Improving survival with metformin: the evidence base today

JHB Scarpello

SUMMARY
Establishing and maintaining control of glycaemia is a key step in the reduction of diabetic microvascular complications. By contrast, macrovascular disease which is the most important complication and shortens the lives of many people with type 2 diabetes is not reduced by glycaemic control alone. The landmark UK Prospective Diabetes Study (UKPDS) showed that intensive glycaemic management with metformin significantly reduced the risk of a range of debilitating and/or life-threatening macrovascular complications, compared with other oral agents, diet and insulin who achieved similar overall glycaemic control. The benefits observed included diabetes-related mortality (reduced by 42%, compared with diet treatment, p = 0.017), all-cause mortality (reduced by 36%, p = 0.011), myocardial infarction (reduced by 39%, p = 0.01), and any diabetes-related endpoint (reduced by 32%, p = 0.002). Other clinical and experimental studies have shown metformin to be associated with improved outcomes and support the conclusions from the UKPDS. In addition, a well-designed retrospective analysis has shown significantly lower mortality rates in patients receiving metformin compared with patients treated with sulphonylurea monotherapy. Metformin provides a greater degree of cardiovascular protection than would be expected from its antihyperglycaemic actions alone and is the first drug of choice for the treatment of type 2 diabetes unless there are contraindications in the individual patient.

Key-words: Metformin · Type 2 diabetes · Diabetic complications · Macrovascular · Microvascular.

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The ultimate goal of diabetes management is to prevent or delay the onset of diabetic complications. Most people with type 2 diabetes will ultimately die from a cardiovascular event, and reducing the risk of macrovascular complications holds the key to optimising clinical outcomes in this population [1]. Indeed, data from the Multiple Risk Factor Intervention Trial (MRFIT) showed that the onset of type 2 diabetes increased the risk of dying from a cardiovascular cause by about 3-fold, compared with non-diabetic individuals [2]. Moreover, MRFIT also showed that the level of cardiovascular risk increases more steeply with each additional risk factor for people with diabetes than for the normoglycaemic population. Analysis of the UK Prospective Diabetes Study (UKPDS) database further confirms the relationship between the presence of diabetes and an increased risk of adverse cardiovascular outcomes [3]. Haffner et al. [4] stated that developing diabetes conferred the same risk of premature cardiovascular death as having undergone a previous myocardial infarction in a non-diabetic individual although this risk is higher than that reported by Donnan et al. from the Diabetes Audit Research in Tayside Study [5]. Overall a patient diagnosed with type 2 diabetes in middle age can expect to lose as much as ten years of life [6].

The main analysis of the UKPDS has shown that establishing effective control of blood glucose through intensive glycaemic management with glibenclamide or insulin significantly reduced the incidence of microvascular complications, compared with less well controlled patients [7]. However, improved control of blood glucose per se did not reduce the incidence of macrovascular complications and there was no reduction in mortality. The UKPDS also included an evaluation of metformin, in comparison with diet-based treatment, in a subgroup of patients who were overweight at baseline [8]. By contrast with all the other therapies analysis showed that metformin significantly reduced the risk of macrovascular complications and premature mortality.

To date, metformin remains the only oral antidiabetic agent proven to reduce the risk of macrovascular complications in overweight type 2 diabetics. This review summarises the current evidence base for cardiovascular protection with metformin.

**Improved clinical outcomes with metformin in the UK Prospective Diabetes Study**

**Design of the UKPDS**

The UKPDS was a randomised comparison of the effects of intensive management of glycaemia, using oral antidiabetic agents or insulin, with those of a conventional management policy based on diet and exercise (provision of dietary advice at 3-monthly intervals). Patients eligible for the UKPDS were newly diagnosed with type 2 diabetes, and those entering the main randomisation group had a fasting plasma glucose concentration of 6.1-15.0 mmol/L (110-270 mg/dL) after 3 months of treatment with diet and exercise. Principal exclusion criteria included retinopathy which required laser treatment, heart failure, angina pectoris, renal dysfunction, malignant hypertension, recent myocardial infarction, or a history of more than one morbid vascular event.

The main analysis of the UKPDS included 4,209 patients, of whom 1,704 were considered to be overweight (> 120% of ideal body weight). Patients were randomly assigned to receive intensive glycaemic treatment with metformin, insulin or a sulphonylurea (glibenclamide or chlorpropamide), or to receive conventional glycaemic management with diet (Fig 1). Patients were followed-up for a median of 11.1 years for glycaemic indices, and a median of 10.0 years for clinical outcomes. A protocol amendment in 1990 led to a subgroup of patients (n = 537) who were receiving the maximum permitted dosage of a sulphonylurea, to be randomised to either...
continuation on sulphonylurea therapy or to the early addition of metformin [8]. The median follow-up for this analysis was 6.6 years.

Benefits beyond blood glucose control

Each of the active treatments initially reduced HbA1c in the first year (Fig 2). Despite careful and intensive management, since type 2 diabetes is a progressive condition, HbA1c increased steadily throughout the follow-up period in all arms of the study. Nevertheless, the intensive glycaemic groups maintained HbA1c at a lower level than the conventional, diet-based patients throughout the study.

The blood glucose-lowering efficacy of all intensive therapies was similar. However, clinical outcomes were superior in patients randomly assigned to metformin, compared with patients receiving other intensive therapies. Specifically, intensive glycaemic management with metformin, but not insulin or a sulphonylurea in comparison with the diet-treated group, was associated with statistically significant reductions in the risk of all-cause mortality (p = 0.011), diabetes-related mortality (p = 0.017), myocardial infarction (p = 0.01), and any endpoint related to diabetes (p = 0.002) (Table I). Thus, metformin provided greater protection against the development of macrovascular complications than would be expected from its effects upon glycaemic control alone.

A recent analysis from the UKPDS group [9] stratified patients according to their total daily dose of metformin (either the average dose during the trial or the dose at the time of a coronary event). The patients were analysed for different daily dosages (< 1,000 mg, 1,000-1,699 mg and 1,700 mg). A proportional hazards model adjusted for gender, ethnicity, lipids, body weight at baseline and blood pressure showed that there were no significant differences in the observed reduction in the risk of coronary artery disease between the three groups. This provides suggestive evidence that the cardiovascular benefits of metformin observed in the UKPDS may be independent of the dose of metformin. Thus patients maintained on lower dosages may still derive substantial cardiovascular benefit. Despite this, it should be emphasised that, in order to achieve best glycaemic control, the dose of metformin should be titrated to the maximum. Any gastrointestinal side effects are not proportionate to the dose and should not inhibit maximum prescription [10].

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Sulphonylurea/insulin</th>
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<tbody>
<tr>
<td></td>
<td>Mean change in risk*</td>
<td>p</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td>42%</td>
<td>0.017</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>36%</td>
<td>0.011</td>
</tr>
<tr>
<td>Any diabetes-related endpoint</td>
<td>32%</td>
<td>0.0023</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>39%</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>41%</td>
<td>0.13</td>
</tr>
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*Compared with conventional therapy based on diet/exercise in overweight patients.

Table I
Clinical outcomes in patients randomly assigned to intensive glycaemic management with metformin, or with a sulphonylurea or insulin, in the UK Prospective Diabetes Study [8].

Figure 2
Glycaemic control in overweight patients in the UK Prospective Diabetes Study [8].
Sub-study of early addition of metformin to a sulphonylurea

A sub-study of the UKPDS evaluated the effects of adding metformin to the regimens of 537 patients who remained hyperglycaemic despite receiving maximal dosages of monotherapy with a sulphonylurea [8]. This analysis showed an apparent excess of diabetes-related mortality in the patients who received the metformin-sulphonylurea combination, compared with a sulphonylurea alone (p = 0.039). Further analysis determined that the apparent excess mortality in the combination group was due to an unexpectedly low mortality rate in the sulphonylurea group, rather than from a true excess mortality in the combination group. A total of 14/269 patients receiving sulphonylurea alone in the sub-study died during 6.6 years of follow-up. Mortality rates from the sulphonylurea monotherapy group in the main UKPDS cohort suggested that 35 deaths would have been predicted for this number of patients and duration of follow-up (p = 0.001 for the difference). The figure exceeds the 26 deaths observed in the combination therapy group. As the UKPDS investigators stated in correspondence to the Lancet, the apparent excess mortality in the combination therapy group was due to “fewer than expected deaths in the sulphonylurea alone group rather than over representation in the sulphonylurea-metformin combined group” [11].

Additional clinical and experimental evidence for cardiovascular protection with metformin

Coronary protection studies

The UKPDS was a prospective, randomised study that was adequately powered to demonstrate the observed improvements in clinical outcomes with metformin. No other study of this magnitude is available for metformin or any other oral antidiabetic agent. However, other smaller clinical studies provide additional evidence to support metformin as conferring additional cardiovascular benefits.

The UKPDS was not designed as a primary prevention study and patients with a recent myocardial infarction or more than one morbid cardiovascular event were excluded. Sgambato et al. [12] had previously reported a 3-year study in 310 patients with ischaemic cardiomyopathy. They evaluated the effects of metformin on rate of reinfarction, and the rates of occurrence of angina pectoris, acute coronary events other than myocardial infarction, and death. This was not a purely diabetic population, although the great majority of patients were dysglycaemic, either through the presence of type 2 diabetes (34%) or impaired glucose tolerance (52%), with only 14% having normal glycaemic function. The incidence of all of the pre-specified outcomes was lower in the metformin group, compared with a control group of patients (Fig 3). The largest effect was on reinfarction rates, which were reduced from 8.9% in the control group to 1.6% in patients receiving metformin. A post-hoc statistical analysis (chi-squared) carried out on data presented in the paper showed that this effect was highly significant (p = 0.003). In addition, the observed reduction in the incidence of symptoms of angina almost achieved statistical significance (p = 0.051).

Patients with angina pectoris are at high risk of a morbid coronary event, and a reduction in the severity of myocardial ischaemia in these patients is likely to provide protection from a subsequent myocardial infarction. The effects of metformin were evaluated in 254 hyperlipidaemic patients, comprising a mixture of hyperglycaemic and normoglycaemic individuals, who were being screened for cardiovascular disease [13]. Within this population, a subgroup of 42 patients who were regular users of glyceryl trinitrate.
(GTN) for angina pectoris was identified, of whom approximately four patients in every five were able to discontinue nitrate use following 6 months of metformin treatment (Fig 4). The presence of ECG abnormalities suggestive of myocardial ischaemia was assessed at baseline and at the end of treatment, using the Minnesota code [14]. The incidence of class 4 ECG abnormalities (mainly T-wave inversions) was reduced by about two-thirds after 6 months of metformin treatment (Fig 4).

Further evidence is provided from an animal based study designed to evaluate the effects of metformin upon infarct size in rats [15]. The rats were treated with various doses of metformin or placebo for 2 days. The left coronary artery was then ligated under anaesthetic, and infarct size was measured after a further 2 days of treatment. The size of the infarct, measured as the proportion of the left ventricle, was significantly reduced in metformin-treated animals, relative to placebo (Fig 5). Despite the short duration of treatment in this study the effects upon infarct size achieved statistical significance and were effectively maximal at a dose of 30 mg/kg, which is comparable with the upper part of the dose range of metformin in man. These data suggest that a reduction in infarct size may contribute to improved outcomes following treatment with metformin. In man there are no published studies concerning the effectiveness of metformin at the time of acute myocardial infarction and at present evidence based treatment suggests the use of intravenous insulin as described by the DIGAMI protocol [16].

Figure 4
Reduced symptoms of cardiovascular disease in patients receiving metformin [13].

Figure 5
Reduction in infarct size with metformin in rats subjected to coronary artery ligation [15].
Vascular protection studies

Patients with type 2 diabetes are at high risk of peripheral vascular disease, due to the development of atherosclerosis in distal arteries. Furthermore, patients with vascular disease occurring anywhere in the body are considered to be at high risk of premature cardiovascular mortality and to require urgent intervention [17].

Intima-media thickening of the carotid artery is a risk factor for coronary death in patients with vascular disease [18]. Intima-media thickness was measured over a period of 3 years in patients receiving metformin plus a sulphonylurea (n = 20), or a sulphonylurea alone (n = 151; 100 glibenclamide and 51 gliclazide), with elevated thickness at baseline [19]. Progression of intima-media thickening was significantly lower in patients receiving metformin-based therapy (0.007 ± 0.068 mm/year), compared with gliclazide or glibenclamide (0.037 ± 0.048 and 0.056 ± 0.056 mm/year, respectively). The lower rate of intima-media thickening in the metformin group was achieved despite those patients having a significantly greater age and duration of diabetes at baseline.

Metformin improved peripheral arterial blood flow in a placebo-controlled crossover study of 15 patients with peripheral arterial disease [20]. Patients received either metformin or placebo for 6 months, and then the other medication for a further 6 months. Peripheral arterial blood flow was measured using quantitative strain-gauge plethysmography following a short period of ischaemia. Little change in arterial blood flow was evident in the placebo group during the first 6 months of treatment (Fig 6, left-hand panel). In contrast, in the metformin group arterial blood flow was improved by 17% after 3 months and by 40% after 6 months (p < 0.05 and p < 0.01 vs baseline, respectively). The beneficial effect of metformin declined when patients were crossed over to placebo for a further 6 months (Fig 6, right-hand panel), while significant improvements compared with baseline were again observed after 3 months (p < 0.05) and 6 months (p < 0.01) in the patients receiving metformin for the first time.

Beneficial changes in systemic haemodynamics may also contribute to the therapeutic profile of metformin. Twelve normotensive type 2 diabetic patients were randomised to receive either metformin (500-2,000 mg/day) or glibenclamide (2.5-20 mg/day) for 4 weeks, followed by crossover to the alternative treatment. Compared with glibenclamide, metformin significantly reduced erect diastolic blood pressure (−12.9% vs −6.8%, p < 0.01), the systemic vascular resistance index (−1.2% vs +6.2%, p < 0.05) and the systolic time interval (+1.7% vs +6.6%, p < 0.05). Total cholesterol was also reduced in the metformin group compared with the glibenclamide group (−0.7 vs −0.2 mmol/L, p < 0.05).

The formation of thrombus can precipitate the development of an ischaemic cardiovascular event. Using anaesthetised rats, Massad et al. [21] evaluated the antithrombotic potential of metformin in prevention of stroke. The vertebral artery was electrocauterised and 24 hours later electrodes were placed around the left common carotid artery. In control animals, application of a current to the carotid artery induced an endothelial lesion that resulted in thrombus formation, usually within 60 minutes. Metformin administered 4 days prior to the experiment increased the time to thrombus formation and was dose dependent, with statistical significance achieved at doses of 35 and 50 mg/kg. The magnitude of the effect achieved with metformin was similar to that achieved with the prostanoids, prostacyclin and iloprost, and greater than that observed with acetylsalicylic acid.

Observational analyses of clinical outcomes with metformin-based therapy

Retrospective analyses are by no means as authoritative as prospective, randomised studies, such as the UKPDS, but they may provide useful information as long as the limitations inherent to their designs are considered. For example, a retrospective analysis by Fisman et al. incorporated the medical records of 2,275 patients who were screened for, but not
enrolled in, a coronary prevention study, of whom about three-quarters had suffered a previous myocardial infarction [22]. It was found that age-adjusted coronary and all-cause mortality rates were lower in patients receiving diet-based treatment (16.2 and 39.5/1,000 patient-years, respectively) than in patients receiving monotherapy with metformin (30.0 and 55.7/1,000 patient-years) or a sulphonylurea (24.5 and 53.6/1,000 patient-years), or co-administered metformin and a sulphonylurea (31.2 and 75.8/1,000 patient-years) after 8 years of follow-up.

However, usual care for patients with type 2 diabetes most often involves initiation of therapy based on diet and exercise, followed by oral antidiabetic monotherapy, and then by oral antidiabetic combination therapy, with successive intensification of treatment occurring when glycaemic control is lost on the previous therapy. The risk of adverse outcomes in type 2 diabetic patients increases with the duration of diabetes [23], so that the outcomes in the retrospective study described above probably tell us more about the patients’ medical histories than the treatments under evaluation.

One advantage of retrospective analyses is that they facilitate the inclusion of data from large numbers of patients, over long-folllow-up periods. One analysis was based upon data from more than 4,000 Polish type 2 diabetic patients over a 26-year period, during which 1,455 patients received either metformin monotherapy or metformin and a sulphonylurea in combination [24]. Odds ratios relative to sulphonylurea alone, calculated using the Cox multiple regression model, were 0.7 [95% CI 0.6-0.9] for all-cause mortality, 0.7 [0.5-1.0] for death from coronary heart disease and 0.6 [0.4-0.9] for death from cerebrovascular disease. This study also included an evaluation of 1,164 patients receiving metformin-sulphonylurea combination therapy. There was no excess mortality in the combination group compared with sulphonylurea alone, as shown by the odds ratios (sulphonylurea = 1.0, as the reference group) for mortality from any cause (1.0 [0.9-1.1]), coronary heart disease (1.1 [0.9-1.3]), or cerebrovascular disease (0.9 [0.7-1.2]).

The results of this analysis conflict with those of Fisman et al., probably at least partly due to methodological differences between the studies. Only patients with diabetes duration of less than 10 years were included in the Polish analysis, which may help to reduce the effect of this confounding factor on the results, in contrast to the Fisman study, where the duration of diabetes was not reported. In addition, patients remained on the stated therapy throughout the 26 years of follow-up, while there is no information on treatment switches in the Fisman analysis. However, the possibility of differences between groups in the underlying severity of diabetes remains.

A further analysis included data from 8,866 patients who received a sulphonylurea, metformin, or sulphonylurea-metformin combination therapy only as first-line pharmacologic therapy [25]. Thus, the confounding effect of different diabetes durations for different treatment groups would be minimised in this analysis and its results may therefore be more reliable than the other retrospective studies. Once again, the odds ratios for all-cause and cardiovascular mortality were significantly lower for metformin, compared with sulphonylurea monotherapy (Table II).

Retrospective analyses must be treated with caution, due to potential difficulties in adjusting for differences between treatment groups, particularly with regard to the duration of diabetes, as described above. However, those analyses which made at least some attempts to limit differences in the duration of diabetes between treatment groups demonstrated improved patient outcomes with metformin, compared with other pharmacologic treatments.

### Conclusions

The UKPDS has shown that metformin exerts protective benefits upon the cardiovascular system of patients with type 2 diabetes above and beyond those expected from improved glycaemic control. These data are supported by the results of other clinical and retrospective studies which demonstrate improved clinical outcomes with metformin. The current evidence identifies metformin as the drug of first choice for inclusion in the antidiabetic regimens of patients in whom there are no contraindications to this oral agent.

### Table II

<table>
<thead>
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<th>All-cause mortality</th>
<th>Change in risk</th>
<th>Cardiovascular mortality</th>
<th>Change in risk</th>
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<tr>
<td>Sulphonylurea monotherapy (reference group)</td>
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<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Metformin monotherapy</td>
<td>0.60 (0.49-0.74)</td>
<td>▼ 40%</td>
<td>0.64 (0.49-0.84)</td>
<td>▼ 34%</td>
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<tr>
<td>Metformin-sulphonylurea in combination</td>
<td>0.66 (0.58-0.75)</td>
<td>▼ 40%</td>
<td>0.64 (0.54-0.77)</td>
<td>▼ 36%</td>
</tr>
</tbody>
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Odds ratios were generated using multivariate logistic regression and were adjusted for age, gender, concurrent disease and nitrate use.
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References