

Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials

João Costa, Margarida Borges, Cláudio David, António Vaz Carneiro

Abstract

Objective To evaluate the clinical benefit of lipid lowering drug treatment in patients with and without diabetes mellitus, for primary and secondary prevention.

Design Systematic review and meta-analysis.

Data sources Cochrane, Medline, Embase, and reference lists up to April 2004.

Study selection Randomised, placebo controlled, double blind trials with a follow-up of at least three years that evaluated lipid lowering drug treatment in patients with and without diabetes mellitus.

Data extraction Two independent reviewers extracted data. The primary outcome was major coronary events defined as coronary heart disease death, non-fatal myocardial infarction, or myocardial revascularisation procedures.

Results Twelve studies were included. Lipid lowering drug treatment was found to be at least as effective in diabetic patients as in non-diabetic patients. In primary prevention, the risk reduction for major coronary events was 21% (95% confidence interval 11% to 30%; $P < 0.0001$) in diabetic patients and 23% (12% to 33%; $P = 0.0003$) in non-diabetic patients. In secondary prevention, the corresponding risk reductions were 21% (10% to 31%; $P = 0.0005$) and 23% (19% to 26%; $P \leq 0.00001$). However, the absolute risk difference was three times higher in secondary prevention. When results were adjusted for baseline risk, diabetic patients benefited more in both primary and secondary prevention. Blood lipids were reduced to a similar degree in both groups.

Conclusions The evidence that lipid lowering drug treatment (especially statins) significantly reduce cardiovascular risk in diabetic and non-diabetic patients is strong and suggests that diabetic patients benefit more, in both primary and secondary prevention. Future research should define the threshold for treatment of these patients and the desired target lipid concentrations, especially for primary prevention.

Introduction

The risk of myocardial infarction in patients with diabetes mellitus without a history of myocardial

infarction is as high as that in patients without diabetes mellitus who have had a myocardial infarction.¹ Diabetes affects virtually all lipids and lipoproteins, and dyslipidaemia is a consistent finding in people with type 2 diabetes. The effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in treating dyslipidaemia and reducing the risk of coronary events has been shown in large scale studies of both primary and secondary intervention to reduce coronary artery disease.² A recent meta-analysis has evaluated the efficacy of lipid lowering drug treatment in patients with type 2 diabetes and showed that both statins and fibrates reduce the cardiovascular risk.³ These data served as a basis for the recent guidelines for lipid control in the management of type 2 diabetes from the American College of Physicians.⁴ The recommendations were that lipid lowering drug treatment should be used for secondary prevention of cardiovascular mortality and morbidity in all patients with known coronary artery disease and type 2 diabetes and that statins should be used for primary prevention against macrovascular complications in patients with type 2 diabetes and other cardiovascular risk factors.

Bearing in mind the limitations of this meta-analysis (search date, number of included trials, outcomes selected, and data for non-diabetic patients), we aimed to evaluate and compare the efficacy of lipid lowering drug treatment in patients with and without diabetes mellitus, by doing a meta-analysis of published unconfounded randomised, prospective, placebo controlled, double blind clinical trials.

Methods

Studies—The criteria for inclusion of trials in the meta-analysis were a lipid lowering/cholesterol drug arm; a placebo arm; adequate concealment of random allocation; double blind assessment; reference to type 2 diabetic patients and non-diabetic patients in both arms; follow-up of at least three years; and a hard end point that was a cardiovascular event as the primary or

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Center for Evidence-Based Medicine, University of Lisbon School of Medicine, Lisbon, Portugal

João Costa
assistant in clinical pharmacology and therapeutics

Margarida Borges
clinical consultant in pneumology

António Vaz Carneiro
clinical professor of medicine

Department of Cardiology, Santa Maria University Hospital, Lisbon
Cláudio David
assistant in clinical pharmacology and therapeutics

Correspondence to: A V Carneiro, Faculdade de Medicina de Lisboa, CEMBE, Piso 6, Av Prof Egas Moniz, 1649-028 Lisboa, Portugal
avc@fm.ul.pt

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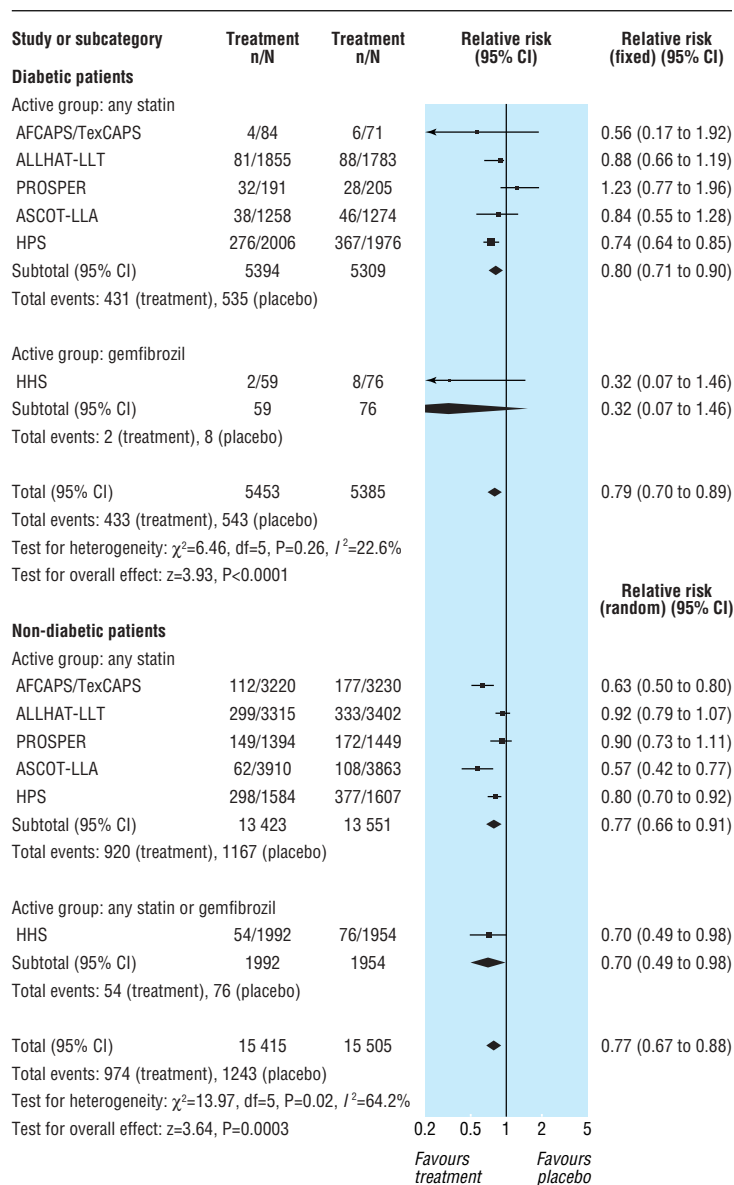


Fig 1 Primary prevention of major coronary events

secondary end point. We considered trials that enrolled patients with or without previous coronary artery disease to evaluate the efficacy in both primary and secondary prevention.

Outcome measures—The primary outcome was a composite of major coronary events defined as coronary artery disease death, non-fatal myocardial infarction, or myocardial revascularisation procedures. Secondary outcomes were coronary artery disease death, non-fatal myocardial infarction, revascularisation procedures, stroke, and changes in concentrations of blood lipids.

Search strategy for identification of studies—We identified published studies through Medline (1966 through April 2004), Embase (1980 through April 2004), and Cochrane Central (1980 through April 2004) and by searching cross references from original articles and reviews. The search terms covered statins, fibrates, diabetes mellitus, and cardiovascular diseases (see bmj.com). We limited the search to English language

papers. We screened titles, keywords, and abstracts and obtained full copies of potentially suitable reports.

Study selection and data extraction—Two authors independently assessed the identified studies. Study details were obtained independently, written on to standardised forms, and cross checked. Disagreements were resolved by consensus.

Data analyses—We tested heterogeneity between trial results, compared the significance of differences between subgroups, and calculated the number needed to treat from meta-analysis estimates. Calculations also took into account the baseline risk, defined as the percentage of patients with events in the control arm. Analysis was done separately for primary and secondary prevention, for diabetic and non-diabetic patients, and for statins and fibrates.

Results

Description of studies

The search yielded a total of 581 reports. Fourteen trials met criteria for inclusion in the final analysis; six trials reported data on primary coronary artery disease prevention, and eight reported on secondary prevention.⁵⁻²³ We excluded two trials because no data were available for diabetic patients.

Event rate

Diabetic patients had a significantly higher risk of major coronary events than non-diabetic patients, in both placebo and treatment groups, in primary and secondary prevention trials (see bmj.com).

Clinical outcomes

In primary prevention, the risk reduction for a major coronary event was 21% (95% confidence interval 11% to 30%; $P<0.0001$) in diabetic patients and 23% (12% to 33%; $P=0.0003$) in non-diabetic patients treated with either statins or gemfibrozil. In secondary prevention, the risk reduction for a major coronary event was 21% (10% to 31%; $P=0.0005$) in diabetic patients and 23% (19% to 26%; $P<0.00001$) in non-diabetic patients treated with either statins or gemfibrozil.

The absolute risk difference was significantly higher in secondary prevention. In primary prevention, the risk difference for major coronary events was -0.02 (-0.04 to -0.00 ; $P=0.1$) in diabetic patients and -0.02 (-0.02 to -0.01 ; $P<0.00001$) in non-diabetic patients (fig 1). In secondary prevention, the risk difference for major coronary events was -0.07 (-0.11 to -0.03 ; $P=0.0003$) in diabetic patients and -0.05 (-0.06 to -0.04 ; $P<0.00001$) in non-diabetic patients (fig 2).

In secondary prevention, we found important differences in secondary outcomes between diabetic and non-diabetic patients. The risk reduction in diabetic and non-diabetic patients treated with either statins or gemfibrozil was 22% (9% to 34%; $P=0.001$) and 26% (22% to 30%; $P<0.00001$) for coronary artery disease death or non-fatal myocardial infarction; 30% (8% to 47%; $P=0.01$) and 21% (5% to 35%; $P=0.01$) for coronary artery disease death; 39% (4% to 62%; $P=0.03$) and 29% (18% to 39%; $P<0.00001$) for non-fatal myocardial infarction; 30% (17% to 41%; $P\leq 0.0001$) and 23% (18% to 27%; $P\leq 0.00001$) for revascularisation procedures; and 36% (17% to 51%;

P=0.0008) and 22% (13% to 30%; P≤0.00001) for stroke.

When we adjusted the results for baseline risk, diabetic patients benefited more than non-diabetic patients in secondary prevention for coronary artery disease death, non-fatal myocardial infarction, revascularisation, and stroke (see bmj.com).

For some outcomes we found significant heterogeneity ($I^2 > 50%$) between study results. As we have taken trials' heterogeneity into account in the analysis, our results probably underestimate the true magnitude of the treatment effect.

Effects on blood lipids

The magnitude of change in blood lipids was similar in diabetic and non-diabetic groups; most trials showed a decrease of 15-20% in total cholesterol and increases of 5-7.5% in high density lipoprotein cholesterol. Trials that used gemfibrozil showed smaller decreases in total cholesterol and low density lipoprotein cholesterol.

Discussion

As the relation between blood cholesterol and cardiovascular risk is continuous,²⁴ no definite threshold exists above which patients must be treated. The decision to treat depends more on the expected absolute risk reduction.²⁵ Consequently, variable entry criteria are found in several clinical trials.

Diabetes is an independent risk factor for cardiovascular disease, and as many as 80% of patients with type 2 diabetes die from cardiovascular complications, a risk that is not completely explained by traditional risk factors.²⁶ Our meta-analysis clearly confirms that reduction of LDL cholesterol concentrations results in an important decrease in major coronary events in diabetic patients and shows similar relative risk reductions for our primary outcomes in both diabetic and non-diabetic patients and in primary and secondary prevention. The absolute risk difference was three times higher in secondary prevention, reflecting the higher baseline cardiovascular risk of these patients, as indicated by the higher rate of coronary events in secondary prevention trials.

We were unable to analyse secondary outcomes in primary prevention, as no data were available from the trials. Indirect comparisons between statins and fibrates should be made with caution, as only one trial evaluated fibrate treatment. The results of some secondary outcomes in secondary prevention clearly show that diabetic patients benefit significantly more from treatment with lipid lowering drugs than do non-diabetic patients.

Limitations of the study

Our meta-analysis has some limitations. Firstly, we included in our primary outcome the results of three studies that report only combined results for coronary events and stroke. Secondly, the definition of diabetes has changed over the years and seven of the 12 studies included have released post hoc analysis for the diabetic patients' subgroup (for the meta-analysis we considered the most updated results and not those from the original reports). Thirdly, we were unable to explore the effect of the dose or individual drugs. None the less, to our knowledge, this

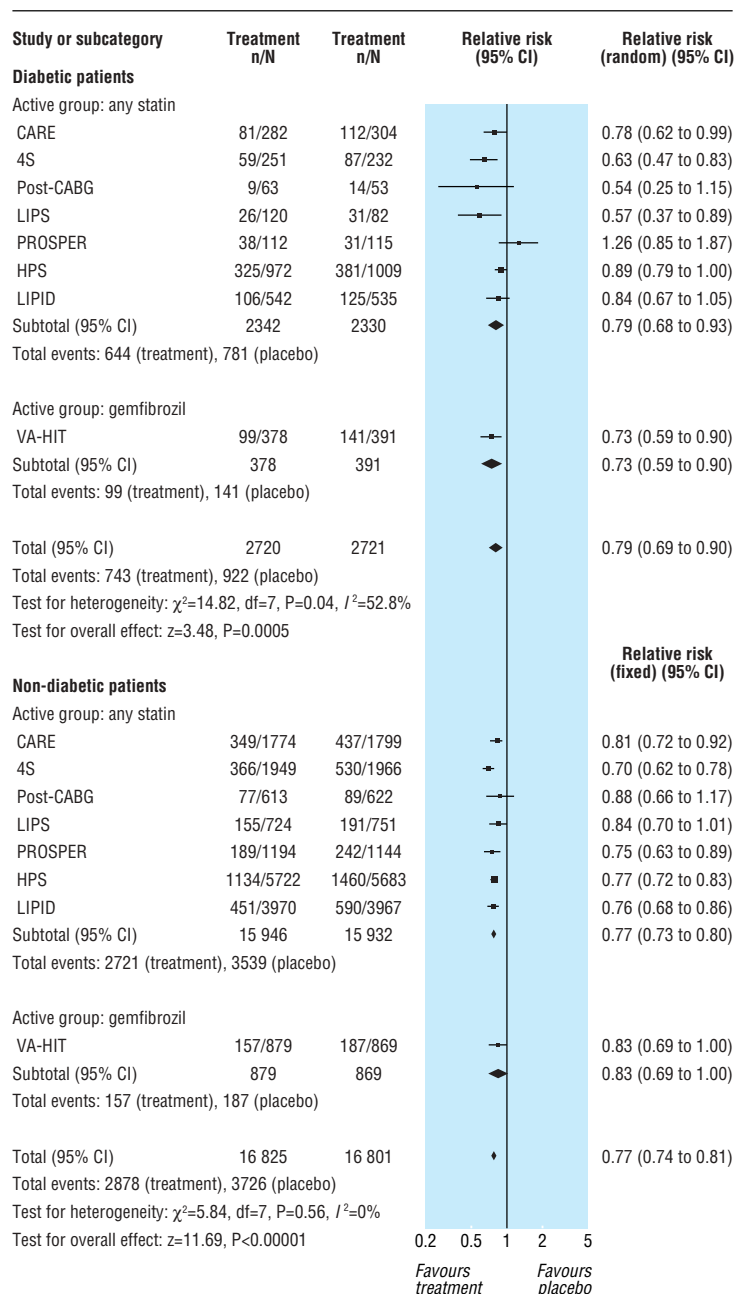


Fig 2 Secondary prevention of major coronary events

is the first meta-analysis that has compared cardiovascular risk reduction in diabetic versus non-diabetic patients.

Implications for practice

Although the benefits of statins for secondary prevention of coronary artery disease have been well documented, they are not being optimally used in patients at higher risk. A recent cohort study of 396 077 patients aged 66 years or more who had a history of cardiovascular disease or diabetes mellitus found that only 19.1% of the patients were prescribed statins.²⁷

Large, prospective, randomised outcome trials designed for diabetic patients that have studied the efficacy of lipid lowering drug treatment are lacking.

What is already known on this topic

Cardiovascular disease is the most common cause of death in the general population and causes even greater morbidity and mortality in people with type 2 diabetes

The effectiveness of lipid lowering drugs in reducing the risk of coronary events has been shown in large scale studies of both primary and secondary prevention

Large randomised outcome trials designed specifically for diabetic patients are lacking

What this study adds

Meta-analysis of published trials showed that patients with diabetes benefit more than non-diabetic patients, in both primary and secondary prevention

This may have important clinical implications, particularly for primary prevention in patients with type 2 diabetes

The angiographic diabetes atherosclerosis intervention study (DAIS) was the first of the lipid intervention studies specifically designed for diabetes mellitus; fenofibrate resulted in 42% less increase in stenosis compared with placebo.²⁸

Although strong data support the efficacy and safety of statins for primary prevention in patients with diabetes mellitus, some controversy still exists about their use in patients with a low risk of coronary disease.²⁹ These ongoing studies will provide the prospective outcome data that are needed for the optimal management of diabetic patients.

Future research should clearly define the threshold over which diabetic patients must be treated and the blood cholesterol target, especially in primary prevention. Until these data are available, our results support the use of statins for secondary prevention and also for primary prevention in these patients.

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