

Inclisiran: A Novel Agent in the Management of Hypercholesterolemia

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Abstract

PCSK9 is a serine protease that binds to the LDL receptors and targets the receptors for lysosomal degradation, thus reducing their recycling and decreasing the removal rate of circulating LDL-C. Monoclonal antibodies directed against PCSK9, such as alirocumab and evolocumab, have been shown to cause a significant reduction in LDL-C levels and improve cardiovascular outcomes. On the other hand, inclisiran is a chemically synthesized siRNA molecule, which lowers LDL-C levels by targeting the hepatic production of PCSK9, as it prevents its translation via degradation of PCSK9 mRNA post-transcription. This review aims to discuss the current evidence regarding the role of inclisiran in the management of hypercholesterolemia.

Keywords

Low-density lipoprotein cholesterol (LDL-C), Proprotein convertase subtilisin/kexin type 9 (PCSK9), Small interfering RNA (siRNA), Inclisiran, Cardiovascular disease (CVD).

Introduction

Dyslipidemia is a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) [1]. Despite a recent decrease in death rates due to cardiovascular disease (CVD), it remains the most frequent cause of mortality universally, as CVD is estimated to cause around 31% of all deaths [2,3]. This decrease is likely attributed to the use of HMG-coenzyme A reductase inhibitors (statins) as the standard of care for low-density lipoprotein cholesterol (LDL-C) lowering [4]. However, there are still several cases in which patients fail to achieve the desired LDL-C goals or are intolerant to statins due to adverse effects (myalgias and weakness). Furthermore, an increased risk for diabetes mellitus, as well as some reports of statin-induced cognitive impairment, have made the Food and Drug Administration (FDA) mandate additional safety labeling warnings [5]. Extensive research is being conducted to identify new LDL-C lowering drugs with favorable side effect profiles, which (used alone or in combination with statin) will produce significant LDL-C reductions and decrease cardiovascular (CV) risk. To that effect proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a novel class of LDL-C lowering agents, administered on a background of statin therapy, have shown marked decrease in LDL-C

levels and improved CV outcomes [6,7]. Inclisiran is a novel synthesized small interfering RNA (siRNA) molecule which lowers LDL-C levels by targeting the hepatic production of PCSK9, as it prevents its translation via degradation of PCSK9 mRNA post-transcription [8,9]. This review discusses the current evidence regarding the safety and efficacy of inclisiran, as well as its impact on long-term CV outcomes.

The Relationship Between LDL-C and PCSK9

LDL receptors (LDLR) bind LDL to the cell surface, which is then engulfed by the hepatocyte. These receptors return to the circulation to bind to more LDL and perform this activity multiple times before their degradation. The degradation of LDLR is mediated by PCSK9. PCSK9, which was first discovered in 2003, is a serine protease that binds to the LDLR and targets the receptors for lysosomal degradation, thus reducing their recycling and decreasing the removal rate of circulating LDL-C [10-14]. This enzyme was linked to hypercholesterolemia and CV risk, as it was established that gain-of-function mutations of PCSK9 in humans correlated with increased LDL-C levels and increased risk for coronary atherosclerosis [15,16], whereas loss-of-function



mutations of PCSK9 correlated with low levels of LDL-C and decreased CV risk [17].

Strategies to Lower PCSK9

Based on the above, strategies to reduce PCSK9 have been developed or are in development, as inhibition of PCSK9 would be an attractive target to maximize the LDL-C-lowering effect of statins and potentially further decrease CV risk. These strategies may include monoclonal antibodies (mAbs) directed against PCSK9, small molecule inhibitors that disrupt the processing of PCSK9, as well as the use of adnectins, which block the binding of PCSK9 to the LDLR [5,18].

Alirocumab and evolocumab are humanized mAbs that bind to circulating PCSK9 and prohibit its binding to the LDLR, thus creating a PCSK9-deficiency state, which results in marked accumulation of LDLR on the membrane of hepatocytes, accelerated clearance of LDL particles, and large decreases in plasma LDL-C levels [19]. In large clinical trials, alirocumab and evolocumab, administered on a background of statin therapy, have been shown to markedly decrease LDL-C levels and significantly improve CV outcomes [6,7].

Another strategy to lower levels of PCSK9 is to decrease its production, which can be mediated by siRNA molecules that block the translation of PCSK9 messenger RNA (mRNA). As mentioned above, inclisiran, a chemically synthesized siRNA molecule, is a novel agent which acts by this mechanism, as it targets the hepatic production of PCSK9 by preventing its translation via degradation of PCSK9 mRNA post-transcription [8,9].

Structure and Function of Inclisiran

Inclisiran is a double-stranded siRNA molecule, which interrupts the translation of PCSK9 by degrading its mRNA post-transcription [8,9]. The siRNAs are in general approximately 20-30 nucleotide RNA molecules, which are involved in the regulation of endogenous genes and in the protection of the genome from invasive nucleic acids [20]. Long double-stranded RNA induces an interferon response, which contributes to the anti-viral defense by causing a generalized shutdown of protein synthesis in most mammalian cells. Thus, long double-stranded RNA cannot be used for specific gene silencing [21]. On the other hand, siRNAs can evade the radar of the mammalian interferon response and induce strong and specific gene silencing [21]. Usually, siRNA interferes with the expression of specific genes with complementary nucleotide sequences by affecting the degradation of mRNA post-transcription thereby preventing translation [8,9].

Inclisiran is a subcutaneously delivered, long-acting, synthetic siRNA molecule. Following injection this siRNA molecule is delivered to the hepatocytes using N-acetyl galactosamine carbohydrate conjugates. These carbohydrates bind to asialo-glycoprotein receptors that are abundantly expressed in the liver, resulting in the uptake of inclisiran into the hepatocytes [22]. Within the hepatocytes, the siRNA binds to the RNA inducing silencing complex (RISC), which then degrades the mRNA that codes for PCSK9 protein. With less PCSK9 protein production in the liver, more LDLR are recycled to surface liver cells, resulting in increased uptake and clearance of LDL-C from the circulation. The inclisiran siRNA duplex comprises 44 modified nucleotides which improve its molecular stability [22,23]. Inclisiran is detectable in the blood one hour after administration and reaches peak concentrations in about 4 hours. It is mainly excreted via the kidneys and evidence suggests that it is safe in patients with renal impairment and dose adjustments are not required in these patients [24]. While the drug is cleared from the plasma within 48 hours, the

siRNA-mediated suppression of PCSK9 production starts shortly after administration and because of its direct RNA targeting, its therapeutic effects of LDL-C reduction lasts up to six months.

Inclisiran: Clinical Trials

Early phase 1 trials included healthy volunteers with LDL-C levels ≥ 100 mg/dL who received inclisiran in single or multiple doses. Administration of 300 mg or more in single or combined doses resulted in both LDL-C and PCSK9 levels for at least 6 months. Multiple-dose regimens resulted in least-squares mean reduction of 59.7% in LDL-C and 83.8% in PCSK9 levels by day 84. The most common adverse effects were back/musculoskeletal pain, cephalgia, cough, diarrhea and nasopharyngitis. However, there were no serious adverse events associated with the use of inclisiran [22].

Early phase 1 studies showed that inclisiran produced sustained reductions in LDL-C and PCSK9 levels and maintained an acceptable safety profile. This supported further clinical investigation of inclisiran, and gave rise to the ORION trial program, which systematically evaluated dosing strategy, LDL-C-lowering efficacy, durability of drug effect, and safety profile across diverse populations. The major ORION studies are summarized in Table 1 and discussed below.

The ORION-1 study was a phase 2, multi-center, double-blind, placebo-controlled trial that enrolled high-risk CV patients with elevated LDL-C levels. This study examined the percentage change of LDL-C levels with different doses of inclisiran at 180 days. A total of 501 participants were enrolled in the study, with mean age of 63 years, 65% men, 69% with established diagnosis of ASCVD, 6% with familial hypercholesterolemia (FH), and 73% on statin therapy. Compared with placebo, a single dose of inclisiran resulted in the least-squares mean reductions in LDL-C level from 27.9% to 41.9%, and two doses resulted in 35.5% to 52.6% ($p < 0.001$ for all comparisons vs. placebo). The greatest effect was observed with two 300 mg doses of inclisiran, resulting in reductions in LDL-C, PCSK9, and hs-CRP of 52.6% ($p < 0.001$), 69.1% ($p < 0.001$), and 16.7% ($p < 0.05$), respectively. Serious adverse events occurred in 11% of patients receiving inclisiran compared to 8% in placebo group, and injection-site reactions occurred in 4% and 7% of patients receiving one and two doses, respectively [9,25].

Glycosylated hemoglobin (HgbA1c) changes did not differ between inclisiran and placebo groups. The most common adverse events (occurring in $>2\%$ of patients) were myalgias, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea and dizziness. The rates of occurrence of these adverse events did not significantly differ between inclisiran and placebo groups [25].

In the one year follow-up of the ORION 1 trial, both the single dose (200, 300, or 500 mg) and two dose regimens of inclisiran (100, 200, or 300 mg on day 1 and day 90) produced dose-dependent reductions in time averaged LDL-C, ranging from 29.5% to 38.7% and 29.9% to 46.4%, respectively. The two dose 300 mg regimen achieved the largest mean LDL-C reduction over one year and yielded the highest proportion of treatment responders. During this period, LDL-C was routinely measured at every 30-day interval clinic visit for up to 365 days to monitor safety and efficacy. Additionally, 50% reduction in LDL-C levels was sustained for at least 6 months after 2 doses of 300 mg of inclisiran on days 1 and 90. The incidence of adverse events was similar up to 1 year of follow-up [26].

The ORION-3 trial was an open-label extension study of the ORION-1 cohort that evaluated the durability and safety of inclisiran treatment over the course of 4 years. Patients either continued inclisiran

Table 1: Summary of inclisiran studies under the ORION trial program.

TRIAL	POPULATION	INTERVENTION vs PLACEBO	PRIMARY ENDPOINT (LDL-C Reduction)	OUTCOME
ORION-1 Phase 2	502 patients with ASCVD or risk equivalents	300 mg twice yearly	-52.6% at day 180 (2 doses)	Dose-dependent reduction, establish 300 mg twice yearly as the inclisiran dose regimen
ORION-3 Phase 2 (extension)	4-year open label extension of ORION-1	300 mg twice yearly vs evolocumab 140 mg biweekly	Sustained LDL-C reduction of ~45-50% over 4 years	Safety and efficacy maintained over 4 years follow-up
ORION-5 Phase 3	56 patients with HoFH	300 mg vs placebo	-1.68% (not significant)	Lowered PCSK9 significantly but failed to reduce LDL-C in HoFH patients
ORION-8 Phase 3 (extension)	3274 patients with ASCVD or risk equivalents. Open label extension of ORION-3, 9-11	300 mg vs placebo	-49.4% at the end of 6.8 years study	78% reached LDL-C target of <70 mg/dL
ORION-9 Phase 3	482 adults with HeFH	300 mg vs placebo	-47.9% at day 510	Twice yearly dose reduced LDL-C effectively in HeFH
ORION-10 Phase 3	1561 patients with ASCVD (USA only)	300 mg vs placebo	-52.3% at day 510	Established most common side effect as mild-to-moderate injection-site reactions
ORION-11 Phase 3	1617 patients with ASCVD or risk equivalent	300 mg vs placebo	-49.9% at day 510	Safety profile similar to placebo, except for injection-site reactions
ORION-13	HoFH (age 12-18)	300 mg vs placebo	-33.3% at day 330	Established safe and effective treatment options for adolescents with HoFH
ORION-4 Phase 3	15,000 patients with ASCVD	300 mg vs placebo	Impact of inclisiran on MACE reduction	Currently investigating with results expected in 2026

ASCVD: Atherosclerotic Cardiovascular Disease, HoFH: Homozygous familial hypercholesterolemia, HeFH: Heterozygous familial hypercholesterolemia, LDL-C: Low-density lipoprotein cholesterol, MACE: Major Adverse Cardiovascular Events.

treatment from ORION-1 or transitioned to receiving 300 mg inclisiran sodium every 180 days if previously assigned to placebo. LDL-C was reduced by 47.5% at day 210, which was sustained over 1440 days. Within the inclisiran-only arm, LDL-C was reduced by 44.2% and PCSK9 was reduced by 62.2% to 77.8% over the 4 years. Additionally, non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB) concentrations were decreased by 30 to 41.7% and 26.5 to 40.4% respectively. Patients who changed from placebo to inclisiran had similar outcomes. The study demonstrated the durability of inclisiran therapy without a loss of efficacy over the 4 years. The most reported side effects were nasopharyngitis in 19% of patients, followed by administration site reactions in 14%. Most of the side effects were mild-to-moderate in severity that were self-limiting [27].

The ORION-10 and ORION-11 studies were two randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trials, which were designed to assess the efficacy, safety and adverse-event profile of inclisiran over a period of 18 months. Both studies included high-risk patients with established ASCVD including coronary heart, cerebrovascular and peripheral arterial diseases. The ORION-10 trial was conducted in the United States while the ORION-11 trial was conducted in Europe and South Africa. Most participants in both trials were on statin treatment (89.2% in ORION-10 and 94.7% in ORION-11). The ORION-10 trial included a total of 1561 participants while the ORION-11 trial included 1617 subjects. All participants were randomly assigned to either placebo or 284 mg of inclisiran, with both being administered subcutaneously in similar intervals; day 1, day 90, followed by every 6 months thereafter over a total period of 540 days. As for enrollment criteria, the ORION-10 trial enrolled adults with ASCVD and LDL-C equal to or greater than 70 mg/dL. In addition to adults with ASCVD and LDL-C equal to or greater than 70 mg/dL, the ORION-11 trial enrolled adults who had an LDL-C level equal to or greater than 100 mg/dL and had an ASCVD risk equivalent (FH, diabetes mellitus, or $\geq 20\%$ 10-year risk of a CV event as assessed by the Framingham Risk Score for CVD or equivalent).

The mean LDL-C concentration at baseline was 104.7 mg/dL in the ORION-10 study and 105.5 mg/dL in the ORION-11 study. At day 510, inclisiran decreased LDL-C levels by 52.3% in the ORION-10 trial and by 49.9% in the ORION-11 trial. The corresponding time-adjusted reductions were 53.8% in the ORION-10 trial and 49.2% in the ORION-11 trial ($p < 0.001$ for all comparisons vs. placebo). Additionally, at day 510, PCSK9 levels were reduced by 69.8% in the ORION-10 trial and 63.6% in the ORION-11 trial with the use of inclisiran. When compared to placebo, this corresponded to between-group differences of 83.3% and 79.3% ($p < 0.001$ for all comparisons). Moreover, inclisiran use was observed in the ORION-10 trial to lower total cholesterol (TC), apoB, non-HDL cholesterol, triglycerides (TG), and lipoprotein(a) [Lp(a)] by 33.1%, 43.1%, 47.4%, 12.6%, and 25.6%, respectively, compared with placebo, while increasing high-density lipoprotein cholesterol (HDL-C) by 5.1%. These reductions were similarly noted against placebo in the ORION-11 trial where it reduced these markers by 29.8%, 38.9%, 43.3%, 7.0%, and 18.6%, respectively, while increasing HDL-C by 6.1%. The overall rate of adverse events was noted to be similar between both the inclisiran and placebo groups in both ORION trials excluding injection-site reactions which were observed to occur more frequently in the inclisiran group compared to the placebo group (2.6% vs. 0.9% in the ORION-10 trial and 4.7% vs. 0.5% in the ORION-11 trial).

These reactions were in general mild and not persistent. Furthermore, the incidence of diabetes mellitus did not significantly differ between inclisiran and placebo groups in both trials [28].

Moreover, inclisiran has been shown to be safe and effective when used in patients with heterozygous familial hypercholesterolemia (HeFH). In the ORION-9 study, a double-blind, randomized, placebo-controlled, phase 3 clinical trial, designed to assess the utilization of inclisiran in adult patients with HeFH who were on a maximally tolerated dose of statin treatment, a total of 482 adults with HeFH were randomized to receive subcutaneous injections of inclisiran sodium (at a dose of 300 mg) vs. matching placebo on days 1, 90,

270 and 450. The average baseline LDL-C level was 153 mg/dL. By day 510, there was a 39.7% reduction in the mean LDL-C in the inclisiran group, while there was an increase of 8.2% in the placebo group yielding a between-group difference of -47.9 percentage points ($p < 0.001$). Similarly, PCSK9 levels at day 510 decreased by 60.7% with inclisiran but increased by 17.7% with placebo, resulting in a -78.4 percent point difference ($p < 0.001$). When averaged over time from day 19 to day 540, there was a reduction of 38.1% in the inclisiran group as opposed to an increase of 6.2% in the placebo group, corresponding to a between-group difference of -44.3 percentage points ($p < 0.001$). It is worth noting that there were reductions in LDL-C observed across all FH genotypes. The rates of adverse and serious adverse events were similar between the two groups [29].

In comparison, the ORION-5 trial evaluated the effect of inclisiran treatment on patients with homozygous familial hypercholesterolemia (HoFH) and did not demonstrate a statistically significant reduction in LDL-C compared to placebo. The ORION-5 trial was a phase 3, randomized, placebo-controlled clinical study that assessed the efficacy, safety and tolerability of inclisiran in HoFH patients already receiving maximally tolerated lipid-lowering therapy. At 150 days, percent change in LDL-C from baseline did not significantly differ between the inclisiran and placebo groups. Notably, a varying degree of impact on LDL-C was observed in the inclisiran group depending on the residual LDLR function. It is important to note that PCSK9 levels after 150 days in the inclisiran group was decreased by 60.6% ($p < 0.0001$) despite discordant LDL-C responses. The ORION-5 study re-demonstrated that inclisiran effectively suppresses PCSK9 but without a reliable control in LDL-C due to severely impaired LDLR function in patients with HoFH [30].

The ORION-8 trial was a multi-center, open-label extension clinical study to evaluate the long-term efficacy, safety and tolerability of inclisiran in patients from the ORION-3, ORION-9, ORION-10 and ORION-11 trials who completed their respective parent trial. A total of 3,274 patients with ASCVD (82.7%) or ASCVD risk equivalents (17.3%) were enrolled in 268 centers in 13 countries and received open-label inclisiran 300 mg subcutaneously twice yearly (following a 0- and 90-day dose) for up to 990 days, with a final end-of-study visit at day 1,080 or ≥ 90 days after the last dose. Most patients were receiving statin treatment (88.6% of patients; 68.5% receiving high-intensity statin therapy); 16.6% of patients were receiving ezetimibe. A total of 2446 patients (74.7%) completed 3 years of the trial. The mean LDL-C concentration at the parent trial baseline was 112 mg/dL (2.9 mmol/L). With a mean cumulative inclisiran exposure of 3.7 years (maximum 6.8 years; $> 12,000$ patient-years across the extension and parent trials), inclisiran treatment reduced LDL-C levels by 49.4%, with 78.4% of patients achieving their pre-specified LDL-C goals of LDL-C < 100 mg/dL for high-risk primary prevention patients and LDL-C < 55 mg/dL for very high-risk patients. Additionally, inclisiran treatment reduced TC and TG by 29.5% and 5.1%, respectively, compared with the parent study baseline, and increased HDL-C by 11.0%.

Treatment did not affect PCSK9, apoB, non-HDL-C or Lp(a), as these parameters were not evaluated in the study. Throughout the study, 77.8% of the patients had treatment-emergent adverse events (TEAEs) and 30.2% had treatment-emergent serious adverse events (TESAEs). The most frequent TEAEs were COVID-19 (13.8%), uncontrolled diabetes mellitus (7%) and hypertension (7%), while the most common TESAEs were coronary artery disease (2%) and acute myocardial infarction (1.3%). For safety topics of special interest, new or worsening diabetes mellitus was observed in 17.8% of patients, followed by major adverse cardiac events (MACE) (9.2%), injection-site reactions (5.9%) and hepatic events (5.1%). Injection-site

reactions were mostly mild-to-moderate in intensity. The ORION-8 trial provides the most extensive long-term clinical trial evidence to date on inclisiran therapy, demonstrating sustained LDL-C reduction for up to 6.8 years with a stable safety profile and minimal treatment burden. These findings support inclisiran as a durable and well-tolerated LDL-C lowering approach when added to standard-of-care lipid-lowering therapy [31].

As for adolescents, the ORION-13 trial was a phase 3, double-blind, placebo-controlled, 2-part multi-center clinical study designed to assess the efficacy and safety of inclisiran in patients 12 to under 18 years of age with genetically confirmed HoFH. Thirteen participants with elevated LDL-C levels despite maximal statin therapy were randomized to receive either inclisiran or placebo at set intervals over one year. The primary outcome was the percentage change in LDL-C from baseline to day 330. Results showed that inclisiran led to a significant placebo-adjusted reduction in LDL-C of 33.3%, with 66.7% of treated patients achieving more than a 15% reduction and 55.6% achieving more than a 20% reduction. Additional benefits included marked reductions in PCSK9, apoB, non-HDL-C and TC. Importantly, no serious adverse events, treatment discontinuations or deaths were reported, and no new safety concerns emerged. These findings support inclisiran as an effective and well-tolerated treatment option for adolescents with HoFH who retain some LDLR activity, addressing a critical need in this high-risk population [33].

Real World Efficacy

The real-world use of inclisiran has been reported across multi-center cohorts and real-world registries, providing a much-needed complement to randomized clinical trial data while illustrating both consistent LDL-C lowering and substantial inter-individual variability in response across diverse health systems. In a real-world multi-center setting in Germany, the German Inclisiran Network enrolled patients who received inclisiran in 14 lipid centers for elevated LDL-C levels between February 2021 and July 2022. This study revealed pronounced heterogeneity in LDL-C reductions after inclisiran, suggesting that effectiveness might be modulated by patient characteristics, prior lipid lowering therapies and local practice patterns rather than a uniform response across all treated individuals [33].

A real-world, single-center experience from a tertiary lipid center at Hammersmith Hospital, Imperial College London National Health Service (NHS) Trust, London, documented the early utilization of inclisiran in 80 patients between December 2021 and September 2022, illustrating its feasibility and tolerability in routine care outside controlled randomized clinical trials. This study confirmed that a single dose of inclisiran led to significant effects after a two month period, with a mean LDL-C reduction of 48.6% (from a baseline of 135 mg/dL (3.5 mmol/L) to 79 mg/dL (1.8 mmol/L)). Broader lipid reductions were also noted, including a 33.3% decrease in TC, a 31.3% decrease in median TG, and a 7.7% increase in HDL-C. These reductions were consistent across diverse demographics (age, sex, ethnicity and FH status). Nearly one-half the cohort (46.3%) achieved at least a 50% LDL-C reduction from baseline and 36.4% achieved LDL-C levels below 54 mg/dL (1.4 mmol/L). Notably, patients on background statin therapy achieved an even greater mean LDL-C reduction of 56% compared to 44.9% in those not receiving statin therapy. The treatment was overall well tolerated, with mild and self-resolving adverse events, including injection-site reactions, headache, and fatigue, occurring in 3.9% of patients at 2 months [34].

Providing robust real-world evidence from Italy, results from the INCLIVEN multi-center registry, which followed 240 patients with elevated CV risk across 12 lipid centers in the Veneto region of Italy,

confirmed significant efficacy consistent with clinical trials, showing a mean LDL-C reduction of 52.3% at 3 months and 50.0% at 9 months, with approximately 64.7% of patients achieving the 2019 European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) LDL-C targets at the 3 month mark. Most notably, multi-variate analysis identified that patients with diabetes mellitus and those on concomitant statin therapy experienced significantly greater LDL-C reductions than those without (59.9% with diabetes mellitus vs. 49.7% without diabetes mellitus), concluding that both diabetes mellitus and background statin therapy are independent predictors for greater LDL-C reduction. The treatment demonstrated a favorable safety profile and high adherence, with only 1.3% of the participants reporting mild injection-site reactions and minimal discontinuation rates [35].

Real World Adherence

When it comes to adherence, real-world evidence demonstrated superior adherence when compared to PCSK9 mABS such as alirocumab or evolocumab. A retrospective, observational clinical study utilized the United States Komodo Health database from January 1, 2021 to February 8, 2023 to evaluate treatment adherence at 6 months for patients with newly initiated inclisiran, alirocumab, or evolocumab since 2022. Adherence was defined as the proportion of days covered (PDC), i.e., the number of days covered by the drug divided by the observational period. Poor adherence was defined as PDC<0.80. This study found the mean 6 month adherence was highest for inclisiran at 0.85 with 69.9% proportion of patients with a PDC>0.8 followed by 0.72 for alirocumab with 51% and 0.70 for evolocumab with 48.6%, respectively [36].

Real World Reductions

A systematic review and meta-analysis published on June 12, 2025, reviewed seven studies comprising 1454 patients. This review noted a median LDL-C reduction of approximately 42.8%, with greater reductions reported when inclisiran was used concomitantly with other lipid-lowering therapies (45.7%) compared with monotherapy (37.5%). This review demonstrated that while real-world LDL-C reductions remained favorable, their magnitude was lower than that of the ORION trial estimates highlighting the need for further real-world data studies to bridge the gaps in effectiveness and to optimize therapeutic outcomes [37].

Real World Implications of Transitioning from PCSK9 mABS to Inclisiran

Real-world evidence suggests a notable and critical divergence in efficacy when it comes to patients transitioning from PCSK9 mABS, such as alirocumab or evolocumab, to inclisiran compared to patients who are not treated with mAB therapy. Multiple observational cohorts have demonstrated attenuated and, in some cases, “paradoxical” responses when transitioning from prior mAB therapy. For instance, data from the Dutch registry indicated that LDL-C paradoxically increased 38% at 3 months and 59% at 9 months when changing therapy from mAB to inclisiran therapy [38]. This finding was corroborated by the German Inclisiran Network, which displayed attenuated LDL-C reductions (23.6%) in patients who were previously on mAB therapy when compared to naive patients (41.1%) [39]. Similarly, a retrospective study from the Middle East displayed a 3 month LDL-C increase of 38% and 9 month increase of 58% [40]. These findings suggest that in clinical practice, inclisiran may be more effective as an alternative therapy for a specific population (such as those struggling with adherence to mAB therapy), rather than as a superior replacement for all patients on PCSK9 mAB therapy.

Taken together, real world studies from Europe, United States, Middle East and North Africa region complemented by the meta-analytical synthesis, support consistent efficacy of LDL-C lowering with inclisiran, particularly among patients not previously treated with PCSK9 mABS. Across cohorts, however, the efficacy and durability appear heterogeneous; shaped by background statin therapy, changing from PCSK9 mAB therapy, co-morbid conditions such as diabetes mellitus and health-system level factors. The existing evidence positions inclisiran as an effective treatment with superior adherence in lipid management, while underscoring the importance of careful patient selection and treatment sequencing to optimize outcomes outside the controlled environment of randomized clinical trials [33-40].

Conclusion and Future Perspectives

While inclisiran is proven to lower LDL-C, large-scale trials to definitively confirm its impact on MACE are ongoing. Several key phase III clinical trials are underway to evaluate the role of inclisiran in the reduction of CV risk.

The PRECAD trial investigates the role of inclisiran treatment in the primary prevention of subclinical atherosclerosis starting at an age younger than conventional practice and is estimated to be completed by 2032. There is growing evidence that subclinical atherosclerosis starts at an early age, even with LDL-C levels and other CV risk factors that are within normal limits. An increased exposure to subclinical atherosclerosis is associated with an increased risk of ASCVD events later in life. The PRECAD trial hypothesizes that participants aged 20 to 39 years without known ASCVD, who maintain LDL<55 mg/dL and control other CV risk factors, will prevent the onset and/or reduce the progression of atherosclerotic burden later in life. If lifestyle modifications fails to meet the goal LDL<55 mg/dL, inclisiran therapy will be initiated among the experimental group. This trial underscores the efficacy of inclisiran treatment in improving adherence among a young population in the setting of primary prevention.

The ADD-VANTAGE trial is investigating efficacy and safety of adding pelacarsen (an Lp(a) lowering therapy) to participants who are already receiving inclisiran (an LDL-C lowering therapy). This trial will study whether the combination of these two therapies can reduce both elevated Lp(a) and LDL-C in those with ASCVD. The trial is estimated to be completed by 2028. Pelacarsen is an investigational antisense drug designed to lower Lp(a). The Lp(a) HORIZON trial is the first outcomes trial that investigates whether lowering Lp(a) reduces MACE and is expected to report results by the end of 2026.

The VICTORION-2P trial is investigating efficacy of inclisiran in reducing MACE in those with known ASCVD and will be completed by 2027. This trial tests the hypothesis that treatment with inclisiran 300 mg subcutaneously on Day 1, Day 90, and every 6 months in addition to high-intensity statin will reduce the risk of MACE (composite of CV death, non-fatal myocardial infarction and ischemic stroke) in participants with established ASCVD compared to controls on placebo and statin therapy.

The VICTORION-INTERVENTION trial is evaluating whether adding inclisiran to standard care will reduce future coronary or peripheral arterial events in high-risk patients who underwent elective or urgent percutaneous coronary or peripheral intervention within two weeks. The study will run until a predetermined number of events occur, with maximum treatment duration of 45 months.

The ORION-4 trial, a double-blind, randomized, placebo-controlled phase 3 outcomes clinical trial, is evaluating the long-term effects of

inclisiran on major CV events in patients with established ASCVD. It is estimated that the trial results will be available in 2026. The primary outcome of the ORION-4 trial is time to first occurrence of MACE or urgent coronary re-vascularization [41].

New Preclinical Data: Comparing Inclisiran with PCSK9 inhibitors

Preclinical dose-escalation studies of inclisiran in rodents and non-human primates demonstrated a robust, dose-dependent reduction in both intracellular hepatic PCSK9 mRNA and secreted plasma protein [42]. The molecule was strategically engineered with 2'-O-methyl and 2'-O-fluoro substituted nucleotides to mitigate exonuclease degradation, significantly extending its cellular half-life [42]. Tissue distribution assays confirmed that subcutaneous administration localized the highest drug concentrations directly within the liver and kidneys, followed by rapid systemic clearance [42]. This contrasts with the systemic circulation required by mABs. Furthermore, emerging in vitro models under cardiotoxic stress suggest that inclisiran may possess distinct immunomodulatory benefits, reducing pro-inflammatory cytokines and MyD88 levels by nearly 48% in mouse cardiomyocytes, a pathway independent of its primary lipid-lowering mechanism [43].

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