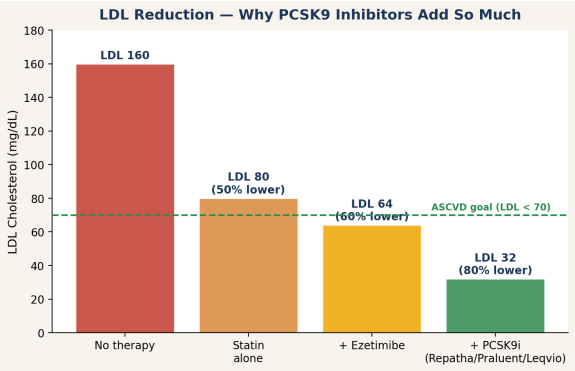
Understanding PCSK9 Inhibitors

Repatha, Praluent, and Leqvio -- when statins aren't enough

Cuts LDL by another 50-60% on top of a statin. Trials show 15% fewer heart attacks and strokes.



Online: https://go.riasalimd.com/pcsk9-guide

Rias KS Ali, MD FACC

Board Certified in Interventional Cardiology & Cardiovascular Disease

4740 Mile Stretch Drive, Holiday FL 34690 | Office: (727) 943-5200 | Fax: (727) 943-5201 | RiasAliMD.com

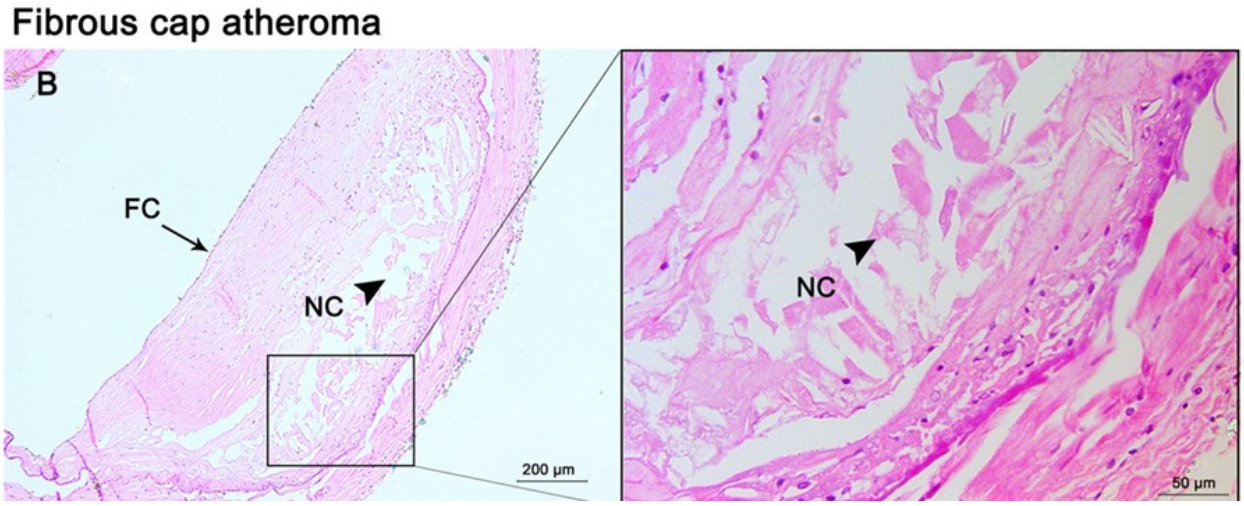
Last Updated: August 2026

Names & Terms You Will Hear

Term	Meaning
PCSK9 inhibitors	A drug class that blocks the PCSK9 protein in the liver. More LDL receptors stay on liver cells. More LDL gets cleared from the blood.
Repatha (evolocumab)	An antibody drug. Given as a shot under the skin every 2 or 4 weeks. Tested in the FOURIER trial.
Praluent (alirocumab)	An antibody drug. Given as a shot under the skin every 2 weeks. Tested in the ODYSSEY-Outcomes trial.
Leqvio (inclisiran)	An siRNA drug -- different method, same target. Given as a shot under the skin twice a year after two loading doses. LDL data is strong; heart-outcome trial (ORION-4) is still running.
LDL receptor recycling	PCSK9 normally marks LDL receptors for removal. Block PCSK9 and the receptors stay put. Your liver then pulls more LDL out of the blood.
Statin-intolerant	Patients who cannot take any statin -- often due to muscle pain. They can use a PCSK9 inhibitor on its own or with ezetimibe.
FH (familial hypercholesterolemia)	A gene-based disorder. LDL is very high from birth. PCSK9 inhibitors work well in both HeFH and HoFH.
MACE	Major adverse cardiovascular events -- a trial measure that combines heart attack, stroke, and CV death.

What Is PCSK9 Inhibitors?

- PCSK9 inhibitors lower LDL cholesterol. They work **in addition to** statins -- they do not replace them. They target a liver protein called PCSK9.
- **How they work:** PCSK9 tells liver cells to destroy their LDL receptors. Block PCSK9 and more receptors stay on the surface. Your liver then pulls more LDL out of the blood.
- **Three FDA-approved choices:** evolocumab (**Repatha**) and alirocumab (**Praluent**) are antibody drugs. You give yourself a small shot every 2 or 4 weeks. Inclisiran (**Leqvio**) uses siRNA to cut how much PCSK9 the liver makes. You only need a shot TWICE A YEAR after two loading doses.
- **LDL impact:** on top of the highest statin dose you can take, PCSK9 inhibitors cut LDL by another 50-60%. Many patients reach LDL below 30 mg/dL -- well under the ASCVD goal of 70.
- **Outcome data:** the FOURIER trial (evolocumab) and ODYSSEY-Outcomes (alirocumab) each showed about a 15% drop in heart attacks, strokes, and CV death -- even in patients already on a statin.



A real fibrous cap atheroma under the microscope -- the exact plaque type PCSK9 inhibitors help stabilize by driving LDL far below goal. FC = fibrous cap; NC = necrotic lipid core (arrowhead). Left: low-power view; right: zoomed-in detail of the core. A thin fibrous cap over a core like this can rupture and cause a heart attack -- deep LDL lowering thickens and stabilizes the cap. Image: Yang et al., Frontiers in Neurology 2017 (CC BY 4.0).

Why It Matters

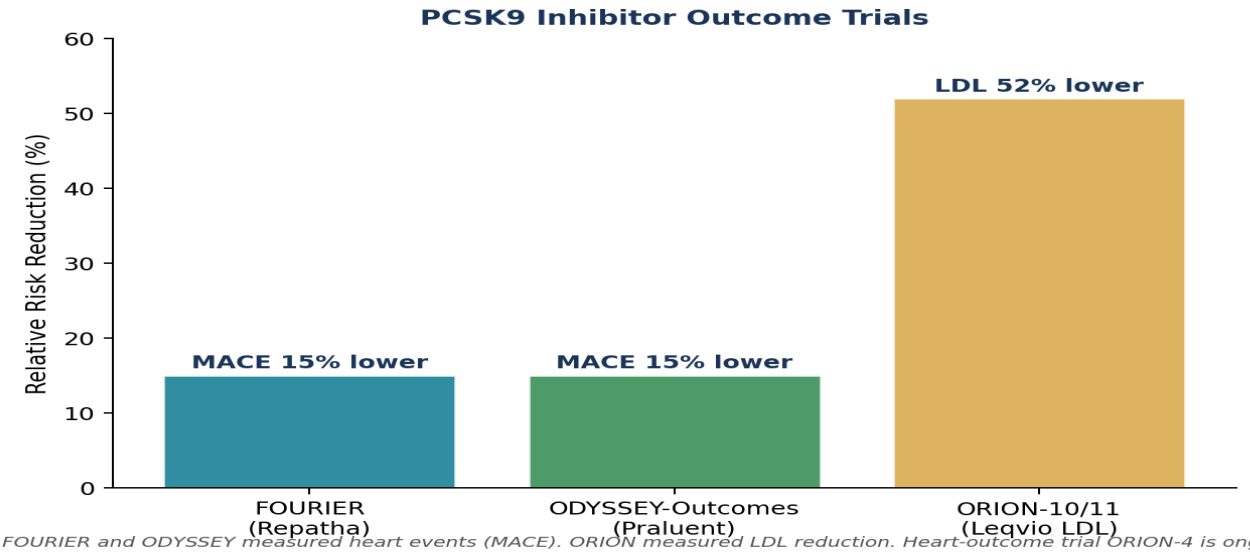
- Some very-high-risk patients have had a prior MI, stroke, or multi-vessel CAD. Even a max statin plus ezetimibe may not bring their LDL low enough. PCSK9 inhibitors close that gap.
- Patients with **familial hypercholesterolemia (FH)** have very high LDL from birth due to a gene change. PCSK9 inhibitors are often the only way to reach the LDL goal. HoFH (both gene copies affected) benefits most.
- Patients who cannot take any statin due to muscle pain or other side effects can use PCSK9 inhibitors on their own or with ezetimibe.
- **Safety:** large trials followed tens of thousands of patients for years. No major safety problems appeared. No memory or thinking issues. No diabetes signal. No extra infections. Even patients who reached very low LDL (below 20 mg/dL) had no harm.
- **Cost:** list price runs about $5,000-7,000 per year. But copay-help programs and insurance often bring your monthly cost to $0-25. Do not let the list price stop you from asking.
- Leqvio only needs two office visits per year after loading. Most patients get it in the cardiology or primary-care office.

Are You a PCSK9 Inhibitor Candidate?

Ideal candidate	Reasonable	Marginal	Not a candidate now
• Prior MI, stroke, or PCI	• Familial hypercholesterolemia	• Primary prevention with added risk factors	• LDL already at goal on statin or ezetimibe
• LDL above 70 on max statin plus ezetimibe	• Multi-vessel CAD	• Family history alone, no ASCVD	• No ASCVD and low risk score
• Strong need for more LDL lowering	• Statin intolerance (documented)	• LDL only a bit above goal	• Very high triglycerides, not yet treated
• Insurance likely to approve	• Repeat CV events on statin	• Insurance approval less certain	• Pregnancy or planned pregnancy

Treatment Options

- **Repatha (evolocumab):** 140 mg shot under the skin every 2 weeks, OR 420 mg shot every 4 weeks. You inject it yourself with a pen or auto-injector. Keep it in the fridge. Let it reach room temp before you inject.
- **Praluent (alirocumab):** 75 mg shot under the skin every 2 weeks. The dose can go up to 150 mg if needed. Self-injected. Store and handle the same way as Repatha.
- **Leqvio (inclisiran):** 284 mg shot on day 0, then again on day 90 (loading doses), then every 6 months. Given in the office -- no self-injection needed. That is only 2 shots per YEAR for upkeep.
- **Use WITH your statin and ezetimibe** for the best result. PCSK9 inhibitors ADD to what you are already taking.
- **Storage:** Repatha and Praluent stay in the fridge. Leqvio is kept at room temp and given in the office.
- **Lab check:** get a lipid panel about 4-8 weeks after starting. Expect a big LDL drop.
- **Missed dose:** Repatha or Praluent -- inject as soon as you recall if it has been only a few days. If it has been longer, just resume your normal schedule. Leqvio -- your office will track your every-6-month schedule.



FOURIER and ODYSSEY measured heart events (MACE). ORION measured LDL reduction. Heart-outcome trial ORION-4 is ongoing.

FOURIER (n=27,564, evolocumab) and ODYSSEY-Outcomes (n=18,924, alirocumab) each showed about a 15% drop in MACE on top of max statin. Leqvio (inclisiran) cuts LDL by about 52%. Its dedicated heart-outcome trial (ORION-4) is still running.

The Three PCSK9 Inhibitors -- Side-by-Side

Drug	Class	Dosing	Evidence
Repatha (evolocumab)	Antibody drug (anti-PCSK9)	140 mg shot q2wk OR 420 mg q4wk	FOURIER (MACE 15% lower)
Praluent (alirocumab)	Antibody drug (anti-PCSK9)	75-150 mg shot q2wk	ODYSSEY-Outcomes (MACE 15% lower)
Leqvio (inclisiran)	siRNA (reduces PCSK9 mRNA)	284 mg shot day 0, 90, then q6mo	ORION 9/10/11 (LDL 52% lower); MACE trial ongoing

Antibody Drug vs siRNA -- Two Routes to the Same Target

- **Antibody drugs (Repatha, Praluent):** bind to PCSK9 in the blood and block it. More LDL receptors stay on liver cells. More LDL gets cleared. The effect lasts 2-4 weeks, so you need a shot that often.
- **siRNA (Leqvio):** works one step earlier. It reduces how much PCSK9 the liver makes. One shot cuts PCSK9 output for about 6 months.
- **LDL drop is about the same:** roughly 50-60% on top of a statin for both types. No head-to-head trial has shown one is clearly stronger.
- **Leqvio has the easiest schedule:** only 2 office visits per year after loading. No self-injection needed. This matters a lot for patients who find biweekly or monthly shots hard to keep up.
- **Outcome data:** FOURIER and ODYSSEY-Outcomes (antibody drugs) have proven MACE benefit. ORION-4 (inclisiran outcomes, about 15,000 patients) results are expected around 2026-2027. Until then, inclisiran's heart benefit is based on its LDL reduction.
- **Choice in practice:** usually driven by insurance, your preference for self-injection vs office visits, and your medical history. All three are good options for the right patient.

Insurance prior auth -- what to show: Your doctor needs to document (1) established ASCVD (prior MI, stroke, PCI, CABG, or multi-vessel CAD), (2) LDL above 70 mg/dL (some plans require above 100) on the highest statin dose you can take, and (3) a trial of ezetimibe or a reason you cannot take it. Also let our office know if you have FH -- that is a separate approval path. Copay-help cards from each maker usually bring cost to **$0-25 per month** once approved.

Risks, Benefits, and Alternatives

Every choice has trade-offs. Use this table to start the shared decision conversation.

Option	Risks	Benefits	Alternatives
PCSK9 antibody drug (Repatha or Praluent)	Shot under the skin every 2-4 weeks. About 5% of people get mild redness at the shot site. Cost is often low with copay cards.	LDL drops 50-60% on top of statin. MACE drops 15%. Long-term safety is well proven.	Leqvio (less frequent shots), ezetimibe alone (less potent), no further treatment.
Leqvio (inclisiran) -- siRNA drug	Shot under the skin only twice a year after loading. Same mild site reactions (~5%). Heart-outcome trial (ORION-4) still running.	Best for adherence -- only 2 office visits per year. LDL drop is the same as antibody drugs (~52%).	Repatha or Praluent (more outcome data), ezetimibe alone, bempedoic acid.
Bempedoic acid (Nexletol)	Oral pill. LDL drops about 20%. Less potent than PCSK9 inhibitors. Slight rise in gout risk.	Oral, lower cost, no shot. Modest MACE reduction shown in CLEAR-Outcomes trial.	PCSK9 inhibitor (more potent), ezetimibe, or a combination.
Ezetimibe alone (after max statin)	Cuts LDL by only about 18-20% more. May not reach goal in very high-risk patients.	Cheap, oral, and very well tolerated. IMPROVE-IT showed CV outcome benefit.	Add a PCSK9 inhibitor if still above goal. Can also add bempedoic acid.
Max statin only -- no add-on therapy	Leaves residual risk in very-high-risk patients. LDL may stay above goal.	No added cost or side effects.	Add ezetimibe or a PCSK9 inhibitor if you are a candidate.

Common Misconceptions

Myth	Reality
PCSK9 inhibitors replace statin therapy.	Not true. They ADD to it. Trials enrolled patients already on the highest statin dose. That is how the 15% MACE benefit was measured. Stopping your statin to start a PCSK9 inhibitor is not the right plan for most people.
PCSK9 inhibitors are only for very high LDL.	They are most often used when LDL stays above 70 mg/dL despite max statin plus ezetimibe AND you have ASCVD or familial hypercholesterolemia. You can qualify even if LDL is only a bit above goal, as long as your event risk is high.
Lowering LDL too far is harmful.	FOURIER and ODYSSEY enrolled patients who reached LDL below 25 mg/dL. No safety problems appeared. No memory issues. No extra hemorrhagic stroke. No diabetes signal beyond the small statin effect.
I cannot afford it.	Do not assume that. Copay-help programs (Repatha Ready, Praluent Connect, Leqvio Patient Support) and insurance prior-auth often bring cost to $0-25 per month. Ask us.
The shot is too hard to learn.	Modern pen and auto-injector devices are made for self-use. Most patients learn in one nurse visit. Leqvio is given in the office twice a year -- no self-injection at all.
PCSK9 inhibitors only have LDL data, not heart data.	Not true for evolocumab and alirocumab. FOURIER (27,564 patients) and ODYSSEY-Outcomes (18,924 patients) both showed about a 15% MACE reduction. Inclisiran (Leqvio) has strong LDL data. Its dedicated heart-outcome trial (ORION-4, about 15,000 patients) is still running.

Possible Complications

Knowing what can go wrong helps you spot problems early. Most complications are uncommon, especially with treatment.

Where / What	What Can Happen
Shot site reactions (~5%)	Mild redness, itching, or swelling at the shot site. This usually clears in 24-48 hours. Rotate shot sites. Let the syringe reach room temp before you inject.
Allergic reactions (rare)	Most are mild -- rash or hives. Severe reactions are very rare. If you have had a severe allergic reaction to an antibody drug before, tell us before starting.
Flu-like symptoms (mild, short-lived)	Some patients feel mild flu-like symptoms in the first few days after a shot. This usually goes away on its own and almost never requires stopping the medicine.
Serious allergic reactions (very rare)	Ongoing shot-site reactions or body-wide symptoms need a doctor visit. Switching to Leqvio is sometimes an option.
Cost and access (the most common barrier)	Without help, list price is $5,000-7,000 per year. Most patients get aid that brings cost to $0-25 per month. The prior-auth paperwork takes some time.
Pregnancy uncertainty	Safety data in pregnancy is limited. We usually hold this medicine during pregnancy and breastfeeding. Talk with your cardiologist and OB.

Points to Know

If you remember nothing else, remember these key points.

- PCSK9 inhibitors ADD to statin therapy -- they do not replace it.
- They cut LDL by 50-60% on top of the highest statin dose you can take.
- MACE reduction in outcome trials: about 15% (FOURIER, ODYSSEY-Outcomes).
- Leqvio is dosed only TWICE A YEAR after loading -- the easiest schedule.
- Insurance plus copay help often brings cost to $0-25 per month.
- Standard candidate: ASCVD plus LDL above 70 on max statin plus ezetimibe.
- Also for: familial hypercholesterolemia (HeFH and HoFH) and statin intolerance.
- Safety is excellent -- no major problems even at very low LDL levels.

When to Call Us - and When to Call 911

If you are not sure, call. We would rather hear from you twice than miss a real problem.

- Large redness or swelling at the shot site that lasts more than 48 hours -- call us this week.
- Severe allergic reaction (rash, swelling, trouble breathing) -- call 911.
- New or worse muscle pain after starting -- call us this week. This is more often a statin issue, but we need to check.
- Cannot get the medicine due to insurance problems -- call us to start the prior-auth process.
- Missed a Repatha or Praluent dose by more than a week -- call to ask about re-loading.
- Planning a pregnancy -- call us. PCSK9 inhibitor safety in pregnancy is not well studied. We usually hold the medicine during pregnancy.
- Major surgery coming up -- usually no need to stop, but check with us first.
- No follow-up lipid panel scheduled -- call us. We want a recheck about 4-8 weeks after you start.

Office: (727) 943-5200

Trusted Resources

The links below are the trusted resources Dr. Ali used to write this guide and that he recommends you visit for more information. Each is a clickable link in the digital version and a Short.io tracked URL on the printed version.

- Repatha -- Patient Support (Amgen) - Maker resources for evolocumab, including copay-card details.
- Praluent -- Patient Support - Maker resources for alirocumab.
- Leqvio -- Patient Support (Novartis) - Maker resources for inclisiran, including office-visit scheduling.
- AHA -- Cholesterol and PCSK9 Inhibitors - AHA patient overview of cholesterol-lowering medicines, including PCSK9 inhibitors.
- Cleveland Clinic -- PCSK9 Inhibitors - Cleveland Clinic patient-friendly overview.
- National Lipid Association -- Patient Resources - NLA patient education on lipid disorders, including PCSK9 inhibitors.

Sources Used to Build This Guide

Every recommendation in this guide is grounded in one or more of the studies, guidelines, or trusted resources below. Short links are tracked so Dr. Ali can see which references patients are reading; nothing personally identifying is captured.

- FOURIER Trial — Evolocumab and Cardiovascular Outcomes (Sabatine et al., NEJM 2017; PMID 28304224) *[Clinical Trial]*
  Pivotal trial: 27,564 patients with ASCVD on max statin; evolocumab reduced MACE by 15% (CV death/MI/stroke/coronary revasc/UA hospitalization).
- ODYSSEY-Outcomes Trial — Alirocumab After ACS (Schwartz et al., NEJM 2018; PMID 30403574) *[Clinical Trial]*
  Pivotal trial: 18,924 ACS patients; alirocumab reduced MACE by 15%; mortality reduction in highest-LDL subgroup.
- ORION-10 / ORION-11 — Inclisiran for LDL Reduction (Ray et al., NEJM 2020; PMID 32302303) *[Clinical Trial]*
  Pivotal trials of inclisiran: 52% additional LDL reduction with twice-yearly dosing after loading.
- 2022 ACC ECDP on the Role of Nonstatin Therapies for LDL-C Lowering (Lloyd-Jones et al., JACC) *[Guideline]*
  ACC expert consensus on when to add ezetimibe, bempedoic acid, PCSK9i, and inclisiran on top of statin therapy.
- 2018 AHA/ACC/AACVPR Guideline on the Management of Blood Cholesterol (Grundy et al.) *[Guideline]*
  Primary US cholesterol guideline; defines very-high-risk ASCVD + LDL > 70 threshold for PCSK9i consideration.
- AHA — Cholesterol Medications *[Clinical]*
  AHA patient overview of cholesterol-lowering medications including PCSK9 inhibitors.
- Cleveland Clinic — PCSK9 Inhibitors *[Clinical]*
  Cleveland Clinic patient guide to PCSK9 inhibitors.
- Mayo Clinic — Cholesterol-Lowering Drugs *[Clinical]*
  Mayo overview of lipid-lowering drug classes including PCSK9i.
- National Lipid Association — Patient Resources *[Clinical]*
  NLA patient education on lipid management including newer agents.

About This Guide

Rias KS Ali, MD FACC | Board Certified in Interventional Cardiology & Cardiovascular Disease

4740 Mile Stretch Drive, Holiday FL 34690 | Office: (727) 943-5200 | Fax: (727) 943-5201 | RiasAliMD.com

Version: 2026-08-15

Reviewer note: Reviewed AHA, ACC, NLA, Cleveland Clinic, and Mayo Clinic patient pages. This guide adds a bar chart of LDL reduction, a drug-class table (antibody vs siRNA), and step-by-step insurance prior-auth guidance.

Disclaimer

This guide is for educational purposes only and does not replace medical advice from your physician. Recommendations may not apply to every patient. Always follow the specific instructions of Dr. Ali and your care team. In an emergency call 911 or go to the nearest emergency department.

Take This Guide With You

Scan or visit: https://go.riasalimd.com/pcsk9-guide

Online: https://go.riasalimd.com/pcsk9-guide

Office: (727) 943-5200

4740 Mile Stretch Drive, Holiday FL 34690 | Office: (727) 943-5200 | Fax: (727) 943-5201 | RiasAliMD.com