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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**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 to the faeces for excretion (Insull 2006). The earlier BAS, colestyramine 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, coleveland, 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; Porthoff 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 (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**

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) (www.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 I² statistic and Tau², the latter calculated from random effects meta-analysis.

We will interpret an I² 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 (I² 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

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

References

Additional references

Besseling 2014

Betteridge 1992

Davidson 1999

Davidson 2011

Deeks 2011

Einarsson 1991

Higgins 2003

Higgins 2011a

Higgins 2011b

Higgins 2011c

Higgins 2011d

Insull 2006

Khela 2016

Lotta 2016

Marina 2012

Mazidi 2017

Miller 1973

Moutafis 1977

Mundal 2014

Nordestgaard 2013

Pasternak 2002

Potthoff 2013

Rosenstock 2012

Ross 2015

Ryan 2015

Shemilt 2011

Shepherd 1980

Slack 1969

Stone 1974

Taylor 2013

Vallejo-Vaz 2016

Versmissen 2008

Yamakawa 2007

* Indicates the major publication for the study

APPENDICES

Appendix I. Search methods - electronic searches

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<th>Strategy</th>
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<tr>
<td>CENTRAL (via the Cochrane Library)</td>
<td>[Search Manager Form] #1 MeSH descriptor: [Hyperlipoproteinemia Type II] this term only #2 (familial or inherited) near/2 (hypercholesterol<em>mia</em>) #3 (Hyperlipoprotein<em>mia</em>) 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 (Colestevam or Cholestagel or Welchol or Lodalis) #8 MeSH descriptor: [Colestevam Hydrochloride] this term only #9 (Colestipol or Colestitd or Cholestably)</td>
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<table>
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<tr>
<th>MeSH descriptor: [Colestipol] this term only</th>
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<td>#11</td>
</tr>
<tr>
<td>#12 MeSH descriptor: [Cholestyramine Resin] this term only</td>
<td>#12</td>
</tr>
<tr>
<td>#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12</td>
<td>#13</td>
</tr>
<tr>
<td>#14 #4 and #13</td>
<td>#14</td>
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**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 Colesid or Cholestabyl).tw.
10. Colestipol/
11. (Cholestyramine or Colestyrmine 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 Colesid 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=study 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)

ClinicalTrials.gov
[Advanced Search form]
OTHER TERMS: sequestrant OR sequestrants OR BAS OR Colesevelam OR Cholestagel OR Welchol OR Lodalis 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 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.

SOURCES OF SUPPORT
Internal sources
- No sources of support supplied
**External sources**

- National Institute for Health Research, UK.

  This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.