# Table of Contents

- Header .................................................. 1
- Abstract ................................................ 1
- Plain Language Summary .............................. 2
- Summary of Findings for the Main Comparison .... 2
- Background ............................................. 5
- Objectives .............................................. 6
- Methods ............................................... 6
  - Figure 1 ............................................. 9
- Results ................................................ 11
  - Figure 2 ............................................. 14
  - Figure 3 ............................................. 15
- Discussion ............................................ 18
- Authors' Conclusions ................................ 19
- Acknowledgements .................................... 19
- References ........................................... 19
- Characteristics of Studies ......................... 23
- Data and Analyses .................................... 38
  - Analysis 1.1. Comparison 1 Colesevelam versus placebo, Outcome 1 Adverse events. ............... 40
  - Analysis 1.2. Comparison 1 Colesevelam versus placebo, Outcome 2 Mortality. ....................... 41
  - Analysis 1.3. Comparison 1 Colesevelam versus placebo, Outcome 3 Mean change in fasting blood glucose from baseline to endpoint. .................................................. 42
  - Analysis 1.4. Comparison 1 Colesevelam versus placebo, Outcome 4 Mean change in HbA1c from baseline to endpoint. .................................................. 43
  - Analysis 1.5. Comparison 1 Colesevelam versus placebo, Outcome 5 Mean change in LDL-cholesterol from baseline to endpoints. ........................................ 44
  - Analysis 1.6. Comparison 1 Colesevelam versus placebo, Outcome 6 Mean change in HOMA-index. .................................................. 45
  - Analysis 1.7. Comparison 1 Colesevelam versus placebo, Outcome 7 Mean change in fasting C-peptide. .................................................. 45
  - Analysis 1.8. Comparison 1 Colesevelam versus placebo, Outcome 8 Mean change in fasting insulin. .................................................. 46
  - Analysis 1.9. Comparison 1 Colesevelam versus placebo, Outcome 9 Mean change in 2-h post-MTT C-peptide. .................................................. 46
  - Analysis 1.10. Comparison 1 Colesevelam versus placebo, Outcome 10 Mean change in 2-h post-MTT insulin. .................................................. 47
- Additional Tables ...................................... 47
- Appendices ............................................. 48
- History .................................................. 61
- Contributions of Authors ............................. 61
- Declarations of Interest ............................... 61
- Sources of Support ..................................... 62
- Differences Between Protocol and Review ........ 62
- Index Terms ........................................... 62
ABSTRACT

Background
Colesevelam is a second-generation bile acid sequestrant that has effects on both blood glucose and lipid levels. It provides a promising approach to glycaemic and lipid control simultaneously.

Objectives
To assess the effects of colesevelam for type 2 diabetes mellitus.

Search methods
Several electronic databases were searched, among these The Cochrane Library (Issue 1, 2012), MEDLINE, EMBASE, CINAHL, LILACS, OpenGrey and Proquest Dissertations and Theses database (all up to January 2012), combined with handsearches. No language restriction was used.

Selection criteria
We included randomised controlled trials (RCTs) that compared colesevelam with or without other oral hypoglycaemic agents with a placebo or a control intervention with or without oral hypoglycaemic agents.

Data collection and analysis
Two review authors independently selected the trials and extracted the data. We evaluated risk of bias of trials using the parameters of randomisation, allocation concealment, blinding, completeness of outcome data, selective reporting and other potential sources of bias.

Main results
Six RCTs ranging from 8 to 26 weeks investigating 1450 participants met the inclusion criteria. Overall, the risk of bias of these trials was unclear or high. All RCTs compared the effects of colesevelam with or without other antidiabetic drug treatments with placebo only (one study) or combined with antidiabetic drug treatments. Colesevelam with add-on antidiabetic agents demonstrated a statistically significant reduction in fasting blood glucose with a mean difference (MD) of -15 mg/dL (95% confidence interval (CI) -22 to -8), P < 0.0001; 1075 participants, 4 trials, no trial with low risk of bias in all domains. There was also a reduction in glycosylated haemoglobin A1c (HbA1c) in favour of colesevelam (MD -0.5% (95% CI -0.6 to -0.4), P < 0.00001; 1315 participants, 5 trials, no trial with low risk of bias in all domains. However, the single trial comparing colesevelam to placebo only (33 participants) did not reveal a statistically significant difference between the two arms - in fact, in both arms HbA1c increased. Colesevelam with add-on antidiabetic agents
demonstrated a statistical significant reduction in low-density lipoprotein (LDL)-cholesterol with a MD of -13 mg/dL (95% CI -17 to -9), P < 0.00001; 886 participants, 4 trials, no trial with low risk of bias in all domains. Non-severe hypoglycaemic episodes were infrequently observed. No other serious adverse effects were reported. There was no documentation of complications of the disease, morbidity, mortality, health-related quality of life and costs.

Authors’ conclusions

Colesevelam added on to antidiabetic agents showed significant effects on glycaemic control. However, there is a limited number of studies with the different colesevelam/antidiabetic agent combinations. More information on the benefit-risk ratio of colesevelam treatment is necessary to assess the long-term effects, particularly in the management of cardiovascular risks as well as the reduction in micro- and macrovascular complications of type 2 diabetes mellitus. Furthermore, long-term data on health-related quality of life and all-cause mortality also need to be investigated.

Plain language summary

Colesevelam for type 2 diabetes mellitus

Colesevelam was originally approved for the treatment of hyperlipidaemia (high blood lipids) in the 2000s but has been shown to improve blood sugar as well. Therefore, we investigated its role in the management of type 2 diabetes mellitus. A total of 1450 patients took part in six studies investigating colesevelam. These studies lasted 8 to 26 weeks. Only one small study compared colesevelam directly to placebo, the other five studies investigated a combination of colesevelam with other antidiabetic agents versus a combination of placebo with other antidiabetic agents. There were no two studies with the same intervention and comparison group. When added to other antidiabetic agents colesevelam showed improvements in the control of blood glucose and blood lipids. However, it is difficult to disentangle the effects of colesevelam from the other antidiabetic agents used because only one study compared colesevelam to placebo. The same is true for adverse effects: three studies reported on just a few non-severe hypoglycaemic episodes, no other serious side effects were observed. No study investigated mortality; complications of type 2 diabetes such as eye disease, kidney disease, heart attack and stroke; health-related quality of life; functional outcomes and costs of treatment. Therefore, long-term data on the efficacy and safety of colesevelam are necessary.
Summary of Findings for the Main Comparison

**Colesevelam compared for type 2 diabetes mellitus**

**Patient or population:** patients with type 2 diabetes mellitus  
**Settings:** outpatient  
**Intervention:** colesevelam (± antidiabetic agents)  
**Comparison:** placebo (± antidiabetic agents)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity</td>
<td>Not estimable</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Not estimable</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>Not estimable</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>Not estimable</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td>Not estimable</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>RR 1.06 (0.97 to 1.15)</td>
<td>1450 (6)</td>
<td>⬤ ⬤ ⬤ ⬤ very low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c change from baseline to end point (%) (follow-up 12 to 26 weeks)</td>
<td>The mean HbA1c change ranged across control groups from -0.8% to 0%</td>
<td>The mean HbA1c change in the intervention groups was 0.4% to 0.6% lower</td>
<td>MD -0.5% (-0.6 to -0.4)</td>
<td>1315 (5)</td>
<td>⬤ ⬤ ⬤ ⬤ very low</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; HbA1c: glycosylated haemoglobin A1c; RR: risk ratio
<table>
<thead>
<tr>
<th>GRADE Working Group grades of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High quality:</strong> Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td><strong>Moderate quality:</strong> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td><strong>Low quality:</strong> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td><strong>Very low quality:</strong> We are very uncertain about the estimate.</td>
</tr>
</tbody>
</table>

1. There was insufficient information on the process of randomisation and incomplete data reporting.
2. There were no two trials with the same intervention and comparison group.
BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is, elevated levels of plasma glucose) with disturbances of carbohydrate, fat, and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy and the risk of cardiovascular disease (CVD) is increased. For a detailed overview of diabetes mellitus, please see under ‘Additional information’ in the information on the Metabolic and Endocrine Disorders Group in The Cochrane Library (see ‘About’, ‘Cochrane Review Groups (CRGs)’). For an explanation of methodological terms, see the main glossary in The Cochrane Library.

Type 2 diabetes mellitus (T2DM) is pandemic globally (IDF 2009). The Asia-Pacific region will face the most challenges of this disease burden (Chan 2009). More than half of the world’s population live here ranging from the richest and most developed countries to the poorest and least-developed ones. There is a predisposition to disproportionate effects on the lower socioeconomic groups as well as middle-aged and older adults (Agadh 2011). In addition, with the poor quality of blood glucose and the associated risk factors control is far from satisfactory (Chan 2009; Cheung 2009; Kolding 2006; Yang 2012). Taken together with the confluence of the recent upsurge of obesity and an ageing population, this will have a far-reaching negative impact on income security, social welfare and medical services (Bruno 2011; Dall 2010; Pan 2010), particularly of the low- and middle-income developing countries in the Asia-Pacific region (Abegunde 2007; Tharkar 2010; Zhang 2010).

CVD is strikingly common, affecting almost 50% of the population with T2DM (Bays 2007; Chan 2009; Lloyd-Jones 2010; NIDDKD 2011), and carries significant morbidity, disability, dependency and mortality (Kalyani 2010). Dyslipidaemia together with hypertension and hyperglycaemia are established risk factors for CVD among the patients with T2DM and are clearly modifiable. Targeting the patients with T2DM and are clearly modifiable. Targeting the patients with T2DM and are clearly modifiable. Targeting the patients with T2DM and are clearly modifiable. Targeting the patients with T2DM and are clearly modifiable. Targeting the patients with T2DM and are clearly modifiable. If the mentioned drugs are given four hours before colesevelam. There is also a potential decrease of absorption of drugs with narrow therapeutic index, such as phenytoin, as well as fat-soluble vitamins (Jacobson 2007; Schmidt 2010).

Adverse effects of the intervention

Compared to its predecessors, the unique polymer structure of this orally administered drug allows for greater tolerability, fewer adverse effects and fewer potential drug interactions (Hanus 2006). Nonetheless, adverse effects are reported to include gastrointestinal (GI) and metabolic effects. Dysphagia, oesophageal obstruction and constipating effects may be aggravated in patients with GI motility disorders (Bays 2008; Davidson 1999; Fonseca 2008; Goldberg 2008; Zieve 2007). These findings further provided the basis for the approval of colesevelam by the US Food and Drug Administration (FDA) in 2008 as an adjunct therapy for glycaemic control in adults with T2DM.

How the intervention might work

Although colesevelam has a favourable effect on glycaemic parameters, the underlying mechanisms remain unclear. Proposed mechanisms include reduction in glucose absorption following binding to the colesevelam molecule and BAs leading to changes in the time course of glucose absorption in the GI tract (Staels 2009). Alternatively, the resulting drug-BA complex may modulate the

Description of the intervention

Colesevelam is a specifically designed second-generation bile acids (BAs) sequestrant for more selective and high-capacity BA-binding (Bays 2003). The non-absorbable polymer along with the hydrophilic and water-insoluble nature further facilitates binding upon BAs in the intestine and formation of a non-absorbable complex for elimination in the faeces (Rosenbaum 1997). Colesevelam was originally approved for the treatment of hyperlipidaemia in 2002 (NCEP 2002). Clinical studies of colesevelam monotherapy demonstrated a lowering of low-density lipoprotein cholesterol (LDL-C) levels from 15% to 19%. When combining with another lipid-lowering agent, LDL-C levels were further reduced between 42% to 48% (Davidson 1999; Insull 2001; Rosenson 2006). Evolving clinical trials also demonstrated improvement of glycaemic control in patients with T2DM (Bays 2008; Fonseca 2008; Goldberg 2008; Zieve 2007). These findings further provided the basis for the approval of colesevelam by the US Food and Drug Administration (FDA) in 2008 as an adjunct therapy for glycaemic control in adults with T2DM.
enterohepatic pathway of bile metabolism or the farnesoid X receptor (Claudel 2005; Herrema 2010; Staels 2009).

The mechanisms of action for lipid control are better understood compared to those of glycaemic control. Binding of colesevelam with BAs in the intestine impedes the re-absorption of BAs. The result is a reduction in LDL-C ranging from 10% at 2.3 g/day to 13% at 3.8 g/day with a threefold increase in faecal BA excretion (Donovan 2005). Accompanying very low-density lipoprotein cholesterol (VLDL-C) production may increase triglyceride levels, but high-density lipoprotein cholesterol (HDL-C) is generally unaffected or slightly increased (Insull 2006).

Why it is important to do this review

Colesevelam differs from other antidiabetic drugs in that it reduces both glucose level and LDL-C through the BA pathways and not the classical interactions among the triumvirate of impaired β-cell function leading to diminished insulin secretion, increased hepatic glucose production and peripheral insulin resistance (DeFronzo 1987; Houten 2006). The majority of the current armamentarium of established pharmacological agents for T2DM have only a glucocentric focus.

The goals for diabetes mellitus reach from glycaemic control to the reduction of all risk factors associated with microvascular and macrovascular disease complications. Apart from education and lifestyle modification (nutrition, weight reduction, exercise and smoking cessation), pharmacological agents are important components of effective treatment of T2DM. However, balancing the multiple goals of ideal T2DM care with the realities of patient adherence, expectations and socioeconomic circumstances are major challenges.

Understanding of the efficacy of colesevelam in the context of T2DM management would have potential implications for the treatment of the disease. Currently, there is still no comprehensive health technology assessment review on colesevelam for T2DM. Previous reviews on the use of colesevelam in clinical trials were focused on the lipid-lowering properties and did not specifically examine the issues in T2DM. One systematic review of colesevelam for T2DM focused on only three clinical trials, even though there were others available (Fonseca 2010). The aim of this review is to identify, examine and assemble comprehensive quality evidence on colesevelam for management of T2DM.

OBJECTIVES

To assess the effects of colesevelam on type 2 diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies
Randomised controlled clinical trials.

Types of participants
All adults of 18 years or above of either gender who had T2DM based on the diagnostic criteria below were included. The level of LDL-C in T2DM that warrants addition of an antihyperlipidaemic pharmacological agent was based on the recommended criteria below.

We excluded individuals with normal fasting blood glucose (FBG) and postprandial glucose levels as well as concomitant endocrinopathy affecting their blood glucose levels.

Diagnostic criteria

Diabetes mellitus
To be consistent with changes in classification and diagnostic criteria of diabetes mellitus through the years, the diagnosis should be established using the standard criteria valid at the time of the beginning of the trial (e.g. ADA 1999; ADA 2008; WHO 1998). Ideally, diagnostic criteria should have been described. If necessary, we used authors’ definition of diabetes mellitus. We planned to subject diagnostic criteria to a sensitivity analysis.

Hypercholesterolaemia
The initiation of a pharmacological agent for treatment of hypercholesterolaemia was based on the recommendations of the American Diabetes Association, American Heart Association and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III). This defined hypercholesterolaemia as a blood LDL-C concentration of 3.36 mmol/L or greater (≥ 130 mg/dL) (ADA 2011; Grundy 2004). If the recommended criteria were not described, we used authors’ definition of hypercholesterolaemia. In such instances, we also planned to subject the recommended criteria to a sensitivity analysis.

Types of interventions
<table>
<thead>
<tr>
<th>Comparison intervention Intervention</th>
<th>Placebo</th>
<th>Placebo with any antihyperglycaemic agent other than colesevelam</th>
<th>Placebo with any antihyperlipidaemic agent other than colesevelam</th>
<th>Placebo with any antihyperglycaemic, antihyperlipidaemic agent other than colesevelam or both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colesevelam</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Colesevelam with another antihyperlipidaemic agent</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Colesevelam with another antihyperglycaemic agent</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Colesevelam with another antihyperglycaemic and antihyperlipidaemic agent</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Types of outcome measures

#### Primary outcomes
- Glycaemic control (measured by HbA1c and glucose levels (fasting and postprandial)).
- Morbidity (both T2DM-related morbidities and cardiovascular-related co-morbidities; all-cause morbidity).
- Adverse effects of colesevelam (all expected and unexpected serious and non-serious adverse events (e.g. hypoglycaemia, gastrointestinal motility effects (especially constipation)).

Classification of hypoglycaemic events was as defined by clinical trial protocols.

#### Secondary outcomes
- Mortality (all-cause and diabetes-related, including death from vascular disease, renal disease and hypoglycaemia).
- Changes in blood-lipid profile (including total cholesterol, LDL-C, HDL-C, triglycerides).
- Obesity measures: body weight, body mass index (BMI), waist circumference, waist to hip-ratio or total body fat.
- Changes in blood insulin, C-peptide levels or insulin resistance.
- Functional outcomes (both physical and cognitive functions).
- Health-related quality of life or well-being.
- Costs.

### Timing of outcome measurement

The outcomes of FBG and two-hour postprandial glucose levels require trials of at least six weeks and over to yield meaningful results. Trials with HbA1c need to be over three months. Other outcomes (such as morbidity) were assessed in the short term (12 to less than 18 weeks), medium term (18 weeks to one year) and long term (more than one year).

### 'Summary of findings' table

We planned to establish a 'Summary of findings' table using the following outcomes listed according to priority:
1. morbidity;
2. mortality;
3. serious adverse events;
4. health-related quality of life;
5. glycaemic control;
6. lipid control.

### Search methods for identification of studies

#### Electronic searches

The following sources were used for the identification of trials:
Searching other resources

We also searched the US FDA and European Medicines Agency (EMA) websites for additional relevant information. The manufacturer of colesevelam was contacted for information of unpublished trials. In addition, we tried to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses and health technology assessment reports. Content experts were contacted for further additional information, additional references, unpublished data and updated results of ongoing interventions.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two review authors (CPO, SCL) independently scanned the abstract, title or both sections of every record retrieved. All potentially relevant articles were investigated as full text. We selected six studies for this review. Where differences in opinion existed, they were resolved by a third party. If resolving disagreement was not possible, the article was added to those 'awaiting assessment' and authors were contacted for clarification. This is summarised in the PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart (Figure 1) of study selection (Liberati 2009).
Data extraction and management

For studies that fulfilled the inclusion criteria, two review authors (CPO, SCL) independently extracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7). Any disagreements were resolved by discussion, or when required by a third party. We attempted to contact the study authors for relevant details on the trials. The results of this survey are displayed in Appendix 8.

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study (Zieve 2007), we maximised the yield of information by simultaneous evaluation of all available data. Zieve 2007 was included as it contained the best usable data for this review.

Assessment of risk of bias in included studies

Two review authors (CPO, SCL) assessed each trial independently. Disagreements were resolved by consensus, or with consultation of a third party.

We assessed the risk of bias using The Cochrane Collaboration’s tool (Higgins 2011). We used the following bias criteria:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding (performance bias and detection bias), separated for blinding of participants and personnel and blinding of outcome assessment;
- incomplete outcome data (attrition bias);
• selective reporting (reporting bias);
• other bias.

We judged the risk of bias criteria as 'low risk', 'high risk' or 'unclear risk' and used the individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We attached a 'Risk of bias graph' figure and 'Risk of bias summary' figure. We assessed the impact of individual bias domains on study results at end point and study levels. The main summary assessments were incorporated into judgements about the 'quality of evidence' in the 'Summary of findings' table, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Data of the main summary assessments were imported into the GradePro software to facilitate the process of creating the 'Summary of findings' table (Brozek 2008).

Measures of treatment effect
Dichotomous data was expressed as odds ratio (OR) or risk ratio (RR) with 95% confidence intervals (CI). Continuous data was expressed as differences in means (MD) with 95% CI.

Unit of analysis issues
We took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome.

Dealing with missing data
We attempted to obtain relevant missing data from authors, if feasible and carefully performed evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT), as-treated and per-protocol (PP) populations. We also investigated attrition rates (e.g. drop-outs, losses to follow-up and withdrawals) and critically appraised issues of missing data and imputation methods (e.g. last observation carried forward (LOCF)).

Assessment of heterogeneity
In the event of substantial clinical or methodological or statistical heterogeneity we did not report study results as meta-analytically pooled effect estimates. We identified heterogeneity by visual inspection of the forest plots and by using a standard Chi² test with a significance level of $\alpha = 0.1$, in view of the low power of this test. We specifically examined heterogeneity employing the I² statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003), where an I² statistic of 75% or more indicated a considerable level of inconsistency (Higgins 2011).

When heterogeneity was found, we attempted to determine potential reasons for it by examining individual study and subgroup characteristics.

We expected the following characteristics to introduce clinical heterogeneity:
• age;
• duration of T2DM;
• presence of complications of diabetes at baseline;
• baseline HbA1c levels;
• baseline blood lipid level;
• compliance with treatment (including medical and nutritional management);
• presence of co-medications (e.g. other antidiabetic agents and antihyperlipidaemic medications).

Assessment of reporting biases
We planned to use funnel plots if we included 10 studies or more for a given outcome to assess small study bias. There are a number of explanations for the asymmetry of a funnel plot (Sterne 2001) and we planned to interpret results carefully (Lau 2006).

Data synthesis
We primarily summarised low-risk of bias data by means of a random-effects model. We performed statistical analyses according to the statistical guidelines referenced in the newest version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Subgroup analysis and investigation of heterogeneity
We planned to carry out subgroup analyses if any one of the primary outcome parameters (see above) demonstrated statistically significant differences between intervention groups to investigate interactions.

We planned the following subgroup analyses:
• age;
• gender;
• patients with and without co-morbidities (e.g. ischaemic heart disease, stroke, peripheral vascular disease);
• patients with and without co-medications (e.g. antihypertensive drugs, statins, aspirin).

Sensitivity analysis
We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:
• restricting the analysis to published studies;
• restricting the analysis taking account risk of bias, as specified above;
• restricting the analysis to very long or large studies to establish how much they dominate the results;
• restricting the analysis to studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.
We also tested the robustness of the results by repeating the analysis using different measures of effect size (RR, OR, etc.) and different statistical models (fixed-effect model and random-effects model).

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies.

For details see Characteristics of included studies and Characteristics of excluded studies. There is no study awaiting classification.

**Results of the search**

The initial electronic searches identified 145 articles (Figure 1). No additional record was identified through other sources as well as no unpublished study was found. We removed 68 duplicates. On reading the titles and abstracts of the remaining 77 records, we excluded another 68 of these articles because they were not related to the review question, were reviews or non-clinical studies.

A total of nine publications describing randomised controlled clinical trials were selected for further assessment (Bays 2008; Fonseca 2008; Goldberg 2008; Goldfine 2010; Kondo 2010; Rosenstock 2010; Schwartz 2010; Zieve 2007). Two publications (Zieve 2007) were analyses from the same trial. One of them was published as 'letter to the editor' and sub-analysed the lipoprotein subclasses in patients with T2DM and HbA1c levels between 7.0% (53 mmol/mol) and 10.0% (86 mmol/mol). The other publication was a pilot study evaluating the effects of colesevelam hydrochloride on glycaemic control in patients with T2DM (Zieve 2007). Zieve 2007 was selected as the primary reference for this review as it contained data relevant to the review question. Goldfine 2010 was an analysis of the extended study period of the three double-blind, placebo-controlled phase III studies (Bays 2008; Fonseca 2008; Goldberg 2008). Those patients who were on placebo from the three phase III studies were given colesevelam. Therefore, this analysis was not an original randomised controlled trial. Two studies (Goldfine 2010; Kondo 2010) were excluded, and details are shown in Characteristics of excluded studies. All the trials were published in the English language.

**Included studies**

For full details, please note the table Characteristics of included studies.
We included six trials in this review (Bays 2008; Fonseca 2008; Goldberg 2008; Rosenstock 2010; Schwartz 2010; Zieve 2007). The details of these trials are summarised in Characteristics of included studies and in Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6 and Appendix 7. There were five multicentre trials (Bays 2008; Fonseca 2008; Goldberg 2008; Rosenstock 2010; Zieve 2007). These centres were in the US, Mexico, Colombia and India. The number of centres ranged from 15 to 56. Only the trial of Schwartz 2010 was of single-centre setting in the US. However, none of the trials reported the clinical settings in which the studies were performed. Colesevelam was supplied by the same manufacturer in all the trials.

The following is the summary of the interventions and controls found in the selected RCTs.

<table>
<thead>
<tr>
<th>Comparison intervention</th>
<th>Placebo</th>
<th>Placebo with any antihyperglycaemic agent other than colesevelam</th>
<th>Placebo with any antihyperlipidaemic agent other than colesevelam</th>
<th>Placebo with any antihyperglycaemic, antihyperlipidaemic agent other than colesevelam or both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colesevelam</td>
<td>Schwartz 2010</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Colesevelam with another antihyperlipidaemic agent</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Colesevelam with another antihyperglycaemic agent</td>
<td>No</td>
<td>Zieve 2007</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Colesevelam with another antihyperglycaemic, anti-</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Bays 2008; Fonseca 2008; Goldberg 2008; Rosenstock 2010</td>
</tr>
</tbody>
</table>
Only one trial compared colesvelam with placebo (Schwartz 2010), while colesvelam or placebo was combined with other hypoglycaemic agents in the remaining five trials (Bays 2008; Fonseca 2008; Goldberg 2008; Schwartz 2010; Zieve 2007).

**Baseline characteristics**

All the trials reported participation of both males and females. There was no significant difference in gender distribution between the intervention and control arms. All patients received general dietary advice. There was no information on the duration of diabetes in five trials (Bays 2008; Fonseca 2008; Goldberg 2008; Schwartz 2010; Zieve 2007). For the trial of Rosenstock 2010, there was no significant difference in the duration of T2DM among patients in the intervention and control groups. None of the publications reported any relevant baseline data on co-morbidities.

**Participants**

A total of 1450 patients with T2DM took part in the six trials ranging from 35 to 461 patients per trial. There were 729 participants in the colesvelam intervention groups and 721 participants in the control groups. These patients came from multi-ethnic backgrounds including: white people, African-Americans, Asians, Hispanics and others. Their mean ages were all above 50 years.

**Diagnostic criteria, inclusion and exclusion criteria, and medications**

All trial participants had T2DM. Criteria for diagnosis in four trials were based on the authors’ definitions (Bays 2008; Fonseca 2008; Goldberg 2008; Schwartz 2010). The American Diabetes Association criteria were used for diagnosis in the other two trials (Rosenstock 2010; Zieve 2007). In all the trials, the patients had inadequate glycaemic control. The inadequacies of glycaemic control as measured by the HbA1c ranged from 7.0% (53 mmol/mol) to 10% (86 mmol/mol) in five trials (Bays 2008; Fonseca 2008; Goldberg 2008; Schwartz 2010; Zieve 2007) and HbA1c 6.5% (48 mmol/mol) to 10.0% (86 mmol/mol) in the remaining trial (Schwartz 2010). Most exclusion criteria consisted of significant obesity (BMI ≥ 40 kg/m²) and diseases such as GI and cardiovascular disorders.

**Co-medications**

Only one trial investigated drug-naive patients (Rosenstock 2010). However, all the patients were given open-label metformin on entry to the trial. The other studies included patients on antidiabetic agents (Bays 2008; Fonseca 2008; Goldberg 2008; Schwartz 2010; Zieve 2007). These agents were metformin monotherapy or metformin in combination with other oral antidiabetic drugs (Bays 2008); sulphonylureas alone or in combination with other oral antidiabetic agents (Fonseca 2008); insulin alone or in combination with oral antidiabetic agents (Goldberg 2008); diet or antidiabetic agents (Schwartz 2010); and sulphonylurea alone, metformin alone or sulphonylurea plus metformin (Zieve 2007). In contrast, in the study of Schwartz 2010, those who met the inclusion criteria at screening were withdrawn from all antidiabetic medications until the end of the trial. Four trials reported the concurrent use of antihypertensives (Bays 2008; Fonseca 2008; Goldberg 2008; Schwartz 2010). Other lipid-altering drugs such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and fibrates were also concomitantly used by patients (Bays 2008; Fonseca 2008; Goldberg 2008; Rosenstock 2010).

**Treatment before study**

Although there were recommendations to follow the appropriate diet, there was no specific, protocol-directed dietary evaluation or dietary recommendations (Bays 2008; Fonseca 2008; Goldberg 2008; Rosenstock 2010). There was no reporting of dietary regimens in two other studies (Schwartz 2010; Zieve 2007). No exercise regimen was documented in all the trials. Four studies reported a placebo run-in period after screening, whereby the patients took six colesvelam-matching placebo tablets daily in addition to their antidiabetic medications (Bays 2008; Fonseca 2008; Goldberg 2008; Zieve 2007). In the study of Schwartz 2010, there was a wash-out period of three days and two weeks for insulin and oral antidiabetic agents, respectively. Rosenstock 2010 did not report any pre-treatment regimens.

**Interventions**

Similar colesvelam hydrochloride tablets (625 mg tablet) and dosing (3.75 g/day) were used for the interventions in all the trials. These tablets were supplied by the same manufacturer. However, the duration of the trials and the complementing management of the disease differed. The duration of treatment ranged from 8 to 26 weeks. There were no complementing antidiabetic agents and
dietary recommendations in the trial of Schwartz 2010, which lasted eight weeks. The intervention was added to the existing antidiabetic regimen for 12 weeks in the trial of Zieve 2007. Both the trials of Goldberg 2008 and Rosenstock 2010 were completed in 16 weeks. The intervention was added to the existing antidiabetic and dietary regimen in Goldberg 2008. In contrast, the patients in Rosenstock 2010 were not receiving any antidiabetic treatment. Finally, both the trials of Bays 2008 and Fonseca 2008 of 26 weeks’ duration, had the intervention added to the existing antidiabetic and dietary regimens.

One trial directly compared colesevelam to placebo as monotherapy (Schwartz 2010). For the other five trials, the control interventions were both placebos and combination therapies (Bays 2008; Fonseca 2008; Goldberg 2008; Rosenstock 2010; Zieve 2007). The placebo consisted of magnesium stearate and microcrystalline cellulose, with a commercially supplied film-coating mixture in two trials (Bays 2008; Goldberg 2008). No information was provided for the content of the placebos in the rest of the trials (Fonseca 2008; Rosenstock 2010; Schwartz 2010; Zieve 2007).

Outcomes

Primary outcomes

For details on outcome data see Appendix 2 and Appendix 5. All included trials reported glycaemic control. Glycaemic control was defined as change in HbA1c from baseline to end of the treatment period in all studies except Schwartz 2010. Change from baseline in glucose disposal rate during the final 30 min of the insulin clamp (M-value) to week eight was used in this study.

Secondary outcomes, additional/other outcomes

Secondary outcomes in these studies consisted mainly of mean changes of fasting plasma glucose (FPG) and lipids from baseline, for the intervals during follow-up periods as well as to end of the treatment period. Mean changes of HbA1c from baseline and for the intervals during the follow-up periods were also included in three trials (Bays 2008; Fonseca 2008; Goldberg 2008). Mean changes in fructosamine as well as changes in postprandial blood glucose, insulin, proinsulin, measurements of beta-cell function, such as homeostasis model assessment index (HOMA-I) and using the hyperinsulinaemic-euglycaemic clamp technique to measure the quantitative insulin sensitivity were also included in some studies. One study also used standard meal tolerance tests (MTT) which were used to analyse plasma glucose, insulin, area-under-the-curve (AUC) insulin, C-peptide AUC and insulin AUC-to-glucose AUC ratio (Schwartz 2010). Safety outcomes mainly comprised treatment-emergent adverse events, vital signs, findings of physical examinations, electrocardiograms (ECG) and body weight. Adverse events reported were usually mild and included hypoglycaemia, constipation, dyspepsia and nausea. Laboratory measurements were composed of routine or standard haematology, serum chemistry and urinalysis. No trial reported outcomes on morbidity, functional outcomes, health-related quality of life, well-being and costs.

Excluded studies

Two studies (Goldfine 2010; Kondo 2010) were excluded (see Characteristics of excluded studies).

Risk of bias in included studies

For details on study populations such as numbers randomised, analysed, ITT and safety population see Table 1. Overall, the publications suggested unclear risk of bias, predominantly in the selection bias domain within and across studies (see Figure 2 and Figure 3). These studies generally had a parallel group randomised controlled, double-blind design, typically employing an ITT analysis. Although blinding of outcome assessors was not described, it was not likely to affect clinical laboratory parameters. There was complete inter-rater agreement for the key quality indicators randomisation, concealment of allocation and blinding. Therefore, no discussion with a third party was necessary.
Figure 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
**Allocation**

All trials did not report adequately on randomisation and allocation concealment.

**Blinding**

Although all trials were described as double-blinded, none reported on the double-blinding procedure.

**Incomplete outcome data**

All publications reported an ITT analysis, and the majority used the LOCF method to impute missing values. Zieve 2007 did not describe any method for handling missing values. Justifications for withdrawals from the trials were reported in all the publications. Although missing data were addressed using the LOCF approach, LOCF procedures can lead to serious bias of effect estimates. In addition, there were 6% to 39% of the patients withdrawn from the respective trials at various stages adding to attrition bias. In particular, the attrition rate in Fonseca 2008 was high and disproportionate. Therefore, data from these publications are at high or
unclear risk of attrition bias.

Selective reporting
All the publications indicated low risk of reporting bias except for Zieve 2007 where the risk was unclear.

Other potential sources of bias
Generally, the risk for other biases was low.

Effects of interventions
See: Summary of findings for the main comparison Colesevelam for type 2 diabetes mellitus

Baseline characteristics
Although all six trials used the similar proprietary colesevelam of the same dose, this drug was combined with a series of different antihyperglycaemic agents. No two trials used the same colesevelam and antihyperglycaemic agent combination. All six trials reported outcomes, including FBG, HbA1c, total cholesterol and subclasses as well as adverse effects. However, no two trials reported similar comparisons (see Appendix 5 for details).

Primary outcomes
For details on primary and secondary outcome data see Data and analyses.

Metabolic control
The general effect of addition of colesevelam to other hypoglycaemic agents showed a reduction in HbA1c in favour of colesevelam (MD -0.5% (95% CI -0.6 to -0.4), P < 0.0001; 1348 participants, 6 trials, no trial with low risk of bias in all domains; Analysis 1.4). However, the single trial comparing colesevelam to placebo only did not reveal a statistical significant difference between the two arms - in fact, in both arms HbA1c increased. Colesevelam with add-on hypoglycaemic agents demonstrated a statistical significant reduction in FBG with a mean difference (MD) of -15 mg/dL (95% CI -22 to -8), P < 0.0001; 1075 participants, 4 trials, no trial with low risk of bias in all domains; Analysis 1.3).

Colesevelam plus metformin monotherapy with or without other antidiabetic agents versus placebo plus metformin with or without oral antidiabetic agents
The trial of Bays 2008 combined colesevelam with metformin only or metformin with other oral antidiabetic drugs. For FBG, the MD between the study arms was -16 mg/dL (95% CI -28 to -4, 301 participants, P < 0.01; Analysis 1.3) in favour of the colesevelam intervention. Similarly, the mean HbA1c difference was also significant (MD -0.6% (95% CI -0.8 to -0.4, 300 participants, P < 0.0001; Analysis 1.4) in favour of the colesevelam intervention.

Colesevelam plus sulphonylurea monotherapy or sulphonylurea plus oral antidiabetic agents versus placebo plus sulphonylurea monotherapy or sulphonylurea plus oral antidiabetic agents
The trial of Fonseca 2008 compared colesevelam and placebo with combinations of other oral antidiabetic agents. There were significant MDs for both FPG and HbA1c in favour of the colesevelam intervention arms. These were -13 mg/dL (95% CI -23 to -2, 435 participants, P < 0.05; Analysis 1.3) and -0.6% (95% CI -0.8 to -0.4, 461 participants, P < 0.0001; Analysis 1.4) for FBG and HbA1c, respectively.

Colesevelam plus insulin monotherapy or insulin plus oral antidiabetic agents versus placebo plus insulin monotherapy or insulin plus oral antidiabetic agents
Colesevelam and placebo were combined with antidiabetic agents in the trial of Goldberg 2008. Significant MDs were found for both FPG and HbA1c in favour of the colesevelam intervention arms. These were -24 mg/dL (95% CI -42 to -6, 280 participants, P < 0.05; Analysis 1.3) and -0.5% (95% CI -0.7 to -0.3, 280 participants, P < 0.0001; Analysis 1.4) for FBG and HbA1c, respectively.

Colesevelam plus metformin versus placebo plus metformin
When comparing metformin plus placebo with colesevelam plus metformin, the latter combination showed more benefit for HbA1c (MD -0.3% (95% CI -0.5 to -0.2, 240 participants, P < 0.0001) Analysis 1.4 (Rosenstock 2010). However, there was no significant treatment difference for FPG at 16 weeks last observation carried forward (LOCF) (treatment difference -6.0 (95% CI -13.0 to 0.0, 275 participants, P < 0.2370)).

Colesevelam versus placebo
Although the results of Schwartz 2010 indicated benefits with colesevelam in lowering the FBG, there were no raw data available for further analysis. However, the authors reported no statistically significant change in mean HbA1c (+0.2% (from 8.2 to 8.5; P = 0.422)) with colesevelam compared with significant changes of +0.6% (from 8.7 to 9.3; P = 0.031) with placebo, from week zero to week eight LOCF.
Colestevam plus antidiabetic agents versus placebo plus antidiabetic agents

The trial of Zieve 2007 combined colestevam with other oral antidiabetic drugs. For FBG, the MD between the study arms was -7 mg/dL (95% CI -26 to -12, 59 participants, P >0.05; Analysis 1.3) which was not significant. However, the mean HbA1c difference was significant, -0.5% (95% CI -0.9 to -0.1, 59 participants, P < 0.006; Analysis 1.4) in favour of the colestevam intervention.

Morbidity

There were no publications reporting data on morbidity outcomes.

Adverse events

For details of adverse events see Appendix 6 and Appendix 7. Adverse events were reported in all the trials and presented in both the intervention and control groups. Most of these reported events were predominantly mild to moderate GI symptoms such as constipation and dyspepsia. Discontinuation owing to adverse effects did not differ significantly between colestevam only or colestevam and other antidiabetic intervention and control arms (RR 1.57 (95% CI 0.89 to 2.75), P = 0.12; 1450 participants, 6 trials; Analysis 1.1). The RRs of adverse events also did not show statistically significant differences between groups. Only three trials reported mild hypoglycaemic episodes (Bays 2008; Fonseca 2008; Goldberg 2008). There was no severe or nocturnal hypoglycaemia reported in all these trials.

Secondary outcomes

Mortality

There were no publications reporting data on mortality outcomes.

Lipid profile

For details of LDL-C see Analysis 1.5
Colestevam with add-on hypoglycaemic agents demonstrated a statistically significant reduction in LDL-C with an MD of -13 mg/dL (95% CI -17 to -9), P < 0.00001; 886 participants, 4 trials, no trial with low risk of bias in all domains; Analysis 1.5. The trials of Goldberg 2008 and Fonseca 2008 reported a significant reduction in triglyceride levels. However, there were no raw data available from the Fonseca 2008 trial for detailed analysis. Nevertheless, secondary data for LDL-C, non-HDL-C, triglycerides, Apo-A1 and Apo-B suggested statistically significant changes favouring colestevam combination with other oral antidiabetic agents.

Obesity measures

There were no publications reporting data on changes in body weight, BMI, waist circumference, waist-to-hip ratio or total body fat.

Changes in blood insulin, C-peptide levels or insulin resistance

There were three publications reporting changes in these parameters (Bays 2008; Rosenstock 2010; Schwartz 2010). Rosenstock 2010 reported both fasting and two-hour post-MTT C-peptide as well as fasting and two-hour post-MTT insulin. There were no statistical significant changes in these parameters between the intervention and control arms. Colestevam plus metformin with or without other oral antidiabetic agents versus placebo plus metformin with or without other antidiabetic agents did not demonstrate any statistical significant mean changes in the levels of fasting C-peptide, fasting insulin and homeostasis model assessment index (HOMA-I) (Bays 2008). Finally, there were no suitable data available in the study of Schwartz 2010 for detailed analysis. However, the authors reported statistically significant increases in whole body insulin sensitivity in the colestevam intervention arm compared with the placebo arm.

Functional outcomes

There were no publications reporting data on functional outcomes.

Health-related quality of life

There were no publications reporting data on health-related quality of life.

Costs

There were no publications reporting data on health economics.

Subgroup analyses

This was not performed owing to lack of data.

Sensitivity analyses

We did not perform sensitivity analyses owing to the different comparisons of intervention and control groups of included studies and insufficient data.

Publication and small study bias

Drawing of funnel plot was not possible owing to insufficient data.
DISCUSSION

Summary of main results
Six studies investigating the treatment of T2DM with colesevelam that met our inclusion criteria were included in this review. A total of 1450 patients with T2DM was randomised to interventions with colesevelam or combinations of colesevelam with other antidiabetic agents. Colesevelam-antidiabetic agents combination therapy resulted in statistically significant reductions in HbA1c compared with the placebo-antidiabetic agents combination therapy in five trials. Significant changes in FBG favouring colesevelam combination therapies as well as significant reductions of LDL-C were also observed. However, no single trial investigated the same intervention and comparison group. Therefore, data on comparisons with active comparators to confirm these findings were limited. Due to the limited number of trials on colesevelam monotherapy or colesevelam combination therapy for T2DM, subgroup and sensitivity analyses were not possible.

Caution is needed when interpreting these findings. The effect estimates were small. The relatively small sample size in each of the colesevelam or colesevelam combination trials contributed to the low power of the studies. Further, there were no data published on mortality, diabetic complications, functional outcomes, costs of treatment and health-related quality of life.

Generally, colesevelam appeared to provide dual benefits of glycaemic control and lowering of LDL-C. Apart from the predominant adverse GI effects, this drug was well tolerated, with no severe hypoglycaemia. So far, in all published randomised controlled trials of colesevelam interventions, only routine adverse effects of symptoms, clinical laboratory measurements and compliance have been reported. Further, there is still no report of pancreatic and thyroid carcinoma in humans despite the theoretical risk demonstrated in animal models (EMEA 2005).

Overall completeness and applicability of evidence
All the six trials selected for this review used similar proprietary colesevelam pharmacological agents in the interventions. Detailed information of the placebos used in the control groups was reported in only two of the six trials (Bays 2008; Goldberg 2008). Further, the time points for assessment of the effects of interventions for the six trials differed. These time points ranged from eight to 26 weeks. No data on outcomes were available beyond 26 weeks. There were also not enough data of similar time points that could be extracted from these publications.

Quality of the evidence
All the six trials had unclear risk of biases in at least two domains. These trials were limited to the same intervention and comparison group. Therefore, data on comparisons with active comparators to confirm these findings were limited. Due to the limited number of trials on colesevelam monotherapy or colesevelam combination therapy for T2DM, subgroup and sensitivity analyses were not possible.

Caution is needed when interpreting these findings. The effect estimates were small. The relatively small sample size in each of the colesevelam or colesevelam combination trials contributed to the low power of the studies. Further, there were no data published on mortality, diabetic complications, functional outcomes, costs of treatment and health-related quality of life.

Generally, colesevelam appeared to provide dual benefits of glycaemic control and lowering of LDL-C. Apart from the predominant adverse GI effects, this drug was well tolerated, with no severe hypoglycaemia. So far, in all published randomised controlled trials of colesevelam interventions, only routine adverse effects of symptoms, clinical laboratory measurements and compliance have been reported. Further, there is still no report of pancreatic and thyroid carcinoma in humans despite the theoretical risk demonstrated in animal models (EMEA 2005).

Potential biases in the review process
There are several limitations in interpretation with this systematic review. First, there are limited trials on colesevelam and the varied colesevelam combinations published. Further, all these published trials had findings of beneficial effects of colesevelam on glycaemic control. Besides possible publication bias, all the included trials have other methodological issues. Potential biases may occur during selection of patients, administration of treatment and the significant number of drop-outs affecting the assessment of outcomes. Therefore, inadequacy in the process of randomisation and blinding may be associated with exaggerated effects of the interventions due to systematic errors (bias). Moreover, methodologically fewer rigorous trials have shown significantly larger intervention effects than trials with more rigour (Egger 2003; Kjaergard 2001; Moher 1998; Schulz 1995).

Second, the small sample size of the trials leading to diminished power of the results may explain the small effect estimates between the interventions and placebo. In other words, the analyses from the size of these trials may not establish with confidence that two interventions have equivalent effects (Piaggio 2001; Pocock 1991). Third, all trials reported end-of-treatment responses, ranging from eight weeks to 26 weeks and long-term responses beyond this period are not known. Fourth, although all the trials provided information on ethnicity of the participants, the number of patients from each ethnic group was insufficient for subgroup analysis. Thus, any significant difference in the results among the different ethnic groups or populations is not known.

This review consists of published data only. Original data from the manufacturers, as well as information from drug regulatory authorities such as the FDA and EMA will be useful. Unfortunately, the original data from manufacturers were not available. Similarly, the search of the FDA and EMA websites yielded no additional information. Finally, it would be difficult to exclude the possibility of biases, as all the selected trials were funded by the same pharmaceutical company.
Agreements and disagreements with other studies or reviews

Previous publications on colesevelam for T2DM focused on a small number of clinical trials. There has been no quality comprehensive systematic review of the effects of colesevelam on T2DM. This review included six available RCTs. These RCTs provided evidence of colesevelam monotherapy and colesevelam combination therapy with antidiabetic agents. Unfortunately, the relatively small sample size and effect estimates of each of the combinations of intervention modality do not provide sufficient evidence for general use of colesevelam for T2DM.

Authors’ Conclusions

Implications for practice

Data provided by landmark clinical trials have left many unresolved issues and paradoxes regarding diabetes control, cardiovascular risk and cardiovascular outcomes. While tight glycaemic control in reducing microvascular diseases is well established, its role in controlling macrovascular risk remains controversial (Duckworth 2009; Gerstein 2008; Patel 2008; UKPDS 1998). Cardiovascular risk accounts for approximately 70% of all mortality in people with diabetes, especially middle-aged people of both genders (Laakso 1999). These mortality and morbidity risks are comparable to non-diabetic individuals who had a cardiovascular event (Haffner 1998). Moreover, treatment focused in reducing other cardiovascular risk factors in addition to hyperglycaemia, appears to be more effective in preventing macrovascular disease than treatment of hyperglycaemia per se (Patel 2007; UKPDS 1998).

Traditionally, the gradual loss of glycaemic control in individuals with T2DM has been attributed to the progressive reduction in beta-cell mass. This has been the major focus in diabetes research. So far, existing oral pharmacological agents for treatments have not been promising in restoring the beta-cell mass typically lost during the natural progression of the disease. Some, such as the sulphonylureas, even hasten beta-cell apoptosis in human islet cells in vitro (Maedler 2005). So far, published data on colesevelam suggest no effects on measurements of beta-cell function in the short term (eight weeks) (Schwartz 2010). However, the ability of colesevelam to reduce blood glucose levels through the alternative novel non-insulin modulated pathways may provide a means of sparing the residual functional beta-cells in individuals with T2DM.

Colesvelam has some theoretical advantages over existing therapies with oral antidiabetic compounds as well as add-on therapy to insulin, metformin, sulphonylureas and other antidiabetic agents. The reduction in both HbA1c and LDL-C may help patients with T2DM to achieve the targeted HbA1c and LDL-C levels. In addition, there is the advantage of a low risk for hypoglycaemic events. Long-term data on efficacy and safety are not available to advocate the widespread use of colesevelam.

Implications for research

More information on the benefit-risk ratio of colesevelam treatment is necessary to assess the long-term effects, particularly in the management of cardiovascular risks as well as reductions in microvascular and macrovascular complications of T2DM. In addition, long-term data on patient-oriented parameters, such as health-related quality of life, diabetic complications and all-cause mortality, also need to be investigated.

Acknowledgements

None.

References

References to studies included in this review

Bays 2008 [published data only]

Fonseca 2008 [published data only]

Goldberg 2008 [published data only]

Rosenstock 2010 [published data only]

Schwartz 2010 [published data only]

**Zieve 2007** [published data only]

**References to studies excluded from this review**

**Goldfine 2010** [published data only]

**Kondo 2010** [published data only]

**Additional references**

**Abegunde 2007**

**ADA 1999**

**ADA 2008**

**ADA 2011**

**Agardh 2011**

**Bays 2003**

**Bays 2007**

**Brown 2010**

**Brozek 2008**

**Bruno 2011**

**Chan 2009**

**Cheung 2009**

**Claudel 2005**

**Colhoun 2004**

**Dall 2010**

**Davidson 1999**
DeFronzo 1987

Donovan 2005

Duckworth 2009

Egger 2003

EMEA 2005

Fonseca 2008

Gaede 2003

Gerstein 2008

Grundy 2004

Haffner 1998

Hanus 2006
Hanus M, Zhorov E. Bile acid salt binding with colesevelam HCl is not affected by suspension in common beverages.
Kolding 2006

Liberati 1999

Lau 2006

Liberati 2009

Lloyd-Jones 2010

Maedler 2005

Mehler 2003

Moher 1998

NCEP 2002

NIDDKD 2011

Pan 2010

Patel 2007

Patel 2008

Piaggio 2001

Pocock 1991

Rosenbaum 1997

Rosenson 2006

Schmidt 2010

Schulz 1995

Staels 2009

Sterne 2001
Tharkar 2010

UKPDS 1998

UKPDS 1999
UK Prospective Diabetes Study Group. Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). *Diabetes Care* 1999;22(7):1125–36.

WHO 1998

Yang 2012

Zhang 2010

* Indicates the major publication for the study
### Characteristics of included studies  
**[ordered by study ID]**

#### Bays 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL, RANDOMISATION RATIO: 1:1, Superiority design</th>
</tr>
</thead>
</table>

**Participants**

- WHO PARTICIPATED: 316 patients with type 2 diabetes mellitus (T2DM)
- SETTING: multicentres in USA (54) and Mexico (2)
- SEX (female:male ratio): 0.92:1
- AGE (mean years (SD)): 56.3 (17.42)
- ETHNIC GROUPS (%): white 51.9%; black 15.5%; Asian 3.5%; Hispanics 22.2%; others 1.0%
- DURATION OF DISEASE (mean years (SD)): no information
- INCLUSION CRITERIA: patients with T2DM aged 18 to 75 years with inadequate glycaemic control (HbA1c level, 7.5% to 9.5%, inclusive), taking a stable dose (for 90 days) of metformin monotherapy or metformin in combination with other oral antidiabetic drugs. Women of childbearing potential engaged in an acceptable form of birth control
- EXCLUSION CRITERIA: patients on glucagon-like peptide-1 analogues and dipeptidyl peptidase IV inhibitors. Other exclusion criteria included BMI > 45 kg/m²; LDL-C level < 60 mg/dL; TG level > 500 mg/dL; uncontrolled hypertension (defined as systolic blood pressure 160 mmHg and diastolic blood pressure 95 mmHg); history of type 1 diabetes mellitus, ketoacidosis, dysphagia, swallowing disorders, or intestinal motility disorders; treatment with colesevelam within 8 weeks of the screening visit; long-term or recently initiated insulin therapy; or treatment with oral corticosteroids, cholestyramine, or colestipol. Patients were also excluded if they had a history of an acute coronary syndrome, coronary intervention, transient ischaemic attack, or a combination within 3 months of the screening visit; severe peripheral vascular disease; any serious disorder that might interfere with the study or affect interpretation of results; or any condition which, in the investigator's opinion, made it inappropriate for the patient to participate
- DIAGNOSTIC CRITERIA: authors' criteria
- CO-MORBIDITIES: no information
- CO-MEDICATIONS: metformin monotherapy or metformin in combination with other oral antidiabetic drugs. Oral anti-diabetic drugs included ≥ 1 of the following: sulphonylureas, thiazolidinediones, α-glucosidase inhibitors, meglitinides or a combination. Other co-medication included oral contraceptives, hormone therapy, thyroid therapy and other lipid-altering drugs (such as HMG-CoA reductase inhibitors, fibrates, niacin, fish oils and cholesterol absorption inhibitors), provided a stable dose had been maintained for ≥ 30 days prior to the initiation of the trial, and dosage changes were not anticipated

| Interventions | INTERVENTION GROUP: colesevelam hydrochloride, 3.75 g/day (6 tablets: 625 mg per tablet) | CONTROL INTERVENTION: 6 colesevelam-matching placebo tablets daily, composed of magnesium stearate and microcrystalline cellulose, with a commercially supplied film-coating mixture. All patients were on recommended T2DM diet regimen during the study |
**Outcomes**

**PRIMARY OUTCOME(S) (as stated in the publication):** mean change from baseline HbA1c level for active drug compared with placebo at week 26 analysed on an ITT basis using the LOCF approach

**SECONDARY OUTCOMES (as stated in the publication):** secondary efficacy parameters included the mean changes in HbA1c, FPG and fructosamine levels from baseline to weeks 6, 12, 18 and 26. Mean changes in HbA1c level from baseline to weeks 6, 12, 18 and 26 were also analysed for both the metformin monotherapy and metformin combination therapy cohorts. An additional secondary efficacy parameter included an assessment of participants who experienced a pre-defined reduction in FPG level of $\geq 30$ mg/dL or an HbA1c level of $\geq 0.7\%$ from baseline at week 26. Finally, other secondary end points included mean change in C-peptide, adiponectin, and insulin levels and HOMA-I from baseline to week 26; mean change and mean % change in concentrations of TC, LDL-C, HDL-C, non-HDL-C, Apo A-I, and Apo B from baseline to week 26; mean change in TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, and Apo B/Apo A-I ratios from baseline to week 26; and median change and median % change in hsCRP and TG levels from baseline to week 26

**ADDITIONAL OUTCOMES:** treatment-emergent AEs, clinical laboratory blood test results, changes in vital signs and findings on physical examinations. Compliance with the medication regimen was evaluated by counting unused tablets at each study visit

---

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Adequate sequence generation        | Unclear risk       | Quote: “.....randomised 1:1 to colesevelam hydrochloride, 3.75 g/d (6 tablets: 625 mg per tablet) or matching placebo ......”
Comment: method of random sequence generation was not described |
| Allocation concealment              | Unclear risk       | Comment: allocation concealment not described                                                                                                           |
| Blinding All outcomes               | Low risk           | Quote: “.....double-blind, placebo-controlled, parallel-group study.......randomised 159 to colesevelam hydrochloride, 3.75 g/d, and 157 to matching placebo......”
Comment: outcomes were primarily clinical laboratory parameters. Although blinding of outcome assessors was not described, it was not likely to affect these outcomes |
| Incomplete outcome data addressed   | High risk          | Quote: “...analysed on an intent-to-treat (ITT) basis using a last-observation-carried-forward (LOCF) approach......Forty- |
Bays 2008  (Continued)

three subjects in the colesevelam group withdrew prior to study completion compared with relative to 51 subjects in the placebo group...."
Comment: although attempts were made to addressed missing data using the LOCF approach, LOCF procedures can lead to serious bias of effect estimates. Further, 28% to 33% of the data were subjected to such an approach

<table>
<thead>
<tr>
<th>Free of selective reporting</th>
<th>Low risk</th>
<th>Comment: important primary and secondary outcomes were adequately reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free of other bias</td>
<td>Low risk</td>
<td>Comment: none detected</td>
</tr>
</tbody>
</table>

Fonseca 2008

Methods

PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL, RANDOMISATION RATIO: 1:1, Superiority design

Participants

WHO PARTICIPATED: 461 patients with T2DM
SETTING: multicentres in USA (49) and Mexico (2)
SEX (female: male ratio): 0.84:1
AGE (mean years (SD)): 56.8 (10.3)
ETHNIC GROUPS (%): White (57.0%); Hispanic (27.1%); African-American (12.4%); Asian (2.4%); other (1.1%)
DURATION OF DISEASE (mean years (SD)): no information
INCLUSION CRITERIA: patients with T2DM inadequately controlled (HbA1c 7.5% to -9.5%, inclusive) on a stable dose of sulphonylureas alone or in combination with additional oral antidiabetic drugs for 90 days. Those on oral contraceptives, hormone replacement therapy, thyroid replacement therapy and lipid-altering drugs (HMG-CoA reductase inhibitors, fibrates, niacin, fish oils, and cholesterol absorption inhibitors) were included provided a stable dose had been maintained for 30 days before the initiation of the study and dosage changes were not anticipated
EXCLUSION CRITERIA: LDL-C 60 mg/dL (1.6 mmol/L); TG 500 mg/dL (5.7 mmol/L); BMI 45 kg/m²; uncontrolled hypertension (blood pressure 160/95 mmHg); history of type 1 diabetes mellitus, ketoacidosis, dysphagia, swallowing disorders or intestinal motility disorders; any serious medical/psychiatric disorder; drug/alcohol abuse within 2 years; hospitalisation within 14 days; treatment with colesevelam within 8 weeks; chronic use or recent initiation of insulin; participation in a weight loss programme with ongoing weight loss; starting an intensive exercise programme within 4 weeks; use of any investigational drug within 30 days of the first dose of study medication; or any condition or therapy that may pose a risk or make participation not in the best interest of the subject. In addition, participants taking oral corticosteroids, cholestyramine and colestipol were excluded
DIAGNOSTIC CRITERIA: authors’ criteria
CO-MORBIDITIES: no information
**CO-MEDICATIONS:** sulphonylurea monotherapy or sulphonylurea in combination with other oral antidiabetic drugs. The sulphonylurea used in the sulphonylurea monotherapy group included glibenclamide, glipizide, glimepiride, tolbutamide or glimeclazide. In the sulphonylurea combination with oral anti-DM group, the sulphonylurea used included glipizide, glibenclamide, glimepiride, tolazamide or biguanides/sulphonylurea fixed dose combination.

Other oral antidiabetes drugs included 1 or more of the following: biguanides, thiazolidinediones, α-glucosidase inhibitors, fixed-dose rosiglitazone/metformin, fixed-dose glipizide/metformin, nateglinide or repaglinide. Other co-medication included oral contraceptives, hormone replacement therapy, thyroid replacement therapy and other lipid-altering drugs (such as HMG-CoA reductase inhibitors, fibrates, niacin, fish oils and cholesterol absorption inhibitors), provided a stable dose had been maintained for ≥ 30 days prior to the initiation of the trial, and dosage changes were not anticipated.

---

| Interventions | **INTERVENTION GROUP:** colesevelam hydrochloride, 3.75 g/day (6 tablets: 625 mg per tablet)  
**CONTROL INTERVENTION:** 6 colesevelam-matching placebo tablets daily. There was no information on the composition of the placebo. All patients were on recommended to follow ADA dietary recommendations |
| --- | --- |

| Outcomes | **PRIMARY OUTCOME(S) (as stated in the publication):** mean change from baseline HbA1c level for active drug compared with placebo at week 26 analysed on an ITT basis using the LOCF approach  
**SECONDARY OUTCOMES (as stated in the publication):** secondary efficacy parameters included the mean change in HbA1c, FPG, fructosamine and C-peptide levels from baseline to week 26. Mean change in HbA1c level from baseline to week 26 was also analysed for both the sulphonylurea monotherapy and sulphonylurea combination therapy cohorts. An additional secondary efficacy parameter included an assessment of participants who experienced a pre-defined reduction in FPG level of ≥ 30 mg/dL or in HbA1c level of ≥ 0.7% from baseline at week 26. Finally, other secondary end points included mean % change in lipids, lipoproteins, and lipid and lipoprotein ratios; and median change and median % change in hsCRP and TGs. For all secondary efficacy parameters, the change from baseline to week 26 was calculated using both LOCF and non-LOCF analyses  
**ADDITIONAL OUTCOMES:** treatment-emergent AEs, clinical laboratory blood test results, changes in vital signs, and findings on physical examinations. Compliance with the medication regimen was evaluated by counting unused tablets |
| --- | --- |

| Notes | Original research journal article |

---

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Adequate sequence generation | Unclear risk | Quote: “.....randomised 1:1 to colesevelam hydrochloride, 3.75 g/d (6 tablets: 625 mg per tablet) or matching placebo ......”  
Comments: method of random sequence generation was not described |
<table>
<thead>
<tr>
<th>Allocation concealment</th>
<th>Unclear risk</th>
<th>Comment: allocation concealment not described</th>
</tr>
</thead>
</table>

**Blinding**

**All outcomes**

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

| Quote: “.....double-blind, placebo-controlled, parallel-group study........randomised 230 to colesevelam hydrochloride and 231 to placebo. ....” |
| Comment: outcomes were primarily clinical laboratory parameters. Although blinding of outcome assessors was not described, it was not likely to affect these outcomes |

**Incomplete outcome data addressed**

**All outcomes**

<table>
<thead>
<tr>
<th>High risk</th>
</tr>
</thead>
</table>

| Quote: “.....an intent-to-treat (ITT) population using a last-observation-carried-forward (LOCF) analysis......64 subjects in the colesevelam group withdrew prior to study completion compared with relative to 90 subjects in the placebo group....” |
| Comment: although attempts were made to addressed missing data using the LOCF approach, LOCF procedures can lead to serious bias of effect estimates. Further, 29% to 39% of the data were subjected to such an approach |

**Free of selective reporting**

<table>
<thead>
<tr>
<th>Unclear risk</th>
</tr>
</thead>
</table>

| Comment: important primary outcomes were adequately reported. However, only the summary of mean changes of the lipid profile using LOCF approach were provided |

**Free of other bias**

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

| Comment: none detected |

---

**Goldberg 2008**

**Methods**

| PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL, RANDOMISATION RATIO: 1:1, Superiority design |

**Participants**

| WHO PARTICIPATED: 287 patients with T2DM |
| SETTING: multicentres in USA (50) and Mexico (1) |
| SEX (female:male ratio): 0.94:1 |
| AGE (mean years (SD)): 56.8 (13.00) |
| ETHNIC GROUPS (%): white (64.0%); black (17.42%); Asian (1.74%); Hispanic (16.38%); other (0.7%) |
| DURATION OF DISEASE (mean years (SD)): no information |
| INCLUSION CRITERIA: patients, aged 18 to 75 years with T2DM not adequately controlled (baseline HbA1c level, 7.5% to 9.5%, inclusive) with insulin alone or in |
Combination with oral antidiabetic agents (a biguanide (metformin hydrochloride), a biguanide-sulphonylurea combination (metformin/glibenclamide), a sulphonylurea (glibenclamide, glimepiride or glipizide), a thiazolidinedione (pioglitazone hydrochloride or rosiglitazone maleate), or a meglitinide (nateglinide or repaglinide)). These patients were receiving a stable (± 10%) dose of insulin (30 to 200 U/day) for ≥ 6 weeks before screening (those receiving oral antidiabetic agents were required to receive a stable dose for ≥ 90 days before screening) and had C-peptide levels > 0.5 ng/mL, LDL-C concentration of ≥ 60 mg/dL and TG levels of ≤ 500 mg/dL.

**EXCLUSION CRITERIA:** BMI (calculated as weight in kilograms divided by height in metres squared) of > 45; uncontrolled hypertension (systolic blood pressure > 160 mmHg, diastolic blood pressure > 95 mmHg, or both); acute coronary syndrome (e.g. myocardial infarction or unstable angina), coronary intervention (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty or similar procedure), or transient ischaemic attacks within 3 months of screening; or a history of pancreatitis, ketoacidosis, type 1 diabetes mellitus, intestinal motility disorders, severe peripheral vascular disease, dysphasia or other swallowing disorders, or AIDS or HIV infection. Patients with T2DM taking oral corticosteroids, cholestyramine resin and colestipol hydrochloride were also excluded. If the HbA1c level of recruited patients with T2DM increased to ≥ 10.0% or FPG levels increased to ≥ 260 mg/dL during the double-blind treatment period, they were also excluded.

**DIAGNOSTIC CRITERIA:** authors’ criteria

**CO-MORBIDITIES:** no information

**CO-MEDICATIONS:** insulin monotherapy or insulin in combination with oral antidiabetic agents (a biguanide (metformin hydrochloride), a biguanide-sulphonylurea combination (metformin/glibenclamide), a sulphonylurea (glibenclamide, glimepiride or glipizide), a thiazolidinedione (pioglitazone hydrochloride or rosiglitazone maleate), or a meglitinide (nateglinide or repaglinide)). Other co-mediations included lipid-altering drugs (such as HMG-CoA reductase inhibitors and fibrates) as well as anti-hypertensives (ACE-inhibitors, angiotensin II antagonists, selective β-blocking agents, dihydropyridine derivatives and thiazides).

**Interventions**

**INTERVENTION GROUP:** colesevelam hydrochloride, 3.75 g/day (6 tablets: 625 mg per tablet)

**CONTROL INTERVENTION:** 6 colesevelam-matching placebo tablets daily, composed of magnesium stearate and microcrystalline cellulose, with a commercially supplied film-coating mixture. All participants were prescribed a diet accepted by the ADA but had no specific, protocol-directed dietary evaluation or dietary recommendations.

**Outcomes**

**PRIMARY OUTCOME(S) (as stated in the publication):** mean change in HbA1c level from baseline to week 16, with participants analysed on an ITT basis, using an LOCF approach.

**SECONDARY OUTCOMES (as stated in the publication):** secondary efficacy parameters included the mean change in FPG, fructosamine and HbA1c levels from baseline to weeks 4, 8 and 16; the arbitrary pre-defined assessment (based on efficacy data for HbA1c and FPG levels from the pilot study with colesevelam 12) of a glycaemic control response: a reduction in the FPG level of ≥ 30 mg/dL or a reduction in the HbA1c level of ≥ 0.7% from baseline by week 16; mean change in C-peptide levels from baseline to week 16; mean change and mean % change in concentrations of TC, LDL-C, HDL-C, non-HDL-C, TGs, and Apo A-I and Apo B levels and in ratios of TC/
**ADDITIONAL OUTCOMES**: vital signs, findings at physical examinations, treatment-emergent AEs, and clinical laboratory test results. Kidney functions were assessed using urine samples at weeks -3 (screening), 0 (randomisation, baseline), 8 and 16 or at an early termination visit, if applicable. Compliance with the medication regimen was evaluated by tablet counts at each visit.

### Notes
Original research journal article

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation</td>
<td>Unclear risk</td>
<td>Quote: “.....randomised 1:1 to colesevelam hydrochloride, 3.75 g/d (6 tablets: 625 mg per tablet) or placebo .......” Comment: method of random sequence generation was not described</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Comment: allocation concealment not described</td>
</tr>
<tr>
<td>Blinding</td>
<td>Low risk</td>
<td>Quote: “.....double-blind, placebo-controlled, parallel-group study.............were randomised: 147 received colesevelam hydrochloride and 140 received placebo.....” Comment: outcomes were primarily clinical laboratory parameters. Although blinding of outcome assessors was not described, it was not likely to affect these outcomes</td>
</tr>
<tr>
<td>Incomplete outcome data addressed</td>
<td>High risk</td>
<td>Quote: “.....subjects were analysed on an intent-to-treat (ITT) population using a last-observation-carried-forward (LOCF) approach......30 subjects in the colesevelam group withdrew prior to study completion compared with 26 subjects in the placebo group....” Comment: although attempts were made to address missing data using the LOCF approach, LOCF procedures can lead to serious bias of effect estimates. Further, about 19% to 20% of the data were subjected to such an approach</td>
</tr>
<tr>
<td>Free of selective reporting</td>
<td>Low risk</td>
<td>Comment: important primary and secondary outcomes were adequately reported</td>
</tr>
</tbody>
</table>
Rosenstock 2010

Methods

WHO PARTICIPATED: 286 patients with T2DM
SETTING: multicentres in USA (16), Colombia (7) and India (5)
SEX (female:male ratio): 1:3:1
AGE (mean years (SD)): 53.3 (14.1)
ETHNIC GROUPS (%): white (14.3%); Hispanic (62.6%); black (1.4%); Asian (21.7%)
DURATION OF DISEASE, years (%): newly diagnosed (23.4%); < 1 year (37.8%); 1 to 5 years (28.3%); > 5 years (10.5%)
INCLUSION CRITERIA: patients with T2DM had HbA1c values of 6.5% to 10.0%, LDL-C levels ≥ 100 mg/dL and TG < 500 mg/dL. All patients never received antidiabetic treatment or had not received treatment for ≥ 3 months before screening. Patients receiving maintenance doses of weight-loss medications (including orlistat and sibutramine) whose weight was stable were eligible for participation. Hormones (oral contraceptives and hormone replacement therapy) and lipid-altering drugs (statins, fibrates, niacin and ezetimibe) were permitted, if a stable dose had been maintained for ≥ 3 months
EXCLUSION CRITERIA: BMI ≥ 40 kg/m²; history of type 1 diabetes mellitus, metabolic acidosis, pancreatitis, dysphagia, swallowing disorders, intestinal motility disorders or long-term insulin therapy (except for gestational diabetes); treatment with a bile acid sequestrant or orally administered corticosteroids within 3 months of screening; acute coronary syndrome, coronary intervention, congestive heart failure, or transient ischaemic attack within 3 months of screening; considerably abnormal haematological or blood chemistry values; clinical or laboratory evidence of hepatic disease; or participation in a weight loss programme with ongoing weight loss
DIAGNOSTIC CRITERIA: authors’ criteria
CO-MORBIDITIES: no information
CO-MEDICATIONS: metformin, ACE inhibitors, angiotensin II antagonists, statins and platelet aggregation inhibitors (excluding heparin)

Interventions

INTERVENTION GROUP: colesevelam hydrochloride, 3.75 g/day (6 tablets: 625 mg per tablet) plus metformin 850 mg to 1700 mg/day (850 mg per tablet)
CONTROL INTERVENTION: 6 colesevelam-matching placebo tablets daily plus metformin 850 mg to 1700 mg/day (850 mg per tablet). There were no specific, protocol-directed dietary evaluation or dietary recommendations were made during the course of the study (e.g. such as would occur through protocol-directed visits with a dietician)

Outcomes

PRIMARY OUTCOME(S) (as stated in the publication): mean change in HbA1c from baseline to week 16 with use of LOCF analysis
SECONDARY OUTCOMES (as stated in the publication): mean change in FPG, fasting insulin, fasting C-peptide, post-MTT glucose, post-MTT insulin, post-MTT C-peptide, change and % change in lipids and Apo, and hsCRP using week-16 LOCF
analyses. The % of patients achieving HbA1c < 7.0%, HbA1c ≤ 6.5%, LDL-C < 100 mg/dL or LDL-C < 70 mg/dL were also evaluated. HbA1c, FPG, lipids, and lipid and Apo ratios were also evaluated at intermediate time points by using observed data (non-LOCF).

**ADDITIONAL OUTCOMES:** safety assessments included changes in vital signs, findings on physical examinations, occurrence and severity of AEs, and clinical laboratory test results. Compliance with the medication regimen was evaluated by tablet count at each study visit.

### Notes
Original research journal article

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation</td>
<td>Unclear risk</td>
<td>Quote: “.....randomly assigned 1:1 to open-label metformin plus blinded unmarked coleselam (metformin/coleselam) or open-label metformin plus blinded coleselam-matching placebo (metformin/placebo).......” Comments: method of random sequence generation was not described</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Comment: allocation concealment not described</td>
</tr>
<tr>
<td>Blinding</td>
<td>Low risk</td>
<td>Quote: “.....double-blind, placebo-controlled, parallel-group study........randomised in this study: 145 to metformin/coleselam and 141 to metformin/placebo....” Comment: outcomes were primarily clinical laboratory parameters. Although blinding of outcome assessors was not described, it was not likely to affect these outcomes</td>
</tr>
<tr>
<td>Incomplete outcome data addressed</td>
<td>High risk</td>
<td>Quote: “...intent-to-treat population......use of last-observation-carried-forward (LOCF) analysis......Overall, 85% of patients completed the 16-week study...” Comment: although attempts were made to addressed missing data using the LOCF approach, LOCF procedures can lead to serious bias of effect estimates. Further, 15% of the data were subjected to such an approach</td>
</tr>
</tbody>
</table>
Rosenstock 2010  (Continued)

<table>
<thead>
<tr>
<th>Free of selective reporting</th>
<th>Low risk</th>
<th>Comment: important primary and secondary outcomes were adequately reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free of other bias</td>
<td>Low risk</td>
<td>Comment: none detected</td>
</tr>
</tbody>
</table>

Schwartz 2010

Methods

PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL, RANDOMISATION RATIO: 1:1, Superiority design

Participants

WHO PARTICIPATED: 35 patients with T2DM
SETTING: single site - Diabetes and Glandular Disease Clinic in USA
SEX (female: male ratio): 1:1
AGE (mean years (SD)): 53.7 (11.34)
ETHNIC GROUPS (%): White (28.6%); black (5.6%); Asian (2.9%); Hispanic (62.9%)
DURATION OF DISEASE (mean years (SD)): no information
INCLUSION CRITERIA: males and females aged 18 to 75 years with diagnosed T2DM (for > 3 months), with an HbA1c of 7.0% to 10.0% (inclusive), being treated with diet or antidiabetic agents (excluding thiazolidinediones), and with a BMI of 25 to 45 kg/m²
EXCLUSION CRITERIA: at screening, had TGs > 500 mg/dL (5.65 mmol/L) or LDL-C < 60 mg/dL (1.55 mmol/L); type 1 diabetes mellitus; a history of diabetic ketoacidosis, allergy or toxic reaction to colesevelam, dysphagia, swallowing disorders, intestinal motility disorders or hyperthyroidism; lipid- or blood pressure-lowering therapy that was not stable for ≥ 3 months; use of any investigational drug within 30 days prior to randomisation; or treatment with colesevelam, cholestyramine or colestipol within 3 months. Exclusionary concomitant medications included all antidiabetic agents (after wash-out), oral corticosteroids, thyroid hormone/levothyroxine, cholestyramine or colestipol
DIAGNOSTIC CRITERIA: authors’ criteria
CO-MORBIDITIES: no information
CO-MEDICATIONS: no information

Interventions

INTERVENTION GROUP: colesevelam hydrochloride, 3.75 g/day (6 tablets: 625 mg per tablet)
CONTROL INTERVENTION: colesevelam-matching placebo tablets daily. There was no information on dietary recommendations

Outcomes

PRIMARY OUTCOME(S) (as stated in the publication): change from baseline in glucose disposal rate during the final 30 min of the insulin clamp (M-value) at week 8
SECONDARY OUTCOMES (as stated in the publication): secondary efficacy parameters included the change from baseline in M-value at week 2; change from baseline in AUCg and AUCi at weeks 2 and 8; acute and chronic effects of colesevelam on postprandial glucose; change from baseline in HbA1c at weeks 0 and 8; change from baseline in FPG and fasting insulin at weeks 2, 4, 6 and 8; and change from baseline in fructosamine at weeks 4 and 8. Baseline was defined as week -1 unless otherwise specified
ADDITIONAL OUTCOMES: safety assessments included changes in vital signs, clin-
Schwartz 2010  

(Continued)

| Laboratory tests, and ECGs, as well as evaluation of the incidence and severity of AEs. Compliance with the treatment regimen was evaluated by counting unused tablets at weeks 4 and 8, or at the early termination visit |

| Notes | Original research journal article. Pilot study |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation</td>
<td>Unclear risk</td>
<td>Quote: “.....randomly assigned 1:1 to coleselam hydrochloride, 3.75 g/d (6 tablets: 625 mg per tablet) or placebo .......” Comments: method of random sequence generation was not described</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Comment: allocation concealment not described</td>
</tr>
<tr>
<td>Blinding</td>
<td>Low risk</td>
<td>Quote: “.....double-blind, placebo-controlled, parallel-group study.......were randomised: 147 received coleselam hydrochloride and 140 received placebo.....” Comment: outcomes were primarily clinical laboratory parameters. Although blinding of outcome assessors was not described, it was not likely to affect these outcomes</td>
</tr>
<tr>
<td>Incomplete outcome data addressed</td>
<td>Unclear risk</td>
<td>Quote: “.....last-observation-carried-forward (LOCF) analysis......1 was lost to follow up (coleselam group)......1 met the protocol-specified discontinuation criteria of FPG &gt; 300 mg/dL on 3 occasions (placebo group).....” Comment: attempts were made to addressed missing data using the LOCF approach and LOCF procedures can lead to serious bias of effect estimates. However, &lt; 6% of the data were subjected to such an approach</td>
</tr>
<tr>
<td>Free of selective reporting</td>
<td>Unclear risk</td>
<td>Comment: important secondary outcomes were not adequately reported</td>
</tr>
<tr>
<td>Free of other bias</td>
<td>Low risk</td>
<td>Comment: none detected</td>
</tr>
</tbody>
</table>
Methods

PARALLEL RANDOMISED CONTROLLED CLINICAL TRIAL, RANDOMISATION RATIO: 1:1, Superiority design

Participants

WHO PARTICIPATED: 65 patients with T2DM
SETTING: 15 clinical sites in USA
SEX (female: male ratio): 0.8:1
AGE (mean years (SD)): 56.2 (9.3)
ETHNIC GROUPS (%): white (53.8%); black (16.9%); Hispanic (26.2%); other (3.1%)
DURATION OF DISEASE (mean years (SD)): no information
INCLUSION CRITERIA: patients, aged 30 to 70 years, had a diagnosis of T2DM (ADA criteria 2°), had a screening HbA1c value of 7.0% to 10.0%, and had been taking a stable dose of a sulphonylurea, metformin, or both as their only antihyperglycaemic medication(s) for > 90 days. Women of childbearing potential were required to practice a medically approved method of birth control throughout the study
EXCLUSION CRITERIA: BMI > 40 kg/m²; a fasting serum TG level > 300 mg/dL; FPG level > 300 mg/dL; a history of dysphagia, swallowing disorders or intestinal motility disorder; any serious disorder that would interfere with the conduct of the study; or any laboratory abnormality that could compromise patient safety
DIAGNOSTIC CRITERIA: authors’ criteria
CO-MORBIDITIES: no information
CO-MEDICATIONS: antihyperglycaemics (sulphonylurea alone, metformin alone, combination of sulphonylurea and metformin) as well as antihypertensives

Interventions

INTERVENTION GROUP: colesvelam hydrochloride, 3.75 g/day (6 tablets: 625 mg per tablet)
CONTROL INTERVENTION: 6 colesvelam-matching placebo tablets daily. There was no information on the composition of the placebo. There was no information on the dietary recommendations

Outcomes

PRIMARY OUTCOME(S) (as stated in the publication): mean change in HbA1c from baseline to week 12
SECONDARY OUTCOMES (as stated in the publication): secondary efficacy parameters included the mean changes in fructosamine levels, FPG levels, the postprandial glucose level and the meal glucose response. Other secondary end points include % changes in lipid parameters (LDL-C, TC, HDL-C, TG, Apo A-I and B, and LDL particle concentration) from baseline to week 12
ADDITIONAL OUTCOMES: AEs were assessed by direct questioning at each visit and by laboratory tests at weeks -5, 0 and 12. Compliance with study medication was assessed by counting unused tablets at clinic visits at weeks -1, 4, 8 and 12

Notes

Original research journal article. Pilot study

Risk of bias

Bias
Authors’ judgement | Support for judgement
| Adequate sequence generation | Unclear risk | Quote: “...randomly assigned to receive either colesevelam hydrochloride 3.75 g/d (six 625 mg tablets) or matching placebo.”

Comments: method of random sequence generation was not described |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Comment: allocation concealment not described</td>
</tr>
</tbody>
</table>
| Blinding                    | Low risk     | Quote: “...double-blind, placebo-controlled, parallel-group study... (31 colesevelam, 34 placebo)...”

Comment: outcomes were primarily clinical laboratory parameters. Although blinding of outcome assessors was not described, it was not likely to affect these outcomes |
| Incomplete outcome data addressed | High risk | Quote: “...intent-to-treat population included all randomised subjects who took >=1 dose of study medication and had both baseline and >1 post baseline efficacy assessments...4 discontinued (colesevelam group)...2 discontinued (placebo group)...”

Comment: there were no attempts made to address missing data (13%) |
| Free of selective reporting | Unclear risk | Comment: important primary and secondary outcomes were not adequately reported |
| Free of other bias           | Unclear risk | Comment: sample-size calculation not performed |

ACE: angiotensin-converting enzyme; ADA: American Diabetes Association; AE: adverse event; Apo: apolipoprotein; AIDS: acquired immune deficiency syndrome; BMI: body mass index; ECG: electrocardiogram; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; HIV: human immunodeficiency virus; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; HOMA-I: homeostasis model assessment index; hsCRP: high-sensitivity C-reactive protein; ITT: intention to treat; LDL-C: low-density lipoprotein cholesterol; LOCF: last observation carried forward; SD: standard deviation; T2DM: type 2 diabetes mellitus; TC: total cholesterol; TG: triglyceride.
### Characteristics of excluded studies

**[ordered by study ID]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldfine 2010</td>
<td>Open-label extension study and not a randomised control study</td>
</tr>
<tr>
<td>Kondo 2010</td>
<td>Colestilan was used for intervention</td>
</tr>
</tbody>
</table>
# Data and Analyses

Comparison 1. Colesevelam versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 Discontinuation due to adverse events</td>
<td>6</td>
<td>3964</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.02 [0.00, 0.04]</td>
</tr>
<tr>
<td>1.2 All adverse events</td>
<td>6</td>
<td>1450</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.02 [-6.23, 0.04]</td>
</tr>
<tr>
<td>1.3 All hypoglycaemic episodes</td>
<td>3</td>
<td>1064</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.04 [-0.01, 0.09]</td>
</tr>
<tr>
<td>1.4 All hypoglycaemic episodes</td>
<td></td>
<td></td>
<td></td>
<td>0.01 [-0.00, 0.02]</td>
</tr>
<tr>
<td>2 Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Mean change in fasting blood glucose from baseline to endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Colesevelam/metformin/antidiabetic agents versus placebo/metformin/antidiabetic agents (26 weeks)</td>
<td>1</td>
<td>301</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-16.1 [-28.14, -4.06]</td>
</tr>
<tr>
<td>3.2 Colesevelam/sulphonylureas/antidiabetic agents versus placebo/sulphonylureas/antidiabetic agents (26 weeks)</td>
<td>1</td>
<td>435</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-12.6 [-23.21, -1.99]</td>
</tr>
<tr>
<td>3.3 Colesevelam/insulin/antidiabetic agents versus placebo/insulin/antidiabetic agents (16 weeks)</td>
<td>1</td>
<td>280</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-24.2 [-42.42, -5.98]</td>
</tr>
<tr>
<td>3.4 Colesevelam/antidiabetic agents versus placebo/antidiabetic agents (12 weeks)</td>
<td>1</td>
<td>59</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-7.20 [-26.29, 11.89]</td>
</tr>
<tr>
<td>4 Mean change in HbA1c from baseline to endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 Colesevelam/metformin versus placebo/metformin (16 weeks)</td>
<td>1</td>
<td>240</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.30 [-0.45, -0.15]</td>
</tr>
<tr>
<td>4.2 Colesevelam/metformin/antidiabetic agents versus placebo/metformin/antidiabetic agents (26 weeks)</td>
<td>1</td>
<td>300</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.60 [-0.82, -0.38]</td>
</tr>
<tr>
<td>4.3 Colesevelam/sulphonylureas/antidiabetic agents versus placebo/sulphonylureas/antidiabetic agents (26 weeks)</td>
<td>1</td>
<td>436</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.60 [-0.78, -0.42]</td>
</tr>
</tbody>
</table>

The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
<thead>
<tr>
<th>Study Description</th>
<th>n</th>
<th>n</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.4 Colesevelam/insulin/antidiabetic agents versus placebo/insulin/antidiabetic agents (16 weeks)</strong></td>
<td>1</td>
<td>280</td>
<td>-0.5 [-0.68, -0.32]</td>
</tr>
<tr>
<td><strong>4.5 Colesevelam/antidiabetic agents versus placebo/antidiabetic agents (12 weeks)</strong></td>
<td>1</td>
<td>59</td>
<td>-0.5 [-0.86, -0.14]</td>
</tr>
<tr>
<td><strong>4.6 Colesevelam versus placebo</strong></td>
<td>1</td>
<td>33</td>
<td>-0.31 [-1.04, 0.42]</td>
</tr>
<tr>
<td><strong>5 Mean change in LDL-cholesterol from baseline to endpoints</strong></td>
<td>4</td>
<td>886</td>
<td>-12.75 [-16.64, -8.87]</td>
</tr>
<tr>
<td><strong>5.1 Colesevelam/antidiabetic agents versus placebo/antidiabetic agents (12 weeks)</strong></td>
<td>1</td>
<td>55</td>
<td>-11.70 [-20.24, -3.16]</td>
</tr>
<tr>
<td><strong>5.2 Colesevelam/insulin/antidiabetic agents versus placebo/insulin/antidiabetic agents (16 weeks)</strong></td>
<td>1</td>
<td>250</td>
<td>-12.8 [-19.38, -6.22]</td>
</tr>
<tr>
<td><strong>5.3 Colesevelam/metformin/antidiabetic agents versus placebo/metformin/antidiabetic agents (26 weeks)</strong></td>
<td>1</td>
<td>316</td>
<td>-11.2 [-18.67, -3.73]</td>
</tr>
<tr>
<td><strong>5.4 Colesevelam/metformin versus placebo/metformin (16 weeks)</strong></td>
<td>1</td>
<td>265</td>
<td>-16.30 [-25.59, -7.01]</td>
</tr>
<tr>
<td><strong>6 Mean change in HOMA-index</strong></td>
<td>1</td>
<td>316</td>
<td>-0.60 [-2.12, 0.92]</td>
</tr>
<tr>
<td><strong>7 Mean change in fasting C-peptide</strong></td>
<td>2</td>
<td>591</td>
<td>-0.55 [-1.35, 0.24]</td>
</tr>
<tr>
<td><strong>8 Mean change in fasting insulin</strong></td>
<td>2</td>
<td>591</td>
<td>-0.22 [-1.93, 1.49]</td>
</tr>
<tr>
<td><strong>9 Mean change in 2-h post-MTT C-peptide</strong></td>
<td>1</td>
<td>271</td>
<td>0.07 [0.01, 0.13]</td>
</tr>
<tr>
<td><strong>10 Mean change in 2-h post-MTT insulin</strong></td>
<td>1</td>
<td>270</td>
<td>2.97 [-5.21, 11.15]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Colesevelam versus placebo, Outcome 1 Adverse events.

Review: Colesevelam for type 2 diabetes mellitus

Comparison: 1 Colesevelam versus placebo

Outcome: 1 Adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>M-H,Fixed,95% CI</th>
<th>Risk Difference</th>
<th>M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Discontinuation due to adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bays 2008</td>
<td>8/159</td>
<td>4/157</td>
<td>8.0 %</td>
<td>0.02</td>
<td>[ -0.02, 0.07 ]</td>
<td>11.6 %</td>
<td>0.04 [ 0.00, 0.08 ]</td>
</tr>
<tr>
<td>Fonseca 2008</td>
<td>18/230</td>
<td>9/231</td>
<td>11.6 %</td>
<td>0.04</td>
<td>[ -0.01, 0.09 ]</td>
<td>7.2 %</td>
<td>0.04 [ -0.08, 0.02 ]</td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>10/147</td>
<td>4/140</td>
<td>7.2 %</td>
<td>0.03</td>
<td>[ -0.08, 0.02 ]</td>
<td>0.9 %</td>
<td>0.00 [ -0.10, 0.10 ]</td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>5/145</td>
<td>9/141</td>
<td>7.2 %</td>
<td>0.04</td>
<td>[ -0.01, 0.09 ]</td>
<td>0.9 %</td>
<td>0.00 [ -0.10, 0.10 ]</td>
</tr>
<tr>
<td>Schwartz 2010</td>
<td>0/17</td>
<td>0/18</td>
<td>0.9 %</td>
<td>0.00</td>
<td>[ -0.10, 0.10 ]</td>
<td>1.6 %</td>
<td>0.04 [ -0.07, 0.14 ]</td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>2/31</td>
<td>1/34</td>
<td>1.6 %</td>
<td></td>
<td>[ -0.07, 0.14 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>729</strong></td>
<td><strong>721</strong></td>
<td><strong>36.6 %</strong></td>
<td><strong>0.02 [ 0.00, 0.04 ]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 43 (Colesevelam), 27 (Control)
Heterogeneity: Chi² = 5.39, df = 5 (P = 0.37); I² =7%
Test for overall effect: Z = 1.90 (P = 0.057)

2 All adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>M-H,Fixed,95% CI</th>
<th>Risk Difference</th>
<th>M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bays 2008</td>
<td>85/159</td>
<td>81/157</td>
<td>8.0 %</td>
<td>0.02</td>
<td>[ -0.09, 0.13 ]</td>
<td>11.6 %</td>
<td>0.04 [ 0.00, 0.17 ]</td>
</tr>
<tr>
<td>Fonseca 2008</td>
<td>145/230</td>
<td>126/231</td>
<td>11.6 %</td>
<td>0.08</td>
<td>[ 0.00, 0.17 ]</td>
<td>7.2 %</td>
<td>0.04 [ -0.07, 0.15 ]</td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>92/147</td>
<td>82/140</td>
<td>7.2 %</td>
<td>0.03</td>
<td>[ -0.13, 0.09 ]</td>
<td>0.9 %</td>
<td>0.14 [ -0.18, 0.46 ]</td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>97/145</td>
<td>97/141</td>
<td>7.2 %</td>
<td>0.02</td>
<td>[ -0.13, 0.09 ]</td>
<td>0.9 %</td>
<td>0.14 [ -0.18, 0.46 ]</td>
</tr>
<tr>
<td>Schwartz 2010</td>
<td>8/17</td>
<td>6/18</td>
<td>0.9 %</td>
<td>0.00</td>
<td>[ -0.23, 0.23 ]</td>
<td>1.6 %</td>
<td>0.14 [ -0.18, 0.46 ]</td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>20/31</td>
<td>22/34</td>
<td>1.6 %</td>
<td></td>
<td>[ -0.23, 0.23 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>729</strong></td>
<td><strong>721</strong></td>
<td><strong>36.6 %</strong></td>
<td><strong>0.04 [ -0.01, 0.09 ]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 447 (Colesevelam), 414 (Control)
Heterogeneity: Chi² = 2.72, df = 5 (P = 0.74); I² =0.0%
Test for overall effect: Z = 1.51 (P = 0.13)

3 All hypoglycaemic episodes

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>M-H,Fixed,95% CI</th>
<th>Risk Difference</th>
<th>M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bays 2008</td>
<td>1/159</td>
<td>0/157</td>
<td>8.0 %</td>
<td>0.01</td>
<td>[ -0.01, 0.02 ]</td>
<td>11.6 %</td>
<td>0.02 [ -0.01, 0.04 ]</td>
</tr>
<tr>
<td>Fonseca 2008</td>
<td>6/230</td>
<td>2/231</td>
<td>11.6 %</td>
<td>0.02</td>
<td>[ -0.01, 0.04 ]</td>
<td>7.2 %</td>
<td>0.00 [ -0.01, 0.01 ]</td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>0/147</td>
<td>0/140</td>
<td>7.2 %</td>
<td>0.00</td>
<td>[ -0.01, 0.01 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>536</strong></td>
<td><strong>528</strong></td>
<td><strong>26.8 %</strong></td>
<td><strong>0.01 [ 0.00, 0.02 ]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 7 (Colesevelam), 2 (Control)
Heterogeneity: Chi² = 2.42, df = 2 (P = 0.30); I² =17%
### Analysis 1.2. Comparison 1 Colesevelam versus placebo, Outcome 2 Mortality.

**Review:** Colesevelam for type 2 diabetes mellitus  
**Comparison:** 1 Colesevelam versus placebo  
**Outcome:** 2 Mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bays 2008</td>
<td>0/159</td>
<td>0/157</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td>Fonseca 2008</td>
<td>0/230</td>
<td>0/231</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>0/147</td>
<td>1/140</td>
<td>0.32 [ 0.01, 7.73 ]</td>
<td></td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>0/145</td>
<td>0/141</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td>Schwartz 2010</td>
<td>0/17</td>
<td>0/18</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>0/31</td>
<td>0/34</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>0.0 [ 0.0, 0.0 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 0 (Colesevelam), 1 (Control)  
Heterogeneity: $\chi^2 = 0.0, df = 0 (P<0.00001)$; $I^2 = 0.0\%$  
Test for overall effect: $Z = 0.0 (P < 0.00001)$  
Test for subgroup differences: Not applicable
### Analysis 1.3. Comparison 1 Colesevelam versus placebo, Outcome 3 Mean change in fasting blood glucose from baseline to endpoint.

**Review:** Colesevelam for type 2 diabetes mellitus

**Comparison:** 1 Colesevelam versus placebo

**Outcome:** 3 Mean change in fasting blood glucose from baseline to endpoint

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Heterogeneity: not applicable</th>
<th>Test for overall effect: Z = 2.62 (P = 0.0087)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Colesevelam/metformin/antidiabetic agents versus placebo/metformin/antidiabetic agents (26 weeks)</td>
<td>149</td>
<td>152</td>
<td>-4.6 (54.55)</td>
<td>11.5 (51.92)</td>
<td>32.1 %</td>
<td>-16.10 [-28.14, -4.06]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>149</td>
<td>152</td>
<td>-4.6 (54.55)</td>
<td>11.5 (51.92)</td>
<td>32.1 %</td>
<td>-16.10 [-28.14, -4.06]</td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.62 (P = 0.0087)</td>
<td>149</td>
<td>152</td>
<td>-4.6 (54.55)</td>
<td>11.5 (51.92)</td>
<td>32.1 %</td>
<td>-16.10 [-28.14, -4.06]</td>
</tr>
<tr>
<td>2 Colesevelam/sulphonylureas/antidiabetic agents versus placebo/sulphonylureas/antidiabetic agents (26 weeks)</td>
<td>218</td>
<td>217</td>
<td>-5.5 (55.63)</td>
<td>7.1 (57.3)</td>
<td>41.2 %</td>
<td>-12.60 [-23.21, -1.99]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>218</td>
<td>217</td>
<td>-5.5 (55.63)</td>
<td>7.1 (57.3)</td>
<td>41.2 %</td>
<td>-12.60 [-23.21, -1.99]</td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.33 (P = 0.020)</td>
<td>218</td>
<td>217</td>
<td>-5.5 (55.63)</td>
<td>7.1 (57.3)</td>
<td>41.2 %</td>
<td>-12.60 [-23.21, -1.99]</td>
</tr>
<tr>
<td>3 Colesevelam/insulin/antidiabetic agents versus placebo/insulin/antidiabetic agents (16 weeks)</td>
<td>144</td>
<td>136</td>
<td>-3.9 (56.58)</td>
<td>20.3 (93.42)</td>
<td>14.0 %</td>
<td>-24.20 [-42.42, -5.98]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>144</td>
<td>136</td>
<td>-3.9 (56.58)</td>
<td>20.3 (93.42)</td>
<td>14.0 %</td>
<td>-24.20 [-42.42, -5.98]</td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.60 (P = 0.0092)</td>
<td>144</td>
<td>136</td>
<td>-3.9 (56.58)</td>
<td>20.3 (93.42)</td>
<td>14.0 %</td>
<td>-24.20 [-42.42, -5.98]</td>
</tr>
<tr>
<td>4 Colesevelam/antidiabetic agents versus placebo/antidiabetic agents (12 weeks)</td>
<td>27</td>
<td>32</td>
<td>-5.1 (40.4)</td>
<td>2.1 (33.2)</td>
<td>12.7 %</td>
<td>-7.20 [-26.29, 11.89]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>27</td>
<td>32</td>
<td>-5.1 (40.4)</td>
<td>2.1 (33.2)</td>
<td>12.7 %</td>
<td>-7.20 [-26.29, 11.89]</td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.74 (P = 0.46)</td>
<td>27</td>
<td>32</td>
<td>-5.1 (40.4)</td>
<td>2.1 (33.2)</td>
<td>12.7 %</td>
<td>-7.20 [-26.29, 11.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>538</td>
<td>537</td>
<td>100.0 %</td>
<td>-14.66 [-21.47, -7.84]</td>
<td>100.0 %</td>
<td>-14.66 [-21.47, -7.84]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.0, Chi² = 1.84, df = 3 (P = 0.61); I² =0.0%

Test for subgroup differences: Chi² = 1.84, df = 3 (P = 0.61), I² =0.0%

---

**Favours colesevelam**

**Favours control**
### Analysis 1.4. Comparison 1 Colesevelam versus placebo, Outcome 4 Mean change in HbA1c from baseline to end point.

**Review:** Colesevelam for type 2 diabetes mellitus

**Comparison:** 1 Colesevelam versus placebo

**Outcome:** 4 Mean change in HbA1c from baseline to end point

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)%</td>
<td>N Mean(SD)%</td>
<td>IV,Random,95% CI</td>
<td>IV,Random,95% CI</td>
<td></td>
</tr>
<tr>
<td>1 Colesevelam/metformin versus placebo/metformin (16 weeks)</td>
<td>122 -1.1 (0.6) 118 -0.8 (0.6)</td>
<td></td>
<td>25.8 % -0.30 [-0.45, -0.15]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>122 118</td>
<td></td>
<td>25.8 % -0.30 [-0.45, -0.15]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.87 (P = 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Colesevelam/metformin/antidiabetic agents versus placebo/metformin/antidiabetic agents (26 weeks)</td>
<td>148 -0.4 (0.97) 152 0.2 (0.95)</td>
<td></td>
<td>18.2 % -0.60 [-0.82, -0.38]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>148 152</td>
<td></td>
<td>18.2 % -0.60 [-0.82, -0.38]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.41 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Colesevelam/sulphonylureas/antidiabetic agents versus placebo/sulphonylureas/antidiabetic agents (26 weeks)</td>
<td>218 -0.4 (0.86) 218 0.2 (1.02)</td>
<td></td>
<td>22.5 % -0.60 [-0.78, -0.42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>218 218</td>
<td></td>
<td>22.5 % -0.60 [-0.78, -0.42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.64 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Colesevelam/insulin/antidiabetic agents versus placebo/insulin/antidiabetic agents (16 weeks)</td>
<td>144 -0.4 (0.68) 136 0.2 (1.02)</td>
<td></td>
<td>21.8 % -0.50 [-0.68, -0.32]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>144 136</td>
<td></td>
<td>21.8 % -0.50 [-0.68, -0.32]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.73 (P = 0.0063)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Colesevelam/antidiabetic agents versus placebo/antidiabetic agents (12 weeks)</td>
<td>27 -0.3 (0.7) 32 0.2 (0.7)</td>
<td></td>
<td>9.1 % -0.50 [-0.86, -0.14]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>27 32</td>
<td></td>
<td>9.1 % -0.50 [-0.86, -0.14]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.73 (P = 0.0063)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Colesevelam versus placebo</td>
<td>16 0.24 (1.1629) 17 0.55 (0.9589)</td>
<td></td>
<td>2.6 % -0.31 [-1.04, 0.42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>16 17</td>
<td></td>
<td>2.6 % -0.31 [-1.04, 0.42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.83 (P = 0.41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 675 673 100.0 % -0.48 [-0.61, -0.36]

**Heterogeneity:** Tau^2 = 0.01; Chi^2 = 8.57, df = 5 (P = 0.13); I^2 =42%

Test for overall effect: Z = 7.80 (P < 0.00001)

Test for subgroup differences: Chi^2 = 8.57, df = 5 (P = 0.13), I^2 =42%

---

**Favours colesevelam vs. Favours control**

---

_**Colesuevelam for type 2 diabetes mellitus (Review)**_

*Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.*
**Analysis 1.5. Comparison 1 Colesevelam versus placebo, Outcome 5 Mean change in LDL-cholesterol from baseline to endpoints.**

Review: Colesevelam for type 2 diabetes mellitus

Comparison: 1 Colesevelam versus placebo

Outcome: 5 Mean change in LDL-cholesterol from baseline to endpoints

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)[mg/dL]</td>
<td>N</td>
<td>Mean(SD)[mg/dL]</td>
<td>IV-Random,95% CI</td>
<td>IV-Random,95% CI</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td>---------</td>
<td>----------------</td>
<td>--------</td>
<td>----------------</td>
</tr>
<tr>
<td>1 Colesevelam/antidiabetic agents versus placebo/antidiabetic agents (12 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>25</td>
<td>-9.6 (19.1)</td>
<td>30</td>
<td>2.1 (11.5)</td>
<td>20.7 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>25</td>
<td>30</td>
<td></td>
<td></td>
<td>20.7 %</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.68 (P = 0.0073)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Colesevelam/insulin/antidiabetic agents versus placebo/insulin/antidiabetic agents (16 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>129</td>
<td>-12.3 (26.69)</td>
<td>121</td>
<td>0.5 (26.4)</td>
<td>34.8 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>129</td>
<td>121</td>
<td></td>
<td></td>
<td>34.8 %</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.81 (P = 0.00014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Colesevelam/metformin/antidiabetic agents versus placebo/metformin/antidiabetic agents (26 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bays 2008</td>
<td>159</td>
<td>-139 (36.55)</td>
<td>157</td>
<td>-2.7 (30.96)</td>
<td>27.1 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>159</td>
<td>157</td>
<td></td>
<td></td>
<td>27.1 %</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.94 (P = 0.0033)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Colesevelam/metformin versus placebo/metformin (16 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>130</td>
<td>-21.4 (38.2)</td>
<td>135</td>
<td>-5.1 (38.92)</td>
<td>17.5 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>130</td>
<td>135</td>
<td></td>
<td></td>
<td>17.5 %</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.44 (P = 0.00058)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>443</td>
<td>443</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.0, Chi² = 0.79, df = 3 (P = 0.85); I² =0.0%

Test for overall effect: Z = 6.44 (P < 0.00001)

Test for subgroup differences: Chi² = 0.79, df = 3 (P = 0.85), I² =0.0%

Favours colesevelam | Favours control

---

Coleselam for type 2 diabetes mellitus (Review)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Analysis 1.6. Comparison 1 Colesevelam versus placebo, Outcome 6 Mean change in HOMA-index.

**Review:** Colesevelam for type 2 diabetes mellitus  
**Comparison:** 1 Colesevelam versus placebo  
**Outcome:** 6 Mean change in HOMA-index

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Bays 2008</td>
<td>159</td>
<td>6.65 (6.83)</td>
<td>157</td>
<td>7.25 (6.91)</td>
<td>-0.60 [-2.12, 0.92]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>159</td>
<td></td>
<td>157</td>
<td></td>
<td>100.0% -0.60 [-2.12, 0.92]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable  
Test for overall effect: Z = 0.78 (P = 0.44)  
Test for subgroup differences: Not applicable

### Analysis 1.7. Comparison 1 Colesevelam versus placebo, Outcome 7 Mean change in fasting C-peptide.

**Review:** Colesevelam for type 2 diabetes mellitus  
**Comparison:** 1 Colesevelam versus placebo  
**Outcome:** 7 Mean change in fasting C-peptide

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)[ng/mL]</td>
<td>N</td>
<td>Mean(SD)[ng/mL]</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Bays 2008</td>
<td>159</td>
<td>2.19 (1.22)</td>
<td>157</td>
<td>3.15 (1.51)</td>
<td>-0.96 [-1.26, -0.66]</td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>138</td>
<td>-0.43 (1.17)</td>
<td>137</td>
<td>-0.28 (1.17)</td>
<td>-0.15 [-0.43, 0.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>297</td>
<td></td>
<td>294</td>
<td></td>
<td>100.0% -0.55 [-1.35, 0.24]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.31$; $\chi^2 = 14.93$, df = 1 ($P = 0.00011$); $I^2 = 93\%$  
Test for overall effect: Z = 1.36 ($P = 0.17$)  
Test for subgroup differences: Not applicable
Analysis 1.8. Comparison 1 Colesevelam versus placebo, Outcome 8 Mean change in fasting insulin.

Review: Colesevelam for type 2 diabetes mellitus

Comparison: 1 Colesevelam versus placebo

Outcome: 8 Mean change in fasting insulin

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD) [uIU/mL]</td>
<td>N Mean(SD) [uIU/mL]</td>
<td>IV(Random),95% CI</td>
<td></td>
</tr>
<tr>
<td>Bays 2008</td>
<td>159 14.5 (10.69)</td>
<td>157 16.15 (14.4)</td>
<td>-2.65 [-4.45, 1.15]</td>
<td>27.2 %</td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>138 -1.59 (4.34)</td>
<td>137 -1.9 (4.56)</td>
<td>0.31 [-0.74, 1.36]</td>
<td>72.8 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>297</td>
<td>294</td>
<td>-0.22 [-1.93, 1.49]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.76; Chi² = 1.65, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Colesevelam versus placebo, Outcome 9 Mean change in 2-h post-MTT C-peptide.

Review: Colesevelam for type 2 diabetes mellitus

Comparison: 1 Colesevelam versus placebo

Outcome: 9 Mean change in 2-h post-MTT C-peptide

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD) [ng/mL]</td>
<td>N Mean(SD) [ng/mL]</td>
<td>IV(Random),95% CI</td>
<td></td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>137 -0.14 (0.24)</td>
<td>134 -0.21 (0.24)</td>
<td>0.07 [0.01, 0.13]</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>137</td>
<td>134</td>
<td>0.07 [0.01, 0.13]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.40 (P = 0.016)
Test for subgroup differences: Not applicable
Analysis 1.10. Comparison 1 Colesevelam versus placebo, Outcome 10 Mean change in 2-h post-MTT insulin.

Review: Colesevelam for type 2 diabetes mellitus

Comparison: 1 Colesevelam versus placebo

Outcome: 10 Mean change in 2-h post-MTT insulin

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Colesevelam</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Random,95% CI</td>
<td></td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>136 -9.3 (25.47)</td>
<td>134 -12.27 (41.14)</td>
<td>100.0 % 2.97 [ -5.21, 11.15 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>136</td>
<td>134</td>
<td>100.0 % 2.97 [ -5.21, 11.15 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Overview of study populations

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention (s) and control(s)</th>
<th>[n] screened</th>
<th>[n] randomised</th>
<th>[n] safety</th>
<th>[n] ITT</th>
<th>[n] finishing study</th>
<th>[%] of randomised participants finishing study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bays 2008</td>
<td>I1: colesevelam + (metformin only or metformin + oadm) C1: placebo + (metformin only or metformin + oadm)</td>
<td>T: 1009</td>
<td>I1: 159 C1: 157 T: 316</td>
<td>I1: 159 C1: 157 T: 316</td>
<td>I1: 149 C1: 152 T: 301</td>
<td>I1: 116 C1: 106 T: 222</td>
<td>I1: 73 C1: 68 T: 70</td>
</tr>
</tbody>
</table>
Table 1. Overview of study populations  (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention Details</th>
<th>ITT</th>
<th>C1: Placebo + (sulphonylureas only or sulphonylureas + oadm)</th>
<th>C1: Placebo + (insulin only or insulin + oadm)</th>
<th>Total 1450</th>
<th>Total Controls 1096</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>All interventions</td>
<td>729</td>
<td>566</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All controls</strong></td>
<td>721</td>
<td>530</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All interventions and controls</strong></td>
<td>1450</td>
<td>1096</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"-" denotes not reported

C: control; I: intervention; ITT: intention to treat; oadm: oral antidiabetic medications; T: total
APPENDICES

Appendix 1. Search strategies

Search terms and databases

Unless otherwise stated, search terms are free text terms.
Abbreviations:
'S': stands for any character; '?' : substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp: exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word

The Cochrane Library

#1 MeSH descriptor Diabetes mellitus, type 2 explode all trees
#2 MeSH descriptor Insulin resistance explode all trees
#3 (impaired in All Text and glucose in All Text and tolerance* in All Text) or (glucose in All Text and intolerance* in All Text) or (insulin* in All Text and resistance* in All Text)
#4 (obes* in All Text near/6 diabet* in All Text)
#5 (MODY in All Text or NIDDM in All Text or TDM2 in All Text or TD2 in All Text)
#6 (non in All Text and insulin* in All Text and depend* in All Text) or (noninsulin* in All Text and depend* in All Text) or (non in All Text and insulindepend* in All Text) or noninsulindepend* in All Text)
#7 (typ? in All Text and (2 in All Text near/6 diabet* in All Text))
#8 (typ? in All Text and (I in All Text near/6 diabet* in All Text))
#9 (non in All Text and (keto* in All Text near/6 diabet* in All Text))
#10 (nonketo* in All Text near/6 diabet* in All Text)
#11 (adult* in All Text near/6 diabet* in All Text)
#12 (matur* in All Text near/6 diabet* in All Text)
#13 (late in All Text near/6 diabet* in All Text)
#14 (slow in All Text near/6 diabet* in All Text)
#15 (stabl* in All Text near/6 diabet* in All Text)
#16 (insulin* in All Text and (defic* in All Text near/6 diabet* in All Text))
#17 (plurimetabolic in All Text and syndrom* in All Text)
#18 (pluri in All Text and metabolic in All Text and syndrom* in All Text)
#19 MeSH descriptor Glucose Intolerance explode all trees
#20 (typ?2 in All Text near/3 diabet* in All Text)
#21 (keto in All Text and (resist* in All Text near/3 diabet* in All Text))
#22 (non in All Text and (keto* in All Text near/3 diabet* in All Text))
#23 (nonketo* in All Text near/3 diabet* in All Text)
#24 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#25 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23)
#26 (#24 or #25)
#27 MeSH descriptor Diabetes insipidus explode all trees
#28 (diabet* in All Text and insipidus in All Text)
#29 (#27 or #28)
#30 (#26 and not #29)
#31 colesevelam* in All Text
#32 (bile in All Text near/6 acids* in All Text and sequestrant* in All Text)
#33 (BA* in All Text and sequestrant* in All Text)
#34 (#31 or #32 or #33)
#35 (#30 and #34)

Colesevelam for type 2 diabetes mellitus (Review)
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
MEDLINE

1. colesevelam.mp.
2. Cholestagel.tw,ot. (5)
3. WelChol.tw,ot. (14)
4. (bile acid* and sequestrant*).tw,ot.
5. BA* sequestrant*.tw,ot.
6. 1 or 2 or 3 or 4 or 5
7. exp Diabetes Mellitus, Type 2/
8. exp Insulin Resistance/
9. 7 exp Glucose Intolerance/
10. (impaired glucos$ tolerance$ or glucos$ intoleranc$ or insulin resistant)$).tw,ot.
11. (obes$ adj3 diabet$).tw,ot.
12. (MODY or NIDDM or T2DM or T2D).tw,ot.
13. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or noninsulin?depend$).tw,ot.
15. ((keto?resist$ or non?keto$) adj6 diabet$).tw,ot.
16. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).tw,ot.
17. or/7-16
18. exp Diabetes Insipidus/
19. diabet$ insipidus.tw,ot.
20. 18 or 19
21. 17 not 20
22. 6 and 21
23. (animals not (animals and humans)).sh.
24. 22 not 23

EMBASE

1. exp colesevelam/
2. colesevelam*.tw,ot.
3. Cholestagel.tw,ot.
4. WelChol.tw,ot.
5. BA* sequestrant*.tw,ot.
6. (bile acid* and sequestrant*).tw,ot.
7. 1 or 2 or 3 or 4 or 5
8. exp Diabetes Mellitus, Type 2/
9. exp Insulin Resistance/
10. (MODY or NIDDM or T2D or T2DM).tw,ot.
11. ((typ? 2 or typ? II or typ?II or typ?2) adj3 diabet*).tw,ot.
12. (obes* adj3 diabet*).tw,ot.
13. (non insulin* depend* or non insulin?depend* or noninsulin* depend* or noninsulin?depend*).tw,ot.
14. ((keto?resist* or non?keto*) adj3 diabet*).tw,ot.
15. ((adult* or matur* or late or slow or stabl*) adj3 diabet*).tw,ot.
16. (insulin* defic* adj3 relativ*).tw,ot.
17. (insulin* resistanc* or impaired glucos* tolerance* or glucos* intoleranc*).tw,ot.
18. or/8-17
19. exp Diabetes Insipidus/
20. diabet* insipidus.tw,ot.
21. 19 or 20  
22. 18 not 21  
23. 7 and 22  
24. limit 23 to human

**CINAHL**

1. MM “colesevelam”  
2. MM “Cholestagel”  
3. MM “WelChol”  
4. MM “bile acid* and sequestrant*”  
5. MM “BA* sequestrant*”  
6. #1 or #2 or #3 or #4 or #5  
7. MM “insulin resistance”  
8. MM “Diabetes Mellitus, Non-Insulin-Dependent”  
9. TX Diabetes Complications  
10. TX MODY or NIDDM or T2DM  
11. TX non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend  
12. TX diabet* N3 (typ* 2 or typ* II)  
13. TX diabet* N6 (keto*resist* or non*keto*)  
14. TI (onset N3 (late or adult* or matur* or slow or stabl*)) and TI diabet*  
15. AB (onset N3 (late or adult* or matur* or slow or stabl*)) and AB diabet*  
16. TI (insulin* defic* or relativ*)  
17. AB (insulin* defic* or relativ*)  
18. TI (insulin* resistanc*)  
19. AB (insulin* resistanc*)  
20. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19  
21. MM “Diabetes Insipidus”  
22. TX diabet* insipidus  
23. # 21 or #22  
24. #20 NOT #23  
25. #6 and #24  
26. AB randomized controlled trial  
27. AB controlled clinical trial  
28. AB cross over OR crossover  
29. TX random* OR blind* OR placebo* OR group*  
30. TX animal* NOT (animal* AND human*)  
31. #26 or #27 or #28 or #29  
32. #31 NOT #30  
33. #25 and #32

**LILACS**

(colesevelam or bile acid$ sequestrant$ or BA$ sequestrant$ or Cholestagel or Welchol) [Subject descriptor] and (Diabetes mellitus or insulin resistance) [Palavras] and (random$ or placebo$ or trial or group$) [Palavras]

**OpenGrey**
Appendix 2. Description of interventions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s) (route, frequency, total dose/day)</th>
<th>Control(s) (route, frequency, total dose/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bays 2008</td>
<td>Colesevelam tablets 3.75 g daily with existing metformin monotherapy or with existing metformin in combination with additional oral antidiabetic agents</td>
<td>Placebo with existing metformin monotherapy or with existing metformin in combination with additional oral antidiabetic agents</td>
</tr>
<tr>
<td>Fonseca 2008</td>
<td>Colesevelam tablets 3.75 g daily with existing sulphonylureas monotherapy or with existing sulphonylureas in combination with additional oral antidiabetic agents</td>
<td>Placebo with existing sulphonylureas monotherapy or with existing sulphonylureas in combination with additional oral antidiabetic agents</td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>Colesevelam tablets 3.75 g daily with existing insulin monotherapy or with existing insulin in combination with additional oral antidiabetic agents</td>
<td>Placebo with existing insulin monotherapy or with existing insulin in combination with additional oral antidiabetic agents</td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>Colesevelam tablets 3.75 g daily and metformin</td>
<td>Placebo and metformin</td>
</tr>
<tr>
<td>Schwartz 2010</td>
<td>Colesevelam tablets 3.75 g daily</td>
<td>Placebo</td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>Colesevelam tablets 3.75 g daily with existing antidiabetic agents</td>
<td>Placebo with existing antidiabetic agents</td>
</tr>
</tbody>
</table>
## Appendix 3. Baseline characteristics (I)

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention (s) and control(s)</th>
<th>Participating population</th>
<th>Country</th>
<th>Sex (%) (female)</th>
<th>Age (mean years (SD))</th>
<th>HbA1c (mean % (SD))</th>
<th>BMI (mean kg/m^2 (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bays 2008</td>
<td>I: colesevelam + (metformin only or metformin + oadm) C: placebo + (metformin only or metformin + oadm)</td>
<td>Participants with T2DM</td>
<td>USA and Mexico</td>
<td>I: 49 C: 47</td>
<td>I: 55.7 (9.6) C: 56.9 (9.5)</td>
<td>I: 8.2 (0.7) C: 8.1 (0.6)</td>
<td>I: 33.9 (5.3) C: 33.0 (6.3)</td>
</tr>
<tr>
<td>Fonseca 2008</td>
<td>I: colesevelam + (sulphonylureas only or sulphonylureas + oadm) C: placebo + (sulphonylureas only or sulphonylureas + oadm)</td>
<td>Participants with T2DM</td>
<td>USA and Mexico</td>
<td>I: 44 C: 47</td>
<td>I: 56.6 (10.3) C: 57.0 (10.3)</td>
<td>I: 8.2 (0.68) C: 8.3 (0.72)</td>
<td>I: 33.1 (5.95) C: 32.5 (5.64)</td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>I: colesevelam + (insulin only or insulin + oadm) C: placebo + (insulin only or insulin + oadm)</td>
<td>Participants with T2DM</td>
<td>USA and Mexico</td>
<td>I: 48 C: 49</td>
<td>I: 56.9 (9.8) C: 56.3 (9.3)</td>
<td>I: 8.3 (0.62) C: 8.3 (0.63)</td>
<td>I: 34.9 (5.82) C: 34.9 (5.91)</td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>I: colesevelam + metformin C: placebo + metformin</td>
<td>Participants with T2DM</td>
<td>USA, Mexico, Colombia and India</td>
<td>I: 52 C: 60</td>
<td>I: 52.7 (11.5) C: 53.9 (10.1)</td>
<td>I: 7.8 (1.0) C: 7.5 (0.9)</td>
<td>I: 30.6 (4.7) C: 29.8 (4.4)</td>
</tr>
<tr>
<td>Schwartz 2010</td>
<td>I: colesevelam C: placebo</td>
<td>Participants with T2DM</td>
<td>USA</td>
<td>I: 41 C: 61</td>
<td>I: 51.4 (12.7) C: 56.0 (7.9)</td>
<td>I: 8.2 (0.9) C: 8.7 (0.9)</td>
<td>I: 35.2 (3.6) C: 33.4 (5.2)</td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>I: colesevelam + oadm C: placebo + oadm</td>
<td>Participants with T2DM</td>
<td>USA</td>
<td>I: 48 C: 41</td>
<td>I: 56.7 (9.7) C: 55.7 (9.1)</td>
<td>I: 7.9 (0.8) C: 8.1 (0.9)</td>
<td>I: 32.5 (5.2) C: 32.2 (5.5)</td>
</tr>
</tbody>
</table>
Appendix 4. Baseline characteristics (II)

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention(s) and control(s)</th>
<th>Duration of disease (n (%)) since diagnosis</th>
<th>Ethnic groups (%)</th>
<th>Duration of intervention</th>
<th>Follow-up</th>
<th>Co-medications</th>
<th>Co-interventions (%)</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bays 2008</td>
<td>I: colesevelam + (metformin only or metformin + oadm) C: placebo + (metformin only or metformin + oadm)</td>
<td>-</td>
<td>I: White: 56 Black: 15 Asian: 4 Hispanic: 25 Others: 1</td>
<td>26 weeks</td>
<td>0, 12, 18, 26 weeks</td>
<td>Antihypertensives Sulphonylureas Thiazolidinediones α-glucosidase inhibitors Meglitinides</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fonseca 2008</td>
<td>I: colesevelam + (sulphonylureas only or sulphonylureas + oadm) C: placebo + (sulphonylureas only or sulphonylureas + oadm)</td>
<td>-</td>
<td>I: White: 59 Hispanic: 29 Black: 10 Asian: 2 Others: 1</td>
<td>26 weeks</td>
<td>0, 12, 18, 26 weeks</td>
<td>Sulphonylureas only or sulphonylureas plus combination therapy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>I: colesevelam + (insulin only)</td>
<td>-</td>
<td>I: White: 64 Black: 16</td>
<td>16 weeks</td>
<td>0, 4, 8, 16 weeks</td>
<td>Insulin only or insulin plus</td>
<td>I: AHT: ACEI 41.5</td>
<td>-</td>
</tr>
<tr>
<td>Study</td>
<td>Design Description</td>
<td>Race/Heritage</td>
<td>Metformin Use</td>
<td>Other Drugs Used</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>I: colesevelam + metformin</td>
<td>&lt; 1 year: 175 (47)</td>
<td>16 weeks</td>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: placebo + metformin</td>
<td>1 to 5 years: 81 (28)</td>
<td>4, 8, 12, 16 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 5 years: 30 (11)</td>
<td>16 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz 2010</td>
<td>I: colesevelam</td>
<td>-</td>
<td>8 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: placebo</td>
<td></td>
<td>0, 2, 4, 6, 8 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>I: colesevelam + oadm</td>
<td>-</td>
<td>12 weeks</td>
<td>Sulphonylureas or metformin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: placebo</td>
<td></td>
<td>1, 4, 8, 12 weeks</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Colesvelam for type 2 diabetes mellitus (Review)
+ oadm  
23 Others: 7  
C: White: 62  
Black: 12  
Hispanic: 27  
Others: 0  
or sulphonylureas plus metformin

**Footnotes**

“-” denotes not reported
ACEI: angiotensin-converting enzyme inhibitors; AHL: antihyperlipidaemics; AHT: antihypertensives; ATII: angiotensin II antagonists; BB: selective β-blocker; BMI: body mass index; C: control; DHP: dihydropyridine derivatives; I: intervention; oadm: oral antidiabetes medications; PI: platelet aggregations inhibitors; SD: standard deviation; TH: thiazides

### Appendix 5. Matrix of study endpoints

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Primary&lt;sup&gt;a&lt;/sup&gt; end point(s)</th>
<th>Secondary&lt;sup&gt;b&lt;/sup&gt; end point(s)</th>
<th>Other&lt;sup&gt;c&lt;/sup&gt; end point(s)</th>
<th>Time period of outcome measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bays 2008</td>
<td>Mean change from baseline HbA1c level</td>
<td>Mean change in HbA1c, FPG and fructosamine levels from baseline to weeks 6, 12, 18 and 26; mean change in C-peptide, adiponectin and insulin levels and homeostasis model assessment (HOMA) index from baseline to week 26; mean change and mean % change in concentrations of TC, LDL-C, HDL-C, non-HDL-C, Apo A-I, and Apo B from baseline to week 26; mean change in TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C and Apo B/Apo A-I ratios from baseline to week 26; and median change and median % change in high-sensi-treatment-emergent adverse events (AEs), clinical laboratory blood test results, changes in vital signs and findings on physical examinations as well as compliance</td>
<td>0, 12, 18, 26 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Fonseca 2008</strong></td>
<td>Mean change from baseline HbA1c level</td>
<td>Mean change in HbA1c, FPG, fructosamine and C-peptide levels from baseline to week 26, pre-defined reduction in FPG level of ≥ 30 mg/dL or in HbA1c level of ≥ 0.7% from baseline at week 26. Other secondary end points included mean % change in lipids, lipoproteins, and lipid and lipoprotein ratios; and median change and median % change in hsCRP and triglycerides</td>
<td>Treatment-emergent AEs, clinical laboratory blood test results, changes in vital signs, and findings on physical examinations as well as compliance</td>
<td>0, 6, 12, 18, 26 weeks</td>
</tr>
<tr>
<td><strong>Goldberg 2008</strong></td>
<td>Mean change from baseline HbA1c level</td>
<td>Mean change in FPG, fructosamine and HbA1c levels from baseline to weeks 4, 8 and 16; mean change in C-peptide levels from baseline to week 16; mean change and mean % change in concentrations of TC, LDL-C, HDL-C, non-HDL-C, TG, and Apo A-I and Apo B levels and in ratios of TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C and Apo B/Apo A-I from baseline to week 16; and median change and median % change in levels of high-sensitivity C-reactive protein and TGs from baseline to week 16</td>
<td>Vital signs, physical examinations, treatment-emergent AEs, and clinical laboratory test results including kidney functions at weeks -3 (screening), 0 (randomisation baseline), 8 and 16 or at an early termination visit, if applicable as well as compliance</td>
<td>0, 4, 8, 16 weeks</td>
</tr>
<tr>
<td><strong>Rosenstock 2010</strong></td>
<td>Mean change from baseline HbA1c level</td>
<td>Mean change in FPG, fasting insulin, fasting C-peptide, post-meal tolerance test (MTT)</td>
<td>Vital signs, physical examinations, occurrence and severity of AEs, clinical laboratory test results</td>
<td>4, 8, 12, 16 weeks</td>
</tr>
<tr>
<td>Study</td>
<td>Change from baseline in glucose disposal rate (insulin clamp)</td>
<td>Change from baseline in M-value at week 2; change from baseline in area under the curve for glucose (AUCg) and insulin (AUCi) at weeks 2 and 8; acute and chronic effects of colesevelam on postprandial glucose; change from baseline in HbA1c at weeks 0 and 8; change from baseline in FPG and fasting insulin at weeks 2, 4, 6 and 8; and change from baseline in fructosamine at weeks 4 and 8</td>
<td>Vital signs, clinical laboratory tests, and ECGs, evaluation of the incidence and severity of AEs as well as compliance</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Schwartz 2010</td>
<td>Change from baseline in glucose disposal rate (insulin clamp)</td>
<td>Change from baseline in M-value at week 2; change from baseline in area under the curve for glucose (AUCg) and insulin (AUCi) at weeks 2 and 8; acute and chronic effects of colesevelam on postprandial glucose; change from baseline in HbA1c at weeks 0 and 8; change from baseline in FPG and fasting insulin at weeks 2, 4, 6 and 8; and change from baseline in fructosamine at weeks 4 and 8</td>
<td>Vital signs, clinical laboratory tests, and ECGs, evaluation of the incidence and severity of AEs as well as compliance</td>
<td></td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>Mean change from baseline HbA1c level</td>
<td>Mean changes in fructosamine levels, FPG levels, the postprandial glucose level, the meal glucose response, % changes in lipid parameters (LDL-C, TC, HDL-C, TG, Apo) A-I and B, and LDL particle concentration</td>
<td>AEs, laboratory tests at weeks -5, 0 and 12 as well as compliance</td>
<td></td>
</tr>
</tbody>
</table>

**Footnotes**

a,b Verbatim statement in the publication; c not explicitly stated as primary or secondary endpoint(s) in the publication

AE: adverse event; Apo: apolipoprotein; AUCg: area under the curve for glucose; AUCi: area under the curve for insulin; ECG: electrocardiogram; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin; HDL-C: high-density lipoprotein cholesterol; HOMA-I: homeostasis model assessment index; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; MTT: meal tolerance test; TC: total cholesterol; TG: triglyceride.
## Appendix 6. Adverse events (I)

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention(s) and control(s)</th>
<th>Deaths (n)</th>
<th>All adverse events (n (%))</th>
<th>Severe/serious adverse events (n (%))</th>
<th>Left study due to adverse events (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bays 2008</strong></td>
<td>I: colesevelam + (metformin only or metformin + oadm) C: placebo + (metformin only or metformin + oadm)</td>
<td>I: 0 C: 0</td>
<td>I: 8 (5) C: 5 (3) T: 13 (6)</td>
<td>I: 4 (3) C: 2 (1) T: 6 (3)</td>
<td>I: 8 (5) C: 4 (3) T: 12 (6)</td>
</tr>
<tr>
<td><strong>Fonseca 2008</strong></td>
<td>I: colesevelam + (sulphonylureas only or sulphonylureas + oadm) C: placebo + (sulphonylureas only or sulphonylureas + oadm)</td>
<td>I: 0 C: 0</td>
<td>I: 145 (63) C: 126 (55) T: 261 (59)</td>
<td>I: 9 (4) C: 7 (3) T: 16 (4)</td>
<td>I: 18 (8) C: 9 (4) T: 27 (6)</td>
</tr>
<tr>
<td><strong>Goldberg 2008</strong></td>
<td>I: colesevelam + (insulin only or insulin + oadm) C: placebo + (insulin only or insulin + oadm)</td>
<td>I: 0 C: 1</td>
<td>I: 92 (63) C: 82 (59) T: 174 (61)</td>
<td>I: 13 (9) C: 11 (8) T: 24 (8)</td>
<td>I: 2 (1) C: 1 (1) T: 3 (1)</td>
</tr>
<tr>
<td><strong>Rosenstock 2010</strong></td>
<td>I: colesevelam + metformin C: placebo + metformin</td>
<td>I: 0 C: 0</td>
<td>I: 97 (67) C: 97 (69) T: 195 (69)</td>
<td>I: 2 (1) C: 1 (1) T: 3 (1)</td>
<td>I: 5 (3) C: 9 (6) T: 14 (5)</td>
</tr>
<tr>
<td><strong>Schwartz 2010</strong></td>
<td>I: colesevelam C: placebo</td>
<td>I: 0 C: 0</td>
<td>I: 8 (47) C: 6 (33) T: 14 (0.4)</td>
<td>I: 1 (6) C: 1 (6) T: 2 (6)</td>
<td>I: 0 (0) C: 0 (0)</td>
</tr>
<tr>
<td><strong>Zieve 2007</strong></td>
<td>I: colesevelam + oadm C: placebo + oadm</td>
<td>-</td>
<td>I: 20 (65) C: 22 (65) T: 42 (65)</td>
<td>-</td>
<td>I: 2 (7) C: 1 (3) T: 3 (5)</td>
</tr>
</tbody>
</table>

**Footnotes**

“-“ denotes not reported

C: control; I: intervention; oadm: oral antidiabetes medications; T: total
### Appendix 7. Adverse events (II)

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention(s) and control(s)</th>
<th>Hospitalisation (n (%))</th>
<th>Outpatient treatment (n (%))</th>
<th>All hypoglycaemic episodes (n (%))</th>
<th>Severe/serious hypoglycaemic episodes (n (%))</th>
<th>Nocturnal hypoglycaemic episodes (n (%))</th>
<th>Symptoms (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bays 2008</strong></td>
<td>I: colesevelam + (metformin only or metformin + oadm) C: placebo + (metformin only or metformin + oadm)</td>
<td>-</td>
<td>-</td>
<td>I: 1 (0.6) C: 0 (0) T: 1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>I: 8 (5) C: 5 (3) T: 13 (6)</td>
</tr>
<tr>
<td><strong>Fonseca 2008</strong></td>
<td>I: colesevelam + (sulphonylureas only or sulphonylureas + oadm) C: placebo + (sulphonylureas only or sulphonylureas + oadm)</td>
<td>-</td>
<td>-</td>
<td>I: 6 (3) C: 2 (1) T: 8 (2)</td>
<td>-</td>
<td>-</td>
<td>I: 145 (63) C: 126 (55) T: 261 (59)</td>
</tr>
<tr>
<td><strong>Goldberg 2008</strong></td>
<td>I: colesevelam + (insulin only or insulin + oadm) C: placebo + (insulin only or insulin + oadm)</td>
<td>-</td>
<td>-</td>
<td>I: 0 C: 0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Rosenstock 2010</strong></td>
<td>I: colesevelam + metformin C: placebo + metformin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>I: 97 (61) C: 97 (69) T: 195 (69)</td>
</tr>
<tr>
<td><strong>Schwartz 2010</strong></td>
<td>I: colesevelam C: placebo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Zieve 2007</strong></td>
<td>I: colesevelam + oadm C: placebo +</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Appendix 8. Survey of authors’ reactions to provide information on trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study author contacted</th>
<th>Study author replied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bays 2008</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Fonseca 2008</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Goldberg 2008</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Rosenstock 2010</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Schwartz 2010</td>
<td>Y</td>
<td>Y (advised to contact manufacturer for data)</td>
</tr>
<tr>
<td>Zieve 2007</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

Footnotes
N: no; Y: yes
Note: to-date the manufacturer has yet to reply
DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia.
- Institute of Gerontology, Universiti Putra Malaysia, Malaysia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Cohen's kappa test for study selection, subgroup analysis and sensitivity analysis was not performed.

INDEX TERMS

Medical Subject Headings (MeSH)

Allylamine [*analogs & derivatives; therapeutic use]; Blood Glucose [metabolism]; Diabetes Mellitus, Type 2 [blood; *drug therapy]; Fasting [blood]; Hemoglobin A, Glycosylated [metabolism]; Hypoglycemic Agents [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans