Cochrane corner: PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease

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INTRODUCTION:

Drug therapies targeted at the reduction of LDL-cholesterol (LDL-C) are mainstream in the treatment of cardiovascular disease (CVD) and particularly for the prevention of coronary heart disease (CHD). In patients who do not have a sufficient response to, or who do not tolerate traditional LDL-C lowering therapies such as statins or ezetimibe, monoclonal antibodies (mAbs) against PCSK9 (PCSK9 inhibitors) may provide an alternative treatment. Non-monoclonal antibody based PCSK9 inhibitors such as inclisiran are also emerging but currently lack robust outcome data[1] and its effects are not considered in the current review. In this synopsis we summarise findings from a recent update of a Cochrane systematic review on the efficacy and safety of PCSK9 inhibitors[2]. This article focuses on the effects on outcomes (CVD and total mortality), safety, and the quality of the evidence in studies of mAb PSCK-9 inhibitors alirocumab and evolocumab. Most of the available studies compared PCSK9 mAb treatment against placebo (against a background of usual care including statin and or ezetimibe), with a smaller group of studies evaluating the effects of PCSK9 mAb directly against statins and/or ezetimibe (none of the trials compared PCSK9 exclusively against statin treatment).

METHODS:

The following databases were systematically searched for suitable randomised controlled trials (RCTs): Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Web of Science, Clinicaltrials.gov and the International Clinical Trials Registry Platform. Parallel-group and factorial RCTs with at least 24 weeks of follow-up were eligible; due to discontinuation of bococizumab and RG7652, studies examining these mAbs were excluded in this update.

SUMMARY OF FINDINGS:

The 24 selected randomised trials (60,997 participants, box 1) predominantly selected high risk patients, for example by enrolling patients with non-optimal LDL-C concentration despite treatment with statins or ezetimibe, or with a history of CVD. The study sample included 1,879 who had familial hypercholesterolaemia (22% of the alirocumab participants and 38% of the evolocumab participants that provided information on FH status), and 18,908 (31%) with a diagnosis of type 2 diabetes mellitus (T2DM) at baseline (32% in alirocumab and 34% evolocumab trials; out of participants with reported T2DM status). Of the included patients 4590 had no history of CVD (10% of the alirocumab patients and 7% of the evolocumab participants). Alirocumab was evaluated in 18 trials and evolocumab in 6 trials. Comparisons were made against placebo in 18 trials, ezetimibe and/or statins in 6 trials. Tables 1 and 2 display the key results of the meta-analysis for both PCSK9 inhibitors compared with placebo and with statins and/or ezetimibe respectively.

Table 1: Comparing PCSK9 inhibitors with placebo (+ background lipid lowering treatment*)

Outcomes	Alirocumab vs. placebo (+ background lipid lowering therapy)		Certainty of evidence (GRADE)	Evolocumab vs. placebo (+ background lipid lowering therapy)		Certainty of evidence (GRADE)
	Risk difference	Relative effect: OR (95% CI)		Risk difference	Relative effect: OR (95% CI)	
CVD	-2%	0.87 (0.80-0.94)	High	-2%	0.84 (0.78-0.91)	High
All-cause-mortality	-1%	0.83 (0.72-0.96)	High	<1%	1.04 (0.91-1.19)	High
Myocardial infarction	-2%	0.86 (0.79-0.94)	High	-1%	0.72 (0.64-0.82)	High
Any stroke	<1%	0.73 (0.59-0.91)	High	<1%	0.79 (0.65-0.94)	High

CI: confidence interval; **CVD:** any cardiovascular disease; **OR:** odds ratio (values <1 beneficial to patients)
Follow-up period 6-36 months
*background lipid lowering treatment comprised either statin, ezetimibe or a combination of these

Risk difference: the difference between the observed risks in the two groups. NB. A value <0 is beneficial to patients

Table 2: Comparing PCSK9 inhibitors vs. statins and/or ezetimibe:

Outcomes	Alirocumab vs. statins and/or ezetimibe		Certainty of evidence (GRADE)	Evolocumab vs. statins and/or ezetimibe		Certainty of evidence (GRADE)
	Risk difference	Relative effect (95% CI)		Risk difference	Relative effect (95% CI)	
CVD	1%	1.37 (0.65-2.87)	Low	-1%	0.66 (0.14-3.04)	Very low
All-cause-mortality	-1%	0.51 (0.18-1.40)	Low	>-1%	0.43 (0.14-1.30)	Very low
Myocardial infarction	1%	1.45 (0.64-3.28)	Low	>-1%	0.66 (0.23-1.85)	Very low
Any stroke	<1%	0.85 (0.13-5.61)	Low	Insufficient data		

CI: confidence interval; **CVD:** any cardiovascular disease; **OR:** odds ratio (values <1 beneficial to patients)
Follow-up period 6-12 months
Risk difference: the difference between the observed risks in the two groups. NB. A value <0 is beneficial to patients

LIMITATIONS:
The GRADE profiler (GRADEpro) methodology was exclusively applied to evaluate the evidence quality of the efficacy endpoints all-cause mortality, any CVD, MI, and any stroke. For studies comparing the effect of alirocumab or evolocumab versus placebo when added to background statin or ezetimibe therapy there was high certainty evidence, however for studies directly comparing PCSK 9 inhibitor efficacy with statins and/or ezetimibe there was only low (in the case of alirocumab) or very low certainty evidence (evolocumab) of their effect to prevent disease.

There were limited data potential safety issues of either evolocumab or alirocumab (Figure 1), precluded strong conclusions on the possible presence *or* absence of effects on influenza, type 2 diabetes incidence, cancer, or hypertension.

AREAS IN NEED OF FUTURE STUDY:
In addition to continued exploration of the long-term safety profiles of PCSK9 inhibitors (e.g. cancer, T2DM, hypertension and influenza) further trials comparing the efficacy of PCSK9 inhibitors and current standard of care i.e. statins and ezetimibe, could help establish if there is any role for replacement therapy with PCSK9 inhibitors in certain patients. Small interfering ribonucleic acids (siRNAs) that block the translation of PCSK9 mRNA (e.g. inclisiran) may offer additional benefits to patients and will require further study as well.

CONCLUSION:
This systematic review and meta-analysis highlights the convincing level of evidence to add PCSK9 inhibitors (alirocumab and evolocumab) to traditional lipid lowering therapies to reduce the risk of CVD, including MI, and stroke, as well as all-cause mortality. In the case of PCSK9 inhibitors directly compared to active treatment (either statins, ezetimibe or combination therapy) the evidence base is weaker and it is not clear if there is a protective or harmful effect in these patients. This review further highlights the absence of sufficient data to rule out possible safety signals on influenza, hypertension, cancer diagnosis or T2DM.

Box 1: Synopsis of collected randomised controlled trial data on PCSK9 inhibitors
▪ No. of studies overall: 24

- No. of RCTs: 24
- Study years: 2011-2018 (see full review).
- No. of patients: 60,997
- Men 71%; Women 29%*
- Race/ethnicity: 83% Caucasian
- Age: 61.57 years (IQR 60.08 to 63.11) for alirocumab and 57.93 years (IQR 56.30 to 59.25) for evolocumab
- Setting: outpatient and home settings
- Countries: International
- PCSK9 inhibitors studied: 43.5% randomised to alirocumab; 56.5% randomised to evolocumab
- Comparisons: PCSK9 mAb compared with (1) placebo, (2) ezetimibe and statin combination therapy
- Primary outcomes: (1) Composite endpoint of CVD, defined as urgent coronary revascularisation, unstable angina pectoris, non-fatal and fatal myocardial infarction (MI), non-fatal and fatal stroke, and CHD death, (2) All-cause mortality, (3) MI, (4) stroke.
- Secondary outcomes: (1) influenza, (2) type 2 diabetes mellitus, (3) cancer, (4) hypertension
- Based on the original Cochrane review: PCSK9 monoclonal antibodies for the primary and secondary prevention of CVD

*for whom gender was reported

Conflict of interest statements

AFS has received Servier funding for unrelated work.

JTW reports consulting fees from 3M unrelated to this work

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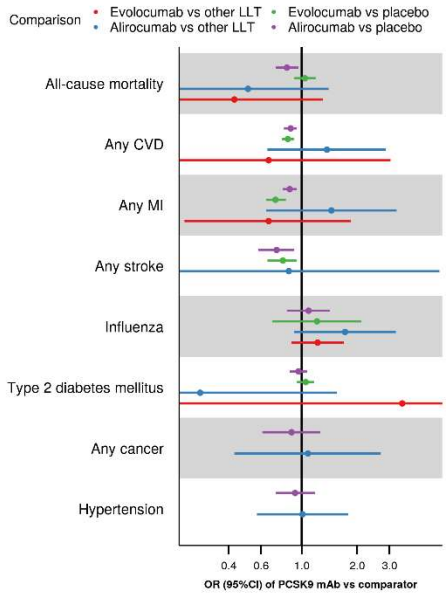
Figure 1 caption: Summary of findings



NB. Associations in the forest plots are given as odds ratios (OR) with 95% confidence interval (CI). Comparisons were made against placebo or lipid lowering therapy consisting of either ezetimibe or ezetimibe and statins. Confidence intervals were truncated were necessary, entries without data are not included. Abbreviations: CVD, cardiovascular disease; and MI, myocardial infarction.

References:

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