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Bile acid sequestrants for primary prevention of ischaemic heart disease in heterozygous familial hypercholesterolaemia (Protocol)

Ryan A, Nevitt SJ, Cook P

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[Intervention Protocol]

Bile acid sequestrants for primary prevention of ischaemic heart disease in heterozygous familial hypercholesterolaemia

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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 BAS 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 level of low density lipoprotein (LDL) cholesterol. Historically, it has been shown that if left untreated, it will lead to at least 50% of men under 50 years old and 30% of women under 60 years old developing ischaemic heart disease (IHD) (Slack 1969; Stone 1974). A more recent observational study showed that the presence of a causative FH mutation may increase the risk of IHD six-fold as compared with those with a similar cholesterol level with no mutation, and a 22-fold risk compared with those with normocholesterolaemia (Khera 2016). FH is an autosomal dominant disorder with the severe homozygous form occurring in one in a million people and the less severe heterozygote form (HeFH) in one in 200 to 500 people (Nordestgaard 2013). Based on these prevalences, it is estimated that FH affects between 13 and 34 million people worldwide; however, due to differences in screening, in many countries less than 1% of individuals have been diagnosed. The diagnosis of FH is based on either clinical criteria or genetic testing (Ryan 2015). Current registry data have shown early diagnosis and treatment reduce 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 guidelines (Nordestgaard 2013).

Description of the intervention

Prior to the introduction of statin therapy, bile acid sequestrants (BAS) were the first-line treatment in managing FH. Current guidance recommends their use as a second- or third-line option in those with statin intolerance or in those individuals failing to achieve LDL targets on statins (Nordestgaard 2013). BAS are non-absorbable resins that bind negatively charged bile acids in the

intestinal lumen. This diverts bile acids from enterohepatic cycling into the faeces for excretion (Insull 2006). The earlier BAS, colestryramine and colestipol, were bulky and unpalatable with doses in adults starting at 4 g to 5 g per day, gradually building up to a maximum of 30 g to 36 g per day (taken in divided doses). The newer BAS, colevelam, is less bulky with doses in adults up to 3.75 g per day in divided doses and was designed to be more palatable and potent than its predecessors (Davidson 1999).

As these drugs are not systemically absorbed, side effects are mainly intestinal, causing constipation at higher doses and malabsorption of fat-soluble vitamins and drugs such as thiazides, digoxin and warfarin. It is possible to avoid such an interaction by altering the timing of drug administration, e.g. taking them at least one hour before or four to six hours after resin ingestion. Interestingly, BAS may also increase triglycerides, particularly in those with already elevated levels of very low density lipoprotein (VLDL), and hence should be avoided in this group (Miller 1973).

How the intervention might work

Interruption in the enterohepatic recycling of bile acid synthesis affects cholesterol metabolism in several ways (Einarsson 1991). Increased faecal bile acid output is compensated by their increased hepatic synthesis from cholesterol, which is a bile acid precursor (Moutafis 1977). This effect is mainly driven by an increase in cholesterol 7α hydroxylase, which is the rate-limiting step for bile acid synthesis. This leads to an increase in the demand for cholesterol by hepatocytes, thus increasing LDL receptor expression (Shepherd 1980). The plasma concentration of LDL is therefore lowered through a combination of these mechanisms; however, it is likely that the increase in LDL receptor expression is the predominant mechanism as BAS lose efficacy in those individuals with null LDL receptor expression (Betteridge 1992).

These resins, however, are believed to have more than just an effect on binding bile acids in the gut. They are thought to inactivate the farnesoid X receptor to increase high density lipoprotein (HDL) production and increase TG5 and GLP-1, thus decreasing fasting glucose and Hba1c (Marina 2012; Potthoff 2013). These effects may be of relevance where other lipid-lowering therapies have been shown to increase risk of diabetes mellitus and are discussed below.

Why it is important to do this review

Recent guidance has highlighted the significant unmet need for both diagnosing and treating FH. Observational data have identified that less than 50% of people with FH are on first-line statin therapy, with similar numbers of individuals failing to achieve LDL targets (Nordestgaard 2013). There is now a growing body of evidence that suggests that additional therapy or alternatives to statin therapy in FH are required (Nordestgaard 2013; Vallejo-Vaz 2016). A systematic review of BAS trials will help evaluate the role of these drugs in the FH-patient care pathway.

There have been concerns regarding the potential diabetogenic effects of statins and more recently PCSK9 inhibitors as suggested by a mendelian randomisation study, particularly in those with pre-existing impaired fasting glucose (Lotta 2016). During trials on dyslipidaemia in people with diabetes it was noted that BAS improved glucose control by unknown mechanisms and there are a number of trials exploring these positive effects on glycaemia (Rosenstock 2012; Yamakawa 2007). There is also a growing body of evidence to suggest that the risk of IHD in HeFH is also influenced by traditional risk factors, such as hypertension, smoking cigarettes and diabetes (Besseling 2014). This suggests that when combined with standard therapy such as statins, any positive effect on glucose may be of benefit and important to the FH-patient care pathway.

A previous systematic review found that BAS reduced LDL with a range of 9.6% to 20.6%; however, this included many studies of less than 12 weeks duration and only one of these was in people with FH, the rest being in people with diabetes (Mazidi 2017). Davidson undertook a systematic review on BAS and FH in 2011; however, this was limited to children and the evidence for adults with FH remained unexplored (Davidson 2011). A mendelian randomisation study on BAS in hypercholesterolaemia has suggested an odds ratio of 0.63 for coronary artery disease; however, FH received limited discussion (Ross 2015). This evidence suggests that BAS have a beneficial effect on reducing risk of cardiovascular disease (CVD) in hypercholesterolaemia, but there is an unmet need for a systematic review that explores the role of BAS in the FH-patient pathway.

OBJECTIVES

To assess the effectiveness and safety of BAS 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.

Types of participants

People of all ages with FH diagnosed either genetically or clinically (based on a referenced, validated FH clinical diagnosis scoring system).

Types of interventions

Active treatment with a BAS (e.g. colsevalam, colestipol) compared to either another BAS, placebo, diet, or with another lipid-lowering agent (e.g. a statin, ezetimibe, or a PCSK9 inhibitor). Eligible studies will be at least one year in duration, with a minimum follow-up of six months (Taylor 2013). This duration was selected in order to provide safety data and longer-term outcome data that would enhance current care for people with FH.

Types of outcome measures

Primary outcomes

1. CVD (a composite end-point defined as urgent coronary revascularization, unstable angina pectoris, non-fatal and fatal myocardial infarction and coronary heart disease death)*
2. Change from baseline in lipid parameters (total cholesterol, LDL-C, HDL-C, triglycerides (mmol/L), apolipoprotein A1 (g/L), apolipoprotein B (g/L) and lipoprotein[a] (mg/dL)) measured as both absolute (mmol/L) and relative (%) changes where possible

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

Secondary outcomes

1. Adverse events (including type 2 diabetes and cancer)
2. All-cause mortality
3. Myopathy or myalgia or creatinine kinase (CK) rise (units/L)*
4. Fasting glucose (mmol/L) and HbA1c (mmol/mol)
5. Upper and lower gastrointestinal disturbance

* Myopathy is defined as any muscle symptom; myalgia where muscle symptoms occur with CK within reference range; myositis where muscle symptoms occur with CK above the reference range (Pasternak 2002).

Search methods for identification of studies

We will search for all relevant published and unpublished studies 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.

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 and the prospective hand-searching of one journal - *Journal of Inherited Metabolic Disease*. 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 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 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 the full search strategies, please see Appendix 1.

Searching other resources

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

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 potentially eligible studies for review. The same two authors will independently assess the full manuscripts (if available) against the inclusion criteria and, where necessary, resolve any disagreements with discussion or the involvement of the third author (PC).

Data extraction and management

Two authors (AR and SN) will independently extract relevant primary and secondary outcome data, with any disagreement resolved either by discussion or by the involvement of the third author (PC).

Assessment of risk of bias in included studies

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

- Random sequence generation
- Allocation concealment
- Intervention blinding
- Outcome blinding
- Missing outcome data
- Selective reporting
- Other biases

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

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 studies using risk ratio (RR) and 95% confidence intervals (CIs) where appropriate. If multiple adverse events are reported in the included studies, we will use 99% CIs to account for multiple statistical testing.

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), we will convert these to SDs using the methodology as described in chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). 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 are not able to enter and analyse these within the Review Manager (RevMan) software, we will report these narratively (Deeks 2011). 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 studies and we aim to combine all the results using the generic inverse variance method. If log HRs are not available, we will extract the 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 2011c).

Unit of analysis issues

Cross-over studies and clustered randomised studies are not appropriate designs and we will not be evaluating these in this review.

If eligible studies have more than one intervention or control arm (e.g. two different BAS compared to a control treatment), we will make separate comparisons of each BAS 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 drop-outs and withdrawals in all intervention groups. 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 treatment group, irrespective of compliance and whether or not the individual is later thought to be ineligible or otherwise excluded from treatment or follow-up (Higgins 2011d).

Assessment of heterogeneity

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

We will assess the between-study 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-study heterogeneity are present (I^2 statistic greater than 75%) which cannot be readily explained, we will not perform meta-analyses. Instead, we will perform a narrative review (Higgins 2003).

Assessment of reporting biases

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

Subgroup analysis and investigation of heterogeneity

We will determine the consistency of the effects of BAS on major cardiovascular events for the following subgroups:

- gender;
- age (under 18 years of age or 18 years and over);
- baseline characteristics (presence of diabetes; LDL-C level (continuous and above 2.5 mmol/L); body mass index (BMI) (less than 25, 25 to 29.99, 30 or more);
- FH genotype.

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

Sensitivity analysis

In order to assess the validity and robustness of the review's results, we will perform sensitivity analyses excluding studies at high risk of bias for one or more domains and compare the direction and magnitude of results of the sensitivity analyses to that of the primary analyses (Deeks 2011).

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; changes in fasting glucose (mmol/L) and HbA1C(mmol/mol). We will also note the genotype of the 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 study; indirectness of the evidence; unexplained heterogeneity or inconsistency; imprecision of results; or a high probability of publication bias. We will downgrade the evidence by one level if we consider the limitation to be 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 studies 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) (Shemilt 2011).

ACKNOWLEDGEMENTS

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REFERENCES

Additional references

Besseling 2014
Besseling J, Kindt I, Hof M, Kastelein JJ, Hutten BA, Hovingh GK. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. *Atherosclerosis* 2014;**233**(1):219–23.

Betteridge 1992
Betteridge DJ, Bhatnager D, Bing RF, Durrington PN, Evans GR, Flax H, et al. Treatment of familial hypercholesterolaemia. The United Kingdom lipid clinics study of pravastatin and cholestyramine. *BMJ* 1992;**304** (6838):1335–8.

Davidson 1999
Davidson MH, Dillon MA, Gordon B, Jones P, Samuels J, Weiss S, et al. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Archives of Internal Medicine* 1999;**159**(16):1893–900.

Davidson 2011
Davidson MH. A systematic review of bile acid sequestrant therapy in children with familial hypercholesterolemia. *Journal of Clinical Lipidology* 2011;**5**(2):76–81.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG, editor(s) on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Einarsson 1991
Einarsson K, Ericsson S, Ewerth S, Reihnér E, Rudling M, Ståhlberg D, et al. Bile acid sequestrants: mechanisms of action on bile acid and cholesterol metabolism. *European Journal of Clinical Pharmacology* 1991;**40 Suppl 1**:53–8.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**

(7414):557–60.

Higgins 2011a
Higgins JPT, Altman DG, Sterne JAC, editor(s) on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b
Higgins JPT, Deeks JJ, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011c
Higgins JPT, Deeks JJ, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011d
Higgins JPT, Deeks JJ, Altman DG, editor(s) on behalf of the Cochrane Statistical Methods Group. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S, editor(s). Cochrane Handbook of Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011e
Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration 2011. Available from handbook.cochrane.org.

Insull 2006
Insull W Jr. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *Southern Medical Journal* 2006;**99**(3):257–73.

Khera 2016
Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, et al. Diagnostic yield of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *Journal of the American College Cardiology* 2016;**67**(22):2578–89.

Lotta 2016
Lotta LA, Sharp SJ, Burgess S, Perry JR, Stewart ID, Willems SM, et al. Association between low-density lipoprotein cholesterol-lowering genetic variants and risk of type 2 diabetes: a meta-analysis. *JAMA* 2016;**316**(13): 1383–91.

Marina 2012
Marina AL, Utzschneider KM, Wright LA, Montgomery BK, Marcovina SM, Kahn SE. Colesevelam improves oral but not intravenous glucose tolerance by a mechanism independent of insulin sensitivity and β-cell function. *Diabetes Care* 2012;**35**(5):1119–25.

Mazidi 2017
Mazidi M, Rezaie P, Karimi E, Kengne AP. The effects of bile acid sequestrants on lipid profile and blood glucose concentrations: a systematic review and meta-analysis of randomized controlled trials. *International Journal of Cardiology* 2017;**15**(227):850–7.

Miller 1973
Miller NE, Cifton-Bligh P, Nestel PJ. Effects of colestipol, a new bile acid sequestering resin on cholesterol metabolism in man. *Journal of Laboratory and Clinical Medicine* 1973; **82**(6):876–90.

Moutafis 1977
Moutafis CD, Simons LA, Myant NB, Adams PW, Wynn V. The effect of cholestyramine on the faecal excretion of bile acids and neutral steroids in familial hypercholesterolaemia. *Atherosclerosis* 1977;**26**(3):329–34.

Mundal 2014
Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierød MB, et al. Mortality among patient with familial hypercholesterolaemia: a registry-based study in Norway, 1999-2010. *JAMA* 2014;**3**(6):e001236.

Nordestgaard 2013
Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *European Heart Journal* 2013;**34**(45):3478–90a.

Pasternak 2002
Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Journal of the American College of Cardiology* 2002;**40**(3):567–72.

Potthoff 2013
Potthoff MJ, Potts A, He T, Duarte JA, Taussig R, Mangelsdorf DJ, et al. Colesevelam suppresses hepatic glycogenolysis by TGR5-mediated induction of GLP-1 action in DIO mice. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2013;**304**(4):371–80.

Rosenstock 2012
Rosenstock J, Hernandez-Triana E, Handelsman Y, Misir S, Jones MR, Nagendran S. Initial combination therapy with metformin plus colesevelam in drug-naïve Hispanic patients with early type 2 diabetes. *Postgraduate Medicine* 2012;**124** (4):7–13.

Ross 2015
Ross S, D'Mello M, Anand SS, Eikelboom J, CARDIoGRAMplusC4D Consortium, Stewart AF, et al.

Effect of bile acid sequestrants on the risk of cardiovascular events: a Mendelian randomization analysis. *Circulation. Cardiovascular Genetics* 2015;**8**(4):618–27.

Ryan 2015
Ryan A, Byrne CD. Importance of early recognition of heterozygous familial hypercholesterolaemia. *Current Opinion in Lipidology* 2015;**26**(4):298–303.

Shemilt 2011
Shemilt I, Mugford M, Byford S, Drummond M, Eisenstein E, Knapp M, et al on behalf of the Campbell and Cochrane Economics Methods Group. Chapter 15: Incorporating economics evidence. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Shepherd 1980
Shepherd J, Packard CJ, Bicker S, Lawrie TD, Morgan HG. Cholestyramine promotes receptor mediated low-density lipoprotein catabolism. *New England Journal of Medicine* 1980;**302**(22):1219–22.

Slack 1969
Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemic states. *Lancet* 1969;**2**(7635): 1380–2.

Stone 1974
Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation* 1974;**49**(3):476–88.

Taylor 2013
Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD004816.pub5

Vallejo-Vaz 2016
EAS Familial Hypercholesterolaemia Studies Collaboration, Vallejo-Vaz AJ, Akram A, Kondapally Seshasai SR, Cole D, Watts GF, et al. Pooling and expanding registries of familial hypercholesterolaemia to assess gaps in care and improve disease management and outcomes: rationale and design of the global EAS Familial Hypercholesterolaemia Studies Collaboration. *Atherosclerosis. Supplements* 2016;**22**:1–32.

Versmissen 2008
Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;**337**:a2423.

Yamakawa 2007
Yamakawa T, Takano T, Utsunomiya H, Kadonosono K, Okamura A. Effect of colestimide therapy for glycemic control in type 2 diabetes mellitus with hypercholesterolemia. *Endocrine Journal* 2007;**54**(1):53–8.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search methods - electronic searches

Database/ Resource	Strategy
CENTRAL (via the Cochrane Library)	[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 sequestrant* #6 BAS #7 (Colesevelam or Cholestagel or Welchol or Lodalis) #8 MeSH descriptor: [Colesevelam Hydrochloride] this term only #9 (Colestipol or Colestid or Cholestabyl)

(*Continued*)

	#10 MeSH descriptor: [Colestipol] this term only #11 (Cholestyramine or Colestyramine or Questran or Prevalite) #12 MeSH descriptor: [Cholestyramine Resin] this term only #13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 #14 #4 and #13
Medline Ovid (1946 to present)	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 5. sequestrant$.tw. 6. BAS.tw. 7. (Colesevelam or Cholestagel or Welchol or Lodalis).tw. 8. Colesevelam Hydrochloride/ 9. (Colestipol or Colestid or Cholestabyl).tw. 10. Colestipol/ 11. (Cholestyramine or Colestyramine or Questran or Prevalite).tw 12. Cholestyramine Resin/ 13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 14. randomized controlled trial.pt. 15. controlled clinical trial.pt. 16. randomized.ab. 17. placebo.ab. 18. drug therapy.fs. 19. randomly.ab. 20. trial.ab. 21. groups.ab. 22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 23. exp animals/ not humans.sh. 24. 22 not 23 25. 4 and 13 and 24 NOTE: Lines #16- #24 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=(sequestrant* OR BAS OR Colesevelam OR Cholestagel OR Welchol OR Lodalis OR Colestipol OR Colestid OR Cholestabyl OR Cholestyramine OR Colestyramine OR Questran OR Prevalite) #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

(*Continued*)

	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)
ClinicalTrials.gov	[Advanced Search form] OTHER TERMS: sequestrant OR sequestrants OR BAS OR Colesevelam OR Cholestagel OR Welchol OR Lodalis OR Colestipol OR Colestid OR Cholestabyl OR Cholestyramine OR Colestyramine OR Questran OR Prevalite STUDY TYPE: Interventional Studies CONDITION/ DISEASE: hypercholesterolemia OR hypercholesterolaemia OR Hyperlipoproteinemia OR Hyperlipoproteinaemia
WHO ICTRP	[Advanced Search Form] CONDITION: hypercholesterolemia OR hypercholesterolaemia OR Hyperlipoproteinemia OR Hyperlipoproteinaemia INTERVENTION: sequestrant OR sequestrants OR Colesevelam OR Cholestagel OR Welchol OR Lodalis OR Colestipol OR Colestid OR Cholestabyl OR Cholestyramine OR Colestyramine OR Questran OR Prevalite RECRUITMENT STATUS: All

CONTRIBUTIONS OF AUTHORS

AR drafted the protocol with input from the other authors.

DECLARATIONS OF INTEREST

All authors: none known.

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