Medicine

OPEN

Effectiveness and safety of Inclisiran in hyperlipidemia treatment
An overview of systematic reviews

Jiayi Li, MD[a,b,c], Xiangguo Lei, MD[a,b,c], Zihao Li, MD[d], Xi Yang, MD[a,b,c,*]

Abstract

Background: This paper aimed to comprehensively evaluate the effectiveness and safety of Inclisiran in treating hyperlipidemia through an overview of systematic reviews (SRs).

Methods: The Cochrane Library, EMBASE, PubMed, CNKI, WANGFANG database, VIP database, ClinicalTrials.gov, and ICRT were searched electronically to collect SRs and meta-analysis of Inclisiran in hyperlipidemia treatment from the establishment of the database till May 2022. Two researchers independently screened the relevant literature, then the assessment of multiple systematic reviews tool was made into assess the methodological quality of the included studies. Data extracted were used to perform the study through RevMan5.3 software. The grading of recommendations assessment, development, and evaluation tool was used to grade the quality of the evidence of the outcomes included in the SRs. Prospero ID: CRD 42022326845.

Results: A total of 10 relevant SRs were included, involving 7 randomized controlled trials. The assessment results of the assessment of multiple systematic reviews tool suggested that the quality of the SRs included needed to be improved. The reduced level of low-density lipoprotein cholesterol of the experimental group was lower than the control group, and the difference in the amount of effectiveness was statistically significant (MD = –50.13, 95%CI: –56.2 to –44.06, $P < .00001$). The grading of recommendations assessment, development, and evaluation results showed that out of 27 outcomes, 8 were high-quality, 3 were of medium quality, 6 were of low quality, and 10 were of the most inferior quality.

Conclusion: 300mg Inclisiran with 2 injections a year has the best therapeutic effect, which can significantly reduce low-density lipoprotein cholesterol and total cholesterol, and increase high-density lipoprotein cholesterol levels in patients with hyperlipidemia. Inclisiran has a favorable safety profile, with no significant difference in the incidence of adverse reactions compared to a placebo. Most of the adverse effects were associated with the reaction on the injection site.

Abbreviations: AMSTAR = assessment of multiple systematic reviews, GRADE = grading of recommendations assessment, development, and evaluation, HDL-C = high-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, RCTs = randomized controlled trials, SRs = systematic reviews, TC = total cholesterol.

Keywords: AMSTAR, an overview of systematic reviews, GRADE, hyperlipidemia, Inclisiran

1. Introduction

Hyperlipidemia refers to abnormally elevated lipid levels or lipoproteins in the blood because of anomalous fat metabolism. The risk factors include smoking, a sedentary lifestyle, obesity, genetic disorders such as familial hypercholesterolemia (FH), or other conditions such as diabetes. Varieties of lipids, such as triglycerides and total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), are related to the regulation of microvascular function.[1] Dyslipidemia is one of the major risk factors for atherosclerotic diseases, where LDL-C in the blood is the main pathogenic factor of atherosclerosis. People with hyperlipidemia are roughly at twice the risk of developing cardiovascular diseases compared to those with normal TC levels.[2]

* Correspondence: Xi Yang, Geriatrics Department of Endocrinology and Metabolism, The First Affiliated Hospital of Guangxi Medical University, Nanning Guangxi 530021, China (e-mail: yangxi@sr.gxmu.edu.cn).

Statins are the conventional treatment method for lowering LDL-C. However, under the treatment of statin, 10% to 20% of high-risk patients still can't reach their LDL-C targets. It is the proprotein convertase subtilisin/kexin type 9 (PCSK9) that is the target of non-statin lipid-lowering drugs discovered in the last few years. Hence, considerable focus has been given to the PCSK9 pathway leading to the development of the human monoclonal antibodies Alirocumab and Evolocumab, which can significantly reduce LDL-C levels. These drugs require a subcutaneous injection every 2 to 4 weeks and are costly, making them susceptible to infection at the injection site and raising concerns regarding the patient's compliance, further affecting the popularization and practical application of the drugs.[3]

Inclisiran, as a chemically modified double-stranded RNA, inhibits the synthesis of PCSK9 in the liver, thereby reducing LDL-C levels.[4] Extensive clinical trials published in the Inclisiran ORION series showed that its twice-yearly regimen has significantly reduced LDL-C levels.[5] Inclisiran is well-tolerated and safe in patients with hyperlipidemia and those who do not respond well to statins. Inclisiran obtained marketing authorization in the European Union that was used in adults with mixed dyslipidemia or hypercholesterolemia in December 2020.[6] Inclisiran has shown significant lipid-lowering effects, and its clinical data are also compelling.

A series of clinical studies were carried out to prove the hypolipidemic effect of this new drug. Inclisiran is effective in lowering blood lipids. With the initial use of ORION-1 followed by 2 doses of 300mg Inclisiran injected within 3 months, there was a 50% decrease in LDL-C in subjects, and it was sustained for at least 6 months.[7] With further research, data from phase III clinical trials ORION-9, ORION-10, and ORION-11 were analyzed by the American Heart Association (AHA) at the 2020 Annual Scientific Meeting[8,9] which showed that Inclisiran injected once every 6 months can achieve the same lipid-lowering effect as PCSK9 monoclonal antibody. In addition, Inclisiran's long dosing cycle provides a more timely and compliant treatment for enhanced lipid control in patients with hyperlipidemia, offering a new drug option for patients who cannot tolerate statins or those on statins whose lipid profile is not up to the standard.

With the continuous improvement of the Inclisiran clinical trial, relevant systematic evaluation has been developed rapidly, and the evidence of effectiveness and safety of the treatment has gradually increased. However, different systematic evaluation has differences in literature quality, analysis methods, outcome indicators, and level of evidence, and there is still a shortage of comprehensive and systematic summary evaluation.

The overview of systematic reviews (SRs) is a method to comprehensively search and collect systematic evaluations on the etiology, diagnosis, treatment, and prognosis of the same disease or health issue and conduct a comprehensive study on them.[10] This paper focused on comprehensively evaluating the safety and effectiveness of Inclisiran in treating hyperlipidemia through the overview of SRs to provide a better decision-making basis for medical personnel.

2. Data and methods

2.1. Inclusion criteria

Study type: This study included systematic evaluation or meta-anal of randomized controlled trials (RCTs); Subjects: The patients with hyperlipidemia who met the diagnostic criteria for hyperlipidemia and had a poor effect after an oral lipid-lowering drug treatment, regardless of the country, race, gender, and age; the patients with atherosclerotic cardiovascular disease (ASCVD) and LDL-C ≥ 70mg/dL (1.8mmol/L) on maximally tolerated statin therapy;[11] Intervention measures: Inclisiran (alone or combined with oral lipid-regulating drugs) was used in the experimental group; Control measures: The control group received oral lipid-lowering drugs/placebo; Outcome indicators: Effectiveness evaluation included TC, LDL-C, HDL-C levels, and

other lipid control results. The safety assessment included the incidence of adverse outcomes and complications after treatment with Inclisiran; The language used was English.

2.2. Exclusion criteria

Repeated literature; Other literature unrelated to Inclisiran in the treatment of hyperlipidemia; Conference abstracts or documents whose full text was not available.

2.3. Literature retrieval strategy

The Cochrane Library, PubMed, EMBASE, CNKI, WANGFANG, VIP, ClinicalTrials.gov, and ICRT were searched electronically. The retrieval method combined subject words and free words. The keywords included "Inclisiran, Leqvio, PCSK9, hyperlipidemia, high-blood-lipid, HLP, HL, hypercholesterolemia, high-blood-cholesterol, systematic review, Meta, Meta-analysis, the meta-analysis, RCT, randomized clinical trial." The retrieval time started from the initial database construction date to May 2022.

2.4. Literature screening and data extraction

Two researchers read the title and abstract of the relevant article. They selected the full text of the literature meeting the inclusion criteria for further research. In case of disagreement, a third party with higher qualifications was consulted for confirmation. Excel was used to extract data from the included literature, including authors, publication year, study types and quantity, interventional and control measures, study quality evaluation methods, outcome indicators, principal conclusions, etc. For the repetition of the same initial studies included in different systematic evaluations, the data in the previously published literature were mainly used to avoid repeated calculations of the same data. The original literature was referred to for confirmation and supplementary data where necessary.

2.5. Literature quality evaluation and evidence grading

Two researchers used the assessment of multiple systematic reviews (AMSTAR) tool to appraise the methodological quality of SRs. The grading of recommendations assessment, development, and evaluation (GRADE) tool was used for assessing the evidence quality of outcome indicators. A third party was consulted in case of any disagreement.

2.6. Data analysis method

Considering the good clinical consistency of the meta-analysis included in this study, RevMan5.3 software (https://training.cochrane.org/online-learning/core-software/revman/revman-5-download) was used to analyze the results and data quantitatively. Relative risk (RR) and 95%CI were used for dichotomous variables, and mean difference (MD) and 95%CI were used for continuous variables. $\chi 2$ test was used to determine whether heterogeneity existed; for $P > .1$ and $I^2 < 50\%$, a fixed effect model was selected. The random effect model was selected for $P \leq .1$ and $I^2 \geq 50\%$. The probability value of effect size $P < .05$ indicated that the combined effect size had statistical significance, while $P > .05$ indicated that the combined effect size had no statistical significance. Descriptive analysis was used for the results of single system evaluation or some data that could not be extracted and combined.

2.7. Ethics approval

This study is based on published systematic reviews and meta-analyze, and does not involve personal data. Therefore, the ethical approvals and patient consent are not necessary.

3. Results

3.1. Literature screening process and results

A total of 588 pieces of literature were retrieved. Among them, 350 literatures were obtained after removing the duplicates. The literature and abstracts were screened, and the full text was read. The research objects, research type discrepancy, results that could not be extracted, and the full text that could not be obtained were excluded. Finally, 10 literatures were included.[8,9,12–19] The screening process of the relevant literature is revealed in Figure 1.

3.2. Evaluation of methodological quality

All the articles included in this study were published in English journals from 2018 to 2021.The AMSTAR evaluation results showed that the included system evaluation's overall methodological quality still needed improvement. Of all the items, 3 were rated as complete (100%), namely Item 6 (describing the characteristics of the included research), Item 7 (evaluating and reporting the science of the included study), and Item 8 (the science of the included research was applied correctly to the derivation of the conclusions). The biggest methodological quality defects of the included systematic evaluations were failure to provide a preliminary design, inability to search comprehensive literature, failure to list excluded literature, and to evaluate the possibility of publication bias. Specific evaluation results are shown in Table 1.

3.3. Main outcome measures and evidence quality grading

The systematic evaluation in this study compared the effects of Inclisiran with placebo, with 27 main outcome measures.

Among them, 8 outcome indexes were high-quality, 3 were of medium quality, 6 were of low quality, and 10 were of the most inferior quality. Important related indicators are analyzed as follows.

3.3.1. Choice of different doses (Phase 1 Trials). In the included RCTs, the experimental groups were divided into subgroups of 100mg, 300mg, and 500mg according to different doses to test whether the different doses affected the therapeutic effect differently.

3.3.1.1. LDL-C indicators. Our analysis showed that 100mg Inclisiran substantially reduced LDL – C (MD=–34.05, 95%CI: –44.66 to –23.45, $P < .00001$). Compared with 100mg Inclisiran, 300mg Inclisiran apparently decreased LDL – C (MD=–51.45, 95%CI: –59.87 to –43.06, $P < .00001$). 500mg Inclisiran was second only to 300mg Inclisiran in reducing LDL – C (MD=–43.22, 95%CI: –49.66 to 36.78, $P < .00001$). The quality of evidence is high, and relevant indicators are shown in Figure 2.

3.3.1.2. TC indicators. The analysis showed that 100mg Inclisiran reduced TC (MD=–19.84, 95%CI: –28.89 to –10.80, $P < .0001$). 300mg Inclisiran had the most significant reduction in TC compared with 100mg Inclisiran (MD=–29.18, 95%CI: –35.64 to –22.71, $P < .00001$). 500mg Inclisiran was second only to 300mg Inclisiran in reducing TC (MD=–27.82, 95%CI: –31.54 to –24.10, $P < .00001$). The quality of evidence is significantly high, and the relevant indicators are demonstrated in Figure 3.

3.3.1.3. HDL – C indicators. The analysis showed that 100mg Inclisiran increased HDL – C levels, but the effect was
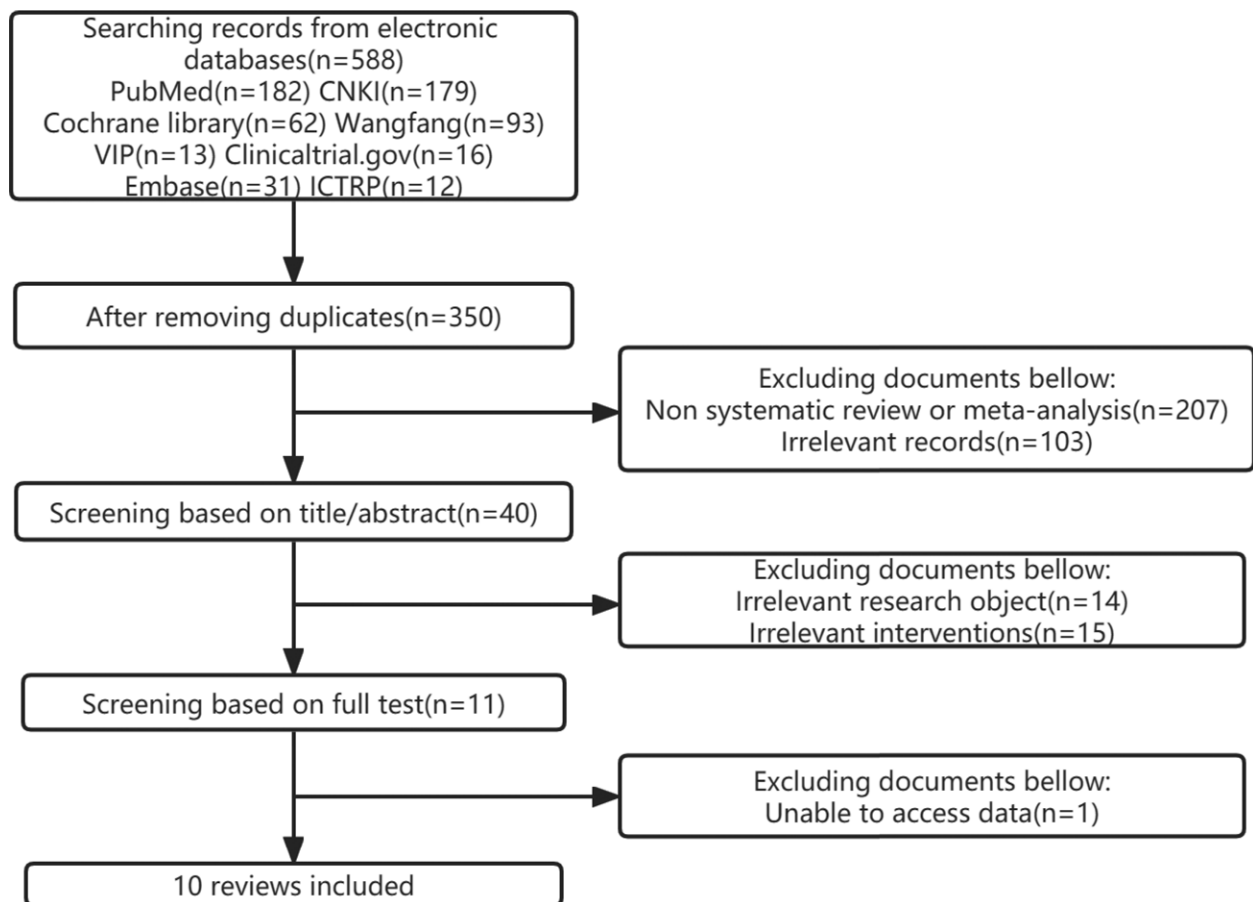

Figure 1. Flow chart of the systematic literature search and selection.

Results of AMSTAR quality assessment.

Reviews	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11
Wright 2021	Y	N	N	N	N	Y	Y	Y	N	N	Y
Asbeutah 2020	N	N	N	N	N	Y	Y	Y	Y	N	Y
Cordero 2020	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Wang 2018	N	Y	N	Y	N	Y	Y	Y	Y	N	Y
Talasaz 2021	N	Y	N	N	N	Y	Y	Y	Y	N	N
Brandts 2021	N	Y	N	N	N	Y	Y	Y	Y	N	Y
Ray 2020	N	Y	N	N	N	Y	Y	Y	Y	N	Y
Raal 2020	N	Y	N	N	N	Y	Y	Y	Y	N	Y
Khan 2020	N	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Ray 2017	Y	Y	N	N	N	Y	Y	Y	Y	N	Y

I1: Was a preliminary design provided? I2: Was there any duplicate research selection and data extraction? I3: Was a comprehensive literature retrieval performed? I4: Was the status of publication included as a criterion? I5: Was a list of inclusion and exclusion provided? I6: Were the characteristics of the inclusion in the study provided? I7: Was the scientific quality of the included research recorded and evaluated? I8: Was the scientific quality of the included research used correctly to draw conclusions? I9: Was it appropriate to combine the results of these research? I10: Was the possibility of publication bias evaluated? I11: Was a conflict of interest demonstrated?.
AMSTAR = assessment of multiple systematic reviews, N = No, Y = Yes.
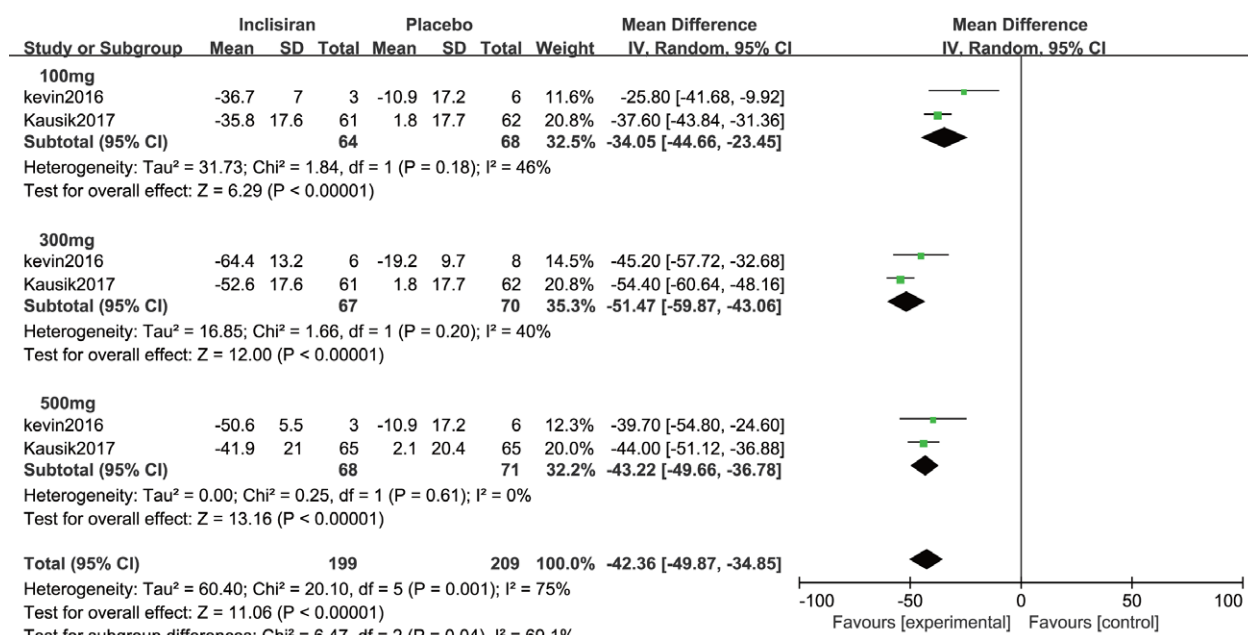

Figure 2. Forest plot of LDL-C comparing different doses of Inclisiran in treating hyperlipidemia. LDL-C = low-density lipoprotein cholesterol.

insignificant (MD = 7.09, 95%CI: 2.75 to 11.44, P = .001). 300mg Inclisiran significantly increased HDL – C level (MD = 8.49, 95%CI: 3.69 to 13.29, P = .0005), and the effect was better than 100mg Inclisiran. 500mg Inclisiran did not increase HDL – C (MD = 2.76, 95%CI: –2.24 to 7.77, P = .24), and the difference was not statistically significant. The quality of evidence is high, and relevant indicators are demonstrated in Figure 4.

3.3.2. Choice of injection frequency (Phase 2 Trials).
The primary efficacy endpoint of ORION-1 was the proportion change from baseline in LDL-C level at day 180.180 days of follow-up showed that LDL-C levels decreased after a single injection of 300mg Inclisiran (MD = –40.50, 95%CI: –47.60 to –33.40) compared with placebo. 300mg Inclisiran was injected twice, and the LDL-C level decreased significantly (MD = –54.40, 95%CI: –60.61 to –48.19) compared with the single injection. The quality of evidence is significantly high, and relevant indicators are demonstrated in Figure 5.

3.3.3. Overall effect (Phase 3 Trials).
The results showed that LDL-C level decreased after the treatment with Inclisiran compared with placebo, and LDL-C level decrease in the experimental group was lower than that in the control group, and the difference in combined effect size was statistically significant (MD = –50.13, 95%CI: –56.21 to –44.06, P < .00001), with high quality and heterogeneity of evidence (I²=81%), as demonstrated in Figure 6. Sensitivity analysis results pointed out that the structure of the forest map did not change.

3.3.4. Adverse reaction (Phase 3 Trials).
Major adverse reaction indicators reported in studies included injection site reactions.[20] Seven of the included SRs compared the adverse reactions between Inclisiran and placebo. The adverse reactions associated with Inclisiran treatment are shown in Figure 7. The overview of SRs showed that the incidence of adverse reactions in the Inclisiran group was equivalent to that in the placebo group compared with the placebo group (RR = 1.0,95%CI = 0.9–1.0). The difference was not statistically significant, and the quality of evidence was low. The incidence of severe adverse reactions was low, with severe adverse reactions (RR = 0.9,95%CI = 0.7–1.0) and irreversible events (RR = 1.2,95%CI = 0.8–1.9), and the quality of evidence was significantly low.
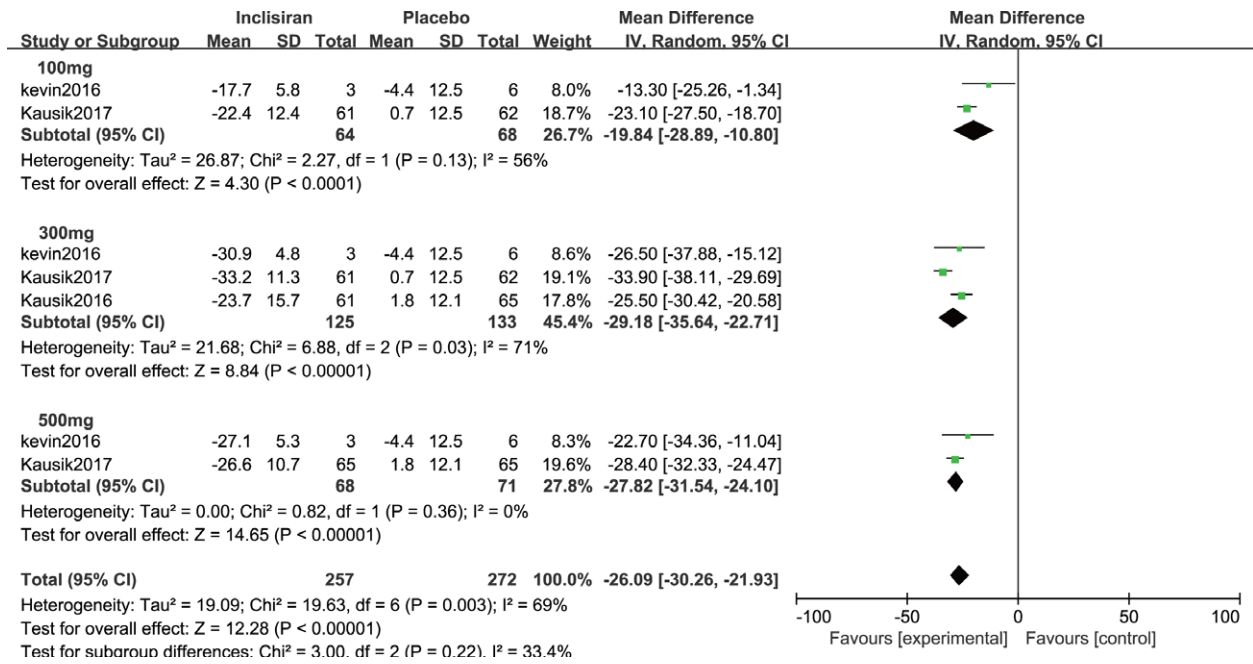
Figure 3. Forest plot of total cholesterol comparing different doses of Inclisiran in treating hyperlipidemia.
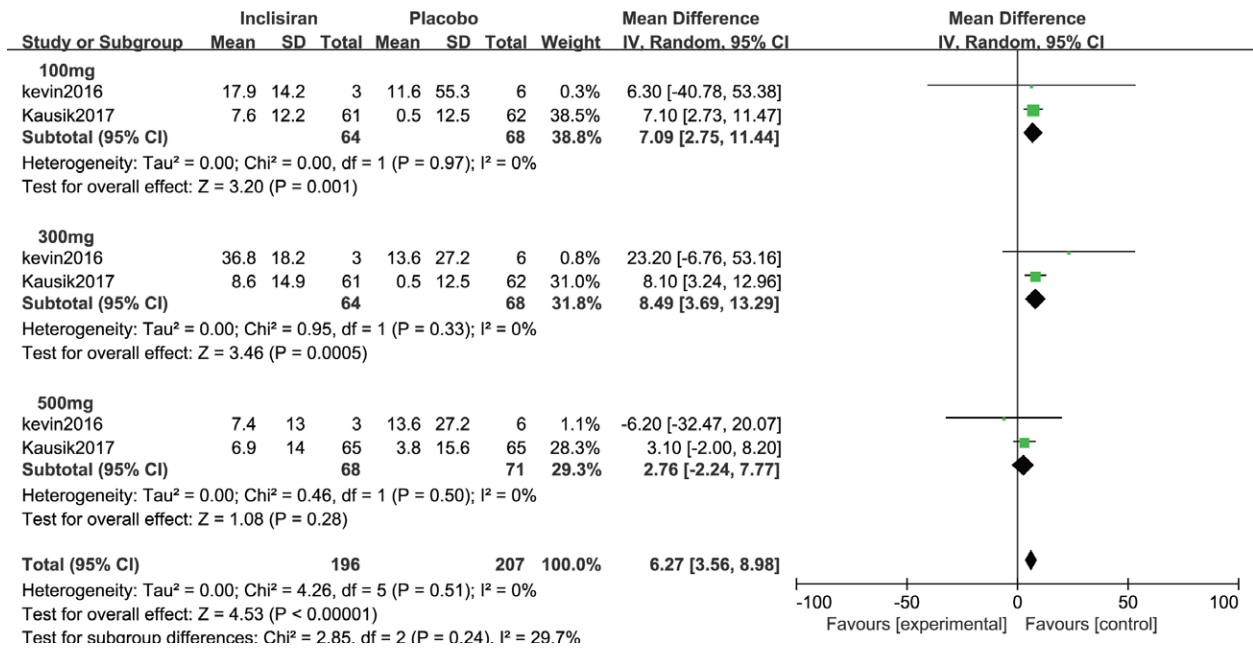

Figure 4. Forest plot of HDL-C comparing different doses of Inclisiran in treating hyperlipidemia. HDL-C = high-density lipoprotein.

The incidence of serious adverse reactions was lower in the Inclisiran group than in the placebo group (RR = 0.9,95%CI = 0.9–1.1). The difference was not statistically significant, and the quality of evidence was intermediate. The incidence of other adverse cardiovascular events was lower in the Inclisiran group than in the placebo group. There were no statistically significant differences in predicting exploratory cardiovascular events (RR = 0.8,95%CI = 0.6–0.9), fatal or non-fatal atrial fibrillation (RR = 0.9,95%CI = 0.4–2.0), fatal or non-fatal stroke (RR = 0.7,95%CI = 0.1–4.2). The evidence is of intermediate quality. The most common adverse reactions were injection site reactions. The incidence was higher in the Inclisiran group than in the placebo group (RR = 6.2,95%CI = 2.6–14.9), with minor injection site reactions (RR = 4.9,95%CI = 1.7–14.4) as the main occurrence. The difference was statistically significant,

and the quality of evidence was high. Other common adverse reactions such as cold (RR = 1.0,95%CI = 0.7–1.4), diabetes (RR = 1.0,95%CI = 0.9–1.2), and hypertension (RR = 1.0,95%CI = 0.8–1.3) were the same in both the groups. The differences were not statistically significant, and the quality of evidence was extremely low. Among them, the incidence rates of back pain (RR = 1.2,95%CI = 0.8–1.9), nasopharyngitis (RR = 1.1,95%CI = 0.8–1.4), gastroenteritis (RR = 1.8,95%CI = 0.7–4.9), bronchitis (RR = 1.5,95%CI = 1.0–2.4), dyspnea (RR = 1.2,95%CI = 0.7–1.9) and arthralgia (RR = 1.5,95%CI = 0.9–2.3) in the Inclisiran group were higher than those in the placebo group, the differences were not statistically significant, and the quality of evidence was very low. The incidence rates of osteoarthritis (RR = 0.8,95%CI = 0.5–1.2) in the Inclisiran group were lower than those in the placebo group, the differences
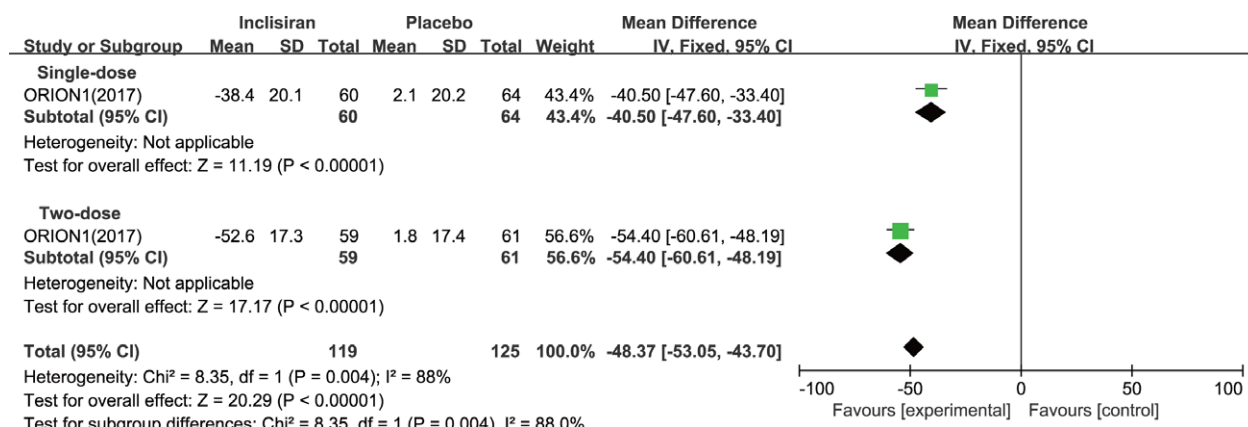
Study or Subgroup	Inclisiran Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Single-dose								
ORION1(2017)	-38.4	20.1	60	2.1	20.2	64	43.4%	-40.50 [-47.60, -33.40]
Subtotal (95% CI)			60			64	43.4%	-40.50 [-47.60, -33.40]
Heterogeneity: Not applicable								
Test for overall effect: Z = 11.19 (P < 0.00001)								
Two-dose								
ORION1(2017)	-52.6	17.3	59	1.8	17.4	61	56.6%	-54.40 [-60.61, -48.19]
Subtotal (95% CI)			59			61	56.6%	-54.40 [-60.61, -48.19]
Heterogeneity: Not applicable								
Test for overall effect: Z = 17.17 (P < 0.00001)								
Total (95% CI)			119			125	100.0%	-48.37 [-53.05, -43.70]
Heterogeneity: Chi² = 8.35, df = 1 (P = 0.004); I² = 88%								
Test for overall effect: Z = 20.29 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.35, df = 1 (P = 0.004), I² = 88.0%								

Favours [experimental]   Favours [control]

Figure 5. Forest plot of LDL-C comparing Inclisiran of injection frequency with placebo in treating hyperlipidemia. LDL-C = low-density lipoprotein cholesterol.
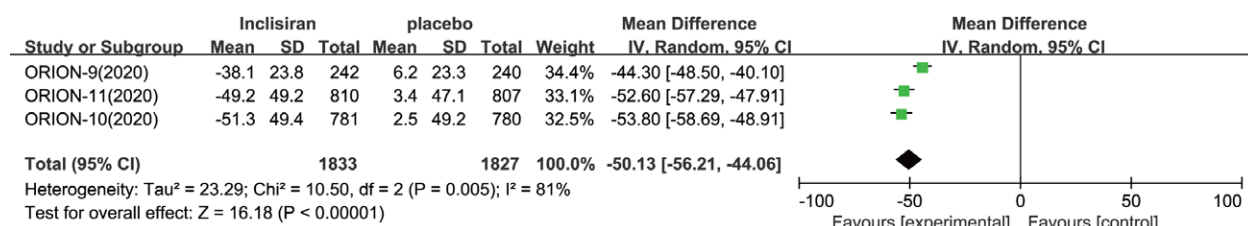
Study or Subgroup	Inclisiran Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ORION-9(2020)	-38.1	23.8	242	6.2	23.3	240	34.4%	-44.30 [-48.50, -40.10]
ORION-11(2020)	-49.2	49.2	810	3.4	47.1	807	33.1%	-52.60 [-57.29, -47.91]
ORION-10(2020)	-51.3	49.4	781	2.5	49.2	780	32.5%	-53.80 [-58.69, -48.91]
Total (95% CI)			1833			1827	100.0%	-50.13 [-56.21, -44.06]
Heterogeneity: Tau² = 23.29; Chi² = 10.50, df = 2 (P = 0.005); I² = 81%								
Test for overall effect: Z = 16.18 (P < 0.00001)								

Favours [experimental]   Favours [control]

Figure 6. Forest plot of LDL-C comparing Inclisiran with placebo in treating hyperlipidemia. LDL-C = low-density lipoprotein cholesterol.

Variable	ORION-9 Inclisiran (N=241)	ORION-9 Placebo (N=240)	ORION-9 Risk Ratio (95%CI)	ORION-10 Inclisiran (N=781)	ORION-10 Placebo (N=778)	ORION-10 Risk Ratio (95%CI)	ORION-11 Inclisiran (N=811)	ORION-11 Placebo (N=804)	ORION-11 Risk Ratio (95%CI)	Total Risk Ratio (95%CI)
Adverse events										
≥1 Adverse event	185	172	1.1(1.0-1.2)	574	582	1.0(0.9-1.0)	671	655	1.0(0.9-1.1)	0.1(0.9-1.0)
≥1 Event lead to discontinuation of trial intervention	3	0	—	19	17	1.1(0.6-2.1)	23	18	1.3(0.7-2.3)	1.2(0.8-1.9)
Serious adverse events										
≥1 Serious adverse event	18	33	0.5(0.3-0.9)	175	205	0.9(0.7-1.0)	181	181	1.0(0.8-1.2)	0.9(0.7-1.0)
Death										
Death from cardiovascular causes	1	0	—	7	5	1.4(0.4-4.4)	9	10	0.9(0.4-2.2)	1.1(0.6-2.2)
From any cause	1	1	1.0(0.1-15.8)	1	3	0.3(0.0-3.2)	3	3	1.0(0.2-4.9)	0.7(0.2-2.4)
New, worsening, or recurrentt cancer	2	3	0.7(0.1-3.9)	26	26	1.0(0.6-1.7)	16	20	0.8(0.1-1.5)	0.9(0.6-1.3)
Other cardiovascular adverse events										
Prespecified exploratory cardiovascular event	10	10	1.0(0.4-2.3)	58	79	0.7(0.5-1.0)	63	83	0.8(0.6-1.0)	0.8(0.6-0.9)
Fatal or nonfatal myocardial infarction	3	1	3.0(0.3-28.5)	20	18	1.1(0.6-2.1)	10	22	0.5(0.2-0.9)	0.9(0.4-2.0)
Fatal or nonfatal stroke	0	0	—	11	7	1.6(0.6-4.0)	2	8	0.2(0.1-0.2)	0.7(0.1-4.2)
Injection-site reaction										
Any reaction	41	4	10.2(3.7-28.1)	20	7	2.9(1.2-6.7)	38	4	9.4(3.4-26.3)	6.2(2.6-14.9)
Mild	37	4	9.2(3.3-25.4)	13	7	1.9(0.7-4.6)	23	3	7.6(2.3-25.2)	4.9(1.7-14.4)
Moderate	4	0	—	7	0	—	15	1	14.9(2.0-112.3)	13.1(3.1-55.4)
Severe	0	0	—	0	0	—	0	0	—	—
Persistent	0	0	—	0	0	—	0	0	—	—
Frequent adverse events										
Upper respiratory tract infection	13	21	0.6(0.3-1.2)	39	33	1.2(0.7-1.9)	52	49	1.1(0.7-1.5)	1.0(0.7-1.4)
Diabetes mellitus	—	—	—	120	108	1.1(0.9-1.4)	88	94	0.9(0.7-1.2)	1.0(0.9-1.2)
Hypertention	—	—	—	42	42	1.0(0.7-1.5)	53	54	1.0(0.7-1.4)	1.0(0.8-1.3)
Back pain	17	10	1.7(0.8-3.6)	39	39	1.0(0.6-1.5)	—	—	—	1.2(0.8-1.9)
Nasopharyngitis	28	20	1.4(0.8-2.4)	—	—	—	91	90	1.0(0.8-1.3)	1.1(0.8-1.4)
Gastroenteritis	11	6	1.8(0.7-4.9)	—	—	—	—	—	—	1.8(0.7-4.9)
Bronchitis	—	—	—	46	30	1.5(1.0-2.4)	—	—	—	1.5(1.0-2.4)
Dyspnea	—	—	—	39	33	1.2(0.7-1.9)	—	—	—	1.2(0.7-1.9)
Arthralgia	—	—	—	—	—	—	47	32	1.5(0.9-2.3)	1.5(0.9-2.3)
Osteoarthritis	—	—	—	—	—	—	32	40	0.8(0.5-1.2)	0.8(0.5-1.2)

Figure 7. Adverse events comparing Inclisiran with placebo while treating hyperlipidemia.

were not statistically significant and the quality of evidence was very low.

4. Discussion

4.1. Evaluation of effectiveness of Inclisiran in hyperlipidemia

Novel lipid-lowering drugs, including PCSK9 inhibitors Evolocumab and Alirocumab, and small interfering ribonucleotide (si-RNA), have obtained promising results in clinical studies. In addition to the efficient and significant reduction of LDL-C, there is still controversy about whether the rapid realization of treatment goals can become a new strategy for lipid-lowering therapy.[21] Inclisiran, as a si-RNA, mainly interferes with the expression of PCSK9 messenger RNA, thus continuously reducing the levels of LDL-C and PCSK9, with good effectiveness.[22] Inclisiran was approved by the European Medicines Agency (EMA) for the first time on December 9, 2020, under the brand name Leqvio.[23] On December 22, 2021, it received marketing approval from the US Food and Drug Administration (FDA). Inclisiran was used as an adjunctive to diet and maximum tolerance of statins for the

favorable treatment of atherosclerosis, primary hypercholesterolemia, and mixed dyslipidemia.[6,24] Long-term oral statin medication compliance was poor, while the Inclisiran administration period of as long as half a year significantly improved patients' compliance.[25] Four of the included SRs compared the effects of Inclisiran with placebo in reducing LDL-C, TC, and increasing HDL-C. The main results showed that compared with placebo therapy, the LDL-C level after Inclisiran decreased (MD = −50.13, 95%CI: −56.21 to −44.06, P < .00001). The results revealed that the LDL-C level of patients with hyperlipidemia was significantly reduced after the treatment with Inclisiran compared with placebo. The LDL-C level of the experimental group was lower than that of the control group, and the difference in the combined effect size was statistically significant. Subgroup analysis showed that 100mg, 300mg, and 500mg Inclisiran could reduce LDL-C and TC. Among them, 300mg Inclisiran had the most significant effect on LDL-C and TC level reduction. 100mg and 300mg Inclisiran could increase HDL-C level; 300 mg Inclisiran had the most obvious effect on HDL-C increase, 500mg Inclisiran could not increase HDL-C level. In conclusion, 300mg Inclisiran had the best therapeutic effect, significantly decreased LDL-C and TC levels in patients with hyperlipidemia, and increased HDL-C levels, thus reducing risk factors for cardiovascular disease and increasing protective factors for the prevention of cardiovascular disease. 300mg Inclisiran was injected twice, and the LDL-C level decreased significantly compared with the single injection. Through durable and potent lowering of LDL-C with 2 injections a year, Inclisiran could yield a persistent lipid-lower therapeutic option in the near future.[19]

4.2. Safety evaluation of Inclisiran in hyperlipidemia

Safety is an essential determinant of drug selection in patients with hyperlipidemia. According to the chemical structure, Inclisiran is a short synthetic siRNA that acts as a guide, can hybridize with the complementary mRNA of PCSK9, and induce its degradation. Due to the unique structural modification of Inclisiran, the drug has prolonged biological activity and better stability.[26] Because of its unique mechanism of action, Inclisiran can degrade both intracellular and extracellular PCSK9 protein levels, leading to a significant, effective, and long-lasting decrease in LDL-C concentration.[27] Inclisiran is safe and well-tolerated in treating dyslipidemia and can reduce the risk of acute vascular events.[5] Although some SRs suggested that the risk rate of adverse reactions in Inclisiran versus placebo needs to be determined,[26,28] data integration from SRs in this paper shows that the risk of adverse events in the Inclisiran group was equivalent to that in the placebo group (RR = 1.0,95%CI = 0.9–1.0). However, the incidence of injectable site reactions in the Inclisiran group was higher than that in the placebo group (RR = 6.2,95%CI = 2.6–14.9). Thus, minor injectable site reactions and other possible adverse reactions mentioned above should be considered while using the Inclisiran group. In addition, there are no research on the long-term effects of Inclisiran on patients with hyperlipidemia, and a large number of clinical studies and longer follow-ups are still needed to observe the long-term effects of the drug on the transformation and outcome of hyperlipidemia. In summary, this research shows that Inclisiran has a favorable safety profile, with no significant difference in its good response compared with placebo. However, ongoing and upcoming clinical trials in a larger patient population are needed to evaluate the long-term tolerability, effectiveness, and safety of Inclisiran.[26]

4.3. Methodological quality of Inclisiran systematic evaluation

Systematic evaluation is a fundamental research method of evidence-based medicine and an important source, which is regarded as the cornerstone of clinical effectiveness evaluation

and clinical guidelines and norms. In general, only systematic evaluation with strict quality control can provide close to real scientific evidence for clinical practice and health-related decision-making.[29] In this study, the AMSTAR tool was used to appraise the methodological quality of the 10 included systematic evaluations. The evaluation results showed that the included systematic evaluations' overall methodological quality needed improvement. This may be related to the fact that most of the articles included were published individually and the lack of quality assurance of SRs such as Cochrane. 100% of the SRs did not indicate whether a bibliographic list of excluded studies was provided, which may be related to the fact that there are space limitations in general academic journals. Editors are less likely to list lengthy exclusions at the end of the paper. 70% of the included system evaluations did not provide the preliminary design scheme, which may affect the rigor of the system evaluation construction process. 80% of the system evaluations did not carry out extensive literature retrieval. It lacked at least 4 authoritative databases, which may affect the comprehensiveness of the system evaluation construction process. 70% of the systematic evaluations did not indicate whether the publication has been considered in the inclusion criteria. The retrieval of unpublished adverse research reports, dissertations, abstractions of conference papers, and various briefs may be missing, and there is a risk of publication bias.[30] In addition, 90% of SRs did not evaluate publication bias, potentially affecting the objectivity and reliability of results.

4.4. Inclisiran evidence strength

The methodological quality of systematic evaluation does not represent the quality of evidence. In order to help users of systematic evaluation accurately understand and correctly apply the evidence provided by this systematic evaluation, the GRADE tool was used in this study to grade the quality of evidence of outcome indicators to evaluate the correct grasp of the effect estimate value.[31] According to GRADE's systematic degradation, this study assessed the evidence quality of 27 outcome indicators, including 10 SRs. The results showed that among the 27 outcome indicators, 8 were high-quality, 3 were of medium quality, 6 were of low quality, and 10 were of very low quality, suggesting that the efficacy and safety of Inclisiran still need to carry out high-quality studies with large sample sizes. Among the 5 degrading factors, the main ones are the inconsistency, limitation, and imprecision of the analysis, which is reflected in the large heterogeneity of some study results. The limitation downgrade of the study indicates that the RCTs included in the systematic evaluation still have some defects in the study design,[32] such as the absence of a randomization process. However, the imprecision degradation of the study is reflected in the fact that the confidence interval of the estimated effect size is too wide, failing to reach the optimal information sample size.[33] These deficiencies significantly reduce the credibility of the results of the systematic evaluation, especially for key outcome measures such as low quality of adverse reactions, suggesting that Inclisiran's adverse reactions were equivalent to placebo and that the results need to be examined with evidence from a larger sample size.

4.5. Closing

Since Inclisiran was available in 2020, the number of randomized controlled trial studies using these drugs was small. Therefore, this overview of SRs provides a direction for researchers to evaluate the indications and contraindications of Inclisiran further. Compared to other studies, we used a more reliable analysis strategy (an overview of SRs) to conduct a more comprehensive and detailed analysis of the effectiveness and safety of Inclisiran. In addition, we performed

subgroup analyses by comparing the effectiveness of different doses of Inclisiran with different LDL-C levels. However, our overview of SRs has some limitations. First, there were few original studies on Inclisiran, and only 10 SRs articles met the requirements. Secondly, fewer than 10 RCTs were included, so we could not compile funnel plots. Thirdly, all relevant studies were carried out abroad, and most of them only included hyperlipidemia patients diagnosed with ASCVD or with ASCVD, thus limiting the generality of the study results. Fourth, some of our results show a high degree of heterogeneity. In general, heterogeneity results from different numbers of participants, different doses, and durations of treatment for various conditions of their participants. The large heterogeneity means that more studies are needed to confirm our findings. This paper's discussion shows that more high-quality RCTs and systematic evaluation articles are expected to provide more reliable evidence.

5. Conclusion

(1) 300mg Inclisiran with 2 injections a year has the best therapeutic effect, which can significantly reduce LDL-C and TC, and can increase HDL-C levels in patients with hyperlipidemia as well.
(2) Inclisiran has a favorable safety profile, with no significant difference in its incidence of adverse reactions compared to placebo. Most of the adverse effects were associated with the reaction on the injection site.

Author contributions

Conceptualization: Jiayi Li, Xi Yang.
Data curation: Jiayi Li, Xiangguo Lei.
Formal analysis: Jiayi Li, Xiangguo Lei.
Investigation: Jiayi Li, Xiangguo Lei.
Methodology: Jiayi Li, Xiangguo Lei, Xi Yang.
Project administration: Xi Yang.
Software: Jiayi Li, Zihao Li.
Writing – original draft: Jiayi Li, Xi Yang.
Writing – review & editing: Jiayi Li, Zihao Li, Xi Yang.

References

[1] Yao YS, Li TD, Zeng ZH. Mechanisms underlying direct actions of hyperlipidemia on myocardium: an updated review. Lipids Health Dis. 2020;19:23.
[2] Karr S. Epidemiology and management of hyperlipidemia. Am J Manag Care. 2017;23:S139–s148.
[3] Hardy J, Niman S, Pereira E, et al. A critical review of the efficacy and safety of inclisiran. Am J Cardiovasc Drugs. 2021;21:629–42.
[4] Smith KW, White CM. Inclisiran: a novel small interfering RNA drug for low-density lipoprotein reduction. J Clin Pharmacol. 2022;62:1079–85.
[5] Banerjee Y, Pantea Stoian A, Cicero AFG, et al. Inclisiran: a small interfering RNA strategy targeting PCSK9 to treat hypercholesterolemia. Expert Opin Drug Saf. 2022;21:9–20.
[6] Kosmas CE, Muñoz Estrella A, Sourlas A, et al. Inclisiran in dyslipidemia. Drugs Today (Barc). 2021;57:311–9.
[7] 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.
[8] Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med. 2020;382:1520–30.
[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] Silva V, Grande AJ, Carvalho AP, et al. Overview of systematic reviews - a new type of study. Part II. Sao Paulo Med J. 2015;133:206–17.
[11] Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2020;105:3613–82.
[12] 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.
[13] Asbeutah AAA, Asbeutah SA, Abu-Assi MA. A meta-analysis of cardiovascular outcomes in patients with hypercholesterolemia treated with inclisiran. Am J Cardiol. 2020;128:218–9.
[14] Cordero A, Santos-Gallego CG, Fácila L, et al. Estimation of the major cardiovascular events prevention with Inclisiran. Atherosclerosis. 2020;313:76–80.
[15] Wang Y, Wang J, Wang S. Comparative effectiveness of inclisiran 100, 300, and 500 mg in a population with hyperlipidemia: a network meta-analysis of randomized controlled trials. Am J Cardiovasc Drugs. 2018;18:271–82.
[16] Talasaz AH, Ho AJ, Bhatty F, et al. Meta-analysis of clinical outcomes of PCSK9 modulators in patients with established ASCVD. Pharmacotherapy. 2021;41:1009–23.
[17] Brandts J, Dharmayat KI, Vallejo-Vaz AJ, et al. A meta-analysis of medications directed against PCSK9 in familial hypercholesterolemia. Atherosclerosis. 2021;325:46–56.
[18] Khan SA, Naz A, Qamar Masood M, et al. Meta-analysis of inclisiran for the treatment of hypercholesterolemia. Am J Cardiol. 2020;134:69–73.
[19] 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.
[20] Banach M, Jankowski P, Jóźwiak J, et al. PoLA/CFPiP/PCS guidelines for the management of dyslipidaemias for family physicians 2016. Arch Med Sci. 2017;13:1–45.
[21] Burger AL, Pogran E, Muthspiel M, et al. New treatment targets and innovative lipid-lowering therapies in very-high-risk patients with cardiovascular disease. Biomedicines. 2022;10:970.
[22] Warden BA, Duell PB. Inclisiran: a novel agent for lowering apolipoprotein B-containing lipoproteins. J Cardiovasc Pharmacol. 2021;78:e157–74.
[23] Lamb YN. Inclisiran: first approval. Drugs. 2021;81:389–95.
[24] Tomlinson B, Chow E, Chan P, et al. An evaluation of the pharmacokinetics of inclisiran in the treatment of atherosclerotic cardiovascular disease. Expert Opin Drug Metab Toxicol. 2021;17:1353–61.
[25] Rogula S, Błażejowska E, Gąsecka A, et al. Inclisiran-silencing the cholesterol, speaking up the prognosis. J Clin Med. 2021;10:2467.
[26] Merćep I, Friščić N, Strikić D, et al. Advantages and disadvantages of inclisiran: a small interfering ribonucleic acid molecule targeting PCSK9-a narrative review. Cardiovasc Ther. 2022;2022:8129513.
[27] Drygas W, Niklas AA, Piwońska A, et al. Multi-centre national population health examination survey (WOBASZ II study): assumptions, methods, and implementation. Kardiol Pol. 2016;74:681–90.
[28] Zijlstra LE, Trompet S, Mooijaart SP, et al. Renal impairment, cardiovascular disease, and the short-term efficacy and safety of PCSK9 targeted by inclisiran. Mayo Clin Proc. 2020;95:12–4.
[29] Pussegoda K, Turner L, Garritty C, et al. Systematic review adherence to methodological or reporting quality. Syst Rev. 2017;6:131.
[30] van Aert RCM, Wicherts JM, van Assen M. Publication bias examined in meta-analyses from psychology and medicine: a meta-meta-analysis. PLoS One. 2019;14:e0215052.
[31] Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490.
[32] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.
[33] Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64:669–77.