

# **Cochrane Corner: PCSK9 monoclonal antibodies from primary and secondary prevention of cardiovascular disease.**

A F Schmidt\* PhD [a,b,c], L S Pearce BSc [d], JT Wilkins[e], JP Casas professor [f], AD Hingorani [a]

- a. Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London WC1E 6BT, United Kingdom.
- b. Groningen Research Institute of Pharmacy, University of Groningen, Groningen, the Netherlands
- c. Department of Cardiology, Division Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands
- d. Department of Non-communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK.
- e. The Department of Medicine (Cardiology) and the Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
- f. Farr Institute of Health Informatics, University College London, London, UK

\* Contact: 0044 (0)20 3549 5625

E-mail address: [amand.schmidt@ucl.ac.uk](mailto:amand.schmidt@ucl.ac.uk) (A.F.Schmidt).

**Word count text:** 1303 (max 1500)

**Number of references:** 3 (max 5)

**Number of tables:** 1

**Number of figures:** 1

## **Summary**

In this synopsis we describe findings from a recent Cochrane review on PCSK9 inhibitors for cardiovascular disease prevention. Compared against placebo, PCSK9 inhibitors show a substantial reduction in atherogenic lipid particles (LDL-C, Apo-B and Lp(a)), and protective effects on: CVD, MI, stroke, and elevated creatinine. There is however only limited, and lower quality, evidence comparing PCSK9 inhibitors against active treatments such as statins or ezetimibe. Furthermore, the current evidence is limited by the relatively short follow-up (at most a median follow-up of 26 months) which likely also relates to the observed beneficial safety profile, showing no clear signals on adverse events such as influenza, myalgia, T2DM or cancers.

## **Introduction**

Despite the availability of effective drug therapies reducing LDL-cholesterol (LDL-C), cardiovascular disease (CVD) remains a significant source of mortality and morbidity. Additional LDL-C reduction may be warranted, especially in patients that are unresponsive to, or unable to take existing LDL-C reducing therapies[1]. Monoclonal antibodies against PCSK9 (PCSK9 inhibitors) may provide such additional LDL-C reduction. In this synopsis we summarize findings from a recent Cochrane systematic review[2] on the safety and effectiveness of PCSK9 inhibitors. Here we particularly focus on the relative effectiveness of PCSK9 inhibitors compared to existing treatments such as statins and/or ezetimibe, and report on the (perceived) quality of the evidence.

## **Methods**

The following databases were systematically searched for eligible Randomized 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 randomized controlled trials (RCTs) with at least 24 weeks of follow-up were included.

## **Summary of Findings**

The 20 identified randomised trials (68 341 participants) predominantly selected high risk patients (Table 1): 7% having familial hypercholesterolemia, 89% a history of CVD, and 39% a type 2 diabetes mellitus (T2DM) diagnosis. The PCSK9 inhibitor alirocumab was evaluated in 13 trials, evolocumab in 3 trials, bococizumab (discontinued agent) in 3 trials, and RG7652 by a single trial. Comparisons were made against placebo in 13 trials, ezetimibe and statins in 5 trials and ezetimibe only in 2 trials. When not used as a randomized comparison treatment, statins or

ezetimibe were often prescribed (i.e., not randomly allocated) as background medication, for example in placebo controlled trials.

PCSK9 inhibitors showed beneficial effects in reducing pro-atherogenic lipid particles (Figure 1). Compared against placebo PCSK9 inhibitor effects on clinical endpoints were: odds ratio (OR) of 0.86 (95% 0.80; 0.92) with CVD events, 0.77 (95%CI 0.69; 0.85) for myocardial infarction (MI), 0.76 (95%CI 0.65; 0.90) for any stroke, and 1.02 (95%CI 0.91; 1.15) for all-cause mortality. The OR with any adverse events was 1.08 (95%CI 1.04; 1.12), selected individual adverse events included a protective association with elevated creatinine 0.85 (95%CI 0.73; 1.00), and potentially harmful signals on influenza and myalgia: 1.19 (95%CI 0.91; 1.55) and 1.11 (95%CI 0.98; 1.26), respectively. After excluding results from the SPIRE trials (using the terminated bococizumab) the associations with any adverse events and myalgia were: 1.01 (95%CI 0.96; 1.06) and 1.17 (95% 0.87; 1.56), respectively. PCSK9 inhibitors did not seem to affect the incidence of T2DM, cancers or neurocognitive events, although precision, number of events, and follow-up time were limited for these endpoints.

Trials comparing PCSK9 inhibitors to ezetimibe and statins showed a protective effect on CVD 0.45 (95%CI 0.27; 0.75) and a risk increasing effect of 1.18 (95%CI 1.05; 1.34) on any adverse event. Data on all-cause mortality and separate CVD elements were unavailable for the ezetimibe and statin comparator trials. Clinical endpoint data were absent for the trials comparing PCSK9 inhibitors to ezetimibe, and no trial were found comparing PCSK9 inhibitors against statins only.

### **Limitations**

Based on the GRADE profiler (GRADEpro) methodology, the quality of the evidence for efficacy endpoints was judged as moderate for the placebo comparisons because of the limited follow-up

(median follow-up FOURIER 26 months, SPIRE-1 7 months, SPIRE-2 12 months). In ezetimibe and statin comparison, the quality of the evidence was graded as very low due to the lack of blinding, small number of events per study and short follow-up. These issues may also explain the larger effect of PCSK9 inhibitors on CVD when compared against ezetimibe and statins versus the smaller effect observed in the placebo comparison. Published data from trials conducted to date shows an adequate safety profile with no increases in the risk of major adverse events such as cancers, T2DM or neurocognitive events. However, the number of neurological events, as well as the duration of follow up was still limited (less than 3 years).

### **Areas in Need of Future Study**

Besides exploring the long-term safety of PCSK9 inhibitors (e.g, cancer, T2DM, cognition) attention should be given to its effects on CVD endpoints other than CHD and stroke (e.g., heart failure, atrial fibrillation) which represents a considerable proportion of first-time presentations for cardiovascular disorders[3]. High quality evidence is limited for PCSK9 inhibitor compared to active treatments (statins and ezetimibe). Finally, little is known on the PCSK9 inhibitor effectiveness and safety in primary prevention settings.

### **Conclusions**

PCSK9 inhibitors showed a substantial reduction in atherogenic lipid particles (LDL-C, Apo-B and Lp(a)), and protective effects on: any CVD, MI (placebo comparison only), stroke (placebo comparison only), and elevated creatinine. PCSK9 inhibitors were associated with an increased risk of any adverse events, which reduced to a neutral effect in the placebo comparison after excluding data from the failed SPIRE trial.

### **Conflict of Interest Statement**

None of the authors of this paper have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

### **Acknowledgement**

We gratefully acknowledge J Overington for his essential contribution to the Cochrane review with the same name as this synopsis.

### **Guarantor**

AFS had full access to all of the data and takes responsibility for the integrity of the data presented.

### **Funding**

AFS is funded by UCLH NIHR Biomedical Research Centre and is a UCL Springboard Population Health Sciences Fellow.

### **Prior postings and presentations**

This study and its results were presented at the 2016 Cochrane colloquium in Seoul South-Korea and are published as a Cochrane systematic review and meta-analysis.

## References

- 1 Knowles JW, O'Brien EC, Greendale K, *et al.* Reducing the burden of disease and death from familial hypercholesterolemia: A call to action. *Am Heart J* 2014;**168**:807–11.
- 2 Schmidt Amand F, Pearce Lucy S, Wilkins John T, *et al.* PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst. Rev. 2015. doi:10.1002/14651858.CD011748
- 3 George J, Rapsomaniki E, Pujades-Rodriguez M, *et al.* How Does Cardiovascular Disease First Present in Women and Men? Incidence of 12 Cardiovascular Diseases in a Contemporary Cohort of 1,937,360 People. *Circulation* 2015;**132**:1320–8.

---

**Table 1 Synopsis of the collected RCT data on PCSK9 inhibitors.**

---

**No. of studies overall:** 20

**No. of randomized controlled trials:** 20

**Study years:** 2011-2017

**No. of patients:** 68 341

**Men 70% Women 30%**

**Race/ethnicity** 86% Caucasian

**Age** 61y (range 52 to 64y)

**Setting:** Outpatient and home settings

**Countries:** International

**Comparisons:** PCSK9 mAb compared against 1) placebo, 2) ezetimibe, and 3) ezetimibe and statin combination therapy

**Primary outcomes:** 1) lipid biomarkers as mean percentage change from baseline, and 2) cardiovascular disease.

**Secondary outcomes:** 1) all-cause mortality, 2) any adverse events, 3) cognitive function, 4) glycaemic biomarkers, and 5) quality of life.

**Based on original Cochrane review:** *PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease*

---

### Figure captions

#### Figure 1 Summary of findings.

N.b. associations in the forest plots are given as odds ratio (OR) with 95% confidence interval (CI). The bottom bar plots provide the mean difference (MD) estimates as mean percentage change from baseline at 6 months of follow-up, with the error bars indicating the 95%CI. Results without data were left empty.