THE DOXAZOSIN ARM ESTABLISHED, AND WHAT IT DID NOT

IT ESTABLISHED	IT DID NOT ESTABLISH
That doxazosin is a worse first drug than chlorthalidone, on an endpoint that matters, by a wide margin ² . Grade A — a harm signal in a randomised comparison, which needs no margin argument.	That alpha-blockers are harmful as an <i>add-on</i> . The comparison was monotherapy against monotherapy, in patients who had a first-line drug substituted rather than a fourth added.
That the reflex sodium retention described in 9.1 has consequences a diuretic comparator would exaggerate — some of the excess heart failure may be a diuretic-versus-non-diuretic artefact rather than doxazosin toxicity.	That the whole class behaves this way. Only doxazosin was studied. That said, this book has just spent Chapter 8 warning against exactly this inference, and it applies here too — in the direction of caution, not exoneration.
That a first-line position has to be earned against the best available comparator, not against placebo.	That the class has no place. PATHWAY-2 gave doxazosin to resistant patients and it lowered pressure — just 4.03 mmHg less than spironolactone did ³ .

9.3 Where this class ranks, and on what

The honest reading

Doxazosin as a first drug: no. Doxazosin as a fourth or fifth drug in a patient already on a diuretic: a different question, which ALLHAT did not ask and PATHWAY-2 answered only by comparison.

TABLE 9.2 — WHERE THE ALPHA-1 BLOCKERS RANK

THE PATIENT	RANK	THE EVIDENCE	GRADE
Uncomplicated hypertension	Not indicated	Heart failure RR 2.04 against chlorthalidone; the arm was stopped early ² .	A — a harm signal. No latitude.
Hypertension with benign prostatic hyperplasia	Strong add-on	Alpha-blockers are first-line for BPH ¹ , and doxazosin, prazosin and terazosin are approved for hypertension though second-line ¹ . One drug, two indications, one tablet, one price.	B for the BPH indication; the hypertension benefit rides along and should not be the reason.
Resistant hypertension, fourth or fifth drug	An option after spironolactone	PATHWAY-2: doxazosin lowered home systolic pressure, 4.03 mmHg less than spironolactone did ³ .	C — it worked, it came second, and this use was not what ALLHAT tested.
Phaeochromocytoma, before surgery	First, and before any beta-blocker	Alpha blockade must precede beta blockade; unopposed alpha stimulation after beta blockade produces a hypertensive crisis. VI-Ch26 and V3.	E as a trial matter — nobody will randomise this — and absolute as a rule of practice.
An older patient at risk of falls	Avoid	First-dose hypotension, syncope and dizziness are “more common in older patients, increasing their risk of falls” ¹ .	B.

This is the only class in the volume whose Grade A row is a prohibition and whose surviving indication is in another organ system. It is not a failure of the drug; it is a drug whose best use was found after its first use was disproved.

9.4 It happened — now what?

TABLE 9.3 — THE THREE THAT MATTER

WHAT HAPPENED	WHAT IT IS	THE MOVE
Collapse or faint after the first dose	“First-dose hypotension, syncope, dizziness, and headache due to vasodilation and vascular smooth muscle relaxation” ¹ .	Prevent it rather than manage it: start at the lowest strength and warn the patient to rise slowly. Terazosin's label fixes the first dose at 1 mg at bedtime for every patient and says it is not to be exceeded ⁴ ; doxazosin's gives 1 mg once daily and names no hour ⁵ . The reasoning carries where the label is silent, and bedtime is the safer hour for the first tablet of any of them. Do not start one in a patient who has just been given a diuretic or a nitrate.
Cataract surgery goes badly	Intraoperative floppy iris syndrome. Long-term use “may lead to dysfunction or atrophy of the iris dilator muscle, potentially resulting in permanent damage”, with iris billowing, prolapse and progressive pupillary constriction. The label carries the warning but prints no incidence ⁶ ; the surgical literature reports 33% to 86%, with tamsulosin most often implicated ¹ .	Tell the patient to tell the ophthalmologist. The surgeon can plan for it if warned and cannot if not. Stopping the drug shortly before surgery does not reliably prevent it, and the physician who prescribed it is the person who should have mentioned it.
The heart rate rises	Reflex tachycardia ¹ — the baroreflex responding to a fall in resistance it can still detect.	Usually settles. If it does not, the pairing that fixes it is a beta-blocker, which blocks the reflex — and this is one of the few places where combining them is the point rather than a hazard.

A distinction worth keeping

The uroselective agents — alfuzosin, tamsulosin, silodosin — have “minimal orthostatic effects” and are first-line for BPH¹. They are prostate drugs that barely touch blood pressure. Doxazosin, prazosin and terazosin are the blood-pressure agents. Do not expect a hypertensive response from tamsulosin, and do not expect tamsulosin’s tolerability from doxazosin.

TABLE 9.4 — THE THREE INTERACTIONS THAT MATTER

THE OTHER DRUG	WHAT HAPPENS, AND WHAT TO DO
A PDE-5 inhibitor — sildenafil, tadalafil, vardenafil	Additive blood-pressure lowering and symptomatic hypotension, on the doxazosin label ⁵ . The man this class exists for — hypertension and a prostate — is the man taking one, and in India he has bought it without telling anyone. Ask. If both are needed, the PDE-5 inhibitor starts at its lowest dose in a patient already stable on the alpha-blocker, never the other way round.
Any antihypertensive newly added, or a diuretic or nitrate started the same day	The first-dose effect returns whenever the vascular tone the patient had adapted to is removed again. Treat every addition as a new first dose: lowest strength, at bedtime, with the warning repeated.
Alcohol, and a hot day	Both amplify the postural fall. Warn before the first tablet, not after the first faint.

One more line belongs with the dose. Doxazosin is cleared by the liver: the label does not recommend it in severe hepatic impairment (Child-Pugh C), and asks for blood pressure and symptoms of hypotension to be watched in lesser degrees of impairment⁵.

9.5 Clinical pearls

Seventeen points that change practice, for a reader who has one minute.

- 1 The site is the alpha-1 receptor on vascular smooth muscle — the sympathetic limb interrupted at its far end¹.
- 2 The same receptor in the prostate and bladder neck is why the class survives¹.
- 3 Blocking at the effector end leaves the baroreflex intact, so reflex tachycardia and sodium retention follow¹.
- 4 **The ALLHAT doxazosin arm was stopped early:** heart failure RR 2.04 (1.79–2.32) against chlorthalidone in 24,335 patients².
- 5 There was no difference on the primary endpoint². The heart failure finding is what ended the class as first-line.
- 6 That comparison was monotherapy against monotherapy. It did not test the class as a fourth drug.
- 7 PATHWAY-2 gave doxazosin to resistant patients and it worked — 4.03 mmHg less well than spironolactone³.
- 8 So: never first, reasonable fifth, and excellent when the man also has prostatic symptoms.
- 9 Give the first dose at bedtime — terazosin's label requires it⁴, doxazosin's leaves the hour open⁵, and it is the safer hour for any of them. First-dose hypotension is preventable and is the reason this class has a bad name.
- 10 Falls risk is higher in older patients¹ — weigh that before adding it to a frail patient's five drugs.
- 11 Intraoperative floppy iris syndrome is on the label⁵; the 33% to 86% incidence and tamsulosin's prominence come from the surgical literature¹. The damage can be permanent.
- 12 **Tell the patient to tell the eye surgeon.** A warned surgeon can plan; stopping the drug late does not reliably help.
- 13 Uroselective agents — alfuzosin, tamsulosin, silodosin — have minimal orthostatic effect and are prostate drugs, not antihypertensives¹.
- 14 Doxazosin, prazosin and terazosin are the antihypertensive members¹.
- 15 In pheochromocytoma, alpha blockade always precedes beta blockade. Reversing that order causes a hypertensive crisis.
- 16 Reflex tachycardia on an alpha-blocker is one of the few places a beta-blocker is the correct partner rather than a hazard.
- 17 Routine monitoring is not recommended for the selective agents¹. The vigilance goes into the first dose, the eye, and the question about sildenafil (Table 9.4).

KEY POINTS

- 1 Alpha-1 blockade interrupts the sympathetic limb at its effector end, where the baroreflex can still compensate. That is the class's structural weakness.
- 2 The ALLHAT doxazosin arm was stopped early for a doubling of heart failure against chlorthalidone, with no difference on the primary endpoint.
- 3 That was a monotherapy comparison. It did not test the class as a fourth or fifth drug, and PATHWAY-2 showed doxazosin does lower pressure there.
- 4 The surviving indication is the man with both hypertension and prostatic symptoms: one receptor, two organs, one tablet.
- 5 First-dose hypotension is preventable — lowest dose, at night, with a warning to rise slowly.
- 6 Intraoperative floppy iris syndrome is common, can be permanent, and the prescribing physician is the person who should warn the patient to tell the eye surgeon.
- 7 Uroselective agents are prostate drugs; doxazosin, prazosin and terazosin are the ones that lower pressure. Do not substitute one for the other.

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CHAPTER 10

PART V · THE SYMPATHETIC LIMB, CONTINUED

Central Sympatholytics

The oldest drugs in this volume, and the ones with the least modern evidence — kept by two situations nothing has replaced them in, and dangerous mainly through the way they are stopped.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- Why interrupting the sympathetic limb at its origin behaves differently from interrupting it at the effector end.
 - Methyldopa in pregnancy: what it rests on, and the two blood tests it obliges you to do.
 - Clonidine rebound — what it is, how fast, and the counselling that prevents it.
 - Where these agents still belong, and the grade of the evidence behind each row.

AT THE POINT OF PRESCRIBING		LAYER 1 · 60 SECONDS
USE WHEN	Pregnancy — methyldopa · resistant hypertension after spironolactone — clonidine · refractory hypertension, where the sympathetic site is what remains	
DO NOT USE	Uncomplicated hypertension · methyldopa in active liver disease, previous liver injury on it, or alongside a MAO inhibitor — and <i>not recommended</i> , rather than barred, in phaeochromocytoma	
WHICH MOLECULE	Methyldopa in pregnancy, 500 mg to 2 g daily in two to four divided doses. Clonidine for resistance; the weekly patch where fasting or adherence is the obstacle.	
FIRST CHECK	Methyldopa: blood count periodically, and liver function in the first 6 to 12 weeks .	
WARN ABOUT	Sedation and dry mouth in most patients. Both settle. A patient not warned stops the drug instead.	
NEVER	Stop clonidine abruptly . Hypertensive crisis, with encephalopathy, stroke and death reported. Reduce the dose gradually over two to four days, and say so at the first prescription.	
IN HOSPITAL	Ask about clonidine in every hypertensive admission. Omitting it is more dangerous than continuing it.	

10.1 Why act here

Chapter 9 blocked the sympathetic signal where it becomes tone. This chapter turns it down where it starts. Methyldopa “is converted to methyl norepinephrine centrally to decrease the adrenergic outflow by alpha-2 agonistic action from the central nervous system, leading to reduced total

peripheral resistance and decreased systemic blood pressure”¹. Clonidine “acts centrally on alpha-2 adrenergic receptors as an agonist”², reducing sympathetic outflow from the central nervous system.

Both are *agonists*, which reads as a contradiction until you locate the receptor. The alpha-2 receptor on a presynaptic terminal in the brainstem is an autoreceptor: stimulating it tells the neurone to release less noradrenaline. **An agonist at the brake is a brake.**

Acting upstream has an advantage and a cost, and they are the same fact seen twice. The advantage is that everything downstream falls together — rate, contractility and resistance — with less reflex compensation than the alpha-blockers provoke. The cost is that the sympathetic nervous system does other things besides holding up blood pressure, and turning it down centrally produces sedation and dry mouth in nearly everyone^{1,2}. It is also why abrupt withdrawal is so dangerous: a system suppressed at its origin rebounds from its origin.

10.2 Where these agents rank, and on what

TABLE 10.1 — WHERE THE CENTRAL AGENTS RANK

THE PATIENT	RANK	THE EVIDENCE	GRADE
Hypertension in pregnancy	First, with labetalol and nifedipine	Methyldopa “is also useful in pregnancy because it has no teratogenic effects” ¹ . Its place rests on decades of safety experience rather than on a modern outcome trial.	B/E — a strong, long-standing safety record, which is a real kind of evidence and a different kind from an endpoint trial. The book says which.
Resistant hypertension after spironolactone	An option	Clonidine is FDA-approved for adult hypertension, “typically for treatment-resistant cases” ² .	E — a licensed indication without a modern comparative outcome trial.
Refractory hypertension — five drugs including an MRA	Worth considering	The mechanistic case: refractory disease carries higher 24-hour urinary normetanephrine than controlled resistant disease, 464.4 against 309.8 µg ³ — a sympathetic problem, and this is the sympathetic site at its origin.	C — a biomarker difference and a mechanism, not an outcome trial in this population.
Uncomplicated hypertension	Not indicated	No modern outcome evidence, and sedation and dry mouth in a patient who has four better-evidenced options.	E , and the answer is still no.
Phaeochromocytoma	Not recommended (methyldopa)	The label does not contraindicate it, but states that methyldopa “is not recommended for the treatment of patients with pheochromocytoma”, under precautions ⁴ — it also interferes with the catecholamine assay used to make the diagnosis ⁴ .	A for not using it here; the bar is a precaution, not a contraindication.
Active liver disease, or previous liver injury on the drug	Contraindicated (methyldopa)	The label’s contraindications are active hepatic disease, a liver disorder previously associated with methyldopa, hypersensitivity, and concurrent MAO inhibitor therapy ⁴ . Haemolytic anaemia on the drug is a warning rather than a listed contraindication, but methyldopa is not to be reinstituted after it ⁴ — and a positive direct Coombs test on its own is explicitly <i>not</i> a bar ⁴ .	A .

This is the least evidence-dense chapter in the volume, and printing it at four pages rather than fourteen is the honest response. What the class has is a licence, a long safety record in pregnancy, and a mechanism that fits the hardest patients. What it does not have is a trial.

10.3 Methyldopa — and the two tests it obliges

Methyldopa is the drug most Indian obstetric practice starts with, and it is prescribed correctly far more often than it is monitored correctly. The dose in adults starts at 250 mg two or three times a day for the first 48 hours; the usual daily dose is then 500 mg to 2 g in two to four divided doses, and the ceiling is 3 g a day⁴. Tablets are 250 and 500 mg — there is no 125 mg strength on the current label⁴.

TABLE 10.2 — WHAT METHYLDOPA OBLIGES YOU TO CHECK, AND WHEN

	WHY, AND WHAT YOU ARE LOOKING FOR
Full blood count — periodically	“Direct Coombs test is reported positive, usually after 6 to 12 months of therapy, but rarely results in fatal hemolytic anemia” ¹ . The instruction that follows is explicit: “periodic testing of hemoglobin, hematocrit, and the red blood cell count is necessary to rule out hemolytic anemia” ¹ . Note the two are not the same thing. A positive Coombs test is common and usually harmless; haemolysis is rare and serious. You are screening for the second, not the first. The label asks for a blood count before treatment and at intervals thereafter, and a direct Coombs test “before therapy and at 6 and 12 months after the start of therapy” ⁴ .
Liver function — first 6 to 12 weeks	“Periodic determinations of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs” ⁴ . The fever clause is the one that catches methyldopa hepatitis early. Active hepatic disease and previous liver disorder on the drug are both contraindications ⁴ .
And what to tell the patient	Sedation and dry mouth are common ¹ and settle in most people over one to two weeks. A woman told to expect that will persist with the drug; a woman not told will stop it, and in pregnancy that matters.

10.4 Clonidine rebound

Every drug in this chapter is safer to start than to stop, and clonidine is the extreme case. The source is unusually direct: “the abrupt discontinuation of clonidine may induce a hypertensive crisis. Therefore, clonidine must be tapered to avoid rebound hypertension”². The label sets the interval, and it is shorter than the habit: “the physician should reduce the dose gradually over 2 to 4 days”⁵ — days, not weeks. It also warns that “rare cases of hypertensive encephalopathy, stroke, and death have been reported”². The weeks-long wind-down belongs to the extended-release tablet, which is licensed for ADHD and carries no hypertension indication.

The mechanism follows from 10.1. Chronic alpha-2 agonism suppresses central sympathetic outflow, and the system adapts by up-regulating. Remove the agonist and a sensitised system fires into a circulation that has been running at low tone. The rebound is not a return to baseline; it overshoots it.

The transfusion trap
The label is precise here: a positive direct Coombs test alone does not interfere with typing or cross-matching; it is the less common positive indirect test alongside it that can complicate the cross-match⁴. The laboratory will not know she is on methyldopa unless somebody says so, and if she is admitted for delivery that is the moment it matters.

TABLE 10.3 — WHERE CLONIDINE GETS STOPPED ABRUPTLY, AND WHAT TO DO ABOUT IT

THE SITUATION	WHAT HAPPENS	THE COUNTERMEASURE
The patient runs out	The commonest cause by far, and it is a supply problem rather than a clinical one.	Never prescribe clonidine without saying, in words, that stopping suddenly can be dangerous. Write it on the prescription. Make sure repeat supply is arranged before the tablets end.
Admitted to hospital and the drug is not on the chart	The drug history is taken, clonidine is missed or deliberately withheld, and the crisis arrives on day two or three.	Ask specifically about it in any hypertensive admission. It is the one antihypertensive whose omission is more dangerous than its continuation.
Nil by mouth for surgery	Same mechanism, and the anaesthetic masks the early signs.	The transdermal patch, changed weekly, exists partly for this ² . Flag it to the anaesthetist before the list, not on the day.
A colleague stops it because the pressure looks low	A well-meant substitution that produces the opposite of what was intended.	Reduce the dose in steps over two to four days rather than stopping outright. If it must come out, replace the sympathetic cover while it does.

Three interactions on the clonidine label are worth knowing before the dose is escalated. A tricyclic antidepressant can reduce clonidine’s hypotensive effect and leave it looking ineffective — so before adding a tablet, ask whether an amitriptyline was started for the neck pain or the sleep⁵. Alcohol, barbiturates and other sedatives compound the sedation that is already the commonest reason patients stop this drug⁵. And with diltiazem or verapamil the label reports sinus bradycardia severe enough to need admission and a pacemaker, and asks for the heart rate to be watched with any agent that slows the sinus node or the AV node — a beta-blocker and digoxin included⁵.

10.5 The molecules, compared

And the same rule, one chapter back

Chapter 8 said never to stop a beta-blocker abruptly for convenience, for a closely related reason — receptor up-regulation during treatment. **Both sympathetic sites punish abrupt withdrawal**, and they punish it hardest together: the risk is greater in a patient taking both, and the label withdraws the beta-blocker several days *before* the clonidine taper begins — never after it, and never at the same time⁵. A patient on either drug should be told so at the first prescription, not at the first crisis.

TABLE 10.4 — THE CENTRAL AGENTS

MOLECULE	DOSE AND FORMS	REACH FOR IT WHEN	WHAT STOPS YOU
Methyldopa	250 mg two or three times daily to start; then 500 mg to 2 g daily in two to four divided doses, maximum 3 g; tablets 250 and 500 mg ⁴	Pregnancy, chiefly — no teratogenic effects ¹ . Long experience is the reason it holds this place.	The labelled contraindications are active liver disease, previous liver injury on the drug, hypersensitivity and a concurrent MAO inhibitor ⁴ . Haemolytic anaemia on the drug is a warning — the drug is not reinstituted after one — and phaeochromocytoma is a precaution, not a bar ⁴ . Sedation and dry mouth in most.
Clonidine	Immediate-release 0.1, 0.2, 0.3 mg — start 0.1 mg twice daily, usual range 0.2 to 0.6 mg daily in divided doses ⁵ ; transdermal patch 0.1–0.3 mg/day, changed every seven days. The extended-release 0.1 mg tablet is an ADHD product and carries no hypertension indication.	Treatment-resistant hypertension ² . The patch where adherence or fasting is the problem.	The withdrawal. Also hypotension, headache, fatigue, nausea, constipation, dry mouth, dizziness and sedation ² . A tricyclic blunts it, sedatives compound it, and verapamil or diltiazem alongside it can stop the sinus node ⁵ (10.4).
Moxonidine, rilmenidine	—	Imidazoline-1 agonists, developed to keep the central sympatholytic effect with less sedation. Where available they are used as later-line agents in resistant hypertension.	The summary of product characteristics contraindicates moxonidine below a GFR of 30 and in severe heart failure, and directs withdrawal over two weeks rather than at once. No outcome trial supports either molecule, so none is printed. Availability differs by country; check the local label rather than this book.

Two other things clonidine does are worth knowing because they explain prescriptions a physician will meet without recognising: it is approved for ADHD in children in extended-release form, for tics in Tourette syndrome, and as an adjunct in severe cancer pain². A patient on clonidine is not necessarily a hypertensive patient — and the withdrawal rule applies to all of them.

10.6 Clinical pearls

Twenty points that change practice, for a reader who has one minute.

- 1 These drugs turn the sympathetic limb down at its origin; Chapter 9 blocks it at its end.
- 2 Both are alpha-2 agonists, which sounds wrong until you notice the receptor is a presynaptic autoreceptor. An agonist at the brake is a brake.
- 3 Methyldopa is converted centrally to methyl noradrenaline and reduces adrenergic outflow¹.
- 4 Clonidine is an imidazoline derivative acting as a central alpha-2 agonist².
- 5 Methyldopa's place in pregnancy rests on the absence of teratogenic effects¹ and long experience — not on a modern outcome trial. That is real evidence of a different kind.
- 6 Dose 500 mg to 2 g daily in two to four divided doses, maximum 3 g, in 250 or 500 mg tablets⁴.
- 7 A positive direct Coombs test appears usually after 6 to 12 months and rarely causes fatal haemolysis¹.
- 8 **A positive Coombs test and haemolysis are not the same thing.** Check haemoglobin, haematocrit and red cell count to rule out the second¹.
- 9 And tell the blood bank she is on methyldopa — the direct Coombs test alone does not interfere with cross-matching, but a positive indirect test alongside it can⁴, and delivery is when that bites.
- 10 Liver function in the first 6 to 12 weeks¹. Active liver disease is a contraindication.
- 11 Warn about sedation and dry mouth. Both settle; a patient not warned stops the drug instead.
- 12 **Abrupt clonidine withdrawal may cause a hypertensive crisis²**; reduce the dose gradually over two to four days⁵.
- 13 Encephalopathy, stroke and death have been reported after abrupt withdrawal².
- 14 The commonest cause of clonidine rebound is running out of tablets. Say so at the first prescription and write it down.
- 15 Ask about clonidine in every hypertensive admission. Omitting it is more dangerous than continuing it.
- 16 The transdermal patch, changed weekly, covers the nil-by-mouth patient².
- 17 Clonidine is also used for ADHD, Tourette tics and cancer pain². The withdrawal rule applies to those patients too.
- 18 In refractory hypertension the sympathetic site is where the biomarker evidence points³ — and this is that site at its origin.
- 19 Methyldopa is not recommended in pheochromocytoma — a precaution on the label rather than a contraindication, and it interferes with the catecholamine assay besides⁴.
- 20 This is the least evidence-dense chapter in the volume. Four pages rather than fourteen is the honest response.

KEY POINTS

- 1 Central alpha-2 agonism reduces sympathetic outflow at its origin, so everything downstream falls together with less reflex compensation than an alpha-blocker provokes.
- 2 The cost is sedation and dry mouth in most patients, and a system that rebounds hard when the drug is removed.
- 3 Methyldopa holds its place in pregnancy on the absence of teratogenicity and decades of experience, not on an outcome trial. The book prints which kind of evidence that is.
- 4 It obliges two monitoring tests: periodic blood counts for haemolysis, and liver function in the first six to twelve weeks.
- 5 A positive Coombs test is common and usually harmless; haemolysis is rare and serious. Screen for the second.
- 6 Abrupt clonidine withdrawal can cause a hypertensive crisis, with encephalopathy, stroke and death reported. Reduce the dose gradually over two to four days.
- 7 The commonest cause of that crisis is a patient running out of tablets, so the counselling belongs at the first prescription.
- 8 Both sympathetic sites — this one and the beta receptor — punish abrupt withdrawal. Say so when you start either, and where a patient is on both, the beta-blocker comes out several days first.

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CHAPTER 11

PART VI · DIRECT VASODILATION, AND THE INTRAVENOUS AGENTS

Direct Vasodilators and the Intravenous Agents

Drugs that dilate an arteriole without asking a receptor’s permission — which is why none of them is given alone, and why the last table in this volume is a selection matrix rather than a protocol.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- Why a drug that dilates directly always needs two companions, and what each companion is for.
 - Hydralazine: the lupus risk, the acetylator phenotype behind it, and the two tests it obliges.
 - Minoxidil, and the effusion that can become tamponade.
 - Choosing an intravenous agent by the situation — and where this volume stops and Volume 3 begins.

AT THE POINT OF PRESCRIBING		LAYER 1 · 60 SECONDS
USE WHEN	Everything else has been tried — oral agents · acute severe hypertension in pregnancy · hypertensive emergency, meaning severe hypertension with acute organ damage — intravenous agents	
DO NOT USE	Hydralazine in coronary disease or aortic dissection — it raises cardiac oxygen demand. Any direct vasodilator alone. Any intravenous agent for a high number in a patient with no acute organ damage — that patient gets an oral drug and a follow-up (Volume 3, Chapter 24).	
THE RULE	A direct vasodilator is given with a beta-blocker and a diuretic, or it is not given. Alone it loses its effect in weeks and keeps every adverse effect.	
HYDRALAZINE	10 mg four times daily to 50 mg four times daily. Drug-induced lupus in 5 to 8% , usually after six months. Check blood count and ANA before and during.	
MINOXIDIL	For hypertension nothing else has controlled. 5 mg once daily to start, usual 10 to 40 mg daily, maximum 100 mg — started under close supervision with a beta-blocker and a loop diuretic already in place. Hypertrichosis, marked fluid retention needing a loop diuretic, and pericarditis that can progress to tamponade.	
INTRAVENOUS, BY SITUATION	Labetalol in pregnancy · esmolol when you may need to stop · nicardipine or clevidipine for titratable control · nitroglycerin for coronary syndrome or pulmonary oedema · phenolamine for catecholamine excess, including clonidine withdrawal	
AND THEN	How far and how fast to lower the pressure is Volume 3. This chapter names the drug and stops.	

11.1 Why act here

Every other class in this volume works through a receptor, an enzyme or a transporter — a control point the body was already using. These drugs bypass all of that and relax the arteriolar smooth muscle cell itself. Hydralazine “inhibits inositol trisphosphate (IP3)-induced calcium release from the smooth muscle cell sarcoplasmic reticulum”¹; minoxidil “directly relaxes arteriolar smooth muscle, with minimal effect on the vein”².

That produces a large fall in resistance and two responses which are the whole of the chapter’s practical content. **The baroreflex answers with tachycardia** — hydralazine’s reduction in vascular resistance “triggers sympathetic activation, causing compensatory tachycardia”¹. **And the kidney answers with sodium retention**, because a fall in perfusion pressure at the afferent arteriole is exactly the signal that releases renin.

So the rule that governs this class is not a caution, it is the prescription: **a direct vasodilator is given with a beta-blocker and a diuretic, or it is not given**. The beta-blocker answers the tachycardia, the diuretic answers the retention, and without them the drug loses its effect within weeks while the patient keeps the side effects. This is the clearest case in the volume of the principle from Opening 1 — the reflex a drug provokes is the argument for its partner.

11.2 Hydralazine

Hydralazine has four indications worth knowing: essential hypertension refractory to other agents, hypertensive emergency, heart failure with reduced ejection fraction in combination with isosorbide dinitrate, and acute severe hypertension in pregnancy¹. The review that lists them also says “urgency”; this book does not. An emergency is severe hypertension with acute organ damage. A high reading on its own is not one, does not need a parenteral drug, and the ESC position document prefers that the word “urgency” not be used at all⁷ — Volume 3, Chapter 24.

Which is also why they are last

Three drugs to deliver what one drug delivers at another site. These agents are for the patient in whom the other sites have been tried, and for the emergency, where the reflexes matter less than the speed.

TABLE 11.1 — HYDRALAZINE AT THE POINT OF PRESCRIBING

	DETAIL
Oral dose	Start 10 mg four times daily, increasing to 25 mg then 50 mg four times daily; maximum 300 mg per day ¹ . Four times daily is a real objection in a chronic disease — Opening 1’s fourth filter applies with force.
Intravenous	20–40 mg by rapid intravenous bolus or intramuscular injection, repeated as necessary⁶ , and the label is explicit that it must not be added to infusion solutions⁶ . The familiar “10 to 20 mg by slow infusion every 4 to 6 hours” is what the review literature prints ¹ ; it is common practice, not label text. Effects appear within 10 to 30 minutes and last 2 to 4 hours, and the “unpredictable response limits first-line use” ³ . The obstetric dose is smaller again — follow the local maternity protocol.
In heart failure	With isosorbide dinitrate: 37.5 mg / 20 mg, up to 75 mg / 40 mg three times daily ¹ . A distinct indication with its own evidence, not a hypertension use.
Contraindications	The label states three: hypersensitivity to hydralazine, coronary artery disease , and mitral valvular rheumatic heart disease⁶ . Aortic dissection is treated as a contraindication in practice and in the review literature ¹ , on the same reasoning, but it is not on the US label. Lactation is a precaution and not a contraindication — hydralazine is excreted in breast milk and the label directs caution ⁶ . The cardiac ones follow directly from the reflex tachycardia — the last thing a dissecting aorta or an ischaemic myocardium needs is a faster, harder-contracting ventricle. Rheumatic mitral disease earns its place in an Indian book: a fixed obstruction upstream of the ventricle tolerates a reflex tachycardia badly, because the filling time is what shortens.
Common adverse effects	Headache, nausea, flushing, palpitations, tachycardia, dizziness ¹ .

And the one that defines the drug. Drug-induced lupus occurs in “roughly 5–8% of hydralazine users”, typically after six months or more, with arthralgia, myalgia and fever; the risk factors are a slow acetylator phenotype and reduced renal function¹. That is not a rare idiosyncrasy — it is one patient in fifteen or twenty on long-term treatment.

The monitoring instruction follows: obtain a full blood count and an antinuclear antibody titre before and during therapy, discontinue immediately if lupus-like symptoms develop, and note that in 95 to 100% of hydralazine-induced lupus the ANA is positive¹.

11.3 Minoxidil

Minoxidil relaxes arteriolar smooth muscle directly, with minimal venous effect². It is the most powerful oral vasodilator available and is reserved for hypertension that has defeated everything else.

Its adverse effects are listed compactly and each one matters: “hypertrichosis, water retention, pericarditis that may progress to tamponade”².

How to read that ANA
A positive ANA on hydralazine, in a patient with no symptoms, is common and is not the diagnosis. Symptoms with a positive ANA are. The test earns its place by being almost always positive when the syndrome is present — so a negative ANA in a symptomatic patient points somewhere else.

TABLE 11.2 — THE THREE THAT DECIDE WHETHER MINOXIDIL IS USABLE

EFFECT	WHAT IT MEANS IN PRACTICE
Hypertrichosis	Hair growth over the face, arms and back. Cosmetically intolerable for many patients, particularly women, and the commonest reason the drug is stopped. It is also why the same molecule is sold as a topical treatment for baldness — a fact worth mentioning before a patient discovers it themselves.
Water retention	Marked, and greater than with hydralazine. A loop diuretic is usually required rather than a thiazide (Chapter 6), and this is one of the few hypertension settings where that is true.
Pericarditis, progressing to tamponade	The one that can kill. A pericardial effusion in a patient on minoxidil is not incidental. Breathlessness, a raised venous pressure or new chest discomfort needs an echocardiogram, not a dose adjustment.
The dose	5 mg once daily to start; the usual effective range is 10 to 40 mg a day and the maximum 100 mg, with at least three days between adjustments because the full response to a dose takes that long ⁸ . The label's boxed warning asks that it be given under close supervision, usually with a beta-blocker against the tachycardia and a diuretic — frequently a loop diuretic — against the fluid, and that malignant hypertension be started in hospital ⁸ .

11.4 Choosing an intravenous agent

This is the last table in the volume and it is deliberately a selection table. Which drug suits which situation is pharmacology and belongs here. **How far and how fast to lower a pressure, in which emergency, is a clinical-situation question and belongs in Volume 3.** Nothing on this page should be read as a target or a rate.

The prescription this drug requires

Minoxidil with a beta-blocker and a loop diuretic, or not at all. A patient on minoxidil alone will retain fluid, become tachycardic, lose the pressure benefit within weeks, and keep every one of the effects above.

TABLE 11.3 — THE INTRAVENOUS AGENTS, AND WHAT DECIDES BETWEEN THEM

AGENT	DOSE AS STATED	WHAT IT SUITS, AND WHAT STOPS YOU
Nicardipine	5 mg/h, increasing by 2.5 mg/h — every 5 minutes for rapid control, every 15 for gradual — to a maximum of 15 mg/h ³⁴	A calcium channel blocker by infusion — the same site as Chapter 4, given where it can be titrated. Steady-state pharmacokinetics are similar in older patients, but the label still directs a low initial dose in the elderly, and gradual titration in renal or hepatic impairment ⁴ . Contraindicated in advanced aortic stenosis — the label's word, not a caution ⁴ .
Clevidipine	1–2 mg/h, doubling every 90 seconds. Most patients need 16 mg/h or less; the lipid load caps this at an average 21 mg/h over 24 hours . Little experience beyond 72 hours ³⁴	The most rapidly titratable agent here. Contraindicated with soy or egg allergy, with a defect of lipid metabolism, and in severe aortic stenosis — the first two because it is formulated in a lipid emulsion, the third because afterload reduction cuts myocardial oxygen delivery ⁴ . Lower doses in the elderly ³ .
Sodium nitroprusside	Start 0.3 mcg/kg/min; maximum 10 mcg/kg/min, and never for more than 10 minutes at that maximum . Cyanide buffering is exhausted at roughly 500 mcg/kg cumulative ³⁴	Powerful and immediate, and the agent with a toxin attached: it “is metabolized to cyanide, and it can lead to cyanide toxicity” ² . Arterial monitoring is recommended, and thiosulfate co-administration advised for longer infusions ³ — thiosulfate provides sulfur, converting cyanide to thiocyanate ² .
Nitroglycerin	5 mcg/min, increasing by 5 mcg/min every 3–5 minutes. Above 20 mcg/min the label allows larger steps of 10–20 mcg/min — there is no stated maximum , and response varies widely ³⁴	A venodilator first. Reserve it for acute coronary syndrome or pulmonary oedema , and avoid it in volume depletion ³ . Contraindicated with a phosphodiesterase-5 inhibitor — sildenafil, tadalafil, vardenafil — or with riociguat , and in tamponade, constrictive pericarditis, restrictive cardiomyopathy and raised intracranial pressure ⁴ . Ask that question before the infusion is started. It is not a general-purpose antihypertensive infusion.

AGENT	DOSE AS STATED	WHAT IT SUITS, AND WHAT STOPS YOU
Labetalol	20 mg over 2 minutes, then 40 or 80 mg at 10-minute intervals; or an infusion at 2 mg/min. Cumulative dose no more than 300 mg ³⁴	Alpha and beta blockade together, which is why it lowers pressure without the reflex tachycardia. The agent of choice in pregnancy — but not at this dose : the ACOG obstetric regimen starts at 10 to 20 mg, repeats 20 to 80 mg every 10 to 30 minutes to a cumulative 300 mg, or infuses at 1 to 2 mg per minute; Volume 3, Chapter 23, Table 23.1, and the maternity protocol. Contraindicated in bronchial asthma, overt cardiac failure, heart block beyond first degree, cardiogenic shock and severe bradycardia ⁴ — Chapter 8's non-selectivity problem, in an emergency, with the conduction and pump limits beside it. Keep the patient supine for the injection and for three hours after it : the label puts symptomatic postural hypotension at 58% in patients tilted or sat up inside that window ⁴ . The label also directs that it not be used in nonallergic bronchospastic disease such as chronic obstructive pulmonary disease ⁶ — and in India the wheezy patient is far more often a biomass-smoke COPD than an asthmatic, so “no asthma” is not the end of the question.
Esmolol	Loading 500 mcg/kg as a bolus over 1 minute — a total dose, not an infusion rate , then 50 mcg/kg/min. For immediate control: 1 mg/kg over 30 seconds, then 150 mcg/kg/min ³⁴	Ultra-short-acting, so it can be switched off. Aortic dissection, perioperative use. Contraindicated in severe sinus bradycardia, sick sinus syndrome, heart block beyond first degree, decompensated heart failure, cardiogenic shock, pulmonary hypertension, and alongside an intravenous cardiodepressant calcium channel blocker such as verapamil ⁴ ; monitor lung function ³ .
Hydralazine	20–40 mg by rapid intravenous bolus or intramuscular injection, repeated as necessary ⁶ . (The familiar “10 mg, every 4 to 6 hours” is common practice, not label text.) This is the general adult dose and is not the obstetric dose — obstetric protocols use substantially smaller increments; follow the local maternity protocol in a pregnant patient ³	Onset 10–30 minutes, lasting 2–4 hours — and an “unpredictable response” that “limits first-line use” ³ . Long-established in obstetric practice; not a titratable agent.
Phentolamine	5 mg intravenously or intramuscularly — 1 mg in a child — one to two hours before surgery for a phaeochromocytoma, and repeated if necessary ; 5 mg intravenously during surgery as indicated ⁶ . The label sets no fixed repeat interval ; the “every 10 minutes” in common circulation is practice, not label text ³	The catecholamine-excess agent , and the only one on this list chosen by cause rather than by organ: phaeochromocytoma, MAO inhibitor interactions, cocaine or amphetamine toxicity, and <i>clonidine withdrawal</i> ³ — the crisis Chapter 10 warned about, met with the drug that answers it. Contraindicated in myocardial infarction, a history of myocardial infarction, coronary insufficiency or angina ⁶ .
Enalaprilat	1.25 mg IV over 5 minutes, every 6 hours — a fixed dose, not a titration . Doses of 5 mg every 6 hours were tolerated in trials but were not more effective, and the label does not recommend them ⁶	Slow onset, about 15 minutes. The labelled contraindications are hypersensitivity and any history of angioedema — on a previous ACE inhibitor, or hereditary or idiopathic ⁶ . Ask before it is given. Pregnancy carries a boxed warning of injury and death to the fetus, and is an absolute bar in practice ⁶ ; bilateral renal artery stenosis sits under precautions rather than contraindications, and myocardial infarction appears among the adverse reactions, secondary to excessive hypotension in a high-risk patient, rather than as a contraindication ⁶ — the cascade rules of Chapter 1, unchanged by the route.
Fenoldopam	0.01–0.3 mcg/kg/min, increasing by 0.05–0.1 mcg/kg/min every 15 minutes. 1.6 mcg/kg/min is the highest rate reported in trials, not a stated ceiling ³⁴	A dopamine-1 agonist, which makes it the renal-perfusion option. Avoid in raised intraocular or intracranial pressure, and in sulfite allergy ³ — cautions taken from the warnings, because the label states no contraindications at all ⁴ .

Read the third column and the same architecture appears one last time. Nicardipine and clevidipine are the calcium channel. Labetalol and esmolol are the sympathetic limb. Enalaprilat is the cascade. Phentolamine is the alpha receptor, chosen when the problem is catecholamine excess. Nitroprusside and

nitroglycerin are the only genuinely new site in the table — nitric oxide donation, acting on the smooth muscle cell directly. **An emergency does not introduce new pharmacology. It introduces a route, a titration and a clock.**

11.5 Where these agents rank, and on what

The handover to Volume 3

Everything above is which drug. Volume 3 is how far, how fast, and in which emergency — the 20 to 25% first-hour rule, its exceptions in aortic dissection, ischaemic stroke, intracerebral haemorrhage and pre-eclampsia or eclampsia, and the organ-by-organ protocols. A reader who takes doses from this page without that volume has half the decision.

TABLE 11.4 — WHERE THE DIRECT VASODILATORS RANK

THE PATIENT	RANK	THE EVIDENCE	GRADE
Uncomplicated hypertension	Not indicated	Hydralazine is licensed for hypertension “refractory to other agents” ¹ . Three drugs to do one drug’s job, with lupus at 5–8% ¹ .	E, and the answer is no.
Resistant hypertension after every other site	An option, with two partners	Licensed use ¹ . No outcome trial in hypertension for either oral agent.	E — licence and practice, not endpoints.
Acute severe hypertension in pregnancy	Established	A stated indication for hydralazine ¹ , at obstetric doses, which are smaller than the general adult doses in the table above ; labetalol is the intravenous agent of choice and enalaprilat is contraindicated ³ .	B/E — long obstetric experience rather than a modern comparative trial.
HFrEF, as hydralazine with isosorbide dinitrate	An established combination	A stated indication with its own dosing ¹ . This is a heart failure use, not a hypertension one.	B for heart failure; it does not transfer to hypertension.
Coronary artery disease, or aortic dissection	Hydralazine contraindicated	Stated contraindications, because it increases cardiac oxygen demand ¹ .	A.
Clonidine withdrawal crisis	Phentolamine	Named for catecholamine excess including clonidine withdrawal ³ ; the crisis itself is described in Chapter 10 ⁵ .	E — mechanism and licence. Nobody will randomise it.

11.6 Clinical pearls

Twenty-two points that change practice, for a reader who has one minute.

- 1 These drugs relax arteriolar smooth muscle directly, bypassing every control point the body was already using^{1,2}.
- 2 Two reflexes follow: tachycardia from the baroreflex, and sodium retention from the kidney.
- 3 **So a direct vasodilator is given with a beta-blocker and a diuretic, or it is not given.** Alone it loses its effect in weeks and keeps every side effect.
- 4 Hydralazine: start 10 mg four times daily, to 50 mg four times daily, maximum 300 mg/day¹. Four times daily is itself an objection.
- 5 Drug-induced lupus in roughly 5–8% of users, usually after six months¹. That is one patient in fifteen to twenty, not a rarity.
- 6 Risk factors are the slow acetylator phenotype and reduced renal function¹.
- 7 Check a full blood count and ANA before and during therapy, and stop immediately if lupus symptoms appear¹.
- 8 The ANA is positive in 95–100% of hydralazine-induced lupus¹ — so a negative ANA in a symptomatic patient points elsewhere.
- 9 Hydralazine is contraindicated in coronary disease and aortic dissection¹. Both follow from the reflex tachycardia.
- 10 Minoxidil causes hypertrichosis, water retention, and pericarditis that may progress to tamponade².
- 11 **An effusion in a patient on minoxidil is never incidental.** Echocardiogram, not a dose change.
- 12 Minoxidil usually needs a loop diuretic rather than a thiazide — one of few hypertension settings where that is so.
- 13 Nicardipine 5 mg/h to 15 mg/h; avoid in advanced aortic stenosis³.
- 14 Clevidipine is the fastest to titrate — and is contraindicated in soy or egg allergy, being a lipid emulsion³.
- 15 Nitroprusside is metabolised to cyanide². Arterial monitoring, and thiosulfate for longer infusions³.
- 16 Nitroglycerin is for acute coronary syndrome and pulmonary oedema, not for general use, and not in volume depletion³.
- 17 Labetalol is the pregnancy agent, and is contraindicated in bronchial asthma, overt cardiac failure, high-grade block, cardiogenic shock and severe bradycardia⁴ — Chapter 8's problem, in an emergency.
- 18 Esmolol can be switched off, which is why it belongs in dissection and perioperative care³.
- 19 Phentolamine is chosen by cause, not organ: phaeochromocytoma, MAO inhibitor interactions, cocaine, and clonidine withdrawal³. It is contraindicated after myocardial infarction, and in coronary insufficiency or angina⁶.
- 20 Enalaprilat is contraindicated by hypersensitivity or any history of angioedema on an ACE inhibitor, and pregnancy carries a boxed warning of fetal injury and death⁶. The route does not change the cascade rules.
- 21 Every intravenous agent here acts at a site already met in this volume, except the nitric oxide donors. An emergency adds a route and a clock, not new pharmacology.
- 22 How far and how fast to lower the pressure is Volume 3. This chapter only says which drug.

KEY POINTS

- 1 Direct vasodilators bypass every physiological control point, so the body answers with tachycardia and sodium retention. The beta-blocker and the diuretic are not optional partners; they are part of the prescription.
- 2 Hydralazine causes drug-induced lupus in roughly 5 to 8% of users, usually after six months, in slow acetylators and in renal impairment. Check FBC and ANA before and during.
- 3 It is contraindicated in coronary disease and aortic dissection, and both follow from the reflex tachycardia rather than from anything idiosyncratic.
- 4 Minoxidil is the most powerful oral vasodilator and carries hypertrichosis, marked fluid retention, and pericarditis that can progress to tamponade. An effusion on minoxidil is never incidental.
- 5 The intravenous agents are chosen by situation: nicardipine and clevidipine for titratable control, labetalol in pregnancy, esmolol where you may need to stop, nitroglycerin for coronary syndromes and pulmonary oedema, phentolamine for catecholamine excess.
- 6 Nitroprusside is metabolised to cyanide and needs arterial monitoring and thiosulfate for longer infusions.
- 7 Every one of those agents acts at a site already met in this volume except the nitric oxide donors. An emergency introduces a route, a titration and a clock — not new pharmacology.
- 8 How far and how fast to lower a pressure is Volume 3. This chapter names the drug and stops.

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Head to Head

Eleven chapters have argued one class at a time. This one puts the direct comparisons side by side and answers the question underneath all of them: when two classes are both allowed, does the choice actually matter?

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 Which class comparisons have actually been run head to head, and which have not.
2 The four situations where the choice between two permitted classes changes outcomes.
3 Why most of the time it does not — and what decides instead.
4 The comparisons nobody has run, and what to do in their absence.

AT THE POINT OF CHOOSING BETWEEN CLASSES		LAYER 1 · 60 SECONDS
>Kaur P, Sakthivel M, Venkatasamy V, et al. India Hypertension Control Initiative: blood pressure control using drug and dose-specific standard treatment protocol at scale in Punjab and Maharashtra, India, 2022. Glob Heart. 2024;19(1):30. doi:10.5334/gh.1305 https://doi.org/10.5334/gh.1305		
IT MATTERS WHEN	The second drug — a calcium channel blocker beats a thiazide alongside a RAAS blocker · left ventricular hypertrophy — an ARB beats a beta-blocker · the fourth drug — spironolactone beats both alternatives · preventing heart failure — a thiazide beats a calcium channel blocker	
IT DOES NOT MATTER	Everywhere else the direct comparisons found equivalence. That is a finding, not a gap, and it hands the decision back to you on legitimate grounds.	
THEN DECIDE IN THIS ORDER	Contraindication → second disease → twenty-four hour cover → tolerability → cost → mechanism	
NOTE WHERE MECHANISM SITS	Last. Below contraindication, a second disease, twenty-four hour cover, tolerability and cost. Reason from the site when those five have not settled it.	
TWO TAUGHT PREFERENCES FAILED	Chlorthalidone over hydrochlorothiazide, and torsemide over furosemide. Both were tested directly and neither was confirmed.	
NEVER ASSUME	That a comparison exists. No outcome trial has compared any two ARBs, or a vasodilating beta-blocker against a calcium channel blocker.	
SAY IT OUT LOUD	“These two are equivalent, so I am choosing on tolerability and cost.” That is evidence-based medicine, not a retreat from it.	

12.1 What has actually been compared

A surprising amount of what a physician believes about class choice has never been tested directly. This table contains every comparison in this volume where two active treatments were randomised against each other, with the result. Everything not on it is inference.

TABLE 12.1 — EVERY HEAD-TO-HEAD COMPARISON IN THIS VOLUME

THE COMPARISON	POPULATION	RESULT	DOES THE CHOICE MATTER?
Thiazide vs CCB vs ACE inhibitor ALLHAT	33,357, aged 55+, one risk factor	Primary endpoint 11.5%, 11.3%, 11.4%. Heart failure worse on amlodipine (RR 1.38) and lisinopril (RR 1.19) than chlorthalidone ¹ .	No, for events. Yes, for heart failure. The largest comparison in the field found a dead heart as the primary endpoint.
CCB-based vs beta-blocker-based ASCOT-BPLA	19,257 with added risk factors	Stroke 3% vs 4%, CV events 14% vs 17%, new diabetes 6% vs 8% ² .	Yes — but the beta-blocker was atenolol, and the regimen was their second drug too.
ARB vs beta-blocker LIFE	9,222 with ECG left ventricular hypertrophy	At 144.1/81.3 vs 145.4/80.9 mmHg: composite 11% vs 13%, stroke 5% vs 7%, new diabetes 6% vs 8% ³ .	Yes, at matched pressures. The cleanest demonstration that two drugs can reach the same number differently.
ACE inhibitor + CCB vs ACE inhibitor + thiazide ACCOMPLISH	11,506 at high risk	Events 9.6% vs 11.8%, HR 0.80, at under 1 mmHg of difference ⁴ .	Yes — and this is the trial that showed the second drug. The thiazide was hydrochlorothiazide.
ACE inhibitor vs ARB vs both ONTARGET	High cardiovascular risk	Telmisartan equivalent to ramipril. The combination gained nothing and cost renal function ^{7,8} .	No between the two. Absent evidence about the third arm.
Chlorthalidone vs hydrochlorothiazide DCP	13,523 veterans over 65	MACE 10.4% vs 10.0%, HR 1.04. Hypokalaemia 6.0% vs 4.4% ⁵ .	No. The preference most clinicians were taught was tested and was not confirmed.
Torsemide vs furosemide TRANSFORM-HF	2,859 after heart failure admission	All-cause mortality 26.1% vs 26.2%, HR 1.02 ⁶ .	No. Better pharmacokinetics, identical outcomes.
MRA vs alpha-blocker vs beta-blocker PATHWAY-2	335 with resistant hypertension	Spironolactone beat placebo by 8.70 mmHg, doxazosin by 4.03, bisoprolol by 4.48, all P<0.0001 ⁹ .	Yes — and uniquely, three classes compared in the same patient.
Alpha-blocker vs thiazide ALLHAT doxazosin arm	24,335	Heart failure RR 2.04. Stopped early. No primary-endpoint difference ¹⁰ .	Yes, decisively, and in the absence of harm.

12.2 The four situations where the choice changes outcomes

Read the last column of that table and the pattern is not the one most clinicians carry. **Class choice changes outcomes in four situations and, on the available evidence, in remarkably few others.**

TABLE 12.2 — WHEN THE CHOICE BETWEEN TWO PERMITTED CLASSES ACTUALLY MATTERS

THE SITUATION	WHAT TO CHOOSE	WHAT THE DIFFERENCE WAS
The second drug alongside a RAAS blocker	A calcium channel blocker rather than a thiazide	A fifth fewer events at the same pressure ⁴ . The single most action-to-head result in hypertension.
Left ventricular hypertrophy	An ARB rather than atenolol	A quarter fewer strokes and a quarter less new diabetes at an identical brachial pressure ³ .
Resistant hypertension, fourth drug	Spironolactone rather than an alpha- or beta-blocker	Four to four and a half millimetres more, against active comparison than placebo ⁹ .
Preventing heart failure specifically	A thiazide-type diuretic	Heart failure was 38% commoner on amlodipine and 19% commoner on lisinopril ¹ — and doubled on doxazosin ¹⁰ .

That is the list. Four rows, from nine head-to-head trials involving well over a hundred thousand patients. A physician who knows those four and nothing else about comparative efficacy is making better choices than one who has absorbed a general impression that some classes are simply better.

12.3 Where the choice does not matter — and what decides instead

The far more common situation is the one ALLHAT describes: two or three classes, permitted, equivalent on hard endpoints, and the guideline declining to choose. **That is not a gap in the evidence. It is a finding,** and it hands the decision back to the clinician on legitimate grounds.

TABLE 12.3 — WHEN THE EVIDENCE IS LEVEL, THESE DECIDE — IN THIS ORDER

	WHY IT OUTRANKS THE ONE BELOW IT
1. A contraindication	Absolute, and it overrides everything above it in the guideline. Pregnancy, gout, asthma, bilateral renal artery stenosis, potassium already at 5.4.
2. A second disease that names a class	Not the blood pressure at all — heart failure, proteinuric kidney disease, atrial fibrillation, prostatic symptoms, aortic aneurysm. Opening 1's first filter and it settles most decisions before phenotype is reached.
3. Whether it covers the day	A drug that lapses before the next dose treats the clinic reading and not the dawn. Two short-acting agents give the regimen that looks controlled and is not.
4. What the patient will tolerate	Ankle oedema, cough, fatigue, erectile dysfunction. A drug not taken has an efficacy of zero, and the difference between adherence and non-adherence is far larger than any difference in this chapter's first table.
5. What it costs	In a patient paying monthly this is a clinical property. The India Hypertension Control Initiative chose its drugs on availability and controlled 70–76% of 159,292 patients at the first protocol step in Punjab and Maharashtra ¹² — with a correct reading of ALLHAT, not a compromise on it.
6. Mechanism and phenotype	Last, deliberately. Renin status, salt sensitivity, arterial stiffness. Powerful reasoning, and it belongs after the first five rather than before them.

12.4 The comparisons nobody has run

A head-to-head chapter has to be as clear about its empty cells as its full ones, because those empty cells are where confident claims come from.

The second chapter makes a point of saying "These are equivalent outcomes" — choosing tolerable. That is, from evidence, medicinal when there been re

TABLE 12.4 — THE TRIALS THAT WOULD SETTLE COMMON ARGUMENTS, AND DO NOT EXIST

THE QUESTION A PHYSICIAN ACTUALLY ASKS	WHAT EXISTS	WHAT TO DO MEANWHILE
ACE inhibitor or ARB?	ONTARGET found them equivalent ⁷ ; a meta-analysis of 158,998 patients found a mortality signal for ACE inhibitors that ARBs did not show ¹² . Two good analyses, different answers.	Let the cough decide. That is a defensible basis for one, and the book says so.
Is a vasodilating beta-blocker different?	Nothing. Atenolol lost twice ^{3,2} and carvedilol and nebivolol were never tested against a calcium channel blocker on outcomes.	Do not assume the class verdict transfers, and assume it does not. Where a beta-blocker is in question, prefer an agent that lowers resistance — on mechanism, labelled as mechanism.
Chlorthalidone or amlodipine as the second drug?	ACCOMPLISH compared against hydrochlorothiazide ⁴ ; ALLHAT compared chlorthalidone with amlodipine as first drugs and found a dead heat ¹ . Neither has been tested as the second drug beside a RAAS blocker, which is the question actually being asked.	If your diuretic is chlorthalidone, ACCOMPLISH answers your question. You are entitled to say so and to say so though rather less firmly since the Diuretic Comparison Project found the two diuretics equivalent on outcomes.
Which ARB, of the seven?	No outcome comparison between any two of them.	Duration of action and tolerability, labelled as pharmacokinetics rather than as endpoints.
Anything, in an Indian population	Almost nothing. Nearly every trial in this volume enrolled predominantly European or North American patients.	Apply the trials as the best available evidence for a related population, and be conscious that you are extending rather than applying.

Four of those five arguments are conducted daily as though the evidence existed. It does not. A physician who knows which cell is empty argues differently — less confidently about the drug, and more confidently about the patient in front of them.

12.5 Clinical pearls

Nineteen points that change practice, for a reader who has one minute.

- 1 Only nine comparisons in this volume randomised two active treatments against each other. Everything else is inference.
- 2 ALLHAT is the largest, and its primary endpoint was a dead heat between three classes in 33,357 patients¹ — the three-arm comparison. The doxazosin arm was stopped early and reported separately, against chlorthalidone alone, in 24,335 patients.
- 3 Class choice changes outcomes in four situations. Learn those four; treat the rest as level.
- 4 **One:** the second drug alongside a RAAS blocker — a calcium channel blocker, a fifth fewer events at the same pressure⁴.
- 5 **Two:** left ventricular hypertrophy — an ARB over atenolol, a quarter fewer strokes at identical pressure³.
- 6 **Three:** resistant hypertension — spironolactone over doxazosin or bisoprolol, by 4.03 and 4.48 mmHg⁹.
- 7 **Four:** preventing heart failure — a thiazide, with amlodipine 38% and lisinopril 19% worse¹, and doxazosin doubled¹⁰.
- 8 Where the evidence is level the decision order is: contraindication, second disease, 24-hour cover, tolerability, cost, then mechanism.
- 9 Mechanism comes last on that list deliberately. It is powerful reasoning and it does not outrank a contraindication or a trial.
- 10 Chlorthalidone against hydrochlorothiazide: no difference in ev hypokalaemia⁵. A taught preference, tested and not confirmed.
- 11 Torsemide against furosemide: mortality 26.1% against 26.2%⁶; pharmacokinetics, identical outcomes.
- 12 Twice now, a pharmacologically superior molecule has failed to beat the older one. Treat pharmacokinetic superiority as a hypothesis about to be tested.
- 13 ACE inhibitor against ARB is genuinely disputed — ONTARGET says equivalent⁷, a 158,998-patient meta-analysis says otherwise¹².
- 14 No trial has compared a vasodilating beta-blocker against a calcium channel blocker on outcomes. The class verdict against beta-blockers is an extrapolation.
- 15 ACCOMPLISH used hydrochlorothiazide. If your diuretic is chlorthalidone, the trial did not test your question.
- 16 No outcome trial has compared any two ARBs. Choose on duration, tolerability, and call it that.
- 17 Almost nothing here was tested in an Indian population. Extending to that population is reasonable; doing it unknowingly is not.
- 18 CAFE is the reason two drugs can reach the same cuff reading at identical brachial pressure, 4.3 mmHg apart at the aortic root¹¹.
- 19 “These two are equivalent, so I am choosing on tolerability and cost.” Evidence-based medicine, not a retreat from it.

KEY POINTS

- 1 Only nine direct class comparisons exist in this volume. A great deal of what physicians believe about class choice has never been tested head to head.
- 2 The choice between two permitted classes changes outcomes in four situations: the second drug, left ventricular hypertrophy, the fourth drug in resistance, and preventing heart failure.
- 3 Everywhere else the trials found equivalence — which is a finding, not a gap, and it hands the decision back on legitimate grounds.
- 4 When the evidence is level, decide in this order: contraindication, second disease, twenty-four hour cover, tolerability, cost, mechanism.
- 5 **Mechanism is last on that list** — below contraindication, a second disease, twenty-four hour cover, tolerability and cost. Reasoning about mechanism is what you reach for when those five have not settled it.
- 6 Two taught preferences — chlorthalidone over hydrochlorothiazide, torsemide over furosemide — were tested and not confirmed.
- 7 Four arguments physicians have daily rest on trials that do not exist. Knowing which cell is empty is what this chapter is for.

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CHAPTER 13

PART VII · COMPARISON

The Patient Who Has Something Else

Chapter 12 found that class choice rarely changes outcomes on its own. The exception is the common case: most hypertensive patients carry a second diagnosis, and it is usually the second diagnosis that decides the drug.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 The four ways — and there are only four — in which a comorbidity changes the answer.
- 2 Which conditions give a drug a second job, which is the best outcome available in prescribing.
- 3 Which forbid a drug absolutely, and which only relatively — a distinction routinely got wrong.
- 4 The precaution that actually gets missed for each, which is usually not the one printed in the guideline.
- 5 What to do when two comorbidities point in opposite directions, and where to stop and refer.

AT THE POINT OF MEETING THE SECOND DIAGNOSIS

LAYER 1 · 60 SECONDS

LOOK HERE FIRST	Does a second diagnosis already name a drug ? Heart failure, post-infarct, angina, atrial fibrillation, prior stroke, proteinuric CKD, aldosteronism, prostatic symptoms, gout, migraine, tremor, osteoporosis, varices. If yes, the argument about class is over.
FOUR MECHANISMS, ONLY FOUR	1 it gives a drug a second job · 2 it forbids a drug · 3 it changes how the drug behaves · 4 it changes what you must watch
ABSOLUTE, NO EXCEPTION	Pregnancy — every RAAS blocker · previous angioedema — every ACE inhibitor, for life · bilateral renal artery stenosis · verapamil or diltiazem in reduced ejection fraction
COMMONLY OVER-APPLIED	A cardio-selective beta-blocker after an infarct is permitted in COPD on the label's own conditions. So is a RAAS blocker in aortic stenosis — that prohibition was never evidenced. Reflex omission costs more than the risk.
NOT FORBIDDEN — CHANGED	Below an eGFR of 30 a thiazide has <i>stopped working</i> , not become dangerous. Switch to a loop. In liver disease use lisinopril or captopril, not the prodrugs.
THE PRECAUTIONS THAT GET MISSED	The eye drops in the asthmatic · the eye surgeon for the man on an alpha-blocker · the standing pressure in the elderly · the RAAS blocker still on the sheet of a woman planning pregnancy
WHEN TWO DIAGNOSES DISAGREE	Rank them by how much is lost if you are wrong , then buy your way out of the weaker constraint rather than surrendering the stronger indication.
KNOW WHERE THE MAP ENDS	Five combinations have no rule a book can print. Recognising one is the skill; referral is the answer.

13.1 Why the second diagnosis usually decides

Chapter 12 reached an uncomfortable conclusion: where two classes are both permitted, the direct comparisons mostly found equivalence, and the choice between them changes outcomes in only four situations³. That is true, and it is regularly misread as meaning the choice does not matter.

It matters constantly, for a reason Chapter 12 deliberately held back. **The class choice is free only until a second diagnosis constrains it — and most hypertensive patients have one.** In India 11.4% of adults have diabetes and a further 15.3% have prediabetes¹; among patients admitted with heart failure the cause is ischaemic in 71.9%². The uncomplicated hypertensive of the trials is not the commonest patient in the clinic.

So this chapter is the fifth situation, and the one a physician meets every day. It runs forwards: condition in, drug out, with the reason attached. **Chapter 15 runs the same map backwards** — and having the map printed here is what allows a reader to check that chapter's codebook rather than take it on trust.

13.2 The four mechanisms, and there are only four

It is tempting to write this chapter disease by disease. That list has no end, and it fails the first time a reader meets a combination it did not print. A comorbidity can only change the answer in four ways, and once those are learned an unlisted condition becomes solvable.

TABLE 13.1 — THE FOUR WAYS A SECOND DIAGNOSIS CHANGES A PRESCRIPTION

#	THE MECHANISM	WHAT IT MEANS AT THE POINT OF PRESCRIBING
1	It gives a drug a second job	One tablet treats two problems. This is the best outcome available in prescribing — better adherence, lower cost, fewer interactions — and it should be looked for before anything else.
2	It forbids a drug	Absolutely, or only relatively. Confusing the two is the commonest error in this chapter , and it usually costs the patient a drug they needed.
3	It changes how the drug behaves	The drug is still permitted but no longer does what you expect — a thiazide below an eGFR of 30, a prodrug in liver disease, furosemide across an oedematous gut.
4	It changes what you must watch	The prescription is unchanged; the follow-up is not. This is the mechanism that gets skipped, because nothing on the sheet looks different.

13.3 When one drug does two jobs

Before asking which antihypertensive suits this patient, ask whether any of their other problems is already treated by an antihypertensive. When the answer is yes, the decision is made and made well.

And a fifth that is not in this volume

A comorbidity can also change the target and the urgency. How far and how fast to lower the pressure is Volume 3. This chapter names the drug and stops.

TABLE 13.2 — CONDITIONS THAT CHOOSE THE DRUG FOR YOU

THE SECOND DIAGNOSIS	THE DRUG IT CHOOSES	WHY, AND HOW STRONG
Heart failure, reduced ejection fraction	ARNI or ACE inhibitor, beta-blocker, mineralocorticoid antagonist, SGLT2 inhibitor	Four drugs, none of them chosen for blood pressure. The pressure becomes a constraint on titration rather than the target.
After myocardial infarction	Beta-blocker and an ACE inhibitor	Mortality indications, not pressure indications ¹⁰ .
Stable angina	Beta-blocker, with a dihydropyridine if more is needed	Rate and oxygen demand fall; the pressure follows.
Atrial fibrillation needing rate control	Beta-blocker, or verapamil / diltiazem	The rate is the target. Chapter 4 explains why the choice between them is not free.
Left ventricular hypertrophy	An ARB in preference to a beta-blocker	LIFE: fewer strokes at the same pressure ⁴ .
Prior stroke or TIA	Perindopril with indapamide	PROGRESS: recurrent stroke fell 43% on the combination and 5% on perindopril alone ⁵ .
Proteinuric CKD, diabetic nephropathy	ACE inhibitor or ARB at maximum tolerated dose	The kidney is protected beyond the pressure effect. Chapter 1.
Primary aldosteronism	Spironolactone	Treating the cause, not the number.
Resistant hypertension	Spironolactone as the fourth drug	PATHWAY-2: it beat both alternatives ⁶ .
Benign prostatic hyperplasia	An alpha-1 blocker	One receptor, two organs, one tablet ¹¹ . The class's surviving indication.
Gout	Losartan among the ARBs	Mildly uricosuric — the one ARB with a second job.
Migraine prophylaxis	Propranolol	A standard prophylactic that happens to lower pressure.
Essential tremor	Propranolol	The same drug, a third job.
Raynaud's phenomenon	A dihydropyridine, usually nifedipine	Peripheral vasodilation is the treatment and the antihypertensive effect at once.

THE SECOND DIAGNOSIS	THE DRUG IT CHOOSES	WHY, AND HOW STRONG
Osteoporosis	A thiazide	Thiazides reduce urinary calcium loss. A rare instance of a metabolic effect working in the patient's favour.
Cirrhosis with varices	A non-selective beta-blocker — propranolol or carvedilol	Portal pressure, not arterial pressure, is the indication. Cardioselective agents do not do this job.

13.4 When the comorbidity forbids

A relative contraindication treated as absolute costs a patient a drug that would have helped them. That error is commoner than the reverse, and it is quieter, because nobody records the benefit that was never given.

The habit worth forming

Read the problem list before the blood pressure. If one of the entries already names a drug, the argument about which class is over, and the consultation can move on to dose, timing and whether the patient will take it.

TABLE 13.3 — ABSOLUTE, OR AS NEAR AS A LABEL GETS — DO NOT, IN ORDINARY CIRCUMSTANCES

THE CONDITION	WHAT IS FORBIDDEN	WHY
Pregnancy, or planning it	Every RAAS blocker — ACE inhibitor, ARB, aliskiren, ARNI	Fetal harm is established and the exposure is entirely avoidable ⁹ . Switch before conception, not after a positive test.
Previous angioedema on an ACE inhibitor	Every ACE inhibitor, for life	A class effect. There is no rechallenge and no substitution within the class.
Bilateral renal artery stenosis	RAAS blockers	Filtration in both kidneys depends on efferent tone.
Heart failure, reduced ejection fraction	Verapamil and diltiazem	Negative inotropy in a failing ventricle. The advice is the same for both; the label is not. Verapamil contraindicates severe left ventricular dysfunction; diltiazem does not bar it at all and puts worsening heart failure under warnings ¹³ .
Severe asthma	Non-selective beta-blockers	Bronchospasm ¹⁰ . See the relative table for what is still permitted.
High-grade AV block or marked bradycardia	Beta-blockers, verapamil, diltiazem	Conduction, already compromised.
Anuria	Diuretics	Nothing to act on.

TABLE 13.4 — RELATIVE — A REASON TO THINK, NOT A REASON TO WITHHOLD

THE CONDITION	WHAT IS DISCOURAGED	WHAT ACTUALLY TO DO
Asthma or COPD, with a strong cardiac indication	Beta-blockers generally	A cardio-selective agent is permitted where the alternatives have failed or are not tolerated, at the lowest possible dose, with a bronchodilator available or given alongside — selectivity is relative and dose-dependent, not absolute ¹⁵ . In COPD especially, withholding it after an infarct costs more than the bronchial risk. Start low, watch, and do not simply omit.
Gout	Thiazides	Use a calcium blocker or a RAAS blocker instead; losartan if an ARB. If the thiazide is doing essential work, treat the gout rather than abandoning the drug.
Diabetes	Beta-blockers; high-dose thiazides	Neither is forbidden. Both need a warning and a plan — see §13.6.
Older patient at risk of falling	Alpha-blockers, and any rapid titration	Lowest dose, at night, and stand the patient up at the next visit ¹¹ .

THE CONDITION	WHAT IS DISCOURAGED	WHAT ACTUALLY TO DO
Potassium above 5.0	RAAS blockers, mineralocorticoid antagonists	Review every other potassium-raising drug first — and never answer a high potassium by adding a second RAAS drug, which raises it further for no benefit ⁷ . §13.7 covers the case where the RAAS blocker is the one drug you most want to keep.
eGFR under 30	Thiazides, spironolactone	The thiazide loses much of its effect rather than becoming dangerous — that is mechanism 3, not mechanism 2. It has not stopped altogether; Chapter 5 gives the stage 4 trial evidence. Spironolactone is a genuine hazard here.
Aortic stenosis	RAAS blockers, by long tradition	The tradition is not supported. The prohibition rested on a theoretical fear of vasodilation across a fixed obstruction; the evidence indicates these drugs are safe, and in one series of patients undergoing valve intervention they were associated with lower cardiovascular mortality ⁸ . Titrate carefully; do not withhold reflexively.

13.5 When the drug stops behaving as expected

The most easily missed of the four, because nothing about the prescription looks wrong. The drug is allowed, the dose is standard, and it is quietly not working.

TABLE 13.5 — THE COMORBIDITY CHANGES THE PHARMACOLOGY, NOT THE PERMISSION

THE SITUATION	WHAT CHANGES	WHAT TO DO INSTEAD
eGFR falls below about 30	A thiazide acts on a segment handling 5% of filtered sodium and must be secreted to reach it. Both fail together.	Switch to a loop diuretic ¹² . Figure 5.1 shows why in one picture.
Liver disease	Ramipril, enalapril and perindopril are prodrugs requiring hepatic activation.	Lisinopril or captopril, both active as given.
Uncertain or changing renal function	Most ACE inhibitors need dose adjustment by eGFR.	Fosinopril needs none at any eGFR — a small convenience that matters in a clinic without recent bloods.
Decompensated heart failure, gut oedema	Oral furosemide is absorbed erratically across an oedematous bowel.	Torsemide, where absorption is the identified problem. Not as a routine upgrade: mortality was the same in 2,859 patients.
Nephrotic syndrome, hypoalbuminaemia	Loop diuretics are protein-bound for delivery to their site.	Higher doses, and the diuretic resistance is expected rather than a failure of adherence.
Advanced age	Baroreflex buffering is reduced; the same dose produces a larger postural fall.	Start lower, titrate slower, and measure standing.

13.6 The precaution that actually gets missed

Every guideline lists monitoring. The rows below are narrower and more useful: for each condition, the one thing that goes wrong in practice, chosen because it is missed rather than because it is important in principle.

TABLE 13.6 — WHAT ACTUALLY GETS MISSED, BY CONDITION

THE PATIENT	WHAT GETS MISSED	WHY IT MATTERS
Diabetic on a beta-blocker	The warning about hypoglycaemia.	The tachycardia and tremor that warn of a low sugar are removed; the hypoglycaemia is not. An unwarned patient loses their alarm.
Anyone started on a RAAS blocker	The potassium and creatinine at one to two weeks.	This is the single most skipped visit in the volume, and it is where the avoidable harm sits.

THE PATIENT	WHAT GETS MISSED	WHY IT MATTERS
Post-infarct patient on a beta-blocker	That it must never be stopped abruptly.	Rebound tachycardia, angina, infarction. Say it at the first prescription, not the fifth.
Woman of childbearing age	The RAAS blocker still on the sheet from before.	Nobody revisits a prescription that was appropriate when it was written.
Asthmatic	The eye drops.	Timolol is a beta-blocker and patients do not count drops as medicines. Ask specifically.
Man on an alpha-blocker	Telling the eye surgeon.	Floppy iris syndrome complicates cataract surgery and can be permanent ¹¹ . The prescriber is the person who should warn.
Older patient, any new drug	The standing blood pressure.	A seated reading conceals the fall that causes the fracture.
Patient on a thiazide	The sodium at two to three weeks.	Hyponatraemia is commonest early and presents as vagueness, not as a symptom anyone reports.
Patient on spironolactone	Warning men about breast tenderness.	About one in ten. An unwarned patient stops the drug and does not say why.
Patient on clonidine	The taper instruction.	Abrupt withdrawal causes a hypertensive crisis. It belongs on every prescription, every time.
Cirrhotic on spironolactone	That the dose is different.	Ascites is treated at doses well above the hypertension range, and the two indications get confused in both directions.

13.7 When two diagnoses disagree

A single comorbidity is a lookup. Two that point in opposite directions is a decision, and it is where a physician actually needs help. The resolutions below share one principle: **rank the two by how much is lost if you are wrong, and buy your way out of the weaker constraint rather than surrendering the stronger indication.**

TABLE 13.7 — CONFLICTS, AND HOW THEY RESOLVE

THE CONFLICT	WHAT EACH SIDE DEMANDS	THE RESOLUTION
Asthma or COPD, after a myocardial infarction	The infarct demands a beta-blocker. The airway forbids one.	Give a cardio-selective beta-blocker on the label's conditions — alternatives first, lowest possible dose, bronchodilator to hand¹⁵ — low and slow, and watch. The mortality benefit after infarction is large and the bronchial risk with a selective agent at low dose is small — in COPD especially ¹⁰ . Reflex omission is the commoner error.
Proteinuric CKD with a potassium of 5.4	The kidney demands a RAAS blocker. The potassium forbids it.	Fight to keep the RAAS blocker. Stop the NSAID and the salt substitute, review every other potassium-raising drug, correct the acidosis, and use a potassium binder if one is available. Surrendering the drug is the easy move and the wrong one.
Diabetes with gout	Neither wants a thiazide.	Neither is an absolute bar. Use a RAAS blocker with a calcium blocker; if an ARB, make it losartan. Keep the thiazide only if the pressure needs it, and treat the gout.
Heart failure with atrial fibrillation needing rate control	Both want rate control; one forbids verapamil.	A beta-blocker does both jobs. Verapamil is contraindicated in severe left ventricular dysfunction, and diltiazem is to be avoided in it¹³ — and verapamil's warning covers any degree of ventricular dysfunction once a beta-blocker is on board, which is exactly this patient. Reaching for either instead of the beta-blocker is a common and dangerous substitution.

THE CONFLICT	WHAT EACH SIDE DEMANDS	THE RESOLUTION
Benign prostatic hyperplasia in a man who has fallen	The prostate wants an alpha-blocker. The falls forbid one.	Separate the jobs: a uroselective agent for the prostate, a different class for the pressure. One tablet doing two jobs is not worth a fracture.
Chronic hypertension and a planned pregnancy	The pressure wants the current regimen. The pregnancy forbids the RAAS blocker.	Switch before conception. Methyldopa, labetalol or nifedipine retard. Waiting for a positive test means weeks of exposure that were avoidable.
Aortic stenosis with hypertension	Tradition forbids RAAS blockade; the pressure needs treating.	Treat the pressure. The prohibition rests on a haemodynamic argument rather than on trial evidence of harm, and an observational series found lower cardiovascular mortality on these drugs ⁸ . Titrate carefully rather than withholding.
Angina in an asthmatic	The angina wants a beta-blocker. The asthma forbids one.	A dihydropyridine or diltiazem with a nitrate. Here the substitution is genuinely good, unlike after an infarct.

13.8 The conflicts with no clean answer

A reference that gives a confident rule for everything teaches its readers to be confident about everything, which is the opposite of what this volume is for. The following combinations do not have a rule that a book can print, and a general physician meeting one should be arranging a specialist opinion rather than looking for a table.

TABLE 13.8 — REFER RATHER THAN RESOLVE

THE COMBINATION	WHY NO RULE FITS
Heart failure with symptomatic hypotension	Every drug that prolongs life lowers the pressure further. The trade cannot be made from a table; it is made at the bedside, over weeks.
Refractory hypertension in advanced CKD	The usual fourth drug is limited by the eGFR rather than barred by it — the label bars only hyperkalaemia, Addison's disease and concomitant eplerenone, and an eGFR of 30 to 50 calls for 25 mg on alternate days ¹⁴ — the diuretic must change class, and the volume state moves week to week.
Pregnancy with pre-existing hypertension and CKD	Two organ systems and two patients, with a drug list narrowed to three agents. This is shared care from the first visit.
The very old with a high systolic pressure and recurrent falls	Treating the pressure and preventing the fall pull in opposite directions, and the right balance depends on things no book knows about this patient.
Hypertension after solid organ transplant	Immunosuppressants raise the pressure, interact with calcium blockers, and the graft changes the renal calculus entirely.

13.9 Clinical pearls

Thirty points that change practice, for a reader who has one minute.

Knowing where the map ends

Every table in this chapter is a beginning. The five rows above are the honest boundary of what a printed rule can do, and a physician who recognises one of them has used the chapter correctly — the recognition is the skill, not the rule.

- 1 Class choice is free only until a second diagnosis constrains it — and most hypertensive patients have one.
- 2 A comorbidity changes the answer in only **four** ways: it gives a drug a second job, forbids a drug, changes how a drug behaves, or changes what you must watch.
- 3 Learn the four and an unlisted condition becomes solvable. A disease list has no end and fails on the first combination it did not print.
- 4 **Read the problem list before the blood pressure.** If an entry already names a drug, the argument about class is over.
- 5 One tablet treating two problems is the best outcome available in prescribing: better adherence, lower cost, fewer interactions.
- 6 Heart failure with reduced ejection fraction chooses four drugs, none of them for blood pressure. The pressure becomes a constraint on titration.
- 7 Prior stroke chooses perindopril with indapamide⁵. Left ventricular hypertrophy chooses an ARB⁴.
- 8 Propranolol has three jobs on its own label: pressure, migraine prophylaxis, essential tremor — and five more besides. Losartan has one licensed job and a useful side effect: it lowers urate as well as pressure.
- 9 A thiazide reduces urinary calcium loss, which makes osteoporosis one of the few comorbidities where the metabolic effect helps.
- 10 Cirrhosis with varices needs a **non-selective** beta-blocker. A cardioselective agent does not do that job.
- 11 **Confusing a relative contraindication with an absolute one is the commonest error in this chapter,** and it is quiet — nobody records the benefit never given.
- 12 Absolute, without exception: a RAAS blocker in pregnancy, an ACE inhibitor after angioedema, verapamil in reduced ejection fraction.
- 13 **A cardio-selective beta-blocker after an infarct is permitted in COPD on the label's conditions — alternatives first, lowest dose, bronchodilator to hand¹⁵ —** and badly underused. Reflex omission costs more than the bronchial risk.
- 14 "Avoid ACE inhibitors in aortic stenosis" is a haemodynamic argument, not a trial finding; an observational series points the other way⁸. Titrate carefully; do not withhold reflexively.
- 15 Below an eGFR of 30 a thiazide loses much of its effect; it does not become dangerous. Switch to a loop where volume is the problem — that is mechanism 3, not mechanism 2.
- 16 In liver disease use lisinopril or captopril: ramipril, enalapril and perindopril are prodrugs needing hepatic activation.
- 17 Fosinopril needs no dose adjustment at any eGFR, which matters in a clinic without recent bloods.
- 18 Diuretic resistance in nephrotic syndrome is expected pharmacology, not poor adherence.
- 19 **The potassium and creatinine at one to two weeks is the most skipped visit in this volume,** and it is where the avoidable harm sits.
- 20 A beta-blocker removes the warning signs of hypoglycaemia but not the hypoglycaemia. Warn the diabetic patient explicitly.
- 21 Ask the asthmatic about **eye drops**. Timolol is a beta-blocker and patients do not count drops as medicines.
- 22 The man on an alpha-blocker must tell his eye surgeon¹¹. The prescriber is the person who should say so.
- 23 Check the sodium at two to three weeks on a thiazide. Hyponatraemia presents as vagueness, which nobody reports.
- 24 In a woman of childbearing age, the danger is the RAAS blocker *already* on the sheet from before.
- 25 When two diagnoses disagree, rank them by how much is lost if you are wrong, then buy your way out of the weaker constraint.
- 26 **Proteinuric CKD with a potassium of 5.4: fight to keep the RAAS blocker.** Stop the NSAID and the salt substitute first. Surrender is the easy move and the wrong one.
- 27 Heart failure with atrial fibrillation: a beta-blocker does both jobs. Verapamil is contraindicated in severe left ventricular dysfunction and diltiazem carries a warning rather than a contraindication¹³; avoid both, and the substitution is common.
- 28 Benign prostatic hyperplasia in a man who has fallen: separate the jobs. One tablet doing two is not worth a fracture.
- 29 Switch off a RAAS blocker **before** conception, not after the test. The waiting is the exposure.
- 30 Some combinations have no rule a book can print. Recognising one of those is the skill; the referral is the right answer.

KEY POINTS

- 1 Chapter 12 found class choice rarely changes outcomes on its own. This chapter is the exception, and it is the common case: the class choice is free only until a second diagnosis constrains it.
- 2 **A comorbidity can change the answer in only four ways** — it gives a drug a second job, forbids a drug, changes how the drug behaves, or changes what must be watched. Learning the four makes an unlisted condition solvable.
- 3 Read the problem list before the blood pressure. When a second diagnosis already names a drug, the argument about class is over and the consultation can move on.
- 4 One tablet doing two jobs is the best outcome in prescribing — and there are sixteen conditions in this chapter where it is available.
- 5 **Treating a relative contraindication as absolute is the commonest error here**, and the quietest: nobody records the benefit that was never given.
- 6 A cardio-selective beta-blocker after an infarct is permitted in COPD on the label's conditions¹⁵, and is badly underused. So is a RAAS blocker in aortic stenosis, where the prohibition rests on a haemodynamic argument rather than a trial⁸.
- 7 Below an eGFR of 30 a thiazide loses much of its effect rather than becoming dangerous — a change in pharmacology, not in permission.
- 8 The precautions that get missed are rarely the ones the guideline emphasises: the eye drops in the asthmatic, the eye surgeon for the man on an alpha-blocker, the standing pressure in the elderly, the RAAS blocker still on the sheet of a woman planning pregnancy.
- 9 When two diagnoses disagree, rank them by how much is lost if you are wrong, then buy your way out of the weaker constraint rather than surrendering the stronger indication.
- 10 **Five combinations have no rule a book can print.** Recognising one of them is the skill this chapter is really teaching.

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CHAPTER

14

PART VII · COMPARISON

When in the Day

The guideline names the drug, the dose and the target, and says almost nothing about the hour. That silence is a real clinical space — and it is settled by sleep, tolerability and adherence, not by chronotherapy.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- 1 What three large trials settled about bedtime dosing — and why the striking earlier claim should not be relied on.
 - 2 Why the hour still matters a great deal, even though it does not change outcomes.
 - 3 The six reasons an hour is ever chosen, and the order in which they apply.
 - 4 How another drug’s pharmacology can decide when the antihypertensive is given.
 - 5 When splitting a dose is reasoning, and when it is habit wearing the costume of reasoning.

AT THE POINT OF CHOOSING AN HOUR		LAYER 1 · 60 SECONDS
FIRST, THE SETTLED PART	The hour does not change outcomes. TIME randomised 21,104 patients for five years: 3.4% against 3.7%. BedMed agrees. Stop optimising chronotherapy.	
WHAT IT DOES CHANGE	Whether the drug is tolerated , and whether it is taken . Both of those change outcomes.	
SIX REASONS, IN ORDER	1 safety at the peak · 2 protecting sleep · 3 another drug owns the hour · 4 a drug-free interval elsewhere · 5 covering a gap · 6 adherence	
IF NONE OF THE SIX APPLIES	There is no timing decision to make. Ask the patient when they will remember, and spend the consultation on dose and second drug instead.	
THE DIURETIC RULE	Last dose no later than mid-afternoon. Twice-daily furosemide is 8 am and 2 pm — never 8 am and 8 pm. A broken night undoes what the dose achieved.	
WHEN TWO DRUGS COMPETE	The one with the hard constraint wins the slot. Levothyroxine cannot move; your drug can.	
SPLITTING A LONG-ACTING DRUG	Loses more than it gains. The test: would the trough be uncovered once daily? Beyond 24 hours of cover, no.	
WRITE IT SO IT SURVIVES	The clock time and an anchor event, not “1-0-1”. On a loop diuretic write the negative half: “not after 2 pm” .	

13.1 The question the guideline does not answer

A guideline will tell you the class, the dose, the target and the review interval. On the hour of the day it is nearly silent, and a protocol programme is silent by design⁸. Yet every prescription in this volume has to land somewhere on a clock, and a consultant makes that choice several dozen times a week.

That silence is not an oversight. It is where the evidence ran out and judgement begins — which makes it exactly the kind of space this book was written for. The danger is that a space with no guideline in it fills up with folklore instead, and the timing of antihypertensives has more folklore attached to it than almost any other question in the field.

13.2 What the trials decided about bedtime dosing

For about a decade the honest answer to “does it matter when?” was that it might matter enormously. A large Spanish trial reported that moving antihypertensives to bedtime cut cardiovascular death and events by around 45%³. If true, that would be the largest effect of any intervention in this volume, achieved by changing nothing but the hour.

It was not true, and the way it unravelled is worth more to a reader than the conclusion. Apply Opening 2’s two grades and the problem is visible before any replication: an effect that large in a population already treated is implausible on its face, and the conduct grade was **weak** on several domains at once.

The shape of this chapter, and why it is not a list of diseases

Hypertension with its complications, plus every comorbidity a patient can carry, is an unbounded list. A chapter built disease by disease would be enormous and would fail the moment a reader met a combination it had not printed. **There are only six reasons an hour is ever chosen.** Learn those, and a scenario this book never listed becomes solvable.

TABLE 14.1 — THE BEDTIME-DOSING QUESTION, AND HOW IT WAS SETTLED

TRIAL	WHAT IT FOUND	GRADE, AND WHY
Hygia 2020	Bedtime dosing reduced cardiovascular death and events by about 45% ³ .	Conduct: weak. Concerns raised include questionable randomisation with baseline differences between groups, an implausibly large effect, no endpoint adjudication or source verification described, an unusually low dropout rate, and fifteen primary endpoints. The European Heart Journal issued an expression of concern ⁴ .
TIME 2022	21,104 patients, 5 years. Vascular death, myocardial infarction or stroke in 3.4% on evening dosing against 3.7% on morning dosing, p = 0.53 ¹ .	Effect grade D — a dead heat. Conduct sound, and large enough that a real difference of any useful size would have shown.
BedMed 2025	3,357 primary-care patients. Major events 9.7% against 10.3%, adjusted hazard ratio 0.96 (95% CI 0.77–1.19) ² .	D again. Different country, different design, same answer.
BedMed-Frail 2025	776 nursing-home residents, median age 88. Major events 40.6% against 41.9%, adjusted hazard ratio 0.88 (0.71–1.11) ² .	D. Including in the frailest population, where a timing effect was most plausible.

The verdict is Grade D, and a dead heat is a finding rather than a gap. Three trials in three settings, one of them with twenty-one thousand patients followed five years, agree that the hour does not change outcomes. A physician can stop worrying about chronotherapy and start using the hour for something that does matter — which is the rest of this chapter.

13.3 Why the hour still matters

It would be easy to read §14.2 and conclude that timing is settled and therefore unimportant. That is the wrong lesson, and the same trials show why.

TIME found **more adverse effects on morning dosing and more non-adherence on evening dosing**¹ — two real, opposite costs that a physician trades against each other every time. Falls, a secondary outcome, occurred in 21.1% on evening dosing against 22.2% on morning dosing¹; a small difference, and not one to prescribe on alone, but not nothing in an older patient. And in the frailest population, unplanned hospital attendance favoured bedtime dosing, hazard ratio 0.74 (0.57–0.96)² — hypothesis-generating rather than practice-changing, and worth knowing.

So the thesis of this chapter is narrow and defensible: the hour does not change what the drug does. It changes whether the patient takes it and whether they tolerate it — and both of those change outcomes. In a country where only 12.6% of hypertensive adults have a controlled pressure⁹, the question of whether the tablet is actually swallowed is not a minor one.

What this episode teaches beyond the answer

A number this book printed for years would have been wrong. The defence was never a bigger literature search; it was the two grades from Opening 2, applied at the time. An implausibly large effect from a weakly conducted trial is a claim to hold loosely, not to teach.

13.4 The six reasons an hour is ever chosen

Below are the only six grounds on which the timing of an antihypertensive is legitimately decided. They are given in the order they apply: a safety reason overrides a sleep reason, which overrides a convenience one. Where none of them is in play — which is the common case — the honest answer is that it does not matter, and the patient should be asked when they will remember.

TABLE 14.2 — THE SIX GROUNDS, IN THE ORDER THEY APPLY

#	THE REASON	WHAT IT LOOKS LIKE, AND THE DRUGS IT APPLIES TO
1	Safety at the peak	A drug whose first or peak effect can drop a patient goes at an hour when they are lying down. Alpha-1 blockers at night , first dose especially ⁷ . Any drug being started in a frail or older patient at risk of falling.
2	Protecting sleep	A diuretic that wakes the patient to pass urine costs more than the dose gains. See §14.5, which is the fullest worked example in this chapter.
3	Another drug owns that hour	Levothyroxine must be taken on an empty stomach, 30 to 60 minutes before breakfast or 3 to 4 hours after dinner, and 4 hours away from iron or calcium ⁵ . It has a hard constraint; the antihypertensive has none. The drug with the constraint wins the slot.
4	A deliberate drug-free interval elsewhere	A long-acting nitrate is given so that a nitrate-free interval falls overnight, to prevent tolerance. Knowing what else is acting, and when it deliberately is not, tells you where the thin hours are.
5	Covering a gap	Only relevant if the drug does not last twenty-four hours. A genuinely short-acting agent may need twice-daily dosing to cover the dawn. A long-acting one does not — see §14.7.
6	Adherence	The hour the patient will actually remember: with a meal they never miss, alongside a tablet they already take, at a time that survives a working day or a fast. When none of the five above applies, this is the whole answer , and the trials support saying so plainly ^{1,2} .

13.5 Protecting sleep — the diuretic rule

A loop diuretic produces its diuresis over a few hours and is short-acting⁶. Given in the evening it produces its effect exactly when the patient is trying to sleep, and the result is nocturia, broken sleep, and often a patient who quietly stops the tablet without saying why.

The rule that follows: the last diuretic dose of the day goes no later than mid-afternoon. A patient needing furosemide twice daily takes it at about 8 am and about 2 pm — not 8 am and 8 pm. The second dose still works; it simply finishes before bedtime.

The reasoning goes one step further, and this is the part worth teaching. Broken sleep is not merely unpleasant. Short and fragmented sleep is consistently associated with higher blood pressure and with the non-dipping pattern described in Volume 1. **An evening diuretic can therefore undo part of what it was given to achieve**, by trading a few hours of natriuresis for a night of sympathetic arousal.

Once the diuretic has taken the morning and early afternoon, the rest of the regimen arranges itself around it. If the patient is comfortable and covered through the day, an antihypertensive with no timing constraint of its own can sit in the evening without difficulty — the trials say the hour is free¹, so use that freedom for the drug that has a reason.

13.6 When another drug owns the hour

Most antihypertensives can be given at any hour with food or without. That flexibility is easy to overlook, and it is the most useful fact in this chapter: **when two drugs compete for a slot, the antihypertensive is almost always the one that can move.**

TABLE 14.3 — DRUGS THAT OWN AN HOUR, AND WHAT THEY DISPLACE

THE DRUG WITH THE CONSTRAINT	WHY THE HOUR IS FIXED	WHAT HAPPENS TO THE ANTIHYPERTENSIVE
Levothyroxine	Empty stomach; 30 to 60 minutes before breakfast, or 3 to 4 hours after dinner. Not within 4 hours of iron or calcium, and not with antacids or proton pump inhibitors ⁵ .	It moves. To breakfast proper, or to the evening. Nothing is lost ¹ .
A bisphosphonate	Empty stomach, upright, water only, and a wait before other tablets.	It moves, for the same reason.
A long-acting nitrate	Timed so the nitrate-free interval falls overnight and tolerance does not develop.	It can occupy the hours the nitrate deliberately leaves uncovered.
Iron or calcium	Separated from levothyroxine by 4 hours ⁵ , which can force a three-way rearrangement of the day.	It fills whichever slot is left.
A short-acting insulin or a meal-tied agent	Fixed to meals by its own action.	It moves.

Reading this table the other way round is the point of Chapter 14: an antihypertensive sitting in an unusual slot often means *another drug* took the obvious one, and the other drug may not be on the prescription you are holding.

13.7 Splitting a dose — reasoning, or habit in costume?

The question to ask yourself

“Which of the six am I acting on?” If the answer is none of them, there is no timing decision to make, and inventing one wastes the patient’s attention on something that does not matter while the things that do — dose, second drug, adherence — go unaddressed.

Grade E, and honestly labelled

No trial has randomised the hour of a diuretic dose against blood pressure or events. The rule above is *reasoning* from the drug’s duration of action and from the association between disturbed sleep and pressure — not a trial finding. This book grades that E. It is still the right thing to do, and a reader is entitled to know which kind of claim it is.

A common sight: telmisartan 40 mg written as 20 mg in the morning and 20 mg at night, usually because a morning reading was high. It looks like sophisticated chronotherapy. Most of the time it is not.

Splitting a long-acting drug generally loses more than it gains. Telmisartan already covers twenty-four hours and beyond; halving each dose halves the peak concentration without extending cover that was not running out, and it converts a once-daily regimen into a twice-daily one — which is a reliable way to lose a dose. The evening trials removed the only justification that would have made the trade worthwhile^{1,2}.

TABLE 14.4 — WHEN SPLITTING IS A DECISION, AND WHEN IT IS A HABIT

SPLITTING IS REASONING WHEN...	SPLITTING IS HABIT WHEN...
The drug is genuinely short-acting — captopril, immediate-release nifedipine, hydralazine, prazosin — and a single dose leaves the trough uncovered.	The drug already covers twenty-four hours. Amlodipine, telmisartan, chlorthalidone and perindopril do not need splitting to reach tomorrow morning.
The peak effect is poorly tolerated — dizziness, flushing, postural symptoms — and spreading it makes the same daily dose bearable.	The reason offered is “the morning reading was high”, with no check of whether the drug was long-acting, at full dose, or the only one.
A loop diuretic needs a second dose and it can be fitted before mid-afternoon (§14.5).	It has simply always been written that way, and nobody has revisited it.

13.8 The high morning reading

Almost every timing decision in Indian practice begins with a high morning reading. Before rearranging the clock around it, three questions are worth more than any change of hour.

The test, in one question
Would the trough be uncovered on once-daily dosing? If the drug’s duration exceeds twenty-four hours, the answer is no, and splitting buys nothing while costing adherence. If you want a lower morning pressure, the useful moves are a fuller dose, a second drug at a second site, or shifting the existing drug to the evening — which the trials say is safe¹.

TABLE 14.5 — BEFORE YOU MOVE ANYTHING, ASK THESE THREE

QUESTION	WHY IT COMES FIRST
Is it real?	One clinic reading taken in the morning is not a morning surge. Home readings or ambulatory monitoring distinguish a genuine dawn pattern from a single number and from white-coat effect. Rearranging a regimen around an artefact is common and entirely avoidable.
Is the regimen actually long-acting and at full dose?	A drug that does not reach twenty-four hours, or one at half its dose, produces a morning rise for a reason that has nothing to do with timing. Fix the drug before you move it.
Is there a second site?	A single agent leaving the dawn uncovered is usually a case for a second drug at a second site, not for splitting the first one. Chapter 12 says which second drug.

If all three are satisfied and the dawn pressure remains high, moving the dose to the evening is a reasonable next step and a safe one^{1,2}. It should be described to the patient as what it is — **a trial of timing, not a treatment** — and reviewed against home readings rather than a single clinic visit.

13.9 The scenarios, resolved

A physician meets these as separate problems. They are not. The value of \$14.4 is that the same six grounds settle all of them, including combinations this book has not printed.

And one cause that is not a drug problem at all

A non-dipping or reverse-dipping pattern with a high morning pressure, in a patient who snores and is sleepy by day, is a reason to think about obstructive sleep apnoea rather than about the clock. Volume 1 covers the phenotype; no rearrangement of tablets treats it.

TABLE 14.6 — COMMON SITUATIONS, AND WHICH OF THE SIX DECIDES THEM

THE SITUATION	WHICH REASON	WHAT IT MEANS IN PRACTICE
CKD, on twice-daily furosemide	2	8 am and 2 pm, not 8 am and 8 pm. The second dose finishes before bedtime and the night is left alone.
Hypothyroid, on levothyroxine	3	The thyroid tablet owns the pre-breakfast slot ⁵ . The antihypertensive moves; nothing is lost by moving it.
Angina, on a long-acting nitrate	4	Know where the nitrate-free interval falls, and place the antihypertensive where the cover is thin rather than where it doubles up.
Older patient who has fallen	1	Peak effect where the patient is safe. Start low, and consider the evening — falls were marginally fewer on evening dosing ¹ .
Starting an alpha-blocker	1	Lowest dose, at night, in bed ⁷ . Not on a day a diuretic or nitrate has just been started.
Night-shift worker	6	“Morning” means on waking, not 8 am. Anchor the dose to the patient’s own day, not the clock’s.
Fasting — Ramadan, a religious fast, a procedure	6	Move doses into the permitted hours, keep once-daily drugs once daily, and be careful with the diuretic on a day of reduced intake. A clonidine patch exists partly for this problem.
Dialysis days	1 and 6	The dialysis day is a different day. Ask what the unit already omits before dialysis, and do not add a second set of instructions that contradicts theirs.
Travel across time zones	6	For a once-daily long-acting drug, shift the dose to the new local time over a day or two. Nothing more elaborate is needed.
Patient on many tablets, adherence poor	6	Collapse to once daily wherever the pharmacology allows, and put everything at one anchor event. This is worth more than any timing refinement in this chapter.

13.10 What to write on the prescription

The reasoning in this chapter is worth nothing if it reaches the patient as an ambiguity. In practice a great deal of timing intent is lost between the consulting room and the strip of tablets.

TABLE 14.7 — WRITING THE HOUR SO THAT IT SURVIVES

INSTEAD OF	WRITE	BECAUSE
“1-0-1”	“8 am and 8 pm”	The notation is read differently by different patients, pharmacists and family members, and it carries no reason with it.

INSTEAD OF	WRITE	BECAUSE
“Twice daily” on a loop diuretic	“8 am and 2 pm — not after 2 pm”	The whole point of the decision is the negative half of it, and the negative half is what gets dropped.
“At night” on a first alpha-blocker dose	“First dose at bedtime, already in bed”	“At night” is compatible with standing at the kitchen sink, which is where the patient falls.
“Morning” for a shift worker	“On waking, whenever that is”	Otherwise the instruction and the patient’s day disagree, and the patient loses.
Nothing at all about stopping	“Never stop clonidine suddenly — tell any doctor you are on it”	This one is not about timing and it belongs on the sheet anyway. It is the most dangerous omission in this volume.

And tie the dose to an event rather than a number wherever possible. **“With breakfast” is remembered; “8 am” is forgotten on a Sunday.** Where the two conflict, the event wins, because the event is what actually happens.

13.11 Clinical pearls

Thirty points that change practice, for a reader who has one minute.

- 1 The guideline names the drug, the dose and the target, and is nearly silent on the hour. That silence is a clinical space, not an oversight.
- 2 A trial once reported that bedtime dosing cut cardiovascular events by about 45%³. Its conduct grade is **weak** and the European Heart Journal issued an expression of concern⁴.
- 3 **TIME randomised 21,104 patients for five years: 3.4% against 3.7%, p = 0.53¹**. BedMed and BedMed-Frail agree².
- 4 The hour does not change outcomes. **Grade D, and a dead heat is a finding, not a gap.**
- 5 What the hour does change is whether the drug is tolerated and whether it is taken — and both of those change outcomes.
- 6 TIME found more adverse effects on morning dosing and more non-adherence on evening dosing¹. You are trading one against the other, every time.
- 7 There are only **six reasons** an hour is ever chosen. Every scenario reduces to one of them.
- 8 **1 — safety at the peak.** A drug that can drop a patient goes when they are lying down.
- 9 **2 — protecting sleep.** A diuretic that wakes the patient costs more than the dose gains.
- 10 **3 — another drug owns the hour.** The drug with the hard constraint wins the slot; the antihypertensive can nearly always move.
- 11 **4 — a deliberate drug-free interval elsewhere**, such as the overnight nitrate-free window.
- 12 **5 — covering a gap**, which only arises if the drug does not last twenty-four hours.
- 13 **6 — adherence.** When none of the other five applies, this is the entire answer, and the trials let you say so plainly.
- 14 Ask yourself which of the six you are acting on. If it is none, there is no timing decision to make.
- 15 **The last diuretic dose of the day goes no later than mid-afternoon.** Twice-daily furosemide is 8 am and 2 pm, never 8 am and 8 pm.
- 16 That diuretic rule is Grade E — reasoning from duration of action and from the association between broken sleep and pressure, not a trial finding. It is still right.
- 17 Levothyroxine must be taken on an empty stomach, 30 to 60 minutes before breakfast, and 4 hours away from iron or calcium⁵. It owns that slot; your drug does not.
- 18 **Splitting a long-acting drug loses more than it gains.** Telmisartan 20 morning and 20 night halves the peak, extends nothing, and doubles the chance of a missed dose.
- 19 The test for splitting: **would the trough be uncovered once daily?** If the drug lasts beyond twenty-four hours, no.
- 20 For a high morning reading, the useful moves are a fuller dose, a second drug at a second site, or a shift to the evening — in that order.
- 21 Before rearranging anything for a morning reading, confirm it is real. One clinic reading is not a dawn surge.
- 22 A high morning pressure in a snorer who is sleepy by day is a reason to think about sleep apnoea, not about the clock.
- 23 For a shift worker, “morning” means on waking. Anchor the dose to the patient’s day, not to the clock’s.
- 24 On a fasting day, move doses into the permitted hours and take particular care with the diuretic.
- 25 The dialysis day is a different day. Ask the unit what they already omit before you add instructions of your own.
- 26 **Write the hour, not the notation.** “1–0–1” is read differently by different people and carries no reason with it.
- 27 On a loop diuretic, write the negative half explicitly: “**not after 2 pm**”. That is the half that gets dropped.
- 28 “At night” is compatible with standing at the kitchen sink. Write “at bedtime, already in bed” for a first alpha-blocker dose.
- 29 Tie a dose to an event rather than a number. “With breakfast” is remembered; “8 am” is forgotten on a Sunday.
- 30 Collapsing a regimen to once daily at one anchor event is worth more than every timing refinement in this chapter put together.

KEY POINTS

- 1 The guideline names the drug, the dose and the target and is nearly silent on the hour. That silence is a real clinical space and it fills with folklore if it is not filled with reasoning.
- 2 A trial once claimed bedtime dosing cut events by about 45%³. Its conduct grade is weak and it carries an expression of concern⁴.
- 3 **Three trials settled it the other way.** TIME randomised 21,104 patients for five years and found 3.4% against 3.7%¹; BedMed and BedMed-Frail agree². Effect grade D.
- 4 The hour does not change what the drug does. It changes whether the patient tolerates it and whether they take it — and both of those change outcomes.
- 5 **There are only six reasons an hour is ever chosen:** safety at the peak, protecting sleep, another drug owning that hour, a deliberate drug-free interval elsewhere, covering a gap, and adherence.
- 6 Every scenario a physician meets — the CKD patient, the hypothyroid patient, the faller, the shift worker, the dialysis day — reduces to one of those six, including combinations this book has not printed.
- 7 **The last diuretic dose of the day goes no later than mid-afternoon**, because an evening dose trades natriuresis for a broken night. Grade E, and labelled as such.
- 8 When two drugs compete for a slot, the antihypertensive is almost always the one that can move. Levothyroxine cannot⁵.
- 9 **Splitting a long-acting drug loses more than it gains.** The test is whether the trough would be uncovered once daily; beyond twenty-four hours of cover, it would not.
- 10 When none of the six applies, the honest answer is that the hour does not matter — and the trials now let you say that to a patient with confidence.

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CHAPTER

15

PART VII · COMPARISON

Reading a Prescription Backwards

Twelve chapters have gone from the patient to the drug. A general physician in India usually meets the problem in the other direction — a patient arrives holding somebody else’s prescription, with no letter and no echo report. This chapter runs the volume in reverse.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- How to build a decoding map that is defensible: forwards from guidelines, then inverted — never asserted.
 - Why the possibility space narrows unevenly as drugs are added, and what each drug count actually tells you.
 - Which drugs are loud and which are silent, and why the non-antihypertensives should be read first.
 - What a prescription cannot tell you — adherence, money — and the confounders that break the method.
 - The rule that makes decoding safe: it produces a question, never an edit.

AT THE POINT OF READING SOMEONE ELSE’S PRESCRIPTION		LAYER 1 · 60 SECONDS
READ THIS FIRST	The composition on every strip, before the brand . Two brands can be one molecule, or one molecule can be hiding inside a combination the patient does not count. Then the non-antihypertensives . Anitrate, an anticoagulant, a high-dose statin, an SGLT2 inhibitor, sodium bicarbonate, a phosphate binder, allopurinol. They localise the patient faster than any blood-pressure drug can.	
THEN COUNT THE DRUGS	One tells you the prescriber’s default · two tells you the phenotype · three tells you severity · four tells you resistance — and tells you about the prescriber	
THE LOUD ONES	Methyldopa — pregnancy · sacubitril/valsartan — an echo exists and the ejection fraction was low · verapamil — rate mattered more than pressure · a loop where a thiazide belonged — eGFR under 30 · minoxidil — refractory, usually renal	
THE SILENT ONES	Amlodipine. Telmisartan. Hydrochlorothiazide inside a combination pill. Their presence means only that somebody treated the blood pressure.	
CHECK WHAT IS MISSING	No RAAS blocker in a diabetic is one of four things · no diuretic in a three-drug regimen is usually why it is not working	
BEFORE YOU CONCLUDE “WRONG”	Rank the reasons: something you cannot see → legacy → a constraint → and only then an error. The first is commonest by a wide margin.	
IT CANNOT TELL YOU	Whether the patient takes the tablets. One sheet is silent on adherence — a <i>sequence</i> of sheets is not.	
THE RULE	Decode to understand and to ask. Never to change. Act at this visit only on the short list in §15.18.	

15.1 The direction a physician actually works in

This volume has been written forwards. A phenotype is identified, a site is chosen, a class follows, a molecule within it follows, and a second drug is added at a second site. That is how a prescription is *made*, and it is how the specialist who made it was taught.

It is not how most Indian physicians meet the problem. In a country where 35.5% of adults are hypertensive but only 14.5% of them are on treatment^{1,2}, the patient who walks in already treated has usually been treated by somebody else — a cardiologist seen once, a discharge summary from a hospital in another city, a prescription written three years ago and refilled ever since. He arrives with a strip of tablets and no reasoning. The general physician must decide whether to continue them, what to check, and what to ask.

That is a decoding problem, and this volume has already supplied every fact needed to solve it. Chapters 1 to 12 go from patient to drug. This chapter runs the same knowledge backwards, from drug to patient. Nothing new is required except a method for doing it honestly.

15.2 The method — build it forwards, then invert it

There is an obvious way to write this chapter and it is the wrong one. It would begin: “Cardiologists commonly use the following fifteen combinations.” That is an empirical claim about prescribing behaviour, it would need a survey nobody has done at national scale, and printing it unsourced would be exactly the kind of confident invention this book refuses everywhere else.

The method used here instead has three steps, and only the first two require any claim at all.

The idea is not wholly new
Inferring a patient’s undisclosed diagnoses from their medication list is taught, mostly to pharmacy students, and there is a published teaching tool built entirely around it¹¹. What has not been built, so far as this book can find, is the codebook — a systematic map from combination to condition, ranked by what is actually common.

TABLE 15.1 — THE THREE STEPS, AND WHAT EACH ONE HAS TO BE DEFENDED BY

STEP	WHAT IT DOES	WHAT DEFENDS IT
1. The prior	Establish what conditions are actually common in Indian adults, because a rare disease and a common one can lead to the same regimen and the common one is the better bet.	Published national prevalence surveys, cited in §15.3.
2. The forward map	For each condition, state the regimen the guidelines and trials direct — then state what each modifier (diabetes, CKD, pregnancy, asthma, gout) adds or removes.	The same guidelines and trials the previous twelve chapters already rest on.
3. The inversion	Read the forward map from the other end. Every condition that leads to regimen X becomes, when X is seen, a candidate — ordered by the prior.	Nothing. It is arithmetic on steps 1 and 2. No new claim is made.

The third step is where the whole chapter lives, and it costs nothing to defend. If the guideline says a patient with proteinuric chronic kidney disease should be on a RAAS blocker at maximum dose with a loop diuretic, then seeing a RAAS blocker at maximum dose with a loop diuretic raises the probability

that the patient has proteinuric chronic kidney disease. That is not a statement about what doctors do. It is a statement about what the guideline says, read from the other end.

15.3 The prior — what is actually common in India

Two conditions can produce the same prescription. A beta-blocker with a RAAS blocker fits heart failure and it fits the year after a myocardial infarction. Which is the better first guess depends on which is commoner in the population the patient came from, and that is a published number rather than an opinion.

The figures below are the ones this book was able to read in a source it could open. Where the national figure does not exist, that is stated rather than filled in.

What the inversion is not

It is not a diagnosis, and it is not a licence to change anything. §15.17 states the rule the chapter ends on. Read that section before using any table in this chapter on a real patient.

TABLE 15.2 — THE INDIAN BASE RATES THIS CHAPTER REASONS FROM

CONDITION	FIGURE	SCOPE, AND THE CAUTION THAT GOES WITH IT
Hypertension	35.5% of adults, about 315 million ¹	National, 113,043 adults, all states. The single most important number in this volume.
— treated	14.5% of those with hypertension; 12.6% controlled ²	National, ages 18–69. Most hypertensive Indians you meet are on nothing. A patient holding a prescription is already unusual.
Diabetes	11.4%, about 101 million; prediabetes 15.3% ¹	National. The commonest modifier you will meet, by a wide margin.
Impaired kidney function	eGFR under 60 in 3.2% ³	National, 25,408 participants. Men 3.8%, women 2.6%; urban and rural did not differ.
Coronary heart disease	Urban over 60: 9–10%, or 2–4% on stringent criteria. Rural over 60: 4–6% ⁵	A review pooling regional surveys, not one national survey. Mortality is national: CHD accounted for 23% of all deaths and 32% of adult deaths in 2010–13.
Heart failure	No national prevalence figure was found. In 10,850 registry patients across 53 centres the cause was ischaemic in 71.9%, and one-year mortality was 22.1% ⁴	Hospital registry, not a population survey. The aetiology figure is what matters here: in India, heart failure usually means coronary disease.
Stroke	Incidence 105–152 per 100,000 per year ⁶	Pooled city registries. No national survey exists.
Atrial fibrillation	Not known nationally. A single-city pilot found 0.196% on one ECG ⁷	4,077 people in Nagpur, mean age 44, single 12-lead ECG — a method that misses paroxysmal AF. This book prints no Indian AF prevalence because none was found.
Asthma / COPD	Asthma 4.38%, COPD 2.1% ⁸	National, but adults 45 and over only, and self-reported diagnosis rather than spirometry.
Hypertensive disorders of pregnancy	About 11% of pregnancies ⁹	Read in a review rather than the primary meta-analysis. Treat as an order of magnitude.

15.4 The forward map — condition to regimen

Read left to right this is a summary of the volume. Read right to left, in §15.6, it becomes the codebook. Nothing in this table is new; every row was argued in an earlier chapter and carries the trial that settled it.

The number that should change your reading

Only 12.6% of hypertensive Indians have controlled blood pressure². When a prescription looks thin for the pressure it is treating, the commonest explanation in this country is not that the prescriber was wrong. It is that nobody has reviewed it since it was written.

TABLE 15.3 — WHAT THE GUIDELINES AND TRIALS DIRECT, BY CONDITION

THE CONDITION	THE REGIMEN IT DIRECTS	WHAT SETTLED IT
Uncomplicated, younger, higher-renin	ACE inhibitor or ARB, alone	Chapter 1. The site matches the phenotype.
Uncomplicated, older, isolated systolic	Thiazide-like diuretic or dihydropyridine CCB	SHEP ¹⁹ ; HYVET above 80 ¹⁵ .
Uncomplicated, needs a second drug	RAAS blocker + dihydropyridine CCB	ACCOMPLISH: a fifth fewer events than the same RAAS blocker with a thiazide ¹² .
High cardiovascular risk, pressure near normal	Ramipril 10 mg	HOPE: a quarter fewer events on a 3.3 mmHg difference ¹⁷ . The drug is treating risk, not the cuff.
Diabetes with albuminuria	ACE inhibitor or ARB first, then a CCB, with an SGLT2 inhibitor	Chapters 1 and 2.
Proteinuric CKD	RAAS blocker at maximum tolerated dose; loop diuretic once eGFR falls below about 30	Chapters 1 and 6. The loop replaces the thiazide because the thiazide stops working.
Heart failure, reduced ejection fraction	ARNI or ACE inhibitor + beta-blocker + mineralocorticoid antagonist + SGLT2 inhibitor	Chapters 7 and 8. Four drugs, none of them chosen for blood pressure.
After myocardial infarction	Beta-blocker + ACE inhibitor + high-dose statin + antiplatelet	Chapter 8.
Angina	Beta-blocker, with a CCB and a nitrate	Chapters 4 and 8.
Atrial fibrillation needing rate control	Beta-blocker, or verapamil or diltiazem — plus an anticoagulant	Chapter 4. The rate is the target; the pressure is incidental.
After stroke or TIA	Perindopril with indapamide	PROGRESS: recurrent stroke fell 43% on the combination and 5% on perindopril alone ¹⁴ .
Left ventricular hypertrophy	ARB in preference to a beta-blocker	LIFE ¹⁶ .
Resistant hypertension	RAAS blocker + CCB + thiazide-like, then spironolactone 25 mg — titrated upwards at two-week intervals if the potassium allows, with a potassium checked within a week of each step ²⁵	PATHWAY-2: spironolactone beat both alternatives as the fourth drug ¹³ .
Pregnancy	Methyldopa, labetalol, or nifedipine retard — and no RAAS blocker at all	Chapters 10 and 11.
Hypertension with prostatic symptoms	An alpha-1 blocker earns a place it does not otherwise have	Chapter 9.
Programme or protocol care	Amlodipine first, then telmisartan, then a thiazide — fixed doses	IHCl, which controlled 70–76% at the first step ²⁴ .

15.5 What each modifier changes

A condition sets the regimen. A modifier bends it — and because bending leaves a visible mark, the modifiers are where the decoding gets specific. A drug chosen *despite* being the second choice for the condition is a drug that is telling you about something else.

TABLE 15.4 — THE MODIFIERS, WHAT THEY CHANGE, AND THE MARK THEY LEAVE

MODIFIER	WHAT IT ADDS	WHAT IT REMOVES	THE MARK IT LEAVES ON THE SHEET
Diabetes	A RAAS blocker — obligatory once there is albuminuria in a hypertensive diabetic, however modest the pressure; an option, not a rule, in a normotensive one. An SGLT2 inhibitor.	Nothing absolutely; a thiazide is relatively disfavoured at higher doses.	Indapamide chosen over hydrochlorothiazide. Telmisartan chosen over other ARBs.
CKD, eGFR under 30	A loop diuretic. Often bicarbonate, a phosphate binder, an erythropoietin.	The thiazide, which no longer works. Spironolactone, on potassium grounds.	A loop diuretic where a cardiologist would have written a thiazide. The single clearest specialty signature in this chapter.
Pregnancy	Methyldopa, labetalol or nifedipine retard.	Every RAAS blocker, absolutely.	Methyldopa in a woman of reproductive age is close to diagnostic on its own.
Asthma or COPD	Nothing.	Non-selective beta-blockers.	A CCB or verapamil where a beta-blocker was clinically indicated. An absent beta-blocker after an infarct.
Gout	Losartan, which is mildly uricosuric. Often allopurinol alongside.	The thiazide.	Losartan chosen over a longer-acting ARB, with allopurinol on the same sheet.
Ankle oedema on a CCB	A RAAS blocker, or lercanidipine.	The higher CCB dose.	Amlodipine at 2.5 mg with a second drug, rather than 10 mg alone.
Age over 80	Indapamide, with perindopril as required.	Aggressive multi-drug escalation.	The HYVET pairing ¹⁵ , at low doses.
Cough on an ACE inhibitor	An ARB.	The ACE inhibitor, permanently.	An ARB in a patient whose condition would ordinarily have earned an ACE inhibitor — after an infarct, say.
Gynaecomastia	Eplerenone.	Spironolactone.	Eplerenone is otherwise rarely first choice; its presence usually means spironolactone was tried.

15.6 The inversion — the codebook

This is the chapter. Every row is the forward map reversed, and the ordering within each row is the prior from §15.3 — the commoner explanation printed first. The last column is the point: **one question or one test that would separate the candidates**. A decode that does not end in a question has not finished.

TABLE 15.5 — THE CODEBOOK — WHAT A REGIMEN IMPLIES, AND WHAT WOULD SETTLE IT

WHAT YOU ARE HOLDING	MOST LIKELY	ALSO POSSIBLE	WHAT WOULD SETTLE IT
Amlodipine alone	Uncomplicated hypertension in an older patient; stiff arteries assumed	A programme or protocol prescription ²⁴ ; or the default of a prescriber who defaults	Age and the pulse pressure. Little else is knowable — and that is a property of the evidence, not a failure of method: ALLHAT found the three first-line classes equivalent on the primary endpoint ¹⁸ , so choosing one of them reveals nothing about the patient.
Telmisartan or ramipril alone	Uncomplicated hypertension, younger patient, higher-renin assumed	Early diabetic or CKD protection at a normal pressure	A urine albumin-creatinine ratio.
Ramipril at 10 mg	Risk is being treated, not pressure¹⁷	Simply a fully titrated dose	Ask what the blood pressure was before it started.
A beta-blocker alone	Something other than hypertension — palpitations, tremor, anxiety, an old infarct	A prescription nobody has revisited in a decade	Ask why it was started. Usually nobody has ever asked.
RAAS blocker + amlodipine	Uncomplicated hypertension needing two drugs ¹²	Diabetes without albuminuria	Nothing needs settling. This is the modern default.
RAAS blocker + thiazide	Salt-sensitive or low-renin phenotype assumed	A retreat from amlodipine after ankle oedema	Ask whether the ankles ever swelled. If chlorthalidone, the prescriber reads trials.
Perindopril + indapamide	Prior stroke or TIA¹⁴ ; or age over 80 ¹⁵	A marketed combination chosen without that reasoning	One question about a previous stroke. This pairing is not accidental.
RAAS blocker + beta-blocker	Not a blood-pressure combination. Heart failure or a past infarct	Rate control in atrial fibrillation	Look for an echo. In India heart failure is ischaemic in 72% of cases ⁴ .
Amlodipine + beta-blocker	Angina	Hypertension where the beta-blocker is legacy	Ask about chest pain on exertion. Look for a nitrate.
Verapamil or diltiazem, anywhere	Rate mattered more than pressure — AF or SVT	Angina where a beta-blocker was contraindicated — the immediate-release preparations carry that indication, the extended-release ones do not; hypertrophic cardiomyopathy, which is a guideline use rather than a licensed one ²⁶	An ECG. And check the ejection fraction was known: verapamil is contraindicated in severe left ventricular dysfunction — the label's example is an ejection fraction below 30% — and diltiazem is to be avoided in it rather than barred ²⁶ .
Losartan + allopurinol	Gout alongside hypertension	Coincidence	Ask about a swollen first toe. Losartan is chosen here for a reason.
Triple: RAAS + CCB + thiazide	Uncontrolled on two, nothing else driving the choice	Any of the above with the comorbidity unrecorded	Are all three at proper doses? If not, this is not yet resistant hypertension.
Quadruple ending in spironolactone 25 mg	Resistant hypertension, treated by someone who knows PATHWAY-2¹³	Primary aldosteronism; heart failure	A potassium and a creatinine, which should already be being checked.
Quadruple ending in a beta-blocker instead	Spironolactone was ruled out by the potassium, or the eGFR made it unattractive — the label bars the first and only reduces the dose for the second ²⁵	There is a cardiac indication; or the prescriber does not know PATHWAY-2	The potassium and the eGFR distinguish the first from the other two.

WHAT YOU ARE HOLDING	MOST LIKELY	ALSO POSSIBLE	WHAT WOULD SETTLE IT
ARNI + beta-blocker + spironolactone	Heart failure with reduced ejection fraction. An echo exists and it was abnormal.	Nothing else. This combination has one meaning	Ask for the ejection fraction by name. Somebody measured it.
Any RAAS blocker + a loop diuretic	Advanced CKD, or heart failure with congestion	Oedema from another cause	An eGFR. The loop replaced a thiazide for a reason.
Methyldopa or labetalol in a young woman	Pregnancy, or planning it	Very little else	Ask directly. And check no RAAS blocker is still on the sheet.
Minoxidil, anywhere	Truly refractory hypertension, usually renal, often dialysis-associated	Nothing benign	Check the beta-blocker and loop diuretic are beside it. Alone it is dangerous.
An alpha-blocker as fourth or fifth drug	Resistance that has run past spironolactone	Coexisting prostatic symptoms in a man	Ask about the urinary stream. Both can be true at once.
Clonidine	The prescriber was near the end of the oral options	Suspected non-adherence being met with escalation	Whatever else you do, never stop it abruptly.

15.7 Loud drugs and silent drugs

The codebook works because drugs differ enormously in how much their presence narrows the field. Amlodipine narrows it barely at all. Methyldopa narrows it almost to a point. Knowing which is which is what turns a list of tablets into a history.

Read the last column twice

Every row ends in one question or one test, and that is deliberate. The purpose of decoding is not to know — it is to know *what to ask*. A physician who reads this table and starts changing drugs has misused it; a physician who reads it and asks the patient one well-aimed question has used it exactly as intended.

TABLE 15.6 — THE INFORMATION VALUE OF A DRUG'S PRESENCE

VALUE	DRUGS	WHAT THEIR PRESENCE BUYS YOU
Silent	Amlodipine, telmisartan, hydrochlorothiazide in a combination pill	Almost nothing. These are the defaults. Their presence means somebody treated the blood pressure.
Quiet	Losartan, enalapril, atenolol	A little about when the prescription was written, and about the prescriber, more than about the patient.
Speaking	Indapamide, chlorthalidone, nebivolol, lercanidipine, eplerenone, torsemide	A specific problem was identified and avoided — a metabolic worry, ankle oedema, gynaecomastia, poor absorption. Each is a second choice picked over a first for a reason.
Loud	Verapamil, diltiazem, spironolactone as a fourth drug, metoprolol succinate, carvedilol, an alpha-blocker	A second diagnosis is present, and usually an investigation was done. Succinate rather than tartrate is a prescriber telling you he knows the difference — which means heart failure.
Diagnostic	Methyldopa, sacubitril/valsartan, minoxidil, finerenone, a potassium binder, sodium bicarbonate	One meaning each, or close to it. Pregnancy. A low ejection fraction. Refractory renal hypertension. Diabetic kidney disease with albuminuria. A fight to keep a RAAS blocker on. Advanced CKD with acidosis.

15.8 Within the class — which molecule, and why that one

Everything so far decodes at the level of the class, and that is where most of the reasoning happens. But it is not where most of the information is. A class is very often simply what a prescriber reaches for; the molecule inside it is where he made a choice — and a choice leaves a trace that a habit does not.

The rule is simple: every class has a default molecule, and picking anything else means somebody had a reason. Amlodipine, telmisartan, hydrochlorothiazide, furosemide, spironolactone and enalapril are the defaults of their classes in Indian practice; seeing one tells you little beyond the class itself. Seeing a different molecule from the same class is often the single most informative mark on the sheet, because the prescriber overrode his own habit to write it.

The most sophisticated signal on any prescription

A potassium binder. It means somebody decided the RAAS blocker was worth keeping and bought the potassium headroom to keep it — rather than doing the easy thing and stopping the drug that was protecting the kidney.

TABLE 15.7 — THE MOLECULE CHOSEN, AND WHAT CHOOSING IT SAYS

CLASS	THE DEFAULT	A DIFFERENT MOLECULE, AND WHAT IT TELLS YOU
ACE inhibitors	Enalapril	Ramipril 10 mg — risk was the target, not the reading ¹⁷ . Perindopril — look for a prior stroke, especially beside indapamide ¹⁴ . Fosinopril — renal function was uncertain; it needs no dose adjustment at any eGFR. Lisinopril or captopril — liver disease; both are active as given.
ARBs	Telmisartan	Losartan — gout, almost always; it is the one uricosuric ARB, and allopurinol is often on the same sheet. Candesartan or olmesartan — tighter binding was wanted, or the prescriber follows the newer literature. Telmisartan itself at 80 mg — the dawn hours were the identified problem.
Calcium blockers	Amlodipine	Lercanidipine — ankle oedema happened, and this was the retreat. Cilnidipine — oedema again, or proteinuria; somebody wanted the second channel. Nifedipine retard in a woman of childbearing age — think pregnancy first . Verapamil or diltiazem — a different chapter altogether; rate, not pressure.
Thiazides	Hydrochlorothiazide	Chlorthalidone — a prescriber who reads trials, though the Diuretic Comparison Project has since unsettled the preference ²² . Indapamide — age over 80, a prior stroke, or a metabolic worry in a diabetic. Metolazone — loud: sequential nephron blockade in resistant oedema, and somebody is watching the electrolytes closely.
Loop diuretics	Furosemide	Torsemide — absorption was identified as the problem, not a general upgrade; mortality was the same in 2,859 patients ²³ . Bumetanide — the same reasoning. Ethacrynic acid — sulfonamide allergy, and almost nothing else.
Aldosterone antagonists	Spironolactone	Eplerenone — gynaecomastia or breast pain occurred; nobody starts here. Finerenone — diagnostic: diabetic kidney disease with albuminuria, and a urine albumin-creatinine ratio exists somewhere. Amiloride — potassium was the goal without touching the receptor.
Beta-blockers	Metoprolol tartrate, or atenolol	Metoprolol succinate or bisoprolol — heart failure, and a prescriber who knows the difference. Carvedilol — heart failure, or portal hypertension. Nebivolol — the prescriber knows the class problem and chose the molecule that does not share it; or a patient complained of something he did not write down. Labetalol — pregnancy. Atenolol still — the prescription has not been revisited.
Alpha-1 blockers	Prazosin	Doxazosin or terazosin — hypertension, as a fourth or fifth drug. Tamsulosin, alfuzosin, silodosin — these are prostate drugs and barely move the pressure . Finding one where a blood-pressure alpha-blocker was intended is a substitution error worth correcting.
Central agents	Clonidine	Methyldopa — pregnancy, and very little else. The clonidine patch — adherence or fasting was the obstacle, and somebody solved it. Moxonidine — tolerability of clonidine was the problem.
Vasodilators	—	Hydralazine with a nitrate — heart failure in someone who cannot take RAAS blockade, usually on potassium or renal grounds. Minoxidil — refractory hypertension, usually renal, and almost never alone: the label says it must <i>usually</i> be given with a diuretic and with a beta-blocker ²⁷ , and the exception is the dialysis patient whose fluid is taken off by ultrafiltration.

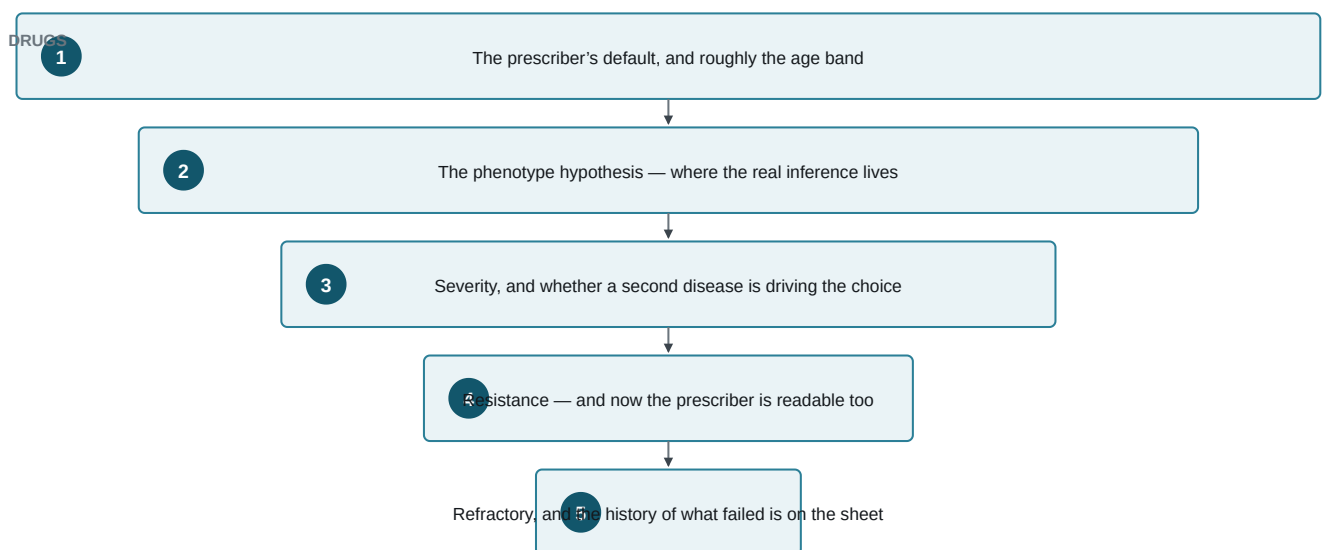
There is a second reading, and it is about the prescriber rather than the patient. **Molecule choice is where sophistication becomes legible.** Succinate rather than tartrate, chlorthalidone rather than hydrochlorothiazide, spironolactone rather than a fourth beta-blocker, 10 mg of ramipril rather than 5 — each is a small decision that only someone who has read the relevant trial makes. A sheet full of defaults is not wrong; it is simply silent. A sheet with three deliberate molecules on it was written by somebody thinking, and that is worth knowing before you change any of it.

The two directions this cuts

A default molecule adds nothing to what its class already told you — do not over-read amlodipine. A non-default molecule almost always encodes a specific event in this patient's history: an oedema, a cough, a gout attack, a gynaecomastia, a pregnancy, a failed absorption. **Ask what happened.** The answer is usually one sentence and it is usually not in any record you can see.

15.9 The narrowing law

FIGURE 15.1 — HOW THE POSSIBILITY SPACE NARROWS, DRUG BY DRUG



width = how many patients this sheet could belong to

The collapse is not even, and the second drug does most of the work. One drug tells you about the prescriber. Two tell you about the patient. Four tell you about both — because by the fourth drug the choice is between known alternatives, and which one was taken says whether the person writing it had read the trial.

Each additional drug narrows the field, but not by the same amount and not in the same way. The second drug is where the phenotype appears. The fourth is where the prescriber's own understanding becomes readable.

TABLE 15.8 — WHAT EACH DRUG COUNT TELLS YOU

DRUGS	WHAT IT TELLS YOU	HOW WIDE THE FIELD STAYS
One	The prescriber's default, and roughly the patient's age band. Almost nothing about the patient.	Very wide.
Two	The phenotype hypothesis. This is where the real inference lives — and where a non-blood-pressure indication first becomes visible.	A handful of candidates.
Three	Severity, and whether a second disease rather than the pressure is driving the choice.	A few.
Four	Resistance — and now the prescriber's sophistication is readable too, because the fourth drug is a choice between known alternatives ¹³ .	Usually one or two.
Five or more	Refractory hypertension, and the history of what has already failed is visible in the sheet itself.	Narrow, but noisy — some of those drugs are fossils.

15.10 Read the non-antihypertensives first

A physician handed a prescription reads the blood-pressure drugs first, because that is what he is being asked about. That is the wrong order. **The companion drugs localise the patient; the antihypertensives then tell you the reasoning.** One nitrate settles more than three antihypertensives can.

TABLE 15.9 — WHAT THE OTHER DRUGS ON THE SHEET LOCALISE

COMPANION DRUG	WHAT IT TELLS YOU
A nitrate (isosorbide mononitrate)	Angina. The beta-blocker beside it is now explained.
An anticoagulant (apixaban, rivaroxaban, warfarin)	Atrial fibrillation or a valve. The rate-controlling drug is now explained.
A high-dose statin with an antiplatelet	Established atherosclerotic disease. With dual antiplatelets, a recent stent — and the duration dates it.
An SGLT2 inhibitor	Diabetes, heart failure, or CKD — and in India the first is much the commonest ¹ .
Sodium bicarbonate	Metabolic acidosis of advanced CKD. Stage 4 or 5.
Calcium acetate or sevelamer	Phosphate retention. Advanced CKD, and someone is managing bone-mineral disease.
Alfacalcidol or calcitriol; cinacalcet	Secondary hyperparathyroidism. Advanced CKD again.
Erythropoietin or parenteral iron	Anaemia of chronic kidney disease.
Allopurinol or febuxostat	Gout — which explains a losartan and the absence of a thiazide.
Ivabradine	Heart failure where the rate stayed high on a maximal beta-blocker; or angina.
Levothyroxine	Hypothyroidism, common enough in India to be worth one question about the dose and the last TSH.

15.11 Absence is information

Decoding usually means reading what is there. Some of the sharpest inferences come from reading what is not — because a guideline-directed drug that is missing was, in most cases, deliberately not given.

TABLE 15.10 — WHAT A MISSING DRUG MEANS, AND THE SHORT LIST OF REASONS

WHAT IS MISSING	WHERE IT SHOULD HAVE BEEN	THE REASONS, AND THERE ARE FEW
Any RAAS blocker	A diabetic, especially with albuminuria	Hyperkalaemia; pregnancy or its possibility; previous angioedema; bilateral renal artery stenosis. Four, and a potassium plus one question separates them.
A beta-blocker	After a myocardial infarction, or in heart failure	Asthma or COPD; bradycardia or heart block; intolerance nobody recorded.
A statin	Established coronary disease	Intolerance; or an oversight, which is commoner. Worth raising.
An anticoagulant	Atrial fibrillation	Bleeding risk; cost; or a gap. This one is worth a direct question, because the stroke it prevents is large.
A diuretic	Resistant hypertension	Almost never justified. A three-drug regimen without a diuretic is usually the reason it is not working.
Spironolactone	Resistant hypertension on three drugs	Potassium above 5.0, or eGFR under 30 ¹³ . If neither, ask why not.

15.12 Dose, timing and packaging

The molecules are only one of four channels. The other three are read less often and are frequently more informative, because they record decisions rather than diagnoses.

The most useful absence in Indian practice

A three-drug regimen with no diuretic in it. It is the commonest correctable reason a prescription is not working, and it is visible without a single investigation.

TABLE 15.11 — WHAT THE DOSE SAYS

WHAT YOU SEE	WHAT IT SAYS
Ramipril 10 mg	The HOPE dose ¹⁷ . Risk was the target, not the reading.
Half doses of two drugs rather than a full dose of one	A sophisticated prescriber. The pressure benefit of doubling a dose is small and the adverse-effect cost is not — and he knows it.
Amlodipine 2.5 mg with a second drug	Usually nothing more than the labelled add-on dose: 2.5 mg is what the label directs when amlodipine is added to another antihypertensive, and the starting dose in a small, frail or elderly patient and in hepatic impairment ²⁸ . Read it as ankle oedema only if the sheet or the patient says so.
Spironolactone 25 mg, not 50	Potassium caution, or a titration that has not finished. PATHWAY-2 opened at 25 mg and doubled to 50 mg at six weeks ¹³ , so 25 mg is where the trial began rather than where it ended.
A beta-blocker started low and climbing over weeks	The heart-failure protocol, not the hypertension one.
A dose that has never changed despite an uncontrolled pressure	Therapeutic inertia. With 12.6% national control ² , this is the commonest finding of all.

TABLE 15.12 — WHAT THE TIMING SAYS

WHAT YOU SEE	WHAT IT SAYS
An alpha-blocker at night	First-dose hypotension was understood by whoever wrote it.
A diuretic in the morning	Somebody thought about the patient's sleep. A small sign of care.
A drug split morning and night	Either twenty-four hour cover was the identified problem — which hints at home readings or ambulatory monitoring — or the peak was deliberately spread for tolerability. On a long-acting drug it is usually neither, and Chapter 14 says why.
Everything at once in the morning	No timing decision was made. Neutral, not negative.

TABLE 15.13 — WHAT THE PACKAGING SAYS

WHAT YOU SEE	WHAT IT SAYS
A fixed-dose combination	Adherence or cost was the priority — or, very often in India, simply that this is the product that exists. See §15.14.
Separate pills where a combination exists	The prescriber wants to move one component independently. He is still titrating. The sharpest packaging signal there is.
A switch to a combination at follow-up	Adherence was identified as the problem.
A weekly patch instead of a daily tablet	Adherence again, and this time it was serious enough to change the route.

15.13 A published Indian series, read backwards

The best demonstration of this chapter is a paper that was not written for it. Two hundred and forty hypertensive patients at a hospital in Pune were studied against the JNC 8 recommendations¹⁰. Read forwards, one finding looks like a failure of guideline adherence. Read backwards, it is not a failure at all.

TABLE 15.14 — WHAT THE PUNE SERIES PRESCRIBED, AND WHAT IT MEANS READ BACKWARDS

WHAT THE PAPER REPORTS	THE FORWARD READING	THE BACKWARD READING
Beta-blockers were 46% of all monotherapy, ahead of diuretics 25%, ARBs 14%, CCBs 12% and ACE inhibitors 3% ¹⁰	JNC 8 removed beta-blockers from first line. This looks like widespread non-adherence.	163 of the 240 patients had heart failure, and 37% had cardiovascular disease. The beta-blocker was never being given for the pressure. The paper reaches the same conclusion itself.
Beta-blocker + diuretic was the commonest two-drug regimen at 20%, then ARB + beta-blocker at 19% ¹⁰	An old-fashioned pairing.	Two heart-failure and post-infarct regimens, in a population where 30% had diabetes with cardiovascular disease.
Sacubitril/valsartan appears in four of the seventeen triple regimens listed ¹⁰	An expensive drug in a hypertension study.	Every one of those patients had an echo, and it showed a reduced ejection fraction. The drug has no other use.
An alpha-blocker appears in five triple regimens; an alpha-2 agonist in two ¹⁰	Unusual choices.	Resistant hypertension that has run past the usual four — or, for the alpha-blocker, a man with prostatic symptoms.
Mean age 62.5 years; 65% male; 44% were in the prehypertension range on admission ¹⁰	A well-controlled population.	A cardiology population already on treatment, which is why the pressures look mild and the drugs look heavy.

The lesson generalises, and it is the most useful thing in this chapter. A prescription that looks non-adherent to a guideline is usually a prescription whose indication you cannot see. The Pune authors could see the indication because they had the charts. A physician holding only the prescription cannot — but he can infer that one exists, and go and ask for it.

15.14 What a prescription cannot tell you

Adherence: a single prescription is silent on it. There is nothing on the sheet that distinguishes a patient taking every tablet from one taking none. Physicians routinely believe otherwise, and are routinely wrong.

A sequence of prescriptions is a different matter, and speaks clearly: a move from twice daily to once daily, a move to a combination pill, a move to a weekly patch, or a dose that never rose across three visits while the pressure

stayed high. Those are adherence decisions and they are legible. One sheet is not a sequence.

Money: weakly, and this is the inference most likely to be wrong and most likely to offend. Generic against brand tells you more about the prescriber and the pharmacy than about the patient. A cheap fourth drug rather than an expensive one may be cost, or may be that the cheap one is better — spironolactone is both¹³. Do not infer a patient’s means from their tablets, and never say it aloud to them.

The past: only weakly. A prescription records what is being given now, not what was tried and abandoned. An absent ACE inhibitor may mean a cough two years ago that nobody wrote down. The only way to recover that history is to ask for it.

What this series is and is not

Two hundred and forty patients in one hospital in one city, weighted towards cardiology. It is a legitimate worked example and it is not a national frequency table. Where the frequency of each pattern across India is concerned, this book has no source and prints no number.

15.15 The confounders that break the method

Every inference in this chapter assumes the prescription records a decision. Often it does not, and in India the first confounder below is powerful enough to overturn a whole reading.

TABLE 15.15 — WHAT ELSE EXPLAINS A PRESCRIPTION, IN ROUGH ORDER OF HOW OFTEN

CONFOUNDER	WHY IT BREAKS THE INFERENCE
The fixed-dose combination market	A combination exists as a marketed pill, so it gets prescribed as a pill. That is a manufacturing fact, not a physiological one. When you decode a combination, ask first whether it is simply a product.
Inertia	The commonest of all. Somebody wrote it once and everybody since has copied it. With 12.6% national control ² , a prescription that has not changed is the norm, not the exception.
Availability	What the hospital pharmacy stocks, or what the local chemist carries. A protocol programme narrows this deliberately ²⁴ ; ordinary practice does not.
Detailing	A molecule promoted this year appears on prescriptions this year, in patterns physiology does not explain.
The patient’s own request	A tablet the patient asked to keep, or asked to stop, with no note of either.
Transcription	A discharge summary copied imperfectly. Strengths in particular go astray, and a wrong strength decodes to a wrong story.

15.16 When the prescription does not fit

Sometimes the sheet makes no sense for the patient in front of you. That is a common experience and it has four explanations, which must be ranked in this order — because a physician who reaches straight for the fourth will be wrong most of the time and will damage a colleague’s work.

TABLE 15.16 — WHY A PRESCRIPTION DOES NOT FIT, IN THE ORDER TO CONSIDER THEM

#	EXPLANATION	WHAT TO DO ABOUT IT
1	Something you cannot see. An echo, a potassium, a urine albumin, a pregnancy, an intolerance.	Go looking. Ask the patient, ask for the reports, ask the prescriber. This is the commonest answer by a wide margin.
2	Legacy. It fitted once and nobody has revisited it.	Legitimate to review — and this is where a general physician adds the most value in Indian practice.
3	A constraint. Cost, stock, tolerability, or what the patient would agree to take.	Ask before assuming. Constraints are usually invisible and usually reasonable.
4	A real error.	Only after the first three have been excluded — except for the short list in §15.18, which needs no deliberation.

15.17 The rule this chapter ends on

This chapter closes a knowledge gap. It is worth being precise about which one, because there are three gaps between a general physician and the specialist who wrote the prescription, and only the first is a book’s to close.

TABLE 15.17 — THREE GAPS, AND WHICH ONE A BOOK CAN CLOSE

THE GAP	WHAT IT IS	CAN A BOOK CLOSE IT?
Knowledge	Why this drug, why this dose, why this combination, and what the trial behind it said.	Yes. That is what this volume is for, and this chapter is its exam.
Data	The echo, the stress test, the potassium, the albumin–creatinine ratio, the pulse under the examining hand.	No. Decoding tells you an echo probably exists. It does not hand you the echo.
Judgement	Knowing when the rule does not apply to this patient.	No. That closes with years, not chapters.

So the output of decoding is a hypothesis and a better question — never an edit. You decode in order to continue the drug correctly, to monitor the right thing rather than the obvious thing, and to ask the patient or the specialist the one question that resolves the uncertainty. A physician who reads this chapter and begins writing four-drug resistant-hypertension regimens without a potassium and without a secondary-cause workup has taken from it the opposite of what it says.

15.18 The short list that needs no deliberation

Everything above says decode and ask. These are the exceptions — combinations where the danger is established, does not depend on information you lack, and should be acted on at the visit.

What this looks like from the other side

The specialist who wrote the prescription cannot see your consultation either. A physician who continues his regimen correctly, monitors the right thing and comes back with one well-aimed question is doing something for that patient no letter between them could achieve.

TABLE 15.18 — ACT AT THIS VISIT, WITHOUT WAITING FOR THE SPECIALIST

WHAT YOU SEE	WHY	WHAT TO DO
An ACE inhibitor and an ARB together	No added benefit and a third more renal impairment ^{20,21}	Stop one. Usually the ACE inhibitor.
Verapamil or diltiazem with a beta-blocker	Two drugs suppressing one node. Bradycardia and block.	Stop one, and find out which was there for the rate.
Any RAAS blocker in a woman who may conceive	Fetal harm is established and the exposure is avoidable.	Stop it and substitute. This does not wait.
A RAAS blocker, a diuretic and an NSAID	The commonest avoidable acute kidney injury in practice.	Stop the NSAID.
Potassium above 5.5 on spironolactone	Established harm, and often several potassium-raising drugs at once.	Review every potassium-raising drug, then reduce or stop.
Clonidine being stopped abruptly	Rebound crisis, with stroke and death reported.	Never stop it abruptly. Taper, and say so at every prescription.
The same drug, or the same class, twice — once loose and once inside a combination pill	The commonest duplication in a market where most products are combinations, and the patient cannot see it because the brand names differ.	Read every strip's composition, not its brand. Stop the duplicate at this visit.

15.19 Clinical pearls

Thirty-two points that change practice, for a reader who has one minute.

And one that is not on this list

A beta-blocker in a hypertensive who does not obviously need one. It looks like an error and usually is not — the Pune series is the demonstration¹⁰. Ask before you stop it.

- 1 This volume runs patient → drug. A physician holding somebody else's prescription runs drug → patient. Same knowledge, opposite direction.
- 2 Never claim what prescribers commonly do — that needs a survey. Build the map forwards from guidelines, then invert it. The inversion is arithmetic, not assertion.
- 3 The inversion needs a prior. Two conditions can give one regimen, and the commoner one is the better first guess.
- 4 35.5% of Indian adults are hypertensive; only 14.5% are treated and **12.6% controlled**^{1,2}. A patient holding any prescription is already unusual.
- 5 **Read the non-antihypertensives first.** A nitrate, an anticoagulant, a statin, bicarbonate or a phosphate binder localises the patient faster than any blood-pressure drug.
- 6 The companion drugs tell you the patient. The antihypertensives tell you the reasoning.
- 7 **Absence is information.** No RAAS blocker in a diabetic means one of four things, and a potassium plus one question separates them.
- 8 A three-drug regimen with no diuretic is the commonest correctable reason a prescription is not working, and it needs no investigation to spot.
- 9 One drug tells you the prescriber's default and the patient's age band. Two tells you the phenotype. Four tells you about resistance — and about the prescriber.
- 10 A beta-blocker alone in a hypertensive almost never means hypertension. Palpitations, tremor, an old infarct, or a prescription nobody has revisited.
- 11 **A RAAS blocker with a beta-blocker is not a blood-pressure combination.** It is heart failure or a past infarct. Look for an echo.
- 12 In India heart failure is ischaemic in 71.9% of registry patients⁴. An echo you cannot see probably showed coronary disease.
- 13 Verapamil means rate mattered more than pressure — and that somebody satisfied themselves the ejection fraction was preserved.
- 14 Perindopril with indapamide is not an accident. Prior stroke¹⁴, or age over 80¹⁵. Ask about both.
- 15 Sacubitril/valsartan has one meaning: an echo exists and the ejection fraction was low.
- 16 Methyldopa in a woman of reproductive age is close to diagnostic. Check no RAAS blocker is still on the sheet.
- 17 **A loop diuretic where a thiazide belonged is the nephrologist's signature.** It usually means eGFR under 30.
- 18 A potassium binder is the most sophisticated signal on any prescription: somebody bought headroom to keep the RAAS blocker rather than surrendering it.
- 19 Metoprolol *succinate* rather than tartrate is a prescriber telling you he knows the difference — which means heart failure.
- 20 Spironolactone 25 mg as the fourth drug means resistant hypertension treated by someone who knows **PATHWAY-2**¹³.
- 21 Half doses of two drugs beat a full dose of one, and a prescriber who does it is telling you he understands the dose-response curve.
- 22 Ramipril at 10 mg means risk was the target, not the cuff¹⁷.
- 23 **Separate pills where a combination exists means the prescriber is still titrating.** A switch to a combination means adherence was the problem.
- 24 A single prescription says nothing about adherence. A sequence of them says a great deal.
- 25 Do not infer a patient's means from their tablets, and never say it aloud to them.
- 26 In India the fixed-dose combination market is the strongest confounder: a combination gets prescribed because it exists as a pill.
- 27 When it does not fit, rank the reasons: something you cannot see, then legacy, then a constraint, and only then an error.
- 28 A prescription that looks guideline-non-adherent is usually one whose indication you cannot see. Beta-blockers were 46% of monotherapy in a Pune series where 163 of 240 patients had heart failure¹⁰.
- 29 The output of decoding is a hypothesis and a better question. **Never an edit.**
- 30 Act without waiting only on the short list: ACE inhibitor with ARB, verapamil with a beta-blocker, a RAAS blocker in a woman who may conceive, the NSAID triple whammy, potassium above 5.5, and clonidine being stopped abruptly.
- 31 Decoding closes the knowledge gap. It does not close the data gap — it tells you an echo exists, not what it showed.
- 32 The commonest single finding in Indian practice is a dose that never changed while the pressure stayed high. That is inertia, and it is correctable at your visit.

KEY POINTS

- 1 Twelve chapters go from the patient to the drug. In Indian practice the physician usually meets the problem from the other end, holding a prescription somebody else wrote with no explanation attached.
- 2 The method is what makes this trustworthy: build the map forwards from guidelines and trials, which are cited, then **invert it**. Seeing a regimen raises the probability of the condition it treats by arithmetic, not by assertion about what prescribers do.
- 3 The inversion needs a prior, and Indian prevalence data supplies it. 35.5% of adults are hypertensive; 14.5% treated; **12.6% controlled**^{1,2}.
- 4 Read the non-antihypertensives first. The companion drugs localise the patient; the blood-pressure drugs then tell you the reasoning.
- 5 Absence is information. A missing guideline-directed drug has a short list of reasons, and one question usually settles which.
- 6 Drugs differ enormously in what their presence buys. Amlodipine is silent; methyldopa, sacubitril/valsartan and minoxidil are close to diagnostic.
- 7 A prescription that looks guideline-non-adherent is usually one whose indication you cannot see — demonstrated on a published Indian series where beta-blockers were 46% of monotherapy because 163 of 240 patients had heart failure¹⁰.
- 8 A single prescription says nothing about adherence and very little about money. A sequence of prescriptions says a great deal about both.
- 9 **The output is a hypothesis and a better question, never an edit** — except for the short list of established dangers in §15.18.
- 10 This chapter closes the knowledge gap between a general physician and a specialist. It does not close the data gap or the judgement gap, and it says so.

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Appendices

Everything in this volume that is consulted rather than read. Nothing here argues; the chapters do that. If you want a dose, a threshold, a trial's numbers or a checklist, it is on one of these pages.

AFTER READING THIS CHAPTER YOU WILL UNDERSTAND

- Dosing for every oral antihypertensive in this volume, in one table.
 - The intravenous agents, with doses and the cautions that decide between them.
 - Renal thresholds, pregnancy status, and the monitoring each drug obliges.
- The trial atlas: every trial in the volume with its numbers and its two grades.
 - A one-page appraisal checklist, and a deviation worksheet to keep in the notes.

A Oral dosing, by class

Starting dose, usual range and frequency. Where no source states a figure, the cell says so rather than carrying a number nothing supports.

TABLE A.1 — ORAL ANTIHYPERTENSIVES — DOSE AND FREQUENCY

CLASS AND DRUG	START	USUAL RANGE	FREQUENCY
ACE inhibitors — ramipril	2.5 mg	2.5–20 mg	Once or twice daily
enalapril, lisinopril, perindopril	Low	See Chapter 1	Once daily
captopril	—	—	Two or three times daily, an hour before food — which rules it out for maintenance
fosinopril	—	—	Once daily. No adjustment at any eGFR
ARBs — losartan to azilsartan	See Chapter 2	—	Once daily; telmisartan has the longest cover
Calcium channel blockers — amlodipine	2.5–5 mg	5–10 mg	Once daily
nifedipine retard (MR)	10–20 mg twice daily	10–40 mg twice daily; maximum 80 mg daily ¹⁷	Twice daily
nifedipine GITS / XL	30–60 mg	90 mg on the coat-core extended-release label; the osmotic GITS label allows titration to 120 mg ¹⁷ . Indian once-daily products are not always the osmotic formulation — treat 90 mg as the ceiling unless the product is.	Once daily — not a twice-daily formulation
felodipine	2.5–5 mg	5–10 mg	Once daily

CLASS AND DRUG	START	USUAL RANGE	FREQUENCY
lercanidipine	10 mg	10–20 mg	Once daily, at least 15 minutes before food
lacidipine	2 mg	4–6 mg	Once daily
cilnidipine	5–10 mg	10–20 mg	Once daily, after breakfast
verapamil SR	120–180 mg	240–480 mg	Once or twice daily
diltiazem CD	180–240 mg ¹⁷	240–360 mg, to 480 mg on the Cardizem CD label; Tiazac's label allows 540 mg ¹⁷ . A 120 mg start is common practice, and within Tiazac's label	Once daily
Thiazide-type — chlorthalidone	12.5 mg	12.5–25 mg ²	Once daily
hydrochlorothiazide	12.5 mg	12.5–25 mg; the label permits 50 mg, at a metabolic cost that buys little pressure ²	Once daily
indapamide	1.25 mg	1.25–2.5 mg ²	Once daily
metolazone	2.5 mg	2.5–5 mg ²	Once daily — rarely for hypertension
Loop — furosemide	20–80 mg (oedema); 40 mg twice daily (hypertension) ²³	Tablets 20, 40, 80 mg ³ . Switch at equivalent dose, not equivalent milligrams: 40 mg is about torsemide 20 mg or bumetanide 1 mg ²³ — Chapter 6	Twice daily usual
torsemide	10–20 mg (heart failure); 5 mg (hypertension) ²³	Tablets 5, 10, 20, 100 mg ³	Once daily
bumetanide	0.5–2 mg ²³	Tablets 0.5, 1, 2 mg ³ ; to 10 mg a day ²³	Twice daily usual
MRA — spironolactone	25 mg	To 50 mg in heart failure, 100 mg in resistant hypertension ⁴	Once daily
eplerenone	50 mg ¹⁷	To 50 mg twice daily if the response is inadequate ¹⁷ . The 25 mg start titrated to 50 mg within four weeks is the post-infarction heart-failure regimen, not the hypertension one¹⁷	Once, then twice daily in hypertension — half-life 3–6 hours ⁵
baxdrostat	2 mg	2 mg; 1 mg if at risk of hyperkalaemia or hyponatraemia ^{14,17}	Once daily
Beta-blockers — carvedilol	6.25 mg twice daily	To 25 mg twice daily; heart failure starts at 3.125 mg twice daily ⁷	Twice daily
nebivolol	5 mg	To 40 mg, titrated at 2-week intervals ¹⁷	Once daily
metoprolol succinate, bisoprolol	Low	See Chapter 8	Once daily
atenolol — not for uncomplicated hypertension; listed because it is what an old prescription carries	50 mg	To 100 mg; above that adds nothing ²⁰ . Renally cleared: maximum 50 mg daily at a creatinine clearance of 15–35 mL/min, 25 mg daily below 15 ²⁰	Once daily

CLASS AND DRUG	START	USUAL RANGE	FREQUENCY
labetalol	100 mg twice daily	200–400 mg twice daily, raised in steps of 100 mg twice daily every two to three days; 1,200–2,400 mg daily in severe hypertension ¹⁸	Twice daily — the oral agent most used in pregnancy. The intravenous regimen in Table A.2 is a different decision
propranolol	—	—	Three or four times daily
Alpha-blockers — doxazosin, prazosin, terazosin	Lowest strength	See Chapter 9	First dose at night — on terazosin's label; doxazosin's names no hour, and the reasoning carries ⁸¹⁷
Central — methyldopa	—	250 mg two or three times daily for 48 hours, then 500 mg–2 g daily in two to four divided doses ; ceiling 3 g. Tablets 250 and 500 mg — there is no 125 mg strength ⁹¹⁷	Two to four times daily — never once
clonidine	—	IR 0.1/0.2/0.3 mg; XR 0.1 mg; patch 0.1–0.3 mg/day weekly ¹⁰	Divided, or weekly patch
Vasodilators — hydralazine	10 mg four times daily	To 50 mg four times daily; maximum 300 mg/day ¹¹	Four times daily
minoxidil	5 mg	Usual 10–40 mg daily; maximum 100 mg; adjustments at least three days apart ²⁴ . The boxed warning asks for close supervision, with a beta-blocker and a diuretic — frequently a loop diuretic — already in place ²⁴ . Chapter 11	Once daily to start ²⁴

B Intravenous agents

Reproduced in one place so the choice can be made at the bedside. **How far and how fast to lower the pressure is Volume 3**; this table names the drug and its dose only.

TABLE A.2 — INTRAVENOUS AGENTS FOR HYPERTENSIVE EMERGENCY

AGENT	DOSE	WHAT STOPS YOU
Nicardipine	5 mg/h, +2.5 mg/h every 5 min (rapid) or 15 min (gradual), max 15 mg/h ¹²¹³	Contraindicated in advanced aortic stenosis. A low initial dose in the elderly; gradual titration in renal or hepatic impairment ¹⁷ .
Clevidipine	1–2 mg/h, doubling every 90 s. Most need ≤16 mg/h; lipid load caps it at an average 21 mg/h per 24 h . Little data beyond 72 h ¹²¹³	Soy or egg allergy, lipid metabolism defect, severe aortic stenosis ¹⁷ . Lower doses in the elderly.
Sodium nitroprusside	0.3 mcg/kg/min, max 10 mcg/kg/min — never more than 10 min at maximum ; cyanide buffering exhausted near 500 mcg/kg cumulative ¹²¹³	Cyanide toxicity. Arterial monitoring; thiosulfate for longer infusions.
Nitroglycerin	5 mcg/min, +5 every 3–5 min; above 20 mcg/min steps of 10–20 are allowed — no stated maximum ¹²¹³	A phosphodiesterase-5 inhibitor or riociguat ; tamponade, constrictive pericarditis, restrictive cardiomyopathy, raised intracranial pressure ¹⁷ . Volume depletion. Reserve for coronary syndrome or pulmonary oedema.

AGENT	DOSE	WHAT STOPS YOU
Labetalol	20 mg over 2 min, then 40 or 80 mg at 10-min intervals; or infusion at 2 mg/min. Cumulative ≤ 300 mg ^{12,13}	Bronchial asthma, overt cardiac failure, block beyond first degree, cardiogenic shock, severe bradycardia ¹⁷ ; the label also directs that it not be used in nonallergic bronchospastic disease such as chronic obstructive pulmonary disease ¹⁷ . The agent of choice in pregnancy — but not at this dose . The obstetric regimen starts at 10 to 20 mg, repeats 20 to 80 mg every 10 to 30 minutes to a cumulative 300 mg, or infuses at 1 to 2 mg per minute ¹⁹ ; Volume 3, Chapter 23, Table 23.1, and the maternity protocol. Supine for the injection and for three hours after it — symptomatic postural hypotension in 58% if sat up sooner ¹⁷ .
Esmolol	500 mcg/kg bolus over 1 min — a total dose, not a rate , then 50 mcg/kg/min. Immediate control: 1 mg/kg over 30 s, then 150 mcg/kg/min ^{12,13}	Severe sinus bradycardia, sick sinus syndrome, block beyond first degree, decompensated heart failure, cardiogenic shock, pulmonary hypertension, and an intravenous verapamil-type calcium channel blocker ¹⁷ .
Hydralazine	20–40 mg by rapid intravenous bolus, repeated as necessary ¹² . Not the obstetric dose — follow the maternity protocol in pregnancy	Unpredictable response limits first-line use. Onset 10–30 min, lasts 2–4 h.
Phentolamine	5 mg intravenously or intramuscularly, repeated if necessary — the label sets no fixed interval ¹⁷	Chosen by cause: phaeochromocytoma, MAOI interaction, cocaine, clonidine withdrawal . Contraindicated after myocardial infarction, or with coronary insufficiency or angina ¹⁷ .
Enalaprilat	1.25 mg over 5 min, every 6 h — a fixed dose, not a titration . 5 mg every 6 h was tolerated but no more effective, and is not recommended ¹⁷	Hypersensitivity, or any history of angioedema on an ACE inhibitor ¹⁷ . Pregnancy — boxed warning, absolute in practice. Slow onset.
Fenoldopam	0.01–0.3 mcg/kg/min, +0.05–0.1 every 15 min. 1.6 mcg/kg/min is the highest rate reported in trials, not a ceiling ^{12,13}	Raised intraocular or intracranial pressure, sulfite allergy.

C Thresholds, monitoring and pregnancy

TABLE A.3 — WHAT EACH CLASS OBLIGES YOU TO CHECK, AND WHAT FORBIDS IT

CLASS	CHECK	WHEN	THE THRESHOLD THAT STOPS YOU
ACE inhibitor / ARB	Potassium, creatinine	1–2 weeks, and after each increase	Pregnancy — absolute . Bilateral renal artery stenosis. Previous angioedema (ACE inhibitor).
Calcium channel blocker	Ankles, heart rate	4 weeks	Verapamil in severe left ventricular dysfunction ¹ ; diltiazem carries a warning there rather than a contraindication, and is avoided for the same reason. Verapamil with a beta-blocker; diltiazem with one only under monitoring. Chapter 4.
Thiazide-type	Sodium, potassium, urate, calcium, creatinine ²	2–4 weeks; potassium through the first three weeks ²	Anuria, and hypersensitivity to a sulfonamide-derived drug ² . A remembered reaction to a sulfonamide antibiotic is not that — Chapter 5. Established gout, relatively.

CLASS	CHECK	WHEN	THE THRESHOLD THAT STOPS YOU
Loop	Weight, electrolytes including magnesium, creatinine	With each dose change	Anuria, and hypersensitivity to the drug ³ . Hepatic coma and severe electrolyte depletion stop bumetanide and torsemide; on furosemide's label they are warnings — improve the state first. Sulfonamide allergy is a warning on all three rather than a bar. Chapter 6.
MRA	Potassium, creatinine	1–2 weeks	Spironolactone: the label bars only hyperkalaemia, Addison's disease and concomitant eplerenone . Do not start above a potassium of 5.0; at an eGFR of 30 to 50 reduce the starting dose rather than withhold; below 30 it is a judgement, not a bar. The familiar figures — eGFR under 30, creatinine above 2.5 mg/dL (men) or 2.0 (women) ⁴ — are initiation thresholds and trial entry criteria, not label contraindications. Chapter 7. Eplerenone: potassium above 5.5 or creatinine clearance 30 mL/min or less, or a strong CYP3A inhibitor — and in hypertension also type 2 diabetes with microalbuminuria, creatinine above 2.0 mg/dL (men) or 1.8 (women), creatinine clearance under 50, or a potassium supplement or potassium-sparing diuretic ¹⁷ .
Beta-blocker	Heart rate, blood pressure	At each visit	Non-selective in asthma ⁶ . Severe bradycardia, high-grade block, decompensated heart failure.
Alpha-blocker	Postural blood pressure	After the first dose	Routine monitoring not otherwise recommended ⁸ .
Methyldopa	Blood count periodically; liver function at 6–12 weeks ⁹	As stated	Active liver disease, previous liver injury on it, previous Coombs-positive haemolysis, phaeochromocytoma ⁹ , and concurrent monoamine oxidase inhibitor therapy — a labelled contraindication ¹⁷ .
Hydralazine	Blood count and ANA before and during ¹¹	Before, then periodically	Coronary artery disease, mitral valvular rheumatic heart disease ¹⁷ ; aortic dissection, in practice ¹¹ .

TABLE A.4 — PREGNANCY, IN ONE PLACE

	STATUS
Contraindicated absolutely	ACE inhibitors, ARBs, direct renin inhibitors — at any dose, at any trimester, and stop at the point pregnancy becomes a plan rather than a fact. Enalaprilat intravenously is contraindicated for the same reason ¹² .
Established in use	Methyldopa — no teratogenic effects ⁹ . Labetalol, oral and intravenous ¹² , at the obstetric dose and not the one in Table A.2 ¹⁹ . Nifedipine — modified-release for maintenance; immediate-release by mouth and swallowed for acute severe hypertension ¹⁹ , never sublingually, and its own label says the capsule is not for the acute reduction of blood pressure ²² . Hydralazine intravenously for acute severe hypertension ¹¹ , at a quarter of the general adult dose ¹⁹ .
Avoid	Atenolol. Thiazides, relatively. Spironolactone, on antiandrogenic grounds.

Lactation is the page that gets missed at discharge. The woman goes home on what she was given on the ward, and the drug most likely to be handed to her is the cheapest beta-blocker in the dispensary.

TABLE A.4B — LACTATION, IN ONE PLACE

	WHAT THE LABEL SAYS
Avoid	Atenolol — excreted in breast milk at 1.5 to 6.8 times the plasma concentration, and clinically significant bradycardia has been reported in breastfed infants; the premature infant and the infant with impaired renal function are at most risk ²⁰ . It is also the cheapest and most widely dispensed beta-blocker in India, which is why it is the one to look for on the discharge sheet.
Weigh	Thiazides — excreted in breast milk; the hydrochlorothiazide label asks for a decision between stopping nursing and stopping the drug ²¹ .
Labetalol	Present in milk at low levels; the label reports no data on the breastfed infant or on milk production ¹⁸ .
The rest	Not read for this table. Check the label of the drug in hand before discharge, and follow the maternity unit's guidance where it has one.

D Trial atlas

One row per trial. The effect grade is how large and on what endpoint; the conduct grade is whether the way it was run supports the number. The two axes are defined in Opening 2, and the key is repeated here so the table can be read alone. **Effect:** A settled — follow it · B strong default — latitude only for a reason specific to this patient · C weak default — a secondary endpoint, a small absolute difference, or a caveat the recommendation does not carry; genuine latitude · D dead heat — the trial found no difference; full latitude · E not a trial finding. **Conduct:** sound · qualified — one survivable defect, and the effect size is an upper bound · weak — two defects, or one that goes to the heart of the comparison. A surrogate endpoint is flagged where it applies: a surrogate is a promise, not a result.

TABLE A.5 — THE TRIALS THIS VOLUME RESTS ON

TRIAL	N	WHAT WAS COMPARED	HEADLINE RESULT	GRADES
SHEP 1991	4,736	Chlorthalidone vs placebo, isolated systolic hypertension	5-year stroke 5.2 vs 8.2 per 100, RR 0.64	Effect A · conduct sound
RALES 1999	1,663	Spironolactone vs placebo, severe HFrEF	Mortality 35% vs 46%, RR 0.70	Effect A · conduct sound
MERIT-HF 1999	3,991	Metoprolol CR/XL vs placebo, HFrEF	Mortality 7.2% vs 11% per patient-year; 34% reduction	Effect A · conduct qualified — stopped early for benefit
HOPE 2000	9,297	Ramipril vs placebo, high CV risk	A quarter fewer events on 3.3 mmHg	Effect A · conduct sound
PROGRESS 2001	6,105	Perindopril ± indapamide vs placebo, prior stroke	Combination 43%, monotherapy 5%	Effect A for treating BP · weak for the combination claim — strata not randomised
ALLHAT 2002	33,357	Chlorthalidone vs amlodipine vs lisinopril	Primary 11.5/11.3/11.4%. Heart failure RR 1.38 and 1.19	Effect D primary, C heart failure · conduct sound
ALLHAT doxazosin 2000	24,335	Doxazosin vs chlorthalidone	Heart failure RR 2.04. No primary difference	Effect A · conduct sound — stopped early for harm, which strengthens rather than qualifies the finding
LIFE 2002	9,222	Losartan vs atenolol, ECG LVH	Composite 11% vs 13%; stroke 5% vs 7%, at matched BP	Effect C for the class verdict · conduct sound

TRIAL	N	WHAT WAS COMPARED	HEADLINE RESULT	GRADES
RENAAL 2001	1,513	Losartan vs placebo, type 2 diabetic nephropathy	ESRD 19.6% vs 25.5%	Effect B · conduct sound
ASCOT-BPLA 2005	19,257	Amlodipine±perindopril vs atenolol±bendroflumethiazide	Stroke 3% vs 4%; CV events 14% vs 17%	Effect C for the class verdict · conduct sound
CAFE 2006	2,073	Central aortic pressure within ASCOT	Brachial identical; central systolic 121.2 vs 125.5	Effect B · conduct sound , surrogate endpoint
ACCOMPLISH 2008	11,506	ACEi+amlodipine vs ACEi+HCTZ	Events 9.6% vs 11.8%, HR 0.80	Effect B/C · conduct sound ; comparator was HCTZ
ONTARGET 2008	—	Telmisartan vs ramipril vs both	Equivalent; combination harmful, NNH 30	Effect A for the prohibition · conduct sound
HYVET 2008	3,845	Indapamide±perindopril vs placebo, age 80+	Primary endpoint, stroke: about 30% lower at p = 0.055, short of conventional significance. Secondary: heart failure HR 0.36, all-cause death HR 0.79	Effect B — the primary endpoint was missed and the mortality and heart-failure findings are secondary · conduct qualified — stopped early for benefit
EMPHASIS-HF 2011	2,737	Eplerenone vs placebo, NYHA II HF rEF	CV death or HF admission 18.3% vs 25.9%	Effect A · conduct sound
ALTITUDE 2012	—	Aliskiren added to RAAS blockade in diabetes	Harm; stopped early	Effect A · conduct sound — stopped early for harm, which strengthens rather than qualifies the finding
Van Vark 2012	158,998	Meta-analysis, ACE inhibitors vs ARBs	Mortality reduction for ACE inhibitors only	Effect C · meta-analysis, disputed by ONTARGET
PATHWAY-2 2015	335	Spironolactone vs doxazosin vs bisoprolol vs placebo	Home systolic -8.70 vs placebo; beat both actives	Effect B — the largest effect on a surrogate endpoint, against three comparators · conduct sound , randomised crossover; 335 patients, 12 weeks, no hard outcomes
SPRINT 2015	9,361	Systolic target <120 vs <140 (protocol held at 135–139)	Events 5.2% vs 6.8%; AKI 4.1% vs 2.5%	Effect A · conduct qualified — stopped early for benefit; open-label; specific BP method
FIDELIO-DKD 2020	5,674	Finerenone vs placebo, type 2 diabetic CKD	Renal composite 17.8% vs 21.1%, HR 0.82	Effect B · conduct sound
CLICK 2021	160	Chlorthalidone vs placebo, stage 4 CKD	24-h systolic -11.0 vs -0.5 mmHg	Effect B · conduct sound , small, surrogate
DCP 2022	13,523	Chlorthalidone vs hydrochlorothiazide	MACE 10.4% vs 10.0%, HR 1.04	Effect D · conduct qualified — open-label, prevalent users
TRANSFORM-HF 2023	2,859	Torsemide vs furosemide after HF admission	Mortality 26.1% vs 26.2%, HR 1.02	Effect D · conduct qualified — open-label, pragmatic
BaxHTN 2025	796	Baxdrostat 1 or 2 mg vs placebo, add-on	Placebo-adjusted systolic -9.8 and -8.7 mmHg	Effect B · conduct sound ; 12 weeks, no outcomes

Five of the twenty-four were stopped early, and the reason matters in each case. ALTITUDE and the doxazosin arm were stopped for harm, where any bias makes the drug look better than it was. SPRINT, MERIT-HF and HYVET were stopped for benefit, where the effect is probably real and the magnitude probably inflated¹⁶.

E Appraisal checklist and deviation worksheet

TABLE A.6 — APPRAISING A TRIAL — EIGHT QUESTIONS IN ORDER

ASK	
1	What was the comparator? Placebo, or an active drug? And was the active drug a fair one, or the weakest member of its class?
2	Who was enrolled? Age, risk, renal function, ethnicity. Would this trial have taken my patient?
3	Was the finding on the primary endpoint? A secondary endpoint is a finding; a subgroup is a hypothesis. All three are printed in the same font.
4	Relative or absolute? A 25% reduction of a 0.4% risk is not a 25% reduction of a 40% risk. Ask for the number needed to treat.
5	Was allocation concealed, and were people blinded? Randomised and concealed are different claims ¹⁵ . An open-label trial of a drug with visible effects is not blinded whatever it says.
6	Who was lost, and how was it analysed? Intention to treat, or per protocol? Per-protocol flatters the drug ¹⁵ .
7	Was it stopped early, and why? For harm, believe it. For benefit, believe the direction and discount the size ¹⁶ .
8	Is the celebrated endpoint the registered one? A result promoted from secondary to headline is a warning ¹⁵ .

TABLE A.7 — DEVIATION WORKSHEET — ONE LINE IN THE NOTES

RECORD	
The recommendation	What the guideline says, and which guideline and year.
Its grade	A, B, C, D or E — and whether the conduct behind it was sound or qualified.
Why this patient differs	Contraindication, intolerance, cost, availability, or falling outside the trial population in a way that matters.
What you did instead	The drug, the dose, and the review date.
The one line to write	“Guideline recommends X; not used because Y; Z prescribed instead, review in four weeks.” That sentence converts an apparent oversight into a visible decision, protects the patient from being switched back blindly, and protects you.

And the boundary around all of it
Where a treatment protocol is **mandatory** rather than advisory — a programme protocol, an institutional formulary, a scheme list, a standing order — none of this applies. Follow it, and raise a concern through whatever reviews it. This worksheet is for clinical discretion, not for overriding a protocol you are bound by.

KEY POINTS

- 1 These pages are consulted, not read. Nothing here argues; the chapters do that.
- 2 A dose you cannot find is a dose you will guess. That is why every dosing table in the volume is on one page rather than nine.
- 3 The trial atlas carries two grades per trial, because how large a result was and whether the trial was run well are independent questions.
- 4 Five of the twenty-four trials were stopped early. Two for harm, which strengthens them; three for benefit, which inflates them.
- 5 The eight appraisal questions fit on one page and will correctly deflate most claims a physician meets.
- 6 The deviation worksheet is one line in the notes. It turns an apparent oversight into a visible decision.
- 7 None of it applies where a protocol is mandatory rather than advisory.

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