

PCSK9 inhibitors

Injectable agents that stop PCSK9 destroying hepatic LDL receptors, so receptors return to the cell surface and clear more LDL cholesterol from the circulation.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/pcsk9-inhibitors>

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Quick revision

One Liner: PCSK9 normally binds hepatic LDL receptors and sends them for lysosomal destruction; block PCSK9 and those receptors are recycled back to the cell surface instead, which is why LDL cholesterol falls by roughly half or more.

1. PCSK9 is made by hepatocytes and secreted into plasma, where it binds LDL receptors and facilitates their lysosomal degradation. [1]
2. Losing LDL receptors reduces receptor density on the cell membrane and therefore reduces clearance of LDL cholesterol from the blood. [1]
3. Inhibiting PCSK9 preserves recycling of the receptor to the cell surface, so more LDL particles are taken up and circulating cholesterol falls. [1]
4. Three agents are approved: alirocumab and evolocumab, which are monoclonal antibodies, and inclisiran, a small interfering RNA. [1]
5. Inclisiran differs mechanistically by silencing PCSK9 gene expression inside the cell rather than binding the circulating protein. [1]
6. LDL cholesterol falls by about 45% to 65%, whether the agent is used alone or added to a statin. [1]
7. All three agents are given by subcutaneous injection; none is available as an oral preparation. [1]
8. Injection-site reactions are the adverse effect common to all three agents. [1]
9. No dose adjustment is required for mild or moderately impaired hepatic or renal function, though data are limited in severe disease. [1]

Overview

1. Proprotein convertase subtilisin/kexin type 9 is made by hepatocytes and secreted into the plasma, where it binds LDL receptors and facilitates their degradation in the lysosome. The consequence is fewer receptors on the hepatocyte membrane and reduced clearance of LDL cholesterol. Blocking PCSK9 reverses that sequence: the receptor is recycled to the cell surface instead of destroyed, uptake of LDL particles increases and circulating cholesterol falls. [1]
2. Three agents are approved. Alirocumab and evolocumab are monoclonal antibodies that neutralise PCSK9 already circulating in plasma, injected subcutaneously at intervals of weeks. Inclisiran is a synthetic double-stranded small interfering RNA directed against the messenger RNA of PCSK9, which prevents the protein being made at all and moves to maintenance dosing every six months after its initial and three-month doses. [1][3]
3. The class lowers LDL cholesterol by roughly 45% to 65%, alone or added to a statin, and two cardiovascular outcome trials support it: FOURIER with evolocumab and ODYSSEY OUTCOMES with alirocumab each reported a 15% reduction in their primary composite endpoint. Tolerability is generally good, with injection-site reactions the shared complaint and hepatotoxicity conspicuously absent. [1][2]

Classification and drug examples

Intro: The class divides by molecular type rather than by potency, because how the drug is built determines how often it must be given and how it intercepts PCSK9 - before the protein is made, or after it has been secreted.

1. Name: Anti-PCSK9 monoclonal antibodies

1. Note: Bind PCSK9 already circulating in the plasma, so the LDL receptor is no longer marked for lysosomal degradation. Given subcutaneously at intervals of weeks.

1. Name: Evolocumab

1. Route: Subcutaneous

1. Note: A human monoclonal antibody to PCSK9 that increases the LDL receptor and so increases uptake of LDL particles; approved use extends to children aged 10 years and over with familial hypercholesterolaemia. [2][1]

2. Name: Alirocumab

2. Route: Subcutaneous

2. Note: Studied in ODYSSEY OUTCOMES; elevated transaminases and rare hypersensitivity vasculitis appear in its adverse effect list. [1] [1]

2. Name: Small interfering RNA directed at PCSK9

2. Note: Acts inside the hepatocyte to silence PCSK9 gene expression, so the protein is never secreted. The long interval between maintenance doses follows from that upstream point of action.

Name: Inclisiran

Route: Subcutaneous

Note: A synthetic double-stranded small interfering RNA against the messenger RNA of PCSK9; no contraindications are listed for it. [3][1] [1][3]

Mechanism of action

Summary: PCSK9 binds hepatic LDL receptors and directs them to lysosomal degradation; inhibiting it - by antibody neutralisation of the secreted protein or by RNA silencing of its synthesis - preserves receptor recycling to the cell surface and increases clearance of LDL cholesterol.

Target: Proprotein convertase subtilisin/kexin type 9 (PCSK9)

Cidal Static: not applicable

Kill Kinetics: not applicable

1. Step: 1

1. Title: PCSK9 is produced and secreted by the hepatocyte

1. Detail: The protein is a product of hepatocytes and is secreted into the plasma, where it is free to interact with LDL receptors. [1]

2. Step: 2

2. Title: It binds the LDL receptor and marks it for destruction

2. Detail: Binding facilitates lysosomal degradation of the receptor, reducing receptor density on the cell membrane. [1]

3. Step: 3

3. Title: LDL clearance falls as receptors are lost

3. Detail: With fewer receptors available, less LDL cholesterol is removed from the circulation, so plasma concentrations rise. [1]

4. Step: 4

4. Title: The drug removes PCSK9 from the equation

4. Detail: An antibody neutralises the circulating protein, while the small interfering RNA prevents it being synthesised by targeting its messenger RNA. [1][3]

5. Step: 5

5. Title: Receptor recycling is preserved and LDL falls

5. Detail: The LDL receptor returns to the cell surface rather than being degraded, uptake of LDL particles rises, and circulating LDL cholesterol falls by roughly 45% to 65%. [1]

Major clinical uses

1. Drug: Evolocumab

1. Organism: Not applicable
1. Indication: Established cardiovascular disease or high cardiovascular risk, to reduce LDL cholesterol further
1. Line: adjunct
1. Note: Supported by the FOURIER trial, which reported a 15% reduction in its primary composite endpoint. [1]
2. Drug: Alirocumab
2. Organism: Not applicable
2. Indication: Primary hyperlipidaemia, including heterozygous familial hypercholesterolaemia
2. Line: adjunct
2. Note: Supported by ODYSSEY OUTCOMES, with greater absolute benefit where baseline LDL cholesterol was higher. [1]
3. Drug: PCSK9 inhibitors as a class
3. Organism: Not applicable
3. Indication: Homozygous familial hypercholesterolaemia, as adjunctive therapy
3. Line: adjunct
3. Note: Used alongside other lipid-lowering treatment rather than as a stand-alone measure in this setting. [1]
4. Drug: Evolocumab
4. Organism: Not applicable
4. Indication: Familial hypercholesterolaemia in children aged 10 years and over
4. Line: targeted
4. Note: A paediatric extension of the indication that applies to this agent rather than to the whole class. [1]
5. Drug: Inclisiran
5. Organism: Not applicable
5. Indication: Heterozygous familial hypercholesterolaemia, or a history of cardiovascular disease with inadequate LDL lowering despite statin therapy
5. Line: adjunct
5. Note: The twice-yearly maintenance schedule is its distinguishing practical feature. [3]

Pharmacokinetics

1. Drug: Evolocumab
1. Route: Subcutaneous
1. Absorption: Subcutaneous administration; no oral formulation exists
1. Csf Penetration: Not clinically relevant for a monoclonal antibody
1. Metabolism: Protein catabolism rather than hepatic enzymes
1. Elimination: See prescribing reference
1. Half Life: Not specified in the source used here
1. Dose Adjust: None required for mild or moderate hepatic or renal impairment [1][2]
2. Drug: Alirocumab
2. Route: Subcutaneous
2. Absorption: Subcutaneous administration at intervals of weeks
2. Csf Penetration: Not clinically relevant for a monoclonal antibody
2. Metabolism: Protein catabolism rather than hepatic enzymes
2. Elimination: See prescribing reference
2. Half Life: Not specified in the source used here
2. Dose Adjust: Mild to moderate hepatic or renal impairment needs no adjustment [1]
3. Drug: Inclisiran
3. Route: Subcutaneous
3. Absorption: Subcutaneous administration, with maintenance dosing every six months after the initial and

three-month doses

3. Csf Penetration: Not clinically relevant

3. Metabolism: Acts intracellularly on the messenger RNA of PCSK9

3. Elimination: See prescribing reference

3. Half Life: The duration of effect greatly exceeds plasma residence

3. Dose Adjust: See prescribing reference [1][3]

1. Every member of this class is injected. That single fact drives much of how the drugs are used, because it introduces device handling, injection-site reactions and, for evolocumab, a latex caution that no oral lipid-lowering drug carries. [1]

2. Response is assessed by rechecking LDL cholesterol several weeks after starting therapy or after any change, before considering further escalation. [1]

3. Data gaps remain for severe renal and severe hepatic disease, which is a limitation of the evidence rather than a demonstrated hazard. [1]

4. This page gives no dose regimens by design. Product-specific amounts and intervals depend on the agent and indication and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Injection-site reactions

1. Detail: Reported with evolocumab, alirocumab and inclisiran alike, and the one adverse effect genuinely common to the whole class. [1]

2. Effect: Nasopharyngitis and myalgia

2. Detail: Both are listed for the two monoclonal antibodies, with headache also reported for evolocumab. [1]

3. Effect: Arthralgia and respiratory or urinary symptoms

3. Detail: Reported with inclisiran, for which no severe events were recorded. [1]

4. Effect: Transient aminotransferase elevation

4. Detail: With inclisiran these arose in fewer than 1% of patients and were invariably transient, mild to moderate, and unaccompanied by symptoms or jaundice. [3]

1. Effect: Hypersensitivity reactions including angio-oedema

1. Detail: Rare, and described with evolocumab; prior hypersensitivity is a contraindication to further use of the antibodies.

1. Action: Discontinue and seek urgent assessment if a hypersensitivity reaction occurs. [1]

2. Effect: Hypersensitivity vasculitis

2. Detail: Listed as a rare reaction to alirocumab.

2. Action: A new vasculitic rash during therapy warrants specialist evaluation. [1]

1. Drug: Evolocumab

1. Effect: Serum ALT or AST above three times the upper limit of normal occurred in 0.4% to 1.8% of recipients compared with 0.6% to 1.6% on placebo, and no instances of acute clinically apparent liver injury were reported. [2]

2. Drug: Inclisiran

2. Effect: Since approval and wider use, no published reports of liver injury have been attributed to it, and it carries the lowest hepatotoxicity likelihood rating. [3]

3. Drug: Alirocumab

3. Effect: Elevated transaminases appear among its listed adverse effects, unlike evolocumab. [1]

Contraindications, precautions and interactions

Previous hypersensitivity reaction to alirocumab or evolocumab. [1]

1. Latex allergy, for which caution is advised with evolocumab because of the delivery device. [1]

2. Severe renal or severe hepatic disease, where the evidence base is incomplete even though mild and moderate impairment need no dose adjustment. [1]

3. No contraindications are listed for inclisiran, which does not mean the drug is free of considerations but that none has been formally recorded. [1]

1. With: Statins

1. Effect: Routinely combined; the LDL reduction of 45% to 65% is described both as monotherapy and alongside statin therapy. [1]

2. With: Cytochrome P450 substrates

2. Effect: Not a concern in the way it is for statins, because antibodies are cleared by protein catabolism and inclisiran acts on messenger RNA rather than through hepatic drug-metabolising enzymes. [1][3]

Comparison tables

Title: The three PCSK9-lowering agents compared

Caption: Molecular type determines the point of interception and the dosing interval. Therapy selection belongs to the treating clinician working from a current prescribing reference.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: type

2. Label: Molecular type

3. Key: point

3. Label: Point of interception

4. Key: interval

4. Label: Administration interval

5. Key: trial

5. Label: Outcome trial

1. Drug: Evolocumab

1. Type: Human monoclonal antibody

1. Point: Neutralises PCSK9 circulating in plasma

1. Interval: Two-weekly to monthly

1. Trial: FOURIER [1][2]

2. Drug: Alirocumab

2. Type: Monoclonal antibody

2. Point: Neutralises PCSK9 circulating in plasma

2. Interval: Two-weekly to four-weekly

2. Trial: ODYSSEY OUTCOMES [1]

3. Drug: Inclisiran

3. Type: Small interfering RNA

3. Point: Silences PCSK9 messenger RNA inside the hepatocyte

3. Interval: Six months for maintenance dosing

3. Trial: Not among the two trials cited here [1][3]

High-yield exam pearls

1. Pearl: PCSK9 is a receptor destroyer, not a cholesterol producer.

1. Why: It does nothing to cholesterol synthesis. Its effect on plasma LDL is entirely indirect, through binding LDL receptors and sending them to the lysosome so that fewer remain to clear LDL. [1]

2. Pearl: Two mechanisms, one target.

2. Why: The antibodies neutralise PCSK9 already circulating in plasma, while inclisiran prevents the protein being made by silencing its messenger RNA. The clinical end point is the same; the point of interception is not. [1][3]

3. Pearl: The dosing interval is the practical difference that patients notice.
3. Why: The monoclonal antibodies are injected at intervals of weeks, whereas inclisiran moves to maintenance dosing every six months after its initial and three-month doses. [1]
4. Pearl: Both outcome trials landed on the same headline number.
4. Why: FOURIER with evolocumab and ODYSSEY OUTCOMES with alirocumab each reported a 15% reduction in their primary endpoint, with greater absolute benefit in patients whose baseline LDL cholesterol was higher. [1]
5. Pearl: This is a remarkably liver-safe class.
5. Why: Evolocumab carries the lowest hepatotoxicity likelihood rating with no reported instances of clinically apparent liver injury, and no published reports of liver injury have been attributed to inclisiran since its approval. [2][3]
6. Pearl: Latex allergy is an easily missed practical caution.
6. Why: Caution is advised with evolocumab in patients allergic to latex, a device-related rather than pharmacological consideration that only matters because these drugs come in injection systems. [1]

Common exam traps

1. Trap: "PCSK9 inhibitors block cholesterol synthesis like a statin."
1. Correction: They do not touch cholesterol synthesis. They prevent degradation of the LDL receptor, so more receptors survive to clear LDL from plasma. [1]
2. Trap: "Inclisiran is just another monoclonal antibody."
2. Correction: It is a synthetic double-stranded small interfering RNA directed against the messenger RNA of PCSK9, so it stops the protein being synthesised rather than neutralising it after secretion. [1][3]
3. Trap: "They are only useful in patients who cannot take a statin."
3. Correction: The 45% to 65% LDL reduction is described both as monotherapy and in combination with statin therapy, and the approved indications include patients on inadequately controlled statin treatment. [1][3]
4. Trap: "Renal or hepatic impairment rules this class out."
4. Correction: No dose adjustment is needed for mild or moderate hepatic or renal impairment. What exists is a data gap in severe disease, which is a different matter from a contraindication. [1]

Self-test questions

1. Question: What does PCSK9 normally do to the LDL receptor?
 1. It increases receptor synthesis in the hepatocyte nucleus
 2. It binds the receptor and facilitates its lysosomal degradation
 3. It transports the receptor from the cytoplasm to the cell surface
 4. It converts the receptor into a triglyceride transporter
1. Explanation: PCSK9 is secreted by hepatocytes into the plasma, binds LDL receptors and facilitates their degradation in the lysosome. Fewer surviving receptors means lower receptor density and reduced clearance of LDL cholesterol. [1]
2. Question: How does inhibiting PCSK9 lower plasma LDL cholesterol?
 1. By blocking hepatic cholesterol synthesis
 2. By binding LDL particles directly and clearing them through the reticuloendothelial system
 3. By preserving recycling of the LDL receptor back to the cell surface, increasing LDL uptake
 4. By preventing intestinal absorption of dietary cholesterol
2. Explanation: With PCSK9 neutralised or not produced, the LDL receptor escapes lysosomal destruction and returns to the membrane. The resulting rise in receptor density increases uptake of LDL particles and lowers circulating cholesterol. [1]
3. Question: How does inclisiran differ mechanistically from alirocumab and evolocumab?
 1. It is a small interfering RNA that silences PCSK9 gene expression rather than binding the circulating protein
 2. It is an oral small molecule inhibitor of PCSK9

3. It blocks the LDL receptor rather than PCSK9
4. It is a monoclonal antibody with a longer half-life
3. Explanation: Inclisiran is a synthetic double-stranded small interfering RNA directed against the messenger RNA of PCSK9, so it prevents the protein being made. The two antibodies instead bind PCSK9 that has already been secreted into plasma. [1][3]
4. Question: What magnitude of LDL cholesterol reduction is described for this class?
 1. About 5% to 10%
 2. About 13% to 20%
 3. About 45% to 65%
 4. About 80% to 90%
4. Explanation: LDL cholesterol falls by roughly 45% to 65%, achieved either as monotherapy or in combination with a statin. That is substantially more than a cholesterol absorption inhibitor achieves on its own. [1]
5. Question: Which pairing of outcome trial and drug is correct?
 1. FOURIER with alirocumab and ODYSSEY OUTCOMES with evolocumab
 2. FOURIER with evolocumab and ODYSSEY OUTCOMES with alirocumab
 3. IMPROVE-IT with evolocumab and FOURIER with inclisiran
 4. ODYSSEY OUTCOMES with inclisiran and FOURIER with ezetimibe
5. Explanation: FOURIER studied evolocumab and ODYSSEY OUTCOMES studied alirocumab, and each reported a 15% reduction in its primary endpoint. IMPROVE-IT is the ezetimibe trial. [1]
6. Question: Which adverse effect is reported across all three agents in this class?
 1. Injection-site reactions
 2. Rhabdomyolysis
 3. Cholelithiasis
 4. Hyperkalaemia
6. Explanation: Injection-site reactions are described for evolocumab, alirocumab and inclisiran alike. Nasopharyngitis and myalgia accompany the antibodies, while arthralgia is listed with inclisiran. [1]
7. Question: What does the evidence show about liver safety in this class?
 1. Clinically apparent liver injury is common and requires quarterly monitoring
 2. Aminotransferase elevations are frequent and progressive
 3. Enzyme elevations are uncommon and no instances of clinically apparent liver injury have been attributed to evolocumab or inclisiran
 4. The class is contraindicated in any chronic liver disease
7. Explanation: Enzyme elevations above three times the upper limit of normal occurred at rates similar to placebo with evolocumab, and inclisiran produced ALT elevations in under 1% of patients that were transient and asymptomatic. Both carry the lowest hepatotoxicity likelihood rating. [2][3]

Frequently asked questions

1. Question: Why can these drugs not be given by mouth?
 1. Answer: Because of what they are. Two are monoclonal antibodies and the third is a double-stranded RNA molecule, none of which survives digestion intact, so all three are given by subcutaneous injection. [1][3]
 2. Question: How much do PCSK9 inhibitors lower LDL cholesterol?
 2. Answer: By roughly 45% to 65%, whether used alone or added to statin therapy. That reduction is the reason the class is reserved for patients whose LDL remains too high despite established treatment. [1]
 3. Question: Is inclisiran a PCSK9 inhibitor in the same sense as the antibodies?
 3. Answer: It lowers PCSK9, but by a different route. The antibodies bind the protein after it has been secreted, whereas inclisiran is a small interfering RNA that prevents the protein from being made at all. [1][3]
 4. Question: Do these drugs need liver monitoring?

4. Answer: Enzyme elevations are uncommon and, with evolocumab, occurred at rates comparable to placebo. No instances of clinically apparent liver injury have been attributed to evolocumab, and none has been published for inclisiran since its approval. [2][3]

5. Question: What evidence supports their use beyond the lipid number?

5. Answer: Two cardiovascular outcome trials. FOURIER studied evolocumab and ODYSSEY OUTCOMES studied alirocumab, each reporting a 15% reduction in its primary endpoint, with greater absolute benefit where baseline LDL cholesterol was higher. [1]

References

[1] PCSK9 Inhibitors (StatPearls). StatPearls Publishing / NCBI Bookshelf 2026.

<https://www.ncbi.nlm.nih.gov/books/NBK448100/>

[2] Evolocumab (LiverTox). LiverTox, NIDDK / NCBI Bookshelf 2012. <https://www.ncbi.nlm.nih.gov/books/NBK548469/>

[3] Inclisiran (LiverTox). LiverTox, NIDDK / NCBI Bookshelf 2012. <https://www.ncbi.nlm.nih.gov/books/NBK588654/>

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