Metformin: drug of choice for the prevention of type 2 diabetes and cardiovascular complications in high-risk subjects

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SUMMARY

The timely series of state-of-the-art reviews contained within this supplement provide a valuable overview of the current state of diabetes care, and the pharmacological interventions we have available. Our experts agree that one of the most important lessons to emerge recently concerns the magnitude of the malign influence on clinical outcomes of the cardiovascular risk factors associated with the dysmetabolic (insulin resistance) syndrome. Metformin is unique in being not only as effective as any other oral antidiabetic therapy in controlling blood glucose, but also having an unparalleled clinical database relating to improved clinical outcomes in pre-diabetic subjects, and patients with established type 2 diabetes.

Key-words: Metformin · Type 2 diabetes · Cardiovascular disease.

Improving cardiovascular outcomes: the next frontier in type 2 diabetes care

There is no doubt that clinical and experimental research in the field of type 2 diabetes is moving forward at an unprecedented rate, with important new publications related to the epidemiology, pathophysiology and natural history of the disease appearing every month. For example, we know the magnitude of the coming type 2 diabetes epidemic, and we can be in no doubt that a greatly increased incidence of cardiovascular disease will be a major part of this challenge [1]. Moreover, we know that damage to the cardiovascular system usually begins years before we have the opportunity to diagnose type 2 diabetes. We often miss the crucial time window where a therapeutic intervention could deliver a real, long-term improvement to the patient’s clinical course thereafter.

Our responsibilities as healthcare professionals are clear. We need to do our utmost to both prevent the onset of type 2 diabetes by timely and aggressive intervention in the pre-diabetic state, and to improve the cardiovascular outlook for those patients who do progress to type 2 diabetes. Lifestyle modification as a means of improving prognosis is well supported by well-designed studies, and will be familiar to cardiologists and diabetologists alike. Such interventions provide the cornerstone of care in either field, and we routinely encourage our patients to take regular exercise, improve their diet, and to shed excess weight. Unfortunately, many type 2 diabetic patients find it extremely difficult to lose weight, and then to maintain the weight loss over a long period of time. We also know, therefore, that we will need alternative strategies for those patients, perhaps the majority, who will not or cannot change their lifestyles to the extent and duration required to prevent the onset of diabetes or cardiovascular diseases.

Addressing cardiovascular risk factors

Controlling blood glucose *per se* is important, but is unlikely to prove sufficient by itself to reverse the rising tide of type 2 diabetes and cardiovascular diseases [2]. An alternative approach focuses on the individual cardiovascular risk factors of the dysmetabolic syndrome (Table I), for example prescribing aspirin, antihypertensive agents or lipid-lowering drugs. Here, we should remember the central role of insulin resistance in the genesis of the dysmetabolic syndrome, impaired glucose tolerance and type 2 diabetes (Fig 1). Metformin improves glycaemia in type 2 diabetes mainly by reducing insulin resistance in skeletal muscle and the liver, and improves clinical outcomes in type 2 diabetic patients by more than would be expected from improved blood glucose control alone. This raises the intriguing hypothesis that much of the proven protection from microvascular and macrovascular complications with metformin may ultimately arise via this central mechanism.

Certainly, our expert reviewers have identified beneficial effects of metformin on weight and body fat composition, lipid profiles, hyperinsulinaemia, and fibrinolysis and coagulation. These effects are consistent with a general improvement in metabolic function and may contribute to an overall lowering of cardiovascular risk in subjects at high risk of a morbid cardiovascular event. In addition, experimental and, in some cases, clinical evidence points to direct and potentially beneficial actions of metformin on the process of atherosclerosis, the microcirculation, the phenomenon of programmed cell death and the interaction of sugar molecules with the amino acid side-chains within proteins in the blood vessel wall. Some of these actions are independent of insulin and are thus completely separate mechanisms from the primary effects of metformin on insulin-mediated glucose metabolism.

These observations render metformin unique. No other pharmacological agent has such a broad range of mechanisms for improving the function of the endocrine and cardiovascular systems, and no other agent has been proven to improve clinical outcomes in type 2 diabetes. We live in an age of evidence-based medicine, and the therapeutic profile of metformin identifies this agent as the treatment of choice for diabetes prevention and for the prevention of cardiovascular complications in patients with type 2 diabetes.

### Table I

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Approximate incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
<td>90%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80%</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>70%</td>
</tr>
<tr>
<td>HbA1C &gt; 6.5%</td>
<td>80%</td>
</tr>
<tr>
<td>HbA1C &gt;7.0%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Figure 1

Insulin resistance: causes and associated diseases.

**References**