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REVIEW

Inclisiran for the treatment of hypercholesterolaemia

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Abstract

Inclisiran is a synthetic small interfering RNA (siRNA) that inhibits the production of proprotein convertase subtilisin/kexin 9 (PCSK9) in hepatocytes by silencing the translation of PCSK9 mRNA. The result of this mechanism is a decrease in PCSK9 synthesis resulting in decreased degradation of the LDL receptor, leading to more LDL receptors being available to clear LDL cholesterol (LDL-C) from the circulation. Inclisiran received FDA approval in 2021 and EMA approval in 2020. The indication for inclisiran use is as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidaemia, including those with heterozygous familial hypercholesterolaemia to reduce LDL-C. Inclisiran has demonstrated consistent LDL-C lowering in the range of 44–54%. Furthermore, inclisiran has been demonstrated to be a safe medication with indications of significant or serious adverse events when compared to placebo. Inclisiran is given as an initial subcutaneous dose followed by a repeat dose at 3 months and every 6 months thereafter. The 2022 American College of Cardiology Expert Consensus Decision Pathway includes inclisiran as an option for non-statin therapy in addition to maximally tolerated statin therapy in those at very high risk of atherosclerotic cardiovascular disease or those with LDL-C >190 mg/dL. The ORION-4, VICTORION-1 PREVENT and VICTORION-2 PREVENT trials are ongoing and designed to evaluate the ability of inclisiran to reduce major cardiovascular events in addition to LDL-C lowering but will not be completed for a few years.

Keywords: atherosclerotic cardiovascular disease, cardiovascular events, dyslipidaemia, heterozygous familial hypercholesterolaemia, hypercholesterolaemia, hyperlipidaemia, inclisiran, proprotein convertase subtilisin/kexin 9, small interfering RNA.

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Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide, with an estimated 17.9 million deaths due to CVD each year.[1] To prevent CVD, both primary and secondary prevention strategies must be considered and employed. Primary prevention focuses on reducing the risk of developing a cardiovascular (CV) event in people with risk factors for CVD, whereas secondary prevention focuses on reducing further CV damage and the risk of another CV event in those with established CVD.[2,3] In both cases of CVD prevention, hyperlipidaemia is a modifiable risk factor that, when treated, can reduce the risk of either a first or subsequent CV event.[4]

Hypercholesterolaemia is defined as elevated low-density lipoprotein cholesterol (LDL-C) levels or total cholesterol levels, whilst hyperlipidaemia refers to elevated lipid levels in the blood, which include lipoid parameters beyond cholesterol. Population estimates suggest that optimal levels of total cholesterol are approximately 150 mg/dL with a corresponding LDL-C level of approximately 100 mg/dL.[3] Both USA and European cholesterol guidelines advocate for the use of statin therapy as first-line treatment for hyperlipidaemia to prevent CVD in primary and secondary prevention populations when the primary lipid abnormality is an increase in total cholesterol and LDL-C.[3,5] Evidence from many randomized, controlled, clinical trials supports the role of statins as first-line therapy to reduce LDL-C levels and to subsequently reduce major CV events (MACE) in patients in both primary and secondary prevention groups.[3]

Statins alone are often not able to lower LDL-C levels to goal, especially in patients with established atherosclerotic CVD (ASCVD); therefore, other drug classes have been studied as adjunctive therapy to statins to further reduce LDL-C levels. Fortunately, several of these other drug classes have demonstrated added CV event

lowering when added to maximal statin therapy. Ezetimibe and proprotein convertase subtilisin/kexin 9 (PCSK9) monoclonal antibodies (mAbs) have demonstrated the ability to reduce the risk of CV events in patients with established ASCVD when added to statin therapy.[6–8] Based on these findings, USA and European cholesterol guidelines recommend the use of ezetimibe and/or PCSK9 mAbs in addition to statin therapy in people with ASCVD who are deemed at high or very high risk.[4,5] Bempedoic acid, an adenosine triphosphate-citrate lyase inhibitor, was approved in 2020 and, whilst not yet reflected in international cholesterol guidelines, can also be used as an adjunct to maximally tolerated statin therapy in adults with established ASCVD or those with heterozygous familial hypercholesterolaemia (HeFH) to further lower LDL-C levels.[9]

One of the newest non-statin approaches to reduce LDL-C is the use of inclisiran, a small interfering RNA (siRNA) conjugated to triantennary *N*-acetylgalactosamine carbohydrates.[10] This narrative review presents and examines current evidence regarding the use of inclisiran for the treatment of hyperlipidaemia and its potential role to reduce CV events.[11] We conducted an English language MEDLINE search through 1 October 2024 using the search terms "inclisiran", "ALN-PCSsc", "hyperlipidemia", "hypercholesterolemia" and "dyslipidemia". A manual search for references identified within these trials and review articles was performed to identify further relevant articles.

Review

Pharmacology

Mechanism of action

PCSK9 is secreted by hepatocytes to regulate the LDL-C receptor in the liver. Inclisiran is a double-stranded siRNA, conjugated on the sense strand with triantennary *N*-acetylgalactosamine carbohydrates to facilitate uptake by hepatocytes.[10,11] Within hepatocytes, inclisiran utilizes the RNA interference mechanism and directly binds to the mRNA precursor for PCSK9, resulting in inhibition of *PCSK9* gene expression, which leads to more LDL-C receptor recycling resulting and subsequently in an increased number of LDL-C receptors available on the hepatocyte cell surface. With more LDL-C receptors available follows an increase in LDL-C uptake in hepatocytes, leading to lower LDL-C levels in the circulation. The specific mechanism of inclisiran allows for less frequent dosing than PCSK9 mAbs.

Pharmacodynamics

Inclisiran is administered as a 284-mg subcutaneous dose on day 1 and then again on day 90, with subsequent dosing administered at 6-month intervals. Following this dosage, the ORION-1 trial demonstrated LDL-C reductions by almost 50% at day 180 and day 240; these results were the primary driver for the approved 284 mg dose.[12] The mean reduction of LDL-C observed at 30–180 days post-dose ranged from 38% to 51%. Additionally, the impact of inclisiran in reducing PCSK9 levels has been demonstrated, with reductions of 75% and 69% at 120 and 180 days post-dose, respectively.

Pharmacokinetics

It has been demonstrated that inclisiran administered at the dose of 284 mg approved by the FDA and EMA reaches peak concentrations within 4 h and reaches undetectable levels between 24 to 48 h despite the prolonged dosing effect allowing for twice-yearly administration for long-term treatment.[10,11] Inclisiran is highly protein bound and has excellent uptake by hepatocytes, with a short half-life of 9 h. Inclisiran is metabolized through nucleases to shorter nucleotides and is not a substrate for CYP450, resulting in low potential for risk of drug interactions. There are no recommended adjustments for inclisiran dosing in individuals with mild or moderate renal or hepatic impairment, and it has not been studied in end-stage liver or renal disease.[10,11] Furthermore, there is no evaluation of the safety or efficacy of inclisiran in the paediatric population. Safety or efficacy have been evaluated in some trials in people over 65 years of age, with no differences observed in relation to adults under 65 years of age. Of note, inclisiran administration must be performed by a health care professional, which is more restrictive than the self-administration of PCSK9 mAbs by patients.

Inclisiran in phase I and II trials

The ORION series of trials has been the main programme evaluating the role of inclisiran as a lipid-lowering therapy. The first trial in this series was the ORION-1 trial, which was a phase II, multicentre, double-blinded, placebo-controlled trial with a mix of patients including those with established ASCVD (69.3% of patients) and those considered at high risk for developing ASCVD.[12] The trial included 501 patients randomly assigned to receive a single dose of placebo or inclisiran 200 mg, 300 mg, or 500 mg or two doses (at days 1 and 90) of placebo or inclisiran 100 mg, 200 mg, or 300 mg.[12] Most patients at baseline were receiving statin therapy and about one-third of patients were on ezetimibe prior to the study. The primary endpoint in the trial was the change in LDL-C from baseline to 180 days. The LDL-C reduction seen with the one-dose inclisiran arms compared with placebo ranged from 27.9% to 41.9% at 180 days compared with 35.5–52.6% in those who received two doses compared with placebo ($p<0.001$ for all doses compared to placebo).[12]

The ORION-3 trial was an open-label extension of the original ORION-1 trial following its completion that followed patients for up to 4 years.[13] This trial included 290 patients

treated with inclisiran from the original trial who continued on a dose of 300 mg every 6 months for the completion of the study. Additionally, there were 92 patients who were randomized in ORION-1 to placebo and then transitioned to evolocumab for up to 1 year before transitioning to inclisiran 300 mg every 6 months up to 4 years of treatment. The trial was able to demonstrate, in the inclisiran-only arm, an LDL-C lowering of 47.5% at 210 days that was sustained at 1440 days. The mean reduction at 4 years in LDL-C was 44.2% with reductions in PSCK9 ranging from 62.2% to 77.8%.[13] In the open-label extension there was no reported difference between treatment arms, as it relates to serious adverse events with injection-site reactions occurring in 14% of patients in the inclisiran-only arm and the group switched to inclisiran. The findings of ORION-3 support that inclisiran is well tolerated and can maintain LDL-C reductions over multiple years with a twice-yearly dosing.

Inclisiran phase III trials

Following the findings from the phase I and phase II ORION trials, a series of phase III trials in larger populations were established evaluating the safety and efficacy of inclisiran (Table 1). The first in this series was ORION-9, which is a phase III, double-blind trial in 482 patients with HeFH who were receiving maximum tolerated doses of statins prior to the trial.[14] Patients were randomized to inclisiran 300 mg subcutaneous injections or placebo on days 1, 90, 270 and 450. The first primary endpoint in the study was LDL-C change from baseline to 510 days and the second was the time-adjusted per cent change in LDL-C from baseline between day 90 and day 540. The median age of patients in the trial was 56 years of age and was evenly split between men and women. The mean LDL-C change from baseline to day 510 was a 39.7% reduction in the inclisiran arm and an 8.2% increase in the placebo arm ($p<0.001$).[14] The time-adjusted per cent change in LDL-C from baseline between day 90 and day 540 was 38.1% lower in the inclisiran arm and a 6.2% lower in placebo-treated individuals ($p<0.001$).[14] There were no noted statistical differences in any serious adverse events or overall adverse events between study arms. Injection-site reactions were the only significant adverse event with a higher rate in the inclisiran *versus* placebo arms. Mild injection-site reactions occurred in 15.4% of inclisiran-treated individuals compared with 1.7% in placebo-treated individuals.

ORION-10 is a phase III, randomized, double-blind, parallel-group study of 1561 adults with known ASCVD who were receiving statins at a maximum tolerated dose with or without ezetimibe and with an LDL-C greater than or equal to 70 mg/dL prior to the trial (Table 1).[15] Patients were randomized to inclisiran 300 mg subcutaneous injections or placebo on days 1 and 90, and every 6 months over a period of 540 days. The first primary endpoint in the study was LDL-C change from baseline to 510 days with the other primary endpoint being time-adjusted percentage change in LDL-C from baseline between day 90 and day 540. The mean LDL-C value in the trial at baseline was 104.7 mg/dL. The median age of patients in the trial was 66 years of age and 70% were men. The mean LDL-C change from baseline to day 510 was a 51.3% reduction in the inclisiran arm and a 1.0% increase in the placebo arm ($p<0.001$).[15] The time-adjusted percentage change in LDL-C from baseline between day 90 and day 540 was a decrease of 51.8% in the inclisiran arm and a 2.5% increase in placebo-treated individuals ($p<0.001$).[15] There were no noted statistical differences in any serious adverse events or overall adverse events between study arms. Injection-site reactions did occur at a slightly higher rate in inclisiran-treated individuals compared with placebo-treated individuals (2.6% *versus* 0.9%, respectively).

The third study in this series is ORION-11, a phase III, randomized, double-blind, parallel-group study of 1617 adults with known ASCVD or ASCVD risk equivalents (i.e. type 2 diabetes, familial hypercholesterolaemia, or a 10-year risk of a cardiovascular event of 20% or greater) who were receiving statins at maximum tolerated doses with or without ezetimibe and with an LDL-C greater than or equal to 70 mg/dL prior to the trial (Table 1).[15] Patients were randomized to inclisiran 300 mg subcutaneous injections or placebo on days 1 and 90, and every 6 months over a period of 540 days. The first primary endpoint in the study was LDL-C change from baseline to 510 days, and the second was the time-adjusted percentage change in LDL-C from baseline between day 90 and day 540. The mean LDL-C value in the trial at baseline was 105.5 mg/dL. The median age of patients in the trial was 65 years of age and with 70% men. The mean LDL-C change from baseline to day 510 was a 45.8% reduction in the inclisiran arm and a 4.0% increase in the placebo arm ($p<0.001$).[15] The time-adjusted percentage change in LDL-C from baseline between day 90 and day 540 was a decrease of 45.8% in the inclisiran arm and a 3.4% increase in the placebo arm ($p<0.001$).[15] There were no noted statistical differences in any serious adverse events or overall adverse events between study arms. Injection-site reactions did occur at a slightly higher rate in inclisiran-treated individuals compared with placebo-treated individuals (4.7% *versus* 0.5%, respectively).

Since the publication of the ORION-9, ORION-10 and ORION-11 trials, there have been multiple other analyses evaluating the published clinical trials in relation to safety. One recent analysis examined the safety and tolerability of seven inclisiran trials, including ORION-1, ORION-3, ORION-5, ORION-9, ORION-10, ORION-11, and the ongoing ORION-8 trial (an open-label extension of ORION-9,

Table 1. Summary of dyslipidaemia phase III trials with inclisiran.

Trial	Design	Participants	Duration (days)	Intervention (mg each dose), *n*	Primary outcome (INC *vs* PL or INC *vs* UC)	Secondary outcomes
ORION-9 (2020)[14]	R, DB, PC	Adults with HeFH 540 with LDL-C ≥100 mg/dL on MTS with or without ezetimibe	540	INC 300 mg, 242 PL, 240	Placebo adjusted LDL-C % change at 510 D (−47.9%); placebo adjusted time average LDL-C % change from 90 D to 540 (−4.3%)	PCSK9 levels decreased by 60.7%; median Lp(a) reduction of 13.5%; mild injection-site reaction (INC 15.4% *vs* PL 1.7%); serious ADE (INC 7.5% *vs* PL 13.8%)
ORION-10 (2020)[15]	R, DB, PC, PG	Adults with ASCVD and LDL-C ≥70 mg/dL on MTS with or without ezetimibe	540	INC 300 mg, 781 PL, 780	LDL-C % change at 510 D (−52.3%); placebo adjusted time average LDL-C % change from 90 D to 540 (−53.8%)	PCSK9 levels decreased by 69.8%; median Lp(a) reduction of 21.9%; mild injection-site reaction (INC 1.7% *vs* PL 0.7%; serious AE (INC 22.4% *vs* PL 26.3%)
ORION-11 (2020)[16]	R, DB, PC, PG	Adults with ASCVD and/or ASCVD risk equivalent and LDL-C ≥70 mg/dL on MTS with or without ezetimibe	540	INC 300 mg, 810 PL, 807	Placebo adjusted LDL-C % change at 510 D (−49.9%); placebo adjusted time average LDL-C % change from 90 D to 540 (−49.2%)	PCSK9 levels decreased by 63.6%; median Lp(a) reduction of 18.6%; mild injection-site reaction (INC 2.8% *vs* PL0.4%; serious AE (INC22.3% *vs* PL 22.5%)
VITORIAN-INITIATE (2024)[18]	R, P, UC, PG, OL	Adults with ASCVD and LDL-C ≥70 mg/dL on MTS with no immediate plan to modify LLT	450	INC 284 mg, 225 UC, 225	UC adjusts LDL-C % change at 330 D (−53.0); statin discontinuation rate INC 6.0% *vs* UC 16.7%	LDL-C <70 mg/dL (INC81.8% *vs* UC 22.2%); LDL-C <55 mg/dL (INC71.6% *vs* UC 8.9%); injection-site reaction (INC 10.3% *vs* UC 2.6%); serious AE (INC 11.5% *vs* UC 13.4%)

AE, adverse event; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; D, days; DB, double blind; E, ezetimibe; HeFH, heterozygous familial hypercholesterolaemia; INC, inclisiran; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein a; MC, multicentre; MTS, maximum tolerated statin; OL, open-label; PC, placebo controlled; PCSK9, proprotein convertase subtilisin/kexin 9; PL, placebo; PG, parallel group; R, randomized; RF, risk factors; UC, usual care.

ORION-10, ORION-11 and ORION-3).[16] This post-hoc analysis included 3576 patients treated with inclisiran for up to 6 years and 1968 patients treated with placebo for up to 1.5 years. The investigators evaluated the cumulative incidence of reported treatment-emergent adverse events (TEAEs). Comparable rates of TEAEs that were serious or led to discontinuation were demonstrated for hepatic, muscle or kidney events, incident diabetes, and elevations in creatine kinase or creatinine.[16] Injection-site reactions were the only TEAEs showing a higher rate in inclisiran-treated individuals compared to placebo (9.3% and 1.8%, respectively). This additional data out to 6 years in some patients further helps support the long-term safety of inclisiran whilst we wait on the major CV outcome trials (CVOTs) to be completed to determine if there is a lowering of CV events with inclisiran use There has been one patient-level, pooled analysis of ORION-9, ORION-10 and ORION-11 which has reported on MACE from these trials. This pooled analysis in 3655 patients evaluated inclisiran 284 mg on days 1 and 90, and every 6 months thereafter for 18 months.[17] The investigators were able to show a statistically significant reduction in

the MACE composite endpoint (odds ratio 0.74, 95% CI 0.58–0.94) showing potential promise for the ongoing CVOTs.[17] The analysis did not show any statistical difference between inclisiran and placebo for the endpoints of fatal or non-fatal myocardial infarction or fatal or non-fatal stroke.

VICTORION-INITIATE is a phase III pragmatic trial evaluating the role of inclisiran added to statin therapy as the second lipid-lowering medication after not achieving an LDL-C of less than 70 mg/dL despite being on maximum tolerated statin therapy (Table 1).[18] Patients were randomized to inclisiran 284 mg subcutaneous injections on days 1, 90 and 270 plus usual care *versus* usual care alone. Usual care included lipid management at the treating physician discretion. The primary endpoint was the percentage change in LDL-C from baseline and statin discontinuation rates. The trial included 450 patients with a mean baseline LDL-C of 97.4 mg/dL and 70% were male.[18] The primary endpoint of change in LDL-C from baseline was 60% *versus* 7.0% in the inclisiran first arm and usual care arms, respectively, at day 330 ($p<0.001$).[18] There was no statistical difference in statin discontinuation rates between the two arms. The secondary endpoints of LDL-C goal achievement of less than 70 mg/dL and less than 55 mg/dL both demonstrated greater achievement with the inclisiran first approach *versus* usual care, respectively (81.8% *versus* 22.2%; $p<0.001$; 71.6% *versus* 8.9%; $p<0.001$).[18] There were no noted statistical differences in any serious adverse events or overall adverse events between study arms. Injection-site reactions did occur at a slightly higher rate in the inclisiran first-treated individuals compared to usual care (10.3% *versus* 2.6%, respectively).

The full findings of the ORION-8 long-term follow-up, which was an open-label extension of ORION-3 (phase II) and ORION-9 and ORION-11 (phase III) trials were reported earlier in 2024.[19] After completion of the parent trials, patients with ASCVD risk equivalents, ASCVD or HeFH received open-label inclisiran twice-yearly for another 990 days with an end-of-study date being 90 days after their last dose or at day 1080. The primary efficacy endpoint in the study was the percentage of participants achieving the LDL-C goal at the end of the study. The pre-defined goals were an LDL-C of less than 70 mg/dL with known ASCVD and less than 100 mg/dL with an ASCVD risk equivalent. The secondary efficacy endpoints evaluated the percentage change in LDL-C and other lipid parameters from baseline until the end of the study. The study enrolled 3274 patients and 2246 patients were followed to the end of the study. Of note, 82.7% of patients had ASCVD at baseline. Patients were treated for a mean exposure time to inclisiran of 3.7 years (including parent trial exposure).[19] The primary efficacy endpoint demonstrated a 78.4% overall LDL-C goal attainment for the full population and 79.4% and 74.3% for the patients with ASCVD and ASCVD risk equivalents, respectively.[19] Exploratory analyses evaluating the benefit of longer-term exposure to inclisiran across the parent trials and through the open-label extension did not demonstrate significant impact on reducing MACE further based on length of exposure. Serious TEAEs were reported in 30.2% of patients in the open-label extension study. Injection-site reactions occurred at a rate of 5.9% with none being considered serious TEAEs, and these findings align with previous phase II and phase III study findings. Results of the ongoing CVOTs are eagerly awaited, although these are still multiple years out from completion and publication.

FDA-approved indication

As previously stated, inclisiran (Leqvio™) was approved by the FDA in 2021 as an adjunct to diet and statin therapy for the treatment of adults with ASCVD or HeFH to reduce LDL-C levels. In 2023, the FDA indication was expanded to allow for use as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidaemia in addition to the previous patient populations.[10] The EMA originally authorized approval for use in 2020 and inclisiran is now indicated in adults with primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidaemia as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.[11] The FDA and EMA approved recommended dose is inclisiran 284 mg administered as a single initial subcutaneous injection initially, another at 3 months, and then every 6 months.[10,11]

Current guideline recommendations

The 2018 American Heart Association/American College of Cardiology (AHA/ACC) guidelines include PCSK9 mAbs (alirocumab and evalocumab) as non-statin therapy recommended in addition to maximum tolerated statin therapy in the very-high-risk ASCVD population.[4] At the time of publication of these guidelines, inclisiran had not been approved by the FDA or EMA and was therefore not included in the guideline recommendations. The 2022 ACC Expert Consensus Decision Pathway (ECDP) has included inclisiran as an option for non-statin therapy in addition to maximally tolerated statin therapy in the very-high-risk ASCVD population or those with LDL-C greater than 190 mg/dL.[20] The American Association of Clinical Endocrinology last published their guidelines in 2020 and, based on inclisiran not having been approved yet by the FDA or EMA, there are no specific recommendations for its use but they do advocate for the use of

PCSK9 mAbs. Based on the literature and FDA approval of inclisiran, its use should be considered as a PCSK9-modulating therapy as an approach to optimize lipid lowering if not achieving LDL-C targets with statin monotherapy.[21] Finally, the European Society of Cardiology last published their dyslipidaemia guidelines in 2019 and do not have specific recommendations for the use of inclisiran.[5] The 2023 AHA/ACC chronic coronary disease guidelines have included a class 2b recommendation for inclisiran to be used in select populations in addition to statin therapy when ezetimibe and PCSK9 mAbs are deemed insufficient or not tolerated, acknowledging that clinical CV outcome data remain unavailable at this time.[22] It is anticipated, as these guidelines are updated over time, that inclisiran will be incorporated into specific recommendations for use to align with their currently approved indications.

Ongoing CVOTs

There are three ongoing CVOTs evaluating ability of inclisiran to reduce future MACE outcomes (Table 2). The ORION-4 began in 2018 and has an estimated enrolment of 15,000 patients and will target patients at least 40 years of age or older with established ASCVD.[23] This study is not anticipated to be completed until 2026 and is focusing on a 5-point MACE outcome of CV death, myocardial infarction, fatal or non-fatal ischaemic stroke, or urgent coronary revascularization procedure. It is anticipated that this will be the first of the three trials to be completed. The second clinical trial, started in 2021, is the VICTORION-2 PREVENT trial, which has an estimated enrolment of 16,500 adult patients with established ASCVD who are 40 years of age or older and taking a maximum tolerated statin dose with or without ezetimibe and have an LDL-C of at least 70 mg/dL.[24] This trial is not estimated to be completed until 2027. The third ongoing CVOT is the VICTORION-1-PREVENT trial, which is evaluating patients with established ASCVD as well as patients with increased risk based on either their 10-year ASCVD risk score and/or elevated coronary artery calcium score.[25] This last trial is not anticipated to be completed until 2029. Additionally, siRNA lipid-lowering therapy is being evaluated for other potential targets, including apolipoprotein C3, angiopoietin-like protein 3 (ANGPTL3), APOB and lipoprotein(a) in phase II–III trials, which may provide further therapeutic options in the future.[26,27]

Implications for practice

Inclisiran has demonstrated the ability to lower LDL-C effectively in a variety of patient populations, including those with established ASCVD considered at very high risk as well as those with primary hyperlipidaemia,

Table 2. Ongoing inclisiran cardiovascular outcome trials.

Trial	Estimated enrolment	Patient population	Start date	Estimated completion date	Primary outcome
ORION-4[23]	15,000	Age ≥40 with established CV disease	October 2018	July 2026	Time to first occurrence of 5-point MACE (up to 5-year follow-up): CV death, MI, fatal or non-fatal ischaemic stroke or urgent coronary revascularization procedure
VICTORION-2 PREVENT[24]	16,500	Age ≥40 with established CV disease	November 2021	October 2027	Time to first occurrence of 3-point MACE (up to 72 months of follow-up): CV death, non-fatal MI or non-fatal stroke
VICTORION-1 PREVENT[25]	14,000	Age 40–79 with CAD, CAC score >100 Agatston units or 10-year ASCVD risk >20%, or 10-year ASCVD risk 7.5% to <20% with at least two risk-enhancing factors	March 2023	April 2029	Time to first occurrence of 4-point MACE (up to 75 months of follow-up): CV death, non-fatal MI, non-fatal ischaemic stroke or urgent coronary revascularization

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CAD, coronary artery disease; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.

including those with HeFH. The dosing scheme of inclisiran is potentially advantageous to help improve lipid-lowering medication adherence due to only needing administration of an injection every 6 months after the initial dose and a follow-up at 90 days. There is a need for further cost analysis when comparing the cost of inclisiran to PCSK9 inhibitors as the dosing of inclisiran is only twice-yearly *versus* 2–4-weekly dosing with PCSK9 inhibitors; however, inclisiran must be administered by a healthcare provider in the office setting. The efficacy in LDL-C lowering should be considered when determining the use of inclisiran as it is highly effective but, across trials, has demonstrated less LDL-C lowering on average than PCSK9 mAbs like alirocumab and evolocumab. The incorporation of inclisiran as a recommendation in the 2022 ACC ECDP as non-statin therapy to add onto statin therapy for those considered at very high risk of being above their LDL-C threshold of 55 mg/dL ideally will allow for more patients to gain access to this medication and optimize their CV risk-lowering therapy.

Conclusions

Inclisiran is a siRNA that inhibits the production of PCSK9 in hepatocytes resulting in decreased degradation of the LDL receptor, leading to the availability of more LDL receptors to clear LDL-C. Inclisiran received FDA approval in 2021 and EMA approval in 2020 and is indicated as adjunct to diet and statin therapy for treatment of adults with primary hyperlipidaemia, including those with HeFH. Inclisiran has demonstrated consistent LDL-C lowering in the range of 44% to 54%. The safety profile for inclisiran when studied *versus* placebo has demonstrated it to be a safe medication with no identified serious adverse effects. The 2022 ACC ECDP includes inclisiran as an option for non-statin therapy in addition to maximally tolerated statin therapy in the very-high-risk ASCVD population or those with LDL-C greater than 190 mg/dL. The ORION-4, VICTORION-2 PREVENT and VICTORION-1 PREVENT trials are ongoing and designed to evaluate the ability of inclisiran to lower MACE but will not be completed for a few years.

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