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PCSK9 inhibition for primary prevention of ischaemic heart disease in heterozygous familial hypercholesterolaemia (Protocol)

Ryan A, Nevitt SJ, Byrne CD, Cook P

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[Intervention Protocol]

PCSK9 inhibition for primary prevention of ischaemic heart disease in heterozygous familial hypercholesterolaemia

Aidan Ryan[1], Sarah J Nevitt[2], Christopher D Byrne[3], Paul Cook[1]

[1]Department of Clinical Biochemistry, University Hospital Southampton NHS Foundation Trust, Southampton, UK. [2]Department of Biostatistics, University of Liverpool, Liverpool, UK. [3]Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton Institute of Developmental Sciences (IDS Building), Southampton, UK

Contact address: Aidan Ryan, Department of Clinical Biochemistry, University Hospital Southampton NHS Foundation Trust, 17 Tremona Road, Southampton, SO16 6YD, UK. aidan.ryan@uhs.nhs.uk.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of PCSK9 inhibitors in the primary prevention of IHD in people with HeFH.

BACKGROUND

Description of the condition

Familial hypercholesterolaemia (FH) is an inherited metabolic disease characterised by an elevated low density lipoprotein cholesterol (LDL-C). Historically it has been shown that, if untreated, FH will lead to at least 50% men under 50 years of age and 30% of women under 60 years of age to develop ischaemic heart disease (IHD) (Slack 1969; Stone 1974). A more recent observational study showed a potential six-fold increase in the risk of IHD in people with the causative FH mutation compared to those without the mutation but with similar cholesterol levels; and a 22-fold risk compared to those with normocholesterolaemia (Khera 2016).
FH is an autosomal dominant disorder with the severe homozygous form occurring in 1 in a million and the less severe heterozygous FH (HeFH) in 1 in 200 to 500 (Nordestgaard 2013). Mutations causing HeFH occur most commonly in the *LDLR* (low density lipoprotein receptor) gene, followed by *APOB* (apolipoprotein B) mutations and less commonly in the *PCSK9* (proprotein convertase subtilisin/kexin type 9) gene (Rader 2003). These mutations cause FH by either affecting LDL uptake in the case of *LDLR*, *APOB* mutations or by increasing LDL receptor degradation in the case of *PCSK9* which leads to an increase in LDL cholesterol due to decreased hepatic clearance. The diagnosis of FH is based on either clinical criteria or genetic testing (Ryan 2015). Current registry data has shown that early diagnosis and treatment reduces the risk of early onset IHD (Mundal 2014; Versmissen 2008). Current methods of risk assessment and treatment used in clinical guidance are mainly adopted from non-FH (Besseling 2014; Nordestgaard 2013; Wong 2016).

Description of the intervention

A number of approaches to inhibition of PCSK9 have been explored in both animal models and in humans (Mullard 2017). These include inhibition at the messenger ribonucleic acid (mRNA) level, small molecule inhibitors and monoclonal antibodies directed against PCSK9. To date the monoclonal antibodies have been the most evaluated. They act by binding to PCSK9 in the extracellular space and preventing the binding of PCSK9 to the LDLR complex. This prevents LDLR degradation, which in turn remains on the liver surface available to remove LDL-C from the bloodstream.

As the monoclonal antibodies are relatively new to the market, approval by regulation bodies has only recently been obtained for both evolocumab and alirocumab (Natarajan 2016). Evolocumab is administered at a dose of 140 mg every two weeks or 420 mg once per month and alirocumab at either 75 mg or 150 mg every two weeks. While the difference in LDL reduction between the agents is minimal, both demonstrate a 59% reduction in LDL-C when compared with placebo.

Alirocumab

Alirocumab is a human monoclonal antibody (IgG1 isotype) that targets PCSK9 and after subcutaneous administration bioavailability is estimated to be 85% with serum levels peaking at day three to day seven post administration. At low doses, elimination is mainly via binding to PCSK9; and at higher doses, it is largely unsaturable via the proteolytic pathway. Its pharmacokinetics are not influenced by age, body weight, gender, race, creatinine clearance or hepatic function. The drug half-life is estimated to be 17 to 20 days, reduced to 12 days in the presence of a statin; however, it is not felt to impact efficacy and also has no effect on statin levels. Adverse effects compared with placebo include injection site reactions, however, most are similar to placebo (EMA 2015a).

Evolocumab

Evolocumab is a human monoclonal IgG2 antibody that targets PCSK9 with maximum suppression of circulating unbound PCSK9 achieved within four hours. After subcutaneous administration, bioavailability was 72% with median peak serum levels occurring after three to four days. Like alirocumab, the effects of body parameters, including creatinine clearance and hepatic function, have not been found to impact on drug pharmacokinetics. The adverse event profile is similar to placebo, apart from an increase in 3% of upper respiratory tract infection. Evolocumab has a half life of 11 to 17 days and there is an approximate 20% reduction in serum levels with concomitant use of high-dose statins, which does not appear to influence efficacy (EMA 2015b).

In people with HeFH on high-dose statins, the systemic exposure of evolocumab was slightly lower than in individuals on a low-to-moderate dose of statins (the ratio of AUC_{last} 0.74 (90% confidence interval (CI) 0.29 to 1.90)). An approximately 20% increase in the clearance is in part mediated by statins increasing the concentration of PCSK9 which does not adversely impact the pharmacodynamic effect of evolocumab on lipids. Population pharmacokinetic analysis indicates no appreciable differences in evolocumab serum concentrations in people with hypercholesterolaemia (non-FH or FH) taking concomitant statins.

How the intervention might work

PCSK9 is an enzyme that plays a crucial role in LDL receptor recycling by acting as a ligand for hepatic LDL receptors, targeting them for degradation via the endo-lysosomal pathway and preventing their return to the cell surface (Horton 2003; Lagace 2006; Maxwell 2005). Genetic case studies have shown that gain of function mutations can lead to HeFH, which leads to increased expression of PCSK9, which in turn leads to increased degradation of the LDLR, resulting in decreased LDL clearance and higher LDL cholesterol (Abifadel 2003; Rader 2003). However, other genetic cohort studies associated with loss of function and decreased PCSK9 expression have suggested an association with very low LDL levels and life-time risk of IHD (Cohen 2006; Rashid 2005). The fact that decreased expression of PCSK9 effectively lowers LDL suggests this has a potential impact as a treatment for FH, where excess LDL burden is a key factor in the risk of IHD in people with HeFH. In vivo the PCSK9 enzyme binds to the extracellular part of the LDLR, targeting it for degradation as described above. Similarly PCSK9 antibody therapies bind extracellularly to PCSK9 preventing it from degrading the LDL receptor (Natarajan 2016). This in turn leads to an increased clearance of LDL cholesterol and a decrease in LDL.

Why it is important to do this review

FH has many unmet needs in the area of diagnosis and risk stratification, but also in treatment, with some studies showing that up to 50% of individuals failed to meet treatment targets or were not on regular statin medication (Nordestgaard 2013; Ryan 2015). The incidence and existence of statin intolerance has received much debate and is controversial given the lack of consensus on intolerance or statin-associated muscular symptoms (Thompson 2016). Dependent on the source, figures suggesting statin-associated muscle symptoms vary from 5% to 20%, being lower in clinical trials than in observational studies, therefore, alternative treatments are required (Parker 2013; Zhang 2013).

Recent guidance on managing HeFH outlines that statins are the first line of treatment, followed by ezetimibe or bile acid sequestrants for those failing to achieve LDL targets (Nordestgaard 2013). The exact role for PCSK9 inhibitors in this pathway remains to be confirmed; however, a recent consensus document from the European Society of Cardiology (ESC) highlights the lack of clinical endpoints from trials to date and suggests that the

use of these drugs should be restricted to those with HeFH, those that are at very high risk of IHD or who are unable to tolerate statin therapy (Catapano 2016).

There are a number of previous systematic reviews on PCSK9 monoclonal antibodies that have included HeFH (Navarese 2015; Schmidt 2017; Zhang 2015). Some have included short-term studies (up to 12 weeks) which are not powered to translate to clinically meaningful outcomes or may lead to bias due to small number of events over a short trial duration (Navarese 2015; Zhang 2015). Furthermore, in all studies there has been limited consideration of the underlying genetic defect on PCSK9 inhibitor effectiveness and discussion regarding the benefit of incorporation into the FH clinical pathway (Navarese 2015; Schmidt 2017; Zhang 2015). This systematic review will include people with FH of all ages.

By not limiting the search to one particular method of PCSK9 inhibition, this review will act as a resource for comparing effectiveness as well as the side effect profile for clinicians managing people with FH. However, within each drug class, this review will consider outcomes based on the individual drugs (rather than combining these studies and analysing a drug class as a whole). This approach is of particular importance given that recent clinical trials of PCSK9 inhibitors have highlighted that even within the same class of drug, there are important differences in side effects and efficacy (Ridker 2017; Sabatine 2017).

In summary, a systematic review will assist with assessing the utility of PCSK9 inhibitors in people with HeFH.

OBJECTIVES

To assess the effectiveness and safety of PCSK9 inhibitors in the primary prevention of IHD in people with HeFH.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials (RCTs).

Types of participants

All ages with either a genetically proven or a clinical diagnosis of HeFH. Clinical diagnosis will be based on recognised diagnostic criteria, e.g. Simon Broome or the Dutch lipid clinic network criteria (Ryan 2015).

Types of interventions

PCSK9 inhibitors given alone versus those given with usual care or versus placebo. Usual care may consist of statin or ezetimibe therapy.

RCTs of at least one year in duration with a minimum follow-up of six months (Taylor 2013). This time point was selected in order to provide safety data and longer-term outcome data that would enhance current care of people with FH.

Types of outcome measures

The ultimate goal of treatment with PCSK9 inhibitors is to reduce the incidence of and mortality from cardiovascular diseases. However, as these drugs are new to the market, RCTs may not yet report such outcome data. Therefore, where mortality data are not available, we will use lipid parameters as surrogate end points for assessing effectiveness. The 'change' means the difference between the values at the beginning and at the end of follow-up. Where possible, we will report the means of both absolute (mmol/L) and relative (%) changes in lipids between groups. An appropriate referenced and validated definition will be used for each of the primary and secondary outcomes where available.

Primary outcomes

1. The composite end-point of IHD (defined as urgent coronary revascularization, unstable angina pectoris, non-fatal and fatal myocardial infarction (as defined by the third universal definition of myocardial infarction (Thygesen 2012)) and coronary heart disease (CHD) death)*
2. Lipid parameters (total cholesterol, LDL-C, HDL-C, triglycerides (mmol/L), apolipoprotein A1 (g/L), apolipoprotein B (g/L) and lipoprotein[a] (mg/dL))

Secondary outcomes

1. Any adverse events (including type 2 diabetes and cancer)
2. All-cause mortality
3. Cognitive function
4. Fasting glucose (mmol/L) and HbA1c (mmol/mol)
5. Myopathy or creatinine kinase rise (units/L)
6. Growth and pubertal development (e.g. z scores or centiles)

* It is anticipated that such outcomes will not be available for those under 18 years of age.

Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We will identify relevant studies from the Group's Inborn Errors of Metabolism Trials Register using the terms: (hypercholesterolaemia OR hypercholesterolemia) AND (PCSK* OR proprotein OR evolocumab OR alirocumab OR IgG1 OR IgG2 OR antibod*).

The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE. Unpublished work is identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS (Scientific Hospital Supplies) Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

We will also search the following databases, registries and resources:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library www.thecochranelibrary.com;
- Medline Ovid (1946 to present);
- Web of Science (1898 to present);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch).

For full search strategies, please see the appendices (Appendix 1).

Searching other resources

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

Data collection and analysis

Selection of studies

Two authors (AR and SN) will independently review the titles and abstracts of articles found in the electronic searches for potential eligible studies for review. The same two authors will independently assess full manuscripts against the inclusion criteria and where necessary resolve any disagreements with discussion or involvement of third author (PC).

Data extraction and management

Two authors (AR and SN) will independently extract relevant primary and secondary outcome data, with disagreement resolved either by discussion or by the involvement of a third author (PC). (See Appendix 2 for the data extraction form.)

Assessment of risk of bias in included studies

Two authors (AR and SN) will independently assess risk of bias, with disagreement resolved either by discussion or by the involvement of a third author (PC). We will assess risk of bias of individual RCTs using the Cochrane 'Risk of bias' assessment tool based on the following items.

- Random sequence generation
- Allocation concealment
- Blinding
- Missing outcome data
- Selective reporting
- Other biases

We will grade the individual items at 'low', 'unclear', or 'high' risk of bias (Higgins 2011c).

Measures of treatment effect

For binary outcome measures (such as adverse events), we will calculate a pooled estimate of the treatment effect for each outcome across trials using the risk ratio (RR) and 95% confidence intervals (CIs) where appropriate. If multiple adverse events are reported in the included trials, we will use 99% CIs to account for multiple statistical testing (Higgins 2011d).

For continuous outcomes (such as lipid parameters and cognitive function), we will record either the mean relative change from baseline for each group or the mean post-treatment or post-intervention values and the standard deviation (SD). If the papers report standard errors (SE) (and if it is possible) we will convert these to SDs. We will present a pooled estimate of treatment effect by calculating the mean difference (MD) and 95% CIs. If we become aware that some data are skewed and therefore we are not able to enter and analyse these within the Review Manager (RevMan) software, we will report these narratively (RevMan 2014). Where data are presented according to different scales (e.g. cognitive functions), we will present the standardised mean difference (SMD) and 95% CIs.

For any time-to-event outcomes included in the review (such as all cause mortality), we plan to extract the log hazard ratio (HR) and SE estimates from the trials and we aim to combine all results using the generic inverse variance method. If log HRs are not available, we will extract log rank P value estimates or survival curve estimates to convert into log HRs and SEs as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Unit of analysis issues

Cross-over trials or clustered randomised trials are not appropriate designs and we will not evaluate these in this review.

If eligible trials have more than one intervention or control arm (e.g. two different PCSK9 inhibitors compared to a control treatment), we will make separate comparisons of each PCSK9 inhibitor invention compared to each control to avoid duplication of participants in the analysis.

Dealing with missing data

Where possible, we will report the numbers and reasons for dropouts and withdrawals in all intervention groups. We will also state whether the papers specify if there were any dropouts or withdrawals. We will contact authors for clarification on missing information, where possible.

In order to allow an intention-to-treat analysis, we will seek data on the number of participants within each outcome event, by allocated treated group, irrespective of compliance and whether or not the individual is later thought to be ineligible or otherwise excluded from treatment or follow-up.

We have chosen not to include cross-over trials due to the risk of treatment carry-over effect, particularly on the LDL receptor. Cluster RCTs will not be appropriate given the variability in FH participants.

Assessment of heterogeneity

We will assess between-trial clinical heterogeneity by examining differences in design, participant characteristics, direction of treatment effect and overlap of treatment effect CIs on forest plots.

We will assess between-trial statistical heterogeneity using the I^2 statistic and Tau^2, the latter calculated from random-effects meta-analysis.

We will interpret an I^2 statistic greater than 50% as an indication of important heterogeneity. Where important heterogeneity is present between studies, we will perform random-effects meta-analysis and we will explore potential sources of heterogeneity through subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Where very high levels of between-trial heterogeneity are present for any outcome (I^2 statistic greater than 75%) which cannot be readily explained, we will not not undertake any meta-analyses but will perform a narrative review.

Assessment of reporting biases

If we are able to include a sufficient number of trials, i.e. 10 or more as recommended by the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011a), we will attempt to assess whether our review is subject to publication bias by using a funnel plot. If we detect asymmetry, we will explore causes other than publication bias.

Data synthesis

If we identify important levels of heterogeneity (as defined above), we will present pooled estimates of the treatment effect using a random-effects model. If this level of heterogeneity is not identified, we will compute pooled estimates of the treatment effect for each outcome under a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We will determine the consistency of PCSK9 inhibitor effect on major cardiovascular events for the following subgroups:

- gender;
- age (younger than 18 years of age or 18 years and over);
- diabetes at baseline; as defined by American Diabetes Association criteria for diabetes mellitus diagnosis (American Diabetes Association 2015);
- baseline LDL-C level (continuous and above 2.5 mmol/L);
- genotype of underlying mutation for HeFH.

We will employ meta-regression (weighted for the inverse variance weights (Thompson 2002)) to explore whether treatment effects differed between trial baseline characteristics on a continuous scale if we are able to include a sufficient number of trials and such an analysis is deemed appropriate.

Sensitivity analysis

To assess the validity and robustness of the review's results, we will perform sensitivity analyses excluding trials at high risk of bias for one or more domains and compare the direction and magnitude of the results of each sensitivity analysis to that of the relevant primary analysis.

Summary of findings and quality of the evidence (GRADE)

We will present a summary of findings table for each comparison made in the review. The following outcomes will be reported in all tables (chosen based on relevance to clinicians and consumers): CVD (composite endpoint); lipid parameters; adverse events; all-cause mortality; cognitive function; genotype of underlying mutation for HeFH.

We will determine the quality of the evidence using the GRADE approach; and downgrade evidence in the presence of a high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results or high probability of publication bias. We will downgrade by one level if considered serious and by two levels if very serious.

We will present results in the Summary of Findings tables in the most appropriate way for the data available, e.g. if included trials report multiple adverse events, we will make a general statement regarding all reported adverse events rather than considering each event separately for brevity and clarity in the tables.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search methods - electronic searches

Database/ Resource	Strategy
Cochrane Central Register of Controlled Trials (CENTRAL)	[Search Manager Form] #1 MeSH descriptor: [Hyperlipoproteinemia Type II] this term only #2 (familial or inherited) near/2 (hypercholesterol*mia*) #3 (Hyperlipoprotein*mia*) near/2 (type II or type IIa or type IIb or type 2 or type 2a or type 2b) #4 #1 or #2 or #3 #5 PCSK-9 or PCSK9 #6 MeSH descriptor: [Proprotein Convertase 9] this term only #7 IgG1 #8 Alirocumab #9 IgG2 #10 Evolocumab #11 MeSH descriptor: [Antibodies, Monoclonal] this term only #12 kexin type 9 #13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 #14 #4 and #13
MEDLINE Ovid (1946 onwards)	1 ((familial or inherited) adj2 hypercholesterol?emia$).tw. 2. Hyperlipoproteinemia Type II/ 3. (Hyperlipoprotein?emia$ adj (type II or type IIa or type IIb or type 2 or type 2a or type 2b)).tw. 4. 1 or 2 or 3

(*Continued*)

	5. PCSK-9.tw. 6. PCSK9.tw. 7. Proprotein Convertase 9/ 8. IgG1.tw. 9. Alirocumab.tw. 10. IgG2.tw. 11. Evolocumab.tw. 12. Antibodies, Monoclonal/ 13. kexin type 9.tw. 14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. 4 and 14 16. randomized controlled trial.pt. 17. controlled clinical trial.pt. 18. randomized.ab. 19. placebo.ab. 20. drug therapy.fs. 21. randomly.ab. 22. trial.ab. 23. groups.ab. 24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 25. (animals not (humans and animals)).sh. 26. 24 not 25 27. 15 and 26 NOTE: Lines#16- #26 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format
Web of Science (1898 to present)	#1 TS=((familial or inherited) NEAR/2 hypercholesterol*emia*) #2 TS=Hyperlipoprotein*emia* #3 TS=(type II OR type IIa OR type IIb OR type 2 OR type 2a OR type 2b) #4 #3 AND #2 #5 #4 OR #1 #6 TS=(PCSK-9 OR PCSK9 OR Proprotein Convertase 9 OR IgG1 OR Alirocumab OR IgG2 OR Evolocumab OR antibody OR antibiodies OR kexin type 9) #7 #6 AND #5 #8 TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) OR TS=(triple blind*) OR TS=(treble blind*) or TS=(singleblind*) OR TS=(doubleblind*) OR TS=(tripleblind*) OR TS=(trebleblind*) OR TS=blinded OR TS=cross* OR TS=RCT #9 #8 AND #7 Note: Line #8 is based on a filter from University of Alberta Libraries http://guides.library.ualberta.ca/c.php?g=248586&p=1655962 (accessed 05 Oct 2017)

(*Continued*)

ClinicalTrials.gov	[Advanced Search Form] OTHER TERMS: PCSK9 OR PCSK-9 OR proprotein OR evolocumab OR alirocumab OR IgG1 OR IgG2 OR antibody OR antibodies OR kexin STUDY TYPE: Interventional Studies CONDITION/ DISEASE: hypercholesterolaemia OR hypercholesterolemia OR hyperlipoproteinemia OR hyperlipoproteinaemia
WHO ICTRP	[Advanced Search Form] CONDITION: hypercholesterolaemia OR hypercholesterolemia OR hyperlipoproteinemia OR hyperlipoproteinaemia [AND] INTERVENTION: PCSK9 OR PCSK-9 OR proprotein OR evolocumab OR alirocumab OR IgG1 OR IgG2 OR antibody OR antibodies OR kexin RECRUITMENT STATUS: All

Appendix 2. Data extraction form

Study selection, quality assessment & data extraction form

First author	**Journal/Conference Proceedings, etc.**	**Year**

Study eligibility			
RCT/Quasi/CCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes / No /Unclear	Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'.

Participants and trial characteristics

Participant characteristics	
	Further details
Age (mean, median, range, etc.)	
Sex of participants (numbers / %, etc.)	

(*Continued*)

Disease status / type, etc. (if applicable)	
Other	

Risk of bias

Allocation of intervention	
State here method used to generate allocation and reasons for grading	Risk of bias (circle)
	Low (Random)
	High (e.g. alternate)
	Unclear

Concealment of allocation	
State here method used to conceal allocation and reasons for grading	Risk of bias (circle)
	Low
	High
	Unclear

Blinding	
Person responsible for participants care	Yes / No
Participant	Yes / No
Outcome assessor	Yes / No
Other (please specify)	Yes / No

Intention-to-treat	
All participants entering trial	
15% or fewer excluded	
More than 15% excluded	
Not analysed as 'intention-to-treat'	
Unclear	

Were withdrawals described? Yes/ No/ not clear
Discuss if appropriate……
…….

Selective outcome reporting	
Have you been able to access the trial protocol?	
Are all outcomes listed in protocol reported in the full trial paper?	

Data extraction	
Outcomes relevant to your review	
	Reported in paper (circle)
Outcome 1 Composite CVD	Yes / No
Outcome 2 Lipid parameters	Yes / No
Outcome 3 Any adverse events	Yes / No
Outcome 4 All cause mortality	Yes / No
Outcome 5 Cognitive function	Yes / No
Outcome 6 Fasting glucose	Yes / No
Outcome 7 Myopathy / creatinine kinase rise	Yes / No

(*Continued*)

Outcome 8 Genotype	Yes / No

For continuous data

Code Of paper	Outcomes (re-name)	Unit of measurement	Intervention group		Control group		Details if outcome only described in text or other data presented, e.g. P value.
			n	Mean (SD)	n	Mean (SD)	

For dichotomous data

Code of Paper	Outcomes (rename)	Intervention group (n)	Control group (n)

(*Continued*)

Other information which you feel is relevant to the results
Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc.; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review

Trial characteristics	
	Further details
Single centre / multicentre	
Country / countries	
How was participant eligibility defined?	
How many people were randomised?	
Number of participants in each intervention group	
Number of participants who received intended treatment	
Number of participants who were analysed	
Drug treatment(s) used	
Dose / frequency of administration	
Duration of treatment (State weeks / months, etc., if cross-over trial give length of time in each arm)	
Median (range) length of follow-up reported in this paper (state weeks, months or years or if not stated)	
Timepoints when measurements were taken during the study	
Timepoints reported in the study	

(*Continued*)

Timepoints you are using in metaview	
Trial design (e.g. parallel / cross-over*)	
Other	

CONTRIBUTIONS OF AUTHORS

AR drafted the protocol with input from the remaining authors.

DECLARATIONS OF INTEREST

All authors: none known.

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