Diabetes: managing dyslipidaemia

Search date June 2007

Jigisha Patel

ABSTRACT

INTRODUCTION: Dyslipidaemia is a major contributor to the increased risk of heart disease found in people with diabetes. An increase of 1 mmol/L LDL-C is associated with a 1.57-fold increase in the risk of coronary heart disease (CHD) in people with type 2 diabetes. A diagnosis of diabetic dyslipidaemia requiring pharmacological treatment is determined by the person's lipid profile and level of cardiovascular risk. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions for dyslipidaemia in people with diabetes? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 21 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: anion exchange resins, combined treatments (for lipid modification), ezetimibe, fibrates, fish oil (for lipid modification), intensive multiple intervention treatment programmes (for lipid modification), nicotinic acid (for lipid modification), and statins.

QUESTIONS

INTERVENTIONS

Key points

- Dyslipidaemia is characterised by decreased circulating levels of high-density lipoprotein cholesterol (HDL-C) and increased circulating levels of triglycerides and low-density lipoprotein cholesterol (LDL-C).

  Dyslipidaemia is a major contributor to the increased risk of heart disease found in people with diabetes.

  An increase of 1 mmol/L LDL-C is associated with a 1.57-fold increase in the risk of CHD in people with type 2 diabetes.

  A diagnosis of diabetic dyslipidaemia requiring pharmacological treatment is determined by the person's lipid profile and level of cardiovascular risk. The classification of cardiovascular risk and lipid targets for drug treatment differ between the USA and the UK, and the rest of Europe. We used the United Kingdom Prospective Diabetes Study (UKPDS) risk calculator to estimate 10-year cardiovascular risk, and categorised a 15% or more risk as "higher risk", and 15% or less as "lower risk" according to the UK clinical guidelines. We found no RCTs of a solely lower-risk population, although some studies were excluded because of insufficient data to calculate risk. In clinical practice, most people with diabetes are increasingly considered at high cardiovascular risk, regardless of the presence or absence of other risk factors.

- Statins are highly effective at improving cardiovascular outcomes in people with diabetes.

  Statins reduce cardiovascular mortality in people with type 2 diabetes with and without known CVD, and regardless of baseline total and LDL-C concentrations.

  Different statins seem to have similar efficacy at reducing LDL-C.

- Combining statins with other treatments (such as ezetimibe or a fibrate) seems to reduce LDL-C more than statin treatments alone.

  Combinations could be useful in people with mixed dyslipidaemia where one drug fails to control all lipid parameters.

- Fibrates seem to have a beneficial effect on cardiovascular mortality and morbidity by reducing triglyceride levels.

In people with mixed dyslipidaemia, statins may also be required.

- Intensive-treatment programmes involving multiple interventions (people seen by a nurse every 4–6 weeks) seem better at reducing cholesterol than usual-care programmes.
- Fish oils may reduce triglyceride levels, but also seem to increase LDL-C levels, making them of limited benefit to most diabetic patients.
- Nicotinic acid seems effective at increasing HDL-C and may reduce triglycerides. However, in clinical practice, nicotinic acid alone is not the preferred treatment for hypertriglyceridaemia, but may be used in combination with a statin in people with mixed dyslipidaemia, or in those unable to tolerate fibrates.

  Nicotinic acid seems to increase the incidence of flushing, particularly in female patients.
- We don't know whether anion exchange resins or ezetimibe are useful in treating dyslipidaemia in people with diabetes, but they could be used in combination with a statin if the statin alone fails to achieve lipid targets.

DEFINITION

The term dyslipidaemia is used to describe a group of conditions in which there are abnormal levels of lipids and lipoproteins in the blood. Abnormalities of lipid metabolism are present in people with both type 1 and type 2 diabetes. The nature of these abnormalities is complex, but the core components of diabetic dyslipidaemia are elevated circulating levels of triglycerides and decreased circulating levels of high-density lipoprotein cholesterol (HDL-C). In addition, the number of small, dense lipoprotein particles is raised. Consequently — although the cholesterol content of these particles may be low — small, dense low-density lipoprotein cholesterol (LDL-C) is raised. Total cholesterol and LDL-C may be normal if glycaemic control is adequate. [1] [2] Triglycerides and cholesterol are the main lipids of interest. The main classes of lipoprotein considered in this review are low-density lipoproteins (LDL) and high-density lipoproteins (HDL). **Diagnosis:** A diagnosis of diabetic dyslipidaemia requiring drug treatment is determined by the person's lipid profile and level of cardiovascular risk. The classification of cardiovascular risk and lipid targets for drug treatment differ between the USA [3] and the UK, [4] and the rest of Europe. [5] While it is accepted that people with diabetes are at high risk of CVD, [6] [7] in the UK and USA this high-risk group is stratified further to target those most likely to benefit from treatment. However, the European guidelines on CVD prevention classify as all high risk people with type 2 diabetes, and with type 1 diabetes and microalbuminuria. Treatment targets for the UK and USA and the rest of Europe are shown in table 1, p 14 . These targets apply to people with type 2 diabetes. It is acknowledged that in the USA, [8] there is a case for offering drug treatment at lower lipid levels in people at high cardiovascular risk. In the USA, an "optional" goal for LDL-C of 1.81 mmol/L (70 mg/dL) is considered in people with high cardiovascular risk; [8] and the Canadian Diabetic Association recommends a goal for LDL-C of 2.0 mmol/L or less in similarly high-risk people. [9] Although these targets apply to people with type 2 diabetes, in clinical practice they are often extrapolated to people with type 1 diabetes. **Population:** For this review, we have included studies of adults with type 1 and type 2 diabetes, including those with concurrent hypertension, and we have used UK (NICE) guidelines to determine level of risk. The UKPDS (United Kingdom Prospective Diabetes Study) tool, which includes data from people with diabetes, was used to calculate level of cardiovascular risk only. [10] Subpopulations are described in detail in the description of individual studies where appropriate. Studies in children were excluded. Studies of adults with diabetes and microalbuminuria or nephropathy are covered in a separate review (see review on diabetic nephropathy).

INCIDENCE/ PREVALENCE

Type 1 diabetes mellitus: In people with well-controlled type 1 diabetes, the incidence of dyslipidaemia is comparable to that in the general population. [6] However, there are no detailed data on the incidence and prevalence of dyslipidaemia in people with type 1 diabetes. **Type 2 diabetes mellitus:** Dyslipidaemia is common in people with type 2 diabetes. A survey of 498 adults with type 2 diabetes [11] (representing a projected population size of 13,369,754 in the US adult general population) estimated that over 70% of people have an LDL-C greater than the US treatment goal of less than 2.6 mmol/L (less than 100 mg/dL; some have estimated this figure at greater than 80% [12]). Over half of men and two thirds of women have an HDL-C level below US recommended goals of greater than 1.0 mmol/L, while over half of men and women have elevated triglyceride levels. Only 28.2% of people with diabetes were taking lipid-modifying drugs, and only 3% were controlled to US targets for all lipids. [11]

AETIOLOGY/ RISK FACTORS

In people with diabetes mellitus, insulin insufficiency or insulin resistance can have an effect on lipid metabolism. [7] **Type 1 diabetes mellitus:** Little is understood about the cause of dyslipidaemia in people with type 1 diabetes. In poorly controlled type 1 diabetes, and in nephropathy, the typical cluster of abnormalities seen in diabetic dyslipidaemia does occur, and is associated with a much greater cardiovascular risk than in people without diabetes. [6] **Type 2 diabetes mellitus:** Impaired insulin action may not be the only cause of dyslipidaemia. Central/visceral obesity may increase the amount of free fatty acids released into the portal circulation, increasing hepatic triglyceride production, while high-fat meals — typical of a Western diet — may exacerbate postprandial hypertriglyceridaemia. [7] Impaired insulin action in people with type 2 diabetes is thought to result in the

loss of suppression of lipolysis (the breakdown of triglycerides into free fatty acids and glycerol) in adipose tissue. This leads to an increased release of free fatty acids into the portal circulation and, consequently, increased delivery of free fatty acids to the liver. This leads to increased production of triglycerides by the liver and a decreased production of HDL-C. In addition, there is impaired clearance of triglycerides from the circulation. This resulting hypertriglyceridaemia alters the activity of other enzymes, which leads to the formation of small, dense LDL particles, and increased catabolism of HDL.

PROGNOSIS

CVD is 2–6 times more frequent in people with diabetes than in people without diabetes, and progresses more rapidly when it occurs. Overall, it is the most common cause of death in people with diabetes, with at least 50% of deaths in type 2 diabetes caused by CHD. [7] Dyslipidaemia is one of the major contributors to this increased cardiovascular risk. Lipid abnormalities are important predictors of CHD in people with type 2 diabetes. High LDL-C, high triglycerides, and low HDL-C have all been reported as predictors for cardiovascular risk. A 1.57-fold increase in CHD risk has been reported to be associated with a 1 mmol/L increase in LDL-C, and a 15% decrease in risk with a 0.1 mmol/L increase in HDL-C concentration. [7]

AIMS OF INTERVENTION

To reduce cardiovascular mortality and morbidity; to reduce all-cause mortality; to improve lipid profile; and to minimise adverse effects of treatment.

OUTCOMES

Primary outcomes: Reduction in cardiovascular morbidity and mortality (including MI, stroke, PVD); a clinically significant improvement in lipid profile as opposed to achieving "target values" per se; quality of life; adverse effects of treatment including muscle events (myalgia, myositis, myopathy); changes in glycaemic control; renal failure; changes in liver enzymes (in clinical practice, an elevation of liver enzymes of at least 3 times the upper limit of normal, or creatine kinase of at least 10 times the upper limit of normal, would warrant stopping treatment). **Secondary outcomes:** All-cause mortality; change in any other risk factor for macrovascular disease.

METHODS

BMJ Clinical Evidence search and appraisal June 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were done using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals. We did not exclude on the basis of loss to follow-up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded, unless blinding was impossible. Studies that compared different intervention options without a placebo arm, but using a double dummy design, were included. We also searched for cohort studies and case control studies on specific harms of interventions. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. **Cardiovascular risk stratification:** In the UK and USA, cardiovascular risk determines whether people are offered pharmacological treatment. We have, therefore, stratified the evidence in a similar way. For this review, we have used the UK (NICE) guidelines to determine level of risk. [4] For each RCT, we categorised the study group as "lower risk" or "higher risk". Studies which stated that the study group had a history of CVD were automatically categorised as higher risk. RCTs where no history was reported, but where patient demographics and baseline lipids were available, were categorised according to the estimated 10-year cardiovascular risk (using the UKPDS risk calculator). Those with a risk of greater than 15% were categorised as higher risk, and those with a risk of less than 15% as lower risk. The UKPDS risk calculator takes into account: duration of diabetes, sex, ethnicity, smoking, systolic blood pressure, HbA1C, total cholesterol, HDL-C, and the presence or absence of atrial fibrillation. The minimum factors used to determine risk were sex, smoking status, systolic blood pressure, and baseline total cholesterol and HDL-C. Ethnicity, HbA1c, and duration of diabetes were included if this information was reported. Most trials assessing the clinical effects of lipid-lowering treatment do not record the presence or absence of atrial fibrillation: this factor was therefore assumed to be absent in the calculation of cardiovascular risk. RCTs were excluded if the authors did not report the presence or absence of a history of manifest CVD, and where the minimum required risk factors as stated above were not recorded. We found no RCTs in people categorised as lower risk. We excluded some studies because the authors did not report sufficient data to calculate risk, [13] [14] [15] [16] and these may have included lower-risk populations. **Clin-**

ical significance criteria for determining changes in lipid profiles: For the outcome of lipid modification, only studies which either reported the proportion of people reaching treatment targets, or which showed a decrease from baseline for LDL-C of 30% or more, or an increase in HDL-C of 5% or more, or a decrease in triglycerides of 30% or more, or a decrease in total cholesterol 20% or more, were considered clinically significant and included. These criteria for clinical significance were based on the findings of large lipid-intervention trials, where a change in lipid parameters was associated with a clinically beneficial effect on cardiovascular morbidity and mortality. [4] **Adverse effects:** Adverse events of interest were muscle effects (myalgia, myositis, and myopathy), change in glycaemic control, an increase in liver enzymes greater than three times the upper limit of normal, an increase in creatine kinase greater than 10 times the upper limit of normal, and any increase in creatinine. RCTs, cohort and case control studies, and phase IV studies addressing the adverse effects of interest were included. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 26).

QUESTION What are the effects of interventions for dyslipidaemia in people with diabetes?

OPTION STATINS

Cardiovascular events

Statins compared with placebo Statins may be more effective at preventing primary and secondary composite outcomes of major coronary events (including coronary artery disease death, non-fatal MI, or myocardial revascularisation procedures) especially in people without a history of CVD (low-quality evidence).

Atorvastatin compared with placebo Atorvastatin is more effective at reducing cardiovascular events in people with diabetes and hypertension but without a history of CVD (moderate-quality evidence).

Change in lipid profile

Simvastatin compared with placebo Simvastatin is more effective at 6–24 weeks at improving triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol (high-quality evidence).

Pravastatin compared with placebo Pravastatin may be more effective at 24 weeks at improving total cholesterol and triglyceride levels (low-quality evidence).

Atorvastatin compared with placebo Atorvastatin is more effective at 30 weeks at improving triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol in people with type 2 diabetes (moderate-quality evidence).

For GRADE evaluation of interventions for dyslipidaemia in diabetes, see table, p 26 .

Benefits:

We found one systematic review (search date 2004) [17] and two subsequent RCTs [18] [19] in people with diabetes at higher risk of macrovascular complications, which compared statins versus placebo for the outcomes of cardiovascular morbidity and mortality (see table 2, p 15). We also found five RCTs comparing statins versus placebo for the outcome of change in lipid profile (see table 3, p 18). [20] [21] [22] [23] [24]

Statins versus placebo for cardiovascular mortality and morbidity:

One systematic review (search date 2004; 4 primary prevention RCTs; 6 secondary prevention RCTs; and 2 primary and secondary prevention RCTs) found that, compared with placebo, statins (pravastatin, simvastatin, atorvastatin, lovastatin, and fluvastatin) significantly reduced cardiovascular risk in both primary and secondary prevention (see table 2, p 15). [17] The primary outcome measured was a composite outcome of major coronary events (defined as coronary artery disease death, non-fatal MI, or myocardial revascularisation procedures). Secondary outcomes were listed as coronary artery disease death, non-fatal MI, myocardial revascularisation procedures, stroke, and changes in blood lipid profile. The review did not report changes in lipid profile in detail. The review carried out subgroup analyses for individual secondary outcomes. It found that statins significantly reduced incidence of stroke and myocardial revascularisation procedures compared with placebo, but the difference between groups in non-fatal MI and death from CHD did not reach significance (see table 2, p 15). None of the RCTs included in the review was solely in people with diabetes. The results presented are from pooled diabetes-specific data. [17] The review found similar relative risk reductions for a major coronary event in primary and secondary prevention in people with diabetes (see table 2, p 15), but it found a significantly higher difference in absolute risk for major coronary event in secondary prevention (risk difference for major coronary events: primary prevention; –0.02, 95% CI –0.04 to 0.00, P = 0.1; secondary prevention; –0.07, 95% CI –0.11 to –0.03, P = 0.0003); these analyses include people treated with gemfibrozil (a fibrate). The characterisation of people with diabetes included in these large intervention trials is poor. This may have implications for the generalisability of results.

Simvastatin versus placebo for cardiovascular mortality and morbidity:
We found no systematic review or RCT assessing the effects of simvastatin on cardiovascular mortality and morbidity. We found three RCTs comparing simvastatin versus placebo for the outcome of change in lipid profile, all of which found significant improvements in lipid levels in people taking simvastatin (see table 3, p 18). [20] [21] [22]

Pravastatin versus placebo for cardiovascular mortality and morbidity:
We found no systematic review or RCT assessing the effects of pravastatin on cardiovascular mortality and morbidity. We found one RCT comparing pravastatin versus placebo for the outcome of change in lipid profile, which found that pravastatin significantly improved total cholesterol and triglycerides compared with placebo (see table 3, p 18). [24]

Atorvastatin versus placebo for cardiovascular mortality and morbidity:
We found two subsequent RCTs, both of which found that atorvastatin significantly reduced cardiovascular events in people with diabetes but no previous CVD. [19] [18] The first RCT found that, compared with placebo, atorvastatin 10 mg daily significantly reduced cardiovascular events at 3.9 years in people with type 2 diabetes without CVD (see table 2, p 15). [19] The trial was stopped 2 years early because of the large treatment effect reported. CVD was defined as history of MI, angina, coronary vascular surgery, cerebrovascular disease, significant PVD defined as that warranting surgery, or high low-density lipoprotein cholesterol (LDL-C). Cardiovascular events were defined as fatal and non-fatal MI, unstable angina, resuscitated cardiac arrest, coronary revascularisation, and fatal and non-fatal stroke. The second RCT comparing atorvastatin versus placebo did a subgroup analysis of 2532 people with type 2 diabetes. [18] The RCT found that, compared with placebo, atorvastatin 10 mg daily significantly reduced the incidence of total cardiovascular events and procedures at 3.3 years in people with diabetes and hypertension, but with no history of CHD, and in people with with cholesterol concentrations that were not markedly elevated (see table 2, p 15). Participants were required to have at least three of the following risk factors: male sex, age at least 55 years, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to high-density lipoprotein cholesterol 6 or greater, a premature family history of CHD, left ventricular hypertrophy, other specified abnormalities on electrocardiogram, previous stroke, or transient ischaemic attack. [18] We found one RCT comparing atorvastatin versus placebo for the outcome of change in lipid profile (see table 3, p 18). [23]

Harms:

Statins:
The systematic review gave no information on adverse effects. [17] Detailed data were not reported. RCTs found that statins may be associated with musculoskeletal adverse effects and may cause elevations of alanine transaminase, aspartate aminotransferase, liver enzymes, and creatine kinase, although results differed among RCTs (see table 2, p 15 and table 3, p 18). The review did not comment on adverse effects among different ethnic groups in the included trials. A drug safety alert has been issued on the increased risk of haemorrhagic stroke associated with high doses of atorvastatin in people with recent stroke. [25]

Comment:

We found no systematic review or RCTs evaluating effects of statins and placebo on outcomes such as quality of life, or change in other risk factors for macrovascular disease. For the surrogate outcome of lipid modification, we defined the size of change in lipid parameters that would qualify as clinically significant, and used this as an inclusion criterion for this review. Our criteria for clinical significance were based on the findings of large lipid-intervention trials where a change in lipid parameters was associated with a beneficial effect on cardiovascular morbidity and mortality. We excluded four RCTs where statistically significant changes in lipid parameters with statins failed to meet our criteria for clinical significance (see methods). [26] [27] [28] [29]

Clinical guide:
Statins reduce cardiovascular mortality in people with type 2 diabetes with and without known CVD. This benefit is present in people without elevated baseline total cholesterol and LDL-C concentrations. Different statins seem similarly effective at reducing LDL-C. Statins seem well tolerated with infrequent serious adverse effects. In UK clinical practice, statins are increasingly used to achieve cholesterol targets lower than those recommended by NICE guidelines, in people with both type 1 and type 2 diabetes at high risk of cardiovascular complications. Some physicians favour starting statin treatment regardless of baseline cholesterol or LDL-C, if the cardiovascular risk is regarded as high enough on an individual patient basis. We found no studies evaluating the effect of statins compared with placebo in people with lower risk of cardiovascular complications. However, some studies were excluded because the authors did not report sufficient data to calculate risk, [13] [14] [15] [16] and these may have included lower-risk populations. Although we found no direct evidence of a beneficial effect of statins in people classified as at lower risk, in clinical practice, most people with diabetes are increasingly considered at high cardiovascular risk, regardless of the presence or absence of other risk factors. Therefore, people classified as “at lower risk of macrovascular complications” may be offered statin treatment at a cholesterol level lower than that recommended

by NICE guidelines (e.g. some will start statin treatment in people aged over 40 years with a cholesterol level of greater than 4.0 mmol/L [154 mg/dL]).

OPTION COMBINED TREATMENTS

Change in lipid profile

Statin plus ezetimibe compared with statin alone A statin plus ezetimibe may be more effective at improving lipid profiles at 6–8 weeks (moderate-quality evidence).

Statin plus fibrate compared with statin alone Fluvastatin plus fenofibrate may be more effective at improving lipid profiles in people with type 2 diabetes, a history of MI (more than 2 years), and dyslipidaemia (low-quality evidence).

Note

We found no clinically important results about the effects of combined treatment compared with monotherapy on cardiovascular morbidity and mortality, quality of life, and changes in other risk factors for macrovascular disease.

For GRADE evaluation of interventions for dyslipidaemia in diabetes, see table, p 26 .

Benefits:

We found no systematic review or RCTs comparing combined treatment versus monotherapy for the outcomes of: cardiovascular morbidity and mortality, all-cause mortality, quality of life, and changes in other risk factors for macrovascular disease. We found three RCTs comparing combined treatments versus monotherapy for the outcome of change in lipid profile (see table 4, p 20). [30] [31] [32]

Statin plus ezetimibe versus statin alone:

Two RCTs found that, compared with statin plus placebo, statin plus ezetimibe significantly improved lipid profile at 6–8 weeks in people with diabetes (see table 4, p 20). [30] [32] In the first RCT (191 people with type 2 diabetes, 53% of the statin-plus-placebo group and 46% of the statin-plus-ezetimibe group had CHD), about 34% of the statin-plus-placebo group and 23% of the statin-plus-ezetimibe group were taking simvastatin, and 36% of the statin-plus-placebo group and 42% of the statin-plus-ezetimibe group were taking atorvastatin. Other statins included in this study were lovastatin, pravastatin, fluvastatin, and cerivastatin. [30] The second RCT included people with diabetes, metabolic syndrome, or neither condition (see table 4, p 20). [32] The RCT carried out a subgroup analysis of people with only type 2 diabetes (1163 people). Atorvastatin was the most frequently used statin (39%), followed by simvastatin (29%), and pravastatin (22%). Fluvastatin and lovastatin were also included. Efficacy analyses were based on ITT population (included all randomised patients with baseline and at least one post-baseline measurement).

Statin plus fibrate versus statin alone:

One RCT (43 people) found that, compared with fluvastatin plus placebo, fluvastatin plus fenofibrate significantly improved lipid profile in people with type 2 diabetes, dyslipidaemia, and history of CHD (see table 4, p 20). [31] CHD was defined as a history of MI more than 2 years before study entry.

Harms:

Statin plus ezetimibe versus statin alone:

One RCT found no significant increase in liver enzymes and creatine kinase with statin plus ezetimibe compared with statin alone. [30] The proportion of people who stopped treatment because of adverse effects was small, and similar in both groups (3%). [30] The second RCT found a similar proportion of people reporting drug-related adverse effects for the two groups (see table 4, p 20). [32] The proportion of people stopping treatment because of drug-related adverse effects was similar for the two groups (see table 4, p 20). The RCT found no significant difference between treatment groups in percentage of patients (included patients with metabolic syndrome and neither syndrome) exceeding predefined limits of change in liver enzymes (alanine and aspartate transaminase) and in muscle creatine kinase (see table 4, p 20).

Statin plus fibrate versus statin alone:

One RCT reported that two people in the fluvastatin plus fenofibrate group and one person in the fluvastatin plus placebo alone group withdrew because of myalgia. [31]

Comment:

Clinical guide:

In clinical practice, a combination of statin plus ezetimibe may be used in people with diabetes at higher cardiovascular risk if a statin alone fails to lower cholesterol adequately. A combination of statin and fibrate may be used in people with mixed dyslipidaemia where one drug fails to control all lipid parameters. In these cases, a statin may be given first, and a fibrate added to treat any remaining hypertriglyceridaemia.

OPTION FIBRATES

Cardiovascular events

Bezafibrate compared with placebo Bezafibrate may be more effective at reducing CHD event rates at 3 years in people with type 2 diabetes and no clinical history of CVD (low-quality evidence).

Gemfibrozil compared with placebo Gemfibrozil may be more effective at preventing primary and secondary major coronary events in men with type 2 diabetes (very low-quality evidence).

Fenofibrate compared with placebo Fenofibrate may be no more effective at reducing total CVD events (first occurrence of non-fatal MI or death from coronary heart disease) in people with type 2 diabetes (low-quality evidence).

Change in lipid profile

Bezafibrate compared with placebo Bezafibrate may be more effective at 3 years at reducing triglycerides and at increasing high-density lipoprotein cholesterol in people with type 2 diabetes with no clinical history of CVD (very low-quality evidence).

Gemfibrozil compared with placebo Gemfibrozil is more effective at 20–24 weeks at reducing triglyceride levels in people with type 2 diabetes (moderate-quality evidence).

For GRADE evaluation of interventions for dyslipidaemia in diabetes, see table, p 26 .

Benefits:

Bezafibrate versus placebo:

We found no systematic review but found one RCT. [33] It found that, compared with placebo, bezafibrate 400 mg daily significantly reduced CHD event rate at 3 years in people with type 2 diabetes with no clinical history of CVD (see table 5, p 22). [33] Bezafibrate also significantly reduced triglyceride concentration and increased high-density lipoprotein cholesterol (HDL-C) (see table 6, p 24). The results of the RCT for cardiovascular outcome should be interpreted with caution, as the primary aim of the study was to evaluate the effects of bezafibrate on progress of ultrasonically measured arterial disease: lipid-modifying effect and CHD morbidity were secondary end points in this study. CHD was assessed annually using history and a 12-lead ECG at rest and during exercise. The primary end point was intima–media thickness, a marker for generalised atherosclerosis.

Gemfibrozil versus placebo:

We found one systematic review (search date 2004; 4 primary prevention RCTs; 6 secondary prevention RCTs; and 2 RCTs on primary and secondary prevention) that assessed the effects of lipid-lowering agents on predominantly cardiovascular outcomes. [17] Two RCTs (three publications) identified by the review compared gemfibrozil (1200 mg daily) versus placebo. [34] [35] [36] None of the RCTs included in the review was solely in people with diabetes. The results presented are from pooled diabetes-specific data. The review carried out a subgroup analysis for the comparison of gemfibrozil versus placebo for primary and secondary prevention of risk of cardiovascular events (see table 5, p 22). [17] The review did not discuss the results from the meta-analysis of the effects of gemfibrozil separately. The analysis found that gemfibrozil significantly improved secondary prevention of major coronary events compared with placebo (see table 5, p 22). However, there was no difference between groups in primary prevention of major coronary events (see table 5, p 22). Primary outcome was a composite of major coronary events (defined as coronary artery disease death, non-fatal MI, and myocardial revascularisation procedures); secondary outcomes were listed as coronary artery disease death, non-fatal MI, myocardial revascularisation procedures, stroke, and changes in blood lipid profile: the review did not report changes in lipid profile in detail. [17] A subgroup analysis of the RCT assessing the effects of gemfibrozil on secondary prevention [35] and identified by the review was also reported separately. [36] It found that, compared with placebo, gemfibrozil significantly reduced the risk of cardiovascular events (see table 5, p 22). [36] A subgroup analysis of the RCT assessing the effects of gemfibrozil on primary prevention [34] identified by the review for people with diabetes was reported separately. [37] The analysis found that gemfibrozil reduced CHD incidence at 5 years in men with type 2 diabetes compared with placebo, but the difference between groups was not significant (see table 5, p 22). The authors of the RCT suggested that gemfibrozil may reduce the risk of MI in people with type 2 diabetes, but warned that this conclusion should be drawn with caution because of the small proportion of men with diabetes in the study. Two RCTs compared gemfibrozil 600 mg twice daily versus placebo for the outcome of change in lipid profile (see table 6, p 24). [38] [39] Both found a clinically significant decrease in triglyceride levels with gemfibrozil compared with placebo. [38] [39] One of the RCTs found that this significant decrease in triglyceride concentration was not linked to a change in low-density lipoprotein cholesterol or total cholesterol (LDL-C). [39] HDL-C increased with both placebo and gemfibrozil, with no significant difference between groups (see table 6, p 24). [39]

Fenofibrate versus placebo:
One RCT (9795 people with type 2 diabetes) found that, compared with placebo, fenofibrate 200 mg daily reduced total CVD events, non-fatal MI, and the need for revascularisation procedures (see table 5, p 22). [40] There was an increase in CHD mortality with fenofibrate, although the difference between groups did not reach significance. The authors found that significantly more people taking placebo began treatment with statins; this may have masked a larger treatment benefit of fenofibrate. The RCT also found that, compared with placebo, fenofibrate significantly reduced the rate of progression to albuminuria, and the proportion of people who developed retinopathy requiring laser treatment.

Harms:

Bezafibrate versus placebo:
The RCT gave no information on adverse effects. [33]

Gemfibrozil versus placebo:
The systematic review [17] and three RCTs gave no information on adverse effects. [36] [37] [39] A fourth RCT found no differences between groups in liver enzymes, urea, or creatinine (significance not assessed; P values not reported). [38]

Fenofibrate versus placebo:
The RCT found that people taking fenofibrate were at a greater risk of pancreatitis and a small increased risk of pulmonary embolism. [40]

Comment:

For the surrogate outcome of lipid modification, we defined the size of change in lipid parameters that would qualify as clinically significant, and used this as an inclusion criterion for this review. Our criteria for clinical significance were based on the findings of large lipid-intervention trials where a change in lipid parameters was associated with a beneficial effect on cardiovascular morbidity and mortality. We excluded one RCT where statistically significant changes in lipid parameters with bezafibrate failed to meet our criteria for clinical significance (see methods). [41]

Clinical guide:
In UK clinical practice, fibrates are used in people with diabetes and higher cardiovascular risk to reduce circulating triglyceride concentrations in those with hypertriglyceridaemia, and in combination with a statin in people with combined dyslipidaemia where a statin alone fails to adequately reduce the triglyceride level.

OPTION INTENSIVE MULTIPLE-INTERVENTION TREATMENT PROGRAMMES

Change in lipid profile
Compared with standard care Intensive intervention by a nurse-led hyperlipidaemia clinic may be more effective at achieving target total-cholesterol levels of less than 5.0 mmol/L (less than 193 mg/dL) in a mixed group of people with type 1 and type 2 diabetes and higher risk for macrovascular complications, but we don't know whether increased frequency of visits to a health professional or changes in medication are beneficial (very low-quality evidence).

For GRADE evaluation of interventions for dyslipidaemia in diabetes, see table, p 26 .

Benefits:

Intensive multiple-intervention treatment programmes versus standard care:
We found no systematic review evaluating effects of intensive multiple-intervention treatment programmes and standard care on cardiovascular mortality, quality of life, or other cardiovascular risk factors. We found one RCT which found that, compared with usual care, randomisation to a specialist nurse-led hyperlipidaemia clinic resulted in a reduction in total cholesterol to below target at 1.5-year follow-up (see table 7, p 24). [42] In the RCT, the usual-care group was seen once by the diabetologist, and was reviewed in primary care as thought necessary by the primary-care physicians. The primary-care physicians were invited to 4-monthly education sessions where guidelines for the management of hypercholesterolaemia were discussed. The specialist nurse-led intervention group was given an individual action plan at their first visit with the specialist nurse, including a discussion of the benefits of treatment and lifestyle changes, drug actions, and potential adverse effects. This group was seen every 4–6 weeks until target cholesterol (less than 5.0 mmol/L [193 mg/dL]) was reached. At these visits, lifestyle modifications were reinforced and cholesterol-lowering medication was titrated according to response to treatment. Medications were “fibrate” or “statin”. Given that the nature of the intervention precluded any blinding, and the ethical restrictions to including a placebo arm, it is difficult to determine which aspect of the intervention (i.e. increased frequency of visits to a health professional or changes in medication) was beneficial.

Harms:

Intensive multiple-intervention treatment programmes versus standard care:
We found no systematic review or RCTs evaluating adverse effects of intensive multiple-intervention treatment programmes and usual care on cardiovascular mortality, lipid modification, all-cause

mortality, quality of life, or change in other risk factors for macrovascular disease. One RCT did not report adverse effects. [42]

Comment: **Clinical guide:**
Intensive multiple-intervention treatment programmes in people with diabetes and higher risk for macrovascular complications would entail intensive management of modifiable CVD risk factors including dyslipidaemia, in addition to other interventions, such as glycaemic control and lifestyle management.

OPTION FISH OILS

Changes in lipid profile
Compared with control Fish oils may be more effective at lowering triglyceride levels in hypertriglyceridaemic people, but may increase low-density lipoprotein cholesterol (low-quality evidence).

For GRADE evaluation of interventions for dyslipidaemia in diabetes, see table, p 26 .

Benefits: **Fish oils versus controls:**
We found one systematic review (search date 2000) evaluating the effects of omega-3 triglycerides (eicosapentaenoic acid, docosahexaenoic acid) compared with vegetable oils (olive oil, linseed oil, safflower oil, corn oil) for cardiovascular morbidity and mortality, lipid profile, glycaemic control, and weight in people with type 2 diabetes. [43] The review also included one RCT comparing fish oils versus saline. The review found no RCTs comparing fish oils versus control for the outcomes of cardiovascular morbidity and mortality. [43] It found that, compared with control, fish oils significantly lowered triglyceride levels and increased low-density lipoprotein cholesterol (LDL-C). It found no significant difference in high-density lipoprotein cholesterol (HDL-C) between fish oils and control (see table 8, p 25). [43] The review found limited evidence, based on indirect comparisons, of a higher reduction of triglycerides and greater increase in LDL-C with fish oils in people with pre-existing hypertriglyceridaemia than in people without pre-existing hypertriglyceridaemia (see table 8, p 25). [43] Most people in the review were male with a duration of diabetes of 5–10 years, and treated with diet or oral hypoglycaemic agents. The doses of fish oils ranged from eicosapentaenoic acid 1.08–5.2 g, and docosahexaenoic acid 0.3–4.8 g. Any type of dietary supplementation with n-3 fatty acids was included. There were no restrictions on dose or formulation. The range of compounds used as controls included olive oil, safflower oil, and corn oil, all of which might be metabolised to n-3 fatty acids.

Harms: **Fish oils versus controls:**
The review found no significant difference in glycaemic control between fish oils and placebo. [43] No other adverse outcomes were reported.

Comment: **Clinical guide:**
Although fish oils may reduce triglyceride concentration in people with hypertriglyceridaemia, this may be accompanied by an increase in LDL-C. In clinical practice, fish oils are not usually prescribed for people with diabetes and higher cardiovascular risk. People with normal triglycerides may be advised to increase their dietary fish oil consumption.

OPTION NICOTINIC ACID GROUP

Changes in lipid profile
Compared with placebo Nicotinic acid in combination with a statin may be more effective at reducing triglyceride levels and at increasing high-density lipoprotein cholesterol in people with type 2 diabetes (very low-quality evidence).

Note
Nicotinic acid has been associated with flushing. We found no direct information about acipomix in the treatment of people with diabetes at risk of macrovascular complications.

For GRADE evaluation of interventions for dyslipidaemia in diabetes, see table, p 26 .

Benefits: We found no systematic review evaluating effects of nicotinic acid and placebo on cardiovascular mortality, quality of life, all-cause mortality, or change in other risk factors for CVD.

Nicotinic acid versus placebo:
We found one RCT comparing the effects on lipid profile of nicotinic acid 1 g and 1.5 g versus placebo. [44] The RCT found that, compared with placebo, nicotinic acid 1 g and 1.5 g significantly increased high-density lipoprotein cholesterol (HDL-C) at 16 weeks (146 people with type 2 diabetes, mean age: 61 ± 1.4 years in placebo group *v* 57 ± 1.4 years in 1 g group *v* 63 ± 1.6 years in 1.5 g group; HDL-C increased with 1 g and 1.5 g nicotinic acid, range: from 13–19% in 1 g group *v*

22–24% in 1.5 g group; P less than 0.05 compared with placebo). The RCT also found that nicotinic acid 1.5 g significantly reduced triglyceride concentration at 16 weeks compared with placebo (median % change range: 28–36%; P less than 0.05 compared with placebo). Nicotinic acid 1.5 g significantly decreased total cholesterol and low-density lipoprotein cholesterol (LDL-C), but these changes were small (6.1 ± 2.1% for total cholesterol and 7.1 ± 3.2% for LDL-C; P less than 0.05 compared with placebo). This study included people treated with diet alone, people treated with insulin and oral hypoglycaemics excluding thiazolidinediones, and people with stable coronary and cerebrovascular disease. About 59% of the placebo group, 40% of the nicotinic acid 1 g group, and 40% of the nicotinic acid 1.5 g group were also taking a statin. [44]

Acipomix versus placebo:
We found no systematic review or RCTs comparing acipomix versus placebo, or comparing different doses for clinical outcomes of interest (cardiovascular mortality, lipid modification, all-cause mortality, quality of life, or change in other risk factors for macrovascular disease), in people with diabetes and higher risk of macrovascular complications.

Harms:

Nicotinic acid versus placebo:
One RCT comparing nicotinic acid 1 g and 1.5 g versus placebo found a small increase in haemoglobin A1c at 16 weeks with nicotinic acid 1 g and 1.5 g (mean ± standard error, HbA1c: from 7.20 ± 0.14% at baseline to 7.40 ± 0.19% at 16 weeks with nicotinic acid 1 g *v* from 7.20 ± 0.11% at baseline to 7.50 ± 0.14% at 16 weeks with nicotinic acid 1.5 g *v* from 7.10 ± 0.12% at baseline to 7.10 ± 0.13% at 16 weeks with placebo; P value reported as not significant for placebo *v* nicotinic acid 1 g, P = 0.048 for placebo *v* nicotinic acid 1.5 g). [44] The RCT reported a higher incidence of flushing with nicotinic acid compared with placebo (75% with nicotinic acid [1 g and 1.5 g] *v* 10% with placebo; absolute numbers and statistical data not reported). The proportion of people reporting any adverse event was not significantly different among treatment groups (69% with nicotinic acid 1 g *v* 77% with nicotinic acid 1.5 g *v* 73% with placebo; reported as non-significant, P value not reported). None of the people included in the trial had myopathy or an elevation in liver enzymes of three times the upper limit of normal or greater. [44]

Acipomix versus placebo:
We found one cohort study evaluating adverse effects of acipomix in people with diabetes. [45] The study found that, in 3009 people (52% female) with type 2 diabetes taking acipomix 250 mg twice daily (82%) or three times daily (18%) for at least 3 months, 263 (9%) people reported adverse events. In 165 (6%) people treatment was withdrawn. Higher doses were associated with a marginal increase in incidence of adverse events (212/2476 [9%] with twice-daily dose *v* 51/533 [10%] with 3 times-daily dose; statistical data not reported). A greater incidence of adverse events (predominantly flushing and pruritus) was found in female compared with male participants (177/1572 [11%] female *v* 86/1437 [6%] male). Acipomix was associated with an 8.5% reduction in HbA1c compared with before treatment (8.20 ± 0.04% before *v* 7.50 ± 0.04% after; P value reported as not significant).

Comment:

For the surrogate outcome of lipid modification, we defined the size of change in lipid parameters that would qualify as clinically significant, and used this as an inclusion criterion for this review. Our criteria for clinical significance were based on the findings of large lipid-intervention trials where a change in lipid parameters was associated with a beneficial effect on cardiovascular morbidity and mortality. We excluded two RCTs where statistically significant changes in lipid parameters failed to meet our criteria for clinical significance (see methods). [46] [47]

Clinical guide:
Nicotinic acid seems effective at increasing HDL-C and may reduce triglycerides, but a significant proportion of people in the reported RCT were also taking statins. In clinical practice, nicotinic acid is not usually preferred treatment for hypertriglyceridaemia. However, it may be used in combination with a statin in people with mixed dyslipidaemia, and in those unable to tolerate a fibrate.

OPTION ANION EXCHANGE RESINS

We found no direct information about whether anion exchange resins (colestyramine, colestipol) are better than no active treatment, or how different anion exchange resins, or different doses compare in the treatment of people with diabetes and high risk for macrovascular complications.

For GRADE evaluation of interventions for dyslipidaemia in diabetes, see table, p 26 .

Benefits:

We found no systematic review or RCTs comparing anion exchange resins (colestyramine, colestipol) versus placebo, or comparing different anion exchange resins, or different doses for clinical outcomes of interest (cardiovascular mortality, lipid modification, all-cause mortality, quality of life, or change in other risk factors for macrovascular disease) in people with diabetes and higher risk for macrovascular complications.

Harms: We found no RCTs.

Comment: **Clinical guide:**
In clinical practice, anion exchange resins are not usually preferred treatment for people with diabetes and higher cardiovascular risk. However, they may be used in combination with a statin where a statin alone fails to achieve lipid targets, or where the person is unable to tolerate a statin.

OPTION EZETIMIBE

We found no direct information about whether ezetimibe is better than no active treatment, or comparing different doses in the treatment of people with diabetes and high risk for macrovascular complications.

For GRADE evaluation of interventions for dyslipidaemia in diabetes, **see table, p 26 .**

Benefits: We found no systematic review or RCTs comparing ezetimibe versus placebo, or comparing different doses for clinical outcomes of interest (cardiovascular mortality, lipid modification, all-cause mortality, quality of life, or change in other risk factors for macrovascular disease) in people with diabetes and higher risk for macrovascular complications. In clinical practice, ezetimibe is not usually preferred treatment, but it may be used in combination with a statin if a statin alone fails to achieve lipid targets.

Harms: We found no RCTs.

Comment: **Clinical guide:**
In clinical practice, ezetimibe is not usually preferred treatment for people with diabetes and higher cardiovascular risk. However, it may be used in combination with a statin where a statin alone fails to achieve lipid targets, or where the person is unable to tolerate a statin.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence 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.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Combined treatments One RCT on the effects of adding ezetimibe to statins added; [32] benefits and harms data enhanced; categorisation unchanged (Likely-to-be-beneficial). The RCT found that, compared with statin plus placebo, statin plus ezetimibe significantly improved lipid profile at 6 weeks in people with diabetes.
Fibrates One systematic review added for the comparison of gemfibrozil versus placebo; [17] benefits enhanced; categorisation unchanged (Likely-to-be-beneficial). The analysis reported by the review found that gemfibrozil significantly improved secondary prevention of major coronary events compared with placebo, but there was no difference between groups in primary prevention of major coronary events.
Statins One systematic review on the effects of statins added; [17] benefits and harms data enhanced; categorisation unchanged (Beneficial). The review found that, compared with placebo, statins (pravastatin, simvastatin, atorvastatin, lovastatin, and fluvastatin) significantly reduced cardiovascular risk in both primary and secondary prevention.

REFERENCES

1. Galton D. *Dyslipidaemia*. Edinburgh: Churchill Livingstone 2003, p14.
2. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 2003;46:733–749.[PubMed]
3. Anon. Diabetic dyslipidaemia. In: *Diabetes and cardiovascular disease review*. *Issue 3*. Alexandria, VA, USA: American Diabetes Association/American College of Cardiology. Available online at http://www.diabetes.org/uedocuments/ADACardioReview3.pdf. Last accessed 21 May 2008.
4. NICE. Type 2 diabetes – management of blood pressure and blood lipids. 2002. Available online at http://www.nice.org.uk/page.aspx?o=38551. Last accessed 21 May 2008.
5. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Atherosclerosis* 2004;173:381–391.[PubMed]
6. Cullen P, von Eckardstein A, Souris S, et al. Dyslipidaemia and cardiovascular risk in diabetes. *Diabetes Obes Metab* 1999;1:189–198.[PubMed]
7. Valabhji J and Elkeles RS. Dyslipidemia in type 2 diabetes: epidemiology and biochemistry. *Br J Diabetes Vasc Dis* 2003;3:184–189.
8. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines *Circulation* 2004;110:227–239. [Erratum in: *Circulation* 2004;110:763][PubMed]
9. Leiter LA, Genest J, Harris SB, et al. Dyslipidemia in adults with diabetes. *Can J Diabetes* 2006;30:230–240.
10. Diabetes Trials Unit. Available online at: http://www.dtu.ox.ac.uk. Last accessed 21 May 2008.
11. Jacobs MJ, Kleisli T, Pio JR, et al. Prevalence and control of dyslipidemia among persons with diabetes in the United States. *Diabetes Res Clin Pract* 2005;70:263–269.[PubMed]
12. Taskinen MR. Diabetic dyslipidemia. *Atheroscler Suppl* 2002;3:47–51.[PubMed]
13. Vinik A, Colwell JA. Effects of gemfibrozil on triglyceride levels in patients with NIDDM. *Diabetes Care* 1993;16:37–43.[PubMed]
14. Raskin P, Ganda OP, Schwartz S, et al. Efficacy and safety of pravastatin in the treatment of patients with type I or type II diabetes mellitus and hypercholesterolemia. *Am J Med* 1995;99:362–369.[PubMed]
15. Ding PY-A, Sheu WH-H, Hu C-A, et al. Efficacy and safety of fluvastatin in patients with non-insulin- dependent diabetes mellitus and hypercholesterolemia. *Acta Cardiol Sinica* 1997;13:138–144.
16. Betteridge DJ, Gibson JM. Effects of rosuvastatin on lipids, lipoproteins and apolipoproteins in the dyslipidaemia of diabetes. *Diabet Med* 2007;24:541–549.[PubMed]
17. Costa J, Borges M, David C, et al. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. *BMJ* 2006;332:1115.[PubMed]
18. Sever PS, Poulter NR, Dahlof B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial – lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005;28:1151–1157.[PubMed]
19. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvas-

tatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004:364:685–696.[PubMed]

20. Miller M, Dobs A, Yuan Z, et al. Effective simvastatin therapy in raising HDL-C in patients with type 2 diabetes and low HDL-C. *Curr Med Res Opin* 2004;20:1087–1094.[PubMed]
21. Sartor G, Katzman P, Kalen J, et al. Simvastatin treatment of hypercholesterolemia in patients with insulin dependent diabetes mellitus. *Int J Clin Pharmacol Ther* 1995;33:3–6.[PubMed]
22. Farrer M, Winocour PH, Evans K, et al. Simvastatin in non-insulin-dependent diabetes mellitus: effect on serum lipids, lipoproteins and haemostatic measures. *Diabetes Res Clin Pract* 1994;23:111–119. [PubMed]
23. Diabetes Atorvastatin Lipid Intervention (DALI) Study Group. The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidaemia: the DALI study: a double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes and diabetic dyslipidemia. *Diabetes Care* 2001;24:1335–1341.[PubMed]
24. Rustemeijer C, Schouten JA, Janssens EN, et al. Pravastatin in diabetes-associated hypercholesterolemia. *Acta Diabetol* 1997;34:294–300.[PubMed]
25. Pfizer. Important new prescribing advice for atorvastatin (Lipitor). Available online at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON2033539 (last accessed 21 May 2008).
26. Visseren FLJ, Bouter PK, Potter van Loon BJ, et al. Treatment of dyslipidaemia with fluvastatin in patients with type 2 diabetes mellitus: effects on lipids, mental state and fibrinolysis. *Clin Drug Invest* 2001;21:671–678.
27. Knopp RH, Frohlich J, Jokubaitis LA, et al. Efficacy and safety of fluvastatin in patients with non-insulin-dependent diabetes mellitus and hyperlipidemia. *Am J Med* 1994;96:69S–78S.
28. Behounek BD, McGovern ME, Kassler-Taub KB, et al. A multinational study of the effects of low-dose pravastatin in patients with non-insulin-dependent diabetes mellitus and hypercholesterolemia. *Clin Cardiol* 1994;17:558–562.[PubMed]
29. Krempf M, Berthezene F, Wemeau JL, et al. Efficacy of low-dose pravastatin in patients with mild hyperlipidemia associated with type II diabetes mellitus. *Diabetes Metab* 1997;23:131–136.[PubMed]
30. Simons L, Tonkon M, Masana L, et al. Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. *Curr Med Res Opin* 2004;20:1437–1445.[PubMed]
31. Derosa G, Cicero AE, Bertone G, et al. Comparison of fluvastatin + fenofibrate combination therapy and fluvastatin monotherapy in the treatment of combined hyperlipidemia, type 2 diabetes mellitus, and coronary heart disease: a 12-month randomized, double-blind, controlled trial. *Clin Ther* 2004;26:1599–1607.[PubMed]
32. Denke M, Pearson T, McBride P, et al. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. *Diabetes Vascular Dis Res* 2006;3:93–102.
33. Elkeles RS, Diamond JR, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St Mary's, Ealing, Northwich Park Diabetes Cardiovascular Disease Prevention (SENCAP) study. *Diabetes Care* 1998;21:641–648.[PubMed]
34. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237–1245.
35. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410–418.
36. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* 2002;162:2597–2604.[PubMed]
37. Koskinen P, Manttari M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992;15:820–825.[PubMed]
38. Avogaro A, Piliego T, Catapano A, et al. The effect of gemfibrozil on lipid profile and glucose metabolism in hypertriglyceridaemic well-controlled non-insulin-dependent diabetic patients. *Acta Diabetol* 1999;36:27–33.[PubMed]
39. O'Neil DN, O'Brien RC, Timmins KL, et al. Gemfibrozil treatment increases low-density lipoprotein particle size in Type 2 diabetes mellitus but does not alter in vitro oxidizability. *Diabet Med* 1998;15:870–877.[PubMed]
40. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–1861.[PubMed]
41. Winocour PH, Durrington PN, Bhatnagar D, et al. Double-blind placebo-controlled study of the effects of bezafibrate on blood lipids, lipoproteins, and fibrinogen in hyperlipidaemic type 1 diabetes mellitus. *Diabet Med* 1990;7:736–743.[PubMed]
42. New JP, Mason JM, Freemantle N, et al. Specialist nurse-led intervention to treat and control hypertension and hyperlipidemia in diabetes (SLINT): a randomized controlled trial. *Diabetes Care* 2003;26:2250–2255.[PubMed]
43. Farmer A, Montori V, Dinneen S, et al. Fish oil in people with type 2 diabetes mellitus. In: The Cochrane Library, Issue 2, 2007. Chichester: John Wiley & Sons, Ltd.
44. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial (AVENT). *Arch Intern Med* 2002;162:1568–1576.[PubMed]
45. Lavezzari M, Milanesi G, Oggioni E, et al. Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipoproteinaemia. *J Int Med Res* 1989;17:373–380.[PubMed]
46. Dean JD, McCarthy S, Betteridge DJ, et al. The effect of acipimox in patients with type 2 diabetes and persistent hyperlipidaemia. *Diabet Med* 1992;9:611–615.[PubMed]
47. Fulcher GR, Catalano C, Walker M, et al. A double blind study of the effect of acipimox on serum lipids, blood glucose control and insulin action in non-obese patients with type 2 diabetes mellitus. *Diabet Med* 1992;9:908–914.[PubMed]
48. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615–1622.[PubMed]
49. ALLHAT-LLT Officers and Coordinators. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002;288:2998–3007.[PubMed]
50. Heart Protection Study Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22.[PubMed]
51. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–1630.[PubMed]
52. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149–1158.[PubMed]
53. Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997;20:614–620. [Erratum in: *Diabetes Care* 1997;20:1048][PubMed]
54. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Eng J Med* 1996;335:1001–1009.
55. Long term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Eng J Med* 1998;339:1349–1357.
56. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;287:3215–3222.[PubMed]
57. Collins R, Armitage J, Parish S, et al. MRC/BHS Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361:2005–2016. [PubMed]
58. Keech A, Colquhoun D, Best J, et al. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care* 2003;26:2713–2721.[PubMed]
59. Hoogwerf BJ, Waness A, Cressman M, et al. Effects of aggressive cholesterol lowering and low-dose anticoagulation on clinical and angiographic outcomes in patients with diabetes: the Post Coronary Artery Bypass Graft Trial. *Diabetes* 1999;48:1289–1294.[PubMed]

Jigisha Patel
Chadburn Lecturer
Royal Free and UCL Medical School
Division of Medicine, Centre for Clinical Science and Technology
London
UK

Competing interests: JP declares that she has no competing interests.

Disclaimer

The information contained in this publication is intended for medical professionals. Categories presented in Clinical Evidence indicate a judgement about the strength of the evidence available to our contributors prior to publication and the relevant importance of benefit and harms. We rely on our contributors to confirm the accuracy of the information presented and to adhere to describe accepted practices. Readers should be aware that professionals in the field may have different opinions. Because of this and regular advances in medical research we strongly recommend that readers' independently verify specified treatments and drugs including manufacturers' guidance. Also, the categories do not indicate whether a particular treatment is generally appropriate or whether it is suitable for a particular individual. Ultimately it is the readers' responsibility to make their own professional judgements, so to appropriately advise and treat their patients. To the fullest extent permitted by law, BMJ Publishing Group Limited and its editors are not responsible for any losses, injury or damage caused to any person or property (including under contract, by negligence, products liability or otherwise) whether they be direct or indirect, special, incidental or consequential, resulting from the application of the information in this publication.

TABLE 1 **Target thresholds for pharmacological treatment of diabetic dyslipidaemia in the UK and USA.**

	Treatment targets (mmol/L [mg/dL])		
	UK	**USA**	**Europe**
TC	Less than 5 (193) or reduced by 20–25%, whichever is lower	-	Less than 4.5 (175)
LDL-C	Less than 3.0 (116) or reduced by 30%, whichever is lower	Less than 2.6 (100)	Less than 2.5 (100)
HDL-C	-	For men greater than 1.2 (45); for women greater than 1.4 (55)	*
Triglycerides	-	Less than 1.7 (150)	*

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol. *European guidelines do not define specific treatment goals for HDL-C or triglycerides, but do acknowledge that HDL-C less than 1.0 mmol/L (40 mg/dL) for men and less than 1.2 mmol/L (46 mg/dL) for women and fasting triglycerides greater than 1.7 mmol/L (150 mg/dL) are markers of increased cardiovascular risk.

TABLE 2 **RCTs assessing the effects of statins on cardiovascular outcomes.** [17] [19] [48] [49] [50] [51] [52] [53] [54] [55] [56]

Study	Population	Intervention	Outcome	RR	NNT	Harms
[17]	People with type 2 diabetes mellitus	Lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin	***Primary prevention:*** coronary artery disease death, non-fatal MI, or myocardial revascularisation procedures	Pooled CHD events: primary-prevention studies (5 RCTs); 431/5394 (8%) with statin *v* 535/5309 (10%) with placebo, RR 0.80, 95% CI 0.71 to 0.90	N/A	The review gave no information on adverse effects
		Two RCTs of gemfibrozil (a fibrate) included (1 primary, the other secondary prevention). The review did a subgroup analysis excluding these studies		Risk reduction (includes people treated with gemfibrozil) 21%, 95% CI 11% to 30%, P less than 0.0001		
			Secondary prevention: coronary artery disease death, non-fatal MI, myocardial revascularisation procedures, stroke, and changes in blood lipid profile	Pooled CHD events: secondary-prevention studies (7 RCTs); 644/2342 (27%) with statin *v* 781/2330 (34%) with placebo,RR 0.79, 95% CI 0.68 to 0.93		
				Risk reduction (includes people treated with gemfibrozil) 21%, 95% CI 10% to 31%, P = 0.0005		
				Pooled secondary-prevention studies on CHD death (3 RCTs): 43/450 (10%) with statin *v* 52/452 (12%) with placebo, RR 0.83, 95% CI 0.57 to 1.21		
				Pooled secondary-prevention studies on non-fatal MI (3 RCTs): 38/450 (8%) with statin *v* 67/454 (15%) with placebo, RR 0.48, 95% CI 0.22 to 1.08		
				Pooled secondary-prevention studies on myocardial revascularisation procedures (4 RCTs): 187/1138 (16%) with statin *v* 269/1124 (24%) with placebo, RR 0.70, 95% CI 0.59 to 0.83		
				Pooled secondary-prevention studies on stroke (3 RCTs): 58/929 (6%) with statin *v* 89/936 (10%) with placebo, RR 0.66, 95% CI 0.48 to 0.90		
Primary prevention RCTs (people without prior CVD) in Costa systematic review [17]						
AFCAPS/TexCAPS [48]	155 people with type 2 diabetes mellitus	Lovastatin 20 mg/day	CHD events, LDL-C	CHD events: 4/84 (5%) with lovastatin *v* 6/71 (9%) with control; RR 0.56, 95% CI 0.17 to 1.92;	NNT 27, CI, and number of years of treatment not reported	
ALLHATT-LLT [49]	3638 people with type 2 diabetes mellitus	Pravastatin 40 mg/day	CHD events, LDL-C	CHD events: 81/1855 (4%) with statin *v* 88/1783 (5%) with placebo; RR 0.88, 95% CI 0.66 to 1.19	Not reported	
HPS [50] [57]	3982 people with type 2 diabetes mellitus	Simvastatin (dose not reported)	CHD events, LDL-C	CHD events: 276/2006 (14%) with simvastatin *v* 367/1976 (19%) with control; RR 0.74, 95% CI 0.64 to 0.85	NNT 21, CI, and number of years of treatment not reported	

Study	Population	Intervention	Outcome	RR	NNT	Harms
PROSPER [51]	396 people aged 70–82 years with type 2 diabetes mellitus	Pravastatin 40 mg/day	CHD events, LDL-C	CHD events: 32/191 (17%) with pravastatin *v* 28/205 (14%) with control; RR 1.23, 95% CI 0.77 to 1.95	NNT 32, CI, and number of years of treatment not reported	
ASCOT-LLA [52]	2532 people with type 2 diabetes mellitus, hypertension, and at least 2 other CHD risk factors	Atorvastatin 10 mg/day	CHD events, LDL-C	CHD events: 38/1258 (3%) with atorvastatin *v* 46/1274 (4%) with control; RR 0.84, 95% CI 0.55 to 1.29	NNT 170, CI, and number of years of treatment not reported	
Primary prevention RCTs (people without prior CVD) subsequent to Costa review [17]						
ASCOT-LAA [18] (detailed subgroup analysis published subsequent to Costa review) [17]	2532 people with type 2 diabetes mellitus, hypertension, and at least 2 other CHD risk factors, but no history of previous MI or currently treated angina	Atorvastatin 10 mg/day	Total cardiovascular events and procedures:	Total cardiovascular events and procedures: HR 0.77, 95% CI 0.61 to 0.98; P = 0.036	NNT not reported (3.3 years of treatment)	There were no significant differences in liver enzyme abnormalities between the atorvastatin and placebo groups. No cases of rhabdomyolysis were reported
			Cardiovascular mortality, non-fatal MI, unstable angina, chronic stable angina, life-threatening arrhythmias, non-fatal heart failure, non-fatal stroke, PAD, retinal vascular thrombosis, revascularisation procedures, transient ischaemic attacks, and reversible ischaemic neurological deficits	Effects with different baseline cholesterol levels less than 5 mmol/L: HR 0.71, 95% CI 0.44 to 1.18 Effects with different baseline cholesterol levels 5.0 to less than 6.0 mmol/L: HR 0.74, 95% CI 0.52 to 1.05 Effects with different baseline cholesterol levels at least 6.0 mmol/L: HR 0.84, 95% CI 0.54 to 1.31		
CARDS [19]	2838 people with type 2 diabetes, without CVD, aged 40–75 years, primary prevention About 15% of people in each group had microalbuminuria, 2% had macroalbuminuria. Mean duration of diabetes 7.90 ± 6.33 years in placebo. Mean HbA1c 7.87 ± 1.42% in atorvastatin group and 7.81 ± 1.39% in placebo group	Atorvastatin 10 mg once daily	Fatal and non-fatal MI, unstable angina, resuscitated cardiac arrest, coronary revascularisation, and fatal and non-fatal stroke	Cardiovascular events over 3.9 years: 83/1428 (6%) with atorvastatin *v* 127/1410 (9%) with placebo; HR 0.63, 95% CI 0.48 to 0.83; P = 0.001 In people with a baseline LDL-C less than 3.1 mmol/L (less than 120 mg/dL): HR 0.63, 95% CI 0.42 to 0.94	NNT 32/3.9 years, CI not reported	Serious adverse events overall did not differ between treatment groups (myalgia: 61/1428 [4%] with atorvastatin *v* 72/1410 [5%] with placebo; creatine kinase rise at least 10 times upper limit of normal: 0.1% with atorvastatin *v* 0.7% with placebo; AST rise at least 3 times upper limit of normal: 1% in both groups; aspartate aminotransferase rise at least 3 times the upper limit of normal: 0.4% with atorvastatin *v* 0.3% with placebo)

Study	Population	Intervention	Outcome	RR	NNT	Harms
Secondary prevention RCTs (people with CVD) in Costa systematic review [17]						
4S [53]	483 people with type 2 diabetes mellitus and heart disease	Simvastatin (dose not reported)	CHD events, LDL-C	CHD events: 59/251 (24%) with simvastatin *v* 87/232 (38%) with control; RR 0.63, 95% CI 0.47 to 0.83		
CARE [54]	586 people with type 2 diabetes mellitus, MI, or angina	Pravastatin 40 mg/day	CHD events, LDL-C	CHD events: 81/282 (29%) with pravastatin *v* 112/304 (39%) with control; RR 0.78, 95% CI 0.62 to 0.99		
HPS [50]	1981 people with type 2 diabetes mellitus	Simvastatin 40 mg/day	CHD events, LDL-C	CHD events: 325/972 (33%) with simvastatin *v* 381/1009 (38%) with control; RR 0.89, 95% CI 0.79 to 1.00		
LIPID [58] [55]	1077 people with type 2 diabetes mellitus and heart disease	Pravastatin 40 mg/day	CHD events, LDL-C	CHD events: 106/542 (20%) with pravastatin *v* 125/535 (23%) with control; RR 0.84, 95% CI 0.67 to 1.05		
LIPS [56]	202 people with type 2 diabetes mellitus and previous percutaneous coronary intervention	Fluvastatin 80 mg/day	CHD events, LDL-C	CHD events: 26/120 (22%) with fluvastatin *v* 31/82 (38%) with control; RR 0.57, 95% CI 0.37 to 0.89		
PostCABG [59]	116 people with type 2 diabetes mellitus and previous CABG	Lovastatin, cholestyramine (doses not reported)	CHD events, LDL-C	CHD events: 9/63 (14%) with lovastatin *v* 14/53 (26%) with control; RR 0.54, 95% CI 0.25 to 1.15		
PROSPER [51]	227 people with type 2 diabetes mellitus	Pravastatin 40 mg/day	CHD events, LDL-C	CHD events: 38/112 (34%) with pravastatin *v* 31/115 (27%) with control; RR 1.26, 95% CI 0.85 to 1.87		

4S, Scandinavian Simvastatin Survival Study; AFCAPS, Air Force Coronary Atherosclerosis Prevention Study; ALLHATT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcome Trial; AST, alanine transaminase CABG, coronary artery bypass grafting; CARDS, Collaborative Atorvastatin (Lipitor™) and Diabetes Study; CARE, Cholesterol And Recurrent Events; C HPS, Heart Protection Study; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; LIPS, Lescol Intervention Prevention Study; MRC/BHS, Medical Research Council/British Hypertension Society; PAD, peripheral arterial disease; TexCAPS, Texas Coronary Atherosclerosis Prevention Study; PostCABG, Post Coronary Artery Bypass; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; Texas Coronary Atherosclerosis Prevention Study.

TABLE 3 **RCTs evaluating the lipid-modifying effects of statins.** [20] [21] [22] [23] [24]

Study	Population	Duration	Statin and dose	Lipids at baseline‡ (mmol/L)	Percentage or absolute change (mmol/L)	P value	Percentage reaching LDL-C treatment target of 2.6 mmol/L or below (placebo)	Harms
Statins versus placebo								
[20]	151 people with type 2 diabetes	Study duration 6 weeks	Simvastatin 40 mg od	LDL-C: 3.5 ± 1.0	–41	Less than 0.001	82%	Drug-related musculoskeletal events (no rise in creatine kinase): 6 people in simvastatin 40 mg od group *v* 2 people in simvastatin 80 mg od group *v* 1 person in placebo group
				HDL-C: 0.9 ± 0.1	+5	Less than 0.001	14%	
				TG: 3.1 (median)	–29	Less than 0.001		
			Simvastatin 80 mg od	LDL-C: 3.5 ± 1.0	–47	less than 0.001*†	87%	Elevated alanine transaminase and aspartate aminotransferase more than 3 times upper limit (2 people simvastatin 80 mg group)
				HDL-C: 0.9 ± 0.1	+8	Less than 0.001*†	14%	
				TG: 3.1 (median)	–31	Less than 0.001	–	
						(= 0.42)†	–	
[21]	25 people with type 1 diabetes	Study duration 16 weeks	Simvastatin up to 20 mg od	LDL-C: 4.6 ± 0.7	2.8 ± 0.3 SD (LDL-C at 16 weeks)	Less than 0.001	–	No difference in liver enzymes or creatine kinase
				TC: 6.7 ± 1.0	4.9 ± 0.4 SD (TC at 16 weeks)	Less than 0.001	–	
[22]	57 people with type 2 diabetes	Study duration 24 weeks	Simvastatin 10 mg od	LDL-C: 5.5 (95% CI 5.4 to 5.6)	–38	Less than 0.001	–	Did not look for adverse effects
				HDL-C: 1.16 (95% CI 1.07 to 1.25)	+9	Less than 0.05	–	
				TC: 7.8 (95% CI 7.6 to 8.0)	–28	Less than 0.001	–	
				TG: 2.6 (95% CI 2.2 to 3.0)	–15	Less than 0.05	–	
[23]	217 people with type 2 diabetes	Study duration 30 weeks	Atorvastatin 10 mg	LDL-C: 3.7 ± 0.1	–40.8	Less than 0.001	71%	No difference in liver and renal enzymes, muscle pain, and myopathy (with creatine kinase rise). No adverse events were reported
				HDL-C: 1.05 ± 0.03	+6	Less than 0.005	36%	
				TC: 5.9 ± 0.1	–29.8	Less than 0.001	–	
				TG: 2.54 + 0.1 (median)	–25.4	Less than 0.001	80%	
			Atorvastatin 80 mg	LDL-C: 3.7 ± 0.1	–52.3	Less than 0.001*	85%	
				HDL-C: 1.03 ± 0.03	+5.2	Less than 0.005	44%	

Study	Population	Duration	Statin and dose	Lipids at baseline‡ (mmol/L)	Percentage or absolute change (mmol/L)	P value	Percentage reaching LDL-C treatment target of 2.6 mmol/L or below (placebo)	Harms
[24]	49 people; 22 with type 1 and 27 with type 2 diabetes, aged 18–70 years	Study duration 24 weeks	Pravastatin 20 mg od	TC: 6.1 ± 0.2	–39.2	Less than 0.001 (Less than 0.005†)	–	1 person in placebo group withdrew with muscle pain No significant changes in biochemical parameters
				TG: 2.85 ± 0.13 (median)	–34.6	Less than 0.001	76%	
				LDL-C: 5.03 ± 0.74	–25.8%	Less than 0.001	–	
				HDL-C: 1.30 ± 0.50	1.8	NS	–	
				TC: 7.35 ± 0.63	–22.2%	Less than 0.001	–	
				TG: 1.93 ± 0.73	13.6%	Less than 0.01	–	

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant; od, once daily; TC, total cholesterol; TG, triglyceride. P values are change compared with placebo unless otherwise stated; *P value compared with placebo and different doses; †P value comparing different doses; ‡values are mean ± standard deviation unless otherwise stated.

TABLE 4 RCTs evaluating the lipid-modifying effects of combination treatment. [30] [31]

Study	Population	Duration	Intervention	Lipids at baseline* (mmol/L)	Change in lipids from baseline (mean)	P value	Percentage reaching LDL-C target of less than 2.6 mmol/L	Harms
[30]	191 people with type 2 diabetes already taking a statin; 60% male; mean age 63 years for placebo group *v* 64 years for ezetimibe group	Mean duration of diabetes not reported, study duration 8 weeks	Statin plus ezetimibe 10 mg od	LDL-C: 3.0 ± 0.1	–27.3%		84%	No significant increase in liver enzymes and creatine kinase with statin plus ezetimibe compared with statin alone. The proportion of people who stopped treatment because of adverse effects was small, and similar in both groups
				HDL-C: 1.30 ± 0.03	+1.5%			
				TC: 5.10 ± 0.01	–18.5%			
				TG: 1.7 (median)	–15.8%			
			Statin plus placebo	LDL-C: 3.1 ± 0.1	–1.2%	Less than 0.001	17%	
				HDL-C: 1.20 ± 0.03	+2.3%	Less than 0.001		
				TC: 5.2 ± 0.1	–0.6%	Less than 0.001		
				TG: 1.8 (median)	–4.9%	Less than 0.001		
[32]	1163 people with diabetes already taking a statin; mean age 61 years for placebo *v* 62 years for ezetimibe ; 47% male in placebo group *v* 50% male in ezetimibe group; over 70% in each group were white and 13% were black; randomisation split was 2:1 (ezetimibe:placebo)	6 weeks	Statin plus ezetimibe 10 mg	Mean LDL-C: 3.14	–27.8%		Not reported	Proportion of people reporting drug-related adverse: 5.2% with placebo plus statin *v* 5.1% with ezetimibe plus statin; proportion of people stopping treatment because of drug-related adverse effects: 1.6% with placebo plus statin *v* 0.9% with ezetimibe plus statin Absolute numbers not reported; significance not assessed; P values not reported
				Mean HDL-C: 1.22	+1.5%			
				Mean TC: 5.25	–19.3%			
				Mean TG: 1.81	–11.1%			
			Statin plus placebo	Mean LDL-C: 3.14	–2.9%	Treatment difference –24.8%, 95% CI –27.0 to –22.6, P less than 0.001		Proportion of people exceeding predefined limits of change in ALT (3 or more times ULN), AST (3 or more times ULN), and CK (10 or more times ULN) (numbers reported for all patients and not just those with diabetes; reported as not significant; P value not reported
				Mean HDL-C: 1.25	–1.2%	Treatment difference 2.7%, 95% CI 1.2 to 4.1, P less than 0.001		

Study	Population	Duration	Intervention	Lipids at baseline* (mmol/L)	Change in lipids from baseline (mean)	P value	Percentage reaching LDL-C target of less than 2.6 mmol/L	Harms
				Mean TC:5.29	–3.3%	Treatment difference –16.0%, 95% CI –17.5 to –14.4, P less than 0.001		
				Mean TG: 1.81	+1.2%	Treatment difference –12.3%, 95% CI –15.9 to –8.7, P less than 0.001		
[31]	43 people with type 2 diabetes, 48% male, mean age ± standard deviation: 61 ± 5 for fenofibrate plus statin group *v* 59 ± 6 for placebo plus statin group, mean duration of diabetes ± standard deviation: 10 ± 2 years with fenofibrate plus fluvastatin *v* 8 ± 3 years with fluvastatin group	Study duration 12 weeks	Fluvastatin 80 mg od plus fenofibrate 200 mg od	LDL-C: 4.9 (0.7)	–35%			Two people in the fluvastatin plus fenofibrate group and one person in the fluvastatin plus placebo alone group withdrew because of myalgia
				HDL-C: 1.1 (0.1)	+34%			
				TC: 6.9 (1.0)	–26%			
				TG: 1.8 (0.4)	–34%			
			Fluvastatin 80 mg od plus placebo	LDL-C: 4.8 (0.5)	–25%	Less than 0.05		
				HDL-C: 1.2 (0.1)	+14%	Less than 0.05		
				TC: 6.7 (0.8)	–20%	NS		
				TG: 1.7 (0.5)	–17%	Less than 0.05		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant; od, once daily; SD, standard deviation; TC, total cholesterol; TG, triglyceride. P values are combination treatment compared with statin plus placebo; *Values are mean ± standard error or mean (standard deviation).

TABLE 5 **RCTs assessing the effects of fibrates on cardiovascular outcomes.** [33] [36] [37] [40]

Study	Population	Intervention	Outcome	Risk reduction	NNT/study duration	Harms
SENCAP* [33]	164 people with type 2 diabetes mean age 50.8 ± 8.0 years for bezafibrate group *v* 50.9 ± 8.1 years for placebo group; more than 65% were men, 30% were Asian, and 8% Afro-Caribbean. Mean duration of diabetes: 5.8 ± 5.7 years for bezafibrate group *v* 4.3 ± 4.3 years for placebo group	Bezafibrate mono 400 mg od	Documented MI or probable ischaemic change on ECG (Minnesota coding), CHD death, stroke, or MI	**CHD event rate at 3 years**: AR: 5/81 (6%) with bezafibrate *v* 16/83 (19%) with placebo; RR = 0.32, 95% CI 0.12 to 0.83	NNT 8, 95% CI 4 to 37, 3 years of treatment (calculated by *BMJ Clinical Evidence* author)*	No information on adverse effects reported
Helsinki Heart Study [34] [17]	Primary prevention of major coronary events: 1 RCT, 135 men with type 2 diabetes and no previous CHD	Gemfibrozil 1200 mg	Primary and secondary prevention of major coronary events	**Primary prevention of major coronary events**: 2/59 (3%) with gemfibrozil *v* 8/76 (11%) with placebo, RR 0.32, 95% CI 0.07 to 1.46		The review gave no information on adverse effects
VA-HIT [35] [36] [17]	Secondary prevention of major coronary events: 1 RCT, 769 men with type 2 diabetes and CHD			**Secondary prevention of major coronary events**: 99/378 (26%) with gemfibrozil *v* 141/391 (36%) with placebo, RR 0.73, 95% CI 0.59 to 0.90 **Secondary prevention of CHD death**: 33/378 (9%) with gemfibrozil *v* 59/391 (15%) with placebo, RR 0.58, 95% CI 0.39 to 0.86 **Secondary prevention of non-fatal MI:** 54/378 (14%) with gemfibrozil *v* 71/391 (18%) with placebo, RR 0.79, 95% CI 0.57 to 1.09		
VA-HIT [36]	Subgroup of 769 men with type 2 diabetes and CHD, mean age ± standard deviation 65 ± 6 years, 627/769 (82%) diabetics diagnosed by clinical history, 142/769 (18%) people with diabetes newly diagnosed by fasting plasma glucose of at least 7.0 mmol/L (at least 126 mg/dL). 323/1748 (18%) without diabetes had impaired fasting glucose of 6.1–6.9 mmol/L (110–125 mg/dL). Number of people receiving placebo not reported	Gemfibrozil 1200 mg od	CHD death, stroke, or MI	**All CVD events diabetics:** RRR 32%; HR 0.68, 95% CI 0.53 to 0.88; P = 0.04 **CHD death, diabetics:** RRR 41%; HR 0.59, 95% CI 0.39 to 0.91; P = 0.02 **Stroke, diabetics:** RRR 40%; HR 0.60, 95% CI 0.37 to 0.99; P = 0.046	NNT not reported, 5.1 years of treatment	No information on adverse effects reported
Helsinki Heart Study [37]	Subgroup of 135 men with type 2 diabetes and no previous CHD, 59 taking gemfibrozil (mean age 48.0 ± 4.7 years), 76 taking placebo (mean age 50.1 ± 4.0 years), 109/135 (81%) mean duration of diabetes 4.5 years, 26/135 (19%) newly diagnosed (fasting blood glucose more than 7.0 mmol/L [126 mg/dL]) on entry to study, people taking oral hypoglycaemic drugs or controlled by diet alone	Gemfibrozil 600 mg bd	Trial end points were definite MI and cardiac death	**CHD incidence:** AR: 3% with gemfibrozil *v* 11% with placebo; P = 0.19	NNT not reported, 5 years of treatment	No information on adverse effects reported

Study	Population	Intervention	Outcome	Risk reduction	NNT/study duration	Harms
FIELD study [40]	9795 people with type 2 diabetes aged 50–75 years not taking statin at entry. 53% of both placebo and fenofibrate groups had a history of previous CVD, MI, stroke, angina, PVD, or coronary revascularisation	Fenofibrate 200 mg od	**Primary outcome:** First occurrence of either non-fatal MI or death from CHD	**All coronary events with placebo *v* fenofibrate:** 256/4895 (5%) with fenofibrate *v* 288/4900 (6%) with placebo; HR 0.89, 95% CI 0.75 to 1.05; P = 0.16	Total CVD events in subgroup with no previous CVD; NNT 50, 5 years of treatment	Similar numbers of people taking fenofibrate and placebo stopped treatment for any cause
				Non-fatal MI: 158/4895 (3%) with fenofibrate *v* 207/4900 (4%) with placebo; HR 0.76, 95% CI 0.62 to 0.94; P = 0.01	Total CVD events for the entire cohort; NNT 70, 5 years of treatment	38/4895 (0.8%) of people taking fenofibrate and 24/4900 (0.5%) taking placebo had possible serious adverse effect
				Death from CHD: 110/4895 (2.2%) with fenofibrate *v* 93/4900 (1.9%) with placebo; HR 1.19, 95% CI 0.90 to 1.57; P = 0.22		
			Secondary outcomes: Major CVD events (CHD events, total stroke, and other cardiovascular death combined) total CVD deaths, CHD death, haemorrhagic and non-haemorrhagic stroke, coronary and peripheral revascularisation procedures, cause-specific non-CHD mortality and total mortality	**Total CVD events:** 612/4895 (13%) with fenofibrate *v* 683/4900 (14%) with placebo; HR 0.89, 95% CI 0.80 to 0.99; P = 0.035		3 people taking fenofibrate and 1 person taking placebo had rhabdomyolysis, which resolved. None of these people were taking statins
				Coronary revascularisations: 290/4895 (6%) with fenofibrate *v* 364/4900 (7%) with placebo; HR 0.79, 95% CI 0.68 to 0.93; P = 0.003		People taking fenofibrate were at greater risk for pancreatitis (40/4895 (0.8%) with fenofibrate *v* 23/4900 (0.5%) with placebo; P = 0.031
				All revascularisations: 380/4895 (8%) with fenofibrate *v* 471/4900 (10%) with placebo; HR 0.80, 95% CI 0.70 to 0.92; P = 0.001		Fenofibrate was also associated with a small increased risk of pulmonary embolism (P = 0.022) and deep venous thrombosis (P = 0.074) compared with placebo
				Progression to albuminuria: 466/4895 (10%) with fenofibrate *v* 539/4900 (11%) with placebo; P = 0.002		Concentrations of creatine phosphokinase more than 5 times the upper limit of normal occurred at least once in 15 people taking fenofibrate and in 10 taking placebo. ALT concentrations reached at least 3 times the upper limit of normal in 38 people taking placebo and in 22 taking fenofibrate
				Development of retinopathy requiring laser treatment: 178/4895 (4%) with fenofibrate *v* 253/4900 (5%) with placebo; P = 0.0003		6 cases of clinical hepatitis were reported in each group

ALT, alanine aminotransferase; bd, twice daily; FIELD, Fenofibrate (TriCor®) Intervention and Event Lowering in Diabetes; od, once daily; SENCAP, St Mary's, Ealing, Northwich Park Diabetes Cardiovascular Disease Prevention; VA-HIT, Veterans Affairs High-density lipoprotein Intervention Trial; *CHD morbidity was a secondary end point for this study; the primary aim was to evaluate the effect of bezafibrate on progress of ultrasonically measured arterial disease.

TABLE 6 **RCTs evaluating the lipid-modifying effects of fibrates.** [33] [38] [39]

Study	Fibrate	Lipids at baseline (mmol/L)	Mean percentage change or absolute change in lipids (mmol/L)	P value	Harms
SENCAP Elkeles 1998 [33] *	Bezafibrate mono 400 mg od	TG: median 2.24 (interquartile range 1.73 to 2.94)	–32.5% with bezafibrate *v* +4.1 with placebo	P = 0.001	No information on adverse effects reported
164 people with type 2 diabetes, study duration 3 years		HDL-C: median 1.02 (interquartile range 0.87 to 1.13)	+6.4 with bezafibrate *v* –2.0 with placebo	P = 0.02	
Avogaro [38]	Gemfibrozil 600 mg bd	TG: 316 ± 84 mg/dL in people given gemfibrozil *v* 318 ± 93 mg/dL in people given placebo	214 ± 82 mg/dL) with gemfibrozil *v* 380 ± 217 mg/dL with placebo	P less than 0.05	There were no significant changes in liver enzymes, urea, or creatinine
217 people with type 2 diabetes, study duration 20 weeks				P less than 0.001*	
O'Neal [39]	Gemfibrozil 600 mg bd	TG: 3.50 ± 1.36	TG: –40% (gemfibrozil compared with placebo [absolute change, mean ± standard deviation]: –1.50 ± 1.42 mmol/L [133 ± 126 mg/dL] with gemfibrozil *v* +1.20 ± 1.25 mmol/L [106 ± 111 mg/dL] with placebo)	P less than 0.001	No information on adverse effects reported
26 people with type 2 diabetes, study duration 24 weeks			Change in HDL-C and LDL-C not statistically significant compared with placebo, and a small decrease in TC which was not clinically significant (absolute change in TC, mean ± SD: –0.2 ± 0.52 mmol/L [7.7 ± 20 mg/dL] with gemfibrozil *v* +0.7 ± 0.45 mmol/L [27 ± 17 mg/dL] with placebo)	P less than 0.05	

bd, twice daily; od, once daily; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; SENCAP, St Mary s, Ealing, Northwich Park Diabetes Cardiovascular Disease Prevention; TC, total cholesterol; TG, triglyceride. P values are compared with placebo unless stated otherwise, *P value compared with baseline. Values are mean ± standard error unless stated otherwise.

TABLE 7 **RCT assessing intensive multiple-intervention treatment programmes (for lipid modification).** [42]

Study	Population	Intervention	Outcome	LDL-C and HDL-C	OR	TC reduction	NNT	Harms
[42]	683 people, aged 50–70 years, type 1 and type 2 diabetes (proportion 1:2), 1.5 years of follow-up	Specialist nurse-led hyperlipidaemia clinic *v* usual care	TC reduction to below target (less than 5.0 mmol/L [193 mg/dL]) at 1.5-year follow-up (interquartile range 1.3 years to 1.8 years	Not reported	AR: 180/345 (52%) with intensive intervention *v* 139/338 (41%) with usual care; OR 1.69, 95% CI 1.25 to 2.29; P = 0.007	–0.28 mmol/L, 95% CI –0.44 mmol/L to –0.13 mmol/L with intensive intervention (11 mg/dL, 95% CI –17 mg/dL to –5 mg/dL); P = 0.0004 Initial TC: 5.8 mmol/L (224 mg/dL) for intervention and control groups falling to 4.9 mmol/L (189 mg/dL) in the intensive-intervention group and 5.2 mmol/L (201 mg/dL) in usual-care group by end of study	9, 95% CI 5 to 27 (calculated by *BMJ Clinical Evidence* author)	No information on adverse effects reported

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

TABLE 8 **RCT assessing fish oil (for lipid modification).** [43]

			Outcomes		
Study	**Population**	**Intervention**	**Cholesterol levels**	**TG levels**	**Harms**
Farmer [43] SR (14 RCTs; 5 parallel, 9 crossover), study duration mean 12 weeks' follow-up	725 people aged 55–65 years with type 2 diabetes	Fish oils *v* vegetable oils or saline	Change in LDL-C *v* control; 11 RCTs, 2 parallel and 9 crossover, 248 people: WMD 0.24 mmol/L, 95% CI 0.05 mmol/L to 0.43 mmol/L (9.3 mg/dL, 95% CI 1.9 mg/dL to 16.6 mg/dL); P = 0.01 over 12 weeks	Change in TGs *v* control: WMD –0.56 mmol/L, 95% CI –0.71 mmol/L to –0.41 mmol/L (–49.6 mg/dL, 95% CI –62.8 mg/dL to –36.3 mg/dL); P less than 0.00001	Few data reported
			Change in HDL-C *v* control; 12 RCTs, 4 parallel and 8 crossover, 685 people: pooled WMD +0.02 mmol/L, 95% CI –0.02 mmol/L to +0.06 mmol/L (+0.8 mg/dL, 95% CI –0.8 mg/dL to 2.3 mg/dL); P = 0.3	Change in TGs *v* control; subgroup analysis: pre-existing hypertriglyceridaemia; 3 RCTs, 2 parallel, 1 crossover, 474 people: WMD –1.45 mmol/L, 95% CI –2.89 mmol/L to –0.01 mmol/L (–128 mg/dL, 95% CI –256 mg/dL to –1 mg/dL); P = 0.05	
			Change in LDL-C *v* control; subgroup analysis: pre-existing hypertriglyceridaemia; 3 RCTs, 2 parallel, 1 crossover, 474 people: WMD 0.60 mmol/L, 95% CI 0.16 mmol/L to 1.04 mmol/L (23 mg/dL, 95% CI 6 mg/dL to 40 mg/dL); P = 0.008	Subgroup analysis; people without pre-existing hypertriglyceridaemia; 11 RCTs, 3 parallel, 8 crossover, 239 people: WMD –0.40 mmol/L, 95% CI –0.61 mmol/L to –0.19 mmol/L (–35 mg/dL, 95% CI –54 mg/dL to –17 mg/dL); P = 0.0002	
			Subgroup analysis; people without pre-existing hypertriglyceridaemia; 11 RCTs, 3 parallel, 8 crossover, 239 people: WMD +0.16 mmol/L, 95% CI –0.05 mmol/L to +0.37 mmol/L (+6 mg/dL, 95% CI –2 mg/dL to +14 mg/dL); P = 0.13		

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

TABLE GRADE evaluation of interventions for dyslipidaemia in diabetes

Important outcomes	Cardiovascular morbidity/mortality, changes in lipid profile, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions for dyslipidaemia in people with diabetes?									
5 (10,703) [17]	Cardiovascular events (primary prevention)	Statins *v* placebo	4	0	0	–2	0	Low	Directness points deducted for composite outcome and for not including diabetics exclusively
7 (4672) [17]	Cardiovascular events (secondary prevention)	Statins *v* placebo	4	0	0	–2	0	Low	Directness points deducted for composite outcome and for not including diabetics exclusively
3 (233) [20] [22] [21]	Change in lipid profile	Simvastatin *v* placebo	4	–1	+1	0	0	High	Quality point deducted for incomplete reporting of results. Consistency point added for dose response
1 (49) [24]	Change in lipid profile	Pravastatin *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (5370) [18] [19]	Cardiovascular events	Atorvastatin *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for subgroup analysis
1 (217) [23]	Change in lipid profile	Atorvastatin *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (1354) [30] [32]	Change in lipid profile	Statin plus ezetimibe *v* statin alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (43) [31]	Change in lipid profile	Statin plus fibrate *v* statin alone	4	–2	0	0	0	Low	Quality points deducted for sparse data and for incomplete reporting of results
1 (164) [33]	Morbidity	Bezafibrate *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for assessing secondary outcomes
1 (164) [31]	Change in lipid profile	Bezafibrate *v* placebo	4	–2	0	–1	0	Very low	Quality point deducted for sparse data and for incomplete reporting of results. Directness point deducted for assessing lipid changes as a secondary outcome
1 (769) [17]	Cardiovascular events	Gemfibrozil *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for subgroup analysis. Consistency point deducted for conflicting results. Directness point deducted for inclusion of small number of people with diabetes
2 (243) [38] [39]	Change in lipid profile	Gemfibrozil *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (9795) [40]	Cardiovascular events	Fenofibrate *v* placebo	4	0	0	–2	0	Low	Directness points deducted for people in placebo group starting treatment with a statin and for composite outcome
1 (683) [42]	Change in lipid profile	Intensive multiple-intervention treatment programmes *v* standard care	4	–2	0	–1	0	Very low	Quality points deducted for blinding flaws and no placebo comparisons. Directness point deducted for uncertainty about intervention of benefit
14 (725) [43]	Change in lipid profile	Fish oils *v* control	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for using different doses/formulations or range of compounds

Important outcomes	Cardiovascular morbidity/mortality, changes in lipid profile, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (146) [44]	Change in lipid profile	Nicotinic acid *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for inclusion of co-intervention

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio