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REVIEW

PCSK9 siRNA INHIBITOR INCLISIRAN AS A TREATMENT OPTION IN HYPERCHOLESTEROLEMIA: A BRIEF REVIEW

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ABSTRACT

Dyslipidemia and hypercholesterolemia are global health issues that require urgent and efficient treatments due to their major impact on cardiovascular disease. The incidence of these illnesses is impacted by population and time differences, with familial hypercholesterolemia and lifestyle changes exacerbating these disorders. Inclisiran, a recently licensed RNA interference therapy, specifically a proprotein convertase subtilisin/kexin type 9 siRNA inhibitor, appears to be a revolutionary treatment method. However, questions about its long-term safety, impact on lipid metabolism, and cost-effectiveness remain unanswered. Evidence from the ORION clinical trials shows that inclisiran is effective at significantly lowering low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B levels. It also demonstrates a low frequency of adverse events and a potential improvement in patient quality of life. Remarkably, inclisiran's low-density lipoprotein cholesterol reduction outperforms statins alone and is comparable to the efficacy of other proprotein convertase subtilisin/ kexin type 9 inhibitors such as evolocumab and alirocumab. It has the potential to revolutionize the coronary preventative medicine market by providing an economically viable long-term cardiovascular risk reduction option. Limited long-term safety data, cost-effectiveness concerns, and clinical experience with the medicine are all barriers to wider acceptance. Despite these obstacles, inclisiran appears to hold promise as an effective, safe, and potentially cost-effective treatment for hypercholesterolemia and dyslipidemia, particularly in high-risk and statin-intolerant patients. However, the precise association between low-density lipoprotein cholesterol lowering and improved cardiovascular outcomes remains unclear, prompting additional investigations. Future research should seek to overcome these knowledge gaps, comprehend inclisiran's broader impact on lipid metabolism, and investigate its usefulness in specific patient populations.

Keywords: Dyslipidemia, hypercholesterolemia, inclisiran, siRNA

INTRODUCTION

Dyslipidemia, a common lipid disorder, is defined by elevated levels of cholesterol and/or triglycerides in the blood, which increase the risk of cardiovascular disease (CVD) (1). Hypercholesterolemia, a type of dyslipidemia, is characterized by high levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, or both (2). The interplay of dyslipidemia, hypercholesterolemia, and CVD is complex and important, necessitating a detailed understanding of their interconnections.

Cardiovascular diseases are the leading cause of mortality across the globe, responsible for 17.9 million deaths, or 31% of all worldwide deaths, in 2017. Over 80% of these fatalities occur in low- and middle-income countries, with more than half of all CVD-related deaths happening before the age of 70 years (3). A variety of factors, including lifestyle changes such as increased dietary fat intake, physical inactivity, and obesity, have contributed to the rising prevalence of dyslipidemia and hypercholesterolemia in recent years (4, 5). Both conditions are strongly correlated with high CVD risk and are considered significant modifiable risk factors for cardiovascular events (6).

It is important to note that the prevalence of hypercholesterolemia and dyslipidemia can vary significantly depending on the population studied and the time. For example, in the United States and China, recent studies have estimated the prevalence of hypercholesterolemia and dyslipidemia among adults aged 18-64 to be 11.4% and 35.5%, respectively (7, 8). However, direct comparisons between these results may be misleading due to differences in the definitions of hypercholesterolemia

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used in each study. Other research findings show an increase in the raw occurrence of initial hypercholesterolemia or mixed dyslipidemia in the United Kingdom from 13.5% in 2009 to 23.5% by 2019 (9), a prevalence of dyslipidemia of 78% among metropolitan overweight adults in South Delhi, India (10), and a prevalence of 75.9% among young adults in Karachi, Pakistan (11).

Hypercholesterolemia is the primary cause of atherosclerotic CVD, while dyslipidemia is also linked to an increased risk of cardiovascular events, death, and increased healthcare resource consumption and expenditures (12). An integral component of these conditions is elevated LDL-cholesterol (LDL-C) levels. As a key modifiable risk factor, LDL is central to the pathogenesis of CVDs and forms a bridge between different types of dyslipidemia, including hypercholesterolemia (7). This highlights how both genetic and lifestyle factors significantly contribute to the development of dyslipidemia and its subtypes, including hypercholesterolemia (13). Of the genetic influences, familial hypercholesterolemia is the most common cause of hypercholesterolemia, affecting 1 in 250 individuals worldwide (14). This autosomal dominant disorder results from mutations in the LDL receptor gene, highlighting the critical role of genetics in this condition (14).

Early diagnosis and intervention are essential in mitigating the risk of CVD associated with dyslipidemia, including hypercholesterolemia (15). Current treatment strategies consist of lifestyle modifications, such as dietary changes and increased physical activity, as well as pharmacological therapies like statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (16). Inclisiran, a recently approved PCSK9 inhibitor, has emerged as a promising treatment option for patients at high risk for CVD events. It functions by targeting the messenger ribonucleic acid (RNA) of the *PCSK9* gene, thereby reducing the expression of the PCSK9 protein, and ultimately decreasing cholesterol levels (17) (Figure 1).

Despite the potential benefits of inclisiran, there are still many unanswered questions surrounding its use in hypercholesterolemia and dyslipidemia. For example, it is unclear how long inclisiran can remain effective in reducing cholesterol levels or how it may affect other aspects of lipid metabolism. Additionally, there is limited data on the safety profile of inclisiran in this patient population. These gaps in knowledge highlight the need for further research into the efficacy and safety of inclisiran as a treatment option for hypercholesterolemia and dyslipidemia.

This narrative review aims to examine the current evidence on inclisiran for dyslipidemia treatment, with a focus on hypercholesterolemia. The review will analyze existing clinical studies, including the conceptual design of the ORION program, to assess the efficacy and safety profile of inclisiran in this patient population. Additionally, this review will identify knowledge gaps surrounding inclisiran's use and provide recommendations for future research.

RESULTS

Clinical Trials

Inclisiran is a double-stranded, modified RNA that binds to the carbohydrate molecule N-acetylgalactosamine (GalNAc), which is expressed by hepatocytes (18). Inclisiran cleaves matrix RNA and decreases PCSK9 protein synthesis after entering hepatocytes, increasing the absorption of circulating LDL by hepatocyte receptors, and reducing LDL levels in circulation (18). The administration schedule of inclisiran is twice a year, which may contribute to the patient compliance and the efficacy of the treatment.

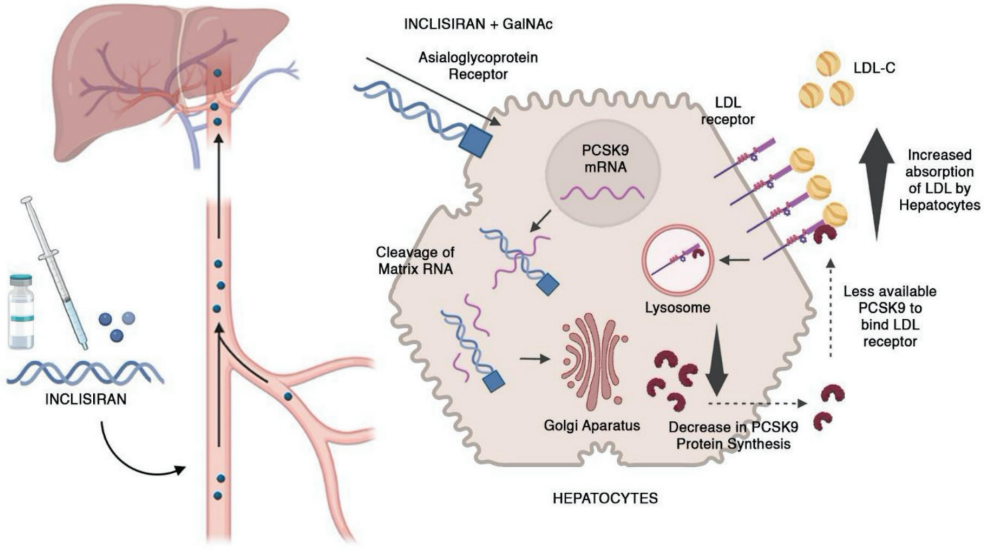

Figure 1: Simplified overview of mechanism of action.

LDL-C: Low-density lipoprotein cholesterol, PCSK9: Proprotein convertase subtilisin/kexin type 9, GalNAc: N-acetylgalactosamine

The ORION clinical initiative consists of a pair of stage 3 investigations, ORION-1, and ORION-2, in addition to an open-label extension examination, ORION-3. The fundamental goal of the ORION initiative was to assess the long-term effectiveness of inclisiran in patients with hypercholesterolemia or dyslipidemia and the well-being of patients. ORION-1 and ORION-2 were randomized, double-anonymous, placebo-controlled experiments that enrolled 2,519 participants. Subjects were administered either 300 mg of inclisiran or a placebo every six months for a maximum of 18 months, with the primary outcome being the LDL-C percentage change from baseline at 18 months (19, 20).

The ORION-1 trial, a randomized, double-anonymous, and placebo-controlled multicenter phase 2 study, aimed to investigate the impact of one or two doses of inclisiran on LDL-C levels (21). The trial enrolled patients who had increased LDL-C despite undergoing maximally tolerated treatment with statins. The primary objective of ORION-1 was to measure the time it took to return to within 20% of baseline for LDL-C levels and time-averaged LDL-C reductions over a year. The results of the study indicated that inclisiran effectively reduces LDL-C levels and lowers the incidence of cardiovascular problems with no clinically significant adverse effects (22).

The ORION-3 trial, an open-label extension study, evaluated the long-term efficacy and safety of inclisiran with four years of follow-up. This trial included patients who had completed the ORION-1 study and received either 300 mg of inclisiran or placebo every six months for an additional 18 months. The results showed that inclisiran significantly reduced LDL-C levels by an average of 53% compared to placebo at 24 months, with these effects sustained for up to 36 months (23).

Inclisiran was also tested in the phase 3 ORION-9 study, which assessed its effectiveness and safety in individuals with homozygous familial hypercholesterolemia. The results showed that inclisiran significantly reduced LDL-C by an average of 52% at day 270 compared to placebo. In addition, inclisiran demonstrated reductions in non-high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (ApoB) levels, with a safety profile similar to that of a placebo. These effects were sustained for up to 12 months (24).

The trials ORION-10 and ORION-11 evaluated the effectiveness and safety of inclisiran in reducing LDL-C levels in individuals with atherosclerotic CVD risk factors. A total of 3,177 patients were randomly assigned to inclisiran (n=1590) or placebo (n=1587). Patients received two subcutaneous doses of either inclisiran 300 mg or placebo at baseline and day 90, with the primary outcome being the percentage change in LDL-C from baseline to day 270. The studies ORION-10 and ORION-11 revealed that inclisiran led to a mean reduction of 52% and 50% in LDL-C levels at day 270 in comparison to the placebo (23, 25). Additionally, inclisiran demonstrated 44% and 47% reductions in non-HDL-C and ApoB levels, respectively, at day 510 (25) (Table 1).

Table 1: Percentage change in LDL-C subgroups.

Trial	Population	Arm	n	Timepoint (days)	Percentage change in LDL-C			
					Change (%)		Difference from placebo (%)	
					Mean	(95% CI)	Mean	(95% CI)
ORION-9 (24)	Overall (HeFH)	Inclisiran	242	510	-39.7	(-43.7, -35.7)	-47.9	(-53.5, -42.3)
		Placebo	240		8.2	(4.3, 12.2)	-	-
ORION-10 (25)	Overall (ASCVD)	Inclisiran	781	510	-51.3	NR	-52.3	(-55.7, -48.8)
		Placebo	780		1	NR	-	-
	Statin at BL	Inclisiran	701		NR		-57.3	(-60.7, -54.0)
		Placebo	692				-	-
	No statin at BL	Inclisiran	80				-54.8	(-62.0, -47.6)
		Placebo	88				-	-
ORION-11 (25)	Overall (ASCVD or RE)	Inclisiran	810	510	-45.8	NR	-49.9	(-53.1, -46.6)
		Placebo	807		4	NR	-	-
	Statin at BL	Inclisiran	766		NR		-53.3	(-56.5, -50.1)
		Placebo	766				-	-
	No statin at BL	Inclisiran	44				-41.6	(-51.1, -32.1)
		Placebo	41				-	-
	ASCVD	Inclisiran	712				-53.3	(-56.6, -50.1)
		Placebo	702				-	-
	ASCVD-risk equivalent	Inclisiran	98				-47.2	(-56.1, -38.3)
		Placebo	105				-	-
ORION-1 (26)	Overall	Inclisiran	59	180	-52.6	(-57.1, -48.1)	NR	NR
		Placebo	61		1.8	(-2.6, 6.3)	-	-

ASCVD: Atherosclerotic cardiovascular disease, BL: Baseline, HeFH: Heterozygous familial hypercholesterolemia, LDL-C: Low-density lipoprotein cholesterol, NR: Not reported, RE: Risk-equivalent, CI: Confidence interval

In terms of safety, reactions at the injection site have been identified as the most seen adverse effects. These were usually mild in severity and did not necessitate medical treatment. They included symptoms such as a slight self-limiting rash, hyperpigmentation, musculoskeletal pain, headaches, back pain, and acute nasopharyngitis or hiccups (26-30). Despite these reactions, no serious side effects from Inclisiran have been observed.

Notably, switching from PCSK9 monoclonal antibodies (mAb) to inclisiran did not affect the drug's efficacy. This finding implies that prior exposure to or treatment with a PCSK9 mAb does not influence inclisiran's effectiveness (31). However, more study is needed to confirm these findings and acquire a better understanding of the long-term effects of this therapeutic strategy.

Additionally, quality of life improvements have been observed in patients receiving inclisiran. Patients who received inclisiran reported improved physical functioning, role functioning, social functioning, and mental health compared to those receiving a placebo (32, 33). These improvements were maintained over 18 months of treatment with inclisiran. These results suggest that inclisiran can improve the quality of life in patients with hypercholesterolemia or dyslipidemia.

Finally, the use of inclisiran is not limited to the adult population. Inclisiran appears to be a promising strategy for controlling hyperlipidemia in younger patients, particularly those with familial hypercholesterolemia, according to the ORION-13 and ORION-16 trials. The investigation of the drug's efficacy, safety, and tolerability in children and adolescents aged 12 to 18 years provides promise for therapeutic choices other than the statins and ezetimibe that have usually been administered for this age range (34, 35).

In conclusion, the findings of these studies suggest that inclisiran has the potential to be an effective, well-tolerated treatment for hypercholesterolemia and dyslipidemia, enhancing patients' quality of life over a wide age range. However, more study is needed to confirm these findings and understand the long-term therapeutic consequences of this developing therapy technique.

Cost-effectiveness

Cost-effectiveness is a crucial aspect of evaluating new treatment options like inclisiran, a novel PCSK9 small interfering RNA (siRNA) inhibitor. Comparing the cost-effectiveness of inclisiran to other treatments for hypercholesterolemia and dyslipidemia is essential to understanding its potential impact on clinical practice. The cost-effectiveness analysis evaluates both the costs and health benefits of various therapies, offering an unbiased evaluation of their merits (32).

The cost-effectiveness of inclisiran in treating atherosclerotic cardiovascular patients with elevated LDL-C despite statin therapy has been studied. With an incremental cost-effectiveness ratio (ICER) of $51,686, inclisiran was assessed to be cost-effective for the US health system at a price just above $50,000 per quality-adjusted life year (QALY) (36). Another study looked at the clinical and economic feasibility of increasing the frequency of use of ezetimibe, alirocumab, evolocumab, and inclisiran in combination with statins in adult patients at very high cardiovascular risk, including those who have not met lipid targets on statin therapy. In comparison to current practice, the study found that increasing the frequency of PCSK9 inhibitor prescriptions, including inclisiran, was cost-effective (37).

According to the ICER Final Report 2021, the evidence was evaluated as sufficient to demonstrate a net health advantage for inclisiran over conventional treatment alone. If priced at parity with current PCSK9 inhibitor prices, the committee determined that inclisiran would provide low-to-intermediate long-term value for money. The $3,600-6,000 annual net price benchmark range for inclisiran is advised by ICER. In addition, inclisiran is cost-effective in terms of QALY gained, with an ICER of $1,686 per QALY gained (38).

Table 2: Advantages and disadvantages of inclisiran.

Advantages	Disadvantages
Reduction in LDL-C levels by approximately 50% compared to placebo (23, 25)	Unknown long-term benefits and safety profile due to its recent approval (31)
Favorable administration regimen (0-90-180 days), which should lead to better compliance (49)	Adverse effects could persist for six months due to its long-acting nature (35, 45)
Reduced plasma PCSK9 levels by approximately 80%, altering lipoprotein profile favorably (23, 29)	Injection site reactions, which were more frequent in the inclisiran group (26-30)
Long-acting duration, remaining effective for up to six months (25)	Uncertainty about whether LDL-C level reduction improves cardiovascular outcomes (45)
Well-tolerated in clinical trials with mostly mild side effects (50)	It's only approved for adults 18 years or older, excluding pediatric patients or those under 18 years of age (49)
Proven efficacy in LDL-C level reduction in familial hypercholesterolemia, patients with elevated cardiovascular risk, statin intolerance, or hyperlipoproteinemia(a) (51)	It is an injectable therapy requiring frequent injections (44)
Rapid liver uptake, a short plasma half-life, and long-lasting effects on PCSK9 inhibition and LDL-C lowering due to Inclisiran's GalNAc attachment (18)	Possible adverse effects that might be noticed in the future after several years of treatment

LDL-C: Low-density lipoprotein cholesterol, PCSK9: Proprotein convertase subtilisin/kexin type 9, GalNAc: N-acetylgalactosamine

In summary, inclisiran appears to be a cost-effective and valuable treatment option for hypercholesterolemia and dyslipidemia. The cost-effectiveness analyses suggest that inclisiran may be an economically viable way to reduce long-term cardiovascular risk in patients with these conditions. Moreover, the clinical effectiveness of inclisiran in reducing LDL-C and major cardiovascular events supports its potential role in managing high-risk patients, including those who are statin-intolerant.

Comparative Analysis

Inclisiran, a novel PCSK9 siRNA inhibitor, was granted authorization for subcutaneous injection and is recommended to be administered every 3 to 6 months (19). This less frequent dose schedule, as compared to statins, adds to the drug's encouraging results in the treatment of hypercholesterolemia and dyslipidemia. In addition to this benefit, inclisiran is associated with more significant decreases in LDL-C levels, with an average 55% reduction in LDL levels after six months of treatment, compared to a 40% reduction with statins alone (22, 39). When combined with statins, inclisiran has demonstrated even greater reductions in LDL-C levels. Combination therapy with atorvastatin and inclisiran reduced LDL-C levels by up to 65%, whereas atorvastatin monotherapy resulted in a reduction of up to 40% (40-42). This shows that combination medication, rather than monotherapy, may be more effective in lowering both LDL-C and non-HDL-C levels.

In terms of potential side effects, the literature has associated statins with a variety of adverse events, including toxicity to the liver, statin-related myopathy, rhabdomyolysis, the development of new diabetes, cataracts, and hemorrhagic stroke (43). On the other hand, none of the research has associated inclisiran with liver toxicity or clinically evident liver injury. Furthermore, alanine transaminase elevations have been reported in less than 1% of patients after inclisiran medication, and they were mild-to-moderate, temporary, and without associated symptoms or jaundice (24). Despite these preliminary findings, additional detailed and direct comparison studies will be required to have a more comprehensive understanding of the adverse effects of inclisiran and statins.

The ORION-3 research evaluated inclisiran's long-term efficacy and safety, finding that it is as effective as other PCSK9 inhibitors in terms of LDL-C lowering and has a comparable safety profile. In the ORION-10 study, inclisiran was found to be equal to evolocumab in terms of LDL-C reduction at day 180, while it was superior to alirocumab at day 270 in the ORION-11 trial. In terms of safety, there were no notable differences between inclisiran and either evolocumab or alirocumab (23, 25). The most prevalent adverse events reported with inclisiran were injection site reactions, along with other PCSK9 inhibitors (25).

Inclisiran has also been used as a public policy to treat patients with coronary heart disease or at a highly elevated risk, representing an innovative way to introduce a drug to the market (44, 45). However, barriers to its widespread use should be analyzed, such as accessibility, cost, and patient acceptance. Moreover, potential candidates for inclisiran therapy include patients who are statin-intolerant or those who require additional cholesterol reduction beyond what can be achieved with statin monotherapy.

Strengths and Limitations of Inclisiran

Inclisiran, an RNA interference therapy, offers several advantages as a treatment option for hypercholesterolemia and dyslipidemia. As a highly targeted therapy, it reduces the expression of specific genes, potentially causing fewer side effects than other treatments (46-48). Inclisiran has proven effective in reducing LDL-C levels, the primary treatment goal for these conditions, with some patients experiencing up to a 50% reduction in LDL-C levels (23, 25). Notably, inclisiran has been associated with significant decreases in LDL-C and PCSK9 levels in both diabetic and non-diabetic patients, implying its potential as a novel therapeutic option for controlling dyslipidemia regardless of diabetes status (19). The long duration of action of inclisiran is another advantage; a single dose can remain effective for up to six months, significantly longer than statins or PCSK9 inhibitors (25). This makes it an appealing option for patients requiring long-term LDL-C level maintenance without frequent injections or other treatments (49).

In clinical trials, inclisiran has demonstrated good tolerability. The most common side effects were mild, quickly resolving injection site reactions (50). This aspect makes it an attractive option for patients concerned about potential side effects from other treatments.

Potential candidates for inclisiran therapy include patients with familial hypercholesterolemia, those with elevated cardiovascular risk, statin intolerance, or hyperlipoproteinemia(a) (51). Inclisiran's GalNAc attachment results in rapid liver uptake, a short plasma half-life, and long-lasting effects on PCSK9 inhibition and LDL-C lowering (18).

However, there are limitations to inclisiran as a treatment option for hypercholesterolemia and dyslipidemia. It is only approved for use in adults aged 18 years or older, excluding those under 18 years of age (49). Although effective in reducing LDL-C levels, it remains unclear whether this reduction translates to improved cardiovascular outcomes, such as reduced heart attack or stroke risk. Long-term benefits are uncertain, and further research is needed to determine if inclisiran can improve patient outcomes over time (44).

The safety profile of inclisiran is relatively unknown due to its recent approval and limited use in clinical practice. There may be potential side effects or adverse events not yet identified. While it has a long duration of action, inclisiran is still an injectable therapy requiring frequent injections to maintain efficacy over time, which may be inconvenient for some patients preferring oral medications or other less invasive treatment options (44, 45) (Table 2).

In conclusion, inclisiran is a promising treatment option for specific patient populations, such as those with familial

hypercholesterolemia, elevated cardiovascular risk, statin intolerance, or hyperlipoproteinemia(a). However, more research is needed to evaluate its long-term safety, efficacy, and cost-effectiveness before it can be widely used in coronary prevention.

CONCLUSION

In summary, the ORION clinical trials have convincingly demonstrated that inclisiran, a siRNA molecule, is an effective and safe treatment for hypercholesterolemia and dyslipidemia. This novel therapeutic agent effectively targets the *PCSK9* gene, leading to significant reductions in LDL-C levels, non-HDL-C levels, and ApoB levels. Additionally, patients receiving inclisiran have reported quality of life improvements, reinforcing its potential value in clinical practice.

Comparative analyses have highlighted inclisiran's superior efficacy and longer duration of action compared to statins, and the combination of the two may offer even greater LDL-C reductions. In terms of efficacy and safety, inclisiran has shown comparable results to other PCSK9 inhibitors. Moreover, the cost-effectiveness analysis suggests that inclisiran could provide value for money, especially considering its potential to reduce long-term cardiovascular risk.

Nonetheless, there are still limitations to consider. Inclisiran is approved for use only in adults aged 18 years or older, and while it effectively reduces LDL-C levels, it is not yet certain whether this will translate into improved long-term cardiovascular outcomes. Furthermore, its safety profile, though seemingly promising, is not fully known due to its recent approval and limited usage. Lastly, as an injectable therapy, some patients may find the administration less convenient than an oral medication.

In conclusion, the evidence presented in this review supports further research into the use of inclisiran as a treatment option for hypercholesterolemia and dyslipidemia. Future studies should focus on long-term safety, efficacy, cost-effectiveness, and potential for reducing other cardiovascular risk factors, considering the insights and experience of the authors to contribute to a comprehensive understanding of inclisiran's potential.

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