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SUMMARY WITH CRITICAL APPRAISAL

PCSK-9 Inhibitors for Hyperlipidemia: A Review of the Comparative Clinical Effectiveness

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Context and Policy Issues

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality.[1-3] In 2012, the World Health Organization (WHO) estimate of death due to CVD was 17.5 million, which represented 31% of all deaths world-wide.[1] There is a substantial societal and economic burden associated with CVD. In Canada, the 2005 estimate for the total cost of the health care resources used and lost productivity related to CVD was C$20.9 billion.[2] This estimate is predicted to increase to C$28.3 billion in 2020.[2]

Hyperlipidemia, which includes hypercholesterolemia, is one of the risk factors for developing CVD.[1,4,5] Familial hyperlipidemia (FH) is an autosomal genetic disorder characterized by very high levels of low density lipoprotein cholesterol (LDL-C) and results in increased cardiovascular risk by up to 20-fold.[6] The two types of FH, include heterozygous FH (HeFH) and homozygous FH (HoFH), which is the more severe type. In Canada, HeFH affects approximately 1 in 500, and HoFH affects approximately 1 in 1,000,000.[6] These numbers are likely underestimated, as many with FH are undiagnosed.[6]

Management of individuals with CVD, or those at risk of CVD, includes life-style changes and appropriate treatment. Treatment includes medication to control cholesterol levels, specifically LDL-C. Statins, which are 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors, have been widely used for controlling cholesterol levels. Also, ezetimibe which inhibits intestinal absorption of cholesterol, has been used alone or in combination with statins for controlling cholesterol levels.[7] However, other treatment options are needed for patients who are intolerant to statin therapy, develop CVD even though on maximal statin therapy, or have severe hypercholesterolemia.[4] Recently, two monoclonal antibodies (alirocumab and evolocumab) that can reduce LDL-C have been marketed. These agents are proprotein convertase subtilisin kexin type 9 (PCSK-9) inhibitors. PCSK-9 is a hepatic protease that attaches to low density lipoprotein (LDL) receptors, which then are internalized into lysosomes and destroyed.[4] As a result, the LDL receptors are no longer available to bind and remove the circulating LDL-C causing LDL-C levels to rise.[8] Inhibition of PCSK-9 increases the number of LDL receptors on the cell surface and increases removal of LDL-C.[3]

Alirocumab and evolocumab are expensive drugs (annual cost per patient > Can $7,000)[2,9] and there appears to be uncertainty around the comparability of these two drugs with respect to the appropriate treatment option for the appropriate patient group. Evidence on comparative effectiveness of these two drugs is needed to assist in coverage policy decisions. The purpose of this report is to review the comparative clinical effectiveness of evolocumab versus alirocumab for the treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease, and who are on maximally tolerated statin therapy and require additional lowering of LDL-C.

Research Questions

1. What is the comparative clinical effectiveness of evolocumab versus alirocumab for the treatment of adults with heterozygous familial hyperlipidemia (HeFH) on maximally tolerated statin therapy who require additional lowering of low density lipoprotein cholesterol (LDL-C)?

2. What is the comparative clinical effectiveness of evolocumab versus alirocumab for the treatment of adults with clinical atherosclerotic cardiovascular disease (CVD) on maximally tolerated statin therapy who require additional lowering of low density lipoprotein cholesterol (LDL-C)?

Key Findings

A single non-randomized study reporting on comparative effects of alirocumab and evolocumab was identified. Considering the limitations of the study, no definitive conclusion on the comparative clinical effectiveness of alirocumab versus evolocumab in patients with heterozygous familial hyperlipidemia or cardiovascular disease was possible

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Medline, Embase, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and May 2, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened titles and abstracts and selected potentially relevant articles for retrieval. A second reviewer assessed the full-text articles for inclusion. The final selection of full-text articles was based on the inclusion criteria in Table 1.

Table 1: Selection Criteria

Population	Q1: Adults with heterozygous familial hyperlipidemia (HeFH) on maximally tolerated statin therapy who require additional lowering of low density lipoprotein cholesterol (LDL-C) Q2: Adults with clinical atherosclerotic cardiovascular disease (CVD) on maximally tolerated statin therapy who require additional lowering of low density lipoprotein cholesterol (LDL-C)
Intervention	Evolocumab
Comparator	Alirocumab
Outcomes	Clinical effectiveness, including: • Mortality • Morbidity (cardiovascular-related; i.e., cardiovascular events, hospitalizations, minimally-invasive cardiovascular interventions (e.g., percutaneous coronary intervention [PCI]) • Changes in LDL-C • Quality of life (HRQoL) • Health care resource utilization • Vascular imaging • Other laboratory parameters (i.e., apolipoprotein B [Apo-B], lipoprotein A [LP-A], non-high density lipoprotein cholesterol [Non-HDL-C], triglyceride [TG], very low density lipoprotein cholesterol

	[VLDL-C]) Harms outcomes (e.g., adverse events, serious adverse events, withdrawal due to adverse events; notable harms include: immune reactions, injection site reactions, muscle symptoms, neurocognitive impairment, Hepatitis C, elevated liver enzymes)
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), and non-randomized studies (NRS)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012.

Critical Appraisal of Individual Studies

The included non-randomized study was critically appraised based on the Downs and Black checklist.[10] Summary scores were not calculated for the included study; rather, a review of the strengths and limitations of the included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 474 citations were identified in the literature search. Following screening of titles and abstracts, 458 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 16 publications were excluded for various reasons, while one publication met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection. The included publication was a non-randomized study.[11]

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Characteristics of the included study are summarized below and details are available in Appendix 2, Table 3.

Study Design

One relevant non-randomized, single-center, open-label study[11] was identified. It was a prospective study following marketing of alirocumab and evolocumab. The median follow-up was 24 weeks.

Country of Origin

The included study was published in 2017 from the USA.

Patient Population

Seventy two patients, with HeFH and/or CVD with suboptimal LDL-C levels despite maximal tolerated cholesterol lowering therapy, including statin doses down to zero, were enrolled in the study. Of the 72 patients, 25 (35%) patients had HeFH, 25 (35%) patients had CVD, and 22 (31%) patients had both HeFH and CVD. These patients had been referred to a regional cholesterol center for diagnosis and treatment of

hypercholesterolemia. Patients were of median age 65 years; 63% were female, 86% were Caucasian, 17% had diabetes, 7% smoked and 63% were on anti-hypertensive medication.

Interventions and Comparators

The interventions compared included alirocumab 75 mg, alirocumab 150 mg, and evolocumab 140 mg.[11]

Outcomes

Outcomes included levels of LDL-C, total cholesterol, triglyceride, and high density lipoprotein cholesterol (HDL-C).[11] Also CVD risks for the next 10 years were calculated using both the American Heart Association (AHA) calculator and the National Institutes of Health (NIH) calculator.[11] Adverse events were also reported. However, only findings for LDL-C levels were reported separately for each of the drugs and each of the patient categories.

Summary of Critical Appraisal

Critical appraisal of the included study is summarized below and details are available in Appendix 3, Table 4.

In the included study[11] the objective was stated, the interventions and outcomes were described, there appeared to be no withdrawals, and the authors mentioned that there were no conflicts of interest. The study provided real world data. The study was a non-randomized, open-label study, hence the potential for selection bias and observer bias cannot be ruled out. Inclusion and exclusion criteria were not stated. Sample size determination does not appear to have been undertaken. Sample sizes for a specific treatment group and specific patient groups were small, ranging between three and 16 participants. Patient characteristics of the subgroups were not described separately hence it was unclear if the characteristics were well balanced between the subgroups.

Summary of Findings

What is the comparative clinical effectiveness of evolocumab versus alirocumab for the treatment of adults with heterozygous familial hyperlipidemia (HeFH) on maximally tolerated statin therapy who require additional lowering of low density lipoprotein cholesterol (LDL-C)?

One relevant non-randomized study[11] involving patients with HeFH was identified. Median follow-up was 24 weeks. Of the 25 patients with HeFH, the proportions of patients achieving LDL-C level <70 mg/dl were 2/5 (40%) with alirocumab 75mg, 2/4 (50%) with alirocumab 150 mg, and 8/16 (50%) with evolocumab 140 mg.

Of the 22 patients with HeFH and CVD, the proportions of patients achieving LDL-C level <70 mg/dl were 5/6 (83%) with alirocumab 75mg, 6/8 (75%) with alirocumab 150 mg, and 3/8 (38%) with evolocumab 140 mg (Table 2). Levels for HDL-C, total cholesterol, and triglyceride; CVD risk assessments; and adverse events were reported for the entire patient population for each intervention and not reported separately for the different patient subgroups (HeFH only, CVD only, and HeFH plus CVD) hence those findings are not presented here but are available in Appendix 4, Table 5. Common adverse events with these interventions included flu-like myositis, respiratory tract infection or symptoms, and injection site reaction. It was reported that for adverse events, there were no significant differences among the three treatment groups ($P > 0.05$).

What is the comparative clinical effectiveness of evolocumab versus alirocumab for the treatment of adults with clinical atherosclerotic cardiovascular disease (CVD) on maximally tolerated statin therapy who require additional lowering of low density lipoprotein cholesterol (LDL-C)?

One relevant non-randomized study[11] on patients with CVD was identified. Of the 25 patients with CVD, the proportions of patients achieving LDL-C level <70 mg/dl (<1.81 mmol/L) were 12/14 (86%) with alirocumab 75mg, 3/3 (100%) with alirocumab 150 mg, and 7/8 (88%) with evolocumab 140 mg (Table 2). Levels for HDL-C, total cholesterol, and triglyceride; CVD risk assessments; and adverse events were reported for the entire patient population for each intervention and not reported separately for the different patient subgroups (HeFH only, CVD only, and HeFH plus CVD) hence those findings are not presented here but are available in Appendix 4, Table 5. Common adverse events with these interventions included flu-like myositis, respiratory tract infection or symptoms, and injection site reaction. It was reported that for adverse events, there were no significant differences among the three treatment groups ($P > 0.05$).

Table 2: Patients who had achieved at least one measurement of LDL-C < 70 mg/dl

Patient group	LDL-C (mg/ dl) level at study entry, 50th percentile (25th percentile, 75th percentile)	Proportion (%) of patients achieving LDL-C < 70 mg/dl		
		Alirocumab 75mg every 2 weeks	Alirocumab 150mg every 2 weeks	Evolocumab 140 mg every 2 weeks
HeFH, (N = 25)	177 (149, 220)	2/5 (40%)	2/4 (50%)	8/16 (50%)
HeFH + CVD, (N = 22)	169 (122, 214)	5/6 (83%)	6/8 (75%)	3/8 (38%)
CVD, (N = 25)	131 (104, 148)	12/14 (86%)	3/3 (100%)	7/8 (88%)
All, (N = 72)	149 (123, 193)	19/25 (76%)	11/15 (73%)	18/32 (56%)

CVD = cardiovascular disease; HeFH = heterozygous familial hyperlipidemia; LDL-C = low density lipoprotein cholesterol

Limitations

The included study is a non-randomized study hence selection bias cannot be ruled out. The authors mentioned that insurance formulary coverage was considered when deciding whether to use alirocumab or evolucumab. It's unclear whether this consideration may have influenced the findings.

The study was relatively small (N = 72) and hence the number of patients in each of the subgroups (HeFH only, CVD only, and HeFH plus CVD) was considerably reduced. Though subgroup analysis was conducted, these subgroups had not been determined a priori.

The characteristics of the patients in each patient subgroup and intervention group were not presented hence it was unclear how comparable they were. Hence it was unclear if there were any differences in patient characteristics that could impact the findings.

This study reported on a surrogate outcome (LDL-C) and not on clinical outcomes such as cardiovascular events. It was not designed to detect such outcomes. The median follow-up was 24 months hence the comparability of these agents in the long-term are unclear. Long term studies are needed to evaluate the effect of these drugs on cardiovascular events.

The included study was conducted in the USA, hence generalizability of the findings to the Canadian setting is unclear.

Conclusions and Implications for Decision or Policy Making

One relevant non-randomized study[11] was identified. No relevant health technology assessment, systematic review, or randomized controlled trial was identified. In the HeFH group, the percentage of patients who had achieved at least one measurement of LDL-C < 70 mg/dl was same (50%) with both evolocumab140 mg and alirocumab 150mg and less (40%) for alirocumab 75mg. In the CVD group, the percentage of patients who had achieved at least one measurement of LDL-C < 70 mg/dl was similar (88%, 86% respectively) with evolocumab140 mg and alirocumab 75mg and higher (100%) with alirocumab 150 mg. However, the statistical significance and the clinical significance of these findings were unclear. It should also be noted that the number of patients for a specific condition (HeFH or CVD) and treated with a specific drug (alirocumab or evolocumab) was small ranging between three and 16 participants. The findings need to be interpreted in the context of the limitations.

The relevant evidence was available from a single non-randomized study; furthermore considering the limitations of the study, definitive conclusions on the comparative clinical effectiveness of alirocumab versus evolocumab in patients with HeFH or CVD, were not possible.

While the focus of this review was on direct comparisons between alirocumab and evolocumab, due to the sparsity of data on this comparison evidence from systematic reviews[3,8,12,13] on alirocumab and evolocumab compared with placebo or another drug such as ezetimibe may be of interest.

One HTA report,[12] which included a systematic review, evaluated the clinical effectiveness of PCSK-9 inhibitors (alirocumab and evolocumab) as a class compared to placebo or ezetimibe, for patients with elevated LDL-C. It also reported findings stratified by dose and type of PSCK-9 inhibitor. This HTA included 25 studies (phase 2 or phase 3), involving overall 10,159 patients. It showed that compared with placebo, the reductions in LDL-C were 52.6% with alirocumab 75 mg every two weeks, 56.2% with alirocumab 150 mg every two weeks, 63.5% with evolocumab 140 mg every two weeks, and 57.3% with evolocumab 420 mg every four weeks. Compared with ezetimibe, the reductions in LDL-C were 31.7% with alirocumab 75 mg every two weeks, 39.3% with evolocumab 140 mg every two weeks, and 37.5% with evolocumab 420 mg every four weeks. The HTA mentioned that LDL-C reduction may be slightly greater with evolocumab than alirocumab but the difference was small and potentially due to differences in the patient populations. It was mentioned that with the lack of head-to-head trials, it was not possible to conclude if one PCSK-9 inhibitor had an advantage over the other.

The systematic review by Gouni-Berhold et al.[3] assessed the efficacy and safety of PCSK-9 inhibitors (alirocumab and evolocumab) compared with placebo or ezetimibe and included 12 studies on alirocumab and nine studies on evolocumab, involving overall 10,000 patients. It reported that up to 87% of patients receiving alirocumab and up to 98% of patients receiving evolocumab achieved the LDL-C goals. These findings were based on comparisons across trials with variations in the patient population, methodologies and follow up durations, hence need to be interpreted with caution.

The systematic review by Mueller et al.[8] included 12 phase 3 RCTs comparing alirocumab or evolocumab with placebo or ezetimibe. It was mentioned in this systematic review that with evolocumab there seemed to be slightly higher percentage reduction in LDL-C but greater adverse effects, especially in the upper respiratory tract.

The systematic review by McDonagh et al.[13] included 17 studies comparing alirocumab or evolocumab with placebo or ezetimibe, and numbers of patients ranging between 49 and 4,465. This systematic review concluded that both alirocumab and evolocumab resulted in improvements in lipid levels; the level of evidence varied depending on the patient population. In patients with high cardiovascular risk who were not at the LDL-C target level, the strength of evidence was greater for alirocumab than evolocumab, whereas in patients with HeFH and patients with varied cardiovascular risk, who were not at the LDL-C target level the strength of evidence was stronger for evolocumab than alirocumab. Details are available in Appendix 5, Table 6. Evidence on adjudicated cardiovascular outcomes did not seem to demonstrate benefit with alirocumab and for evolocumab the evidence was insufficient to draw any conclusion. The authors cautioned that the comparability of these agents with respect to long term effects is unclear.

There was considerable overlap in the studies included in these systematic reviews hence findings are not exclusive.

While many available studies focus on reduction of LDL-C, there is some evidence that reduction in LDL-C levels does not always translate into greater reduction in cardiovascular outcomes.[12] In one RCT with 15,000 patients, torcetrapib decreased LDL-C levels by 25% but increased cardiovascular events by 25% and total mortality by 58%.[12] On the other hand, the IMPROVE-IT trial with a median follow-up of five years showed that ezetimibe lowered LDL-C levels and reduced cardiovascular events by 6% (95% CI 1% to 11%).[12] However, treatment with statins which reduce LDL-C levels, has been associated with decreased risk of cardiovascular mortality.[14] Studies designed with cardiovascular events as primary outcomes will determine if lowering LDL-C levels results in reduced cardiovascular events. Examples of such studies include, the FOURIER study (NCT 01764633) and the ODYSSEY-OUTCOMES study (NCT 01663402).[15] The FOURIER study on evolocumab was recently published.[16] In the FOURIER study the median duration of follow up was 2.2 years and the primary outcome was major cardiovascular events, defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The study showed that compared with placebo, evolocumab statistically significantly reduced the risk of the primary outcome (hazard ratio [HR] 0.85; 95% confidence interval [CI], 0.79 to 0.92; [*P* <0.001]). For other outcomes (not the primary outcome), compared with placebo, evolocumab statistically significantly reduced the risk of stroke (HR, 0.79, 95% CI, 0.66 to 0.95; *P* = 0.01) but the difference between the evolocumab and placebo groups was not statistically significant for risk of cardiovascular death (HR, 1.05; 95% CI, 0.88 to 1.025); *P* =0.62). The ODYSSEY-OUTCOMES study on alirocumab is ongoing and is expected to be completed in December 2017.[17] Results from these studies will provide a better insight into the clinical efficacy of these PCSK-9 inhibitors. Long term studies with PCSK-9 inhibitors are also needed to determine adverse effects such as neurocognitive impairment and cancer, which may not be evident in short-term studies.

Currently, with the available evidence, it is not possible to definitively conclude if one PCSK-9 inhibitor has an advantage over the other.

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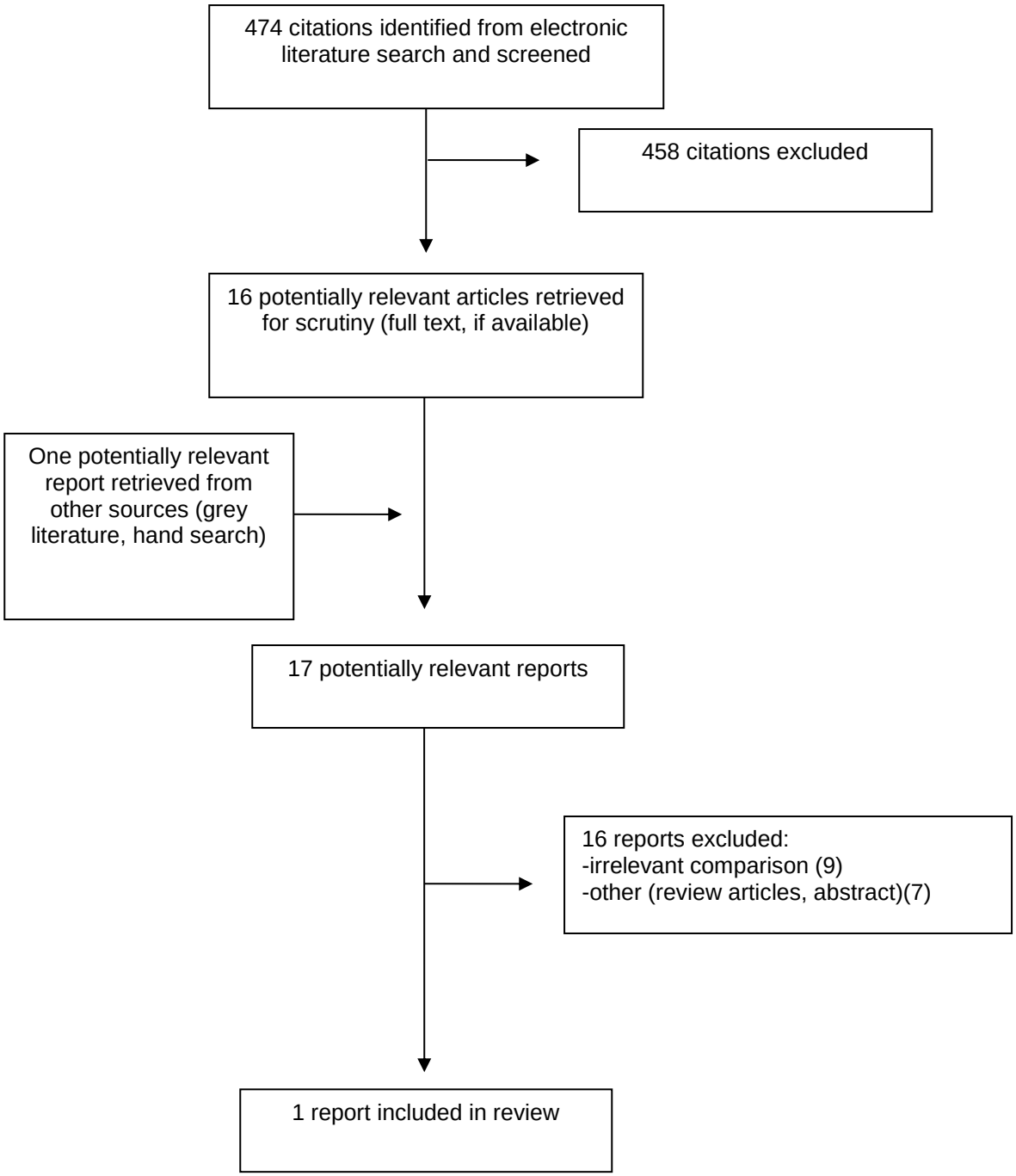
Abbreviations

AHA	American Heart Association
CVD	cardiovascular disease
FU	follow-up
HDL	high density lipoprotein
HDL-C	high density lipoprotein cholesterol
HeFH	heterozygous familial hyperlipidemia
HoFE	homozygous familial hyperlipidemia
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
Mg	milligram
NIH	National Institute of Health
PCSK-9	proprotein convertase subtilisin kexin type 9
RR	relative risk
SD	standard deviation
WHO	World Health Organization

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 3: Characteristics of Included Clinical Studies

First author, Year, Country	Study Design	Population characteristics	Comparison	Outcome, Follow-up
Shah,[11] 2017, USA	Nonrandomized study (post-commercialization study). Insurance formulary coverage was taken into account In deciding on whether to treat with alirocumab or evolocumab, If at entry, LDL-C ≤130 mg/dl, alirocumab 75 mg was used and for LDL-C >130 mg/ml alirocumab 150 mg was used. Evolocumab 140 mg was used for any LDL-C level at study entry	Patients with HeFH and/or CVD with suboptimal LDL-C levels despite maximal tolerated cholesterol lowering therapy, including statins dose down to zero. HeFH was determined by presence of tendon xanthomas and LDL-C ≥190mg/dl, and/or personal or family history of premature CVD, and/or history of severe hypercholesterolemia. CVD was defined as carotid artery disease, history of stroke/TIA, coronary artery disease, congestive heart failure associated with CVD, and peripheral vascular disease. N = 72 (25 with HeFH, 25 with CVD, and 22 with HeFH + CV) Age (median) (years): 65 % Female: 63% Statin intolerant: 58% Treatment before starting study drugs: 16 patients on statin, 5 patients on statin+ ezetimibe, 2 patients on statin+ colesevelam, 7 patients on statin+ ezetimibe+ colesevelam, 11 patients on ezetimibe and/or colesevelam, and 31 patients on nothing	Alirocumab - 75mg, vs Alirocumab - 150mg, vs Evolicumab -140 mg. All agents were administered every two weeks. These agents were given in addition to the maximal tolerated cholesterol lowering treatments which patients were already receiving. prior to study entry	LDL- C, HDL-C. total cholesterol, and triglyceride levels; and adverse events. Only LDL-C levels were reported separately for the three different subgroups (HeFH only, CVD only, and HeFH + CVD) Follow-up (median): 24 weeks

CVD = cardiovascular disease;

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Non-randomized Studies using Downs and Black checklist

Strengths	Limitations
Shah,[11] 2017, USA	
• The objective was clearly stated • Interventions and outcome were described. • There appeared to be no withdrawals • *P*-values were reported in some cases but not for the subgroups that are relevant for this report • The authors mentioned that there was no conflict of interest	• Non-randomized, open-label study. • The inclusion and exclusion criteria were not stated • Patient characteristics were described for the entire patient population not for the different subgroups that are relevant for this report.. • Unclear if adequate sample size was used; it was unclear if sample size had been determined.

Appendix 4: Main Study Findings and Author's Conclusions

Table 5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Shah,[11] 2017, USA	

Cholesterol and triglyceride levels in patients with HeFH and/or CVD with alirocumab and evolocumab treatments

Parameter	Time point or *P* value[a]	Effect size (mg/ dl), 50th percentile (25th percentile, 75th percentile)		
		Alirocumab 75mg, FU = 24 weeks, N = 25	Alirocumab 150mg, FU = 26 weeks, N = 15	Evolocumab 140mg, FU = 24 weeks, N = 32
LDL-C	At entry	117 (100, 143)	175 (133, 214)	165 (143, 211)
	At FU	62 (47, 84)	57 (49, 86)	69 (46, 109)
	P value[a]	<0.0001	<0.0001	<0.0001
	Change (%)	-54 (-27 to -63)	-63 (-72 to -56)	-63 (-40 to -71)
	P value[b]	<0.0001	<0.0001	<0.0001
HDL-C	At entry	53 (41, 61)	51 (40, 57)	56 (45, 68)
	At FU	51 (40, 65)	52 (44, 65)	58 (47, 75)
	P value[a]	0.070	0.0075	0.0028
Total cholesterol	At entry	192 (172, 231)	259 (227, 294)	252 (222, 299)
	At FU	155 (118, 177)	145 (114, 181)	157 (117, 203)
	P value	<0.0001	<0.0001	<0.0001
Triglyceride	At entry	135 (96, 173)	160 (124, 317)	145 (101, 167)
	At FU	106 (80, 154)	105 (76, 161)	106 (80, 142)
	P value[a]	0.0051	0.0015	0.0069

FU = follow-up
[a]*P* value (Paired Wilcoxon)
[b]P value (Wilcoxon)

Evaluation of CVD risk changes with alirocumab and evolocumab treatments using different tools

Evaluation of CVD risk over the next 10 years using a calculator	Time point or *P* value[a]	Risk estimate (%), 50th percentile (25th percentile, 75th percentile)		
		Alirocumab 75mg, FU = 24 weeks, N = 25	Alirocumab 150mg, FU = 26 weeks, N = 15	Evolocumab 140mg, FU = 24 weeks, N = 32
Using the AHA calculator	At entry	6.2 (3.9, 18.0)	9.3 (5.4, 20.4)	11.5 (4.3, 18.6)
	At FU	6.2 (3.3, 10.1)	7.0 (2.3, 15.1)	6.7 (2.9, 20.2)
	P value	0.0001	0.0043	<0.0001
Using the NIH calculator	At entry	11.2 (6.8, 19.8)	17.2 (10.6, 25.7)	17.4 (9.6, 26.4)
	At FU	7.4 (4.3, 11.7)	6.5 (5.1, 12.3)	8.0 (5.3, 12.0)
	P value	<0.0001	0.0001	<0.0001

AHA = American Heart Association, CVD = cardiovascular disease, FU = follow-up, NIH = National Institute of Health
[a]*P* value (Paired Wilcoxon)

Common adverse events in the three treatment groups

Adverse event	Alirocumab 75mg, FU = 24 weeks, (N =	Alirocumab 150mg, FU = 26 weeks, (N =	Evolocumab 140mg, FU = 24 weeks, (N =

"In patients with HeFH and/or CVD, LDLC was lowered by 63% on EVO and ALI 150 mg, and 54% on ALI 75 mg. Adverse events were minimal and tolerable. ALI and EVO represent paradigm shifts in LDLC lowering. Long term, post-commercial safety and efficacy remain to be determined." Page 2 of 12

Main Study Findings				Author's Conclusion
	25)	15)	32)	
Flu-like myositis	1 (4%)	5 (33%)	2 (6%)	
Respiratory tract infection or symptoms	1 (4%)	1 (7%)	4 (13%)	
Injection site reaction	1 (4%)	1 (7%)	6 (6%)	
Any adverse events	5 (20%)	7 (47%)	10 (31%)	
FU = follow-up				

AHA = American Heart Association; ALI = alirocumab; CVD = cardiovascular disease; EVO = evolocumab; FU = follow-up; HeFH = heterozygous familial hyperlipidemia; NIH = National Institute of Health

Appendix 5: Systematic Review[13] not Satisfying the Inclusion Criteria but with Information of Potential Interest

Table 6: Findings from the Systematic review[13]

Comparison	Study, Patient Number (N), Endpoint	PCSK 9 Inhibitor Dose, Concomitant Lipid Therapy, Baseline LDL-C	Difference in LDL-C change, *(level of evidence)*[a]	Difference in % Achieving LDL-C target, *(level of evidence)*[a]	Harms, *(level of evidence)*[a]
Population: HeFH					
Ali vs placebo	2 RCTs, N = 99, 12 weeks	Ali: 150 mg, 200 mg, or 300 mg every 4 weeks or 150 mg every 2 weeks, High-dose statin (51.0%-77.0%) + ezetimibe, 151-170 mg/dL,	-8.0% to -57.4%, *(low)*	NR	*(insufficient)*
Evo vs placebo	2 RCTs, N = 499, 12 weeks	Evo: 140 mg every 2 weeks to 420 mg every 4 weeks, High-intensity statin (89.7%) + ezetimibe, 150-155 mg/dL	-44.1% to -61.3%, *(high)*	NR	No differences for overall AEs (55.0%-66.1% vs. 43.0%-58.9%; pooled RR = 1.12; 95% CI = 0.94-1.33), SAEs (3.0%-4.0% vs. 4.0%-5.0%; pooled RR = 0.81; 95% CI = 0.28-2.33), and injection-site reactions (6.3% vs. 3.6%; pooled RR = 0.76; 95% CI = 0.76-5.21). *(insufficient)*
Population: varied CV risk (LDL-C targets <100 mg/dL [2.59 mmol/L] or <70 mg/dL [1.18 mmol/L] not achieved)					
Ali vs placebo	2 RCTs, N = 124, 10 weeks	Ali: 150 mg every 2 weeks, Statin, range of doses (0.0%-66.3%), 123-124 mg/dL	-49.0% to -67.0%, *(low)*	LDL < 100 mg/dL: 100.0% vs. 16.1% to 52.0% (150 mg every 2 weeks), *(low)*	*(insufficient)*
Evo vs placebo	2 RCTs,	Evo: 420 mg every	52 weeks: -57.0%	52 weeks: LDL	52 weeks: no

Comparison	Study, Patient Number (N), Endpoint	PCSK 9 Inhibitor Dose, Concomitant Lipid Therapy, Baseline LDL-C	Difference in LDL-C change, *(level of evidence)*[a]	Difference in % Achieving LDL-C target, *(level of evidence)*[a]	Harms, *(level of evidence)*[a]
	N = 1,375, 12 and 52 weeks	4 weeks, Statin, range of doses according to risk level (29.0%-37.5%), 104 mg/dL	± 2.1 SD) *(moderate)*, 12 weeks: -53.0% (95% CI = 56.0-44.6) to -70.5% (95% CI = -79.8 to -61.2)	target < 70 mg/dL: 82.3% vs. 6.4% (*P* < 0.001) *(moderate)*. 12 weeks: LDL target < 70 mg/dL: 71.8%-94.5% vs. 0%-9.3% (*P* < 0.001) *(high)*	differences, *(low to moderate)* 12 weeks: more overall AEs (60.0% vs. 42.0%), no difference in WAEs, SAEs, or injection site reactions *(moderate to high)*
Population: high CV risk ((LDL-C targets <100 mg/dL or <70 mg/dL not achieved)					
Ali vs placebo	2 RCTs, N = 2,656, 24 weeks	Ali: 75 to 150 mg every 2 weeks, High-dose statin (46.8%-63.1%,), 100-123 mg/dL	-45.9% to -61.9% (*P* < 0.001) LDL target < 70 mg/dL: RR = 9.65 (95% CI = 7.7-12.0), *(high)*	LDL target < 70 mg/dL: RR = 9.65 (95% CI = 7.7-12.0), *(high)*	No difference in overall AEs, WAEs, SAEs. *(moderate to high)*. No difference in injection-site reactions (pooled RR = 1.4; 95% CI = 0.98-2.1) or neurocognitive events (pooled RR = 1.8; 95% CI = 0.37-8.5). *(low)*
Evo vs placebo	1 RCT, N = 310, 12 weeks	Evo: 420 mg every 4 weeks, High-dose statin (5.9%; 24.8% per Japanese standard, 139 mg/dL	-63.9% (*P* < 0.001), *(low)*	LDL target < 100 mg/dL: 96.0% vs. 1.0% (*P* < 0.001); LDL target <70 mg/dL: 82.0% vs. 0.0% (*P* < 0.001), *(low)*	*(insufficient)*
Ali vs ezetimibe (10 mg)	1 RCT, N = 720, 24 weeks	75 to 150 mg every 2 weeks, Statin, range of doses (66.6%), 106 mg/dL	-29.8% (*P* < 0.001), *(moderate)*	LDL targetl < 70 mg/dL: RR = 1.70 (95% CI = 1.46-1.95), *(moderate)*	No differences for overall AEs, WAEs, or SAEs. *(moderate)*. More injection site reactions with Ali (2.5% vs. 0.8%). *(low)*

Comparison	Study, Patient Number (N), Endpoint	PCSK 9 Inhibitor Dose, Concomitant Lipid Therapy, Baseline LDL-C	Difference in LDL-C change, *(level of evidence)*[a]	Difference in % Achieving LDL-C target, *(level of evidence)*[a]	Harms, *(level of evidence)*[a]
Evo vs ezetimibe (10 mg)	1 RCT, N = 329, 12 weeks	420 mg every 4 weeks, Statin, range of doses (37.5%), 126-129 mg/dL or 92-94 mg/dL	NR	LDL target <70 mg/dL with Atorvastatin 10 mg: 85.8% vs. 5.6%; unadjusted RR = 5.22 (95% CI = 3.00-9.69) LDL target <70 mg/dL with atorvastatin 80 mg: 92.5% vs. 62.3%; unadjusted RR = 1.47 (95% CI = 1.23-1.88), *(low)*	Similar rates of overall AEs, *(low)* For other harms outcomes, *(insufficient)*

AE = adverse event; Ali = alirocumab; CV = cardiovascular; Evo = evolocumab, HeFH = heterozygous familial hypercholesterolemia; LDL-C = low density lipoprotein cholesterol; NR = not reported; PCSK 9 = proprotein convertase subtilisin kexin type 9; RCT = randomized controlled trial, RR = relative risk; SAE = serious adverse event; SD = standard deviation; vs = versus, WAE = withdrawal due to serious adverse event

[a]Level of evidence: high, moderate, low, or insufficient to draw conclusions

Appendix 6: Additional References of Potential Interest

Systematic reviews and/ or meta-analyses (alternate comparator) that did not meet the selection criteria.

Milionis H, Barkas F, Ntaios G, Papavasileiou V, Vemmos K, Michel P, et al. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors to treat hypercholesterolemia: effect on stroke risk. Eur J Intern Med. 2016 Oct;34:54-7.

Sahebkar A, Di GP, Stamerra CA, Grassi D, Pedone C, Ferretti G, et al. Effect of monoclonal antibodies to PCSK9 on high-sensitivity C-reactive protein levels: a meta-analysis of 16 randomized controlled treatment arms. Br J Clin Pharmacol. 2016 Jun;81(6):1175-90.

Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017 Apr 28;4:CD011748.

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