OVERVIEW

Cardiovascular risk reduction in diabetes: underemphasised and overdue. Messages from major trials

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Diabetes markedly increases the risk of coronary artery disease and death, but is underrecognised as a cardiovascular risk factor, despite the existence of effective treatments. Because patients with diabetes are at high risk for coronary disease, they have more to gain from prevention. There is evidence from clinical trials that select cardiovascular therapies may work better in diabetes, beyond their expected benefit, and may prevent diabetes itself.

Diabetes more than doubles the risk of heart disease[1]. This increase is made more serious by figures showing that cardiovascular disease is already the most common cause of death in the general population. In the UK, 35% of all deaths are attributable to cardiovascular disease[2]; in people with type 2 diabetes this figure reaches almost 60%[3]. Myocardial infarction (MI) is the most common and the most costly complication in diabetes, as well as the number one cause of death. Despite this, doctors and patients apparently do not perceive diabetes to be a major risk for cardiovascular disease. Trials have identified a number of effective means of reducing cardiovascular complications in patients with diabetes. This article will highlight differences between diabetes and other known cardiovascular risk factors and, using examples from large trials, discuss why interventions:

- may be more important in diabetes
- work better in diabetes
- work beyond their expected benefit
- may prevent diabetes itself.

Differences between diabetes and other risk factors

There are several differences between diabetes and other well-acknowledged risk factors for cardiovascular disease, but perhaps the most important is the lack of prominence and import accorded to diabetes. The under-recognition of diabetes was admitted in 1997 by officials from the US National Institutes of Health who convened a special emphasis panel on the prevention and treatment of cardiovascular disease in diabetes. The panel concluded that:

> *much remains unknown about the way diabetes increases the risk for cardiovascular disease ... this area has been neglected relative to the intensive intervention studies of other major cardiovascular risk factors*[4].

As further evidence, patients with diabetes appear less likely to receive cardiovascular prevention. Aspirin reduces the risk for cardiovascular events in patients with diabetes, hypertension and coronary artery disease to a degree equivalent to other hypertensive patients[5], but rates of aspirin use for cardiovascular prophylaxis are poor. US national survey data show that only 32% of individuals with both diabetes and cardiovascular disease take aspirin[6]. Diabetic patients admitted for suspected MI are less likely to receive treatment with thrombolysis and aspirin[7], while diabetic patients discharged following MI are less likely to receive aspirin[8].

Diabetes and cardiovascular disease have been shown to be equivalent in terms of the risk increase for MI[9]. However, among over 15,000 patients enrolled in the MRC/BHF HPS only 7% of those with diabetes but without coronary artery disease reported taking aspirin compared to 77% of patients with coronary artery disease[10] (see end of text for explanation of trials). Aspirin trials for primary prevention in diabetes have not been performed, but there is no obvious reason to believe that aspirin would be less effective or lead to more unwanted effects in patients with diabetes. Fortunately, diabetes now appears to be gaining recognition in cardiovascular prevention guidelines[11].

The most obvious difference between diabetes and other risk factors for cardiovascular disease is that patients with diabetes are hyperglycaemic. Since diabetic individuals are also more likely to have higher blood pressure and dyslipidaemia[12], it has not been innately obvious whether hyperglycaemia *per se* is associated with cardiovascular complications. Recent data based on observational analyses of the UKPDS show that the degree of hyperglycaemia in patients with diabetes, as measured by glycated haemoglobin (HbA1c), is strongly associated with the rate of occurrence of MI[13]. Moreover, the associ-

ation, estimated to be a 16% increase in MI rate for each 1% increase in HbA1c, remains following adjustment for other risk factors, which takes into account the possibility that patients with poor glycaemic control might have a constellation of cardiovascular risk factors.

Better control, fewer complications

The knowledge that hyperglycaemia increases the risk of MI is of little practical value unless lowering blood glucose lowers the risk of cardiovascular complications. The UKPDS considered whether rates of complications were lower among newly diagnosed type 2 diabetic patients who achieved near normal glycaemia (defined as fasting plasma glucose values below 6.0 mmol/l) following randomisation to treatment with insulin or sulphonylurea, compared with patients randomised to conventional blood glucose control (defined as fasting plasma glucose levels below 15 mmol/l and achieved primarily through diet). At any given time during follow-up, patients allocated to intensive therapy were less likely to have had any diabetes-related complication. After a median 10 years follow-up, the difference in MI amounted to a risk reduction of 16% ($p = 0.052$)[14].

Some practitioners have interpreted this as a negative study and therefore do not advocate good glycaemic control as a means of reducing the risk of MI. They assume that the statistical convention of a p value less than or equal to 0.05 as a cut-off can be directly interpreted into clinical significance. Attention to the p value, a measure of the *strength* of the association, detracts from interpretation of the *magnitude* of the association, measured by the relative risk reduction which for MI was similar to observational analyses[13]. Not even Fisher, the originator of the concept, suggested that this cut-off be dogma, but wrote:

> *the evidence would have reached a point which may be called the verge of significance; for it is convenient to draw the line at about the level ... which we may call 5% ... would be indicated, though very roughly*[15].

However, the risk reduction and strength of the association for intensive treatment and microvascular disease (25% risk reduction, $p = 0.0099$) alone justify treatment of hyperglycaemia. Moreover, physicians cannot accurately predict which patients will develop macrovascular complications, microvascular complications, or both.

High priority for diabetes

Interventions that prevent heart disease are more important in diabetes than in its absence, based on the notion that patients with diabetes are at higher risk, and therefore have more to gain from preventive measures. For example, patients with diabetes might be expected to have an annual risk of heart disease of 2%, or 24% in 12 years, whereas a lower risk group might experience a 12% risk of heart disease in 12 years. It follows that an interventional therapy associated with a 25% risk reduction – comparable to the risk reduction associated with statins or angiotensin-converting enzyme (ACE) inhibitors for primary prevention of heart disease[16,17] – would prevent six of 100 patients with diabetes and three of 100 without diabetes having a cardiac event in 12 years. For the same reason, the higher the risk of disease the greater the cost-effectiveness[18]. By this logic, patients with diabetes have higher blood glucose values and are at greater risk, making any cardiovascular risk reduction more important.

Key Points

- **Among patients with diabetes, the greater the HbA1c, the greater the risk for cardiovascular disease; this relationship is independent of other cardiovascular risk factors**
- **Because patients with diabetes are at high risk for cardiovascular disease, effective interventions will prevent more myocardial infarctions amongst patients with diabetes than in lower risk patients**
- **Metformin is associated with a 39% risk reduction for myocardial infarction in overweight patients, suggesting that metformin does more than lower blood glucose**
- **Coronary angioplasty and bypass are equivalent treatments in patients without diabetes, while in patients with diabetes, coronary artery bypass is superior**
- **There is evidence that statins and ACE inhibitors may delay the onset of diabetes; current trials are addressing these questions**

Better than expected

Metformin

For a drug to prevent complications is desirable; for it to work beyond its expected benefit is a bonus. Among antidiabetic therapies, metformin appears to have this property in that it has been associated with a greater risk reduction for cardiovascular disease in type 2 diabetes than might have been anticipated. Evidence from the UKPDS showed that overweight patients with newly diagnosed type 2 diabetes randomised to intensive blood glucose control with metformin had a 39% risk reduction for MI relative to patients randomised to conventional blood glucose control[19]. Yet the patients on metformin had a median HbA1c only 0.6% lower than those allocated to conventional therapy. A 0.6% reduction in HbA1c would be expected to reduce the risk of MI by approximately 5–10%[13]. The confidence interval around the estimate of risk reduction for MI associated with metformin includes the possibility that the risk reduction is as low as 11% but also as great as 59%. One logical explanation for this large effect is that metformin does more than lower blood glucose. A prospective study noted favourable changes in lipids as well as in blood pressure[20]. The large risk reduction associated with MI makes the use of metformin economical. Indeed, its economic attractiveness extends beyond cost-effectiveness to cost-saving: that is, it is cheaper to pay for

treatment with metformin than for the complications which result in its absence[21].

There are currently no trial data of cardiovascular end-points using metformin in non-overweight patients with type 2 diabetes. Metformin is rarely associated with hypoglycaemia, its action being 'antihyperglycaemic' rather than 'hypoglycaemic'[22], so it is of potential use in patients with blood glucose readings that are elevated but not sufficiently high for the diagnosis of diabetes. It is conceivable that metformin could reduce the raised risk for heart disease in this group[23,24]. It is also possible that metformin will reduce the greater incidence of diabetes in subjects with impaired glucose tolerance[25], a question currently being evaluated in the DPP[26]. Metformin reduces insulin requirements in patients with type 1 diabetes[27]. An intriguing, but unaddressed, question is whether it might also reduce the increased risk of cardiovascular disease which accounts for 67% of deaths in patients with type 1 diabetes who live past the age of 40[28].

Beta-blockers and angiotensin-converting enzyme inhibitors

Based on UKPDS results, beta-blockers and ACE inhibitors are also associated with risk reductions for cardiovascular complications to a greater degree than would be expected from blood pressure lowering[29]. These complications include diabetes-related deaths (due mostly to cardiovascular disease), stroke and heart failure. In the UKPDS a 10 mmHg difference in systolic blood pressure between those randomised to less tight blood pressure control versus tight blood pressure control resulted in 56% and 44% risk reduction in heart failure and in stroke, respectively[30]. In the placebo-controlled HOPE trial, more modest differences in systolic blood pressure (2–3 mm Hg) following randomisation to ramipril were associated with a 25% risk reduction in cardiovascular end-points[17]. This result, and the fact that only 56% of the patients had hypertension, led the HOPE investigators to conclude that:

> *ramipril is most appropriately viewed for this study as a preventive intervention with multiple mechanisms of benefit, including lowering of blood pressure*[17].

It follows that many clinicians wonder whether all diabetic patients would benefit from ACE inhibition, or at least from ramipril. In support of this notion, subjects in HOPE appeared to be representative of diabetic patients in general in that they had at least one other risk factor for coronary artery disease, as do 98% of US patients in a national sample[6]. Since the UKPDS showed no difference between ACE inhibitors and beta-blockers[31], some clinicians opt for beta-blockers over ACE inhibitors for first-line therapy in hypertensive diabetic patients. However, as few patients remain on a single antihypertensive therapy[30], there is a good chance that patients will require both ACE inhibitors and beta-blockers. Moreover, ACE inhibitors, but not beta-blockers, appear to delay the occurrence of new proteinuria[32], in addition to slowing the course of existing proteinuria[33]. Current trials and meta-analyses will provide information about ACE inhibitors, angiotensin II antagonists, diuretics, calcium channel blockers and their relative merits[34].

Statins

Statins also appear to have benefits beyond their role in cholesterol lowering[35]. This is of particular importance for patients with diabetes who, in general, do not have elevated levels of cholesterol or low-density lipoprotein yet are at high risk for cardiovascular disease. Whether statins will reduce the risk of cardiovascular disease and death in patients with diabetes but without hypercholesterolaemia is addressed in trials currently underway[36]. The anti-atherosclerotic properties of statins are hypothesised to influence plaque and endothelial thrombogenicity, cellular migration into plaques, platelet reactivity, and coagulation[37].

Practical aspects of glycaemic control

Although the initial standard treatment for patients with type 2 diabetes is diet and exercise, the great majority require pharmacological therapy[38], most of them multiple therapies[39]. Dosage requirement increases over time for patients on insulin[14]. In the past, physicians stopped oral hypoglycaemic agents once a type 2 diabetic patient started insulin. The clinical implication of the apparent non-glycaemic related benefit of metformin means that overweight patients on insulin may benefit from the addition of metformin to their insulin regimen. Also of practical value in the management of glycaemia is the fact that patients on beta-blockers require more antidiabetic therapies than those not on beta-blockers[31]. Sulphonylurea leads to weight gain, and insulin to even more weight gain[14]. Thiazolidinediones have not yet been shown to reduce complications but their use is encouraged when alternatives fail as they are effective in lowering blood glucose[40,41].

The definition of a target HbA1c is of great appeal to practitioners, yet the definition of a target is far from easy. Ideally, there is a level of HbA1c below which the risk of diabetic complications falls markedly. This level would be an obvious target to guide patient care. However, there appears to be no threshold, and the risk of complications falls steadily with decreasing HbA1c. This implies that the lower the HbA1c level in individuals with diabetes, the lower the risk of cardiovascular complications. This relationship extends to the non-diabetic range. Recent data from Britain show that among non-diabetic individuals, lower HbA1c levels were associated with a lower risk of death[42]. Despite no obvious biological threshold, a HbA1c of below 6% is considered normal, and below 7% the goal in diabetes[43].

Better or unequal in diabetes?

There is an intriguing possibility that therapies to reduce cardiovascular risk may work better in diabetes. This deviates from the assumption that an intervention brings about a proportional risk reduction regardless of the baseline risk of

cardiovascular disease[16]. In contrast, the 4S, a simvastatin placebo-controlled, multicentre trial, raised the possibility that patients with coronary artery disease and diabetes may experience greater reduction from statins than patients without diabetes. Simvastatin was associated with 55% and 32% reductions in major coronary events in subjects with and without diabetes, respectively[44]. The subgroup of diabetic patients was small (n = 202), resulting in imprecise estimates which suggested, but did not prove, the possibility of a greater effect among diabetic patients.

To investigate whether a treatment works better in one or another subgroup is reasonable, but to be discouraged unless the analysis is specified a *priori*[45] because of the increased possibility of a chance finding, as in the case of treatment for MI and astrological sign[46]. Investigators may find it hard to resist performing subgroup analyses. Investigators in the VA-HIT wrote:

> *Although the study was not designed to have adequate power for subgroup analyses, we performed exploratory analyses in predefined subgroups*[47].

Two therapies may work equally well in patients without diabetes but unequally in patients with diabetes, as with coronary revascularisation. To define which coronary revascularisation procedure was associated with the lower mortality, the BARI trial enrolled 1,829 patients from 18 centres. All the patients had symptomatic multivessel coronary artery disease and 19% of them had diabetes. They were randomised to coronary angioplasty (percutaneous transluminal coronary angioplasty (PTCA)) or to coronary artery bypass grafting (CABG) as a first revascularisation procedure. Investigators had in advance specified a subgroup analysis of the diabetic patients in the protocol. Seven years following randomisation, an equivalent proportion (87%) of patients without diabetes was alive in each treatment group. However, among the diabetic patients, those randomised to CABG were more likely to be alive (76.4%) than those who underwent PTCA (55.7%) ($p = 0.0011$)[48]. There were similar findings in another trial[49]. In summary, while PTCA and CABG are reasonable alternatives in patients without diabetes, CABG appears superior in diabetic patients.

Prevention of diabetes with cardiovascular drugs

One way of preventing cardiovascular complications in diabetes is to prevent diabetes itself. A trial has recently shown that it is possible to prevent or delay diabetes with diet and exercise[50]. In addition, recent reports have associated the use of ACE inhibitors and statins with a lower risk of diabetes. In the HOPE trial patients randomised to ramipril had a 34% risk reduction for new diabetes (p <0.001)[17]. However, as diabetes was not a pre-defined study end-point it remains possible that patients randomised to placebo were incidentally diagnosed with diabetes because of their higher rate of cardiovascular events and hospitalisation. Prior evidence for a preventive role of ACE inhibitors and diabetes had been reported[51] which has compelled investigators to incorporate ramipril into a diabetes prevention trial, DREAM, which will include 4,000 individuals at high risk for diabetes.

Statins, too, may prevent diabetes. Secondary analysis of hypercholesterolaemic men in the WOSCOPS trial showed that randomisation to pravastatin was associated with a 30% risk reduction for new diabetes[52]. Hypothesised mechanisms include triglyceride lowering, anti-inflammatory effects, and improved endothelial function. Thus, in addition to their proven efficacy in preventing heart disease in patients with diabetes, ACE inhibitors and statins may in future be used to *prevent* diabetes.

Conclusions

Diabetes increases the already substantial risk of heart disease, yet this has not been accorded appropriate concern. Recent trials have provided evidence for the efficacy of preventive interventions for cardiovascular disease in diabetes. Drugs primarily aimed at lowering blood pressure, glucose or cholesterol have been shown to have multiple beneficial effects. It follows that patients with diabetes who have an elevated risk for cardiovascular disease, possibly even in the absence of hypertension, hyperglycaemia or hypercholesterolemia, may materially benefit from these drugs.

Trial acronyms

DPP	Diabetes Prevention Program
MRC/BHF HPS	Medical Research Council/British Heart Foundation Heart Protection Study
UKPDS	UK Prospective Diabetes Study
HOPE	Heart Outcomes Protection Evaluation
4S	Scandinavian Simvastatin Survival Study
VA-HIT	Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial
BARI	Bypass Angioplasty Revascularization Investigation
DREAM	Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications
WOSCOPS	West of Scotland Coronary Prevention Study

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