Is diabetes still a state of premature cardiovascular death?

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Abstract  
The association between diabetes and cardiovascular disease is now well accepted. For the Arnold Bloom lecture 2016 I described the great improvements in the management of cardiovascular disease that have occurred in the last 20 years in people with diabetes. Meta-analysis has shown reductions in microvascular and macrovascular complications with control of blood pressure, but there is still some uncertainty as to how low the target systolic blood pressure should be. Meta-analysis has also demonstrated that reductions in cholesterol decrease macrovascular complications, and larger doses of statins should be used in people with established atherosclerotic disease.

The initial results of intensive glycaemic control trials in diabetes did not demonstrate reductions in macrovascular outcomes during the study period, but long-term epidemiological follow up has shown long-lasting benefits. Follow up of DCCT and UKPDS has shown reductions in cardiovascular events and total mortality, and shorter follow up of VADT and ADVANCE has shown reductions in a composite of cardiovascular outcomes and end-stage renal disease respectively. Metformin, pioglitazone, empagliflozin and liraglutide have demonstrated specific effects, although use of pioglitazone is falling because of side effects.

Future reductions in cardiovascular events in people with diabetes can be anticipated if these beneficial antidiabetes drugs can be used more widely in appropriate patients.

Key words  
cardiovascular risk; intensive glycaemic control; empagliflozin; liraglutide

Introduction
Arnold Bloom’s contribution to diabetes care in the UK is celebrated in the Arnold Bloom lecture. Arnold was a consultant physician at the Whittington Hospital from 1952 to 1980. He was an active member of the British Diabetic Association (BDA), which later became Diabetes UK. His overall approach was essentially that of a teacher and clinician rather than an original research worker, but he also collaborated in several research trials. His qualities of humour, good nature and intelligence made him an ideal colleague and a splendid clinician.1

At a meeting of the BDA in 1996, I delivered a state-of-the-art lecture on heart disease and diabetes. Routine diabetes practice at that time was focused on glycaemic control and the prevention of microvascular complications. To increase awareness of macrovascular disease, I suggested that diabetes should be redefined as ‘a state of premature cardiovascular death, that may also be associated with blindness and renal failure’. I later featured this redefinition in a leader for a themed edition of Practical Diabetes on cardiovascular disease.2

For the 2016 Arnold Bloom lecture I revisited my presentation from 1996 and illustrated how the results of large randomised controlled trials and meta-analyses have transformed the cardiovascular prognosis for people with diabetes in the intervening 20 years.

Background
Twenty years ago I was concerned that heart disease in diabetes was a Cinderella sub-specialty. Diabetologists and diabetes research were focused on microvascular complications and pregnancy. Cardiologists and cardiac surgeons were sceptical that anything could be done to reduce cardiovascular events in people with diabetes, as outcomes appeared less satisfactory than in non-diabetic subjects. Furthermore, patients with diabetes were older, more overweight and had atypical symptoms.

The modern approach to cardiovascular risk and disease in diabetes now concerns all of these specialties, with important involvement from primary care and the person with
diabetes. Addressing cardiovascular risk factors, especially blood pressure (BP) and cholesterol, is now part of routine diabetes care. Cardiologists have realised that around one-third of patients with atherosclerotic vascular disease (myocardial infarction, stroke, peripheral arterial disease) or chronic heart failure (CHF) have diabetes, and one-third can be defined as pre-diabetic. Emergency percutaneous coronary interventions (PCIs) reduce mortality following acute coronary syndromes in people with diabetes, and as the relative risk reduction is similar to the non-diabetic population the absolute risk reduction is greater because of the higher event rate, so more lives are saved. Coronary artery bypass grafting is more effective than PCI for diabetic patients with triple vessel disease and stable coronary artery disease, and modern cardiac interventions such as implantable cardioverter defibrillators and cardiac resynchronisation therapy are all effective in patients with diabetes.3

Treatment of hypertension

Treatment of hypertension was the first intervention proven to reduce cardiovascular risk in people with diabetes. A recent systematic review and meta-analysis identified 45 trials that either reported diabetic subgroups or included only diabetic patients; 26 studies compared the addition of a BP lowering drug versus placebo, 17 compared different classes of drugs against each other, and seven compared BP lowering to different target levels.4 Forty trials, involving 100 554 participants, were judged to be at low risk of bias and were included in the analysis. Each 10mmHg reduction in BP was associated with significant reductions in microvascular and macrovascular outcomes, including heart failure and total mortality. Few differences were observed in the associations between the class of medication and the outcome, except that diuretics and angiotensin receptor blockers were better at reducing heart failure. No association was found between lower achieved BP levels and lower risk of cardiovascular events, and a linked editorial questioned how low to go when treating hypertension in patients with diabetes.5

How low to go with BP targets when treating hypertension in diabetes is an area of continuing uncertainty. As part of the ACCORD trial, half of the participants (n=4733) were allocated to a BP sub-study comparing intensive BP lowering (target systolic BP <120mmHg) versus standard treatment (target <140mmHg). No benefit was demonstrated in the primary endpoint of major adverse cardiovascular events (MACE), comprising cardiovascular death, non-fatal myocardial infarction, non-fatal stroke.6 There was a slight but statistically significant reduction in the secondary outcome of strokes, but side effects were more common in the intensive treatment group, with more hypotension, hyperkalaemia, and renal dysfunction.

SPRINT was a study comparing the same target BPs in 9361 non-diabetic subjects, and deliberately excluded people with known diabetes.7 SPRINT was halted early because of clear benefit in the primary outcome (a composite of acute coronary syndrome, stroke, heart failure and cardiovascular death) and total mortality. In retrospect, the ACCORD BP study may have been underpowered to show a difference, and in one of two accompanying editorials it was suggested that the results of SPRINT and ACCORD were generally consistent.8 Epidemiological follow up of the ACCORD BP study in ACCORDION may provide further information.

Treatment of lipids

Cholesterol lowering, particularly using statins, is also of clear and proven benefit in reducing cardiovascular risk in people with diabetes. A meta-analysis by the Cholesterol Treatment Trials’ (CTT) Collaborators published in 2008 included data from 18 686 patients with diabetes who had been included in 14 randomised trials of statin therapy.9 Each 1mmol reduction in LDL cholesterol was associated with significant reductions in major coronary events, strokes, cardiovascular death and total mortality. The proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease (secondary prevention) or not (primary prevention).

These findings were extended by CTT in 2010 by a meta-analysis of 26 randomised trials, including five trials comparing more versus less intensive statin therapy. High-dose statin treatment further reduced major coronary events, coronary revascularisations and strokes, and in the overall analysis the proportionate reduction was similar in people with diabetes.10

Most guidelines recommend that statin treatment is started in middle-aged people with diabetes, and that higher doses should be used in patients with established atherosclerotic disease. The diabetes meta-analysis included 1466 subjects who

Blood pressure key points

- Treatment of hypertension was the first intervention proven to reduce cardiovascular events in people with diabetes
- Blood pressure lowering in people with diabetes significantly reduces total mortality, coronary heart disease, stroke, heart failure, cardiovascular disease, retinopathy and albuminuria
- It is uncertain whether more intensive blood pressure lowering, with a target systolic blood pressure of less than 120mmHg is of any additional benefit in people with diabetes

Cholesterol key points

- Cholesterol lowering with statins is also proven to reduce cardiovascular disease in people with diabetes
- High-dose statins, e.g. atorvastatin 80mg, should be used in people with diagnosed atherosclerotic disease (coronary heart disease, cerebrovascular disease, peripheral arterial disease)
- It is uncertain when statin therapy should be started in younger patients

BP study in ACCORDION may provide further information.
were categorised as having type 1 diabetes, and the benefits were similar. An area of continuing debate and uncertainty is when to treat younger diabetic patients with statins. Expert opinion ranges from treating everyone with diabetes from teenage years, to avoiding statins below the age of 40 years unless there is existing vascular disease or high cardiovascular risk, e.g. persisting microalbuminuria.

### Does intensive glycaemic control reduce cardiovascular risk?

Faced with overwhelming evidence that treatment of hypertension and lipids reduce cardiovascular risk in people with diabetes, some have questioned whether a focus on intensive glycaemic control is warranted. The DCCT in people with type 1 diabetes, and VADT in people with type 2 diabetes all attempted to address whether intensive glycaemic control reduced cardiovascular events; the results are summarised in Table 1.

It is disappointing that no significant reduction in cardiovascular events was demonstrated at the end of the intervention in any of these studies, and ACCORD was stopped prematurely because of an increase in total mortality, particularly sudden cardiovascular deaths. These negative results, however, were not unexpected as blood glucose is a less important risk factor for the development of cardiovascular disease than hypertension or LDL cholesterol, so even if a wide separation in HbA1c could be safely obtained it would take a long time for cardiovascular benefit to accrue. A detailed description of ACCORD is beyond the scope of this review, and has previously been published in *Practical Diabetes*. Serious concerns with the intensive glycaemic treatment in that trial were the rapid escalation of therapies, the early use of large doses of insulin, massive weight gain and frequent hypoglycaemia.

At the end of these intervention studies the subjects returned to routine diabetes care. The clear reduction in microvascular events with intensive control was adopted into routine care so glycaemic control improved in the subjects who had been receiving conventional therapy. On the other hand, glycaemic control deteriorated outside the supported study environment in subjects who had previously been in the intensive control groups. Within one year of finishing the intervention study, HbA1c concentrations were similar in the two groups.

We are fortunate that longer-term epidemiological follow up has been performed in all of these studies, and a clear pattern of cardiovascular benefit has emerged (Table 2). In DCCT/EDIC we now have 30 years of total follow up, which has demonstrated reductions in cardiovascular events and total mortality with seven years of earlier intensive glycaemic treatment. In UKPDS, post trial monitoring with 20 years of total follow up has shown reductions in myocardial infarctions and total mortality. Shorter overall follow up of the VADT (10 years) has shown a significant reduction in the primary outcome of major cardiovascular events (heart attack, stroke, new or worsening congestive heart failure, amputation for ischaemic gangrene, or cardiovascular-related death). By contrast, follow up of the ADVANCE study in ADVANCE-ON demonstrated reductions in end-stage renal disease with 10 years of follow up, but no significant effect on cardiovascular events.

Even in the epidemiological follow up of ACCORD in ACCORDION, the excess increase in total mortality that was seen during 3.5 years of intensive treatment was reduced by returning to conventional control, so that there was no difference in total mortality after a total of nine years of follow up and the increase in cardiovascular deaths was obstained.

Collectively, the results of these studies confirm the long-term benefits of intensive glycemic control, with the exception of ACCORDION which showed no difference in total mortality compared to conventional control.

### Table 1. Results of studies of intensive glycaemic management on microvascular outcomes, macrovascular outcomes and total mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Effects on microvascular complications</th>
<th>Effect on macrovascular complications</th>
<th>Effect on total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>Reduced retinopathy, nephropathy, neuropathy</td>
<td>No effect on major cardiovascular and peripheral vascular events</td>
<td>No effect</td>
</tr>
<tr>
<td>UKPDS</td>
<td>Reduced microvascular endpoints</td>
<td>No effect on myocardial infarctions</td>
<td>No effect</td>
</tr>
<tr>
<td>ACCORD</td>
<td>Reduced retinopathy, nephropathy, neuropathy</td>
<td>No effect on major adverse cardiovascular events (MACE)</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Reduced nephropathy</td>
<td>No effect on MACE</td>
<td>No effect</td>
</tr>
<tr>
<td>VADT</td>
<td>Reduced albuminuria progression</td>
<td>No effect on major cardiovascular events</td>
<td>No effect</td>
</tr>
</tbody>
</table>

### Table 2. Results of epidemiologic follow up of studies of intensive glycaemic management on microvascular outcomes, macrovascular outcomes and total mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Effects on microvascular complications</th>
<th>Effects on macrovascular complications</th>
<th>Effect on total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT/EDIC</td>
<td>Reduced retinopathy, nephropathy, neuropathy</td>
<td>Reduced MACE</td>
<td>Reduced mortality</td>
</tr>
<tr>
<td>UKPDS-PTM</td>
<td>Reduced microvascular disease</td>
<td>Reduced myocardial infarctions</td>
<td>Reduced mortality</td>
</tr>
<tr>
<td>ACCORDION</td>
<td>Reduced retinopathy</td>
<td>No effect on MACE</td>
<td>No longer increased</td>
</tr>
<tr>
<td>ADVANCE-ON</td>
<td>Reduced end-stage renal disease</td>
<td>No effect on MACE</td>
<td>No effect</td>
</tr>
<tr>
<td>VADT</td>
<td>Not available</td>
<td>Reduced major cardiovascular events</td>
<td>No effect</td>
</tr>
</tbody>
</table>
of intensive glycaemic control in reducing cardiovascular events, and suggest that the method of obtaining intensive control should be based on the packages of care used in UKPDS, ADVANCE, and VADT, avoiding the aggressive approach that was devised for ACCORD.

Are there benefits of specific antidiabetic drugs? Metformin

Prior to the publication of the UKPDS in 1998, the mainstays of diabetes treatment were sulphonylureas and insulin. Metformin was not widely used because of concerns about the development of lactic acidosis. The data sheet for metformin from 1996 stated that it was contraindicated in heart failure and recent myocardial infarction, it should be used with caution in patients with angina, and it might possibly be used in patients with chronic stable heart failure.

Results of the small metformin subgroup in UKPDS, which included overweight patients with recently diagnosed diabetes and excluded patients with recent myocardial infarction or heart failure, demonstrated a significant reduction in myocardial infarctions and all-cause mortality.25 As this benefit was not demonstrated in larger groups treated with sulphonylureas or insulin, it was concluded that metformin was reducing cardiovascular events through mechanisms other than glucose lowering.

Support for the cardiovascular benefits of metformin comes from secondary outcomes from the Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME) study, and from the SPREAD-DIMCAD trial.26,27 For patients with CHF, epidemiological studies suggest a possible benefit in diabetic patients with CHF compared to other diabetes therapies, often sulphonylureas.28 There was an attempt to formally study metformin versus placebo in a randomised controlled trial in diabetic patients with CHF but this was halted because of futility.29 Current recommendations are that metformin can be used in patients with CHF but should be interrupted during episodes of acute heart failure, when the risk of hypoxia and lactic acidosis increases.

Metformin can be re-started once the acute failure has been treated.

Pioglitazone

PROactive was the first double-blind, placebo-controlled, randomised controlled trial to examine the effects of a specific antidiabetes drug, pioglitazone, on hard cardiovascular endpoints in patients with diabetes and existing atherosclerotic vascular disease.30 The results of the study were controversial. The main secondary endpoint of cardiovascular death, myocardial infarction and stroke was significantly reduced by pioglitazone, but the primary endpoint which included peripheral vascular events and interventions was not significantly reduced. Secondly, an increase in heart failure was seen with pioglitazone, and the mechanism of this increase was uncertain.

Further research on pioglitazone identified that glitazones increased renal retention of sodium and water, unmasking undiagnosed heart failure, and pioglitazone is contraindicated in patients with previous heart failure. Further large randomised controlled trials with glitazones identified an increase in fractures. Initially it was thought that the fractures were in small bones and only in women, but cohort studies have demonstrated increases in hip fractures and in men.31

The recent IRIS trial compared pioglitazone with placebo in non-diabetic patients with a recent stroke and markers of insulin resistance on HOMA-IR.32 Similar to PROactive there was a significant reduction in the composite primary outcome of fatal or non-fatal stroke or myocardial infarction. Careful collection of adverse events showed a significant increase in bone fractures requiring surgery or hospitalisation, as well as the expected increase in weight. It is unlikely that this proof of concept study will translate into clinical use because of these side effects. For people with diabetes there are now newer therapies that are not associated with weight gain, fluid retention or fractures, and the clinical role of pioglitazone is limited.

DPP-4 inhibitors

Following the rosiglitazone controversy, where rosiglitazone was suspected to be associated with an increase in non-fatal myocardial infarctions, all new non-insulin antidiabetes drugs have to demonstrate cardiovascular safety before receiving a licence from the FDA. This usually includes a placebo-controlled randomised control cardiovascular safety trial at either phase 3 or phase 4 of the development programme.

We now have the results of three cardiovascular safety trials with saxagliptin (SAVOR-TIMI),33 alogliptin (EXAMINE),34 and sitagliptin (TECOS).35 The results have been disappointing but not unexpected, as DPP-4 inhibitors have no significant effects on cardiovascular risk factors. All three showed neutral effects on the primary endpoint which

Metformin key cardiovascular points

- In the UKPDS trial, metformin reduced myocardial infarctions and total mortality in a small subgroup of overweight patients with recently diagnosed diabetes
- Support for cardiovascular benefit with metformin comes from the HOME and SPREAD-DIMCAD studies
- Metformin appears safe in patients without heart disease, in patients with coronary heart disease, following acute coronary syndromes, and with chronic heart failure

Pioglitazone key cardiovascular points

- In the PROactive trial, pioglitazone reduced a main secondary endpoint of cardiovascular death, myocardial infarction and stroke, but increased hospitalisation for heart failure
- Support for a reduction in atherosclerotic events with pioglitazone comes from studies of surrogate cardiovascular outcomes (intima-media thickness and intravascular ultrasound) and from a study in non-diabetic stroke patients
- The side-effect profile of pioglitazone, with an increase in weight, fluid retention, increased hospitalisation for heart failure, and increased fractures, limits the use of pioglitazone for cardiovascular protection in modern diabetes practice
Three large cardiovascular safety studies with sitagliptin, saxagliptin and alogliptin have shown neutrality, with no beneficial effect or harmful effect on major adverse cardiovascular events.

Saxagliptin increased hospitalisation for heart failure in the SAVOR-TIMI trial, but there was no increase in hospitalisation for heart failure with sitagliptin in the TECOS trial.

When choosing a DPP-4 inhibitor, sitagliptin is preferred for patients with existing cardiovascular disease or high cardiovascular risk.

In the EMPA-REG OUTCOME trial, empagliflozin reduced cardiovascular events, cardiovascular mortality, total mortality, and hospitalisation for heart failure in people with existing atherosclerotic vascular disease.

The use of empagliflozin should be considered in patients with existing cardiovascular disease, including patients on insulin, to improve glycaemic control and reduce cardiovascular events.

It is not known at present if this is a class effect, and further cardiovascular studies with other SGLT2 inhibitors will be completed over the next few years.

In the LEADER trial, liraglutide at full dose reduced cardiovascular events, cardiovascular mortality, and total mortality, but had no effect on hospitalisation for heart failure.

The use of liraglutide, at a dose of 1.8mg, should be considered in patients with longstanding diabetes and existing cardiovascular disease or high cardiovascular risk, to improve glycaemic control and reduce cardiovascular events.

No cardiovascular benefit was seen with lixisenatide in the ELIXA trial, and the results of studies with other available GLP-1 receptor agonists are awaited with interest.

was either MACE (SAVOR-TIMI, EXAMINE) or MACE plus hospitalisation for unstable angina (TECOS).

An unexpected finding was an increase in hospitalisation for heart failure in the saxagliptin group of SAVOR-TIMI. This was adjudicated blindly by an events adjudication committee, using a definition that has been used in heart failure studies. An increase in heart failure was also seen in a subgroup of subjects in EXAMINE, whereas sitagliptin had no effect on hospitalisation for heart failure in TECOS. DPP-4 inhibitors inhibit the breakdown of multiple peptides in addition to inhibiting breakdown of GLP-1, including peptides with cardiovascular effects such as brain natriuretic peptide. These non-GLP-1 effects may differ among the DPP-4 inhibitors, and further mechanistic studies are required. Two cardiovascular safety studies with lixinaglitin are comparing lixinaglitin with glimepiride (CAROLINA) and linaigliptin with placebo (CARMELINA). These will be analysed for atherosclerotic events in the primary outcomes and heart failure as secondary outcomes.

A once-weekly DPP-4 inhibitor, omari-gliptin, is phase 3 development, and the development programme included a large cardiovascular safety study (OMNEON-18). This study was recently halted by the manufacturer and omari-gliptin will not be marketed in the US or the EU.

Empagliflozin and SGLT2 inhibitors
The first completed cardiovascular safety study with an SGLT2 inhibitor was EMPA-REG OUTCOME, which compared empagliflozin with placebo in 7020 people with type 2 diabetes and existing atherosclerotic disease.

I described the results with enthusiasm in an editorial for Practical Diabetes and my enthusiasm has not diminished in the year since its presentation to applause at the EASD meeting in Stockholm.

Further publications have demonstrated reductions in events in patients both with and without heart failure at baseline and reductions in incident or worsening nephropathy and reductions of a post hoc composite renal outcome (doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease) have been added to the significant reductions in MACE, cardiovascular death, hospitalisation for heart failure, and total mortality.

There are now several hypotheses to explain the cardiovascular and renal benefits of empagliflozin, including metabolic explanations and haemodynamic explanations. Multiple mechanistic studies are underway.

The results of the cardiovascular safety studies with canagliflozin (CANA-VAS, CANAVAS-R) and dapagliflozin (DECLARE-TIMI) are eagerly awaited in 2017 and 2019, respectively.

Liraglutide and GLP-1 RAs
The first cardiovascular safety study with a GLP-1 receptor agonist (RA) was the ELIXA trial with lixinaglitin, and this was neutral, with no effect on the primary endpoint of MACE plus hospitalisation for unstable angina, or heart failure as a secondary endpoint.

The LEADER trial was the cardiovascular safety study with liraglutide, and the results were revealed shortly after the Arnold Bloom lecture. LEADER included subjects with established cardiovascular disease plus subjects with high cardiovascular risk. A significant reduction was demonstrated in MACE, cardiovascular mortality and total mortality. In contrast to EMPA-REG OUTCOME, there was no reduction in hospitalisation for heart failure. Again, the mechanisms of benefit are uncertain, but may include an effect on the progression of atherosclerosis; mechanistic studies are underway, and the results of cardiovascular studies with once-weekly GLP-1 RAs will be scrutinised in detail for atherosclerotic and heart failure outcomes.

Conclusions
Epidemiological studies from the Emerging Risk Factors Collaboration provided up-to-date information on the relative risk of vascular disease in people with diabetes compared to the non-diabetic population. Cardiac and stroke events, including cardiovascular death, were doubled, indicating that
diabetes remains a state of premature cardiovascular death. We should not be pessimistic about these findings, however, as older epidemiological data, e.g. from Framingham, demonstrated a four- to six-fold increase in vascular events. The reduction in excess cardiovascular risk can be attributed to the widespread prescribing of statins, treatment of hypertension, intensive control of glycaemia (mostly to reduce microvascular events) and cardiological interventions for established disease.

Future reductions in risk may come from greater use of high-dose statins and newer cholesterol-lowering therapies, lower targets for the control of hypertension, a broader acceptance of intensive glycaemic control to reduce cardiovascular events, and increasing use of modern anti-diabetes drugs with proven cardiovascular benefits, such as empagliflozin and liraglutide.

Future guidelines may start with metformin, add an SGLT2 inhibitor as second line, and then a GLP-1 RA as third line, with the additional benefits for the person with diabetes that all three are associated with reductions in weight.

Declaration of interests
Prof Fisher was an investigator in the HOPE, CARDS, ADVANCE, PROactive, and EXAMINE trials, and is currently an investigator in CANVAS. He has received payment for lecturing and advisory boards from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, MSD, Novo Nordisk, Novartis, Pfizer, Roche, Sanofi Aventis, and Takeda.

Prof Fisher supports full disclosure and his details are available on the ABPI database (https://abp-et-ag.s.emaec.crm.cegedim.com/Aggregate Spend360/Posting/ExpenseReport.aspx?postedreporttype=pCcrQFT-mU5SGXW6yEjsGDIHzD&Data Value=&q(WEIR12&LCID=2057).

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