Metformin and vascular protection: a diabetologist’s view

AJ Garber

SUMMARY

The diabetologist’s short-term priority is often to gain rapid control of severe and symptomatic hyperglycaemia, with the longer term objective of preventing or delaying the onset of the debilitating and life-threatening complications that result from continued poor glycaemic control. Indeed, guidelines for the management of type 2 diabetes are centred firmly on measures of glycaemic control, based on evidence from the landmark UK Prospective Diabetes Study and Diabetes Control and Complications Trial. Nevertheless, we must remember that most type 2 diabetic patients ultimately die from a cardiovascular cause. A comprehensive approach is needed, where effective control of blood glucose takes place alongside aggressive management of cardiovascular risk factors. A substantial database of clinical evidence, including the ground-breaking UK Prospective Diabetes Study, underpins the place of metformin both as an effective oral antihyperglycaemic agent and for reducing the risk of morbid cardiovascular events.

Key-words: Type 2 diabetes · Metabolic syndrome · Glycaemic control · Cardiovascular risk factors.

Beyond blood glucose control

Uncontrolled severe hyperglycaemia can be a clinical emergency, with a high risk of coma and death. Even lower severities of hyperglycaemia may present with common and distressing symptoms, such as polyuria and polydipsia. As diabetologists, our initial priority for our type 2 diabetic patients is often to gain prompt control of blood glucose, to gain a rapid improvement in our patient’s well-being. In the longer term, sub-optimal glycaemic control leaves our patient at risk of a series of devastating microvascular complications that threaten to reduce both the quality and duration of his or her life. For example, in the USA, diabetes accounts for 35-40% of all new cases of end-stage renal disease and diabetic individuals represent the fastest-growing group of candidates for renal dialysis or transplantation [1, 2]. After 20 years of diabetes, retinopathy afflicts virtually patients with type 1 diabetes, and some two-thirds of all patients with type 2 diabetes [3]. These shocking statistics exclude other major causes of diabetes-related microvascular morbidity, such as diabetic neuropathy or diabetic foot. It is not surprising, then, that the diagnostic criteria for diabetes have been, and still are, centred firmly on measurements of blood glucose or HbA1c [4].

Two landmark trials, the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), conducted in patients with type 2 and type 1 diabetes, respectively, have proven beyond doubt that intensive glycaemic management with pharmacological intervention provides significantly greater protection against these complications than conventional treatment with diet and exercise alone. In the UKPDS [5], intensive glycaemic management with a sulphonylurea or insulin reduced the incidence of microvascular endpoints by 25% (p = 0.00099), compared with diet treatment alone. Intensive glycaemic management with insulin in the DCCT, compared with conventional therapy, reduced the risk of developing retinopathy by 75%, and reduced the risk of developing microalbuminuria or albuminuria by 39% and 54%, respectively [6]. The results of each of these landmark clinical trials have set a new standard for diabetes care, and have strongly influenced the development of guidelines and glycaemic targets for the management of diabetes [7, 8].

It is reasonable, then, to regard establishing control of the patient’s HbA1c and plasma glucose as an urgent clinical priority. Nevertheless, the burden of type 2 diabetes is by no means restricted to those complications that are associated most strongly with long-term hyperglycaemia. Recent years have provided much epidemiological data concerning the fate of patients with type 2 diabetes, and the message from these studies is clear and unequivocal: cardiovascular events, such as heart attacks and strokes, are the major cause of premature mortality among the type 2 diabetic population [9-11]. If we are to improve the overall clinical outcomes of type 2 diabetic patients, it will be necessary to take a holistic view of their management, where the aggressive management of glycaemia takes place within a framework of care that addresses their high risk of cardiovascular death.

These aims are not mutually exclusive. Intensive control of blood glucose, with an insulin secretagogue or with insulin itself, did provide some degree of protection from cardiovascular endpoints in the UKPDS [5]. For example, the reduction in the risk of myocardial infarction almost achieved statistical significance for intensive glycaemic control vs diet (p = 0.056). We should remember that the average difference in HbA1c between the intensive glycaemic management and diet therapy groups in the UKPDS was only 1%, and we are as yet unable to exclude the possibility that the study underestimated the true potential of correction of glycaemia for reducing the burden of cardiovascular mortality in type 2 diabetes [12]. An epidemiological analysis of the UKPDS data adds support to this view, as each and every 1% reduction in HbA1c was associated with a reduction in the risk of myocardial infarction or diabetes-related deaths of 14%, and 21%, respectively [13]. However, the UKPDS also showed that metformin was markedly more effective in improving macrovascular outcomes, with significant protection from myocardial infarction (risk reduction 39%, p = 0.01) and diabetes-related death (risk reduction 42%, p = 0.017) [14]. It is important to note that metformin is as effective as other classes of oral antidiabetic agents [15] and the quality of blood glucose control was essentially identical in patients randomly assigned to receive intensive glycaemic management with either metformin, or an insulin secretagogue or insulin. The UKPDS therefore proves beyond doubt that metformin provides cardiovascular protection above and beyond that available from tight glycaemic control.

Evidence base

An unparalleled database of clinical and experimental experience supports the use of metformin in the management of type 2 diabetes. Metformin has been available for clinical use in Europe since 1957, though we physicians in the USA have only been able to prescribe it since 1995. Despite being one of the longest-established oral antidiabetic agents available, it continues to inspire intensive biomedical research. Indeed, a search of the National Institutes of Health Medline database for “metformin” on 25 April 2003 provided more than 2,000 references. Few other pharmacological agents in clinical use, and none in the field of diabetes, are supported by such a solid evidence base.

One of the most striking features of metformin is the breadth of clinical mechanisms that may give rise to vascular protection [16]. Perhaps the most important is its amelioration of insulin resistance, which sits at the centre of the cluster of cardiovascular risk factors associated with the dysmetabolic syndrome. Insulin resistance is intimately connected with the process of atherosclerosis which leads
directly to coronary or cerebrovascular thrombosis, and cardiovascular death [17]. By reducing insulin resistance, metformin also reduces circulating insulin levels and blood glucose in parallel, and improves lipid metabolism, especially where these are abnormal before treatment [15]. Interestingly, these actually represent metformin’s indirect effects. Increasingly strong and well-researched evidence, including that presented within this collection of manuscripts, points to direct and potentially beneficial effects of metformin on the fibrinolytic system, the vascular endothelium, glycation of proteins, the structure of the blood vessel wall, and vascular redox balance. The net result is an improvement in each of a number of important functional cardiovascular parameters, concerned with optimising vascular structure and function before, and even after, the onset of ischaemia.

**Risk/benefit**

It is important to consider the overall risk/benefit ratio for metformin, as with any pharmacological agent. Metformin is not without side-effects [18], and the increased incidence of gastrointestinal adverse events (particularly diarrhoea) will be familiar to all who have prescribed this agent. However, these are usually minimised or avoided using slow titration of therapy or a reduction in dosage, and few patients discontinue treatment for this reason. A substantial minority of type 2 diabetic patients have contraindications to metformin, and it is essential that the contraindications are respected. Metformin-associated lactic acidosis is much discussed in the medical literature, but is actually extremely rare (3 cases/100,000 patient-years of treatment) when used according to its labelling [19]. Given the substantial protection from cardiovascular complications provided by metformin, discussed within this supplement, there is no doubt that the risk/benefit ratio for metformin is strongly positive when used either in the settings of primary or secondary prevention of cardiovascular events [20].

**Metformin: foundation therapy for type 2 diabetes**

In summary, maintaining effective control of blood glucose will remain high on the list of clinical priorities when designing therapeutic interventions for a patient with type 2 diabetes. However, we must look beyond blood glucose control, to implementing therapy that will provide the best overall outcome for our patients, particularly with regard to cardiovascular outcomes. A therapeutic regimen based on metformin is consistent with both of these objectives. The evidence base today strongly supports metformin as the foundation therapy for patients with type 2 diabetes.

**References**


