Clínica e Investigación en Arteriosclerosis 36 (2024) 100730

Sociedad Española de Arteriosclerosis

CLÍNICA E INVESTIGACIÓN EN ARTERIOSCLEROSIS

www.elsevier.es/arterio

REVIEW ARTICLE

Efficacy, benefit and safety of inclisiran☆

José López-Miranda*

Unidad de Lípidos y Arteriosclerosis, Departamento de Medicina Interna, Hospital Universitario Reina Sofía, Universidad De Cordoba, IMIBIC, CIBEROBN, Cordoba, Spain

Received 17 July 2024; accepted 22 July 2024

KEYWORDS
Inclisiran;
LDL-cholesterol;
PCSK9;
Efficacy;
Safety

Abstract Hypercholesterolemia is a causal factor of atherosclerotic cardiovascular disease (ASCVD), which is one of the main causes of morbidity and mortality in Spain. The reduction of LDL cholesterol (LDL-C) decreases the risk of ASCVD and adverse cardiovascular events. Targeted therapy for the proprotein convertase subtilisin/kexin type 9 (PCSK-9) has emerged as a novel tool for the treatment of hyperlipidemia. Inclisiran is a small double-stranded small interfering RNA that acts by blocking PCSK-9 transcription in hepatocytes, leading to a marked and sustained reduction in circulating LDL-C levels. In contrast to other lipid-lowering therapies such as statins, ezetimibe and monoclonal antibodies PCSK-9 inhibitors, Inclisiran proposes an infrequent dosing regimen of twice times a year. Its prolonged effect represents an advantage over non-compliance of the treatment, which is one of the main reasons why LDL-C goals are not achieved with standard therapy. This review aims to present and discuss current scientific data regarding the efficacy, tolerability and safety of Inclisiran in the treatment of hypercholesterolemia. Inclisiran has been shown to provide significant long-term reductions in LDL-C levels associated with notable decreases in levels of PCSK9 and other atherogenic lipoproteins with a highly favourable side effect profile similar to placebo. The convenience of a twice-yearly dosing regimen promotes adherence to therapy and facilitates achievement of LDL-C goals. Results from ongoing trials designed to determine its effect on cardiovascular events are expected to provide further information about the cardiovascular benefit of inclisiran in patients with ACVD and in patients at high cardiovascular risk.

PALABRAS CLAVE
Inclisiran;
Colesterol-LDL;
PCSK9;
Eficacia;
Seguridad

Eficacia, beneficio y seguridad de inclisiran

Resumen La hipercolesterolemia es un agente causal la enfermedad cardiovascular aterosclerótica, que es una de las principales causas de morbilidad y mortalidad en España. La reducción del colesterol LDL (c-LDL) produce una disminución del riesgo de enfermedad cardiovascular aterosclerótica y de eventos cardiovasculares adversos. La terapia dirigida a la proproteína

DOI of original article: https://doi.org/10.1016/j.arteri.2024.07.003
☆ Please cite this article as: J. López-Miranda, Eficacia, beneficio y seguridad de inclisiran, Clinica e Investigacion en Arteriosclerosis, https://doi.org/10.1016/j.arteri.2024.07.003
* Corresponding author.
E-mail address: jlopezmir@uco.es

convertasa subtilisina/kexina tipo 9 (PCSK9) ha surgido como una herramienta novedosa para el tratamiento de la hiperlipidemia. Inclisiran es un ARN pequeño de doble cadena, que actúa inhibiendo la transcripción de PCSK-9 en los hepatocitos, lo que conduce a una reducción marcada y sostenida del c-LDL. En contraste con otras terapias hipolipemiantes, como estatinas, ezetimibe y anticuerpos monoclonales inhibidores de PCSK9, inclisiran propone un régimen de dosificación infrecuente de dos veces al año. Su efecto prolongado representa una ventaja frente al incumplimiento del tratamiento, que es una de las principales causas por las que no se alcanzan los objetivos de c-LDL con la terapia estándar. Esta revisión tiene como objetivo presentar y discutir los datos científicos actuales con relación a la eficacia, tolerabilidad y seguridad del inclisiran en el tratamiento de la hipercolesterolemia. Se ha demostrado que inclisiran proporciona reducciones significativas a largo plazo en los niveles de c-LDL asociado a disminuciones notables en los niveles de PCSK9 y otras lipoproteínas aterogénas con un perfil de efectos secundarios muy favourable similar a placebo. La conveniencia de un régimen de dosificación dos veces al año promueve la adherencia a la terapia y facilita la consecución de los objetivos de c-LDL. Se espera que los resultados de los ensayos en curso diseñados para determinar su efecto sobre los eventos cardiovasculares aporten más información acerca del beneficio cardiovascular de inclisiran en pacientes con ACVD y en pacientes de alto riesgo cardiovascular.

Inclisiran in lowering LDC cholesterol levels

The efficacy of inclisiran in lowering LDL cholesterol (LDL-C) was initially evaluated in Phase 1 clinical trials in healthy volunteers with LDL-C levels greater than 100 mg/dl. Fitzgerald et al.[1] conducted a randomised, single-blind, placebo-controlled trial in adults with LDL-C of 116 mg/dl. Subjects were randomised 3:1 to receive a dose of ALN PCSsc (inclisiran precursor molecule), with doses ranging from 0.015 to 0.400 mg/kg. Participants in the higher dose group achieved reductions in LDL-C and proprotein convertase subtilisin/kexin type 9 (PCSK9) of 40% and 70%, respectively ($p < .001$). In a second study,[2] published 3 years later, 70 volunteers aged 18–75 years were randomly assigned in a 3:1 ratio to receive subcutaneous injections of inclisiran (ALN PCSsc) or placebo in a single-ascending-dose phase (at a dose of 25, 100, 300, 500, or 800 mg) or a multiple-dose phase (125 mg weekly for 4 doses, 250 mg every other week for 2 doses, and 300 or 500 mg monthly for 2 doses, with or without concurrent statin therapy). In the single-dose phase, LDL-C levels were significantly reduced compared to placebo on day 84 following treatment with a dose of 100 mg or more of inclisiran, with least-squares mean reductions ranging from 36.7%–50.6%; the largest reduction was observed with the 500 mg dose of inclisiran. In the group of subjects randomised to the multiple-dose phase, a significant reduction in LDL-C was observed, with a least-squares mean change at day 84 after the first dose ranging of 45.1%–59.7% for all inclisiran regimens except the cohort that received 125 mg weekly for 4 weeks. The effect on cholesterol, PCSK9, and LDL-C was sustained for at least 180 days after treatment initiation, and there was little variation over a 6-month period after the first dose.

Based on previous findings, the ORION programme, a series of separate global clinical trials, was initiated to evaluate the efficacy of inclisiran in a variety of individuals, including those at high risk of atherosclerotic cardiovascular disease (CVD), those with established CVD, and those with familial hypercholesterolaemia (FH).

ORION-1 was a Phase 2, multicentre, randomised, double-blind, placebo-controlled, multiple-ascending-dose trial of inclisiran in patients at high risk for ASCVD with elevated LDL-C levels.[3] Five hundred and one subjects were randomly assigned to receive a single dose of 200, 300, or 500 mg of inclisiran or two doses (on days 1 and 90) compared to placebo. A reduction in LDL-C levels was observed from day 14 after the first injection. At day 30, the reduction in LDL-C ranged from 44.5%–50.5% below baseline for all doses of inclisiran tested. In addition, a nadir was observed at approximately day 60 for the single-dose regimens and at day 150 for the two-dose group. For the single-dose regimen, the reduction in LDL-C at day 180 was 27.9%–41.9% compared to a 2.1% increase with placebo ($p < .001$). At day 180, subjects in the 2-dose arm experienced a mean reduction in LDL-C of 35.5%–52.6% compared to a 1.8% increase in the placebo group ($p < .001$). PCSK9 levels were also significantly reduced at 180 days in patients treated with inclisiran. In the one-year follow-up of the ORION-1 trial, a single dose of inclisiran and two doses on days 1 and 90 were shown to reduce time-averaged LDL-C levels over one year by 29.5%–38.7% and 29.9%–46.4%, respectively, according to the dose. A 50% reduction in LDL-C was maintained for at least 6 months after 2 doses of 300 mg of inclisiran on days 1 and 90. In addition, this 2-dose regimen of 300 mg of inclisiran produced the greatest mean reduction in LDL-C over more than one year.[4] A subsequent analysis of this trial showed that inclisiran reduced LDL-C levels by a similar percentage in both diabetic and non-diabetic patients.[5] This represents an advantage of inclisiran over other ther-

apies with a shorter duration of action. Relative stability in achieved LDL-C levels over time can be achieved despite prolonged dosing frequency (6 months), which, in theory, could attenuate short-term fluctuations in LDL-C that may result from intermittent use of concurrent statin therapy in subjects with poor adherence.

Inclisiran in familial hypercholesterolaemia

ORION-9 was a phase 3, double-blind trial, in which a total of 482 adults with heterozygous FH were randomly assigned 1:1 to receive inclisiran (300 mg) or placebo on days 1, 90, 270, and 450. In this trial, the percent change in LDL-C from baseline to day 510 was a 39.7% (95% CI: −43.7 to −35.7) reduction in the inclisiran group and an 8.2% (95% CI: 4.3−12.2) increase in the placebo group, for a between-group difference of −47.9% (95% CI: −53.5 to −42.3; p < .001). In addition, inclisiran was associated with lower levels of TC, non-HDL-C, Apo B, Lp(a), and triglycerides (TG) and higher levels of HDL-C compared to placebo. Importantly, this trial found a significant reduction in LDL-C across all FH genotypes.[6]

ORION-5 was an open-label, double-blind, placebo-controlled, multicentre, phase 3 study that determined the efficacy, safety, and tolerability of inclisiran in 56 patients with homozygous familial hypercholesterolaemia (HoFH) and elevated LDL-C levels after maximum tolerated doses of LDL-C-lowering therapy with or without lipoprotein apheresis.[7] The placebo-corrected percent change in LDL-C level from baseline to day 150 was −1.68% (95% CI: −29.19−25.83; p = .90), and the difference was not statistically significant between the inclisiran and placebo groups. Preliminary data in this population subgroup were obtained from ORION-2,[8] a phase 2, open-label, single-arm, multicentre, pilot study in which 4 subjects with a genetic or clinical diagnosis of HoFH were assigned to standard therapy plus inclisiran 300 mg on day one and either day 90 or 104 if mean PCSK9 levels were not suppressed by >70% compared with baseline at day 60 or 90. In this study, inclisiran showed reductions in LDL-C of 11.7%−33.1% at day 90 and 17.5%−37.0% at day 180 in 3 individuals, although one of the cases had increased LDL-C at days 90 and 180; however, this latter participant also had a history of poor response to both currently marketed PCSK9 inhibitors.[8]

Inclisiran in patients with cardiovascular disease

ORION-10 and ORION-11 were two randomised, phase 3, double-blind, placebo-controlled, parallel-group clinical trials.[9] The ORION-10 trial was conducted in the USA and included 1561 adults with ASCVD with an LDL-C level ≥70 mg/dl, while ORION-11 was conducted in Europe and South Africa and included 1617 patients with ASCVD and an LDL-C level ≥70 mg/dl or an equivalent risk of ASCVD, type 2 diabetes, FH, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score with LDL-C≥100 mg/dl. Results obtained in the ORION-10 trial indicated a percentage change in LDL-C level at day 510 of 1.0% in the placebo group and −51.3% in the inclisiran group, resulting in a between-group difference of −52.3% (95% CI: −55.7 to −48.8; p < .001). The time-adjusted change in LDL-C level after day 90 and up to day 540 as compared to baseline was 2.5% with placebo and −51.3% with inclisiran, representing a between-group mean difference of −53.8% (95% CI: −56.2 to −51.3; p < .001). In the ORION-11 trial, the corresponding percentage change in LDL-C at day 510 was 4.0% in the placebo group and −45.8% in the inclisiran group, resulting in a between-group difference of −49.9% (95% CI: −53.1 to −46.6; p < .001). In both clinical trials inclisiran lowered TG and Lp(a) levels, and increased HDL-C levels at day 510. Similarly, the proportion of patients likely to have a 50% reduction in LDL-C was higher in the inclisiran group than in the placebo group.[9]

A post-hoc analysis of these studies showed that inclisiran was equally effective in reducing LDL-C levels in patients with and without acute myocardial infarction (AMI),[10] in patients with cerebrovascular disease,[11] in patients with polyvascular disease,[12] and in primary prevention patients without clinical manifestations of ASCVD.[13]

Finally, the VICTORION-INITIATE study has recently been published, which evaluated the implementation strategy of giving inclisiran immediately upon failure to achieve LDL-C targets (<70 mg/dl) despite maximally tolerated statins in patients with ASCVD compared to a usual care strategy.[14] The inclisiran first implementation strategy resulted in significantly greater LDL-C lowering (60.0 vs. 7.0%; p < .001) compared to the usual care strategy, which was maintained until the end of the study, with no major safety issues compared to usual care. In addition, a higher proportion of patients randomised to inclisiran first achieved LDL-C targets than those randomly assigned to usual care (<70 mg/dl: 81.8% vs. 22.2%; <55 mg/dl: 71.6% vs. 8.9%; p < .001). These results highlight the importance of early initiation of inclisiran in the management of these patients and the urgent need to improve routine care of patients with ASCVD in the US.

Real-life studies

To date, 4 real-life studies have been published,[15–18] most of them with several important methodological limitations (retrospective design, short follow-up, variable LDL-C measurement time, heterogeneous populations, non-standardisation of LDL-C measurement, etc.), which may explain the wide variability of results among them in terms of lowering of mean LDL-C levels (−31.9%−49%). We can highlight 2 of these studies. First Padam P et al.[16] performed a retrospective analysis of the first 80 patients who received a single dose of inclisiran in their lipid clinic between 1 December 2021 and 1 September 2022. Within 2 months of treatment initiation, mean baseline LDL-C was reduced by 48.6% (from 3.5 ± 1.1−1.8 ± 1.0 mmol/l). Moreover, results from the Israeli National Health Registry in 503 patients show that inclisiran effectively reduces LDL-C (40%) in patients treated with inclisiran alone and 46% in patients treated with other oral lipid-lowering drugs.[15] More prospective, well-protocolised studies in real-world populations with longer

Table 1 Ongoing trials to determine the effect of inclisiran on the incidence of cardiovascular events or progression of atherosclerotic cardiovascular disease.

Trial	Population	Intervention	Comparator	Primary endpoint
ORION-4 NCT03705234	ASCVD (N = 16,124)	Inclisiran	Placebo	MACE (coronary heart disease death, MI, fatal or non-fatal ischaemic stroke, urgent coronary revascularisation)
VICTORION-2 PREVENT NCT05030428	ASCVD (N = 17,006)	Inclisiran + statins maximum tolerated dose	Placebo + statins maximum tolerated dose	3P-MACE (CV death, AMI, and non-fatal ischaemic stroke)
VICTORION-1 PREVENT NCT05739383	Patients at high cardiovascular risk without a previous CV event (n = 14,000)	Inclisiran	Placebo	4P-MACE (CV death, non-fatal MI and non-fatal ischaemic stroke, and urgent coronary revascularisation)
VICTORION-PLAQUE NCT05360446	Non-obstructive coronary artery disease without a previous CV event (n = 600)	Inclisiran + statins	Placebo + statins	Percentage change in total atheroma plaque volume as determined by CT angiography

AMI: Acute Myocardial Infarction; ASCVD: Atherosclerotic Cardiovascular Disease; CT: Computed Tomography; CV: Cardiovascular events.

follow-up are therefore needed to reach higher-evidence conclusions.

Inclisiran in the prevention of cardiovascular events

All of the studies reviewed above clearly demonstrated that inclisiran significantly reduced LDL-C in phase 2–3 trials. However, it has not yet been established whether lowering of LDL-C with inclisiran translates into a lower risk of cardiovascular (CV) events. In this regard, the recently conducted patient-level pooled analysis of the ORION-9, -10, and -11 included patients with heterozygous FH, ASCVD, or ASCVD risk equivalent on maximum tolerated statin-therapy who were randomised 1:1 to receive 284 mg of inclisiran or placebo. Inclisiran or placebo on days 1, 90, and then every 6 months for 18 months. The pre-specified exploratory endpoint of major cardiovascular events (MACE) included CV death, cardiac arrest, non-fatal MI, and fatal and non-fatal stroke, which were assessed as part of the safety evaluations. Of the 3655 patients followed for 18 months in these trials, 303 (8.3%) experienced a MACE, including 74 (2.0%) fatal and non-fatal MIs, and 28 (.8%) fatal and non-fatal strokes. Inclisiran significantly reduced composite MACE by 26% (OR .74, 95% CI .58–.94).[19] This preliminary analysis is consistent with all previous studies that have observed a parallel and proportional reduction in MACE with a reduction in LDL-C levels.

A number of studies have been initiated with the ultimate goal of demonstrating the effect of inclisiran on reducing the risk of MACE in different settings and populations (Table 1).

To this end, ORION-4, a phase 3, double-blind, randomised, placebo-controlled, double-blind trial (NCT03705234), is being conducted to evaluate the effects of inclisiran on clinical outcomes of major cardiovascular event incidence in patients with ASCVD. The study started in October 2018 with an estimated completion date of July 2026.

VICTORION-2 PREVENT is a phase 3 study evaluating the benefits of inclisiran on the incidence of MACE in patients with established cardiovascular disease (CVD). The objective of the study is to test the hypothesis that treatment with inclisiran sodium 300 mg administered on day 1, month 3 (day 90), and every 6 months thereafter, in addition to well-tolerated high-intensity statin therapy in participants with established CVD, will significantly reduce the risk of a 3-point MACE (3P-MACE), defined as a composite outcome of CV death, non-fatal MI, and non-fatal ischaemic stroke. This study has enrolled 17,006 patients and is expected to be completed in October 2027.

VICTORION-1 PREVENT is a phase 3 trial designed to test the hypothesis that treatment with inclisiran sodium 300 mg on day 1, day 90, and every 6 months thereafter in patients at high cardiovascular risk without a prior ASCVD event will significantly reduce the risk of 4-point MACE (4P-MACE), defined as a composite outcome of CV death, non-fatal MI, non-fatal ischaemic stroke, and urgent coronary revascularisation, compared to placebo. More than 14,000 patients have been enrolled, and the trial is expected to be completed in April 2029.

Finally, VICTORION-PLAQUE is a trial to determine whether treatment with inclisiran compared to placebo, when added to standard lipid-lowering statin therapy, can effectively reduce the total amount of plaque formed in the coronary arteries as measured by coronary computed tomography (CT) angiography from baseline to month 24. This study is being conducted in eligible participants with a diagnosis of non-obstructive atherosclerotic coronary artery disease with stenoses greater than 50% and no prior cardiovascular events. The objective of the study is to evaluate the efficacy of inclisiran compared to placebo in addition to statin therapy at the maximum tolerated dose in reducing total coronary atheroma volume as assessed by coronary CT angiography from baseline to month 24. Participants will receive 300 mg of inclisiran on day 1, month 3 (day 90), and every 6 months until month 21. Participants will undergo CT angiography at baseline and at month 24 at the end of the study visit.

Safety

In the ORION-1 trial[3] over a 180-day follow-up period, serious adverse events were reported in 11% of participants receiving inclisiran and 8% of those receiving placebo. Injection site reactions occurred in 4% and 7% of patients receiving one and two doses of inclisiran, respectively. The most common adverse events (occurring in >2% of patients) were myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhoea, and dizziness, with similar incidences in both groups (inclisiran and placebo). Patients with diabetes had no clinically significant changes in HbA1c. The ORION-3 trial (an open-label phase 2 extension study of the ORION-1 trial) showed no change in the overall safety profile over 3 years of follow-up.[20]

A meta-analysis pooled data from the phase 3 ORION-9, -10, and -11 trials that were registered over the 540-day study period, for a size of n = 3655 (1833 participants assigned to inclisiran and 1822 participants assigned to placebo). Emergent adverse events leading to drug discontinuation were reported in 2.5% of the inclisiran group and 1.9% of the placebo group. Most emergent adverse events were mild or moderate; treatment-emergent adverse events at the injection site (erythema, hypersensitivity, and local pruritus) were more frequent with inclisiran than with placebo (5.0% vs. .7%); other adverse events included worsening of glycaemic control (11.6% of participants assigned to inclisiran and 11.4% of participants assigned to placebo). Some events did not exceed 10% in both groups (nasopharyngitis, upper respiratory tract infection, and hypertension), while others were less than 5.0% in both groups (back pain, urinary tract infection, diarrhoea, bronchitis, cough, headache, angina pectoris, dizziness, osteoarthritis, pain in extremity, dyspnoea, increased blood CPK), non-cardiac chest pain, influenza, sinusitis, fatigue, coronary artery disease, pneumonia, atrial fibrillation, injection site reaction, musculoskeletal pain, myalgia, peripheral oedema, anaemia, pain, and congestive heart failure). Serious adverse events were reported in 20.4% of participants receiving inclisiran and 23% of those receiving placebo. The same number of deaths (n = 27) occurred in both the inclisiran and placebo

groups. Rates of new, worsening, or recurrent cancer were less than 3% in both groups.[21]

An analysis of the phase 1 ORION-7 and phase 2 ORION-1 trials evaluated the safety of inclisiran in patients with renal impairment compared to those with normal renal function. It included 31 ORION-7 and 247 ORION-1 subjects with various stages of renal function who received 300 mg subcutaneous inclisiran or placebo. Cough (12.5%) was the most common adverse event in the population with reduced renal function (GFR<60 mL/min per 1.73 m^2), followed by headache (6.3%) and fatigue (6.3%). It was concluded that the safety profile of inclisiran was similar in patients with normal and impaired renal function, and therefore no dose adjustment of the drug is required in this patient group.[22] Similarly, data from pharmacokinetic studies suggest that no dose adjustment is required in patients with mild to moderate hepatic impairment.[23]

Long-term efficacy and safety

A post-hoc safety analysis was recently conducted that included patients treated with 300 mg inclisiran sodium or placebo in the completed (ORION-1, -3, -5, -9, -10, and -11) and ongoing (ORION-8) trials. This analysis included 3576 patients treated with inclisiran for up to 6 years and 1968 patients treated with placebo for up to 1.5 years, representing 9,982.1 and 2,647.7 patient years of exposure, respectively. Kaplan–Meier curve analyses showed that serious or discontinuation-related adverse events, hepatic, muscle, and renal events, incident diabetes, and CPK or creatinine elevations accrued at a comparable rate between groups for up to 1.5 years, with similar trends continuing beyond this period. This study demonstrated that long-term treatment with inclisiran was well tolerated in a diverse population, supporting the safety of inclisiran in patients with dyslipidaemia.[24]

Results have recently been published from ORION-8, a multicentre long-term extension of the phase 2 (ORION-3) and phase 3 (ORION-9, ORION-10, and ORION-11) trials involving 3275 patients with ASCVD or heterozygous familial hypercholesterolaemia or ASCVD risk equivalent. The mean percentage change in LDL cholesterol across the entire trial population was −49.4% (−50.4% to −48.3%) at the end of a mean treatment and follow-up period of 3.7 years, with a maximum of up to 6 years of treatment. This trial therefore demonstrates that inclisiran maintains LDL-C lowering efficacy in the long term (mean treatment period of 3.7 years with a maximum of 6 years). In conclusion, this trial has shown that inclisiran induces a sustained and effective reduction in LDL cholesterol with a favourable long-term safety and tolerability profile.[25]

Conclusions

Inclisiran has been shown to provide significant long-term reductions in blood LDL-C levels, associated with marked reductions in PCSK9 levels and other atherogenic lipids, with a favourable safety profile similar to placebo. The convenience of a twice-yearly dosing regimen promotes adherence and facilitates the achievement of LDL-C targets. This drug has emerged as a promising therapeutic option for the treatment of hypercholesterolaemia. As mentioned above, results from ongoing trials investigating its effect on cardiovascular events are expected to provide further information on the cardiovascular benefits of inclisiran in patients with ASCVD and those at high cardiovascular risk.

Funding

This work was funded by the Spanish Arteriosclerosis Society.

Additional information

This article is part of the supplement entitled ''New horizons in the treatment of hypercholesterolemia'', which was funded by the Spanish Society of Arteriosclerosis, with sponsorship from Novartis.

Declaration of competing interest

The author of this article declares that he has received financial compensation for giving lectures and/or attending scientific advisory meetings from Sanofi, (JL-M), Amgen, Novartis, Dr, Esteve, Ferrer laboratories.

References

1. Fitzgerald K, Frank-Kamenetsky M, Shulga-Morskaya S, et al. Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial. Lancet. 2014;383:60–8.
2. Fitzgerald K, White S, Borodovsky A, et al. A highly durable RNAi therapeutic inhibitor of PCSK9. N Engl J Med. 2017;376:41–51.
3. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med. 2017;376:1430–40.
4. Ray KK, Stoekenbroek RM, Kallend D, et al. Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels: one-year follow-up of the ORION-1 randomized clinical trial. JAMA Cardiol. 2019;4:1067–75.
5. Leiter LA, Teoh H, Kallend D, et al. Inclisiran lowers LDL-C and PCSK9 irrespective of diabetes status: the ORION-1 randomized clinical trial. Diabetes Care. 2019;42:173–6.
6. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med. 2020;382:1520–30.
7. Raal F, Durst R, Bi R, et al. Efficacy, safety, and tolerability of inclisiran in patients with homozygous familial hypercholesterolemia: results from the ORION-5 randomized clinical trial. Circulation. 2024;149:354–62.
8. Hovingh GK, Lepor NE, Kallend D, Stoekenbroek RM, Wijngaard PLJ, Raal FJ. Inclisiran durably lowers low-density lipoprotein cholesterol and proprotein convertase subtilisin/kexin type 9 expression in homozygous familial hypercholesterolemia: the ORION-2 pilot study. Circulation. 2020;141:1829–31.
9. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382:1507–19.
10. Landmesser U, Koenig W, Leiter LA, et al. Inclisiran in patients with prior myocardial infarction: a post hoc pooled analysis of the ORION-10 and ORION-11 Phase 3 randomised trials. Atherosclerosis. 2023;386:117354.

11. Koenig W, Ray KK, Landmesser U, et al. Efficacy and safety of inclisiran in patients with cerebrovascular disease: ORION-9, ORION-10, and ORION-11. Am J Prev Cardiol. 2023;14:100503.
12. Koenig W, Conde LG, Landmesser U, et al. Efficacy and safety of inclisiran in patients with polyvascular disease: pooled, post hoc analysis of the ORION-9, ORION-10, and ORION-11 phase 3 randomized controlled trials. Cardiovasc Drugs Ther. 2024;38:493–503.
13. Ray KK, Kallend D, Leiter LA, et al. Effect of inclisiran on lipids in primary prevention: the ORION-11 trial. Eur Heart J. 2022;43:5047–57.
14. Koren MJ, Rodriguez F, East C, et al. An ïnclisiran Firstẗstrategy vs usual care in patients with atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2024;83:1939–52.
15. Naoum I, Saliba W, Aker A, Zafrir B. Lipid-lowering therapy with inclisiran in the real-world setting: initial data from a national health care service. J Clin Lipidol. 2024.
16. Padam P, Barton L, Wilson S, et al. Lipid lowering with inclisiran: a real-world single-centre experience. Open Heart. 2022:9.
17. Makhmudova U, Schatz U, Perakakis N, et al. High interindividual variability in LDL-cholesterol reductions after inclisiran administration in a real-world multicenter setting in Germany. Clin Res Cardiol. 2023;112:1639–49.
18. Mulder J, Galema-Boers AMH, Roeters van Lennep JE. First clinical experiences with inclisiran in a real-world setting. J Clin Lipidol. 2023;17:818–27.
19. Ray KK, Raal FJ, Kallend DG, et al. Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. Eur Heart J. 2023;44:129–38.
20. Ray KK, Troquay RPT, Visseren FLJ, et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. Lancet Diabetes Endocrinol. 2023;11:109–19.
21. Wright RS, Ray KK, Raal FJ, et al. Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolemia or atherosclerosis. J Am Coll Cardiol. 2021;77:1182–93.
22. Wright RS, Collins MG, Stoekenbroek RM, et al. Effects of renal impairment on the pharmacokinetics, efficacy, and safety of inclisiran: an analysis of the ORION-7 and ORION-1 studies. Mayo Clin Proc. 2020;95:77–89.
23. Kallend D, Stoekenbroek R, He Y, Smith PF, Wijngaard P. Pharmacokinetics and pharmacodynamics of inclisiran, a small interfering RNA therapy, in patients with hepatic impairment. J Clin Lipidol. 2022;16:208–19.
24. Wright RS, Koenig W, Landmesser U, et al. Safety and tolerability of inclisiran for treatment of hypercholesterolemia in 7 clinical trials. J Am Coll Cardiol. 2023;82:2251–61.
25. Wright RS, Raal FJ, Koenig W, Landmesser U, Leiter LA, Vikarunnessa S, et al. Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial. Cardiovasc Res. 2024;120:1400–10.