Inclisiran Treatment for Cardiovascular Disease Risk Reduction: A Systematic Review and Meta-Analysis

Ya-Fang Chen, Si Li, Mei-Juan Wang, Meng-Yuan Wu, Zi-Chen Du and Li-Ping Wei

Department of Cardiology, Tianjin Union Medical Center, Tianjin, China

ABSTRACT

This study was a meta-analysis of patient data to investigate the therapeutic effects of inclisiran on LDL-C, PCSK9, and TC in patients with atherosclerosis. Authors searched the Cochrane Library, Pubmed, EMBASE, and Web of Science databases for randomised controlled trials. Data of 4,731 subjects from five randomised clinical trials were included in this analysis. Patients treated with the PCSK9 inhibitor inclisiran had significantly lower LDL-C levels than those treated with placebo or a statin (mean difference (MD) -1.477; 95% CI -1.551 to -1.403; p <0.001; I^2 = 7.2%). The average level of PCSK9 was also relatively lower ((MD) -2.579; 95% CI -2.694 to -2.464; p <0.001; I^2 = 36%). They exhibited significant reductions in total cholesterol protein levels ((MD) -1.477; 95% CI -1.585 to -1.369; p <0.001; I^2 = 46.7%). Inclisiran reduced LDL-C and PCSK9 levels as well as TC and Apo B levels significantly in patients with atherosclerotic cardiovascular disease (ASCVD).

Key Words: *Inclisiran, Low-density lipoprotein cholesterol, Atherosclerosis, Adverse events, Meta-analysis.*

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INTRODUCTION

The development of atherosclerotic cardiovascular disease (ASCVD) is no longer concentrated in industrialised Western countries but has spread worldwide.[1] ASCVD currently accounts for majority of deaths worldwide.[2] Atherosclerosis is a chronic progressive disease,[3] and a major driver of risk for ASCVD is lifelong exposure to elevated cumulative LDL-C levels, especially when effective cholesterol-lowering therapy is not administered in a timely manner.[4] Over time, leading to worsening LDL-C levels, existing lipid-lowering treatments maintain sustained and effective reductions in LDL-C levels but are partially hampered by adherence. Achieving LDL-C goals in practice is often limited by liver or kidney injury due to concerns about the risk of liver injury and kidney injury, even when statins plus ezetimibe or acipimox are administered.[5] Indeed, the ideal LDL-C-lowering therapy should achieve both LDL-C control and a reduced propensity for liver injury and kidney damage.

Circulating PCSK9 is the strongest regulator of cholesterol trafficking in the body.[6] Inclisiran is a new class of injectable LDL-C-lowering drug that acts primarily in the liver, which is the main site of PCSK9 production, and therefore reduces circulating concentrations of PCSK9 and LDL-C.[7]

Correspondence to: Dr. Li-Ping Wei, Department of Cardiology, Tianjin Union Medical Center, Tianjin, China
E-mail: chenkaihua@aeroindustries.cn

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The reduction in LDL-C levels with inclisiran treatment was similar to that with the PCSK9 monoclonal antibody treatment. Inclisiran has been proven to reduce LDL-C levels by more than 50%[8,9] and does not require frequent dosing therapy. The benefits of inclisiran for cardiovascular disease have been demonstrated in the secondary prevention setting.[10] However, the optimal role of these compounds in lowering LDL-C in the treatment of ASCVD has not been determined and still needs to be explored in additional trials.

In such a situation, there is great interest in the potential benefits of inclisiran treatment, with strong physiological and clinical theories supporting this strategy. Above all, a potential advantage of inclisiran is that LDL-C levels remain relatively stable over time, despite infrequent dosing regimens.[11] Specifically, the molecular structure of inclisiran confers important therapeutic benefits, and chemical modification of the molecular structure reduces the immunogenic potential of inclisiran[12] and increases its molecular stability, thus improving its durability and clinical efficacy. Second, due to the liver specificity of inclisiran, systemic exposure is limited, and inclisiran concentrations are no longer detectable in the circulation after 2 days of dosing in patients with common and mild to severe renal impairment.[13,14] Finally, as far as the current trial studies indicate, inclisiran appears to have relatively benign side effects with only rare flu-like symptoms of immune activation,[15] but large trials will be needed to accurately capture the long-term side effects of inclisiran in the future.

Inclisiran improves patient adherence to lipid-lowering therapy and prevents atherothrombotic events. Consequently, to comprehensively assess the clinical impact and quality of the data, authors conducted a systematic analysis of data from indi-

vidual clinical trials to determine the impact of inclisiran treatment on key outcomes, such as decreased LDL-C, PCSK9, and total cholesterol (TC) levels, in patients with ASCVD.

METHODOLOGY

The authors used existing search strategies to search the EMBASE, Pubmed, Cochrane Library, and Web of Science databases for literature published prior to 12 October 2022. Additionally, they used a retrospective approach, which involved reviewing the references of the identified articles and retrieved abstracts published at relevant scientific meetings from 2010 to 2022.

All studies targeting elevated LDL-C levels in specific ASCVD populations were included. It excluded studies using monoclonal antibody therapy targeting PCSK9 to assess LDL-C reduction with inclisiran and studies that did not report clinical outcomes. They also excluded duplicate publications, literature for which specific data were not available, observational and retrospective articles, and articles that were not based on random assignments. There were no restrictions on the language of the study or publication status of the literature. The search strategy, inclusion criteria, and data extraction for this paper followed the Cochrane collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the risk of bias was assessed according to PRISMA recommendations.

The primary efficacy endpoint was the LDL-C level, with the PCSK9 level and total cholesterol (TC) level serving as key secondary endpoints. The secondary safety endpoints included the serum ALB concentration, high-density lipoprotein cholesterol (HDL-C) level, lipoprotein (a) (Lp (a)) level, non-high-density lipoprotein cholesterol (non-HDL-C) level, and triglyceride level. Individual trials were divided into intervention and control groups, with the placebo group considered the control group and the treatment group classified as the intervention group.

People used the revised Cochrane risk of bias tool to assess the risk of bias for each trial. The strength of evidence for each article was categorised as low, medium, or high by using this standardised tool. Two researchers individually assessed five areas of bias for each outcome including randomisation process, deviation from the intended intervention, missing outcome data, outcome measures, and choice of reported outcomes.

All the statistical analyses were performed using Stata 16 software. According to standard methods, fixed-effects model (FEM) analysis (the Mantel–Haenszel method) was used when no heterogeneity in composite indicators was found, risk ratios (RRs) were calculated using binary data with 95% confidence intervals (CIs) for categorical data, and means ± standard deviations were used for differences in continuous outcomes. When there was evidence of significant heterogeneity, the random-effects model (REM) analysis (I-V heterogeneity) method was used. Cochran's Q χ^2 test was used to assess whether there was a trend in the analysis between studies. All p-values were calculated by a statistically significant test, with a p-value of 0.10 or less being considered significant, and the I^2 test was used to measure consistency. An I^2 value of 0% indicated that no heterogeneity was present, and larger values indicated increased heterogeneity.

RESULTS

A total of 728 references were retrieved, and the two evaluators removed duplicates and filtered them; a total of five trials were eligible for full-text review;[8,16-19] one study included two trials of different durations, Figure 1). A total of 4,654 patients were randomly assigned to the inclisiran group (n = 2,573) or the placebo or statin treatment group (n = 2,081).

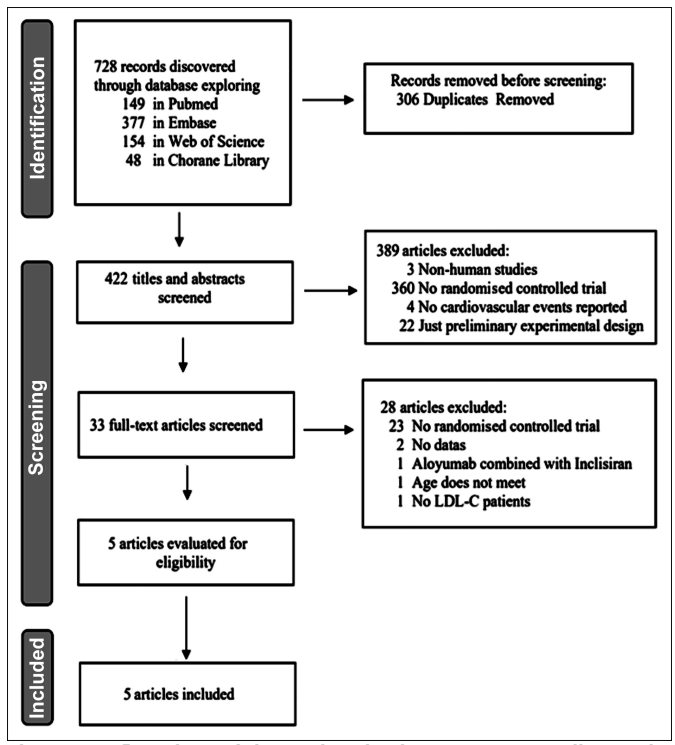

Figure 1: A flow chart of the study selection process according to the PRISMA guidelines.

Table I shows the baseline levels of the patients included in the meta-analysis. A total of 4,654 patients were enrolled, of whom, 4,495 (96.6%) had definite atherosclerosis with abnormally elevated LDL-C levels; one study included 69 (3.4%) patients who did not have definite atherosclerosis but were enrolled because of hypercholesterolaemia, and some of these patients were taking statins. The mean age of the participants was 60.8 years, with men composing the majority (64.5%). Most patients had hypertension (70.0%) and a history of diabetes mellitus (24.4%) before randomisation to the group. Most patients were taking statins as well as ezetimibe prior to enrolment in the inclisiran group.

Two trials by Ray *et al*. 2020 reported 18-month follow-up results, as did the Raal team trial; additional trials by Ray *et al*. in 2017 and 2019, each reported 12-month *versus* 8-month follow-up results; and the Fitzgerald trial by reported 6-month follow-up results. Few individual participants were lost to follow-up in any of the trials.

Table I: Baseline characteristics reported in the included trials.

	Mean age	Male (%)	White race (%)	Previous ASCVD (%)	Hypertension (%)	Diabetes (%)	Smokers (%)	Heterozygous familial hypercholesterolaemia (%)	Statin treatment (%)	Ezetimibe treatment (%)
Ray *et al.*	66 years	69%	85.7%	100%	90.6%	45%	15%	1.3%	89.2%	9.9%
Ray *et al.*	64.8 years	72%	98.1%	89.9%	80.5%	35.1%	18.1%	2.1%	94.7%	7.1%
Raal *et al.*	56 years	47%	93.98%	27.4%	42.1%	10%	11.6%	100%	90.5%	52.9%
Ray, *et al.*	63.3 years	65%	92.8%	69.3%	68.8%	10.8%	13.3%	5.6%	72.9%	31.2%
Fitzgerald *et al.*	51 years	70%	75.4%	0%	NA	0%	NA	NA	28.9%	NA
Ray *et al.*	63.3 years	64%	92.01%	68.9%	67.9%	21%	13.2%	5.6%	70.1%	30.3%

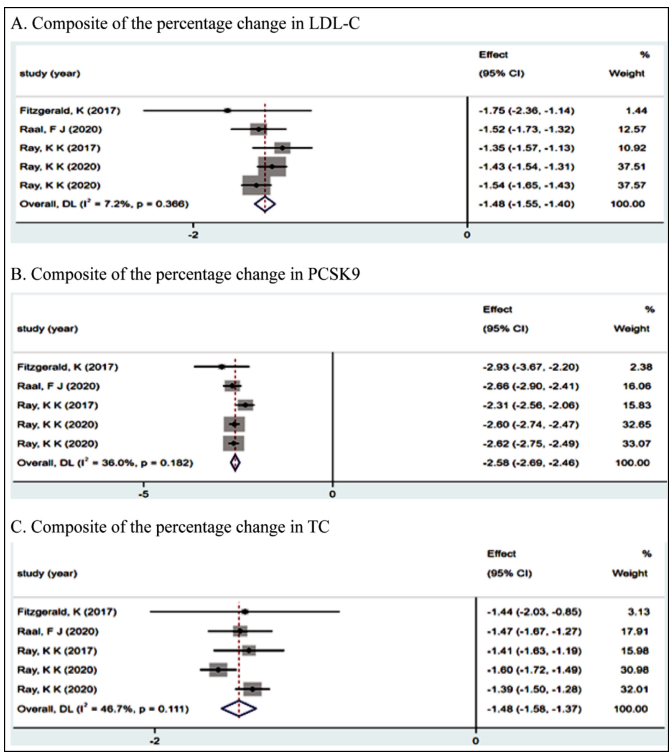

Figure 2: Primary and secondary endpoints.

The primary efficacy endpoint and key secondary endpoints are summarised in Figure 2. A pooled analysis of five studies assessing the proportion of participants with LDL-C at the end of the intervention included a total of 4,226 patients. The results showed a general increase in LDL-C levels in patients given placebo and a substantial decrease in LDL-C levels in patients given subcutaneous inclisiran ((MD) -1.477; 95% CI -1.551 to -1.403; p <0.001; I^2 = 7.2%; Figure 2A). For the key secondary endpoint of treatment, compared with those in the placebo group, PCSK9 levels (MD -2.579; 95% CI -2.694 to -2.464; p <0.001; I^2 = 36%; Figure 2B) and total cholesterol (TC) levels ((MD) -1.477; 95% CI -1.585 to -1.369; p <0.001; I^2 = 46.7%; Figure 2C) were significantly lower.

The treatment effect was consistent in the direction of the secondary safety endpoint composite analysis (Figure 3). Overall, inclisiran significantly reduced the level of Apo B ((MD) -1.501; 95% CI -1.606 to -1.396; p <0.001; Figure 3A), with high heterogeneity (I^2 = 43.7%; p = 0.130; Figure 3A). Compared with those in the placebo or statin treatment group, the Lp (a) ((MD) -0.363; 95% CI -0.435 to -0.291; p <0.001; I^2 = 16.2%; Figure 3B), non-HDL-C ((MD) -1.398; 95% CI -1.483 to -1.313; p <0.001; I^2 = 23.4%; Figure 3C) and triglyceride ((MD) -0.304; 95% CI -0.381 to -0.227; p <0.000; I^2 = 23.6%; Figure 3D) levels were significantly lower than the baseline levels. In contrast, the HDL-C ((MD) 0.357; 95% CI = 0.280 to 0.435; p <0.000; I^2 = 23.8%; Figure 3E) levels were significantly greater after inclisiran intervention.

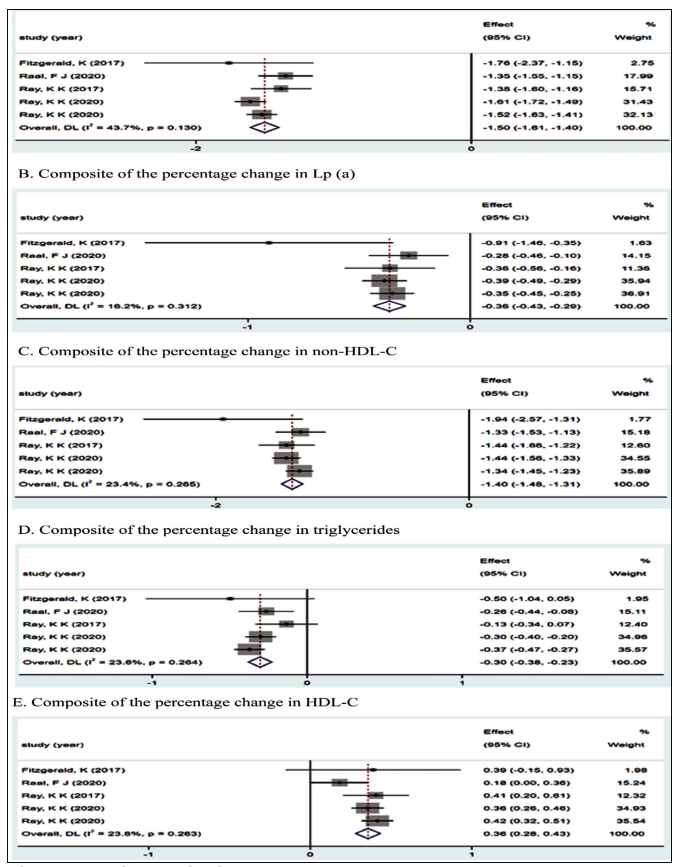

Figure 3: Other endpoints.

Figure 4 shows the safety endpoints of the trial treatment. Pooling this information showed that compared to the other treatment groups, inclisiran subcutaneous injection ((RR) 6.504; 95% CI 3.08 - 13.735; p <0.000, I^2 = 40.3%; Figure 4A) caused reactions at the injection site, but most of the reactions were mild. According to the statistical analysis of the deaths, authors did not observe a difference in all-cause mortality ((RR) 1.073; 95% CI = 0.635 - 1.813; p = 0.793, I^2 = 0%; Figure 4B). Overall, there was no difference in the risk of new cancer between the assigned inclisiran or placebo groups ((RR) 0.896; 95% CI = 0.60 - 1.338; p = 0.59, I^2 =

0%; Figure 4C). On the other hand, inclisiran treatment was significantly unrelated to abnormalities in the renal function creatinine ((RR) 0.855; 95% CI 0.552-1.326; p = 0.485, I^2 = 0%; Figure 4D) or muscle creatine kinase ((RR) 1.162; 95% CI 0.68-1.986; p = 0.584, I^2 = 0%; Figure 4E) indicators.

Finally, the authors performed an individual study assessment of the possible risk of bias. Four studies were considered to have a low overall risk of bias, and two studies had some problems. All six randomised controlled trials reported adequate randomisation, no trial was terminated early, and all trials were multicentric studies.

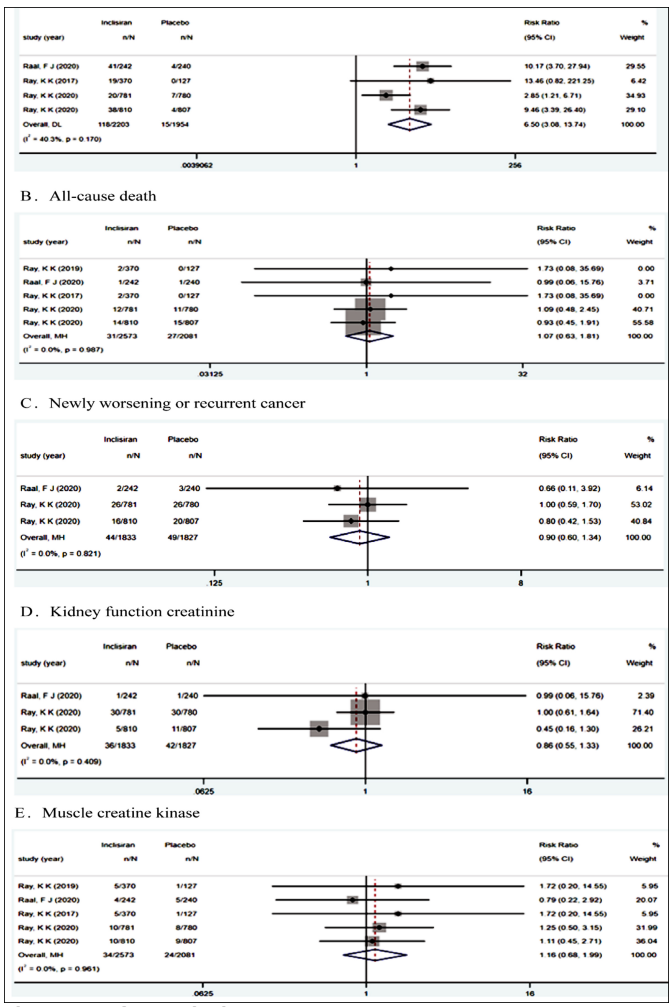

Figure 4: Safety endpoints.

DISCUSSION

In this analysis, authors compared the precautionary effects of treatment with the PCSK9 inhibitor inclisiran with those of placebo or statins in patients with established or risk of atherosclerotic cardiovascular disease. The key findings of this study can be summarised as follows. Firstly, LDL-C, PCSK9, and TC levels were significantly lower in subjects treated with inclisiran compared with those treated with placebo or statins. Secondly, Apo B, HDL-C, Lp (a), non-HDL-C, and triglyceride levels were obviously different between patients treated with inclisiran and those treated with placebo or statins. Thirdly, adverse reactions occurred at the injection site in patients treated with inclisiran but most were mild, and the occurrence of other adverse events was not statistically significant according to the group treatment.

In the treatment of ASCVD, the goal of any cholesterol-lowering regimen is to maintain a consistent, long-term safe reduction in LDL-C exposure.[20] The achievement of ideal LDL-C targets is hampered by the limitations of the available treatments. The use of some lipid-lowering therapies (e.g., statins and ezetimibe)[21] and poor patient compliance with the drug lead to unfavourable long-term stabilisation of LDL-C levels, which in turn increases the risk of cardiovascular events,[22] which is an adverse effect in ASCVD patients. Some patients taking statins experience elevated transaminase levels in a dose-dependent manner; while some patients experience elevated creatinine levels and even protein haematuria.[23] Furthermore, a recent study has shown that statin therapy may be related to an increased rate of diabetes diagnosis, with more frequent statin therapy resulting in a greater rate of diabetes.[24] In addition, myalgia is one of the most common statin-related adverse effects and, in severe cases, may lead to myositis and rhabdomyolysis, forcing patients to discontinue the medicine.[25] The incidence of myalgia reported during statin therapy varies from 1-30%.[26] As the severity of myopathy increases, the number of patients at high cardiovascular risk increases.[27] In this context, the PCSK9 inhibitor inclisiran is considered a novel therapeutic agent for addressing this management dilemma by stabilising LDL-C levels while maintaining cardiovascular-related risk.

Inclisiran is a double-stranded cholesterol-lowering small interfering RNA (siRNA) that inhibits gene transcription,[28] essentially by blocking the post-transcriptional regulatory process by which the protein is explicitly produced. Inclisiran is able to reduce circulating plasma levels of PCSK9 protein-related genes by interfering with their transcription.[29] A short half-life and rapid elimination from plasma may result in increased effects on lipid metabolism and a decreased incidence of adverse events in the liver, muscle, and kidney.[30]

A key insight from the analysis was the absolute benefit of subcutaneous inclisiran treatment relative to basal oral statins or other lipid-lowering agents in lowering LDL-C. Although sustained inclisiran injections may attenuate the overall relative lipid-lowering benefit of treatment, this effect is still beneficial. In addition, the significant reduction in LDL-C was accompanied by a significant reduction in PCSK9 levels and a significant difference in TC. This evidence demonstrates the beneficial effects of inclisiran compared with oral statins and other lipid-lowering agents and suggests that inclisiran combined with a statin should be considered in the treatment of patients with very high LDL-C levels. Moreover, these data support important improve-

ments in the management of atherosclerosis. Specifically, the use of the long-acting synthetic siRNA inclisiran as a therapeutic strategy could achieve desirable long-term outcomes in the management of ASCVD. If offers effective lipid-lowering capacity with a reduced risk of liver, kidney, and muscle damage.

CONCLUSION

Compared with statins, PCSK9 inhibitor inclisiran monotherapy is associated with a lower risk of myocardial infarction and a comparable risk of stroke among patients with established atherosclerosis. The benefit favouring inclisiran monotherapy is, however, of debatable clinical relevance in view of the high number needed to treat to prevent atherosclerosis and the absence of any effect on all-cause and vascular death.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
YFC: Conducted the statistical analysis and wrote the manuscript.
YFC, SL: Literature search and extracted data on the study design, patient characteristics, and outcomes.
MYW, ZCD: Conceived and designed the review.
MJW: Data review and quality assessment.
LPW: Acquired funding and resources and provided supervision, revised, and reviewed the manuscript.
All authors approved the final version of the manuscript to be published.

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