

Diabetes and lipids

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ABSTRACT The benefits of statin therapy to lower cholesterol in patients with coronary heart disease are well established. Patients with type 2 diabetes have a high prevalence of coronary heart disease, and, while some consider type 2 diabetes a coronary risk factor, others consider it a disease equivalent. This raises the question 'Should all diabetic patients receive statin therapy regardless of the presence of coronary heart disease?' Review of the major secondary prevention lipid-lowering trials: the Scandinavian Simvastatin Survival study (4S study), the CARE trial, and the LIPID trial demonstrates that statin therapy is effective in reducing the incidence of major coronary events in diabetic patients. This supports the use of statin therapy in diabetic patients with known CHD, and the more recent HPS extends this recommendation to include patients with 'low to normal' cholesterol levels. The evidence for primary prevention in patients with diabetes has, until recently, been less clear, as the early primary prevention lipid-lowering studies had too few diabetic subjects to provide conclusive data. However, HPS and the recently published CARDS have shown that statin therapy results in a significant reduction in cardiovascular events, including coronary events, in patients with type 2 diabetes and no previous history of cardiovascular disease. Once again these benefits were seen in patients without 'elevated' cholesterol levels. On the basis of all of these studies it seems reasonable to treat all diabetic patients with statins regardless of previous cardiovascular disease or pre-treatment cholesterol levels.

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LIST OF ABBREVIATIONS Cholesterol and Recurrent Events (CARE), Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID), coronary heart disease (CHD), Heart Protection Study (HPS), Collaborative Atorvastatin Diabetes Study (CARDS), Myocardial Infarction (MI), West of Scotland Coronary Prevention Study (WoSCoPS), Airforce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), peripheral vascular disease (PVD), low density lipoprotein (LDL), Scottish Intercollegiate Guideline Network (SIGN), UK Prospective Diabetes Study (UKPDS)

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OVERVIEW

Introduction

It is well established that type 2 diabetes leads to an increased and premature morbidity and mortality from cardiovascular disease. Coronary heart disease is the leading cause of death in patients with type 2 diabetes. Data from the Framingham cohort, which have been mirrored by many further studies, demonstrated at least a doubling of all-cause mortality in diabetic males, and at least a threefold increase in mortality in females when compared to their non-diabetic counterparts.

On a more positive note there are many strategies that can reduce cardiovascular risk in this group of people (Table 1). Over the last decade convincing evidence has emerged that lowering cholesterol with statins reduces cardiovascular mortality in diabetic patients with established CHD (secondary prevention) and those at risk

(primary prevention) (see Figure 1). Indeed, the prescription of a statin is probably the single most effective measure to prolong life in the person with diabetes. Early in 2004, the American College of Physicians performed a systematic review of pharmacological lipid-lowering therapy in type 2 diabetes, and on the basis of this review recommended a clinical practice guideline.

In this overview we will examine some of the important studies that were included in the review, with the addition of the recent CARDS that was published after the review was completed.

Secondary prevention trials

There have been three pivotal randomised, double-blind, placebo-controlled trials assessing the effect of statins on cardiovascular risk in patients with pre-existing cardiovascular disease: the Scandinavian Simvastatin Survival study (4S study), the CARE trial which was

TABLE 1 Reduction of cardiovascular risk in the person with diabetes.**Treatment of hyperglycaemia**

- Metformin of particular benefit
- Sulphonylureas/insulin of some benefit on long-term follow-up of UKPDS
- Thiazolidenediones of theoretical benefit, currently under investigation for cardiovascular outcomes

Treatment of hypertension

- Multiple hypotensive agents of proven efficacy
- Better outcomes with lower blood pressures in diabetic patients
- ACE inhibitors usually first choice as additional cardiovascular qualities
- Multiple agents may be required to reach target

Treatment of dyslipidaemia

- Statins of proven benefit for secondary prevention
- Statins of proven benefit for primary prevention in diabetic patients
- Not certain if a lower cholesterol leads to better protection
- Fibrates theoretically more suitable for the typical dyslipidaemia of diabetes, under investigation in cardiovascular end-point studies

Other pharmacological therapy

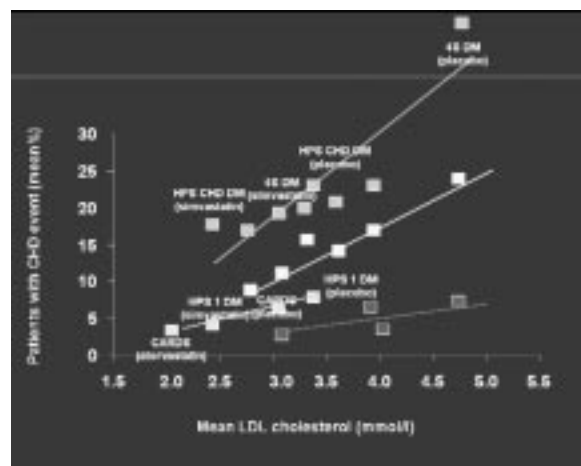
- Antiplatelet therapy with aspirin or clopidogrel reduces cardiovascular events, but frequent side-effects
- ACE inhibitors (ramipril, perindopril) reduce cardiovascular events separate from effects on blood pressure and heart failure

Lifestyle

- Smoking cessation difficult and little specific evidence in diabetic patients
- Increase physical activity/weight loss, reduce blood pressure, and improve glycaemic control in the short term, long-term effects on cardiovascular outcomes under investigation

conducted in the US and Canada, and the Long-term Intervention with Pravastatin in Ischaemic Disease trial carried out in Australia and New Zealand (LIPID) (Table 2).

In 4S, active treatment with simvastatin was associated with a significant reduction in all-cause mortality, CHD-related death, and non-fatal MI. There were two *post hoc* subgroup analyses of the data from diabetic patients. The first examined patients with known diabetes at the start of the study, and revealed significant reductions in CHD events. Although there was a larger reduction in all-cause mortality in this group when compared with the whole trial population, this did not reach statistical significance, probably as a result of the relatively small size of the subgroup ($n = 202$, 5% of the total). The second *post hoc* analysis included people diagnosed as having diabetes using the new WHO criteria (i.e. fasting glucose ≥ 7.0 mmol/l), as well as known diabetic patients ($n = 483$, 11% of the total), and the reduction in major coronary events was similar.



Primary and secondary cholesterol lowering statin trials illustrating the percentage of patients with a CHD event (CHD death or non-fatal MI) against the mean LDL cholesterol during the study in the statin intervention and placebo groups. Data for secondary prevention for all subjects is in dark blue, and for subjects with diabetes is in grey. Data for primary prevention for all subjects is in light blue, and for subjects with diabetes is in purple. The event rate for diabetes secondary prevention is greater than for secondary prevention overall. The event rate for diabetes primary prevention is greater than for primary prevention overall, but not as high as secondary prevention overall.

Key: CHD = coronary heart disease, CARES = Collaborative AtoRvastatin Diabetes Study, HPS I DM = Heart Protection Study primary prevention diabetes subjects, HPS CHD DM = Heart Protection Study diabetes subjects with CHD, 4S = Scandinavian Simvastatin Survival Study

FIGURE 1 Relationship between achieved mean cholesterol and percentage of patients with a CHD event in published trials.

This was the first trial-based evidence that cholesterol lowering with a statin reduced the risk of major CHD events and other atherosclerotic events in diabetic patients. The results in the diabetic subgroups in CARE and LIPID were very similar comparing pravastatin with placebo.

Primary prevention

The evidence that cholesterol lowering in diabetic patients plays a role in the primary prevention setting has been less compelling until recently, as there were very few diabetic subjects in the classic WoSCoPS and the AFCAPS/TexCAPS (Table 2).

The HPS was a large study designed to address the question of whether lowering cholesterol with a statin was of benefit in subjects who were not included in the previous studies (Table 3). Its aim was to study the effects of lipid-lowering within subgroups for which there was limited existing evidence, including subjects with a cholesterol level below previously accepted thresholds for treatment, subjects with diabetes, females, the elderly, and those with non-coronary occlusive arterial disease. The HPS randomised patients with known CHD or risk factors such as PVD, stroke, diabetes,

TABLE 2 Results of end-points for all subjects and subjects with diabetes in the three early secondary prevention studies and two early primary prevention studies with statins.

Trial	Drug	Total subjects (n)	Diabetic subjects (n (%))	Primary end-point (all)	Primary end-point (diabetes)	Major coronary events (CHD death, non-fatal MI) (all)	Major coronary events (CHD death, non-fatal MI) (diabetes)	Comments
Primary prevention								
AFCAPS / TexCAPS	Lovastatin 20–40 mg	6,605	155 (2%)	Primary end-point fatal or non-fatal MI, unstable angina, or sudden cardiac death from 11% to 7%	Data not provided	Data not provided for combined end-point	Data not provided	
WoSCoPS	Pravastatin 40 mg	6,595	76 (1%)	Reduced CHD mortality or non-fatal MI from 8% to 5.5%	Data not provided	Primary end-point	Data not provided	
Secondary prevention								
4S	Simvastatin 20–40 mg	4,444	202 (5%)	Reduced total mortality from 12% to 8%	Reduced total mortality from 24% to 15% (NS)	Reduced from 28% to 19%	Reduced from 44% to 23%	
CARE	Pravastatin 40 mg	4,159	586 (14%)	Reduced CHD mortality or non-fatal MI from 13% to 10%	Insignificant effect	Primary end-point	Primary end-point, insignificant effect	Statistically significant reduction in expanded end-point in diabetes (CHD death, MI, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA))
LIPID	Pravastatin 40 mg	9,014	1,077 (12%)	Reduced CHD mortality from 8% to 6%	Data not provided	Reduced from 15% to 12%	reduced MACE from 23% to 19% (NS)	Statistically significant reduction in any cardiovascular end-point in diabetes (CHD death, MI, CABG, PTCA, stroke)

and hypertension. It included patients who had random total cholesterol of >3.5 mmol/l, which is considerably lower than the levels used previously in most major trials.

There were 5,963 diabetic subjects within the study group of 20,536 (29% of the total) and most of these were classified as having type 2 diabetes. Patients with diabetes and prior MI or CHD had the highest event rate of any group in the study, with a first major vascular event rate (major coronary event, stroke, or revascularisation) of 38% in five years in the placebo group that was reduced to 33% with simvastatin 40 mg, extending the results of 4S, CARE, and LIPID studies to diabetic patients with lower

cholesterol concentrations. This was also the first study to demonstrate a reduction in strokes with statins in addition to the reduction in coronary events in people with diabetes. A total of 2,912 diabetic patients had no prior occlusive vascular disease (primary prevention), and simvastatin reduced the primary end-point of first vascular event from 13.5% down to 9.3% in this group of patients.

CARDS

The Collaborative Atorvastatin Diabetes Study was initially set up as a secondary prevention study of diabetic patients with previous MI. When the evidence for benefit from

statins in secondary prevention became overwhelming it was decided that it was unethical that half of the subjects would receive placebo, and the secondary prevention study was abandoned. It was replaced by the first primary prevention study with subjects with type 2 diabetes only. Randomisation of the 2,838 male and female participants in this multicentre, randomised, double-blind, placebo-controlled trial was completed in June 2001. The participants, aged 40–75 years, all had a diagnosis of type 2 diabetes and a minimum of one other risk factor for cardiovascular disease, but were required to have a serum LDL cholesterol of <4.14 mmol/l (i.e. not a markedly elevated cholesterol level). Follow-up was initially planned to be for a minimum of four years, but the trial was stopped earlier than expected due to the obvious benefit seen in the subjects taking atorvastatin 10 mg. Significant reductions were seen in acute coronary heart disease events, coronary revascularisations, and strokes. Importantly, the benefit was observed irrespective of their cholesterol or triglyceride levels at the start of the study.

Discussion

The benefits of cholesterol lowering with statins are now well established for primary and secondary prevention of CHD in diabetic patients with both elevated and relatively 'normal' serum cholesterol. This appears to hold true for a number of different statins, suggesting that this is a class effect and not simply dependent on the individual drugs used. However, evidence of efficacy is not the same as evidence of safety, and it should be remembered that cerivastatin was withdrawn because of unacceptable muscle side-effects when used widely in routine clinical practice. It is suggested, therefore, that either simvastatin, pravastatin, or atorvastatin is prescribed in at least moderate doses for any diabetic patient with cardiovascular disease, regardless of baseline cholesterol concentration, as these drugs have both proven benefit and safety in large studies.

The role of statins in primary prevention of CHD in diabetic subjects has also been established in a number of studies, but this does not necessarily help decide which patients should be started on this therapy. The SIGN guideline number 55 on the management of diabetes suggested the use of risk tables. However, risk estimation tables used for establishing CHD risk and influencing both statin and antihypertensive treatments (e.g. The Joint British Societies Coronary Risk Prediction Charts) do not adequately represent the diabetic population. This is because these tables are based on Framingham data which included few diabetic subjects. This complicates the issue of which diabetic patients should be treated with statins in the primary prevention setting. The American College of Physicians offers a simplified version of this approach and suggests statins for primary prevention in patients with type 2 diabetes and other risk factors.

The high incidence of CHD within diabetic patients has led many to believe that diabetes should be considered

as a CHD risk equivalent, and therefore all patients should receive a statin. This is the approach taken by Adult Treatment Panel III in the US, and also the revised Joint British recommendations. These have yet to be published in full, but a summary is contained within recent British Hypertension Society guidelines, which recommend the use of statin therapy in all hypertensive patients with type 2 diabetes, as most are aged >50 years or have been diagnosed for 10 years and have a 10-year CHD risk equivalent to having had an MI. This approach will currently apply to most patients with type 2 diabetes, but will not include the rapidly increasing number of younger patients developing type 2 diabetes.

This is also the approach that is inferred indirectly in the new British general medical services contract, where a target cholesterol of less than 5.0 mmol/l is indicated for every diabetic patient. As the majority of patients will have a baseline total cholesterol above 5.0 mmol/l this implies the use of a cholesterol-lowering agent. It should not be forgotten, however, as described previously, that patients who have a baseline cholesterol below 5.0 mmol/l will also benefit. It is not clear at what age therapy should start, and the evidence for benefit in patients with type 1 diabetes is not strong. We believe a pragmatic approach for the time being is to treat all people with diabetes who would have been eligible for enrolment in HPS or CARDS, i.e. all diabetic patients over 40 years old, and to consider the use of statins in higher risk younger patients, e.g. smokers or those with hypertension.

The American College of Physicians offers useful practical advice and suggests that for patients with type 2 diabetes who are taking statins, routine monitoring of liver function tests or muscle enzymes is not recommended except in specific circumstances, e.g. if the patient has symptoms or is taking other drugs that interact with statins to increase the risk for adverse events, and we endorse that approach.

HIGHLIGHTS

- Patients with type 2 diabetes have a high prevalence of CHD.
- Trial evidence supports the use of statin therapy in all diabetic patients with previous cardiovascular disease.
- Current cardiovascular risk prediction tables should not be used to determine the use of statin therapy for primary prevention of cardiovascular disease in diabetic patients.
- Trial evidence supports the use of statin therapy in most diabetic patients for primary prevention of cardiovascular disease
- We recommend the use of simvastatin, pravastatin, or atorvastatin in all diabetic patients over the age of 40 years regardless of previous cardiovascular disease or pre-treatment cholesterol.

TABLE 3 Results of endpoints for all subjects and subjects with diabetes in the recent secondary prevention studies and primary prevention studies with statins.

Trial	Drug	Total subjects (n)	Diabetic subjects (n (%))	Primary endpoint (all)	Primary endpoint (diabetes)	Major coronary events (CHD death, non-fatal MI) (all)	Major coronary events (CHD death, non-fatal MI) (diabetes)	Comments
HPS	Simvastatin 40 mg	20,536	5,963 (29%)	Reduced total mortality from 15% to 13% Reduced fatal or non-fatal vascular events from 25% to 20%	Reduced fatal or non-fatal vascular events from 25% to 20%	Reduced from 12% to 9%	Reduced from 13% to 9%	Diabetes subgroup contains patients with known CHD, other vascular disease, or no cardiovascular disease
ALLHAT-LLA (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial Lipid Lowering Arm)	Pravastatin 40 mg	10,355	3,638 (35%)	No significant reduction in all-cause mortality	No significant reduction in all-cause mortality	No significant reduction	No significant reduction	Small difference in total cholesterol between groups, high rates of non-compliance in treatment group, high uptake of non-study statins in placebo group
ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm)	Atorvastatin 10 mg	10,305	2,532 (25%)	Reduced fatal CHD and non-fatal MI from 3.0% to 1.9%	No significant reduction	Primary endpoint	Primary endpoint	Low number of total CHD events in diabetes group, high use of open-label statins in diabetes placebo group
PROSPER (PROspective Study of Pravastatin in the Elderly at Risk)	Pravastatin 40 mg	5,804	623 (11%)	Reduced CHD death or non-fatal MI or fatal or non-fatal stroke from 16% to 14%	Higher rate of CHD death or non-fatal MI, or fatal or non-fatal stroke in treatment group (23%) vs placebo group (18%) (NS)	Reduced from 12% to 10%	Data not provided	
CARDS	Atorvastatin 10 mg	2,838	2,838 (100%)	Significant reduction in acute coronary heart disease event, coronary revascularisation, or stroke from 9% to 6%	All subjects had diabetes	Significant reduction from 5.5% to 3.6%	All subjects had diabetes	

FURTHER READING

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