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EFFICACY AND SIDE EFFECT PROFILE OF PCSK9 INHIBITORS: WHAT DO META-ANALYSES SAY? A REVIEW

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ABSTRACT

Introduction: Hypercholesterolemia is associated with increased risk of heart disease and stroke. Heart disease is the first leading cause of death and the stroke is the fifth leading cause of death. In the world, 33% of ischemic heart disease is due to hypercholesterolemia (total blood cholesterol ≥ 200 mg/dL) which causes approximately 4.5% of the total death globally and 2% of total disability-adjusted life year, and its global prevalence is about 39%. In the US, 2 in 5 (40%) adults (≥20 years) and almost 7% of children and adolescents (6 to 19 years) have hypercholesterolemia. **Methods:** We conducted a literature search and a review of meta-analyses in Pubmed, Chochrane library and Google published up to November 4, 2022. The key words used for literature search were hypercholesterolemia, PCSK9 inhibitors and hyperlipidemia. Meta-analyses consisting effects of PCSK9 inhibitors on lipid profile, cardiovascular events and side effect profile were included in the study. **Results:** PCSK9 inhibitors significantly reduced LDL-C, TC, TG, LP(a) and increased HDL-C. PCSK9 inhibitors reduced the all-cause death and cardiovascular events. However, these effects were not statistically significant. Additionally, these drugs were associated with lower risk of MI, stroke and cardiac revascularization ($P<0.05$). PCSK9 inhibitors may increase blood sugar level and HbA1c. Nevertheless, these drugs are not associated with increased risk of neurocognitive adverse events ($P = 0.91$), liver enzymes elevations ($P = 0.34$), rhabdomyolysis ($P = 0.58$), or new-onset diabetes mellitus ($P = 0.97$). **Conclusion:** PCSK9 inhibitors in combination therapy reduced the LDL-C, TC, TG, LP (a) levels and increased HDL-C and their use was associated with a statistically significant reduction in MI, stroke, and coronary revascularization. PCSK9 inhibitors were not significantly associated with neurocognitive adverse events, incident or worsening of preexisting diabetes mellitus, creatine kinase increase, myalgia, and increase in alanine or aspartate aminotransferase.

INTRODUCTION

In the world, 33% of ischemic heart disease is due to hypercholesterolemia (total blood cholesterol ≥ 200 mg/dL) which causes approximately 4.5% of the total death globally and 2% of total disability-adjusted life year, and its global prevalence is about 39%.[1] In the United States, 2 in 5 (40%) adults (≥20 years) and almost 7% of children and adolescents (6 to 19 years) have hypercholesterolemia and it is associated with increased risk of heart disease and stroke.[2] Heart disease is the first leading cause of death, and the stroke is the fifth leading cause of death.[3]

Cardiovascular disease is the leading cause of morbidity and mortality globally.[4] Atherosclerosis is responsible for a significant amount of cardiovascular disease known as atherosclerotic cardiovascular disease (ASCVD).[5,6] Dyslipidemia is an important risk factor for atherosclerotic cardiovascular disease. Dyslipidemia consists of higher blood levels of low-density lipoprotein cholesterol (LDL-C), Lipoprotein (a) (Lp(a)), very low-density lipoprotein (VLDL) and triglycerides (TG).[7-10]

Statins are highly beneficial to decrease high blood cholesterol and prevent the risk of ASCVD. Nevertheless, many patients may do not have adequate control on their blood cholesterol despite high dose of statins therapy. Additionally, some patients may not tolerate high doses of statins.[11,12] So, the search for alternative therapies for control of high blood cholesterol is a continuous process. Results of monotherapy and combination therapy of ezetimibe are not very much promising.[13] Findings in the literature have shown that the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors- evolocumab and alirocumab are associated with decrease in LDL cholesterol and risk of ASVD.[14-16] PCSK9 is synthesized by hepatic inactive proprotein convertase, and it circulates in the blood either in free form or bound to atherogenic lipoproteins, such as Lp(a) and LDL-C.[17] PCSK9 increases

degradation of LDL receptors resulting in the decreased removal of LDL-C from the blood.[18-20] Therefore, drugs that inhibit PCSK9 can increase the expression of LDL-C receptor on the surface of hepatocytes and reduce LDL-C and subsequently major cardiovascular events.[21-23] The two monoclonal antibodies inhibiting PCSK9, alirocumab and evolocumab, have been approved in many countries.[17] So, the present study focuses on efficacy and side effect profile of PCSK9 inhibitors-evolocumab and alirocumab.

We conducted a literature search and a review of meta-analyses in Pubmed, Chochrane library and Google. We used the following key words hypercholesterolemia, PCSK9 inhibitors, hyperlipidemia and meta-analysis to search the literature up to November 4, 2022. Steps followed in identification, screening, and inclusion of the published meta-analyses during literature search have been shown in Figure 1. Meta-analyses consisting effects of PCSK9 inhibitors on lipid profile, cardiovascular events and side effect profile were included in the study.

METHODS

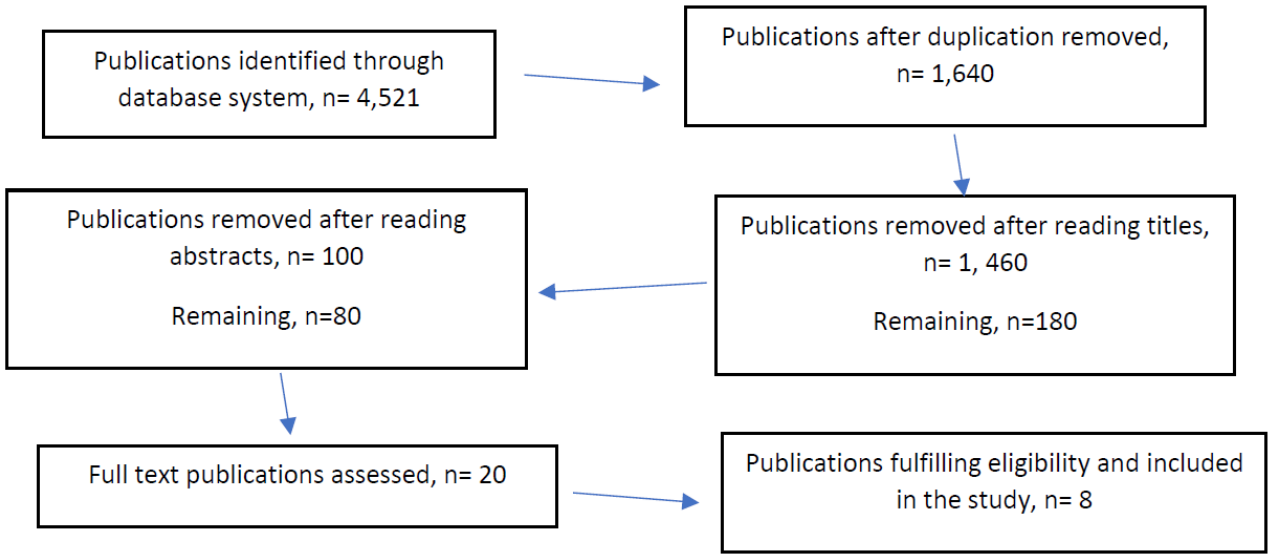

Fig 1: Steps in identification, screening and inclusion of the published meta-analyses, n= number.

RESULTS

Meta-analyses consisting of the effects of PCSK9 inhibitors LDL-C, total cholesterol (TC), TG, apoprotein B (ApoB), Lp(a), and mean/median follow-up times are shown in table 1. PCSK9 inhibitors significantly reduced LDL-C, TC, TG, Lp(a) and increased HDL-C 9 (table 1). Meta-analyses consisting of the effects of PCSK9 inhibitors on lipid profile, all-cause mortality, cardiovascular death, myocardial infarction, stroke, and mean/median follow-up times, and adverse effect profile are shown in table 2. PCSK9 inhibitors reduced the all-cause death and cardiovascular events. However, these effects were not statistically significant. Additionally, these drugs were associated with lower risk of MI, stroke and cardiac revascularization (P<0.05). PCSK9 inhibitors may increase blood sugar level and HbA1c. Nevertheless, these drugs are not associated with increased risk of neurocognitive adverse events (P = 0.91), liver enzymes elevations (P = 0.34), rhabdomyolysis (P = 0.58), or new-onset diabetes mellitus (P = 0.97) (table 2).

Table 1: Meta-analyses consisting of the effects of PCSK9 inhibitors LDL-C, TC, TG, ApoB, LP(a), HDL-C and mean/median follow-up times.

Meta-analysis	No. of RCTs and Patients	% Reduction in LDL-C	% Reduction in TC	% Reduction in TG	% Reduction in ApoB	% reduction in Lp(a)	% Increase in HDL-C	Mean/median follow-up time after PCSK9 inhibitor therapy
Yue Zhang et al., 2022*[15]	14 RCTs N= 52,586	-46.86, 95% CI (-54.99 to -38.72), P < 0.00001]	-31.92, 95% CI (-39.47 to -24.38), P < 0.00001	-8.13, 95% CI (-10.48 to -5.79), P < 0.00001	-38.44, 95% CI (-42.23 to -34.65), P < 0.00001	-26.69, 95% CI (-27.93 to -25.44), P < 0.00001	6.27, CI (5.17 to 7.36), P < 0.00001	24 weeks
Geng Q et al., 2022**[24]	45 RCTs N= 97, 297	Alirocumab –51.29% (95% CI – 55.83 to –	Alirocumab -30.31% (95% CI – 34.26 to –	Alirocumab –10.31% (95% CI – 13.81 to –			Alirocumab 5.63% (95% CI 4.86 to 6.40, p <	8-134 weeks

		46.75, p < 0.05) Evolocumab –53.99% (95% CI –58.45 to –49.54, p < 0.05)	26.36, p < 0.05) Evolocumab –34.2% (95% CI –36.18 to –32.21, p < 0.05)	6.81, p < 0.05) Evolocumab –8.86% (95% CI –13.17 to –4.55, p < 0.05)			0.05) Evolocumab 7.05% (95% CI 5.55 to 8.54, p < 0.05)	

*Experimental group: PCSK9 inhibitor therapy besides statins alone or with ezetimibe in You Zhang et al., study; **control group- either placebo or ezetimibe in Geng et al., study, RCTs: randomized controlled trials, N: number of patients, values are expressed in mean deviation with confidence interval, LDL-c: low density lipoprotein- cholesterol, TC: total cholesterol, TG: triglyceride, ApoB: apoprotein B, Lp: non-high density lipoprotein (a), HDL-C: high density lipoprotein- cholesterol.

Table 2: Meta-analyses consisting of the effects of PCSK9 inhibitors on lipid profile, all-cause mortality, cardiovascular death, myocardial infarction, stroke, and mean/median follow-up times, and adverse effect profile.

Meta-analysis	No. of RCTs and Patients	Effects of PCSK9 inhibitors on lipid profile, and all-cause and cardiovascular mortality	Side effects of PCSK9 inhibitors
Wang X et al., 2022[25]	9 RCTs N=54,311	Alirocumab was associated with reductions in all-cause mortality compared with control (RR 0.83, 95% CrI 0.72–0.95)	alirocumab was associated with decreased risk of serious adverse events (RR 0.94, 95% CrI 0.90–0.99)
Burnett H et al., 2022[16]	23 RCTs	Alirocumab % change in LDL-c compared to placebo -7.79 (-14.8-1.12) 98.8%	
Paul Guedeney et al., 2022[26]	39 RCTs N= 66, 478	Overall, the effects of PCSK9 inhibition on all-cause death and cardiovascular death were not statistically significant (P = 0.15 and P = 0.34, respectively); median follow-up of 2.3 years PCSK 9 inhibitors were associated with lower risk of MI (1.49 vs. 1.93 per 100 patient-year; RR 0.80, 95% CI 0.74–0.86; I^2 = 0%; P < 0.0001), ischaemic stroke (0.44 vs. 0.58 per 100 patient-year; RR 0.78, 95% CI 0.67–0.89; I^2 = 0%; P = 0.0005), and coronary revascularization (2.16 vs. 2.64 per 100 patient-year; RR 0.83, 95% CI 0.78–0.89; I^2 = 0%; P < 0.0001), compared with the control group.	PCSK9 inhibitors was not associated with increased risk of neurocognitive adverse events (P = 0.91), liver enzymes elevations (P = 0.34), rhabdomyolysis (P = 0.58), or new-onset diabetes mellitus (P = 0.97)
Huang Y-T et al., 2022[27]	22 RCTs N=42,786	The lipid reductions in LDLC, ApoB, and Lp(a) with add-on PCSK9 inhibitors vs. placebo in statin-treated patients across all trials were 50–63%, 43–52%, and 23–31%, respectively	No significant risk difference of adverse events between PCSK9 inhibitors and placebo was found
Luiz Sérgio F et al., 2018[28]	20 RCTs N= 68,123		PCSK9 inhibitor increased fasting blood glucose (weighted mean difference 1.88 mg/dL [95% CI 0.91–2.68]; I^2 = 0%; P < 0.001) and HbA_{1c} (0.032% [0.011–0.050]; I^2 = 15.5%; P < 0.001) when compared with placebo;

			with median follow-up of 78 weeks
Aris Karatasakis et al., 2017[29]	35 RCTs n= 45,539	PCSK9 inhibitor was associated with a lower rate of myocardial infarction (2.3% versus 3.6%; odds ratio [OR]: 0.72 [95% confidence interval (CI), 0.64–0.81]; P<0.001), stroke (1.0% versus 1.4%; OR: 0.80 [95% CI, 0.67–0.96]; P=0.02), and coronary revascularization (4.2% versus 5.8%; OR: 0.78 [95% CI, 0.71–0.86]; P<0.001). Overall, no significant change was observed in all-cause mortality (OR: 0.71 [95% CI, 0.47–1.09]; P=0.12) or cardiovascular mortality (OR: 1.01 [95% CI, 0.85–1.19]; P=0.95), mean follow-up time 85.5 weeks	No significant change was observed in neurocognitive adverse events (OR: 1.12 [95% CI, 0.88–1.42]; P=0.37), myalgia (OR: 0.95 [95% CI, 0.75–1.20]; P=0.65), new onset or worsening of preexisting diabetes mellitus (OR: 1.05 [95% CI, 0.95–1.17]; P=0.32), and increase in levels of creatine kinase (OR: 0.84 [95% CI, 0.70–1.01]; P=0.06) or alanine or aspartate aminotransferase (OR: 0.96 [95% CI, 0.82–1.12]; P=0.61).

RCTs: randomized controlled trials, N: number of patients

DISCUSSION

This study aimed to conduct a review of meta-analyses for the effects of treatment with PCSK9 inhibitors on the blood levels of lipid profile, reduction on over-all and cardiovascular mortality and side effect profile. Meta-analysis by Yue Zhang et al. found that PCSK9 combination therapy resulted in beneficial and comprehensive modulation of serum LDL-C, TC, TG, ApoB, Lp(a), non-HDL-C, HDL-C, and ApoA1 levels in patients with cardiovascular disease- high risk. The results of their study showed that the all-cause mortality and cardiovascular mortality were not statistically different between with or without PCSK9 inhibitors.[15] Results of another meta-analysis by Geng Q et al. also showed that PCSK9 inhibitors could lead to marked reduction in LDL-C, TC, TG, and increase in HDL-C.[24] These findings were in consonant with other studies.[16, 27]

According to the Wang X et al. analysis, the use of alirocumab was associated with reductions in the all-cause mortality and serious adverse event. Furthermore, use of evolocumab was associated with decreased risk of myocardial infarction.[25] As per the study by Paul Guedeney et al., administration of PCSK9 inhibitors was associated with lower risk of MI, ischemic stroke, and coronary revascularization compared with controls. There were no significant differences between PCSK9 inhibitors and the control group in terms of major side effect profile including neurocognitive adverse events, rhabdomyolysis, liver enzymes elevations, new-onset diabetes mellitus, or allergic reactions.[26]

Huang Y-T et al., found that statin add-on PCSK9 inhibitors such as evolocumab and alirocumab vs. placebo or ezetimibe, significantly reduced the levels of LDL-C, ApoB, and Lp(a). The statin used in the included randomized controlled trials were maximally tolerated statin doses, example, atorvastatin 20, 40, or 80 mg once a day; rosuvastatin 20 or 40 mg once a day; and simvastatin 40 mg or 80 mg once a day.[27] Moderate-to-high doses of statin therapy causes 30 to 50% LDL-C reduction.[30]

Luiz Sérgio F et al., observed that there was a small but significant increase in plasma levels of glucose and HbA1c after a short-term (1.5-year) treatment with PCSK9 inhibitor, and the effect was proportional to the decrease in plasma LDL-C. However, they opined that the cohort of patients and under the short period of time, the increase was not sufficient to impact on incident diabetes.[28]

Meta-analysis by Aris Karatasakis et al., showed that, compared with no PCSK9 inhibitor use, treatment with PCSK9 inhibitors was associated with a statistically significant reduction in MI, stroke, and coronary revascularization. However, treatment with PCSK9 inhibitors was not significantly associated with all-cause or cardiovascular mortality. Moreover, use of PCSK9 inhibitors was not significantly associated with neurocognitive adverse events, incident or worsening of preexisting diabetes mellitus, creatine kinase increase, myalgia, increase in alanine or aspartate aminotransferase, or treatment-emergent serious adverse events.[29] They also found that treatment with PCSK9 inhibitors was associated with consistent and favorable changes in lipid fractions[29] which are consistent with other similar studies.[15,16,24,25]

Limitations of the study

The limitations of the study are several. The doses of PCSK9 inhibitors and different follow-up durations might have affected heterogeneity to the results. Several studies have control groups with a mixture of placebo or ezetimibe and/or baseline statin therapies in high-risk patients.[24] Additionally, the publication and selection bias cannot be ruled out.

CONCLUSION

PCSK9 inhibitors in combination therapy reduced the LDL-C, TC, TG, Lp(a) levels and increased HDL-C. treatment with PCSK9 inhibitors was associated with a statistically significant reduction in MI, stroke, and coronary revascularization. However, treatment with PCSK9 inhibitors was not significantly associated with all-cause or cardiovascular mortality. Additionally, use of PCSK9 inhibitors was not significantly associated with neurocognitive adverse events, incident or worsening of preexisting diabetes mellitus, creatine kinase increase, myalgia, and increase in alanine or aspartate aminotransferase.

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