AN EVIDENCE-BASED READER'S GUIDE

Advanced Atherosclerosis (ASCVD) Educational Handbook

What causes coronary artery disease, how it is measured, and what the evidence says can stop and reverse it

Compiled from the research library of

CURINGHEARTDISEASE.COM

The Premiere Heart Health Education Platform
Founded by Peter Megdal, PhD

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Please read this first

This handbook is an educational document. It is not medical advice, it is not a treatment plan, and it cannot account for your particular history, your other conditions, or the medications you already take. Nothing in it should replace a conversation with a qualified healthcare professional who knows you.

It was assembled from the published research library at CuringHeartDisease.com, a reader-supported education platform founded by Peter Megdal, PhD, after his own diagnosis with severe, inoperable coronary artery disease at age 55. That library draws on peer-reviewed primary literature — randomized trials, genetic studies, imaging trials, and clinical guidelines — and every article on the site is reviewed and verified by Peter Megdal, PhD, before publication. Megdal is a research scientist, not a physician.

Three cautions are worth stating plainly, because this handbook covers ground where acting alone can cause harm:

- **Never start, stop, or change a prescription medication** — including statins, PCSK9 inhibitors, aspirin, hormone therapy, or diabetes drugs — on the basis of anything you read here. Aspirin in particular carries a real bleeding risk that has to be weighed against benefit for your specific situation.
- **Do not treat a target number as a personal prescription.** The lipid targets in Part III are drawn from published guidelines and trials. Which tier applies to you is a clinical judgment.
- **Chest pain, unusual breathlessness, a sudden drop in exercise capacity, or a feeling that something is wrong is a reason to seek medical attention now**, not a reason to read another chapter.

> **HOW THIS HANDBOOK USES EVIDENCE**
>
> Where the underlying science is settled — that apolipoprotein B-containing particles cause atherosclerosis, for example — the handbook says so directly. Where evidence is contested, thin, or mostly observational, it says that too, and names what would settle the question. Sections that describe what one person did, including Megdal, are labeled as a case, not as a protocol for anyone else.

Some of the source articles were drafted with the assistance of AI research and writing tools, then reviewed, corrected, and verified against the primary literature by Peter Megdal, PhD, who is responsible for the published content. The site publishes an editorial and AI transparency policy describing this process.

How to use this handbook

You do not have to read this front to back. It is built in eight parts, and each answers a different kind of question.

If you want to know…	Start at
What this disease actually is, and whether it can really be reversed	Part I — The Disease
Why it happens, and what the single most important number is	Part II — The Cause
Which tests to ask for and how to read the results	Part III — Knowing Your Numbers
What to eat — and how the diet arguments actually resolve	Part IV — Food
How much exercise, what kind, and what it can and cannot do	Part V — Movement
What the drugs do, who they are for, and what the trials showed	Part VI — Medication
Menopause, testosterone, inherited cholesterol, athletes, diabetes	Part VII — Special Situations
A concrete plan, a tracking sheet, and questions for your doctor	Part VIII — Putting It Together

Three conventions

- **Crimson boxes** carry the single most important takeaway of a section.
- **Teal boxes** flag nuance, a caveat, or a place where the evidence is weaker than the popular claim.
- **Units.** Lipid values are given in mg/dL, the convention used in the United States. To convert LDL cholesterol to mmol/L, divide by 38.7.

THE ONE-PARAGRAPH VERSION

Coronary artery disease is caused by apolipoprotein B (ApoB) particles crossing into the artery wall and getting trapped there. Risk tracks how many particles you have and how long you have had them — a cumulative exposure, accruing silently from childhood. It is usually symptomless until it is not. It can be measured directly with a blood test and a scan rather than estimated from a risk calculator. And when particle exposure is driven low enough, for long enough, plaque stops growing, stabilizes, and in a meaningful fraction of people partially regresses. Almost everything else in this handbook is detail hanging off that sentence.

Contents

PART I

The Disease

Before anything else: what is actually happening inside an artery, when it starts, why our species is vulnerable to it, why it stays hidden for decades, and what the word "reversal" honestly means.

CHAPTER 1

What atherosclerosis actually is

The popular image — cholesterol as sludge gradually clogging a pipe — is wrong in ways that matter. The real process is a retention and inflammation problem in the wall of the artery, not a plumbing problem in its channel.

An artery is not a pipe. It is a living, three-layered tissue. The innermost layer, the intima, is lined by a single sheet of endothelial cells that sits between the blood and everything behind it. Atherosclerosis is a disease of what gets stuck *behind* that lining.

The sequence, as the current evidence describes it, runs like this. Lipoprotein particles carrying apolipoprotein B — LDL principally, but also VLDL remnants, IDL, and lipoprotein(a) — cross the endothelium. Most cross back out. Some do not. ApoB-100 carries positively charged regions that bind electrostatically to the negatively charged sulfate groups on proteoglycans in the arterial matrix. That binding is the pivotal event: it converts a particle passing through into a particle retained. This is why the framework is called **response-to-retention**.

Once trapped, a particle is chemically modified — oxidized, enzymatically altered. Modified lipoproteins behave like danger signals. They activate the endothelium, recruit circulating monocytes, and are swallowed by macrophages through scavenger receptors that, unlike the normal LDL receptor, have no off switch. The macrophages engorge with cholesteryl ester and become foam cells — the earliest visible lesion of atherosclerosis. Cholesterol crystals and oxidized particles then activate the NLRP3 inflammasome inside those macrophages, releasing interleukin-1-beta and IL-18, driving IL-6 signaling, and instructing the liver to produce C-reactive protein. Inflammation is not a separate disease running alongside the lipid problem. It is the wall’s response to the lipid problem.

> **THE ONE MECHANISM TO REMEMBER**
>
> Atherosclerosis begins when ApoB-containing particles are *retained* in the artery wall and trigger a maladaptive immune response. Everything downstream — foam cells, the necrotic core, the fibrous cap, calcification, rupture — follows from that. The more particles are circulating, the more get retained. This is the reason particle count matters more than the cholesterol cargo those particles happen to be carrying.

What a plaque is made of, and why composition beats size

A mature plaque is not uniform. It has a lipid-rich necrotic core — dead foam cells, cholesterol crystals, debris — separated from the bloodstream by a fibrous cap of smooth muscle cells and collagen. The dangerous plaque is not necessarily the big one. It is the one with a large necrotic core and a thin, inflamed cap.

This is why the old measure — percent narrowing of the channel, or stenosis — is a poor guide to risk on its own. Most heart attacks arise from lesions that were not severely narrowing the artery before they ruptured. When a thin cap tears, the thrombogenic core is exposed to flowing blood, a clot forms in seconds, and a vessel that was 40 percent narrowed becomes 100 percent occluded.

Positive remodeling: why arteries hide their own disease

Early in the disease, as plaque accumulates in the wall, the artery compensates by expanding outward. The lumen — the channel blood flows through — stays the same size. This is called positive, or Glagov, remodeling. Substantial disease can therefore be present while an angiogram, which images only the channel, looks entirely normal.

The same phenomenon runs in reverse during treatment, and it is a source of confusion for patients. Plaque volume can fall measurably while the lumen does not visibly widen, because the wall contracts inward as the burden shrinks. The site's articles call this the **lumen paradox**. A treatment can be working at the level of the artery wall without producing a dramatic "opening" on a picture of the channel.

> **WHY THIS MATTERS FOR WHAT YOU GET TOLD**
>
> If your only test is one that images the lumen, a "normal" result means the channel is open. It does not mean the wall is clean. Chapter 13 covers the tests that see the wall itself.

CHAPTER 2

A disease you are born with

Atherosclerosis is managed as a disease of aging. The pathology record puts its earliest lesions before birth and its imaging-detectable form in most middle-aged adults.

Autopsy series, pediatric pathology, and population imaging converge on an uncomfortable picture: the process starts far earlier than the age at which anyone is screened for it. Fatty streaks appear in the aorta in childhood and in the coronary arteries in adolescence. By the second and third decades, a substantial minority of people have lesions that are no longer merely streaks.

One distinction does a lot of work here, and the site's life-course review insists on it: **adaptive intimal thickening is not the same thing as a lipid-retaining lesion**. Arteries normally thicken at branch points in response to shear stress. That is development, not disease. Pathology begins when lipid is being retained. Much of the historical disagreement about "when atherosclerosis starts" dissolves once those two things are counted separately.

Latency is not absence

Between the first retained particle and the first symptom lie decades. During that window the disease is real, progressive, and — critically — invisible to most routine testing. This is why a young adult with severe hypercholesterolemia can have a completely clean coronary CT scan and why that clean scan proves very little. Zero detectable plaque is the expected finding during biological latency, not evidence of protection.

> *"You feel fine" and "nothing is wrong" describe two different states. For thirty or forty years, most people with progressing coronary disease are in the first.*

The practical consequence

If the disease begins in childhood and accumulates for decades, then the useful question is not "do I have heart disease?" at age 60. It is "how much exposure have I accumulated, and how fast am I still accumulating it?" — asked as early as anyone will ask it. That reframing drives most of Part II.

NOT A COUNSEL OF DESPAIR

Early onset does not mean fixed fate. It means the relevant clock started earlier than you were told, and that the sooner exposure comes down, the more of the curve you avoid. The evidence on regression in Chapter 5 is the reason this is worth acting on at any age.

CHAPTER 3

Why humans get this disease

Two popular stories about the deep history of heart disease are both wrong: that our ancestors were immune to it, and that it is the unavoidable price of getting old. The evidence points somewhere more useful than either.

If atherosclerosis were purely a disease of industrial food, preindustrial people should not have it. If it were purely a consequence of aging, every long-lived population should have it. Neither prediction survives contact with the data.

The mummies: our ancestors were not immune

The Horus study performed whole-body computed tomography on 137 mummified remains from four geographically and dietarily diverse preindustrial cultures spanning more than four millennia: ancient Egyptians, Peruvians, Ancestral Puebloans, and Unangan hunter-gatherers of the Aleutian Islands. Probable or definite arterial calcification was identified in 47 of the 137 remains — 34 percent — and it was present in all four populations, including the hunter-gatherer group with no access to processed food, refined sugar, tobacco, or a sedentary life. Mean age at death was higher among affected than unaffected individuals, reproducing the age-relationship seen in modern populations.

This finding is genuinely inconvenient for the ancestral-diet argument in its strong form. Atherosclerosis is not a modern invention, and no preindustrial dietary pattern examined has conferred immunity to it.

The Tsimane: but exposure still decides

Set against that, the Tsimane forager-horticulturalists of the Bolivian Amazon have the lowest prevalence of coronary artery disease of any population yet recorded. Among 705 adults aged 40 and older, 85 percent had a coronary artery calcium score of zero. Among those over 75 — an age at which more than half of comparable US adults have significant calcification — 65 percent still scored zero, and only 8 percent scored 100 or above. That is roughly a five-fold lower prevalence of significant coronary calcification than the MESA reference population.

> **THE DETAIL THAT MATTERS MOST ABOUT THE TSIMANE**
>
> They achieve this *despite* a high chronic infectious and inflammatory burden from parasite exposure — conditions that ought to produce plaque if inflammation alone were sufficient. What they do not have is high lifetime ApoB exposure. This is one of the cleanest natural demonstrations that inflammation propagates atherosclerosis but does not initiate it without the lipid substrate. In wild-type animal models, similarly, systemic inflammation does not generate atherosclerosis in the absence of hyperlipidemia.

Reconciling the two

The apparent contradiction dissolves under the cumulative exposure model of Chapter 7. The Horus mummies show that the disease is available to any human with enough exposure and enough years — several of those populations ate substantially from animal sources, and some lived long enough to accumulate meaningful burden. The Tsimane show that when lifetime exposure is low, the disease largely does not develop, even into old age and even under heavy inflammatory load. Era is not the variable. Exposure is.

Our ancestors were not protected by living in the past. Some of them were protected by low lifetime particle exposure, and some of them were not protected at all.

What is a "normal" cholesterol for a human?

One argument built on this comparative evidence holds that physiologically normal LDL cholesterol for our species sits somewhere between 50 and 70 mg/dL — the range reported in human neonates, in wild non-human primates, and in the least-exposed human populations. On that reading, conventional laboratory reference intervals do not describe a healthy state at all; they describe a population with pathological exposure.

HANDLE THIS ARGUMENT CAREFULLY

It is a coherent and interesting position, and it aligns with everything in Part II. But it is advanced principally in narrative reviews and opinion articles rather than original research, and several of the comparative lipid values it rests on are asserted with limited primary documentation. Treat it as a well-motivated hypothesis about what our species' baseline looks like — not as an established measurement, and not as a personal target.

Why the animal evidence translates

The primate work described in Chapter 5 carries weight for an evolutionary reason. Unlike rabbits or rodents, non-human primates share our lipoprotein distributions, our ApoB biology, and our coronary arterial architecture. Given sufficient dietary exposure they develop genuinely human-like lesions — fibrous caps, lipid-rich necrotic cores, matrix remodeling, calcification, occasionally spontaneous infarction — and when exposure is lowered, those lesions partially regress along the same lines. The disease is not a human peculiarity. It is a property of the ApoB transport system we inherited.

One human-specific vulnerability

There is, however, at least one plausible way in which our particular lineage made itself more vulnerable. Roughly 2 to 3 million years ago, around the emergence of the genus *Homo*, an Alu-mediated deletion inactivated the CMAH gene. CMAH is the enzyme that converts the sialic acid Neu5Ac into Neu5Gc, and its loss means humans — alone among great apes — do not make Neu5Gc.

The fixation of that mutation across the whole population implies intense selection rather than drift. The leading hypothesis is a host-pathogen arms race: ancestral hominins were likely devastated by a malarial parasite that used Neu5Gc-rich red blood cells as its docking receptor, and losing the receptor was suddenly life-saving. A complementary hypothesis involves reproductive isolation — a CMAH-null female would develop anti-Neu5Gc antibodies from dietary exposure, and those antibodies would attack the heavily sialylated sperm of a wild-type male, selecting hard against mixed pairings over many generations.

THE MODERN CONSEQUENCE

We still absorb Neu5Gc — from red meat in particular — and incorporate it into our own tissues, including the vascular endothelium, where our circulating anti-Neu5Gc antibodies can react against it. The result is a chronic, low-grade inflammatory stimulus in the vessel wall from a molecule our species stopped recognizing as self two million years ago. This is a well-argued mechanism, not a demonstrated driver of human events — the same caution that Chapter 20 applies to TMAO applies here.

The other inheritance: fat storage

The same logic explains visceral adiposity. The thrifty gene hypothesis holds that efficient energy storage in adipose tissue conferred a survival advantage across long stretches of intermittent famine. The anatomy that made that advantageous — visceral fat draining directly into the portal circulation, delivering free fatty acids and inflammatory mediators straight to the liver — is precisely what makes it dangerous when famine never arrives. Chapter 34 returns to this.

The conclusion this points to

Nothing about the human cardiovascular system is defective. It is operating as built, under three conditions it was never selected for: an ApoB exposure sustained at magnitudes that were rare in our history, over a lifespan far longer than the one it was optimized for, and without the periodic scarcity that used to interrupt it. Atherosclerosis is best understood as a mismatch disease.

WHAT THIS CHANGES PRACTICALLY

It undercuts "eat like our ancestors" as a guide. The mummy evidence shows ancestral populations — including hunter-gatherers — developed the disease. Ancestry is not a warrant for any particular macronutrient ideology.

It reframes what a low number means. An LDL-C of 60 mg/dL is not an unnaturally suppressed value produced by drugs. It is plausibly closer to the range our species spent most of its existence in.

It explains why this is worth treating at all. A mismatch disease is, by definition, one where changing the exposure changes the outcome.

CHAPTER 4

Why feeling fine is the problem

For a large share of people, the first symptom of coronary artery disease is the event itself. Fitness, in particular, can mask it.

Coronary disease produces no reliable warning in its long accumulating phase. Angina, when it appears, generally requires a lesion that limits flow — and most infarctions arise from lesions that were not flow-limiting. So the absence of chest pain is close to uninformative about whether plaque is present.

The athlete’s version of the problem

Endurance training makes this harder, not easier, and the site returns to this theme repeatedly because its founder lived it. Several adaptations that make trained people healthier also blunt the signals that would otherwise reveal disease:

- **Exercise-induced hypoalgesia.** Regular hard training raises pain thresholds. Ischemic discomfort that would stop a sedentary person may register as ordinary effort.
- **Collateral circulation.** Repeated demand promotes arteriogenesis — the enlargement of existing collateral vessels — which can perfuse territory beyond a narrowing well enough to prevent symptoms.
- **Enormous physiological reserve.** A large drop in cardiac performance can still leave an athlete performing at or above the level of an untrained peer.

The result is a population that presents late, or presents with something that does not look cardiac at all. In the founding case behind this platform, the presenting complaint was not pain. It was an unexplained 14 percent fall in 20-minute maximal cycling power that persisted through four more years of harder training. The eventual workup showed ST-segment depression at 90 percent of VO2max, and the angiogram that followed found five lesions, including obstructive disease not amenable to stenting or bypass because of where it sat.

> **A SIGNAL WORTH TAKING SERIOUSLY**
>
> An unexplained, sustained decline in exercise capacity — power, pace, breathlessness at efforts that used to be easy — that does not respond to training adjustment or rest deserves a cardiac evaluation, not a training-plan revision. This is one of the few "symptoms" the silent phase reliably produces in trained people.

Silent infarction and MINOCA

Two further patterns break the classic story. Unrecognized myocardial infarction — scar found on imaging in someone who never knew they had had a heart attack — is not rare, particularly in older and in diabetic populations. And myocardial infarction with non-obstructive coronary arteries (MINOCA) is a genuine infarction in someone whose angiogram shows no significant stenosis, driven by plaque disruption or erosion, spasm, embolism, or microvascular dysfunction rather than by a flow-limiting blockage. Both are reminders that "the arteries looked open" is not the same as "the arteries are healthy."

CHAPTER 5

What "reversal" really means

The claim that coronary disease can be reversed is both true and routinely overstated. It is worth being precise about which part of the plaque changes, by how much, and under what conditions.

Start with the strongest evidence, which is not from humans. Between the 1950s and the 1980s, primate studies established that diet-induced atherosclerosis in animals whose lipoprotein biology closely resembles ours could not only be halted but partially undone. Lowering severe hypercholesterolemia depleted intracellular and extracellular cholesteryl ester pools, resolved necrotic debris, and restored endothelial vasomotor function. Dense fibrosis and macrocalcification largely persisted.

That last sentence is the honest boundary of the claim, and it holds in humans too. What regresses is the soft, lipid-rich, rupture-prone compartment. What does not regress is the fibrous and calcified scaffolding. This is not a disappointment — the lipid-rich compartment is the dangerous one — but it means that a calcium score may not fall, and may even rise, while the disease is being successfully treated. Chapter 13 returns to this.

Compartment of plaque	Responds to intensive treatment?	What it means for you
Lipid-rich necrotic core	Yes — depletes measurably	This is the compartment that ruptures. Shrinking it is the main goal.
Fibrous cap	Yes — thickens and stabilizes	A thicker cap is less likely to tear. Stabilization is itself a win.
Inflammatory activity	Yes — falls with lipid lowering and with anti-inflammatory therapy	Tracked clinically with hsCRP.
Dense fibrosis	Largely no	Structural scarring persists.
Calcification	No — and may increase	Densely calcified plaque is more stable. A rising calcium score under treatment is not necessarily failure.

How the different compartments of an atherosclerotic plaque respond to intensive lipid lowering and lifestyle change.

What the human trials show

Serial imaging trials using intravascular ultrasound, coronary CT angiography, and quantitative coronary angiography have converged on a dose relationship rather than a switch. Achieved LDL cholesterol below roughly 70 mg/dL is broadly associated with halted progression; deeper lowering, into the 30 to 40 mg/dL range achievable with combination therapy, is where measurable regression is most consistently reported. The magnitude varies with baseline plaque burden, the imaging method, the achieved ApoB, and background therapy.

A NUMBER WORTH NOT OVER-TRUSTING

A figure of 70 mg/dL is often quoted as *the* threshold below which regression begins. The site's own verification work flags this as a convenient summary rather than a demonstrated biological cliff. The relationship looks continuous: lower achieved exposure, more regression, without a clean cut point inside the ranges studied.

Cure versus reversal

The site draws a distinction that is easy to lose. **Curing** a pathological process means stopping the active biology driving it. **Reversing** structural damage means undoing what that process already built. The first is achievable and reasonably well documented: hold ApoB low enough and the retention-and-inflammation engine largely stops. The second is partial. Expect the process to be arrestable and the architecture to be partly, not wholly, remodeled.

> *The realistic goal is not a photograph of clean arteries. It is a plaque that has stopped growing, lost its dangerous core, and thickened its cap — in a person whose particle exposure no longer feeds it.*

PART II

The Cause

One molecule explains most of this disease. Understanding what ApoB is, why duration matters as much as level, and where LDL cholesterol misleads is the highest-yield thing a reader can do.

CHAPTER 6

ApoB: the number that counts particles

Every atherogenic lipoprotein particle carries exactly one apolipoprotein B molecule. That one-to-one relationship turns a blood test into a particle count.

The liver builds VLDL, which becomes IDL, which becomes LDL. Each of these carries a single ApoB-100 molecule, and so does lipoprotein(a). The molecule is not exchanged between particles. Measure plasma ApoB and you have counted, directly, how many potentially artery-damaging particles are in circulation.

Why does count beat cholesterol mass? Because retention in the artery wall is a particle event. A particle either crosses the endothelium and binds a proteoglycan or it does not. How much cholesterol that particle happened to be carrying is close to irrelevant to whether it gets stuck. Two people can have identical LDL cholesterol values while one has considerably more particles, because their particles are smaller and each carries less cargo.

> **IF YOU REMEMBER ONE NUMBER**
>
> ApoB is the best single circulating measure of atherogenic particle burden, and the unifying causal driver of atherosclerotic cardiovascular disease. If you can get one additional test beyond a standard lipid panel, this is usually the one to ask about.

Why the causal claim is strong

The evidence that ApoB-containing lipoproteins cause atherosclerosis — rather than merely accompanying it — rests on three independent lines that agree:

1. **Mechanism.** The response-to-retention pathway described in Chapter 1 supplies a complete, physically specified route from circulating particle to plaque.
2. **Genetics.** Mendelian randomization across dozens of genetic instruments — variants in LDLR, PCSK9, HMGCR, NPC1L1, APOB, ANGPTL3, LPL, CETP — shows that people randomly assigned by inheritance to lifelong lower ApoB have proportionally lower lifetime disease, regardless of which gene does the lowering. The relationship holds down to very low concentrations.
3. **Randomized trials.** Lowering ApoB-containing lipoproteins by any of several mechanistically unrelated drugs lowers events, and the size of the benefit tracks the size of the reduction.

Convergence across mechanism, natural genetic experiment, and randomized intervention is about as strong as causal evidence gets in chronic disease epidemiology.

Where ApoB earns its keep clinically

ApoB and LDL cholesterol usually agree. The clinically important situations are the ones where they do not — a state called **discordance** — and it is concentrated in exactly the populations that are hardest to risk-stratify: insulin resistance, metabolic syndrome, type 2 diabetes, high triglycerides, obesity. In those states, LDL particles become small and cholesterol-depleted. The particle count runs high while the cholesterol number looks acceptable.

DISCORDANCE IN ONE SENTENCE

If you have high triglycerides, insulin resistance, or type 2 diabetes, an "acceptable" LDL cholesterol is more likely to be hiding a high particle count — which is why guidelines increasingly recommend measuring ApoB in precisely these patients.

A measurement advantage as well

Most reported LDL cholesterol is not measured; it is calculated, historically by the Friedewald equation, which degrades when triglycerides are elevated or the sample is non-fasting. ApoB is measured directly by internationally standardized immunoassays, with lower analytic bias and better reproducibility. It also does not require fasting.

CHAPTER 7

Cumulative exposure: longer, higher, worse

Risk is not set by today's cholesterol value. It is set by the area under the curve — how high, multiplied by how long.

Consider two people with an LDL cholesterol of 118 mg/dL at age 52. One has been at 118 since her twenties. The other was at 190 until a diagnosis at 48 and is now treated. A single cross-sectional measurement assigns them the same risk category, the same treatment threshold, and the same follow-up interval. Their arteries have had entirely different lives.

The more faithful construct is **ApoB-years** (or, in its more commonly reported proxy form, LDL-C-years): particle concentration integrated over time. It is more mechanistically honest than any single value, because retention accumulates. Each year of exposure deposits material that does not simply wash out when the number improves.

> *Atherosclerosis is a disease of cumulative exposure that we still assess almost exclusively with a snapshot.*

What the modeling implies

Working from a widely used heuristic threshold of roughly 5,000 mg/dL-years of cumulative LDL exposure — the neighbourhood in which clinically meaningful disease tends to become apparent — the arithmetic is stark. These are model-derived projections from the cumulative-exposure hypothesis, not measured incidence:

Lifetime average LDL-C	Age at which ~5,000 mg/dL-years is reached	Interpretation
~200 mg/dL (untreated heterozygous FH)	Around age 25	Explains the premature disease that defines familial hypercholesterolemia.
~125 mg/dL (very common, often called "normal")	Around age 40	A value most people are never treated for still crosses the threshold in midlife.
~80 mg/dL	Not until the seventh decade	The same disease, deferred past most of a lifespan.

Model-derived illustration of how lifetime average exposure shifts the timing of disease rather than merely its probability.

The young-adult inflection

Analyses of exposure during early adulthood have identified an inflection at a usual ApoB of roughly 75 mg/dL sustained across ages 18 to 40, above which risk begins to climb. On that basis, an ApoB below about 75 mg/dL has been proposed as a goal for maintaining low risk in young adults — a group almost never screened and almost never treated.

WHY THIS ARGUES FOR ACTING EARLY

Lowering ApoB at 60 prevents future exposure. It does not refund the exposure already accumulated. Two decades of elevated particle burden during a formative window leaves a residue that even aggressive later therapy does not fully erase. The cheapest intervention in this entire handbook is knowing your ApoB in your twenties.

A caution about the concept

ApoB-years is a research framework, not a validated clinical instrument. There is no standard way to reconstruct your historical exposure, no accepted target expressed in those units, and no trial that has randomized people on the basis of it. Treat it as a way of thinking that reframes urgency — not as a number to chase.

CHAPTER 8

Where LDL cholesterol misleads

LDL-C remains the standard therapeutic target and it is not wrong. It is simply a proxy, and proxies fail in predictable places.

There is a rhetorical trap on both sides of the cholesterol debate. One side treats LDL-C as the whole story; the other points to its failures and concludes that cholesterol does not matter. Both mistakes come from confusing the marker with the mechanism. The mechanism is particle retention. LDL-C is a usually-adequate estimate of how many particles there are.

The four situations where the estimate breaks

- **High triglycerides.** Calculated LDL-C loses accuracy as triglycerides rise, and triglyceride-rich remnant particles — each carrying its own ApoB — go uncounted.
- **Insulin resistance and type 2 diabetes.** The small dense LDL phenotype means more particles per unit of cholesterol.
- **Already-treated patients.** At achieved LDL-C below about 70 mg/dL, residual particle burden is where the remaining risk lives, and ApoB resolves it better.
- **Elevated lipoprotein(a).** Lp(a) cholesterol is counted inside the LDL-C number, which can make LDL-C look worse than the modifiable component actually is — and hides a risk that behaves differently. See Chapter 9.

The "normal cholesterol" problem

A very large share of heart attacks occur in people whose cholesterol was called normal. This is not evidence against the lipid model. It is evidence that "normal" was defined against a population in which the disease is close to universal. A US population median ApoB sits around 93 mg/dL and the conventional upper reference limit is about 130 mg/dL — values comfortably inside the range that produces atherosclerosis over decades. Reference ranges describe what is common. They do not describe what is safe.

> **COMMON IS NOT OPTIMAL**
>
> A lab result flagged as "within normal limits" tells you that you resemble the population the range was drawn from. In a population where most middle-aged adults have detectable coronary plaque, that is faint reassurance.

How low is too low?

The natural objection to aggressive lowering is that cholesterol is essential — which it is, for membranes, steroid hormones, and bile acids. But peripheral tissues synthesize their own cholesterol; they are not dependent on circulating supply in the way intuition suggests. Modeling of the transport system suggests the circulating pool required for structural and delivery functions is far below concentrations that are typical, and far below concentrations that cause disease.

Empirically, open-label extension data from PCSK9 inhibitor trials have followed people at LDL-C below 20 mg/dL without a signal of harm, and event reduction has continued rather than plateauing — no J-curve, no

therapeutic floor identified within the studied range. Concerns about neurocognitive harm at very low LDL-C, including Alzheimer’s risk, have been examined specifically in the genetic and trial evidence and have not been borne out; the genetic evidence points, if anything, the other way. That said, "no harm observed in trials of this length" is not the same as "no harm possible over fifty years," and honest practice acknowledges the difference.

CHAPTER 9

Lipoprotein(a): the inherited one

A common, largely genetic, mostly unmeasured risk factor that behaves differently from everything else on the lipid panel.

Lp(a) is structurally an LDL particle with an extra protein — apolipoprotein(a) — bolted on by a disulfide bond to its ApoB-100. That addition changes its behavior substantially, and some estimates place it as several-fold more potent per particle than ordinary LDL.

Genetically fixed, lifelong stable

Concentration is controlled principally by the LPA gene, is roughly 70 to 90 percent heritable, and stays broadly stable across a lifetime. Diet, weight loss, and exercise move it very little. Between individuals it varies enormously — over a thousand-fold — driven largely by copy-number variation in the kringle IV type 2 repeats: fewer repeats, smaller isoform, higher plasma concentration.

Two mechanisms, not one

- **Atherogenic and inflammatory.** Like any ApoB particle it can enter and be retained in the intima. It is also the major carrier of oxidized phospholipids in plasma, which are potent inflammatory ligands driving endothelial activation and plaque instability.
- **Thrombotic and antifibrinolytic.** Apo(a) closely resembles plasminogen, and competes with it for binding sites on fibrin. That impairs clot breakdown, raising the chance that a plaque disruption becomes an occlusive event rather than a silent one.

> **TEST IT ONCE**
>
> Because Lp(a) is genetically set and lifelong stable, a single measurement is generally informative for life. It is inexpensive, widely available, and still routinely omitted. Elevated Lp(a) combined with a coronary calcium score of 100 or above identifies particularly high risk in cohort data.

What to do if it is high

Lifestyle does not meaningfully lower it and statins do not lower it. Targeted RNA-based therapies are in late-stage development, and until outcome trials report, the established response is indirect: an elevated Lp(a) is a reason to treat everything else more aggressively — to drive ApoB and LDL-C lower than the standard tier would suggest, control blood pressure, and screen family members, since the trait is inherited.

CHAPTER 10

Inflammation and residual risk

Lipids initiate. Inflammation propagates. Both are measurable, and treating only one leaves risk on the table.

The chicken-and-egg framing — is atherosclerosis a lipid disease or an inflammatory disease? — has largely resolved. ApoB retention is the initiating event; the inflammatory cascade it provokes is what turns a retained particle into a growing, destabilizing lesion. Neither description is complete alone.

hsCRP as the practical marker

High-sensitivity C-reactive protein is the best-standardized inflammatory marker in routine use. It does not localize inflammation — an infection, arthritis, or recent injury will raise it — but persistent low-grade elevation, conventionally hsCRP at or above 2 mg/L, correlates with vascular inflammatory risk and future events.

The JUPITER trial made the point sharply by enrolling apparently healthy people with LDL-C below 130 mg/dL — below usual treatment thresholds — but hsCRP at or above 2 mg/L, and demonstrating benefit from statin therapy in that group. Later work went further: among patients already on statins with achieved LDL-C below 70 mg/dL, residual *inflammatory* risk predicted recurrent events more strongly than residual cholesterol risk.

THE TRIAD WORTH KNOWING

ApoB — how many atherogenic particles are circulating.

Lp(a) — whether an inherited, thrombotic particle subtype is stacked on top.

hsCRP — whether the vessel wall is actively inflamed.

These three stack. When all are elevated, risk runs well above what a standard lipid panel suggests — and standard panels measure none of them.

What lowers it

Lipid lowering itself reduces hsCRP, because removing the substrate quiets the response. Beyond that, weight loss — particularly visceral fat loss — smoking cessation, exercise, and dietary pattern all move it. Dedicated anti-inflammatory therapy targeting the IL-1-beta to IL-6 axis has demonstrated event reduction in trials, establishing inflammation as a treatable target in its own right rather than merely a marker, though such therapy is not part of routine prevention.

PART III

Knowing Your Numbers

Risk calculators estimate. Tests measure. This part covers which blood work to ask for, what the targets are and where they come from, what the imaging can and cannot see, and how to read a family history.

CHAPTER 11

The panel to ask for

A standard lipid panel was designed in an era of population risk estimation. Four additions turn it into a measurement of your actual biology.

Nothing here is exotic, expensive, or unavailable. Most of it is ordered routinely in preventive cardiology and simply is not ordered in general practice unless someone asks.

Test	What it tells you	How often
Standard lipid panel	Total cholesterol, LDL-C, HDL-C, triglycerides. The baseline everything else is read against.	Annually; more often when treatment is being adjusted
ApoB	Direct count of atherogenic particles. The single most informative addition, especially if triglycerides are high or LDL-C looks acceptable.	With each lipid panel where available
Lipoprotein(a)	Inherited, lifelong-stable particle subtype with added thrombotic risk.	Once in a lifetime is generally sufficient
hsCRP	Systemic and vascular inflammatory activity. Interpret only when well and free of recent infection or injury.	Periodically; repeat to confirm any elevation
Fasting glucose, HbA1c, fasting insulin	Insulin resistance — the state in which LDL-C most often understates particle burden.	Annually
Blood pressure	Independent driver of endothelial injury and plaque; also the cheapest thing on this list to measure.	Regularly, ideally at home as well as in clinic
Lipid panel in children of affected families	Screening for familial hypercholesterolemia, which is treatable and commonly missed.	See Chapter 14

IF YOUR CLINICIAN IS UNFAMILIAR WITH APOB

It is a standardized, inexpensive, directly measured immunoassay, endorsed as a treatment target or risk-refining measure by the National Lipid Association, the European Society of Cardiology and European Atherosclerosis Society, and — as a class 2a recommendation for intensification decisions — by the American College of Cardiology and American Heart Association. It does not require fasting.

CHAPTER 12

Targets, and which tier applies

Published targets vary by risk category and by guideline body. Here is what the major societies actually say — and the caveat that matters more than the numbers.

Risk tiers are clinical determinations. Broadly: **very high risk** means established cardiovascular disease, often with recurrent events or additional high-risk conditions; **high risk** covers primary prevention with major risk factors, familial hypercholesterolemia, diabetes with organ damage, or documented subclinical plaque; **moderate or intermediate** covers most everyone else with some elevation. Where you sit is not something to self-assign.

Risk tier	LDL-C goal	ApoB goal	Source
Very high risk / secondary prevention	Below 55 mg/dL	Below 65 mg/dL	ESC/EAS 2019
High risk	Below 70 mg/dL	Below 80 mg/dL	ESC/EAS 2019
Moderate risk	Below 100 mg/dL	Below 100 mg/dL	ESC/EAS 2019
Very high risk	Aligned with LDL-C below 55 mg/dL	~60 mg/dL	NLA 2024 consensus
High risk	—	~70 mg/dL (90 mg/dL borderline-intermediate)	NLA 2024 consensus
Threshold for intensifying therapy	At or above 70 mg/dL	130 mg/dL and above is a risk-enhancing factor	AHA/ACC 2018
Young adults, low-risk maintenance	—	Below ~75 mg/dL	Cumulative-exposure analyses

Published lipid goals by risk category. US and European frameworks differ in structure: European guidelines set explicit absolute goals, while the AHA/ACC framework works from thresholds for intensifying therapy.

READ THIS BEFORE USING THE TABLE ABOVE

These are population targets from guideline documents, not a prescription. Which tier applies to you depends on your history, your imaging, your family, and your other conditions. Bring the table to your clinician as a basis for a conversation about which row describes you — not as a number to pursue independently.

Targets for regression are lower than targets for prevention

The goals above are event-prevention goals. If the objective is documented plaque regression rather than event avoidance, the imaging literature points lower still: progression broadly halts below about 70 mg/dL, and measurable regression is most consistently reported at achieved LDL-C in the 30 to 40 mg/dL range. In one commonly cited framing of secondary prevention practice, the parallel ApoB goals would be below 80 mg/dL for high-risk primary prevention and below 90 mg/dL for standard primary prevention.

The other numbers

- **hsCRP.** Below 2 mg/L is the conventional dividing line for residual inflammatory risk.
- **Blood pressure.** Follow current guideline targets with your clinician; hypertension amplifies endothelial injury and accelerates everything in Part I.
- **Lp(a).** There is no target, because there is not yet an approved way to lower it. Its role is to shift how aggressively the modifiable numbers are pursued.
- **Triglycerides.** Above 200 mg/dL is a specific trigger for measuring ApoB, because discordance becomes likely.

CHAPTER 13

Imaging: seeing the disease directly

The shift from estimating risk to measuring disease is the most consequential change in preventive cardiology in a generation.

Risk calculators — Framingham, the Pooled Cohort Equations — estimate the probability that someone with your characteristics will have an event. They do not tell you whether *you* have plaque. Imaging does.

Coronary artery calcium

A non-contrast CT scan, quick and low-dose, producing an Agatston score. It measures calcified plaque only. A score above zero establishes that subclinical disease is present; higher scores stratify risk steeply.

The power of zero, and its limits

A calcium score of zero is one of the strongest negative risk markers in preventive cardiology, conferring low short-term event risk in appropriately selected asymptomatic people, and it is embedded in both AHA/ACC and ESC/EAS guidance as a decision aid. But the reassurance is conditional in three ways that the site's articles emphasize:

- **It sees only calcium.** CT angiography studies find detectable atherosclerosis in roughly 15 to 17 percent of low-to-intermediate-risk people with a zero calcium score, and non-calcified plaque in a smaller subset even in populations where the negative predictive value for obstructive disease remains very high.
- **It is age-dependent.** In a young person with high ApoB, zero more likely reflects biological latency than protection. In the MESA analysis of participants with LDL-C at or above 190 mg/dL, 37 percent had a calcium score of zero — younger age, female sex, and absence of diabetes predicted it.
- **It is short-term.** Events in people with zero calcium typically arise from rupture or erosion of non-calcified lesions, from systemic inflammation, or from microvascular dysfunction. Zero is a strong statement about the next several years, not about the next thirty.

CT angiography and AI-based quantification

Coronary CT angiography uses contrast to visualize the artery wall as well as the lumen, and it sees the soft, lipid-rich, non-calcified plaque that calcium scoring misses. Newer AI-driven quantitative analysis (AI-QCT) goes further, measuring plaque volumes by type — total, non-calcified, low-attenuation — and characterizing features associated with instability, including positive remodeling and perivascular inflammation.

The direction of travel in the field is toward individualized, disease-based assessment rather than population-based estimation. A large Swedish general-population imaging cohort of nearly 25,000 adults aged 50 to 64 without known cardiovascular disease was published in JAMA in late 2025 as a marker of that shift.

WHICH TEST, AND WHEN

Calcium score is inexpensive, widely available, and excellent for refining risk in intermediate-risk adults — particularly for deciding whether to start therapy.

CT angiography is the test that sees the wall, and is the more informative choice when the question is whether soft plaque is present despite a reassuring calcium score, or when someone is young with a strong risk profile.

Both involve radiation and, for CTA, contrast. Neither is appropriate for everyone. This is a decision to make with a clinician who knows your history.

Reading a calcium score under treatment

This is where patients most often get frightened unnecessarily. Because calcification is part of how plaque stabilizes, a calcium score can rise while treatment is working — the soft, dangerous compartment shrinking as the remaining lesion becomes denser and more stable. Athletes in particular show a pattern of higher calcium scores composed predominantly of stable calcified plaque rather than the rupture-prone mixed plaque more typical of sedentary people. A rising score is a reason to look at plaque composition, not to abandon therapy.

Other measures

- **Carotid ultrasound** can detect plaque and measure intima-media thickness in a different vascular bed, without radiation.
- **Exercise stress testing** detects ischemia — flow limitation — rather than plaque. It is a test of consequence, not of presence, and a normal result does not exclude substantial non-obstructive disease.
- **Invasive angiography** images the lumen with high resolution and remains the reference for obstructive disease, but as Chapter 1 explained, a normal-looking lumen can coexist with a diseased wall.

CHAPTER 14

Family history and genetics

Family history is one of the most informative risk signals available and one of the most crudely collected. It is also not destiny in either direction.

Most risk tools reduce family history to a checkbox. The information that matters is finer: *who* was affected, *what* happened, and *how early*. A father with a bypass at 45 and a grandfather with a stroke at 88 are not the same datum. Premature events in first-degree relatives — conventionally before 55 in men and 65 in women — carry the most weight.

Familial hypercholesterolemia

Heterozygous FH is common — far more common than most people assume — inherited, treatable, and badly underdiagnosed. A lifetime average LDL-C near 200 mg/dL crosses the cumulative exposure threshold around age 25, which is why untreated FH produces events decades early. Adults with LDL-C at or above 190 mg/dL warrant evaluation regardless of anything else on their panel.

Homozygous FH, in which both gene copies are affected, is ultra-rare and far more severe: untreated LDL-C above 400 to 500 mg/dL from birth, cumulative exposure reaching the threshold by roughly age 12, and — before modern therapy — myocardial infarction or sudden death in childhood. Current consensus advises suspecting HoFH in anyone with untreated LDL-C above 400 mg/dL, since genetically confirmed cases often fall below the historical 500 mg/dL definition. Chapter 31 covers this population in more detail.

> **IF FH RUNS IN YOUR FAMILY**
>
> Cascade screening — testing first-degree relatives of an affected person — is one of the highest-yield interventions in preventive medicine, and it includes children. Identifying a child with FH allows exposure to be controlled before decades of it accumulate.

The "good genes" question

Two mirror-image beliefs are both wrong, and the site addresses each directly.

The first is that a clean family history protects you from high lipids. It does not, or not much. Absent family history slightly modifies risk; it does not neutralize the causal effect of a high particle burden sustained for decades. Someone with LDL-C at or above 190 mg/dL and no affected relatives still has LDL-C at or above 190 mg/dL.

The second is that bad genes make effort pointless. Genome-wide association work has identified genuinely protective variants — a "super-resilient" vascular phenotype in some individuals — but resilience is partial, and the same body of genetic work is the strongest evidence that lowering ApoB lowers disease. Genetics sets the starting position, not the trajectory.

A family history is a statement about probability under the conditions your relatives lived in. It is not a statement about the conditions you choose.

CHAPTER 15

Talking to your doctor

The purpose of this handbook is not to make you your own physician. It is to let you walk into an appointment able to ask better questions.

Appointments are short. What follows is organized so that you can take one section rather than all of it, depending on where you are.

If you have never been assessed

- Can we measure ApoB in addition to a standard lipid panel?
- Can I have a one-time lipoprotein(a) measurement?
- Given my age and family history, is a coronary calcium score reasonable for me?
- What is my blood pressure trend, not just today's reading?
- Do my glucose, HbA1c, and triglycerides suggest insulin resistance?

If you have been told your cholesterol is "fine"

- Fine relative to what — a population reference range, or a target for my risk tier?
- What is my ApoB, and is it concordant with my LDL-C?
- If my triglycerides are elevated, could my particle count be higher than my LDL-C suggests?
- What would change your recommendation — a calcium score above zero? An elevated Lp(a)?

If you already have diagnosed disease

- What is my achieved LDL-C and ApoB, and which target are we aiming for?
- If I am not at target on my current therapy, what is the next step — ezetimibe, a PCSK9 inhibitor, something else?
- Is my hsCRP elevated despite treatment, and does that change anything?
- Is there a role for imaging to track plaque over time in my case?
- How does what I eat fit into this plan, specifically?

If you have been told to stop a medication because of side effects

- Is it worth trying a different statin, or a lower dose, before abandoning the class?
- Would a non-statin agent — ezetimibe, bempedoic acid, a PCSK9 inhibitor — be appropriate for me?
- Can we confirm whether the symptoms track with the drug by a structured rechallenge?

ONE THING NOT TO DO

Do not arrive with a printout and an argument. Arrive with questions and a willingness to be told that something does not apply to you. The clinicians who engage most readily with informed patients are the ones being asked, not told.

PART IV

Food

The diet debates look intractable from outside. They are far more tractable once you separate two different questions that get asked as if they were one.

CHAPTER 16

The two ladders

Which diet is best for the heart is not one question. It is two, and they have different answers.

Almost every unresolvable argument about nutrition and heart disease comes from conflating these:

1. **Which dietary pattern reduces cardiovascular events** in a broad population over years of follow-up?
2. **Which dietary pattern produces documented regression of existing coronary plaque** in people who already have significant disease?

These are different endpoints, tested in different populations, with different evidence bases and different amounts of it. A pattern can be excellent at the first and unproven at the second. The site frames this as two separate evidence ladders, and treating them as one is the source of most of the noise.

	Ladder 1: Event reduction	Ladder 2: Plaque regression
Question	Fewer heart attacks and deaths across a population	Measurable shrinkage of existing plaque on serial imaging
Typical evidence	Large cohorts and randomized outcome trials	Small randomized trials with serial angiography or imaging
Strongest performers	Mediterranean, plant-predominant, DASH, Portfolio patterns	Ultra-low-fat whole-food plant-based, generally alongside lipid-lowering drugs
Who it is for	Most people, most of the time	People with established disease seeking documented reversal
Certainty	Good, though methodologically imperfect	Thinner: fewer trials, smaller, older, and confounded by concurrent medication

The two-ladder framework: separating the evidence for reducing events from the evidence for reversing existing plaque.

THE FORK IN THE ROAD

For general prevention, a Mediterranean or plant-predominant pattern is well supported and sustainable. For someone with established coronary disease who wants documented regression, the ultra-low-fat whole-food plant-based protocol is the only dietary intervention with prospective angiographic evidence behind it — and even there, most participants were also on lipid-lowering medication.

One thing both ladders agree on

Whatever the pattern, the mechanism runs through ApoB. Diet is the largest modifiable lifelong determinant of particle exposure in most populations. Migration and cohort studies show lifetime incidence tracking lifelong exposure to ApoB-raising dietary patterns. A diet that does not lower your ApoB is not, whatever else it does, treating your atherosclerosis.

CHAPTER 17

The regression diet

What the ultra-low-fat whole-food plant-based protocol involves, what it has shown, and the limitations of that evidence.

The protocol is quantitative rather than qualitative: total fat below roughly 10 percent of calories, achieved by eliminating animal products and all added oils. That threshold is low enough that even nominally healthy high-fat plant foods — nuts, avocado, seeds — are restricted in the strictest versions.

The Lifestyle Heart Trial

The most direct randomized evidence comes from Ornish and colleagues. Patients with moderate-to-severe angiographically documented coronary disease were randomized to a program combining a diet below 10 percent fat with aerobic exercise, stress management, and smoking cessation, or to standard care.

Measure	Intensive lifestyle group	Standard care control
Diameter stenosis, baseline	40.7%	41.3%
Diameter stenosis, 1 year	38.5%	42.3%
Diameter stenosis, 5 years	37.3%	51.9%
Relative change over 5 years	7.9% regression	27.7% progression
Angina frequency	72% decrease	36% decrease
Risk ratio for any cardiac event	1.0 (reference)	2.47 (95% CI 1.48–4.20)

Lifestyle Heart Trial, five-year outcomes (Ornish D et al. JAMA 1998;280:2001-7). Figures from the sub-cohort with complete angiographic follow-up; the original 1990 Lancet report of the full cohort gives directionally consistent results.

Note what is and is not demonstrated here. The intervention was multi-component — diet, exercise, stress management, smoking cessation — so the dietary contribution cannot be cleanly isolated. The cohort was small. But the direction and magnitude, sustained over five years with a nearly two-and-a-half-fold event difference, are not easily explained away.

The Esselstyn cohort

The largest dataset for the no-oil version comes from Esselstyn’s 2014 observational study of 198 patients with significant disease, many of whom had already failed conventional treatment including repeated revascularization. Among the 177 who adhered over a mean of 3.7 years, one cardiovascular event occurred — an event rate of 0.6 percent. Among the 21 who did not adhere, 13 events occurred. Follow-up angiography documented reversal in 22 percent of adherent participants.

THE HONEST CAVEAT

Most patients in the Esselstyn cohort were also taking cholesterol-lowering medication, which makes it impossible to separate the dietary contribution from the pharmacological one. The study was observational, and adherent and non-adherent groups may differ in ways beyond diet. The size of the gap between them is striking; it is not the same as a randomized result.

The biochemical targets that go with it

The regression literature associates documented reversal with total serum cholesterol below about 150 mg/dL and LDL-C below roughly 70 to 85 mg/dL — in the Esselstyn framing, total cholesterol below 150 mg/dL and LDL-C below 80 mg/dL, with 73 percent of adherent patients showing reversal by angiographic and clinical assessment. These are difficult to reach through diet alone on any higher-fat pattern, which is much of why the regression and prevention ladders diverge.

Is it necessary? Is it sustainable?

Two fair objections. On necessity: for most people, no — a plant-predominant pattern that meaningfully lowers ApoB, combined with medication where indicated, will achieve target numbers without the strictest version. On sustainability: the protocol is demanding, and a diet followed for three months is worth less than a good diet followed for thirty years. Adherence is the variable that dominates every comparison in this chapter.

CHAPTER 18

The Mediterranean pattern, examined

Strong evidence for preventing events, thinner evidence for reversing plaque, and a headline trial with real methodological problems.

The Mediterranean pattern belongs to the qualitative paradigm: total fat can run 30 to 45 percent of calories provided saturated and trans fats are replaced by monounsaturated and polyunsaturated ones. It is palatable, culturally durable, and genuinely associated with fewer cardiovascular events.

What the trials actually tested

PREDIMED is the most-cited randomized trial supporting the pattern, reporting roughly a 30 percent reduction in major cardiovascular events in 7,447 high-risk participants. It also carries serious methodological problems that are often omitted when it is quoted: randomization failures affecting a substantial share of participants, early termination that likely inflated the effect estimate, and — most relevant to the debate in Chapter 16 — a control arm that never became low-fat, reaching 37 percent of calories from fat by study end. PREDIMED therefore shows that among two high-fat patterns the Mediterranean is better. It does not test it against a genuinely low-fat comparator.

The Lyon Diet Heart Study is methodologically cleaner and, in some ways, more impressive: a 73 percent reduction in cardiac death and non-fatal infarction over 27 months in post-infarction patients on an alpha-linolenic-acid-enriched Mediterranean pattern versus a standard post-infarction diet, stopped early for benefit. Its comparator, though, was a standard Western diet, not a whole-food plant-based one.

CORDIOPREV confirms Mediterranean superiority over a modestly low-fat comparator at around 28 to 30 percent fat. It does not test the below-10-percent threshold either.

> **WHAT THE MEDITERRANEAN EVIDENCE SUPPORTS**
>
> A robust case for primary prevention in the general population, and a good case for secondary prevention against a standard Western diet. What it has not demonstrated is angiographic plaque regression comparable to the ultra-low-fat protocol — because no trial has run that comparison.

Population evidence, in both directions

The North Karelia Project remains one of the most compelling population demonstrations of the substitution model. Systematically shifting a Finnish population from saturated dairy fat toward rapeseed oil and vegetables — butter on bread falling from over 90 percent of the population in 1972 to under 5 percent by 2012 — accompanied roughly an 84 percent reduction in coronary mortality among men aged 35 to 64 over four decades.

Two things can be true: replacing saturated fat with unsaturated fat produces enormous population benefit, and it is not the same intervention as removing nearly all fat in someone with established plaque.

CHAPTER 19

Fats and oils

Coconut oil, olive oil, seed oils, fish oil. Four arguments, four different answers, and one recurring pattern about who funds the evidence.

Coconut oil

The gap between marketing and evidence is wide here. Coconut oil is a concentrated source of saturated fat, and randomized trials and meta-analyses consistently show it raises LDL cholesterol relative to non-tropical unsaturated oils. The usual defense — that it also raises HDL — does not rescue it: HDL-raising interventions have repeatedly failed to reduce events in trials, and Mendelian randomization does not support raising HDL as causally protective. Claims about weight loss, thyroid function, and metabolic advantage are weakly supported, inconsistent, or borrowed from studies of purified MCT preparations that are not coconut oil.

Nor is dietary saturated fat physiologically necessary. The body synthesizes saturated fatty acids readily; the fats that are genuinely essential are unsaturated.

Olive oil

A more interesting case, because the answer is neither "health food" nor "no better than butter." The question the site poses is whether extra-virgin olive oil is *independently* cardioprotective — that is, whether the benefit is in the oil itself or in what it displaces. On the available data, the apparent benefit tracks the displacement of atherogenic animal fat rather than any intrinsic property of the olive oil lipid backbone. The evidence base is also unusually dependent on industry funding, including olive oil and nut industry involvement in the headline trials, which is a reason for care rather than dismissal.

> **THE DISPLACEMENT PRINCIPLE**
>
> Much of nutrition science is about substitution, not addition. "Is olive oil good for you" is an incomplete question. Good compared to butter — clearly. Good compared to the whole olives, or to no added oil at all, in someone chasing an ultra-low-fat threshold — that is a different and much less settled comparison.

Seed oils

The claim that omega-6-rich industrial seed oils drive inflammation and cardiovascular disease has become widespread. It is not well supported. Increasing dietary linoleic acid does not reliably raise tissue arachidonic acid in adults eating Western diets, and systematic reviews of randomized trials do not show linoleic acid raising inflammatory markers in healthy people. The historical evidence cited against seed oils — recovered data from the Minnesota Coronary Experiment and the Sydney Diet Heart Study — is genuinely complicating and deserves to be taken seriously, but it does not overturn the broader body of trial and mechanistic evidence. Repeatedly heated frying oil is a separate issue from the oils themselves.

Fish oil, and the important distinction

"Fish oil" is not one thing, and treating it as one thing explains most of the confusion. Over-the-counter omega-3 supplements — mixed EPA and DHA preparations — have repeatedly failed to reduce major cardiovascular

events in randomized trials. Purified prescription icosapent ethyl, which is EPA alone at high dose, is a different agent, and REDUCE-IT provided strong randomized evidence of reduction in major ischemic events in the population it studied, with supporting imaging data from EVAPORATE.

BEFORE YOU TAKE OMEGA-3 FOR YOUR HEART

The trial evidence supports a specific prescription drug in specific patients, not the capsules on a supermarket shelf. Omega-3 therapy at these doses also carries a real, dose-dependent increase in atrial fibrillation risk, which has to be part of the decision. This is a prescribing conversation, not a supplement choice.

CHAPTER 20

Animal foods, the gut, and TMAO

A mechanism that connects red meat to arterial disease through gut bacteria — and an honest account of how strong that evidence is.

Dietary precursors in animal foods — choline, phosphatidylcholine, carnitine — are metabolized by gut bacteria into trimethylamine, which the liver converts to trimethylamine N-oxide, or TMAO. Elevated TMAO has been associated with cardiovascular events across multiple meta-analyses, and mechanistic work links it to foam cell formation, platelet reactivity, and impaired reverse cholesterol transport.

Whether TMAO is *causal* or a marker of the dietary pattern and metabolic state that produce it is genuinely unsettled. The site's review of this literature is notable for an unusual reason: it carries an editorial note documenting that an earlier version had opened with a striking statistic that could not be located in any published meta-analysis, traced back to a commercial testing website, and had to be replaced with verified figures from the three principal meta-analyses. That is worth mentioning because the TMAO field is commercially active and the citation chain is not always trustworthy.

The Neu5Gc pathway

A second, independent mechanism links red meat to arterial inflammation. Humans lost the ability to synthesize the sialic acid Neu5Gc, but we absorb it from red meat and incorporate it into our own tissues, where circulating anti-Neu5Gc antibodies can then react against it — a chronic, low-grade autoimmune-like inflammatory stimulus in the vessel wall. It is a plausible and well-argued mechanism; it is not yet demonstrated to drive events in humans.

> **HOW TO WEIGH MECHANISMS LIKE THESE**
>
> Both TMAO and Neu5Gc are reasons to be interested in reducing red meat. Neither is the main reason. The main reason remains that dietary patterns high in animal fat raise ApoB, and ApoB causes atherosclerosis by a pathway that is far better established than either of these.

Not all plant-based diets are equal

A large French cohort — over 63,000 adults followed for a mean of nine years — found that the *type* of plant-based diet matters substantially. Plant-based eating built on refined grains, sugar, and ultra-processed meat analogues does not deliver the benefit of one built on whole foods. Removing animal products is not the same intervention as eating well.

CHAPTER 21

Alcohol

The most durable piece of good news in cardiology has been steadily dismantled over the past decade.

For decades, observational data showed a J-shaped or U-shaped curve: light-to-moderate drinkers appeared to have lower coronary heart disease and ischemic stroke risk than both abstainers and heavy drinkers. The mechanism stories were plausible — HDL, platelet effects, polyphenols in red wine — and the finding was enormously popular.

Two developments have undermined it. First, better adjustment for confounding: the abstainer reference group in these studies has always been contaminated by former drinkers who quit because they were ill, which biases the comparison in favor of moderate drinking. Second, Mendelian randomization — using genetic variants that influence alcohol consumption to approximate randomization — largely fails to reproduce the protective effect, and in several analyses shows a monotonic relationship in which less is better.

Meanwhile the harms are not in doubt: dose-dependent hypertension, atrial fibrillation risk that begins at modest intake, alcoholic cardiomyopathy at higher intake, and cancer risk that has no identified safe threshold. The 2025 American Heart Association scientific statement on alcohol and cardiovascular disease reflects this changed picture.

THE PRACTICAL SUMMARY

There is no established cardiovascular reason to start drinking, and the case for continuing on cardiac grounds has substantially weakened. If you drink, less is better. The specific beverage matters far less than the amount.

CHAPTER 22

Protein, and a paradox about age

The optimal protein intake for cardiovascular and metabolic health appears to change direction somewhere in the seventh decade.

The protein debate is unusually confusing because two strong bodies of evidence point opposite ways, and both are largely right — for different people.

In midlife, high intake of animal protein is associated with worse metabolic and mortality outcomes, mediated partly through mTOR signaling, IGF-1, and reduced autophagy — the same anabolic pathways implicated in aging biology. Chronic over-activation of mTORC1 shows up across model organisms as a contributor to functional decline rather than a neutral correlate.

After roughly age 65, the calculus shifts. Sarcopenia — progressive loss of muscle mass and function — becomes a dominant threat to independence, mobility, and survival. Anabolic resistance means older adults extract less muscle protein synthesis from the same protein dose. The intake that minimized risk at 45 can contribute to frailty at 75.

> **THE PARADOX, STATED PLAINLY**
>
> What may kill you younger than 65 can help keep you alive over 65. Protein restriction and protein sufficiency are both defensible positions; which one applies depends heavily on age, muscle mass, activity level, and kidney function. This is a genuinely individual decision and a good one to make with a clinician or dietitian rather than from a rule.

Source still matters

Across the age range, the source of protein carries independent weight. Plant protein sources come without the ApoB-raising saturated fat load, without dietary cholesterol, without the TMAO precursors of Chapter 20, and with fiber. Where higher protein intake is warranted in later life, the same reasoning that governs the rest of this part still favors plant-dominant sources — a pattern that longevity cohort research broadly supports, with attention to vitamin B12, vitamin D, iron, and omega-3 adequacy.

PART V

Movement

Exercise is one of the most powerful interventions available and one of the most misunderstood. It does not do what most people think it does to plaque — what it does instead is arguably more useful.

CHAPTER 23

What exercise does to arteries

It does not scrub plaque out. It changes the plaque that is there, and it changes the vessel around it.

Regular exercise generates pulsatile laminar shear stress across the endothelium. That mechanical signal increases endothelial nitric oxide synthase activity and nitric oxide bioavailability, and activates anti-atherogenic transcription programs including KLF2 signaling, while pushing macrophages toward anti-inflammatory phenotypes. The vessel becomes a less hospitable place for particle retention.

The stabilization effect

What exercise does to existing plaque is best described as compositional rather than volumetric. Plaque characterization studies show that older endurance athletes carry a predominance of calcified, stable plaque, in contrast to the rupture-prone mixed plaque more typical of sedentary people with similar burden. The site's headline for this — that exercise turns plaque to stone rather than erasing it — is blunt but accurate.

Direct volume reduction has been observed under intensive protocols: in the CENIT trial, six months of supervised high-intensity interval training reduced total atheroma volume in stable coronary artery disease. But the reliable, reproducible contribution of exercise is stabilization plus everything it does to the rest of the risk profile — blood pressure, insulin sensitivity, visceral fat, inflammation, and cardiorespiratory fitness itself.

Deconditioning masquerading as aging

Much of what is attributed to cardiovascular aging is disuse. The Dallas Bed Rest and Training Study, following participants across three decades, found that 20 days of total bed rest in healthy 20-year-old men produced a fall in cardiovascular capacity more severe than 30 years of natural aging in the same individuals. The heart shrinks and stiffens primarily because of reduced loading, not the passage of time.

> **AORTIC AGE**
>
> Using the Modelflow method developed in Benjamin Levine's laboratory, sedentary seniors have aortic ages matching their chronological age, while competitive masters athletes who have trained vigorously for more than 25 years have aortas biologically 25 to 30 years younger. Arterial stiffening is not simply a clock.

CHAPTER 24

The dose

Frequency, intensity, and the window in which the heart is most plastic.

Levine's work quantifies a dose-response relationship that varies by vessel size, which is unusual and useful:

Vessel	Dose associated with preserved compliance	Comment
Large central arteries (aorta)	Committed exercise 4–5 sessions per week, sustained over decades	The compartment that matters most for heart failure risk, and the hardest to maintain
Middle-sized arteries (carotid)	Moderate exercise 2–3 sessions weekly	A more accessible dose still minimizes stiffening
Small peripheral arteries	Limited structural benefit demonstrated	Benefits here are largely functional rather than structural

Dose-response of lifelong exercise on arterial stiffness by vessel size, from the Levine laboratory.

The middle-age window

There appears to be a period during which the heart remains plastic enough to be meaningfully remodeled. In adults aged 45 to 64, a two-year structured program improved VO2max by roughly 18 percent and increased left ventricular compliance by about 25 percent. Similar interventions started after 65 show diminished reversibility. The Norwegian 4x4 interval session — four intervals of four minutes at high intensity, with active recovery between — is a central component of the protocol.

> **THIS IS NOT A REASON FOR ANYONE OVER 65 TO STOP**
>
> Diminished reversibility of ventricular compliance is not the same as diminished benefit. Fitness, blood pressure, insulin sensitivity, muscle mass, and mortality all respond to training at every age. The window applies to one specific structural adaptation, not to the value of exercise.

Resistance training is not optional

Cardiovascular prevention has historically been prescribed as aerobic exercise. The cohort data do not support treating resistance training as a supplement. In a pooled analysis of 117,025 women from the Nurses' Health Study cohorts, at least two hours of resistance training per week was associated with roughly 20 percent lower risk of incident major cardiovascular disease compared with none. Combining three behaviors — at least 15 MET-hours per week of aerobic activity, roughly equivalent to 150 minutes of moderate-to-vigorous exercise; at least one hour per week of resistance training; and under two hours per day of sedentary television viewing — performed better than any single one.

Is there an upper limit?

Risk reduction for all-cause and cardiovascular mortality is maximized at roughly 150 minutes per week of vigorous physical activity. Beyond that, benefits plateau and may follow a slight reverse-J. Very high lifetime

endurance volumes carry specific considerations — atrial fibrillation risk in particular, and the coronary calcium findings of the next chapter — but the population-level message is that the large gains come early. Going from nothing to something matters far more than going from a lot to more.

> *The steepest part of the benefit curve is between zero and modest. Almost nobody is failing to prevent heart disease because they trained 5 hours a week instead of 8.*

CHAPTER 25

The athlete’s paradox

Lifelong endurance athletes often have more coronary calcium than sedentary controls — and still live longer. Both halves of that sentence are true.

Picture two men in their mid-fifties in the same clinic on the same day. One has barely exercised in a decade. The other has run more than 40 marathons and still logs 60 miles a week. Both have identical coronary calcium scores that their cardiologist flags as concerning. The first man is at greater risk — and understanding why is the key to this entire chapter.

Why athletes accumulate calcium

Several explanations are on the table and they are not mutually exclusive: mechanical shear and wall stress from decades of high cardiac output; transient inflammatory and oxidative stress from repeated intense efforts; possibly altered coronary microenvironment facilitating particle entry and retention. The site’s mechanistic hypothesis frames it in cumulative-ApoB terms — decades of very high coronary flow may alter the conditions of subendothelial entry and retention.

In one athlete cohort, 11 percent had calcium scores above 300 Agatston units. What distinguishes them is composition: the plaque is predominantly calcified and stable, not lipid-rich and rupture-prone.

> **HOW TO READ A HIGH CALCIUM SCORE IN A TRAINED PERSON**
>
> A high score in an athlete carries different prognostic weight than the same score in a sedentary person, because the plaque is compositionally different and everything else about the risk profile differs. It is a reason for CT angiography to characterize the plaque and for aggressive attention to ApoB — not a reason to stop training, and not a reason to dismiss the finding.

The masking problem again

Chapter 4 covered why fitness hides disease: exercise-induced hypoalgesia, collateral circulation, and vast physiological reserve. This is where those converge with the calcium findings into a specific risk — a population with more detectable subclinical disease and fewer detectable symptoms. Silent ischemia and unrecognized infarction are documented contributors to longitudinal performance decline in masters athletes, which is why an unexplained drop in performance deserves a cardiac workup.

The aorta, and atrial fibrillation

Two further athlete-specific considerations. Aortic dilation in trained athletes exists on a spectrum from physiological adaptation to genuine aortopathy, and distinguishing them matters enormously because the consequences of missing an aneurysm are catastrophic. And endurance training is a dose-dependent risk factor for atrial arrhythmias; for a masters athlete who has already been treated for atrial fibrillation by ablation or medication, continuing high-volume intense training carries a substantial probability of recurrence, and training modification rather than training continuation is the evidence-supported response.

PART VI

Medication

What the drugs do, how they differ mechanistically, what the trials showed, and how to think about side effects without abandoning effective therapy on weak grounds.

CHAPTER 26

The lipid-lowering toolkit

Five mechanisms, deployed in sequence. What matters is not which drug you are on but how far your ApoB has come down.

The armamentarium has expanded well beyond statins, which matters because it means that being unable to tolerate one class is no longer a reason to abandon lipid lowering.

Class	Mechanism	Notes
Statins	Inhibit HMG-CoA reductase, upregulating hepatic LDL receptors	The most extensively validated class. High-intensity statin is the usual first step.
Ezetimibe	Inhibits NPC1L1, blocking intestinal cholesterol absorption	Oral, well tolerated, additive to statin. IMPROVE-IT and imaging trials support incremental benefit.
Bempedoic acid	Inhibits ATP-citrate lyase, upstream of HMG-CoA reductase	Activated in liver rather than muscle, which is the rationale for use in statin-intolerant patients.
PCSK9 inhibitors (monoclonal antibodies)	Block PCSK9, preventing degradation of LDL receptors	Injectable every 2–4 weeks. Reductions exceeding 60 percent, reaching very low LDL-C. FOURIER and ODYSSEY OUTCOMES established event reduction.
Inclisiran	Small interfering RNA silencing hepatic PCSK9 production	Twice-yearly dosing after loading — the shift from daily pills to biannual injections.
Other targets	ANGPTL3 inhibition, CETP inhibition, oral PCSK9 inhibitors, gene-based approaches	An active pipeline moving toward durable, infrequent, or one-time therapy.

Sequential escalation

The practical approach described in the literature is stepwise: high-intensity statin first; add ezetimibe if not at target; add a PCSK9 inhibitor — or inclisiran for dosing convenience — if still not at target; consider bempedoic acid in statin-intolerant patients. The endpoint is the achieved number, not the number of drugs.

> **THE MOST COMMON FAILURE MODE**
>
> It is not intolerance. It is stopping at "controlled." A patient with an LDL-C of 95 mg/dL on a statin is technically below 100 and may be well above what their risk tier demands. The magnitude of additional benefit from escalating beyond statin monotherapy is routinely underestimated.

How low, revisited

The imaging trials that document regression — ASTEROID, GLAGOV, PACMAN-AMI, EVAPORATE, the PARADIGM registry — consistently show progression halting below about 70 mg/dL and measurable regression

in a majority of treated subjects at 30 to 40 mg/dL. In secondary prevention, targets in that range are sometimes treated as aspirational when the evidence supports treating them as operational.

CHAPTER 27

Statin side effects, honestly

Muscle symptoms are real, common as a complaint, much less common as a drug effect, and the difference matters because the alternative to a tolerable statin is often no therapy at all.

Two things are true at once and the debate usually insists on only one. Statins can cause genuine muscle toxicity through identified cellular mechanisms, and pharmacogenomic variation — notably in SLCO1B1, which governs hepatic uptake — modifies individual susceptibility. Rhabdomyolysis, though rare, is real.

And: blinded randomized and n-of-1 rechallenge studies consistently find that most reported muscle symptoms occur at similar rates on placebo — the nocebo effect. Expectation of harm produces the symptom. This is not an accusation that patients are imagining things; nocebo symptoms are experienced exactly as real symptoms are. It is an observation about attribution.

WHAT TO DO ABOUT IT

The productive response is neither "push through it" nor "stop the class." It is a structured conversation with your prescriber about:

- Trying a different statin — tolerance is often molecule-specific
- Lowering the dose or reducing dosing frequency
- A formal rechallenge to establish whether symptoms actually track the drug
- Switching to a non-statin agent — ezetimibe, bempedoic acid, a PCSK9 inhibitor — if statins genuinely are not workable

It is worth naming the specific case that founded this platform, because it cuts both ways. Megdal experienced muscle pain on statins severe enough to degrade cycling performance, and moved to evolocumab, a PCSK9 inhibitor, reaching an LDL-C of 40 mg/dL. The lesson is not that statins are bad. It is that intolerance to one agent is a reason to change agents, not to accept untreated risk.

CHAPTER 28

Aspirin

The benefit-risk balance differs fundamentally between people who already have cardiovascular disease and people who do not.

This is the chapter where acting on general information is most likely to cause direct harm, because aspirin's risk is bleeding and bleeding is immediate.

Setting	What the evidence supports
Secondary prevention — established cardiovascular disease	The benefit-risk balance generally favors aspirin. This is well-established territory and not usually controversial.
Primary prevention — no established disease	Much narrower. US Preventive Services Task Force guidance recommends an individualized decision only for adults aged 40–59 with a 10-year cardiovascular risk of 10 percent or higher who are not at increased bleeding risk, and recommends against initiating aspirin in adults aged 60 or older.

Coronary calcium scoring has been studied as a way to personalize the primary prevention decision, identifying subgroups in whom the ischemic benefit is more likely to exceed the bleeding cost. Body weight and dose also interact in ways that individual-patient-data analyses have explored.

TWO RULES

If you are on aspirin for established cardiovascular disease, **do not stop it on your own**. Stopping antiplatelet therapy after an event or a stent can be dangerous.

If you are taking daily aspirin for prevention without established disease and have never discussed it with a clinician, that conversation is worth having — guidance has changed substantially, and many people are taking it on the basis of advice from an earlier era.

CHAPTER 29

The metabolic drugs

GLP-1 receptor agonists were approved for diabetes, then for obesity. Their cardiovascular effects appear to run partly independent of both.

Placebo-controlled outcome trials of GLP-1 receptor agonists — LEADER, SUSTAIN-6, REWIND, and SOUL in type 2 diabetes, and SELECT in obesity without diabetes — have demonstrated reductions in major adverse cardiovascular events in the range of roughly 12 to 26 percent, with SELECT reporting about 20 percent.

What makes this interesting mechanistically is that benefit appears to begin before substantial weight loss accrues, which points to direct vascular and anti-inflammatory effects rather than weight reduction alone. Imaging work using PET has shown reduced coronary artery inflammation under GLP-1 therapy. There are parallel signals in heart failure with preserved ejection fraction and in chronic kidney disease.

WHERE THIS FITS

These are not lipid drugs and they do not replace lipid lowering. They act on a different and complementary part of the risk picture — the insulin-resistant, visceral-adipose, inflammatory phenotype in which, as Chapter 8 explained, LDL-C most often understates particle burden. In the right patient they address both a metabolic problem and a vascular one.

Visceral fat as the target

The reason this phenotype matters is anatomical. Visceral adipose tissue drains directly into the portal circulation, activates glucocorticoids locally, and behaves as an endocrine organ secreting inflammatory mediators — which is why it carries disproportionate cardiometabolic risk relative to total body fat. Waist circumference is a cruder measure than imaging but a far better one than weight alone.

CHAPTER 30

Stents, bypass, and treating the biology

Revascularization treats a blockage. It does not treat the disease that produced the blockage.

For acute coronary syndromes, revascularization is life-saving and not in dispute. The question that has shifted over two decades of randomized trials is what to do in **stable** coronary disease — and there, the evidence has reframed management away from a reflexively interventional model toward one in which guideline-directed medical therapy and intensive lifestyle modification are central.

The logic is straightforward once Chapter 1 is in place. A stent opens the lumen at one location. The disease is distributed across the arterial tree, and most future events arise from lesions that are not currently flow-limiting — precisely the lesions no one is stenting. Systemic therapy that lowers ApoB and quiets inflammation acts everywhere at once, including on the lesions that have not declared themselves.

> *Treating the pipes addresses the symptom of a plumbing problem. Treating the biology addresses the reason the pipes keep failing.*

AN IMPORTANT BOUNDARY

This is a statement about *stable* coronary disease and about how the field weighs upfront revascularization against optimal medical therapy. It is not advice to decline a recommended procedure. Symptom relief is a legitimate indication, anatomy varies, and the decision belongs with your cardiologist. The point is that a stent is not a cure and does not reduce the need for everything else in this handbook.

PART VII

Special Situations

The general framework holds. But inherited lipid disorders, the menopausal transition, testosterone therapy, insulin resistance, and advanced age each change what the framework implies in practice.

CHAPTER 31

Inherited cholesterol: FH and HoFH

The clearest natural experiment in cardiovascular medicine, and the population where early detection changes the most.

Familial hypercholesterolemia is the cumulative-exposure model made visible. In heterozygous FH, one defective gene copy raises LDL-C from birth; a lifetime average near 200 mg/dL crosses the cumulative exposure threshold around age 25, roughly two decades earlier than someone at 125 mg/dL. That single fact explains the premature disease that defines the condition, and it explains why treatment started in the twenties is worth so much more than treatment started at fifty.

Homozygous FH

The homozygous form is the extreme edge of the same biology, and it is genuinely severe. Near-complete inability to clear LDL from circulation produces untreated LDL-C historically defined as above 500 mg/dL, though current European Atherosclerosis Society consensus advises suspecting HoFH above 400 mg/dL because many genetically confirmed cases fall below the older cutoff. Cumulative exposure reaches the threshold at which disease becomes clinically manifest by roughly age 12. Children with the most severe null-receptor mutations have historically experienced myocardial infarction or sudden cardiac death before the age of ten.

> **WHY "DO BABIES NEED STATINS" IS NOT A RHETORICAL QUESTION**
>
> It sounds absurd until you hold the exposure model in mind. If atherosclerosis is driven by particle-years and begins accumulating from the first decade, then for a child with a severe inherited disorder, waiting until adulthood to intervene means allowing the damage the treatment is meant to prevent. Pediatric lipid management in FH is established practice, not a fringe position — and it is a specialist decision, not a general one.

For adults

- LDL-C at or above 190 mg/dL warrants evaluation for FH regardless of family history.
- Absent family history does not rule it out and does not neutralize the risk.
- Cascade screening of first-degree relatives is among the highest-yield interventions in preventive medicine.
- Modern combination therapy — statin plus ezetimibe plus a PCSK9 inhibitor, with newer agents for the most severe forms — can achieve reductions that were impossible a generation ago.

CHAPTER 32

Women, menopause, and hormone therapy

The menopausal transition is a cardiovascular event as much as a reproductive one, and the hormone therapy question is more nuanced than either of its popular answers.

Menopause is a neuroendocrine reconfiguration, not simply the end of reproductive function. Estradiol acts as a coordinator of cerebral and vascular bioenergetics, and its decline coincides with measurable shifts in lipid profile, visceral fat distribution, insulin sensitivity, vascular reactivity, and inflammatory tone. Risk that appeared low in the premenopausal years does not so much appear as become visible.

Why the hormone therapy literature is confusing

The reputation of menopausal hormone therapy was shaped almost entirely by trials of one oral regimen — conjugated equine estrogens plus medroxyprogesterone acetate — given largely to women a decade or more past menopause. That is a specific drug combination, a specific route of administration, and a specific timing. Generalizing from it to all hormone therapy at all times was an error that took years to correct.

When the lens shifts to early initiation and to transdermal 17-beta-estradiol with micronized progesterone, the signal points differently. The DOPS randomized trial, the Women's Health Initiative estrogen-alone subgroup aged 50 to 59, meta-analyses of early initiators, and randomized carotid imaging data from ELITE all point toward a more favorable cardiovascular profile when therapy begins near menopause.

> **THE HONEST STATE OF THE EVIDENCE**
>
> Transdermal estradiol with micronized progesterone, started near menopause, has a more favorable cardiovascular risk profile than the oral regimen that shaped the field's reputation. But hard-outcome evidence remains limited, the timing hypothesis is not fully proven, and hormone therapy is prescribed for symptom relief and bone health with cardiovascular effects as a consideration — not as a cardiovascular preventive. This is a discussion with a clinician who knows your full history, including breast and clotting risk.

What does not change

The framework in Parts II and III applies identically. ApoB causes atherosclerosis in women as in men. Women are more likely than men to have a coronary calcium score of zero at a given age, which makes the limitations of calcium scoring in Chapter 13 especially relevant, and women are over-represented among MINOCA presentations. Underdiagnosis in women is a documented and persistent problem; knowing your ApoB, your Lp(a), and your imaging status is a partial defense against it.

CHAPTER 33

Men and testosterone

Total testosterone is a routinely misleading measurement, and testosterone therapy is a cardiovascular decision as well as a hormonal one.

Most circulating testosterone is bound to plasma proteins of widely differing affinity, with sex hormone-binding globulin acting as the principal regulator of how much hormone actually reaches tissue. A total testosterone value can therefore look reassuring while bioavailable testosterone is low, or look low while bioavailable levels are adequate. SHBG itself varies with age, obesity, insulin resistance, thyroid status, and liver function.

THE MEASUREMENT POINT

If testosterone status is being assessed, bioavailable or free testosterone alongside SHBG is substantially more informative than total testosterone alone. Interpreting a total value in isolation is the most common error in this area.

On the cardiovascular side, therapy interacts with lipids, hematocrit, blood pressure, and sleep-disordered breathing, and the appropriate framing is individualized restorative therapy under supervision rather than either blanket enthusiasm or blanket avoidance. As with every other agent in this handbook, the ApoB question does not go away because a hormone question has been added.

CHAPTER 34

Insulin resistance, diabetes, and visceral fat

The phenotype in which standard lipid testing is least reliable and standard risk estimation most often fails.

Everything in this chapter follows from one fact established in Chapter 8: in insulin-resistant states, LDL particles become small and cholesterol-depleted, and triglyceride-rich remnants proliferate. Particle count runs high while LDL cholesterol looks acceptable. This is the population in which measuring ApoB changes management most often.

Why visceral fat specifically

White adipose tissue is an endocrine organ, and where it sits determines what it does. Visceral adipose tissue drains directly into the portal circulation, delivering free fatty acids and inflammatory mediators straight to the liver; it has enhanced local glucocorticoid activation; and it secretes a more inflammatory profile of adipokines than subcutaneous fat. This is why waist circumference and visceral adiposity predict cardiometabolic risk better than body weight or BMI.

THE PRACTICAL PANEL FOR THIS PHENOTYPE

- ApoB, not LDL-C alone — discordance is the rule here, not the exception
- Triglycerides above 200 mg/dL is itself a trigger to measure ApoB
- HbA1c and fasting insulin alongside fasting glucose
- hsCRP, because inflammatory burden runs high in this state
- Waist circumference, tracked over time

On treatment, this is where the metabolic drugs of Chapter 29 and the dietary patterns of Part IV do double duty — improving insulin sensitivity and visceral adiposity while lowering particle burden and inflammation. It is also where resistance training earns particular attention, given its effects on glucose disposal and lean mass.

CHAPTER 35

Aging well

After roughly 65, the objective shifts from minimizing a single risk to balancing several that pull in opposite directions.

The tensions are real. Protein restriction that looks protective in midlife contributes to sarcopenia later. Aggressive training loads that build fitness also carry arrhythmia risk in aged atria. Weight loss that improves metabolic markers can cost muscle mass that predicts survival. Chapter 22 covered the protein version of this; the principle generalizes.

VO2max as the through-line

Cardiorespiratory fitness is among the strongest available predictors of all-cause and cardiovascular mortality, and it is modifiable at every age. It also declines far more slowly in trained masters athletes than in sedentary peers, which makes it a useful longitudinal marker for exactly the reason Chapter 4 described: an unexplained deviation from your own trajectory is informative in a way that a population reference range is not.

The anabolic pathways

The longevity literature on mTOR describes it as a metabolic switchboard integrating energy status, growth factors, and amino acid availability, coordinating protein synthesis against autophagy. Chronic over-activation of mTORC1 is associated with functional decline across model organisms; suppressed anabolic signaling, though, is precisely what drives sarcopenia. The interesting question in later life is not how to minimize the pathway but how to cycle it — periods of anabolic stimulus from resistance training and adequate protein, against periods of autophagic clearance.

WHAT IS WELL ESTABLISHED VERSUS WHAT IS PROMISING

Established: cardiorespiratory fitness, muscle mass, blood pressure control, and ApoB exposure all matter for how the next decades go.

Promising but unsettled: most of the specific anti-aging molecular interventions. The mechanistic work is genuinely interesting; the human outcome data are not there yet. Treat this field with interest and skepticism in equal measure.

CHAPTER 36

Beyond the heart

The same particles, in different vascular beds, producing different diseases.

If atherosclerosis is a systemic response to retained ApoB particles, there is no reason it should stop at the coronary arteries — and it does not. Elevated ApoB relates to disease across vascular, metabolic, hepatic, renal, and neurologic territory, with the strength of evidence varying considerably by endpoint.

Endpoint	Strength of the ApoB link
Coronary artery disease	Causal, established by mechanism, genetics, and randomized trials
Ischemic stroke	Causal and outcome-proven
Peripheral arterial disease	Causal and outcome-proven
Chronic kidney disease	Associated; contributory in a shared vascular pathway
Alzheimer's disease and vascular cognitive impairment	Plausible and increasingly supported, but contested

The Alzheimer's question

The dominant framework defines Alzheimer's biologically by amyloid and tau, treating vascular pathology as a frequent but secondary modifier. An alternative reading — argued at length in the site's library — holds that lifelong ApoB exposure is a causal upstream driver of the cerebrovascular and small-vessel injury that in a substantial subset of patients precedes and accelerates Alzheimer's-defining pathology.

This should be held as a serious hypothesis rather than a settled finding. What can be said with more confidence is the negative version: the concern that driving LDL-C very low harms cognition has been examined in genetic and trial evidence and has not been supported. If anything, the genetic evidence on PCSK9 and lifelong low lipid exposure points the other way.

> *The strongest reading of the evidence is not that lowering ApoB is a treatment for dementia. It is that the vascular contribution to cognitive decline is larger than the neurocentric model allows — and that contribution is modifiable.*

PART VIII

Putting It Together

The synthesis: one documented case, a twelve-month sequence, a tracking sheet, and a set of common claims answered briefly.

CHAPTER 37

One case, three pillars

What Peter Megdal, PhD, actually did, what was measured, and what a single case can and cannot establish.

This handbook exists because of one person's diagnosis, and the case is worth setting out plainly — including its limits as evidence.

The diagnosis

A competitive cyclist of forty years noticed an abrupt 14 percent reduction in 20-minute maximal power output with no explanation. His coach attributed it to aging. He trained harder for four years with no recovery. In 2014, at 55, a maximal exercise stress test at Massachusetts General Hospital showed ST-segment depression at 90 percent of VO2max. The angiogram that followed found five significant lesions, including obstructive disease that could not be stented or bypassed given its location. There had been no prior cardiac symptoms.

The response

With no surgical option, he spent months in the medical literature — the work of Ornish, Esselstyn, and Campbell forming the dietary foundation — and assembled a three-part protocol.

Pillar	What it consisted of	Rationale
Diet	Whole-food plant-based: all animal products and added oils eliminated. Approximately 12 percent of calories from fat, 75 percent carbohydrate, 13 percent protein, no dietary cholesterol.	The ultra-low-fat protocol of Chapter 17, targeting the lowest achievable particle burden through diet.
Lipid therapy	Statins caused intolerable muscle pain and degraded cycling performance. He moved to evolocumab, a PCSK9 inhibitor.	Chapter 27: intolerance to one agent is a reason to change agents, not to accept untreated risk.
Training	Elite-level endurance training maintained throughout, with VO2max and 20-minute maximal power measured serially under the same protocol.	Endothelial function and plaque stabilization per Part V — and objective, repeatable measurement.

What was measured

- Total cholesterol fell from 200 to 150 mg/dL, and LDL-C from 140 to 100 mg/dL, on diet alone before any medication.
- LDL-C ultimately reached 40 mg/dL on the PCSK9 inhibitor.
- VO2max rose by approximately 20 percent over three years, from about 56 to 65 mL/kg/min.
- Follow-up exercise stress testing showed no detectable cardiac ischemia, where it had been present on all prior tests.
- Serial angiograms from 2014 to 2018 documented objective changes in lumen diameter and plaque burden.

- Athletic trajectory moved from state-ranked to a fourth-place finish at the Masters World Track Championships, and subsequently to national and world hour-record performances — the current world record set at age 65, more than a decade after diagnosis.

WHAT ONE CASE ESTABLISHES, AND WHAT IT DOES NOT

This is a documented, peer-reviewed case report with serial angiography, stress testing, lipid panels, and VO2max data — far better evidenced than a testimonial. It is still one person, with a multi-component intervention, no control, and no way to apportion the result between diet, drug, and training. It demonstrates that this outcome is *possible*. The trial evidence in Chapters 5, 17, and 25 is what establishes that it is not a fluke.

CHAPTER 38

Your first twelve months

A sequence rather than a prescription. Every clinical step below belongs in a conversation with your own clinician.

Months 1–2: Measure

- Book an appointment specifically to discuss cardiovascular risk, not as an add-on to something else.
- Ask for the panel in Chapter 11: lipids plus ApoB, a one-time Lp(a), hsCRP, and metabolic markers.
- Assemble a real family history — who, what, and at what age — rather than a yes or no.
- Discuss whether coronary imaging is appropriate for you, and which test.
- Establish a home blood pressure routine.

Month 3: Interpret

- Establish with your clinician which risk tier you are in and therefore which target in Chapter 12 applies.
- Identify whether ApoB and LDL-C are concordant. If not, ApoB governs.
- Decide whether medication is indicated, and if you are already on it, whether you are at target or merely "controlled."

Months 3–6: Change what is changeable

- **Diet.** Choose the ladder from Chapter 16 that matches your situation. For most people that means a plant-predominant, whole-food pattern; for established disease with a regression goal, discuss the ultra-low-fat protocol.
- **Movement.** Build toward the dose in Chapter 24: aerobic work most days, resistance training at least twice weekly, and reduced sedentary time. Start below where you think you should.
- **Alcohol.** Reduce it. There is no cardiovascular case for maintaining intake.
- **Smoking.** If this applies, nothing else in this handbook comes close in magnitude.
- **Sleep and blood pressure.** Both are load-bearing and both are frequently ignored.

Month 6: Recheck

- Repeat lipids and ApoB. Diet effects are usually visible by now.
- If you are not at target, this is the point to discuss escalation rather than waiting another year.
- Recheck hsCRP if it was elevated.

Month 12: Consolidate

- Full repeat panel and a review of the whole picture.
- Discuss whether repeat or first-time imaging is warranted.
- Ask the question that matters most: is the plan producing the numbers, and if not, what changes?

THE SINGLE MOST IMPORTANT HABIT

Measure, change one thing at a time where you can, and re-measure. Most people fail not because they choose the wrong intervention but because they never find out whether the one they chose worked.

CHAPTER 39

The tracking sheet

Photocopy this page, or rebuild it in whatever you already use. The point is the trend, not any single row.

Bring completed rows to appointments. A clinician looking at four years of ApoB values makes better decisions than one looking at today's.

Measure	Baseline	Month 6	Month 12	Year 2	Year 3
ApoB (mg/dL)					
LDL-C (mg/dL)					
Total cholesterol					
Triglycerides					
HDL-C					
hsCRP (mg/L)					
Lp(a) — once					
HbA1c (%)					
Fasting glucose					
Blood pressure					
Waist circumference					
Weight					
Resting heart rate					
VO2max or fitness proxy					
Calcium score / imaging					
Current medications					

THREE QUESTIONS TO BRING WITH THE SHEET

- Is my ApoB at the target for my risk tier — and which tier am I in?
- If not, what is the next escalation step and when do we take it?
- What in this table has moved in the wrong direction, and why?

CHAPTER 40

Claims, answered briefly

Common statements about heart disease, and where the evidence in this handbook leaves them.

Claim	Where the evidence leaves it
"My cholesterol is normal, so I am fine."	Normal means typical for a population in which most middle-aged adults have detectable plaque. Ask for ApoB and, if appropriate, imaging. (Ch. 8, 13)
"Heart disease is a disease of old age."	The lesions begin in childhood; the symptoms arrive in later life. Latency is not absence. (Ch. 2)
"A calcium score of zero means I am safe."	It is a strong short-term negative marker with three real limits: it sees only calcium, it is age-dependent, and it is short-term. (Ch. 13)
"My calcium score went up on treatment, so treatment failed."	Calcification is part of how plaque stabilizes. Composition matters more than the number. (Ch. 5, 13)
"Statins are poison."	Muscle symptoms are real but occur at similar rates on placebo in blinded rechallenge. Intolerance is a reason to change agents, not to stop treating. (Ch. 27)
"Cholesterol is essential, so lowering it must be harmful."	Tissues synthesize their own. Trial data extend below 20 mg/dL LDL-C without a harm signal or a floor effect. (Ch. 8)
"Coconut oil is a health food."	It raises LDL relative to unsaturated oils. The HDL rise does not rescue it. (Ch. 19)
"Seed oils cause inflammation."	Not well supported. Linoleic acid does not reliably raise inflammatory markers in randomized trials. (Ch. 19)
"Olive oil is independently cardioprotective."	The benefit tracks what it displaces more than the oil itself, in a literature heavily industry-funded. (Ch. 19)
"Fish oil prevents heart attacks."	Over-the-counter mixed omega-3 has repeatedly failed. Prescription icosapent ethyl in selected patients is a different question. (Ch. 19)
"A glass of red wine is good for the heart."	The J-curve largely does not survive better confounder control or Mendelian randomization. (Ch. 21)
"I am fit, so my heart is fine."	Fitness masks this disease through hypoalgesia, collaterals, and reserve. (Ch. 4, 25)
"Exercise cleans out your arteries."	It stabilizes plaque and transforms risk. It does not scrub the artery. (Ch. 23)
"No family history means I am protected."	It modifies risk slightly. It does not neutralize high particle exposure. (Ch. 14)
"I got a stent, so I am fixed."	A stent treats one lesion. Most future events come from lesions no one stented. (Ch. 30)
"It is too late for me."	Regression and stabilization have been documented in people with advanced disease. The exposure you avoid from today still counts. (Ch. 5, 17)

CHAPTER 41

Glossary

Term	Meaning
ApoB (apolipoprotein B-100)	The structural protein carried by every atherogenic lipoprotein particle, one per particle. Measuring it counts particles directly.
Atherosclerosis	Disease of the artery wall in which retained lipoprotein particles provoke a chronic inflammatory response, producing plaque.
CAC / Agatston score	Coronary artery calcium score from a non-contrast CT. Measures calcified plaque only.
CCTA	Coronary CT angiography. Contrast-enhanced CT that visualizes the artery wall as well as the lumen, including non-calcified plaque.
AI-QCT	AI-driven quantitative analysis of CT angiography, measuring plaque volumes by type and characterizing high-risk features.
Cumulative exposure / ApoB-years	Particle concentration integrated over time. The construct that explains why duration matters as much as level.
Discordance	The situation in which ApoB and LDL-C disagree about risk — common in insulin resistance, high triglycerides, and diabetes.
Endothelium	The single-cell lining separating blood from the artery wall. Its dysfunction permits particle entry.
FH / HoFH	Familial hypercholesterolemia, heterozygous or homozygous. Inherited disorders of LDL clearance producing lifelong elevated exposure.
Fibrous cap	The collagen-rich layer separating a plaque’s necrotic core from the bloodstream. Thin caps rupture.
hsCRP	High-sensitivity C-reactive protein. Marker of systemic and vascular inflammation; 2 mg/L is the conventional dividing line.
Lp(a) / lipoprotein(a)	An LDL-like particle with apolipoprotein(a) attached. Largely genetic, lifelong stable, both atherogenic and prothrombotic.
Lumen	The channel through which blood flows. Distinct from the wall, where the disease lives.
Lumen paradox	Plaque volume falling under treatment without visible widening of the lumen, because the wall remodels inward.
MINOCA	Myocardial infarction with non-obstructive coronary arteries — a genuine infarction without significant stenosis on angiography.
Necrotic core	The lipid-rich, debris-filled centre of a mature plaque. The compartment that regresses under treatment, and the one that ruptures.
Mendelian randomization	A method using inherited genetic variation as a natural randomization to test causality in observational data.

Term	Meaning
PCSK9	A protein that degrades hepatic LDL receptors. Inhibiting it — by antibody or by RNA silencing — markedly lowers LDL-C.
Positive (Glagov) remodeling	Outward expansion of the artery as plaque accumulates, keeping the lumen open and the disease hidden.
Regression	Measurable reduction in plaque burden, principally of the lipid-rich compartment. Not the same as elimination.
Response-to-retention	The framework describing atherosclerosis as initiated by retention of ApoB particles in the arterial intima.
Sarcopenia	Progressive age-related loss of muscle mass and function.
Small dense LDL	Cholesterol-depleted LDL particles typical of insulin resistance. More particles per unit of cholesterol.
TMAO	Trimethylamine N-oxide, a gut-bacterial metabolite of dietary choline and carnitine, associated with cardiovascular risk.
VO2max	Maximal oxygen uptake. The standard measure of cardiorespiratory fitness and a strong predictor of mortality.
WFPB	Whole-food plant-based. In the regression literature, typically also meaning no added oils and total fat below 10 percent of calories.

Where to read more

Every chapter in this handbook condenses one or more full-length articles from the research library at CuringHeartDisease.com, each with its primary-literature citations. The site presents most topics at two depths — a plain-language overview and a fully technical deep dive — and also publishes audio and video versions. If a chapter here raised a question it did not answer, the source article is where to go.

If you want more on…	Look for articles on
The biology of plaque (Part I)	Response-to-retention and molecular traffic in the artery wall; the life-course continuum of atherosclerosis; plaque regression, stabilization, and cross-modal imaging harmonization; whether heart disease can be cured
ApoB and cumulative exposure (Part II)	Why ApoB matters; cumulative ApoB exposure and the apoB-years framework; ApoB, insulin resistance and diabetes; the ApoB–Lp(a)–CRP triad; which came first, the lipid or the inflammation
Testing and imaging (Part III)	Advanced paradigms in cardiovascular risk assessment; the power of zero; coronary calcium and athletic risk; AI-driven quantitative CT angiography; the illusion of "normal" coronary arteries at 60
Diet (Part IV)	Optimal fat thresholds for prevention and regression; Mediterranean versus whole-food plant-based; the coconut oil myth; olive oil and seed oils examined; TMAO and the gut; alcohol and the vanishing J-curve; the protein paradox
Exercise (Part V)	Turning back the cardiovascular clock; the athlete’s paradox of plaque buildup; exercise, plaque composition and calcification; resistance training and cardiovascular risk; how fitness can hide a heart attack
Medication (Part VI)	Comparative review of lipid-lowering therapeutics; from daily pills to twice-a-year shots; aspirin in primary and secondary prevention; incretin therapies in cardiovascular medicine; revascularization versus intensive lifestyle medicine
Special populations (Part VII)	Menopause and cardiovascular risk; transdermal estradiol; bioavailable testosterone; homozygous FH; do babies need statins; visceral adiposity; does Alzheimer’s start in the arteries
The founding case (Part VIII)	Peter’s Story; the published case study; the Megdal serial angiogram 2014–2018; how a world-class cyclist discovered silent heart disease

TOOLS ON THE SITE

The platform also publishes an educational family-history heart risk calculator for Android and iPhone, a heart health plan simulator for exploring how lifestyle and treatment choices interact, and a search tool that answers questions using only the site’s own published content rather than generating an answer when none exists.

A closing note

The central claim of this handbook is not that heart disease is easy to reverse. It is that heart disease is *measurable* — and that a disease you can measure is a disease you can manage.

For most of the last century, coronary artery disease was treated as something that happened to you, discovered at the moment it became an emergency. What has changed is that its cause is now identified with unusual confidence, its presence can be detected decades before symptoms, its progression can be tracked with numbers on a lab report, and its trajectory can be altered. None of that requires you to become an expert. It requires you to ask for the right tests, understand what the answers mean, and work with someone qualified to act on them.

That is what this document is for. It is not a substitute for a clinician, and the best outcome from reading it is a better conversation at your next appointment — not a decision made alone.

ONCE MORE, BECAUSE IT MATTERS

Nothing in this handbook is medical advice. Do not start, stop, or change any medication on the basis of it. If you have chest pain, unusual breathlessness, or a sudden unexplained fall in exercise capacity, seek medical attention now.

Compiled from the research library of CuringHeartDisease.com
The Premiere Heart Health Education Platform · founded by Peter Megdal, PhD
Independent, evidence-based, and reader-supported — not funded by the pharmaceutical or food industries.