A GENMEDS GUIDE · CARDIOVASCULAR PREVENTION · UPDATED JULY 2026

The best way to lower *LDL cholesterol* and prevent heart disease

Of all the things that cause heart attacks, heart failure, and stroke, **LDL cholesterol** is the one you can do the most about. Decades of research point to one rule: the lower your LDL, and the longer you keep it there, the better.

AUTHORS

Braidwell AI
Alex Karnal
Nick Myerberg
Dr. Josh Sims
Dr. Robert Stoekenbroek
Dr. Andrew Badley
Dr. Nihar Desai

ABOUT THIS DOCUMENT

A living guide, updated in as close to real-time as we and our Braidwell AI system can, reviewing every FDA-approved LDL-lowering medicine and the science behind them, written for everyone.

READING TIME

~20 minutes

LAST SUBSTANTIVE REVIEW

July 17, 2026

§01 — WHAT WE RECOMMEND

What we tell our *friends and family*

We tell our friends and family to start treatment early — before damage to the arteries has begun. There is no level of LDL that is "too low." Your cells make all the cholesterol they need on their own. So we say start with the medicines that bring LDL down the most, with the fewest side effects. The goal is to get LDL under 50 mg/dL. This is the level we are naturally born with, that hunter-gatherer populations maintain throughout life, and the range where atherosclerosis largely stalls instead of actively progressing.

PCSK9 inhibitors are a class that now includes five approved medicines: **evolocumab (Repatha)**, **alirocumab (Praluent)**, **lerodalcibep (Lerochol)**,**inclisiran (Leqvio)**, and enlicitide (Lipfendra). We prefer to start treatment with these. They produce the largest LDL reductions of any approved medicines. In clinical trials involving tens of thousands of patients, rates of side effects were comparable to placebo. [1] [3]

Recently, the first oral PCSK9 inhibitor was approved. Statins are oral medications that have been on the market for many years. But the statin FDA labels warn of muscle damage, liver enzyme abnormalities, and increases in blood sugar that can lead to new-onset diabetes. In real-world studies, roughly 10-25% of statin users report muscle symptoms. [44] [52]

The relationship between LDL and heart disease is continuous — there is no biological threshold below which the benefit stops. In a prespecified analysis of the `FOURIER[1]` trial, patients who achieved the lowest LDL levels continued to see fewer heart attacks and strokes, with no increase in side effects, all the way down well below 20 mg/dL. So once a PCSK9 inhibitor has done the heavy lifting, it may be worth adding a second and third medicine on top — depending on how much further you want to push your risk down. [17]

The medicines in this guide are FDA-approved. They work. They have different strengths and trade-offs. The right choice depends on your numbers, your preferences, and your ability to afford them — not on which drug a guideline committee ranked first many years ago.

One thing we will say directly: there is no level of LDL cholesterol that is "too low." Every cell in your body makes all the cholesterol it needs. You do not depend on circulating LDL for any essential function. The data — from clinical trials, genetics, and decades of observation — confirm this. The evidence is summarized below.

*For personalized lifetime risk and treatment benefit estimates from your own profile, see the **GenMeds CV Risk Calculator**.*

§02 — THE BOTTOM LINE

The benefit *compounds* with duration. Start earlier. Go lower

Heart disease is driven by cumulative exposure to LDL particles over time — what researchers call "LDL-years." This makes intuitive sense. LDL particles carry most of the cholesterol — a fatty substance — in our blood. LDL particles are small and can penetrate the arterial wall and accumulate, leading to the formation of atherosclerotic plaques. The more particles and the longer arteries are exposed, the more accumulation, the more plaque, and the higher the risk of heart attacks and strokes. Every year of elevated LDL-C adds to a running total of arterial damage. Conversely, the earlier and lower you go, the more you prevent. There is no threshold below which benefit stops. [4][15]

People born with naturally low LDL, because of genetic variants in PCSK9 or other genes, have **50–90% less coronary heart disease** than the general population, despite only modestly lower LDL levels (15–40 mg/dL lower). [11] A 5-year statin trial, by contrast, produces roughly a 22% risk reduction despite achieving a similar or even larger absolute LDL-C drop. [4]

The difference is time. The genetic experiment delivers decades of lower exposure starting from birth; a statin trial delivers a few years starting in middle age. The implication: to maximize the impact of LDL lowering, one has to start earlier in life, before significant damage to the arterial wall has occurred.

MODEL SNAPSHOT · LOWER & LONGER

How much risk you avoid depends on how low you go, and for how long.

Based on the CTT relationship of ~22% relative risk reduction per ~39 mg/dL of LDL-C lowering [4], scaled to treatment duration per the Ference / EAS Consensus formula. [15]

STARTING LDL-C
160 mg/dL

ACHIEVED LDL-C
55 mg/dL

YEARS OF SUSTAINED TREATMENT
20 yrs

RELATIVE RISK REDUCTION IN MAJOR CARDIOVASCULAR EVENTS
72.6%

LDL-C DROP
105 mg/dL · 66%

TIME COMPOUNDS · FERENCE 2017

Time matters more than intensity

Risk reduction per 1 mmol/L of sustained LDL-C lowering grows with the number of years on treatment. [15]

This is the most important insight in cardiovascular prevention: **the benefit compounds with duration.** Starting earlier matters. Going lower matters. **Lower for longer is better; lowest for longest is best.**

§03 — WHY THIS WORKS

What the science *actually* shows

Genetics and direct visualization converge on the same picture.

People born with less PCSK9 almost never get heart disease

In 2006, researchers found people carrying natural loss-of-function mutations in the PCSK9 gene, the same target that PCSK9 inhibiting medicines hit with a drug. These people have had lower LDL since birth, not because of any medication, but because of their DNA. [11]

COHEN ET AL., 2006 — CORONARY PROTECTION BY LIFELONG PCSK9 REDUCTION N ≈ 12,000

GROUP	HOW MUCH LOWER THEIR LDL	LESS CORONARY HEART DISEASE
Black participants with nonsense mutations	**28%** lower (~40 mg/dL less)	**88% less**
White participants with missense mutation	**15%** lower (~21 mg/dL less)	**47% less**

Notice the asymmetry: a modest LDL difference (15–28%) produced an outsized reduction in disease (47–88%). That is the power of lifelong exposure. A statin trial achieves a larger percentage LDL drop over 5 years and delivers ~22% risk reduction — still worthwhile, but far less than what decades of lower exposure produce. [4] The implication: start as early as makes sense for your risk, and stay on treatment.

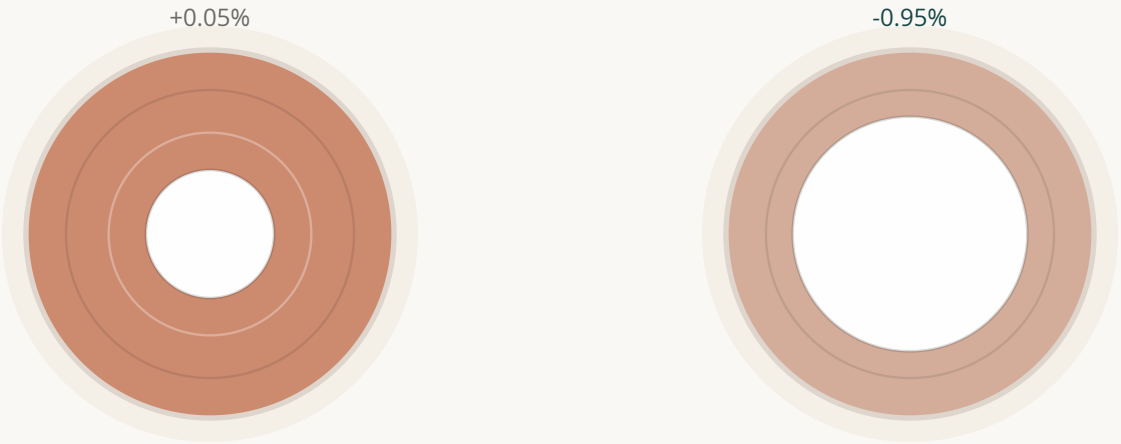
The disease physically gets smaller when treated

You can see the disease getting smaller on a screen, reversing its course. The people who went lowest in their LDL-C had the most regression. There was no level at which the benefit plateaued. This is what "lower is better" looks like inside an artery.

You can watch the disease shrink.

GLAGOV · IVUS · N=846

In the GLAGOV[14] trial, researchers used intravascular ultrasound — a tiny camera inside the coronary arteries — to directly measure atherosclerotic plaque in 846 patients already on statins. Half received evolocumab (Repatha) on top. The people who went lowest over 76 weeks had the most regression.



Statin alone

LDL **93 mg/dL**

47% SAW PLAQUE REGRESSION

Statin + evolocumab

LDL **37 mg/dL**

64% SAW PLAQUE REGRESSION

47 %	**64** %	**-56** mg/dL
Patients with plaque regression with statin alone	Patients with plaque regression with statin + evolocumab	Achieved LDL-C difference between arms

The PACMAN-AMI[43] trial (n=300) replicated this finding with alirocumab post-acute heart attack: percent atheroma volume regressed by -2.13% vs -0.92% with placebo (p<0.001). Different drug, different trial, same geometry — the disease gets smaller when LDL goes lower.

§05 — WHAT CHANGED IN 2025

The two largest barriers to PCSK9 access just *fell away*

The FDA expanded evolocumab's (Repatha) label based on data from the VESALIUS-CV[2] trial: in 12,257 patients without prior heart attack or stroke, evolocumab reduced 3-point MACE by 25% (HR 0.75, p<0.0001) and heart attack alone by 36% over 4.6 years. The new label covers **adults at increased risk for cardiovascular events** — no prior event required, no step therapy needed. Alirocumab (Praluent) followed with a parallel label expansion. [3]

Separately, Amgen launched **AmgenNow**, a direct pricing program that brought the cash price of Repatha down to **$239/month** at over 70,000 pharmacies — roughly 60% below the previous list price and less than many branded oral therapies. [51]

Lerodalcibep (Lerochol), approved by the FDA in December 2025, brought the floor lower still. At $199/month cash with monthly rather than biweekly dosing and room-temperature storage, it is both the least expensive PCSK9 inhibitor available and the most logistically forgiving.

Together, these changes removed the two largest barriers to PCSK9 inhibitor access: the indication restriction and the price.

25%
VESALIUS-CV reduction in 3-point MACE in patients **without prior heart attack or stroke**

36%
VESALIUS-CV reduction in heart attack alone over 4.6 years

$239/mo
Cash price of Repatha at **70,000+ pharmacies** via AmgenNow

$199/mo
Cash price of Lerochol, the lowest price for any PCSK9 inhibitor

§06 — WHAT TO MEASURE

Not every test matters equally. We rank by whether the result *changes what you do.*

A note on family history

A first-degree relative with a documented heart attack, stroke, or cardiovascular death before age 55 in men or 65 in women raises ASCVD risk by approximately 50% above what your measured biomarkers and risk factors capture. [33][34] Part of the excess risk may be mediated through Lp(a), which is one reason to measure it. [37]

Essential — measure these

TEST	WHY IT MATTERS	HOW OFTEN	TARGET
LDL-C	The primary driver of atherosclerotic cardiovascular disease. This is the number to track and lower.	Baseline + 8-12 weeks after any change in medication. At least yearly thereafter.	Lower is better. No floor. We recommend targeting 50 mg/dL to halt plaque build-up in arteries for most people, and potentially lower in people with established plaque.
Lp(a)	Genetically determined, independent risk factor. Lp(a) particles are effectively LDL particles with added characteristics that make them even more dangerous. Elevated in ~20% of people. Does not change with lifestyle or most drugs. Measure once. Usually not part of a standard lipid panel, so this needs to be requested separately.	Once	<50 nmol/L or <20-25 mg/dL. If elevated, it strengthens the case for aggressive LDL-C lowering. No approved Lp(a)-lowering therapy yet.
HbA1c	Diabetes is an ASCVD risk equivalent. Metabolic health and insulin resistance directly affect cardiovascular risk. HbA1c is a measure of your blood glucose over a 2 to 3 month period. It is more stable than a direct blood glucose measurement, which varies greatly during the day and between days.	Annually	<5.7% normal; ≥6.5% = diabetes.
Blood Pressure	Independent and synergistic. Hypertension significantly increases ASCVD risk at any LDL level.	Every visit	120/80 mmHg for most adults.

Optional — measure if your doctor recommends

TEST	WHY IT MATTERS	WHEN TO CONSIDER	TARGET / NOTES
ApoB	Counts every atherogenic particle directly — more precise than LDL-C, especially when triglycerides are elevated or LDL-C and clinical risk seem discordant.	Diabetes, elevated triglycerides, or discordant LDL-C and clinical risk	<45 mg/dL
hsCRP	Measures inflammatory risk, a second causal axis of heart disease beyond cholesterol. CANTOS proved that inflammation alone drives cardiovascular events. [20]	Baseline; after treatment	<2.0 mg/L conventional; <1.0 mg/L ideal.
CAC Score	Direct visualization of coronary plaque burden. A score of 0 in otherwise low-risk people is reassuring. >100 reclassifies risk upward.	Once, when risk classification is uncertain	0 is optimal; >100 = treat aggressively.

§07 — GENERAL PRINCIPLES

Four principles that apply to *every* LDL-C lowering therapy

Before choosing a specific therapy, understand the principles that apply to all of them.

01 Lower for longer is better. Lowest for longest is best

Every ~39 mg/dL of LDL-C reduction lowers major cardiovascular events by ~22% over 5 years, starting from any baseline. This relationship is log-linear and does not plateau. [4] People who achieve LDL-C below 20 mg/dL in trials continue to show benefit with no excess harm. [16] [17] [18]

The benefit compounds over time. People with genetically low LDL from birth get 3–4x more risk reduction per unit of LDL lowered than people who start in their 50s because they have had decades more exposure to the benefit. [11] [15] A lipid lowering treatment started at 35 and continued through 75 produces benefits closer to lifelong genetic protection than to a 5-year clinical trial.

02 The mechanism does not matter

Statins, ezetimibe, PCSK9 inhibitors, and bile acid sequestrants produce the same cardiovascular benefit for each given LDL-C reduction. The only thing to focus on is the magnitude of the LDL-C reduction. PCSK9s offer the greatest LDL-C reduction and therefore the greatest cardiovascular benefit over time, generally with fewer side effects than statins. [12]

CONCORDANCE PRINCIPLE · FERENCE 2015 & 2016

It does not matter how you lower LDL. Only that you do

A landmark Mendelian randomization study compared the genetic equivalents of three drug mechanisms. Per 10 mg/dL of LDL-C reduction, the benefit is statistically indistinguishable. [12] [13]

Every mechanism that reduces the number of LDL particles in your blood produces the same proportional benefit. There is no special sauce — just fewer particles, for longer. This means the choice between therapies should be driven by your preferences (cost, convenience, side effects), not by any belief that one mechanism is biologically superior to another.

Choose the option that fits your life — cost, convenience, side effects, dosing — not the one with a particular mechanism.

03 Lifestyle runs in parallel, not as a prerequisite

Diet, exercise, sleep, weight management, and smoking cessation are good for everyone, regardless of medication. They improve cardiovascular risk through multiple pathways beyond LDL-C (blood pressure, insulin sensitivity, inflammation, endothelial function). But lifestyle alone typically reduces LDL-C by only 5–15%, which is rarely sufficient for people at meaningful risk. [9]

Do not treat lifestyle as Step 1 and medication as Step 2. They are concurrent. A person who needs an LDL-C reduction of 50% will not get there with diet alone, and delaying medication while "trying lifestyle first" costs time — and time is the variable that matters most.

04 There is no LDL level that is too low

This is the most important safety principle in the guide. The concern is understandable: if cholesterol is essential for cell membranes and hormones, won't low levels cause harm?

No. Here is why:

Every cell in your body makes all the cholesterol it needs. Cholesterol is synthesized de novo via the mevalonate pathway in every nucleated cell. The brain produces approximately 95% of its cholesterol locally, behind the blood-brain barrier. Circulating LDL does not cross this barrier in meaningful amounts. [25]

Steroid hormones do not depend on LDL. Steroidogenic tissues primarily use HDL-delivered cholesterol via the SR-BI receptor and their own de novo synthesis. The `DESCARTES[23]` evolocumab substudy directly measured cortisol, testosterone, and estradiol in people achieving LDL below 15 mg/dL. There was zero correlation between LDL-C change and any hormone level. [46] [47]

The clinical data confirm the safety of achieving very low LDL levels at scale:

Cognition: The `EBBINGHAUS[16]` study performed serial formal neuropsychological testing in patients on evolocumab whose LDL-C reached a median of ~30 mg/dL, with many below 20 mg/dL. No differences appeared on any cognitive domain. A broader analysis of 22,655 FOURIER participants found no cognitive decline even in the 2,338 people who reached LDL-C below 20 mg/dL. [17]

Hemorrhagic stroke: In `ODYSSEY OUTCOMES[18]`, among 730 people who transiently reached LDL-C below 15 mg/dL: zero hemorrhagic strokes. A meta-analysis of 39 PCSK9 inhibitor RCTs (66,478 patients) found no hemorrhagic stroke excess. [36]

New-onset diabetes: In `FOURIER[1]`, HR was 1.05 (95% CI 0.94–1.17). In `ODYSSEY OUTCOMES[3]`, HR was 1.00 (0.89–1.11). No statistically significant increase appeared in either trial. [4]

Cancer: CTT Collaboration meta-analysis of 170,000+ people: RR 1.00 (95% CI 0.96–1.04) — no relationship. Observational associations between low LDL and cancer are reverse causation. [4] [26]

People with lifelong very low LDL are healthy. PCSK9 loss-of-function carriers show 47–88% less coronary disease, normal neurocognition, normal adrenal function, and normal fertility. [11] [19] There is no clinical syndrome associated with having too-low LDL.

> ✓ **Bottom line:** the safety concerns that held back early PCSK9 utilization are not supported by the data. The risk is in keeping LDL too high, not in lowering it too far.

Every LDL-C-lowering therapy has a place. The right choice *depends on you*.

Every approved LDL-C-lowering therapy has a place. The right choice *depends on what matters to you:* how much LDL-C reduction you need, whether you prefer a pill or an injection, how often you want to deal with it, what side effects you are willing to accept, and what you can afford. We describe each option objectively along these dimensions.

LARGEST LDL-C REDUCTIONS & CLEANEST SAFETY

PCSK9-based therapies

The strongest LDL-C lowering class in the guide. Various therapies available within this class.

Lerochol

lerodalcibep · PCSK9 fusion protein

LDL-C REDUCTION **~56-62%**

FORMAT	DOSING	PRICE
Prefilled syringe	Monthly	$199/mo

MECHANISM

Small recombinant fusion protein (~77 kDa) consisting of a PCSK9-binding adnectin fused to human serum albumin. It binds and neutralizes PCSK9, preventing degradation of LDL receptors — the same mechanism as Repatha and Praluent, but in a different molecular format, not a monoclonal antibody.

TRIALS & OUTCOMES

`LIBerate Phase 3[29]` showed ~56-62% LDL-C reduction, ApoB reductions of ~36-45%, Lp(a) reductions of ~25-33%, and sustained lowering over 2+ years in the open-label extension with no attenuation [30].

SAFETY

Well-tolerated. Injection site reactions such as pain and redness in 12-18% are the most common adverse event — slightly higher than for PCSK9 antibodies, likely due to the larger injection volume.

COST & ACCESS

As low as $199/month.

FDA LABEL

Adjunct to diet and exercise in adults with hypercholesterolemia.

THE TRADE-OFF

Monthly dosing and room-temperature storage are practical advantages. The potential disadvantages may be slightly higher rates of injection site reactions and the fact that it is currently administered via a prefilled syringe rather than an autoinjector.

Repatha

evolocumab · PCSK9 antibody

LDL-C REDUCTION **~60%**

FORMAT	DOSING	PRICE
Autoinjector	**Every 2 weeks** or monthly	**$239/mo**

MECHANISM

Monoclonal antibody that blocks PCSK9 protein, preventing it from degrading LDL receptors on liver cells. More LDL receptors on the liver surface means more LDL cleared from the blood. LDL-C reduction is ~60% as monotherapy — materially more than what most statins achieve.

TRIALS & OUTCOMES

Cardiovascular outcomes are established. **FOURIER[1]** showed a 15% reduction in the primary composite endpoint and a 20% reduction in CV death, heart attack, or stroke. **VESALIUS-CV[2]** extended benefit into patients without prior heart attack or stroke, showing a 25% reduction in the primary composite endpoint and a 36% reduction in heart attack, supporting the 2025 label expansion. PCSK9 antibodies also lower Lp(a) by ~24–27%; in ODYSSEY, mediation analyses suggested that Lp(a) reduction contributed independently to benefit.

SAFETY

Comparable to placebo in **FOURIER[1]**. Mild injection-site reactions around 2%. No myopathy, hepatotoxicity, or new-onset diabetes. Cognitive safety has been formally tested at LDL <20 mg/dL and cleared. [16] [17] Steroid hormones are unaffected.

COST & ACCESS

$239/month through the AmgenNow direct pricing program at over 70,000 pharmacies. [51] This is less than Nexletol ($431/month) and comparable in annual cost to some specialty oral therapies. Patient assistance programs are available.

FDA LABEL

Adjunct to diet and exercise in adults with hypercholesterolemia, and to reduce the risk of major adverse cardiovascular events in adults at risk of these events.

THE TRADE-OFF

Injectable. Some people dislike needles. The injection itself takes seconds via autoinjector and most people adapt quickly, but this is a real preference issue for some.

Lipfendra

enlicitide · PCSK9 inhibitor

LDL-C REDUCTION **~60%**

FORMAT	DOSING	PRICE
Oral tablet	Once daily (20mg)	$315/mo

MECHANISM

An oral macrocyclic peptide that blocks the PCSK9 protein - the same target as the injectable PCSK9 antibodies (Repatha, Praluent) - preventing PCSK9 from degrading LDL receptors on liver cells. More LDL receptors on the liver surface means more LDL cleared from the blood. It is the first PCSK9 inhibitor to achieve antibody-level LDL lowering in a once-daily pill rather than an injection.

TRIALS & OUTCOMES

The Phase 3 CORALreef program enrolled more than 19,000 participants. In **CORALreef Lipids[56]**, enlicitide reduced LDL-C by ~56% versus placebo at 24 weeks, and also had meaningful reductions in non-HDL-C, ApoB, and Lp(a), similar to the monoclonal antibodies. [57] [58] A dedicated cardiovascular outcomes trial, **CORALreef Outcomes[60]**, is still ongoing - so, unlike Repatha and Praluent, hard cardiovascular-event data are not yet available. Because the LDL-C lowering is similar to the antibodies and Lipfendra works through the identical mechanism, it is highly unlikely that the cardiovascular benefit would be any different than the monoclonal antibodies (although trial design differences such as duration play a big role in the ultimate number produced in the trial).

SAFETY

In the Phase 3 program, adverse events were comparable to placebo with low discontinuation rates. [50] As an oral peptide it does not carry the injection-site reactions seen with the injectables.

COST & ACCESS

Launching at ~$315/month. That is more than Repatha at cash prices. As a brand-new launch (FDA approval July 16, 2026) [59], formulary placement and prior-authorization requirements are still being set; expect most insured access to require prior authorization initially, as with the rest of the class. Cash/self-pay is likely to be the fastest route at launch.

FDA LABEL

Adjunct to diet and exercise to reduce LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH). Approved July 16, 2026.

THE TRADE-OFF

The first PCSK9 that is a once-daily pill: no needles, no injection-site reactions, room-temperature convenience - at antibody-level LDL lowering and a lower price than the injectables. The main caveat is that although orals are more convenient for some, many people forget to take them. In addition, one has to take LIPFENDRA on an empty stomach in the morning with water, black coffee, or plain tea, and cannot eat or drink anything else for 30 minutes afterwards.

Praluent

alirocumab · PCSK9 antibody

LDL-C REDUCTION **~60%**

FORMAT	DOSING	PRICE
Autoinjector	Every 2 weeks or monthly	$533/mo

MECHANISM

Same target and mechanism as evolocumab: blocks PCSK9 protein, preserves LDL receptors, clears more LDL from the blood. LDL-C reduction is ~60% as monotherapy.

TRIALS & OUTCOMES

ODYSSEY OUTCOMES[3] showed 15% reduction in the primary composite endpoint after acute coronary syndrome. PCSK9 antibodies reduce Lp(a) by ~24-27%, and Lp(a) lowering contributed to event reduction independently of LDL-C lowering in ODYSSEY mediation analysis.

SAFETY

Consistent with Repatha. [3] [18]

COST & ACCESS

~$533/month cash. Patient assistance through Sanofi.

FDA LABEL

Adjunct to diet and exercise in adults with hypercholesterolemia, and to reduce the risk of major adverse cardiovascular events in adults at risk of these events.

THE TRADE-OFF

Injectable, and the cash price is higher than Repatha.

LOW COST · BROAD EVIDENCE

Statins

Daily oral medicines with the deepest outcomes evidence and the lowest cash prices.

Leqvio

Inclisiran · PCSK9 siRNA

LDL-C REDUCTION **~50%**

FORMAT	DOSING	PRICE

Atorvastatin

Statin

LDL-C REDUCTION **35-55%**

FORMAT	DOSING	PRICE
Oral tablet	**Daily**	**$4-15/mo**

MECHANISM

Inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. The liver compensates by upregulating LDL receptors, pulling more LDL from the blood. LDL-C reduction is 35-55% depending on drug and dose; high-intensity regimens (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) achieve the upper end.

TRIALS & OUTCOMES

The deepest evidence base of any drug class in medicine. CTT meta-analyses across 170,000+ people and 26 trials: 22% reduction in major vascular events per 1.0 mmol/L (~39 mg/dL) LDL-C reduction, including ~10% all-cause mortality reduction. [4] As of May 2026, statins remain the only LDL-lowering class to have demonstrated a statistically significant all-cause mortality benefit in randomized trials — likely reflecting shorter trial durations for newer agents rather than a biological difference, but still worth noting.

SAFETY

Muscle symptoms are a common reason people stop. In observational studies, statin-associated muscle symptoms are reported by roughly 10-25%. [52] [44] Based on trials where people do not know whether they are taking a statin or placebo, much of it is not caused by the statin [7] [8]. Genuine statin myopathy is uncommon, affecting roughly 1 per 1,000 to 1 per 10,000 people per year and is dose dependent. [52] [53] Rhabdomyolysis is rarer still: 1 per 10,000 person-years. [54] New-onset diabetes: odds ratio 1.09 (95% CI 1.02-1.17), equivalent to roughly 1 additional case per 255 patients treated for 4 years [48]; risk is greater with higher intensity therapy and most new diagnoses occur in people whose blood glucose is already near the diabetes threshold. [10] [49]

COST & ACCESS

$4-15/month for generic atorvastatin or rosuvastatin. No prior authorization. Available everywhere. This is the least expensive option by a wide margin.

FDA LABEL

Broad indication for hyperlipidemia, ASCVD risk reduction, and lipid disorders.

THE TRADE-OFF

Daily pill — and most people stop taking it within a few years, which eliminates the benefit entirely. Real though rare myopathy risk. New-onset diabetes risk at high doses.

Rosuvastatin

Statin

LDL-C REDUCTION **35-55%**

FORMAT	DOSING	PRICE
Oral tablet	Daily	$4-15/mo

MECHANISM

Same class as atorvastatin: inhibits HMG-CoA reductase, causing the liver to upregulate LDL receptors and pull more LDL from the blood. Slightly more potent at the high end of the dose range.

TRIALS & OUTCOMES

The deepest evidence base of any drug class in medicine. CTT meta-analyses across 170,000+ people and 26 trials: 22% reduction in major vascular events per 1.0 mmol/L (~39 mg/dL) LDL-C reduction, including ~10% all-cause mortality reduction. [4] JUPITER[10] demonstrated benefit in people with elevated hsCRP. As of May 2026, statins remain the only LDL-lowering class to have demonstrated a statistically significant all-cause mortality benefit in randomized trials — likely reflecting shorter trial durations for newer agents rather than a biological difference, but still worth noting.

SAFETY

Same class considerations as atorvastatin: reported muscle symptoms, rare true myopathy, diabetes risk concentrated near the diabetes threshold, hepatic monitoring, and rare rhabdomyolysis.

COST & ACCESS

$4-15/month generic. No prior authorization. Available everywhere.

FDA LABEL

Hyperlipidemia and ASCVD risk reduction.

THE TRADE-OFF

Same trade-offs as atorvastatin.

ADD-ONS AND ALTERNATIVES

Other LDL-lowering medicines

Oral add-ons, statin alternatives, and emerging non-statin pathways that lower LDL.

Ezetimibe

Cholesterol absorption inhibitor

LDL-C REDUCTION **18-20%**

FORMAT	DOSING	PRICE
Oral tablet	Daily	$10-25/mo

MECHANISM

Blocks intestinal cholesterol absorption via the NPC1L1 transporter — a completely different pathway from statins or PCSK9 inhibitors.

TRIALS & OUTCOMES

LDL-C reduction is ~18-20% as monotherapy, or as an add-on to any other therapy. Ference Mendelian randomization data confirm that each 10 mg/dL of LDL-C reduction from ezetimibe produces the same cardiovascular benefit as from a statin or PCSK9 inhibitor. [12]

SAFETY

Well-tolerated. Minimal side effects, mostly mild GI symptoms.

COST & ACCESS

$10-25/month generic. No prior authorization.

FDA LABEL

Hyperlipidemia, primary or in combination with statins.

THE TRADE-OFF

Modest incremental effect. This is a booster, not a primary driver. Useful when you need more LDL-C reduction on top of another therapy, or as part of a low-cost oral combination.

Nexletol

bempedoic acid · ACL inhibitor

LDL-C REDUCTION **18-38%**

FORMAT	DOSING	PRICE
Oral tablet	Daily	$431/mo

MECHANISM

Inhibits ATP citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase in the cholesterol synthesis pathway. Acts only in the liver because it is a prodrug activated by a liver-specific enzyme, which is why it does not cause the muscle symptoms seen with statins.

TRIALS & OUTCOMES

LDL-C reduction is ~18% as monotherapy. When combined with ezetimibe as Nexlizet, ~38%. `CLEAR Outcomes[6]` showed 13% reduction in the 4-point MACE primary composite — a real but modest effect consistent with the modest LDL-C reduction.

SAFETY

`CLEAR Outcomes[6]` showed elevated uric acid 10.9% vs 5.6%, gout 3.1% vs 2.1%, tendon rupture as an FDA labeled Warning and Precaution (0.5% vs. 0%), gallstones 2.2% vs. 1.2%, and hepatic enzyme elevations 4.5% vs 3.0%. No excess myalgia — this is its one clear advantage over statins.

COST & ACCESS

~$431/month cash. At the uninsured cash price, this is more expensive than Repatha at AmgenNow while delivering substantially less LDL-C reduction.

FDA LABEL

1) Adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia. 2) To reduce the risk of major adverse cardiovascular events in adults at increased risk who are unable to take recommended statin therapy.

THE TRADE-OFF

Useful for genuine statin intolerance when PCSK9 inhibitors are not accessible or tolerated. For everyone else, modest efficacy, real safety issues, and high cost make it hard to justify as a first choice.

Prices reflect US cash/self-pay rates as of early 2026. Verify with manufacturer programs, GoodRx and your pharmacy.

§10 — HOW TO GET PCSK9 INHIBITORS

Access has *improved dramatically*. Here's the current landscape

Statins and ezetimibe are cheap, generic and available at any pharmacy. PCSK9 inhibitors are newer and historically harder to obtain, so this section focuses on them.

01 · CASH PAY

No insurance needed

Repatha `$239/mo`

AmgenNow at 70,000+ pharmacies via GoodRx. Available regardless of insurance status, including Medicare.

Lerochol `$199/mo`

Lerodalcibep (Lerochol), approved by the FDA in December 2025, brought the floor lower still. At $199/month cash, it is the least expensive PCSK9 inhibitor available.

02 · THROUGH INSURANCE

Prior authorization

Coverage

Most plans still require prior authorization. Approval rates are rising after the VESALIUS-CV label expansion.

Appeals

Document LDL-C level, risk factors, and prior therapies. Appeals often succeed; persistence matters.

What to ask your doctor

01 "I'd like my LDL-C and Lp(a) measured."

02 "Based on my risk, what are my options for lowering LDL-C?"

03 "Can we look into PCSK9 inhibitor access, including cash pricing?"

04 "What does my insurance require for coverage, and is there a patient-assistance program?"

§11 — WHAT WE STILL DON'T KNOW

The honest open questions

?

Anti-inflammatory therapy beyond colchicine

CANTOS proved the axis. Colchicine is approved but adoption is low and the drug-drug interaction profile limits use. Targeted IL-6 and IL-1beta agents may offer cleaner benefit-risk profiles.

?

Lp(a) lowering

Pelacarsen and olpasiran are in Phase 3. We do not yet know whether lowering Lp(a) reduces cardiovascular events.

§12 — SOURCES

Every claim, grounded

We cite throughout. Hover any [n] in the text for a one-line summary; click to highlight the entry below. Source links open the underlying paper when available.

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How we made this guide

Randomized Controlled Trials — Reviewed FOURIER, VESALIUS-CV, ODYSSEY OUTCOMES, IMPROVE-IT, CLEAR Outcomes, CANTOS, LoDoCo2, COLCOT, SAMSON, StatinWISE, GLAGOV, PACMAN-AMI, EBBINGHAUS, DESCARTES, the LIBerate Phase 3 program, and GLP-1 RA cardiovascular outcomes trials. Prioritized large, well-powered, placebo-controlled trials with hard cardiovascular endpoints. **Genetic and Epidemiologic Evidence** — Integrated Mendelian randomization data (concordance principle, LDL-years framework), PCSK9 loss-of-function cohorts, and the EAS consensus statement on LDL causality. **Safety at Very Low LDL** — Reviewed cognitive, hormonal, hemorrhagic stroke, diabetes, and cancer safety data, including genetic evidence from PCSK9 loss-of-function carriers. **Pricing** — Confirmed current US cash prices through GoodRx, manufacturer direct programs, and pharmacy benefit databases as of early 2026.

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