Metformin: an agent of minimal harm and maximal benefit in type 2 diabetes?

Peter Burrill takes a rational look at the evidence base for metformin use in type 2 diabetes. He finds evidence to show it can provide clinically important benefits to these patients, both by controlling blood glucose and by reducing all cause mortality. Indeed, metformin appears to provide a greater degree of cardiovascular protection than might be predicted from its antihyperglycaemic actions alone. In the face of such good clinical evidence Peter Burrill asks: 'How can we maximise the use of 'stormin' metformin?'

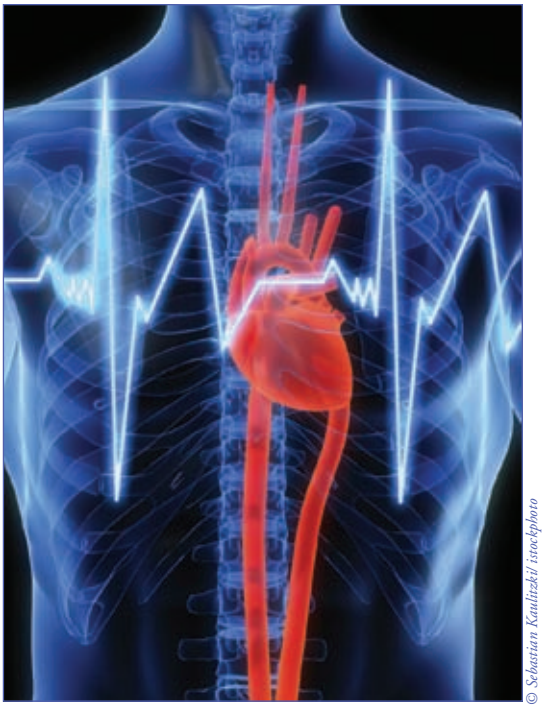
The UK prospective diabetes study (UKPDS) showed that metformin was associated with reduced all cause mortality regardless of the degree of glucose control — something not seen in patients treated with sulphonylureas or with insulin.[1] This is not to say that control of blood glucose is not important for control of symptoms, simply that to provide greatest benefit to patients with type 2 diabetes we need to maximise the use of metformin.

This includes explaining to patients the pros of taking metformin and building up the dose slowly to avoid gastrointestinal (GI) upsets, which can cause patients to give up. Use of the modified release preparation may also help. Despite the evidence base for the benefits of metformin, concerns remain about its side-effects and especially about the perceived risk of lactic acidosis in the presence of renal, hepatic, respiratory or cardiac failure. Perhaps as a result of this, some patients with type 2 diabetes are denied metformin treatment.

Should we use metformin as first-line agent?

A recent systematic review has compared the effectiveness and safety of oral medications for type 2 diabetes.[2] The authors considered 216 controlled trials and cohort studies and two systematic reviews that addressed benefits and harms of using metformin.

The strength of evidence was moderate-to-high that most oral agents — such as metformin, glitazones and repaglinide — improved glycaemic control to the same degree as sulphonylureas, producing a decrease in glycosylated haemoglobin (HbA1c) levels of about 1%. Nateglinide and acarbose may have slightly weaker effects on HbA1c levels on the basis of indirect comparisons of placebo-controlled trials. There was moderate evidence that most agents, other than metformin, increased body weight by about 1kg to 5 kg. Metformin had no effect on body weight in placebo-controlled trials.



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Can metformin be used in patients with cardiac failure? Decisions should be based upon each patient's assessed risk

Glitazones were associated with adverse effects on low density lipoprotein cholesterol (LDL-C) levels and higher risk for congestive heart failure, with an absolute risk of 1% to 3% (NNH of 33 to 100). The review did not find evidence of an elevated risk for lactic acidosis in patients taking metformin compared with other oral diabetes agents. The authors comment that the evidence for metformin-induced lactic acidosis stems mainly from about 300 case reports and most reported cases were

associated with severe underlying illnesses. They stated: 'We suspect that apparent cases of 'metformin-induced lactic acidosis' may have been over reported. However, we could not rule out the possibility that metformin conferred additional risk in the presence of severe underlying cardiac or renal disease'.[2]

Metformin has the best benefit to risk profile

The authors concluded that metformin has the best profile of benefit to risk and should be initial pharmacotherapy for type 2 diabetes. Second-generation sulphonylureas also fared well against other agents, apart from the increased risk for hypoglycaemia. The second-generation sulphonylureas remain an alternative as second-line therapy.[2] The study authors commented: 'Compared with newer agents, metformin and second-generation sulphonylureas share three additional advantages: lower cost, longer use in practice, and more intensive scrutiny in long-term trials with clinically relevant end points'.[2]

Which hypoglycaemic agents can be used in people with heart failure?

Another systematic review examined the relationship between antidiabetic treatment and outcomes in people with heart failure and diabetes.[3] Eight studies were included in the review.

Insulin use

Three of four studies found that insulin use was associated with increased risk for all cause mortality, but the authors comment that it is difficult to tell whether this is a true adverse effect of insulin or whether it is confounding by indication.[3]

Metformin use

Metformin was associated with significantly reduced all cause mortality in two studies and a similar trend was seen in a third. Metformin was not associated with increased hospital admission for any cause or for heart failure specifically. No study found an increase in adverse events with metformin and the results of both studies that evaluated all cause hospital admissions in metformin users suggested that it is associated with a lower rate than other antidiabetic drugs.[3]

Glitazone use

The pooled effect of four studies that assessed the effect of glitazones on all cause mortality suggested that treatment may be associated with reduced all cause mortality. However, glitazones were associated with increased risk of hospital admission for heart failure.

The authors concluded that of the current antidiabetic agents, metformin is the only one not associated with any measurable harm in people with diabetes and heart failure and is associated with reduced mortality.

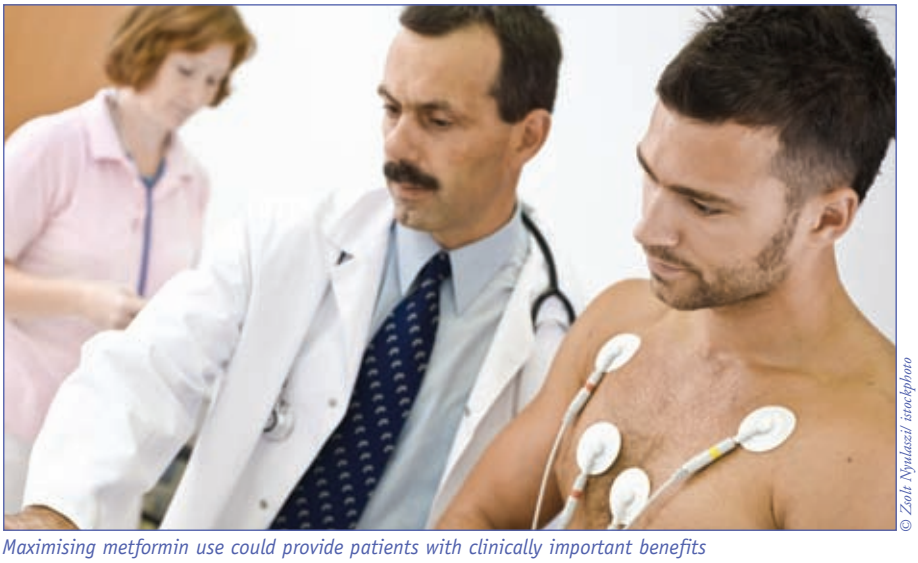
Does metformin cause lactic acidosis?

While there is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis if prescribed under study conditions, concerns remain about its possible side-effects and especially the perceived risk of lactic acidosis if used in the presence of renal, hepatic, respiratory, or cardiac failure. Perhaps as a result of this, some patients with type 2 diabetes are denied metformin treatment.

An increasing body of evidence challenges the so-called 'contraindications' to metformin. Indeed, a recent review[4] asked the question: 'Metformin, heart failure and lactic acidosis: is metformin absolutely contraindicated?' Most of the evidence for the association between metformin and lactic acidosis is historical data for phenformin, which was withdrawn in 1977. Metformin and phenformin have different pharmacological characteristics that could explain the much lower incidence of lactic acidosis with metformin.

> Treatment with metformin is not absolutely contraindicated in patients who have isolated heart failure, and it may be beneficial.

Several reports found that physicians have increasingly ignored contraindications to prescribing metformin and yet the incidence of lactic acidosis has remained very low. A study in Scotland found that 24.5% of patients receiving metformin had contraindications to its use, including myocardial infarction (MI), cardiac failure, renal impairment, or chronic renal disease. Despite this, only one episode of lactic acidosis occurred in 4600 patient years, and this was in a 72-year-old patient with acute MI complicated by acute renal failure. It was estimated that between 2 and 9 cases per 100,000 patients-years would be the expected rate of lactic acidosis in people



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Maximising metformin use could provide patients with clinically important benefits

> An increasing body of evidence suggests that metformin treatment alone will not result in lactic acidosis unless other contributing factors coexist.

with type 2 diabetes not receiving metformin. Another study found that 73% of metformin treated patients had at least one contraindication to its use. Nonetheless, no cases of lactic acidosis were seen.[4] The evidence from these reports reinforces the viewpoint that metformin is an extremely rare cause of lactic acidosis in patients with type 2 diabetes, even in the presence of contraindications including renal, hepatic, and cardiac failure.

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Patients with contraindications to the use of metformin have been treated without succumbing to lactic acidosis

The authors make the following conclusions:[4] 'an increasing body of evidence suggests that metformin treatment alone will not result in lactic acidosis unless other contributing factors coexist. More importantly, treatment with metformin is not absolutely contraindicated in patients who have isolated heart failure, and it may be beneficial. The risk of lactic acidosis due to metformin is negligible in these patients and is unrelated to the plasma concentration of metformin. The presence of other organ failure, such as renal failure, in addition to heart failure might pose a risk of lactic acidosis. Metformin provides a greater degree of cardiovascular protection than would be expected from its anti-hyperglycaemic actions alone and is the first drug of choice for the treatment of type 2 diabetes. The decision to stop or continue metformin in the presence of heart failure should be individualised to the particular patient until further evidence is available'.

Declaration of competing interests
The author declares that he has no competing interests.

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