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REVIEW

Small Interfering RNA (siRNA) in Dyslipidemia: A Systematic Review on Safety and Efficacy of siRNA

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Introduction: RNA interference (RNAi) therapy represents an evolving advancement in the management of dyslipidemia. One prominent form of RNAi therapy is small interfering RNA (siRNA), which has emerged as a promising therapeutic strategy. This study aims to critically analyze the efficacy and safety of siRNA in the treatment of dyslipidemia.

Methods: PubMed, Scopus, and Web of Science servers were used to conduct a systematic search in compliance with the PRISMA guidelines.

Results: A total of 20 studies with 6651 participants were included in the analysis. The drugs used in the studies were. Inclisiran led to a notable 44.09% reduction in LDL and 37.5% in apolipoprotein levels among individuals with hypercholesterolemia. In hyperlipoproteinemia(a), therapies like Lepodisiran and Olpasiran achieved a 75.69% drop in apolipoproteins and 16.25% in LDL. For hypertriglyceridemia, agents such as ARO-APOC3 and Plozasiran showed over 50% reductions in both VLDL and triglycerides. In mixed hyperlipidemia and chylomicronemia, Plozasiran significantly reduced triglycerides by up to 79% and apolipoproteins by 87.5%. The 5 most common adverse effects reported were nasopharyngitis, diabetes mellitus (including new-onset diabetes mellitus and worsening diabetes mellitus), injection site adverse effects, back pain, and hypertension.

Conclusion: In conclusion, the benefits of siRNA therapy in dyslipidemia management appear to outweigh its potential drawbacks, demonstrating promising efficacy and safety profiles. However, further research is necessary to fully understand its long-term effects and optimize its therapeutic potential.

Keywords: small interfering RNA, RNA interference therapy, inclisiran, ALN-PCS, ARO ANG3, lipodisiran, zerlasiran, Plozasiran, zodasiran, ARO-APOC3, SLN360, olpasiran

Introduction

Dyslipidemias are among the most frequently identified and treated chronic illnesses. Research on dyslipidemias is still ongoing and continues to expand; recent studies have provided insights into their genetic and molecular origins, as well as their role in the development of atherosclerosis.[1] Over the last few decades, progress in genetics, analytical tools, and knowledge of signaling molecules has revealed a wide range of new mechanisms that can be targeted for therapy to reduce cholesterol levels.[2] Rapid progress has been made in developing advanced methods that use small molecules, biological agents, or nucleic acids to target these recently identified mediators. Selective suppression of the synthesis of particular proteins is now achievable due to the engineering of antisense RNA and small interfering RNAs (siRNAs).

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New treatment strategies targeting hepatocytes, important cells involved in lipid metabolism, have been made possible by these technologies.[3]

RNA interference (RNAi) therapies have generated considerable interest, with recent approvals highlighting their potential for treating cardiovascular and metabolic disorders, cancers, and other diseases. These therapies primarily use siRNAs, which are double-stranded RNA molecules designed to target specific genetic sequences, and antisense oligonucleotides (ASOs), which are single-stranded RNA or DNA molecules engineered to modify gene expression.[4] Initially targeting rare genetic disorders, RNAi treatments have demonstrated their effectiveness and now present new opportunities for managing more prevalent conditions, such as cholesterol imbalances.[5] The most advanced RNAi treatment available to manage dyslipidemia is Inclisiran, which targets PCSK9 and was approved in late 2021.[6]

The 2019 ESC/EAS (European Society of Cardiology/European Atherosclerosis Society) Guidelines for managing dyslipidemias prioritize cardiovascular risk assessment using tools like the SCORE (Systematic Coronary Risk Evaluation) system.[7] It categorizes patients into low, moderate, and high-risk groups. In terms of pharmacological treatments high-intensity statins are the first-line therapy for most patients. If statins alone are insufficient, ezetimibe can be added to lower lipid levels. PCSK9 inhibitors (Alirocumab and Evolocumab) are used for very high-risk patients with inadequate LDL-C (Low-Density Lipoprotein- Cholesterol) reduction despite other therapies. Monitoring and adjusting treatment are crucial to meeting lipid goals.[8] RNAi therapy remains in the research phase and has not yet been incorporated into the guidelines. However, the promising outcomes demonstrated in recent studies highlight its potential as a therapeutic approach.

In 2014, Fitzgerald et al published a Phase I trial to prove the safety and efficacy of single-dose administration of ALN PCS, RNAi targeting PCSK9 synthesis. This study is the first definitive clinical proof of concept in human beings of an RNAi drug being used to lower PCSK9, thereby resulting in favorable outcomes of decreased LDL cholesterol.[9]

This study presents a comprehensive analysis of various RNA interference (RNAi) therapeutics used in the management of a broad spectrum of dyslipidemias, including hypercholesterolemia, hyperapolipoproteinemia(a), hypertriglyceridemia, mixed hyperlipidemia, and chylomicronemia. Additionally, it evaluates the impact of RNAi therapy on key lipid parameters and provides a summary of the associated adverse effects, aiming to expand physicians' understanding of this emerging therapeutic approach.

Methods

The Systematic review was done according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The review was registered on PROSPERO (ID: CRD42024564012).

Data Sources and Search Strategy

A comprehensive search was conducted in PubMed, Scopus, and Web of Science databases without publication period restriction. The keywords used are summarized in Table 1. The search process was completed separately by two researchers. The studies' significance level was further screened by appropriately evaluating the publications' titles, abstracts, and full text. A total of 19 articles were included and reviewed.

Table 1 Keywords Used in Searching Data Sources

Treatment terms	"RNA interference therapy" OR "RNAi" OR "siRNA" OR "Small interfering RNA"
Disease terms	"Dyslipidemia" OR "hyperlipidemia"

Abbreviations: RNA, Ribonucleic acid; RNAi, Ribonucleic acid interference.

Eligibility Criteria

The studies were included or excluded as per the defined inclusion and exclusion criteria. The inclusion criteria followed were:

(1) The study must be a randomized control trial.
(2) The study consists of the demographic details of the patients.
(4) The intervention used is a siRNA targeting PCSK9/ANGPTL3/APO C3/Lp(a)
(5) The study includes data on any outcomes (LDL [Low-density lipoprotein], total cholesterol, triglycerides, apolipoprotein, apoc3) or reports any adverse effects of RNAi therapy usage.

The following exclusion criteria were considered:

(1) Case-control studies, cohort studies, and non-original studies, including conference abstracts, review articles, protocols, case reports, animal studies, and editorials.
(2) Articles in a language other than English.
(3) Unavailability of full texts.

Study Selection

Revman software was used to organize the search results and remove duplicates. Eight authors independently screened 232 non-duplicated records and the conflicts were resolved after a discussion with DA, SSM, and RGB.

Data Extraction

Nine authors of the research team extracted the required data: the first author's name, the year of the study, the place of the study, the number of participants, the mean age, gender, the drug used, the route of administration, the treatment duration, adverse effects, and the outcomes of the intervention. The results of the included articles are discussed in Tables 2 and 3. The first author investigated the extracted data and settled any disagreements among the other authors.

Quality Assessment

The Cochrane RoB 2 (Risk of Bias 2) tool was used for randomized control trials (RCT). Nine authors independently assessed the risk of bias.

Table 2 Characteristics of the Studies Included in the Systematic Review

Author	Year	Country	Events (N)	Male (%)	Mean age	Research Type
Ray et al[10]	2020	USA	T1: 781; C1: 780	T1: 68.5; C1: 70.3	T1: 66.4±8.9; C1: 65.7±8.9	Randomized controlled trial
		Europe, South Africa	T2: 810; C2: 807	T2: 71.5; C2: 72	T2: 64.8±8.3; C2: 64.8±8.7	
Ray et al[11]	2023	USA, Canada, Netherlands, Germany, United Kingdom	T: 290; C: 92	T: 65; C: 60	T: 63·3±11·1; C: 61·9±10·6	Randomized controlled trial
Raal et al[12]	2020	USA, Canada, Netherlands, South Africa, Spain, Denmark, Sweden	T: 242; C: 240	T: 46.3; C: 47.9	T: 56; C: 56	Randomized controlled trial

(*Continued*)

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Table 2 (Continued).

Author	Year	Country	Events (N)	Male (%)	Mean age	Research Type
Ray et al[13]	2017	USA, Canada, Netherlands, Germany, United Kingdom	T1: 60, T2: 61, T3: 65; C: 65	T1: 65, T2: 67, T3: 71; C: 65	T1: 63.9±10.8, T2: 63.9±12.8, T3: 62.1±12.5; C: 62.0±11.4	Randomized controlled trial
Luo et al[14]	2023	China	T1: 15, T2: 15, C: 10	T1: 26.7, T2: 20.0; C1: 40.0	T1: 62.6±10.53, T2: 59.5±7.45; C1: 57.3±9.59	Randomized controlled trial
Yamashita et al[15]	2024	Japan	T: 255 C: 57	T: 75.7 C: 68.4	T: 63.6±10.5 C: 63.8±11.1	Randomized controlled trial
Kallend et al[16]	2022	USA	T: 48; C1: 48, C2: 48	T: 68.8; C1: 68.8, C2: 68.8	T: 36.0±10.12 C1: 36.0±10.12, C2: 36.0±10.12	Randomized controlled trial
Fitzgerald et al[9]	2013	United Kingdom	T: 24 C: 8	T: 90; C: 100	T: 51.0 C: 41.5	Randomized controlled trial
Kallend et al[17]	2022	USA	T1: 10 T2: 6; C: 12	T1: 50, T2: 83.3; C: 50	T1: 56±11.6 T2: 51.2±14.2 C: 53.8±13.8	Randomized controlled trial
Watts et al[18]	2022	New Zealand, Australia	T1: 6, T2: 6, T3: 6, T4: 6, T5: 4, T6: 4, T7: 4, T8: 6, C: 19	T1: 66.7, T2: 50, T3: 83.3, T4: 83.3, T5: 50, T6: 100, T7: 50; C: 75 T8: 50; C: 66.7	T1: 37.5 T2: 51 T3: 42.5 T4: 50.0 T5: 53 T6: 44.5 T7: 29.5 C: 39.5. T8: 54.5 C: 45.0	Randomized controlled trial
Nissen et al[19]	2023	USA, Singapore	T1: 6, T2: 6, T3: 6, T4: 6, T5: 6, T6: 6; C: 12	T1: 83.3, T2: 83.3, T3: 50.0, T4: 50.0, T5: 66.7, T6: 83.3; C: 50.0	T1: 40.5±11.7 T2: 44.3±8.3 T3: 50.7±11.3 T4: 47.8±10.4 T5: 51.8±9.5 T6: 38.5±15.6 C: 50.3±11.1	Randomized controlled trial
Nissen et al[20]	2024	USA, Netherlands, United Kingdom, Australia	T1: 5, T2: 6; C1: 3, T3: 9, T4: 9, T5: 9; C2: 9	T1: 40, T2: 50; C: 0 T3: 77.8, T4: 44.4, T5: 55.6; C: 55.6	T1: 57.8±14.6 T2: 43.7±17.5 C: 54.3±17.0 T3: 59.8±8.6 T4: 61.3±6.8 T5: 56.9±12.2 C: 47±8.2	Randomized controlled trial
Ballantyne et al[21]	2024	USA, Europe, New Zealand, Australia, Canada	T1: 67, T2: 67, T3: 66, T4: 66; C: 87	T1: 54, T2: 55, T3: 56, T4: 65; C: 53	T1: 60.2±11.7 T2: 61.3±11.3 T3: 62.6±10.5 T4: 61.3±11.8 C: 58.9±9.7	Randomized controlled trial

(*Continued*)

Table 2 (Continued).

Author	Year	Country	Events (N)	Male (%)	Mean age	Research Type
Gaudet et al[22]	2024	USA, Europe, New Zealand, Australia, Canada	T1: 54, T2: 55, T3: 57; C: 60	T1: 85, T2: 78, T3: 72; C: 77	T1: 53±10 T2: 56±11 T3: 54±11 C: 56±11	Randomized controlled trial
Gerald et al[23]	2024	Australia, Canada, USA, Belgium	T1: 26, T2: 24, C: 25	T1: 12, T2: 11, C: 14	T1: 47.9±14.4 T2: 42.6±10.9 C: 47.4±13.9	Randomized controlled trial
Rosenson et al[24]	2024	4 countries (Names not mentioned)	T1: 51, T2: 51, T3: 51; C: 51	T1: 51, T2: 57, T3: 53; C: 53	T1: 60.4±12.7 T2: 60.0±9.9 T3: 61.5±12.5 C: 60.2±11.3	Randomized controlled trial
Gaudet et al[25]	2023	Australia, Canada, New Zealand	T1: 6, T2: 6, T3: 6, T4: 6; C: 16	T1: 83.3, T2: 83.3, T3: 50.0, T4: 66.7; C: 56.3	T1: 31.5 T2: 44.5 T3: 47.0 T4: 27.0 C: 28.0	Randomized controlled trial
Raal et al[26]	2023	Hong Kong, Israel, Russia, Serbia, South Africa, Taiwan, Turkey, Ukraine	T: 37; C: 19	T: 37.8; C: 42.1	T: 43.8±13.4 C: 40.7±12.1	Randomized controlled trial
Nissen et al[27]	2022	USA, United Kingdom, Australia	T: 24; C: 8	T1: 67, T2: 67, T3: 33, T4: 50; C: 25	T1: 45.5 T2: 46.3±12.3 T3: 58.7±13.2 T4: 43.7±17.5 C: 52.9±12.0	Randomized controlled trial
O'Donoghue et al[28]	2021	North America, Europe, Australia, Japan	T1: 58; C: 54	T1: 79, T2: 60, T3: 73, T4: 60; C: 67	T1: 63.4±9.5 T2: 61.3±9.2 T3: 59.7±10.1 T4: 61.8±9.4 C: 63.4±8.9	Randomized controlled trial

Abbreviations: T, Test group; C, Control group.

Statistical Analysis

All data were extracted onto a predesigned Excel sheet and represented in percentages, mean, and standard deviation for appropriate variables.

Results

A total of 20 studies were included in the final analysis. Study characteristics of the included studies are included in Table 2 and data on the outcomes from the included studies are presented in Table 3. The selection process of articles is shown in the PRISMA diagram (Figure 1).

Patient Characteristics

The review included 6651 patients. Among the 20 studies, 2701 (76%) and 1677 (55%) males were in the test and control groups, respectively. The mean age of the participants in the test group was 54.32±6.7 years, while the mean age in the control group was 54.2±8.3 years.

Table 3 Table Representing the Data Extracted From the Articles

First Author	Drug	Gene targeted	Dosage	Route of Administration	Treatment Duration	Outcome (% Change)
Ray et al[10]	Inclisiran	PCSK9	300 mg	SC	540 days	LDL T1: −51.3 C1: 1
			300 mg			LDL T2: −45.8 C2: 4
Ray et al[11]	Inclisiran	PCSK9	300 mg	SC	570 days	LDL T: −38.2 C: −48.6 Total Cholesterol T: 22.9 VLDL T: −10.1
Raal et al[12]	Inclisiran	PCSK9	300 mg	SC	540 days	LDL T: −39.7 C: 8.2
Ray et al[13]	Inclisiran	PCSK9	200 mg	SC	210 days	LDL T1: −27.9 C: 2.1 Total Cholesterol T1: −17.6 C: 1.8 Triglycerides T1: 1.1 C: 6.4 Apolipoprotein T1: −22.9 C: 1.7 VLDL T1: −11.6 C: 2.4
			300 mg			LDL: −38.4 Total Cholesterol: −23.7 Triglycerides: −12.8 Apolipoprotein-30.8 VLDL: −23.8
			500 mg			LDL: −41.9 Total Cholesterol: −26.6 Triglycerides: −12.2 Apolipoprotein: −33.1 VLDL: −14.6
Luo et al[14]	Inclisiran	PCSK9	100 mg	SC	90 days	LDL T1: −49.6 C1: −19.3
			300 mg			LDL: −58.3

(*Continued*)

Table 3 (Continued).

First Author	Drug	Gene targeted	Dosage	Route of Administration	Treatment Duration	Outcome (% Change)
Yamashita et al[15]	Inclisiran	PCSK9	100 mg	SC	360 days	LDL T1: −56.6 C: −0.6 Total Cholesterol T1: −23.8 C: 0.2 Triglycerides T1: −12.4 C: −0.7 Apolipoprotein T1: −42.1 C: −5 VLDL T1: −17.3 C: −0.3
			200 mg			LDL: −60.9 Total Cholesterol: −28.2 Triglycerides: −14.5 Apolipoprotein: −46.7 VLDL: −19.4
			300 mg			LDL: −65.3 Total Cholesterol: −31.6 Triglycerides: −15.7 Apolipoprotein: −49.4 VLDL: −20.6
Kallend et al[16]	Inclisiran sodium	PCSK9	900 mg	SC	180 days	LDL T: −44.8
Kallend et al[17]	Inclisiran	PCSK9	300 mg	SC	60 days	Total Cholesterol T1: −24.0; C: −32.6 Triglycerides T1: 12.6 C: −1.4
			300 mg			Total Cholesterol: −19.7 Triglycerides: −21.2 [Moderate hepatic impairment}
Raal et al[26]	Inclisiran	PCSK9	300 mg	SC	720 days	LDL T: 0.70 C: 2.39

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Table 3 (Continued).

First Author	Drug	Gene targeted	Dosage	Route of Administration	Treatment Duration	Outcome (% Change)
Fitzgerald et al[9]	ALN-PCS	PCSK9	T1: 0.015 mg/kg T2: 0.045 mg/kg T2: 0.045 mg/kg T3: 0.090 mg/kg T4: 0.150 mg/kg T5: 0.250 mg/kg T6: 0.400 mg/kg	IV	180 days	LDL T1: −14.4 T2: −19.3 T3: −30.4 T4: −35.0 T5: −35.5 T6: −36.1 C: −24
Watts et al[18]	ARO ANG3	ANGPT L3	35 mg (day 1)	SC	85 days	LDL T: −22.30 C: −3.74 Total Cholesterol T: −38.2 C: −6.2 Triglycerides T: 18.79 C: 7.53 APOC3 T: −2.372 C: −0.405 VLDL T: 16.56 C: 6.08
			100 mg (day 1)		85 days	LDL: −27.97 Total Cholesterol: −54.5 Triglycerides: −35.36 APOC3: −5.225 VLDL: −32.86
			200 mg (day 1)		85 days	LDL: T3: 4.71 Total Cholesterol: −32.3 Triglycerides: −49.46 APOC3: −7.755 VLDL: −46.12
			300 mg (day 1)		85 days	LDL: −12.88 Total Cholesterol: −49.2 Triglycerides: −51.05 APOC3: −6.418 VLDL: −49.22
			100 mg (day 1, 29)		113 days	LDL: −42.87 Total Cholesterol: −86.8 Triglycerides: −62.33 APOC3: −5.930 VLDL: −59.7

(*Continued*)

Table 3 (Continued).

First Author	Drug	Gene targeted	Dosage	Route of Administration	Treatment Duration	Outcome (% Change)
			200 mg (day 1, 29)		113 days	LDL: −43.62 Total Cholesterol: −90.5 Triglycerides: −72.69 APOC3: −7.198 VLDL: −61.23
			300 mg (day 1, 29)		113 days	LDL: −36.82 Total Cholesterol: −78.8 Triglycerides: −65.42 APOC3: −7.170 VLDL: −62.67
			200 mg (day 1, 29)		113 days	LDL T8: −35.6 C: −9.54 Total Cholesterol T8: −72.3 C: −5.3 Triglycerides T8: −46.5 C: 91.0 Apolipoprotein T8: −1.77 C: −13.63 APOC3 T8: −7.273 C: 1.9 VLDL T8: −10.8 C: 10
Nissen et al[19]	Lepodisiran	LPA	T1: 4 mg T2: 12 mg T3: 32 mg T4: 96 mg T5: 304 mg T6: 608 mg	SC	336 days	Apolipoprotein T1: −41 T2: −59 T3: −76 T4: −90 T5: −96 T6: −97 C: −5
Nissen et al[20]	Zerlasiran	LPA	Single dose: T1: 300 mg T2: 600 mg Multiple doses: T3: 200 mg T4: 300 mg T5: 450 mg	SC	365 days (T1, T2) 201 days (T3, T4, T5)	Apolipoprotein: T1: −30 T2: −29 T3: −60 T4: −90 T5: −89 C1: 14 C2: 0.3

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Table 3 (Continued).

First Author	Drug	Gene targeted	Dosage	Route of Administration	Treatment Duration	Outcome (% Change)
Ballantyne et al[21]	Plozasiran	APOC3	10 mg	SC	336 days	LDL: −4.1 Triglycerides T1: −33.2 C: 1.7 Apolipoprotein: −23.8
			25 mg			LDL: −2.7 Triglycerides: −42.8 Apolipoprotein: −23.8
			50 mg			LDL: −13.6 Triglycerides: −50.2 Apolipoprotein: −9
			50 mg			Triglycerides: −55.0
Gaudet et al[22]	Plozasiran	APOC3	10 mg	SC	336 days	LDL T1: 33.5 C: 21.3 Triglycerides T1: −31.4 C: −6.6 Apolipoprotein T1: −34.3 C: 4.4
			25 mg			LDL: 34.4 Triglycerides: −58.0 Apolipoprotein: −48.1
			50 mg			LDL: 44.6 Triglycerides: −53.4 Apolipoprotein: −46.9
Gerald et al[23]	Plozasiran	APOC3	25 mg	SC	304 days	Triglycerides: T1: −80 C: −17 Apolipoprotein: T1: −87 C: 8
			50 mg			Triglycerides: -78 Apolipoprotein: -88
Rosenson et al[24]	Zodasiran	ANGPTL3	50 mg	SC	252 days	LDL: −12.0 Triglycerides: −34.1 Apolipoprotein: −3.3
			100 mg			LDL: −7.0 Triglycerides: −37.9 Apolipoprotein: −12.2

(*Continued*)

Table 3 (Continued).

First Author	Drug	Gene targeted	Dosage	Route of Administration	Treatment Duration	Outcome (% Change)
			200 mg			LDL: −7.3 Triglycerides: −51.2 Apolipoprotein: −6.0
Gaudet et al[25]	ARO-APOC3	APOC3	10 mg	SC	113 days	LDL T1: −10.7 C: −0.5 Triglycerides T1: −41.2 C: −29.5 Apolipoprotein T1: −55.7 C: −9.0 VLDL T1: −41.3 C: −21.6
			25 mg			LDL: −20.4 Triglycerides: −56.0 Apolipoprotein: −80.8 VLDL: −55.2
			50 mg			LDL: −13.1 Triglycerides: −61.4 Apolipoprotein: −79.6 VLDL: −58.3
			100 mg			LDL: −20.6 Triglycerides: −68.7 Apolipoprotein: −93.8 VLDL: −60.7
Nissen et al[27]	SLN360	Apolipoprotein(a)	30 mg	SC	150 days	LDL T1: 1 C: −4 Total Cholesterol T1: 2 C: −1 Apolipoprotein T1: −46 C: −10
			100 mg			LDL: −21 Total Cholesterol: −9 Apolipoprotein: −86
			300 mg			LDL: −19 Total Cholesterol: −10 Apolipoprotein: −96

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Table 3 (Continued).

First Author	Drug	Gene targeted	Dosage	Route of Administration	Treatment Duration	Outcome (% Change)
			600 mg			LDL: −26 Total Cholesterol: −18 Apolipoprotein: −98
O'Donoghue et al[28]	Olpasiran	LPA	T1: 10 mg T2: 75 mg T3: 225 mg T4: 225 mg	SC	336 days	Apolipoprotein T1: −66.9 T2: −93.8 T3: −97.5 T4: −96.9 C: 3.6

Abbreviations: LDL, Low-density lipoprotein; VLDL, Very low-density lipoprotein; SC, Subcutaneous; IV, Intravenous; PCSK9, Proprotein convertase subtilisin/kexin type 9; ANGPTL3, Angiopoietin-like protein 3; LPA, Lipoprotein(a); APOC3, apolipoprotein C3.

Drugs and Dosages

The drugs used in the studies were Inclisiran, ALN-PCS, ARO ANG3, Lepodisiran, Zerlasiran, Plozasiran, Zodasiran, ARO-APOC3, SLN360, and Olpasiran. The duration of the trials included in this study ranges from 60 days to 720 days.

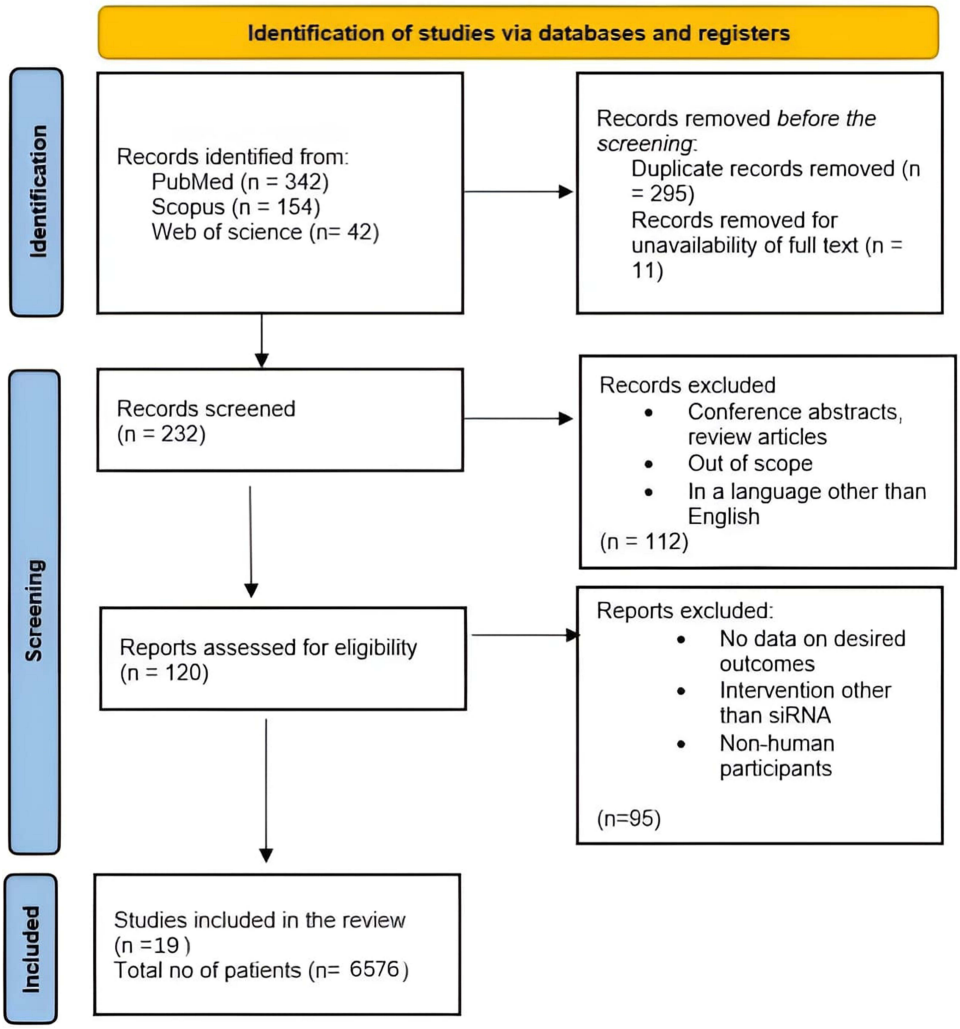

Figure 1 Search results from different databases.

Most of the trials preferred the subcutaneous route ie, 19 of them which makes it 95% of trials, and in only 1 study the venous route was chosen.

Inclisiran has been evaluated in nine clinical studies involving 4873 participants, with a mean follow-up duration of 363.3 days.[10–17,26] The administered doses ranged from 300 mg to 900 mg. The mean reduction in LDL cholesterol levels was dose-dependent, with reported reductions of 53.1% (100 mg), 44.4% (200 mg), 42.0% (300 mg), 41.9% (500 mg), and 44.8% (900 mg). Notably, the reduction in LDL-C was more pronounced compared to total cholesterol, very-low-density lipoprotein (VLDL), triglycerides, and apolipoprotein levels, as detailed in the accompanying Table 4.

ALN-PCS has been evaluated in a single clinical study involving 32 participants over a follow-up period of 180 days.[9] The administered doses ranged from 0.015 mg/kg to 0.4 mg/kg. The mean reduction in LDL-C levels varied between 14.4% and 36%, depending on the dosage. A dose-dependent relationship was observed, with higher doses resulting in greater LDL-C reduction, as shown in the accompanying table.

ARO-ANG3 was evaluated in a single clinical study comprising eight subgroups and a total of 61 participants.[18] Four subgroups followed a single-dose regimen, receiving doses ranging from 35 mg to 300 mg over 85 days. The remaining four subgroups received a double-dose regimen, with 100–300 mg of ARO-ANG3 administered on days 1 and 29, followed by a 113-day follow-up period. Lipid parameter reductions were more pronounced in the double-dose regimen compared to the single-dose regimen, with total cholesterol levels decreasing by 86.8%, 72.69%, and 78.8% for the 100 mg, 200 mg, and 300 mg doses, respectively.

Lepodisiran was assessed in a single study involving 48 participants over a 336-day period.[19] Doses ranged from 4 mg to 608 mg. The reduction in apolipoprotein levels varied between 41% and 97%, with higher doses leading to greater reductions. This dose-dependent effect is illustrated in the accompanying table, Table 3.

Zerlasiran was evaluated in a single clinical study comprising five subgroups and a total of 50 participants.[20] Two subgroups followed a single-dose regimen, receiving 300 mg or 600 mg over 365 days. The remaining three subgroups received a multiple-dose regimen, with 200 mg administered every four weeks and 300 mg or 450 mg administered every eight weeks, over a follow-up period of 201 days. A predominant reduction in apolipoprotein levels was observed, with greater reductions in the multiple-dose regimen compared to the single-dose regimen—60%, 90%, and 89% for the 200 mg, 300 mg, and 450 mg doses, respectively.

Plozasiran has been evaluated in three clinical studies involving a total of 654 participants, with a mean follow-up duration of 325.3 days.[21,22] Administered doses ranged from 10 mg to 50 mg. The mean reduction in triglyceride levels

Table 4 Lipid Profile Variations Across Different Doses of Inclisiran

	LDL	Total Cholesterol	VLDL	Triglycerides	Apolipoprotein
100 mg	T: −53.1% C: −9.95% (n= 2)	T: −23.8% C: 0.2% (n= 1)	T: −17.3% C: −0.3% (n= 1)	T: −12.4% C: −0.7% (n= 1)	T: −42.1% C: −5% (n= 1)
200 mg	T: −44.4% C: 0.75% (n= 2)	T: −22.9% C: 1% (n= 2)	T: −15.5% C: 1.05% (n= 2)	T: −6.7% C: 2.85% (n= 2)	T: −18.7% C: −1.65% (n= 2)
300 mg	T: −42% C: −6.6% (n= 8)	T: −15.22% C: −10.2% (n= 4)	T: −18.17% C: 1.05% (n= 3)	T: −9.2% C: 1.43% (n= 3)	T: −40.1% C: −1.65% (n= 2)
500 mg	T: −41.9% C: 2.1% (n= 1)	T: −26.6% C: 1.8% (n= 1)	T: −14.6% C: 2.4% (n= 1)	T: −12.2% C: 6.4% (n= 1)	T: −33.1% C: 1.7% (n= 1)
900 mg	T: 44.8% (n= 1)	–	–	–	–

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was dose-dependent, that is, 32.3% for 10 mg, 60.3% for 25 mg, and 51% for 50 mg. The decrease in triglyceride concentration was more pronounced compared to other lipid parameters.

Zodasiran was evaluated in a single clinical study involving 204 participants over a 252-day period. Administered doses ranged from 50 mg to 200 mg.[24] The reduction in triglyceride levels was more significant than that of other lipid parameters, with mean decreases of 34.1% for 50 mg, 37.9% for 100 mg, and 51.2% for 200 mg. A dose-dependent effect was observed, with higher doses leading to greater reductions in triglyceride levels.

ARO-APOC3 was evaluated in a single clinical study involving 40 participants over a 113-day period.[25] Administered doses ranged from 10 mg to 100 mg. The reduction in apolipoprotein levels was more pronounced than in other lipid parameters, with mean decreases of 55.7% for 10 mg, 80.8% for 25 mg, 79.6% for 50 mg, and 93.8% for 100 mg. Additionally, the study reported reductions in LDL, triglyceride, and VLDL levels.

SLN360 was evaluated in a single clinical study involving 32 participants over a 150-day period, with subcutaneous doses ranging from 30 mg to 600 mg.[27] The reduction in apolipoprotein levels was more pronounced than in other lipid parameters and demonstrated a dose-dependent effect: 46% for 30 mg, 86% for 100 mg, 96% for 300 mg, and 98% for 600 mg. Additionally, the study reported reductions in LDL and total cholesterol levels at higher doses of SLN360 (100–600 mg).

Olpasiran was evaluated in a single clinical study involving 112 participants, with a mean follow-up duration of 336 days.[28] Administered doses ranged from 10 mg to 225 mg. The mean reduction in apolipoprotein concentration was 66.9% for 10 mg every 12 weeks, 93.8% for 75 mg every 12 weeks, 97.5% for 225 mg every 12 weeks, and 96.9% for 225 mg every 24 weeks.

Outcomes

Seven studies were conducted on individuals with hypercholesterolemia, all of which investigated Inclisiran as the intervention. The participants exhibited a predominant reduction in LDL levels by 44.09%, followed by a decrease in apolipoprotein levels by 37.5%. Additionally, reductions were observed in total cholesterol (−18.37%), VLDL (−16.77%), and triglycerides (−11.08%).

Four studies were conducted on individuals with hyperlipoproteinemia(a), evaluating the effects of Lepodisiran, Zerlasiran, Olpasiran, and SLN360. The participants demonstrated a predominant reduction in apolipoprotein levels by 75.69%, followed by a decrease in LDL levels by 16.25%. Additionally, a reduction of 8.75% was observed in total cholesterol levels.

Two studies investigated the effects of ARO-APOC3 and Plozasiran in individuals with hypertriglyceridemia. The results showed a substantial reduction in apolipoprotein levels by 62.74%, followed by decreases in VLDL levels by 53.9% and triglycerides by 52.87%.

Two studies examined the effects of Zodasiran and Plozasiran in individuals with mixed hyperlipidemia. The findings revealed a prominent reduction in triglyceride levels by 43.48%, followed by a decrease in apolipoprotein levels by 13.01%.

A study was conducted on individuals with chylomicronemia to evaluate the effects of Plozasiran. The results demonstrated a substantial reduction in apolipoprotein levels by 87.5%, followed by a decrease in triglyceride levels by 79%.

Adverse Effects

A comprehensive analysis of 20 global studies shows that RNA interference therapy in dyslipidemia patients faced significant adverse effects. The most common adverse effects include diabetes mellitus (including new-onset diabetes mellitus and worsening diabetes mellitus), affecting 379 participants (13.54%), and injection site adverse effects, reported by 331 participants (6.96%). Nasopharyngitis was noted in 428 participants (7.8%). Other notable adverse effects include hypertension in 95 participants (5.97%), back pain in 127 participants (4.7%), and bronchitis in 63 participants (3.39%). Additionally, 64 participants (3.40%) reported dyspnea and 41 participants (2.15%) had abnormal liver function tests. COVID-19 was reported in 114 cases (13.8%), and pyrexia affected 40 participants (13.70%). Less common adverse effects included myocardial infarction (n=33, 1.80%), stroke (n=13, 0.82%), and increased creatine levels (n=20, 1.26%). Other reported conditions were headache (n=78, 8.7%), urinary tract infections (n=21, 5.01%), and gastrointestinal

effects (n=30, 3.61%). The rare adverse effects included angina (n=5, 1.53%), influenza (n=45, 6.98%), myalgia (n=61, 5.85%), lethargy (n=3, 4.05%), paresthesia (n=5, 8.33%), dysuria (n=5, 12.50%), rash/pruritis (n=17, 15.18%), and dizziness (n=4, 5.56%). Additionally, 43 deaths (1.41%) were noted.

In the control groups, the most common adverse effects were upper respiratory tract infections (9.4%), new onset/worsening diabetes mellitus (8.08%), and hypertension (4.02%). Other notable effects included back pain (2.6%), COVID-19 (2%), injection-related events (1.60%), myocardial infarction (1.45%), osteoarthritis (1.42%), elevated liver enzymes (1.35%), dyspnea (1.31%), influenza (1.35%), and arthralgia (1.31%). Less common adverse effects included bronchitis, headache, increase in creatinine, myalgia, stroke, Urinary tract infections, gastroenteritis, malaise, diarrhea, pyrexia, rash, and angina pectoris. Additionally, 30 deaths (1.06%) were reported.

Discussion

RNAi therapy utilizes siRNA, a ds-RNA, to selectively silence genes. siRNA includes a guide strand that directs the RNA-induced silencing complex (RISC) to degrade target mRNA, achieving gene silencing.[29] Figure 2 represents various siRNA drugs that target lipid synthesis genes. PCSK9 inhibitors (Alirocumab and Evolocumab) bind to free PCSK9, which prevents it from attaching to the LDL receptor. Decreased free PCSK9 results in more LDL receptor recycling, a greater density of LDL receptors on the surface of the hepatocyte, and significant reductions in circulating

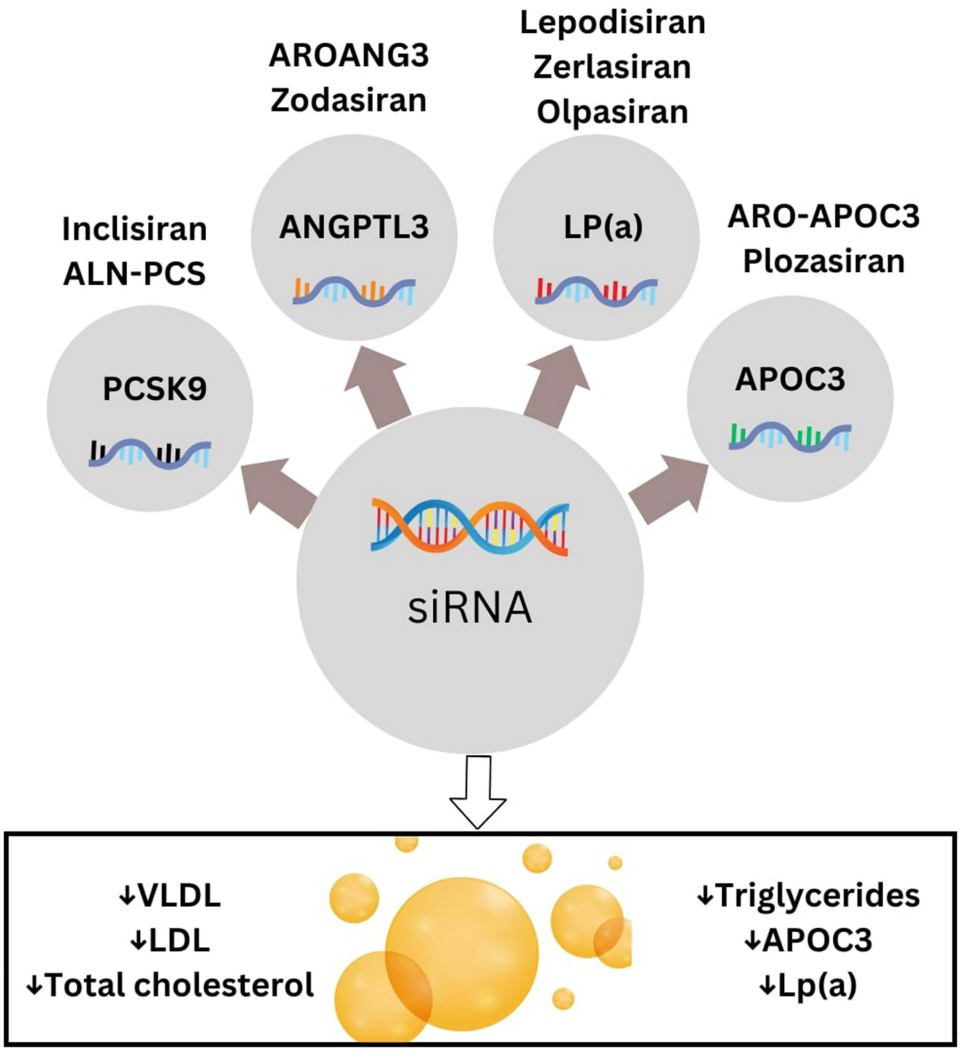

Figure 2 Drugs under siRNA target various lipid synthesis genes.

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LDL-C.[30] Drugs targeting the *PCSK9* gene for dyslipidemia management include Inclisiran and ALN-PCS, both of which have demonstrated a significant reduction in LDL cholesterol levels. Inclisiran, at a 100 mg dose, has been shown to reduce LDL-C by 53.1%, aligning with findings from a meta-analysis by Khan et al, which reported a 51% decrease in LDL cholesterol levels.[31]

The present study identified Lepodisiran, Zerlasiran, and Olpasiran as therapeutic agents targeting the LPA (Lipoprotein (a)) gene. Olpasiran achieved a relative reduction in apolipoprotein(a) levels by 99.6%, followed by Lepodisiran at 97%, and Zerlasiran at 90%, at their highest doses. Additionally, SLN360, which targets the Apo(a) gene, resulted in a 98% relative reduction in apolipoprotein(a) levels compared to the placebo group.

Apo C3 is a liver and intestine-synthesized glycoprotein that decreases triglyceride-rich lipoprotein (TRL) metabolism and hepatic uptake by inhibiting the lipoprotein lipase (LPL), hence increasing the serum level of circulating chylomicrons and other TRL (Triglyceride rich lipoproteins).[22] The expression of APOC3 can be reduced by gene silencing of APOC3 RNA and one such small interfering RNA (siRNA) is Plozasiran which is conjugated with N-Acetylgalactosamine.[21] ARO-APOC3 and Plozasiran are RNAi therapies targeting Apolipoprotein C3 (APOC3) that have been evaluated for their effects on lipid levels. Plozasiran demonstrated a more pronounced reduction in triglyceride levels, with a 51.8% decrease at the highest dose, consistent with findings from a meta-analysis by Hasan et al, which reported a 50.57% reduction in triglyceride levels.[32]

Similarly, Angiopoietin-Like 3 (ANGPTL3) is a regulator of lipoprotein and lipid metabolism, which acts by reversibly inhibiting the LPL, endothelial lipase, and LDL receptor-independent hepatic lipoprotein uptake.[24] Decreased expression of ANGPTL3 leads to enhanced LPL and Endothelial lipase activity and decreased TRL levels. The messenger RNA for ANGPLT3 is another target for gene silencing therapies. Both ARO ANG3 and Zodasiran, which target ANGPTL3, demonstrated significant lipid-lowering effects in their respective test groups. Zodasiran also led to notable reductions in lipid levels within its test group, though the effects were generally less pronounced compared to ARO ANG3. These results underscore the effectiveness of both ARO ANG3 and Zodasiran in lowering LDL, triglycerides, and other key lipid parameters by targeting ANGPTL3, with ARO ANG3 showing a powerful impact. Solbinsiran, a novel siRNA therapeutic targeting ANGPTL3, has demonstrated a significant reduction in ANGPTL3, triglycerides (TG), non-HDL cholesterol (non-HDL-C), and apolipoprotein B (apoB) levels in the latest randomized controlled trial (RCT) conducted by Ray et al.[33]

Statins, or HMG-CoA Reductase Inhibitors, are among the most widely used drugs worldwide and are the cornerstone of treatment for hypercholesterolemia. However, Statin intolerance (SI) and discontinuation of treatment have been an ongoing concern, with a worldwide prevalence of 9.1%.[34] A few factors associated with SI are older, female patients, Asian or African-American race, diabetes, obesity, chronic liver and renal disease, alcohol use, and hypothyroidism. Higher doses of statin and concomitant use of antiarrhythmic agents also implicated a higher risk. The intolerance stems from statin-associated muscle symptoms, including myalgia, myopathy, myositis, with or without elevation of creatine kinase, and even rhabdomyolysis. Few studies also acknowledge the side effects of tendinopathies, arthralgias, and transaminitis. Another rare side effect includes Statin-Induced Necrotizing Autoimmune Myopathy (SINAM), which presents with proximal muscle weakness and marked CK elevation.[35] Unlike other statin-associated myopathies, SINAM persists even after discontinuation of the drug and may cause irreversible muscle damage without immunosuppressive therapy.

The current systematic review on RNA interference therapy reported 43 deaths (1.41%) among the test participants. The 5 most common adverse effects reported were nasopharyngitis, diabetes mellitus (including new-onset diabetes mellitus and worsening diabetes mellitus), injection site adverse effects, back pain, and hypertension. Some of the adverse effects reported with other anti-hyperlipidemic drugs like statins include muscle symptoms like myalgia (mostly from rosuvastatin), myopathy, and rhabdomyolysis,[36,37] liver dysfunction primarily from atorvastatin and lovastatin; renal insufficiency, and eye conditions (cataracts). Compared to pitavastatin, atorvastatin, and rosuvastatin exhibited a greater risk of diabetes.[36] Fibrates are associated with an increase in creatinine levels, increased altered liver function tests, and an increase in pancreatitis. Patients using bile acid sequestrants are more likely to complain of constipation, while those taking niacin are more likely to experience flushing, diabetes, gastrointestinal and musculoskeletal problems, pruritus, and rash. The risk of atrial fibrillation is increased in patients taking docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).[37] These adverse effects associated with other lipid-lowering drugs are relatively absent

or minimal in RNAi therapy, underscoring its significance as a safer and more targeted approach in the management of hyperlipidemia.

The therapeutic use of RNAi therapy is limited by several challenges. Some of these are potential off-target effects and the induction of innate immune responses, which can result in the release of cytokines and other immune reactions.[38,39] The targeted transport of RNA interference (RNAi) molecules into the cytoplasm of target cells constitutes a significant challenge, further complicated by their susceptibility to nuclease-mediated degradation and unfavorable physicochemical characteristics.[39,40] In addition, these molecules have difficulties with endosomal escape, short half-lives, fast clearance rates, and systemic stability.[41] Their delivery is made more complicated by their inability to cross vascular endothelium and break through cell membranes. As demonstrated by the withdrawal of multiple clinical trials over safety concerns, these problems indicate the necessity of delivery technologies and chemical modifications to improve stability, facilitate localization, and guarantee successful intracellular delivery.[38]

Limitations

This systematic review has several limitations that should be acknowledged. First, the scarcity of adequate articles on RNA interference therapy in dyslipidemia limits the availability of evidence. Second, incomplete or missing data in some of the included studies posed challenges in conducting a thorough analysis, potentially affecting the accuracy of the findings. Lastly, the heterogeneity between studies, including variations in study design, patient populations, treatment protocols, and outcome measures, complicates the comparability of results and reduces the overall generalizability of the conclusions drawn from this review.

Conclusion

Inclisiran was studied in individuals with hypercholesterolemia, showing significant reductions in LDL, apolipoproteins, total cholesterol, VLDL, and triglycerides. Various RNA therapies were evaluated for hyperlipoproteinemia(a), with notable decreases in apolipoproteins, LDL, and total cholesterol. Studies on hypertriglyceridemia and mixed hyperlipidemia demonstrated reductions in apolipoproteins, triglycerides, and VLDL. In chylomicronemia, Plozasiran significantly lowered apolipoproteins and triglycerides. Besides, these therapies have the advantage of biannual dosing and hence offer better adherence compared to the daily regimen needed with statins. However, some patients developed severe side effects, including diabetes, injection site reactions, and respiratory infections, with a reported 1.41% mortality rate among participants, which pointed out the continuous monitoring required for these patients. Further research should soon focus on the refinement of methods of RNAi delivery, the reduction of side effects, and working on broader applications regarding the management of lipids while ensuring its safety and efficacy in a larger population of patients.

Disclosure

The authors declare no conflicts of interest in this work.

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