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CONTEMPORARY REVIEW

Harnessing RNA Interference for Cholesterol Lowering: The Bench-to-Bedside Story of Inclisiran

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ABSTRACT: Lowering low-density lipoprotein cholesterol (LDL-C) is a cornerstone of reducing risk for atherosclerotic cardiovascular disease. Despite the approval of nonstatin therapies for LDL-C lowering over the past 2 decades, these medications are underused, and most patients are still not at guideline-recommended LDL-C goals. Barriers include poor adherence, clinical inertia, concern for side effects, cost, and complex prior authorization processes. With atherosclerotic cardiovascular disease-related mortality increasing globally, there remains a need for additional therapeutic options for lowering LDL-C as part of an atherosclerotic cardiovascular disease prevention strategy. Following the identification of PCSK9 (proprotein convertase subtilisin/kexin type 9) as a promising therapeutic target, inclisiran was developed using the natural process of RNA interference for robust, sustained prevention of hepatic PCSK9 synthesis. Twice-yearly maintenance subcutaneous inclisiran (following initial loading doses at Day 1 and Day 90) reduces circulating LDL-C levels by ≈50% versus placebo when added to maximally tolerated statins. Long-term safety and tolerability of inclisiran have been assessed, with studies underway to evaluate the effects of inclisiran on cardiovascular outcomes and to provide additional safety and effectiveness data. In 2021, <20 years after the discovery of PCSK9, inclisiran became the first RNA interference therapeutic approved in the United States for LDL-C lowering in patients with established atherosclerotic cardiovascular disease or familial hypercholesterolemia and has since been approved for use in patients with primary hyperlipidemia. This article reviews the journey of inclisiran from bench to bedside, including early development, the clinical trial program, key characteristics of inclisiran, and practical points for its use in the clinic.

Key Words: atherosclerotic cardiovascular disease ■ inclisiran ■ low-density lipoprotein cholesterol ■ proprotein convertase subtilisin/kexin type 9 ■ small interfering RNA

See Viewpoint by Gidding

Cardiovascular disease is the leading cause of death globally and is increasing in incidence worldwide.[1] Atherosclerotic cardiovascular disease (ASCVD), which accounts for up to 80% of cardiovascular-related deaths, is associated with substantial morbidity/mortality and economic burden on health care systems.[1] Persistently elevated low-density lipoprotein cholesterol (LDL-C) is a well-established causal factor in ASCVD[2]; lowering LDL-C levels reduces ASCVD risk in a log-linear relationship and is an important strategy for primary and secondary prevention of ASCVD.[2–4]

In addition to lifestyle modifications, most patients with elevated LDL-C require pharmacological therapy for lipid lowering.[3] β-Hydroxy β-methylglutaryl-coenzyme A reductase inhibitors (statins) revolutionized ASCVD management following their discovery in the 1970s and US Food and Drug Administration (FDA) approval in 1987[5]; they became the cornerstone of pharmacological therapy for ASCVD prevention.[3,5] Despite the wealth of evidence from randomized controlled trials demonstrating the clinical benefit of statin therapy, statins are underused in real-world clinical practice due to issues including patient adherence, concerns about side effects (including statin-associated muscle symptoms), and clinical inertia.[6–8] Additionally, for many patients, including those at very

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Nonstandard Abbreviations and Acronyms

LNP	lipid nanoparticle
LLT	lipid-lowering therapy
RNAi	RNA interference

high risk of cardiovascular events, LDL-C lowering remains suboptimal with statin therapy alone.[3,4,9–11]

Risk associated with LDL-C is driven by both magnitude of LDL-C elevation and cumulative duration of exposure to high LDL-C levels. Thus, the most effective strategy for reducing lipid-related risk of ASCVD is early lowering of LDL-C and maintaining low levels over a long duration.[12] As such, to optimize ASCVD prevention, there remains an unmet need for therapies to further reduce LDL-C levels in addition to statin therapy alone. Following the introduction of nonstatin lipid-lowering therapies (LLTs), including ezetimibe and anti-PCSK9 (proprotein convertase subtilisin/kexin type 9) monoclonal antibodies, guidelines recommended increasingly lower LDL-C goals, suggesting the addition of nonstatin LLTs in patients for whom LDL-C lowering was insufficient with statins.[3,4,13] Despite these recommendations, registry studies demonstrated poor uptake of anti-PCSK9 monoclonal antibodies, ezetimibe, or combinations of these and maximally tolerated statins.[8,14–17] Studies estimate that ≈60% to 80% of people with ASCVD are not at LDL-C goals in the United States.[8,17]

Inclisiran, a novel small interfering RNA (siRNA), lowers LDL-C by inhibiting hepatic production of PCSK9 with twice-yearly maintenance dosing. Following clinical trials,[18,19] inclisiran was approved by the European Medicines Agency in 2020 for the treatment of adults with primary hypercholesterolemia or mixed dyslipidemia on maximally tolerated statin therapy, followed by FDA approval in 2021 for the treatment of adults with clinical ASCVD or heterozygous familial hypercholesterolemia (FH) on maximally tolerated statin therapy.[20,21] In July 2023, the FDA approved an expanded indication for inclisiran for LDL-C lowering in patients with primary hyperlipidemia.[22] Here, we summarize the development of inclisiran over the past 20 years (Figure 1)[18,20–44] and discuss practical guidance for the use of inclisiran in clinical practice.

PCSK9: IDENTIFICATION OF A NOVEL TARGET FOR LDL-C LOWERING

PCSK9 Discovery and Insights From Genetic Studies

PCSK9 is a proprotein convertase that acts nonenzymatically to increase endosomal and lysosomal degradation of cell surface receptors, most notably the LDL receptor (LDLR).[45] The *PCSK9* gene was first discovered in 2003 when Abifadel et al linked autosomal dominant FH in a French family with a gain-of-function point mutation in a locus on chromosome 1p32.[23] Following its initial discovery, numerous other loss- or gain-of-function mutations in this highly polymorphic gene were identified and associated with low or high levels of circulating LDL-C, respectively.[23,46–48] An individual heterozygous for 2 inactivating mutations in *PCSK9*, identified during the Dallas Heart Study, with no immunodetectable circulating PCSK9 and extremely low circulating LDL-C, appeared to have normal long-term reproductive and cognitive function, was normotensive, and had normal liver and renal function.[49] In a study of 653 Black African women in Zimbabwe, a nonsense variant of *PCSK9*, *C679X*, was found in 3.7% of participants and resulted in a 27% reduction in LDL-C compared with noncarriers.[50] Similar results were reported in the Atherosclerosis Risk in Communities study, in which nonsense mutations in *PCSK9* were present in 2.6% of Black participants, and were associated with a 28% LDL-C reduction and 88% reduction in the risk of coronary heart disease versus noncarriers.[47] Further evidence from a Mendelian randomization study demonstrated that variants in *PCSK9* and *HMGCR* (the gene encoding β-Hydroxy β-methylglutaryl-coenzyme A reductase, the enzyme inhibited by statins) have almost the same effect on cardiovascular event risk reduction per unit LDL-C lowering.[51] Taken together, this evidence identified PCSK9 as a target for LDL-C lowering and ASCVD risk reduction.

PCSK9: A Breakthrough in Cholesterol Homeostasis

Following the discovery of the *PCSK9* gene and its role in FH, the PCSK9 protein was identified as a predominantly hepatically synthesized, ≈75-kDa precursor protein (proPCSK9) inhibited by a prodomain.[45] The prodomain is autocatalytically cleaved in the endoplasmic reticulum but remains associated with the protein, forming a PCSK9/inhibitory prosegment complex that is secreted from the cell via the cis-Golgi.[52]

Hepatic uptake of LDL particles via the LDLR has a vital role in maintaining physiological cholesterol homeostasis. At the time of PCSK9 discovery, most regulation of the LDLR was thought to occur intracellularly.[53] However, in animal and in vitro models, PCSK9 protein was found to exert its effects predominantly extracellularly via interaction with the LDLR epidermal growth-factor-like domain A.[52] Binding of PCSK9 to the LDLR leads to a conformational change that prevents its recycling to the hepatocyte surface and results in PCSK9-LDLR lysosomal degradation.[45] PCSK9-driven

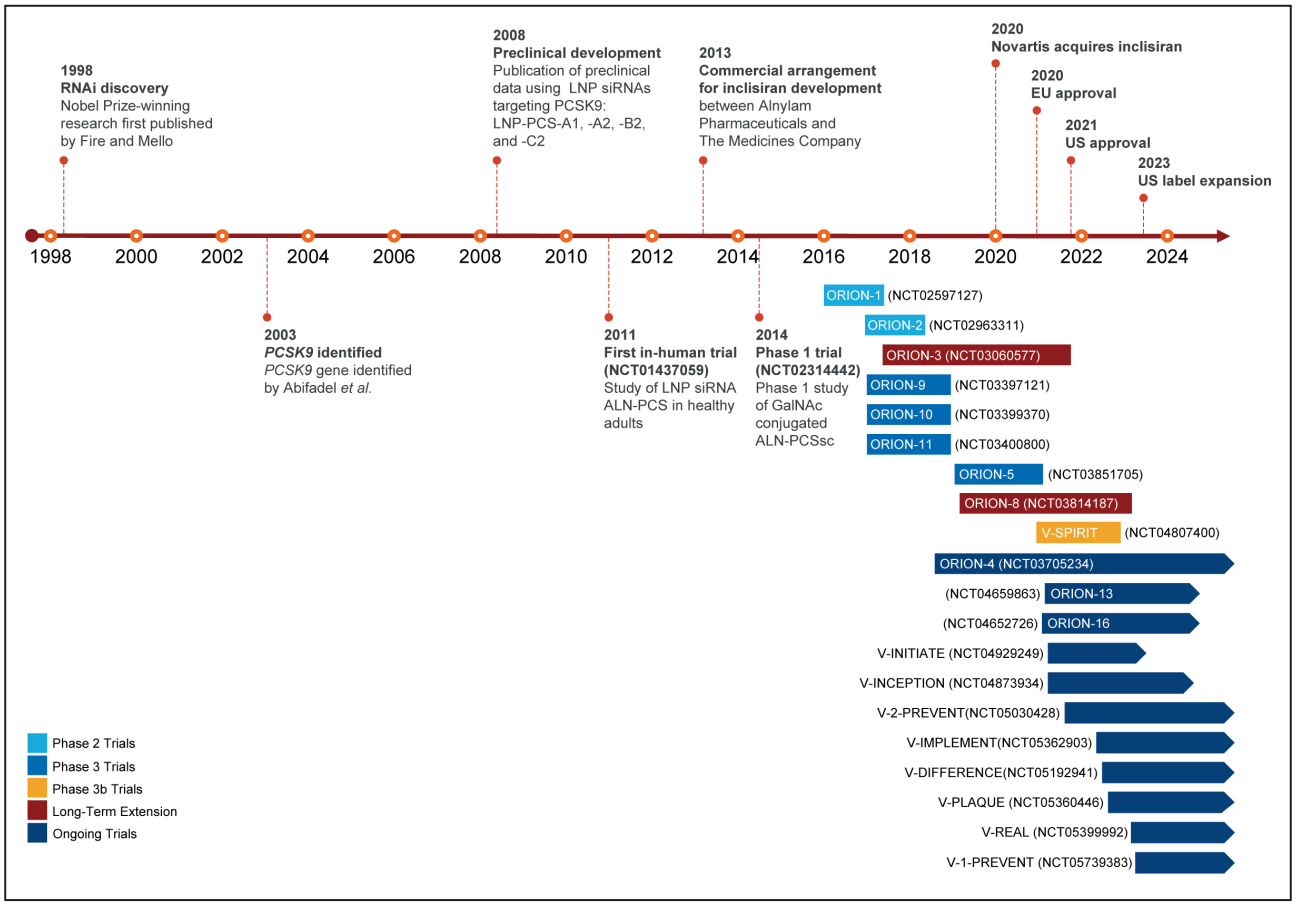

Figure 1. Timeline of inclisiran development.[18,20–44]
The start and estimated completion dates are correct as of the article submission date. EU indicates European Union; GalNAc, triantennary *N*-acetylgalactosamine; LNP, lipid nanoparticle; PCSK9, proprotein convertase subtilisin/kexin type 9; RNAi, ribonucleic acid interference; siRNA, small interfering RNA; US, United States; and V, VICTORION.

degradation of the LDLR and decreased intracellular LDLR recycling result in fewer LDLR available on the hepatocyte membrane and, thus, reduced LDL clearance from the blood.[52] This discovery presented a potential target for a pharmacological intervention designed to disrupt cholesterol homeostasis.

Inhibiting PCSK9 for Lipid Lowering

The interaction surface between PCSK9 and the epidermal growth-factor-like domain A in the LDLR is challenging to target pharmaceutically.[52] The PCSK9 proteolytic site is not required for its interaction with the LDLR, suggesting that any small molecule inhibitors designed to antagonize PCSK9 catalytic activity would need to enter the endoplasmic reticulum to inhibit PCSK9 cleavage and would not affect the extracellular PCSK9–LDLR interaction.[54]

Antibodies to reversibly neutralize extracellular PCSK9 were shown to successfully disrupt the PCSK9–LDLR interaction and to reduce LDLR degradation in proof-of-concept in vitro and animal studies.[55,56] Following promising results in mice and nonhuman primates,[56] 2 anti-PCSK9 monoclonal antibodies, alirocumab and evolocumab, were evaluated in clinical trials. These demonstrated LDL-C reductions of up to 60% to 70%, and in patients with a history of ASCVD, an ≈15% relative reduction in cardiovascular event risk versus standard of care when added to maximally tolerated statins, and were the first approved therapies targeting PCSK9 (Box 1).[57–61]

In addition to LDL-C lowering, anti-PCSK9 monoclonal antibodies reduce levels of lipoprotein (a) (LP(a)), an LDL-like particle identified as an independent, causal, genetically determined ASCVD risk factor, by ≈25% in clinical trial populations not enriched for patients with elevated Lp(a).[62,63] There are currently no approved therapies to treat elevated Lp(a), but RNA-targeted therapies that reduce Lp(a) by inhibiting the synthesis of apolipoprotein(a) are in clinical development, including the antisense oligonucleotide pelacarsen and the siRNA therapies olpasiran, zerlasiran (SLN360), and lepodisiran (LY3819469).[64]

Despite high rates of adherence to prescribed anti-PSCK9 monoclonal antibodies in clinical trials,

evidence from registry studies has demonstrated poor clinical uptake of anti-PCSK9 monoclonal antibodies and high rates of discontinuation in real-world clinical practice.[8,14,65] One study reported that <1% of patients with dyslipidemia, coronary artery disease, or coronary heart disease were prescribed anti-PCSK9 monoclonal antibodies in the United States between 2015 and 2017.[14] Potential historical reasons for poor uptake include burden of self-administration, high cost, and complex prior authorization processes.[8,14,15,65,66] Registry studies suggest that up to ≈80% of people with ASCVD are not at LDL-C goals despite the availability of anti-PCSK9 monoclonal antibodies and other oral LLTs,[8,16,17] suggesting there remains an unmet need for additional LLTs and strategies to improve patient access to existing LLTs.

INCLISIRAN: DEVELOPMENT AND CHARACTERISTICS

Harnessing RNA Interference for Pharmacological Therapy

The 2006 Nobel Prize-winning discovery that exogenously introduced RNA can interfere with gene expression was described by Fire and Mello in their 1998 pivotal research in *Caenorhabditis elegans*.[24] Following the discovery that gene expression can be silenced using exogenously introduced RNA, this was applied to targets such as PCSK9.

One method to prevent *PCSK9* gene expression is antisense oligonucleotide technology, which involves introducing short, single-stranded nucleotides that bind directly to mRNA. Although a second-generation antisense oligonucleotide was shown to reduce *PCSK9* mRNA and LDL-C levels by 92% and 38%, respectively, in preclinical mouse studies,[67] development was terminated due to binding affinity. A triantennary *N*-acetylgalactosamine (GalNAc)-conjugated antisense oligonucleotide that showed LDL-C reductions of >70% after 12 weeks' monthly subcutaneous dosing in phase 2b trials was discontinued for commercial reasons.[68]

Gene expression can also be silenced by exogenously introduced sequence-specific 21-/22-nucleotide double-stranded RNA by harnessing cells' natural mechanism to degrade mRNA, known as RNA interference (RNAi).[69] Inside the cytoplasm, these exogenously introduced double-stranded RNAs are cleaved to form siRNAs with a sense strand that facilitates uptake into the RNA-induced silencing complex (RISC) and an antisense strand that is complementary to the target mRNA. The sense strand is degraded while the antisense strand remains loaded in the RISC, acting as a template to hybridize with the target mRNA, leading to its catalytic cleavage.[70]

The discovery of RNAi, a natural process with a role in the regulation of protein synthesis and immunity,[70] led to the exploration of siRNA as a therapeutic strategy; however, key challenges in siRNA development included targeted delivery, stability, and off-target effects.[70,71] In the following years, modifications to improve biostability and novel delivery systems to facilitate selectivity, such as lipid nanoparticles (LNPs) or conjugation with triantennary GalNAc, were developed.[71] These advances led to the 2018 US FDA approval of patisiran (ALN TTR02), an LNP-formulated siRNA for hereditary transthyretin amyloidosis, as the first commercial RNAi-based therapeutic.[70,71] As of 2022, the siRNA therapeutics givosiran, lumasiran, and vutrisiran have also been approved by the US FDA for use in rare disease indications.[72]

RNAi as a therapeutic strategy for LDL-C lowering was first demonstrated in proof-of-concept preclinical studies. LNP-formulated siRNAs targeting PCSK9 (LNP-PCS-A1, -A2, -B2, and -C2) were shown to reduce PCSK9 mRNA levels by 60%–70% with reductions in cholesterol of up to 60% in rodents.[25] A single intravenous bolus of LNP-PCS-A2 or LNP-PCS-B2 in nonhuman primates resulted in rapid, durable (3 weeks) reduction in PCSK9 and LDL-C, with no significant effect on high-density lipoprotein cholesterol.[25] In a first-in-human study (n=32), a 1-hour intravenous infusion of LNP-formulated siRNA, ALN-PCS, demonstrated a safety profile similar to placebo and a mean 40% placebo-corrected reduction from baseline in LDL-C (nadir Day 10) at the highest dose (0.4 mg/kg; n=6).[26] Although LNP-formulated siRNAs targeting PCSK9 demonstrated efficacy, repeat intravenous doses were required for sustained silencing.[73] GalNAc conjugation facilitates liver-selective siRNA delivery via uptake by asialoglycoprotein receptors (ASGPRs), which are highly expressed on hepatocytes.[73] In early preclinical studies, GalNAc-conjugated siRNAs demonstrated robust and durable hepatic mRNA silencing with increased potency versus previous molecules, allowing for subcutaneous dosing.[73] This led to phase 1 clinical trials with GalNAc-conjugated ALN-PCSsc (inclisiran).[70]

Inclisiran Characteristics and Mechanism of Action

Inclisiran is a double-stranded RNA comprising a 21-base sense (passenger) strand and 23-base antisense (guide) strand; the antisense strand is highly specific and designed to hybridize with human PCSK9 mRNA, which may minimize the risk of off-target effects.[74,75] Inclisiran incorporates several important modifications that enhance stability and enable subcutaneous delivery. First, to protect the siRNA from rapid degradation in the plasma by exonucleases and endonucleases, 1 2′-deoxy, 12 2′-fluoro, and 31 2′-O-methyl

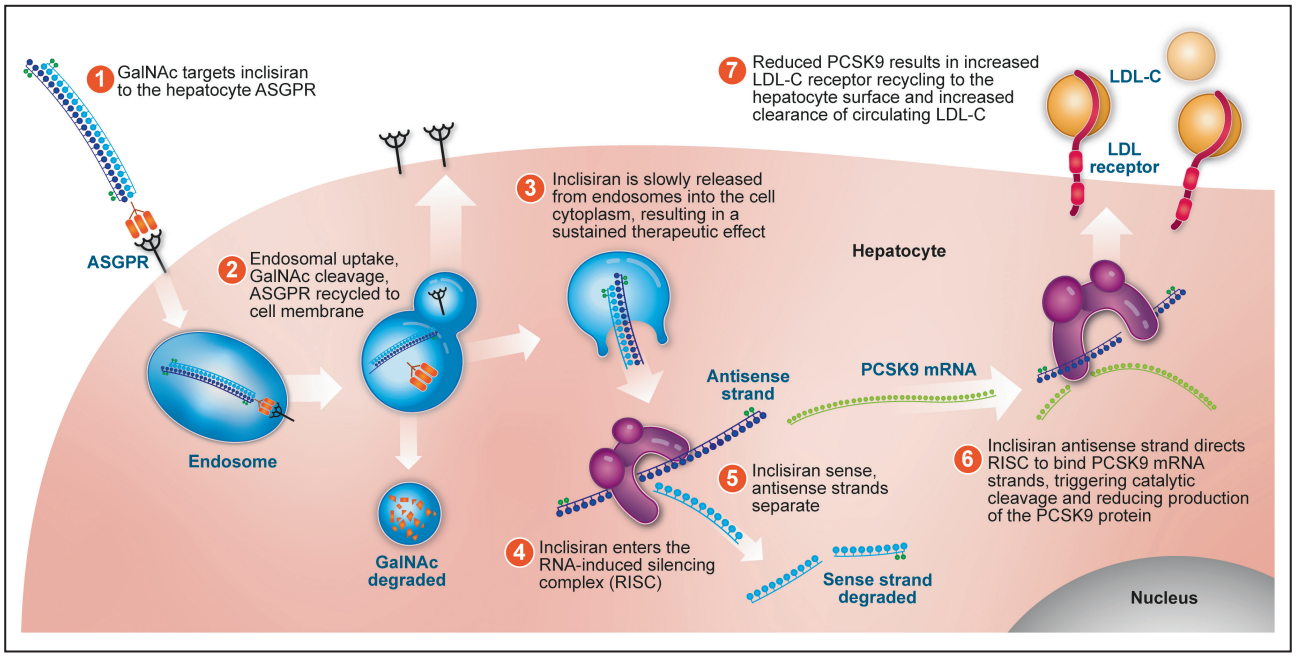

Figure 2. Inclisiran mechanism and key characteristics.[70,75]
(1) Inclisiran is conjugated with a triantennary GalNAc moiety at the 3′ end of the passenger strand. GalNAc is specifically recognized by ASGPR, which is widely expressed on hepatocytes; 1 2′-deoxy, 12 2′-fluoro, and 31 2'-O-methyl ribose-modified nucleotides confer stability; 5′-phosphorothioate modifications facilitate RISC loading. (2) The inclisiran-ASGPR interaction modifies the hepatocyte membrane, forming clathrin-coated vesicles and promoting the formation of endosomes in which the inclisiran-ASGPR complex enters the cell; ASGPR is recycled to the hepatocyte membrane, while the GalNAc moiety is degraded within the lysosome. (3) Inclisiran gradually exits the endosome, which may act as an intracellular store of inclisiran, increasing the duration of action from a single dose. (4) Active inclisiran is then loaded into the RISC. (5) The sense strand is degraded while the antisense strand remains within the complex; RISC protects the antisense strand from nucleases. (6) The antisense strand hybridizes with PCSK9 mRNA within the RISC, triggering its catalytic cleavage, thereby preventing translation and PCSK9 production; once loaded, one complex can prevent the translation of multiple copies of PCSK9 mRNA. (7) Decreased PCSK9 protein production results in increased LDLR recycling, leading to increased hepatic LDL-C clearance. ASGPR indicates asialoglycoprotein receptor; GalNAc, triantennary *N*-acetylgalactosamine; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; and RISC, RNA-induced silencing complex. Reproduced from Soffer et al 2022,[77] available under creative commons license CC BY-NC-ND 4.0.

ribose-modified nucleotides are included.[75] Inclisiran also incorporates 5′-phosphorothioate modifications[22] designed to prevent dephosphorylation within cells and to facilitate RISC loading. GalNAc conjugation permits rapid and selective entry to hepatocytes through interaction with ASGPRs; this substantially lowers the risk of off-target effects and allows for low cumulative doses.[74,75]

The mechanism of action of inclisiran is reviewed in detail elsewhere and is summarized in Figure 2 and Box 1.[70,75]

Clinical Development of Inclisiran

The inclisiran clinical development program, including preclinical and early clinical studies, is reviewed in detail elsewhere[74,76,77]; however, a summary of the key clinical trials is included here. Initial clinical studies of inclisiran gave an early indication of its favorable safety profile.[27,74,78] Pharmacokinetic studies reported that inclisiran plasma concentrations typically peak at ≈4 hours post-dose, with an elimination half-life from the plasma of ≈9 hours. In most individuals, inclisiran is not detectable in the blood 48 hours after dosing due to rapid GalNAc-mediated hepatic uptake.[74,78] Inclisiran remains active within the liver to exert its effects for several months, with an acceptable safety and tolerability profile.[18,74,78] Pharmacokinetic studies also identified no significant interactions with hepatic cytochrome P450 enzymes, suggesting a low risk of drug–drug interactions and rapid elimination in patients with hepatic or renal impairment.[74,78,79]

A proof-of-concept, ascending-dose phase 1 trial (NCT02314442) in healthy individuals demonstrated sustained mean reductions from baseline of 47.8% to 74.3% in PCSK9 levels and 35.2% to 47.8% in LDL-C levels 180 days after single subcutaneous doses of inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) or more (300 mg: n=3; 500 mg: n=2; 800 mg: n=4).[27] These results led to the phase 2 ORION-1 trial (NCT02597127), which included 501 patients with a history of ASCVD or ASCVD risk-equivalent and elevated LDL-C despite maximally tolerated LLT. The greatest LDL-C reduction was seen at Day 180 (52.6% LDL-C reduction from baseline) in patients who received 2

doses of inclisiran 284 mg subcutaneously at Days 1 and 90 (N=59).[28] At Day 240, LDL-C was reduced by 47.2% from baseline, with a time-averaged reduction of ≈46% maintained at the 1-year follow-up.[28,80] Inclisiran was well tolerated, both as monotherapy and in combination with statins, with no drug–drug interactions reported.[28,80] Based on these results, a 2-dose regimen of inclisiran on Day 1 and Day 90, with maintenance dosing every 6 months, was selected for further investigation.

The efficacy and safety of inclisiran were investigated in three phase 3 randomized controlled trials, ORION-9 (NCT03397121), ORION-10 (NCT03399370), and ORION-11 (NCT03400800), in which over 1800 patients on maximally tolerated statins or other nonstatin LLT if statin-intolerant, with either heterozygous FH (ORION-9), ASCVD (ORION-10 and ORION-11) or ASCVD risk-equivalent (type 2 diabetes, FH, or a 10-year risk score ≥20% [12.6% of patients in ORION-11]) received inclisiran.[18,19] In each trial, participants were administered either 300 mg of inclisiran sodium or placebo subcutaneously on Days 1, 90, 270, and 450. Pooled analysis of these 3 studies reported a mean placebo-corrected percentage change in LDL-C at Day 510 of –50.7% in patients who received inclisiran.[19] In addition, the majority of patients reached prespecified LDL-C goals of <70 mg/dL (86.6%) and <50 mg/dL (74.6%) at any time after baseline.[19] Inclisiran also lowered levels of total cholesterol (–32.4%), non-high-density lipoprotein cholesterol (–46.3%), apolipoprotein B (–41.7%), Lp(a) (–20.2%), and triglycerides (–9.9%), while increasing high-density lipoprotein cholesterol (6.2%) at Day 510 versus placebo.[19] Inclisiran was well tolerated, with a comparable safety profile to placebo. Of the most common (incidence ≥2%) treatment-emergent adverse events (AEs), rates were similar between inclisiran and placebo, except for treatment-emergent AEs at the injection site (5% inclisiran versus 0.7% placebo; risk ratio 7.54 (95% CI, 4.14–13.71), which were mostly mild and none were severe or persistent), and mild-to-moderate bronchitis (4.3% inclisiran versus 2.7% placebo; risk ratio 1.55 (95% CI, 1.09–2.20)).[19]

Prespecified subgroup and post hoc analyses of data from the ORION phase 3 clinical program provide further insights into the efficacy and safety of inclisiran.[81,82] In an exploratory analysis of 3655 patients (ORION-9, ORION-10, and ORION-11), the addition of inclisiran was associated with a 26% reduced probability of major adverse cardiovascular events (MACE) and a numerically lower risk of fatal and nonfatal myocardial infarction compared with placebo.[81] A subgroup analysis including 203 high-risk primary prevention patients from ORION-11 (patients with type 2 diabetes, FH, or 10-year risk score ≥20% and LDL-C ≥100 mg/dL) demonstrated a placebo-corrected –43.7% LDL-C reduction at Day 510.[82] These preliminary observations will support data from ongoing trials (eg, VICTORION-1 PREVENT [NCT05739383])[29] that are underway to further explore cardiovascular outcomes and long-term safety.

The ORION-3 (NCT03060577) open-label long-term extension study to ORION-1, reported a mean 47.5% LDL-C reduction from levels at ORION-1 baseline to Day 210 (ORION-3).[30] Patients who completed ORION-9, ORION-10, ORION-11, or ORION-3 were invited to participate in the ORION-8 long-term extension study (NCT03814187), which was designed to assess the efficacy and safety of inclisiran for up to an additional 3 years' total follow-up from phase 3 trial baseline. The primary completion date was reached in February 2023.[43] At the end-of-study visit, LDL-C was reduced by 49.4% on average and no new safety signals were identified,[83] demonstrating the consistent LDL-C-lowering effect and safety and tolerability profile of inclisiran (Box 1).

ONGOING STUDIES AND REAL-WORLD EVIDENCE

Although the phase 3 clinical trial program and subsequent exploratory analyses have provided robust evidence for the clinical efficacy and safety of inclisiran, there are still unanswered questions regarding the long-term efficacy and safety of inclisiran and its effect on atherosclerosis and cardiovascular outcomes. In addition, it is important to note that the highly controlled

Box 1. Inclisiran and anti-PCSK9 monoclonal antibodies: what are the key similarities and differences?

Inclisiran and anti-PCSK9 monoclonal antibodies target PCSK9 with the aim of increasing hepatic LDLR availability and thereby increasing LDL clearance. The mechanism by which this is achieved differs between the two classes. Anti-PCSK9 monoclonal antibodies bind to the catalytic domain of extracellular PCSK9, blocking the PCSK9/LDLR interaction.[56,76] In contrast, inclisiran reduces circulating PCSK9 levels by inhibiting PCSK9 protein synthesis within hepatocytes via RNA interference, resulting in a long duration of action.[75]

When added to maximally tolerated statins, self-administered biweekly or monthly anti-PCSK9 monoclonal antibodies reduce LDL-C by ≈60% (depending on dose and frequency), whereas twice-yearly inclisiran (administered by a health care professional) reduces LDL-C by ≈50% (after initial doses at baseline and 3 months).[18,44,61] Both classes also modestly reduce Lp(a) and triglycerides, and inclisiran modestly increases high-density lipoprotein cholesterol.[18,44,61] In clinical trials to date, evolocumab, alirocumab, and inclisiran have all been well tolerated. Although injection-site reactions have been reported more frequently for each of these agents versus placebo, they have been mostly mild.[18,44,61]

For anti-PCSK9 monoclonal antibodies, cardiovascular outcomes trials in patients with established ASCVD have reported a 15% to 20% lower risk of major adverse cardiovascular events (MACE),[61] while long-term cardiovascular outcomes data are awaited for inclisiran from 2 large ongoing cardiovascular outcome trials.

nature of these trials limits their ability to reflect the complexity and diversity of real-world clinical practice. Furthermore, the majority of participants in the phase 3 clinical trial program were White (92%) or male (67%).[19] Therefore, evidence from further clinical studies and real-world data will be required to fully understand the long-term effects of inclisiran, its impact on cardiovascular outcomes, and its safety and efficacy in people from diverse racial, ethnic, and socioeconomic groups. As of 2023, several trials are underway, or have recently been completed, that may provide a broader picture of inclisiran effectiveness and implementation. Completed and ongoing clinical trials of inclisiran are summarized in Figure 1.

ORION-13 (NCT04659863) and ORION-16 (NCT04652726) are ongoing phase 3 trials evaluating the efficacy and safety of inclisiran added to maximally tolerated statin therapy in adolescents (12–17 years of age) with homozygous FH and heterozygous FH, respectively. Both trials will comprise a 1-year double-blind phase (inclisiran versus placebo) followed by a 1-year open-label phase and are expected to reach completion in late 2024.[31,32]

Ongoing trials designed to assess the effect of inclisiran on MACE include ORION-4 (NCT03705234), VICTORION-2 PREVENT (NCT05030428), and VICTORION-1 PREVENT (NCT05739383).[29,33,34] ORION-4 will assess rates of 4-point MACE in 15 000 patients with a history of myocardial infarction, ischemic stroke, or peripheral arterial disease over a median 5-year follow-up, with primary completion expected in 2026.[33] VICTORION-2 PREVENT aims to evaluate rates of 3-point-MACE over 72 months in patients with established cardiovascular disease and LDL-C ≥70 mg/dL on stable LLT and is expected to complete in 2027.[34] VICTORION-1 PREVENT will assess the incidence of 4-point MACE in patients without ASCVD at high risk of their first ASCVD event over a minimum of 3 years follow-up; primary completion is expected in 2029.[29]

The ongoing VICTORION-PLAQUE (NCT05360446) study will include participants with nonobstructive coronary artery disease to evaluate the effect of inclisiran on atherosclerotic plaque progression (assessed using coronary computed tomography angiography). The trial is currently enrolling patients and is expected to complete in 2025.[35]

Several studies are ongoing to investigate the implementation of inclisiran into real-world clinical practice. These include VICTORION-INITIATE (NCT05030428) and VICTORION-INCEPTION (NCT04873934), which have been designed to assess the efficacy of the addition of inclisiran earlier in the treatment pathway in a setting designed to mimic real-world clinical practice by comparing inclisiran to usual care at the discretion of the treating physician (including allowing changes in background LLT).[36,37] Anti-PCSK9 monoclonal antibodies and other LLTs may be prescribed in the usual-care arm but not in patients receiving inclisiran. In addition, the treating physician may order lipid panels at their discretion to reflect real-world monitoring more accurately. VICTORION-INITIATE includes patients with established ASCVD who have not reached LDL-C goals on maximally tolerated statin therapy, and VICTORION-INCEPTION enrolled patients who have had a recent hospitalization for an acute coronary syndrome.[36,37]

Beyond clinical trials, early real-world experiences with inclisiran have been reported.[84–86] In a UK-based, retrospective analysis including 80 patients prescribed inclisiran at a single center between December 2021 and September 2022, the mean reduction in LDL-C from baseline was 48.6% (P<0.0001) 2 months after inclisiran initiation.[84] LDL-C lowering was significantly greater in patients receiving statins at baseline compared with those who were not (n=40 versus n=36; 56.0% versus 44.9% LDL-C reduction; P=0.01).[84] At 2 months, AEs were reported in 3.9% of patients; all had spontaneously resolved by the 2-month follow-up, and no serious AEs were reported.[84] This provides an early indication that inclisiran likely offers similar effectiveness and tolerability in real-world practice compared with the clinical trial setting.[84] In a US, single-center, real-world study of 61 patients who received at least 1 dose of inclisiran, among patients who did not discontinue their background LLT or switch from an anti-PCSK9 monoclonal antibody (n=25), mean LDL-C (measured at least 30 days from first inclisiran dose) was reduced from 139±44 mg/dL to 72±30 mg/dL (49%; P<0.001).[85] Inclisiran was generally well tolerated.[85] Further real-world evidence from ongoing observational studies is awaited to provide greater insights into the effectiveness of inclisiran in the clinic.

INCLISIRAN IN THE CLINIC: WHAT DO HEALTH CARE PROFESSIONALS NEED TO KNOW?

Current Lipid Management Guidelines and Medical Society Recommendations

As inclisiran first received US FDA approval in 2021, after the publication of the 2018 Cholesterol Clinical Practice Guidelines, recommendations on its use were not included.[3] A recent American College of Cardiology Expert Consensus Decision Pathway (ECDP) focusing on nonstatin therapies has emphasized the need for intensification of LLT for patients with elevated LDL-C in the secondary prevention setting.[13] The ECDP recommends the addition of nonstatin LLT (ezetimibe and/or anti-PCSK9 monoclonal antibodies, or inclisiran, or bempedoic acid) in patients with ASCVD who require further LDL-C lowering, with differing LDL-C thresholds

for the addition of therapies based on the patient's level of risk (eg, LDL-C reduction ≥50% and LDL-C <55 mg/dL or <70 mg/dL for very high-risk ASCVD or not very high-risk ASCVD, respectively).[13] The ECDP suggests that inclisiran be considered for primary prevention in patients with severe primary hypercholesterolemia (LDL-C ≥190 mg/dL) and for patients with poor adherence to anti-PCSK9 monoclonal antibodies, with anti-PCSK9 monoclonal antibody-related side effects, or in those unable to self-inject.[13] It should be noted that the American College of Cardiology ECDP recommendations for inclisiran consider the current absence of long-term cardiovascular outcomes data, which are expected in 2026.[33]

In the United Kingdom, inclisiran is recommended for use in patients with a history of acute coronary syndrome, coronary or other arterial revascularization, coronary heart disease, ischemic stroke, or peripheral arterial disease, and who have LDL-C persistently ≥100 mg/dL, despite maximally tolerated LLT (ie, maximally tolerated statins with or without other LLT, or statin intolerance).[87] A flow chart summarizing recommendations for prescribing inclisiran, adapted from the recent American College of Cardiology ECDP and the National Health Service England guidance, is presented in Figure 3.[13,88]

Factors to Consider in Discussions With Patients When Prescribing Inclisiran

Shared decision-making is recommended by lipid management guidelines and pathways,[3,4,13] and its implementation in cardiology practice has been linked with benefits including increased medication adherence, patient satisfaction, and quality of life.[89]

For patients who have not reached target LDL-C thresholds, it is important for health care providers to understand the role of side effects or poor adherence/persistence with the prescribed LLT and to discuss the risks and benefits of therapies. When initiating a new LLT with a patient, the potential for additional LDL-C lowering and ASCVD risk reduction should be discussed in the context of the risk of clinically significant AEs or drug–drug interactions, costs, and patient preferences and considerations (eg, convenience factors, patient perceptions). Because inclisiran is administered twice yearly by a health care professional, it may offer a convenient option for patients with a history of nonadherence to LLT or those who are unable or unwilling to self-inject. In other therapy areas, in-office administration of medication has led to increased treatment adherence through directly observed therapy.[90,91]

From a practical perspective, it is important for health care professionals to understand that the in-office administration of inclisiran can potentially affect insurance authorization and out-of-pocket costs for patients. For example, for patients with Traditional Medicare insurance, inclisiran is typically provided under Medicare Part B. Under Medicare Part B, services are 80% covered and the remaining costs may be covered by supplemental insurance, if the patient has a supplemental policy.[86] The limited evidence available suggests that out-of-pocket costs vary for patients with other forms of insurance (eg, Medicare Advantage Plan or coverage through a health maintenance organization or preferred provider organization)[86] but can be estimated using prior authorization and benefits investigations, similar to other LLTs. Additional data from the real-world use of inclisiran may provide further insights into the typical costs for patients and challenges related to patient access to therapy.[85]

As inclisiran was first approved in the United States in 2021, long-term real-world safety data are not yet available, and patients may have concerns about the duration of side effects given inclisiran's extended duration of action. Patients should be informed that inclisiran is rapidly cleared from the circulation (within 24–48 hours), although it remains in the liver for several months post-dose,[83] and that no significant off-target toxicity or drug–drug interactions have been reported in clinical trials to date. In phase 3 clinical trials, the incidence of AEs at the injection site was significantly higher with inclisiran versus placebo (8.2% versus 1.8%),[22] but these were mostly mild and short lived.[18,19,79] Data on inclisiran use for up to 6.8 years (≈4.5 years on average) are now available from ORION-8.[83] In ORION-8, injection-site treatment-emergent AEs occurred in 5.9% of patients, and the most frequently reported serious treatment-emergent AEs were coronary artery disease (1.9%), COVID-19 (1.5%), and acute myocardial infarction (1.3%), none of which was study drug-related.[83] Ongoing studies are further investigating the long-term effects of inclisiran, including its effect on cardiovascular outcomes, with results expected from 2026.[33,34]

Safety data have been available for anti-PCSK9 monoclonal antibodies since 2015, and there appear to be no long-term effects from sustained inhibition of PCSK9. Despite potential concerns regarding the impact of PCSK9 inhibition on cognitive function, evolocumab (added to statins) was not found to affect cognitive function compared with placebo in a randomized clinical trial including patients at high risk of ASCVD.[92] In addition to clinical trials, a small prospective real-world study found no association between evolocumab or alirocumab and cognitive decline,[93] and a large Mendelian randomization study using single-nucleotide polymorphisms in *PCSK9* as a proxy for inhibition found no association between PCSK9-related LDL-C lowering and neuropsychiatric effects, including cognitive decline and mental health conditions.[94]

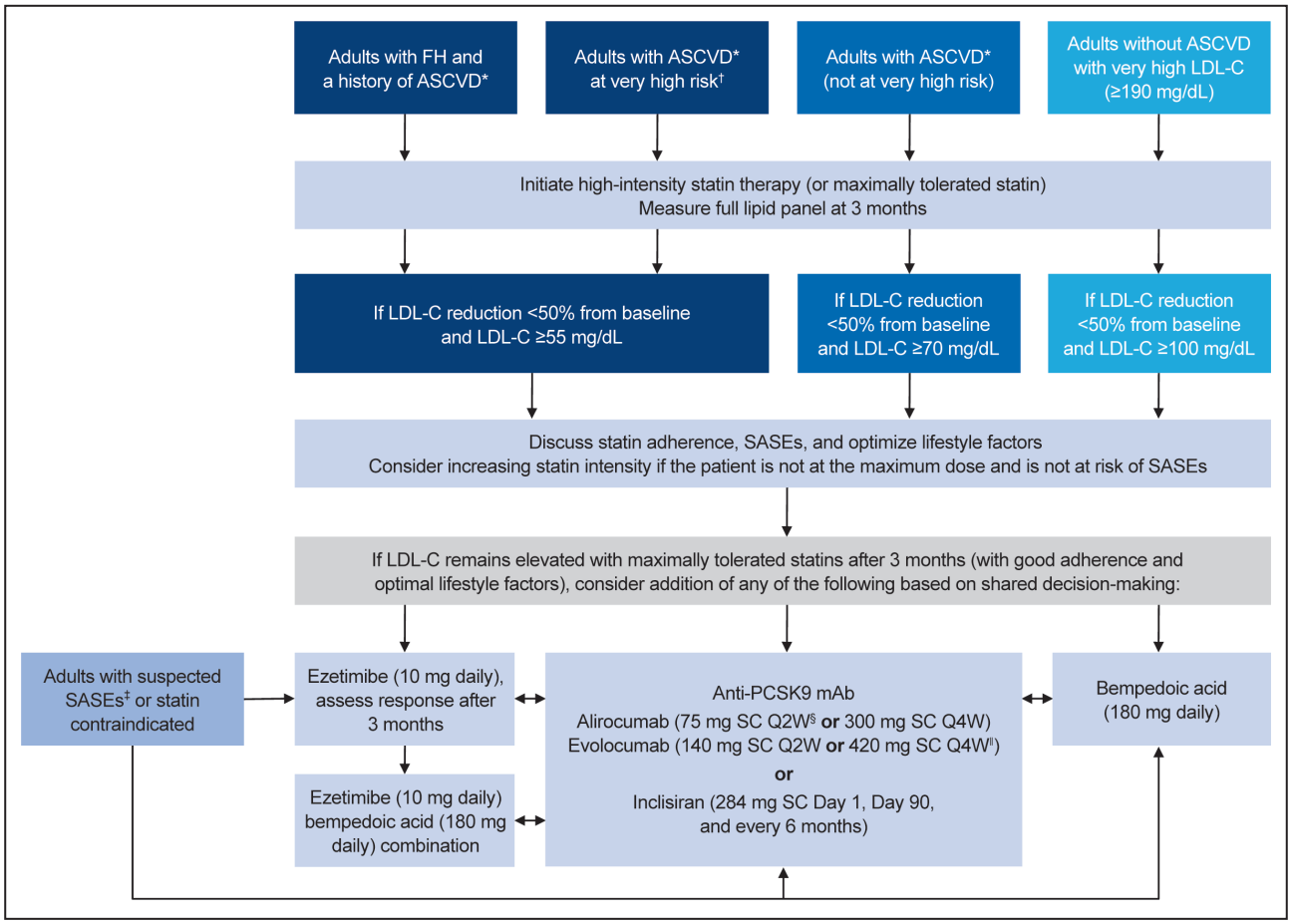

Figure 3. A pathway for managing patients with FH or ASCVD, or at risk of ASCVD, adapted from the UK NHS pathway and ACC ECDP.[13,88]

*ACS, history of MI, stable/unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD; †History of multiple major cardiovascular events (ACS [past 12 months], history of MI, ischemic stroke, symptomatic PAD), or a major cardiovascular event plus high-risk conditions (≥65 years of age, heterozygous FH, history of coronary artery bypass, diabetes, hypertension, chronic kidney disease, smoking, LDL-C ≥100 mg/dL despite maximally tolerated LLT, history of congestive heart failure); ‡Intolerant of ≥2 statins with 1 attempt at lowest recommended dose; §Increase to 150 mg Q2W if required; ‖At 12 weeks increase to 420 mg Q2W, if required. ACC indicates American College of Cardiology; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; ECDP, Expert Consensus Decision Pathway; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; NHS, National Health Service; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; Q4W, every 4 weeks; SASE, statin-associated side effect; SC, subcutaneously; TIA, transient ischemic attack; and UK, United Kingdom.

A summary of key points for US health care professionals on the use of inclisiran in the clinic, including key safety and efficacy data, use in special populations, and considerations for cost, acquisition, and reimbursement in the United States, is provided in the Table.

CONCLUSIONS

Management guidelines have recommended increasingly aggressive LDL-C thresholds for patients with ASCVD or at risk for ASCVD, emphasizing rapid intensification of therapy when goals are not met.[3,4,13] However, for a variety of reasons, LDL-C levels remain inadequately controlled in the majority of patients.[17] Inclisiran, a first-in-class LDL-C–lowering siRNA therapy, was developed following the identification of PCSK9 as a novel target for ASCVD prevention, and the discovery of RNAi.[23,24,74] Inclisiran is administered subcutaneously, and GalNAc conjugation facilitates targeted drug delivery to the hepatocyte. Inclisiran uses cells' natural mechanism of RNAi to prevent PCSK9 production, thus increasing LDLR availability and clearance of LDL-C from the circulation.[24,74,75,77]

In phase 3 trials, inclisiran administered twice yearly (after an initial dose and a second dose at 3 months), demonstrated sustained LDL-C lowering with an acceptable safety and tolerability profile when added to maximally tolerated statin therapy in patients with elevated LDL-C.[18,19,74,75] The potential long-term adverse

Table. Practical Points and Frequently Asked Questions Surrounding the Use of Inclisiran in US Clinical Practice[19,20,22,30,33,34,82,86,95]

What is the mechanism of action?	Inclisiran uses the natural process of RNA interference to degrade PCSK9 mRNA and reduce the production of PCSK9 protein, thus increasing LDL receptor expression and promoting greater clearance of circulating LDL-C.[22]
What is the US Food and Drug Administration-approved indication?	For lowering LDL-C in adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) as an adjunct to diet modifications and statin therapy.[22]
What is the formulation?	A 284 mg/1.5 mL (189 mg/mL) solution in a single-dose prefilled syringe and should be stored at controlled room temperature 20–25 °C (68–77 °F) for up to 3 y.[20,22]
How is it administered?	By subcutaneous injection in the abdomen, upper arm, or thigh. Inclisiran is administered by a health care professional.[22]
What is the dosing schedule?	Subcutaneous injections on Day 1, at 3 mo, and then every 6 mo.[22]
By how much does it lower LDL-C?	Following a single subcutaneous administration of 284 mg of inclisiran, LDL-C reduction was apparent within 14 d post-dose.[22] In phase 3 studies, inclisiran lowered LDL-C levels by 48%–52% at Day 510.*[19]
What are the common AEs?	In a pooled analysis of 3 phase 3 studies, AEs at the injection site occurred in more patients treated with inclisiran (8.2%) than placebo (1.8%).[22] These were mostly mild and nonpersistent.[19] Patients should be reassured that despite every 6-mo dosing of inclisiran, the risk of long-lasting adverse effects with inclisiran is low.
What do we know about potential long-term risks or AEs?	Results are available from a study of ≈500 people with ASCVD or at risk of ASCVD, who were followed for up to 4 y.[30] This study has not identified any new safety concerns compared with previous trials.[30] Ongoing studies are investigating the long-term effects of inclisiran, including cardiovascular outcomes, with results expected from 2026 onwards.[33,34]
How long does inclisiran stay in the body?	Blood inclisiran concentration peaks at ≈4 h after dosage; in most people, inclisiran is not measurable in the blood after 48 h[22] due to rapid triantennary *N*-acetylgalactosamine-mediated hepatic uptake. Inclisiran remains in the liver for several mo post-dose.[83]
Can inclisiran be combined with other medications?	Inclisiran is not expected to cause drug–drug interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes.[22] Inclisiran can be used in combination with statins (or other background therapy such as ezetimibe).[22] In large clinical trials, almost all patients included were taking statins.[19] No safety concerns were identified from concurrent switching between evolocumab and inclisiran.[30]
Can I use inclisiran in patients with hepatic or renal impairment or a history of solid organ transplant?	Inclisiran may be used without any changes to dosing in patients with mild, moderate, or severe renal impairment.[22] Inclisiran should not be used in patients with end-stage kidney disease, as inclisiran has not been studied in this population.[22] Inclisiran may also be prescribed for patients with mild or moderate hepatic impairment but not for those with severe hepatic impairment, as inclisiran has not been studied in this population.[22] Inclisiran has not been studied in patients with a history of solid organ transplant.
Can inclisiran be used during pregnancy and peri-pregnancy?	Inclisiran has not been studied in patients who are pregnant and should be discontinued during pregnancy.[22] In preclinical models, inclisiran was found to cross the placenta when administered during gestation, with no evidence of embryo–fetal toxicity. Inclisiran was also detected in the milk of lactating rats. There are no data regarding inclisiran excretion in human milk; however, it is unlikely that low levels of inclisiran in milk would adversely affect an infant due to its low oral bioavailability.[22]
How is inclisiran acquired and reimbursed? What are the costs to the patient?	The price of inclisiran in the United States (2023) is $3290.63 per dose.[95] The cost to the patient depends on the type of insurance and coverage. For example, for patients with traditional Medicare insurance, inclisiran is typically provided under Medicare Part B. Under Medicare Part B, services are covered 80%, and the remaining costs may be covered by supplemental insurance, if the patient has a supplemental policy. Limited available evidence suggests that out-of-pocket costs for patients with other forms of insurance (eg, Medicare Advantage plans, preferred provider organization, health maintenance organization) are variable but can be estimated using prior authorization and benefits investigations before initiation of inclisiran, similar to other lipid-lowering therapies.[86] Additional data from real-world use of inclisiran may provide further insights.
When should I draw a lipid panel following inclisiran administration?	No specific recommendations exist on the timing of LDL-C measurement after initiation of inclisiran; however, based on the results of clinical trials, drawing a lipid panel 90 d after initiation of therapy is reasonable.

*In combination with statins±ezetimibe.

AEs indicates adverse events; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9.

effects of inclisiran and its effects on cardiovascular outcomes have yet to be fully elucidated; however, the efficacy and favorable safety profile of agents targeting PCSK9 are already well established. Additional studies in the real-world setting, as well as greater inclusion of underrepresented populations in future clinical trials, will be required to provide crucial evidence on the efficacy and safety profile of inclisiran in patients from diverse backgrounds. Thus, after making the journey from bench to bedside in under 20 years from the discovery of PCSK9, inclisiran has been found to be a well-tolerated and effective therapy for lowering LDL-C and is an important addition to the clinician's toolbox for LDL-C–lowering therapies.

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