Reducing cardiovascular risk in type 2 diabetes mellitus

David Preiss

Naveed Sattar

Abstract

The last decade has seen a radical change in our assumptions about the best ways to lower cardiovascular risk in patients with type 2 diabetes mellitus. In the past, considerable emphasis was placed on reduction of plasma glucose as the key to lowering cardiovascular risk and there were misplaced perceptions of benefit from aspirin in all patients. There is now overwhelming evidence that lowering cholesterol with statin therapy and lowering blood pressure with antihypertensive agents, at least to a systolic value of 130 mmHg, are the keys to success in achieving such benefits. Indeed, recent reductions in cardiovascular mortality in diabetes have largely been driven by greater use of statins and antihypertensive agents. Trial and meta-analytical evidence has shown that aspirin therapy for primary prevention of vascular events is unwarranted, intensive glucose lowering actually achieves limited reductions in cardiovascular events, and fibrate therapy has no clear effect upon vascular events in type 2 diabetes despite favourable changes in lipid subfractions.

Keywords cardiovascular risk; intensive glucose lowering; meta-analysis; randomized controlled trial; statin; type 2 diabetes

What's new?

- Lipid-lowering therapy: statins have been confirmed as the only effective class of agents; fibrate therapy and nicotinic acid have been shown to be ineffective in reducing cardiovascular events
- Glucose-lowering therapy: results from three important trials (ACCORD, ADVANCE, VADT) showed that intensive glucose lowering modestly reduces the incidence of myocardial infarction and major cardiovascular events, particularly in patients with type 2 diabetes and without overt vascular disease. However, the incidence of all-cause death and cardiovascular death appeared to rise (although this was not statistically significant) and the explanation for these divergent findings remains unknown. Numerous major trials are under way to assess the cardiovascular safety of new glucose-lowering agents, namely dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists and sodium glucose co-transporter 2 inhibitors
- Blood pressure-lowering therapy: meta-analyses have shown that blood pressure lowering reduces cardiovascular disease regardless of the agent used. However, ACCORD surprisingly found no further advantage in lowering systolic blood pressure below 120 mmHg
- Antiplatelet therapy: while it is well established that aspirin is effective for secondary prevention, any potential slight benefit achieved in primary prevention is probably matched by the risk of serious bleeding

Introduction

Morbidity and mortality in patients with type 2 diabetes mellitus are higher than in those without diabetes and this elevation in risk is especially marked in those with concomitant microalbuminuria or a history of cardiovascular events. Major modifiable cardiovascular risk factors in type 2 diabetes include smoking, dyslipidaemia, hypertension and, potentially, hyperglycaemia. Numerous large randomized trials have investigated the effect of agents that lower serum cholesterol, blood pressure or plasma glucose on cardiovascular outcomes and death. In addition, antiplatelet agents have been tested in primary and secondary prevention trials in diabetes. In this article, we will examine the relevant findings in these four key areas with particular focus on randomized controlled trials and meta-analyses of these trials.

Lipid-modifying therapy

Whereas most large trials of lipid-lowering agents have included mainly participants without diabetes, many of these trials have included sufficient numbers of patients with type 2 diabetes to allow data to be combined statistically in robust meta-analyses. A few important trials have been conducted specifically in participants with diabetes. Of the agents investigated in these studies, statins and fibrates have been examined more thoroughly than other agents. Statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) act by reducing cholesterol synthesis; the major effect of this inhibition is to increase low-density lipoprotein cholesterol (LDL-C) uptake by the liver with a resultant fall in circulating LDL-C. The mechanism of action of fibrates is not fully understood but they help to correct hypertriglyceridaemia and low high-density lipoprotein cholesterol (HDL-C), both of which are features of insulin resistance. Data have also emerged recently for nicotinic acid, a medicine that raises the concentration of HDL-C.

Statin therapy

The beneficial effect of statin therapy on cardiovascular outcomes in type 2 diabetes has mirrored those found in individuals without diabetes. The four published statin trials with the biggest populations of patients with diabetes have been the Heart Protection Study (HPS), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) and the Collaborative Atorvastatin Diabetes Study (CARDS). Of these, only CARDS was conducted specifically in patients with diabetes whereas the others included both diabetic and non-diabetic patients. In the Cholesterol Treatment Trialists' (CTT) meta-analysis of outcomes in over 18,000 patients with diabetes from all relevant statin trials, including the four noted

David Preiss *PhD MRCP FRCPath is a Clinical Senior Lecturer in Metabolic Medicine at the BHF Glasgow Cardiovascular Research Centre, University of Glasgow, UK. Competing interests: none declared.*

Naveed Sattar *PhD FRCPath FRCP FRSE is Professor of Metabolic Medicine at the BHF Glasgow Cardiovascular Research Centre, University of Glasgow, UK. Competing interests: I have consulted for AstraZeneca, BMS, Lilly, Boehringer Ingelheim, Sanofi and Amgen.*

above,[1] a 1-mmol/litre reduction in LDL-C reduced the combined endpoint of coronary heart disease (CHD) death and non-fatal myocardial infarction (MI) by 22% (hazard ratio [HR] 0.78; 99% confidence intervals [CI] 0.69–0.87), cardiovascular disease (CVD) events by 21% (HR 0.79; 99% CI 0.72–0.86), vascular death by 13% (HR 0.87; 99% CI 0.76–1.00) and all-cause death by 9% (HR 0.91; 99% CI 0.82–1.01) with no effect on non-vascular death. Similarly, coronary revascularization was reduced by 25% and stroke by 21%. The results are summarized in Figure 1. *Relative* benefits were similar in patients with and without pre-existing vascular disease and in those with and without a history of hypertension. Furthermore, benefits were similar in men and women, in various body mass index (BMI) categories, and in smokers and non-smokers. Accordingly, it is important to appreciate that the benefits of statin therapy are greater in *absolute* terms in those who are already at higher risk of cardiovascular events. For example, using data from the CTT meta-analysis, lowering LDL-C by 1 mmol/litre in 1000 patients with diabetes and existing baseline CVD (i.e. secondary prevention) over 5 years would reduce the number of major vascular events by 57, while treatment in patients with diabetes free of CVD at baseline (primary prevention) would lead to 36 fewer events. Of note, it was recently demonstrated that statin therapy slightly elevates the risk of developing diabetes.[2] It is not definitively known whether statin therapy has any detrimental effect on glycaemic control in those with established diabetes or on the intensity of therapy needed to maintain a certain level of glycaemic control.

Benefits of statin therapy per 1 mmol/litre reduction in LDL-cholesterol in patients with and without diabetes (from the Cholesterol Treatment Trialists' meta-analysis)

Major vascular event and prior diabetes	Treatment	Control	RR (CI)
Major coronary event			
Diabetes	776 (8.3%)	979 (10.5%)	0.78 (0.69–0.87)
No diabetes	2561 (7.2%)	3441 (9.6%)	0.77 (0.73–0.81)
Any major coronary event	**3337 (7.4%)**	**4420 (9.8%)**	**0.77 (0.74–0.80)**
Test for heterogeneity within subgroup: χ^2_1=0.1; p=0.8			
Coronary revascularization			
Diabetes	591 (5.2%)	627 (6.7%)	0.75 (0.64–0.88)
No diabetes	2129 (6.0%)	2807 (7.9%)	0.76 (0.72–0.81)
Any coronary revascularization	**2620 (5.8%)**	**3434 (7.6%)**	**0.76 (0.73–0.80)**
Test for heterogeneity within subgroup: χ^2_1=0.1; p=0.8			
Stroke			
Diabetes	407 (4.4%)	501 (5.4%)	0.79 (0.67–0.93)
No diabetes	933 (2.7%)	1116 (3.2%)	0.84 (0.76–0.93)
Any stroke	**1340 (3.0%)**	**1617 (3.7%)**	**0.83 (0.77–0.88)**
Test for heterogeneity within subgroup: χ^2_1=0.8; p=0.4			
Major vascular event			
Diabetes	1465 (15.6%)	1782 (19.2%)	0.79 (0.72–0.86)
No diabetes	4889 (13.7%)	6212 (17.4%)	0.79 (0.76–0.86)
Any major vascular event	**6354 (14.1%)**	**7994 (17.8%)**	**0.79 (0.77–0.81)**
Test for heterogeneity within subgroup: χ^2_1=0.8; p=0.4			

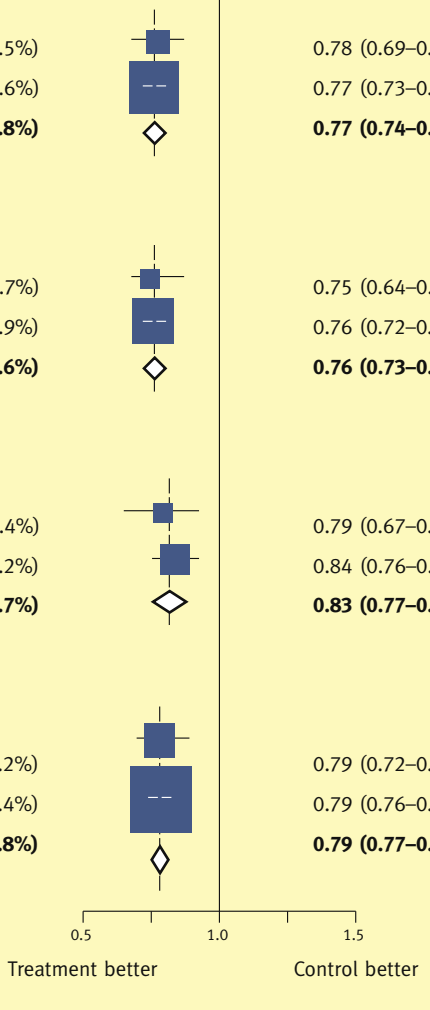

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Figure 1