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Metformin therapy and clinical uses

JOHN HB SCARPELLO, HARRY CS HOWLETT

Abstract

Metformin is now established as a first-line antidiabetic therapy for the management of type 2 diabetes. Its early use in treatment algorithms is supported by lack of weight gain, low risk of hypoglycaemia and its mode of action to counter insulin resistance. The drug's anti-atherosclerotic and cardio-protective effects have recently been confirmed in prospective and retrospective studies, and appear to reflect a collection of glucose-independent effects on the vascular endothelium, suppressant effects on glycation, oxidative stress and formation of adhesion molecules, stimulation of fibrinolysis and favourable effects on the lipid profile. Although avoidance of troublesome gastrointestinal tolerability issues requires careful dose titration, the risk of serious adverse events is considered low provided that contra-indications (especially with respect to renal function) are observed. As many of its actions go beyond glucose lowering, emerging evidence indicates potential benefits in other insulin-resistant states and possibly tumour suppression.

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Key words: cardiovascular protection, insulin resistance, metformin, type 2 diabetes.

Antihyperglycaemic mechanisms of metformin

The blood glucose-lowering actions of metformin result primarily from an amelioration of insulin resistance, mainly in liver and muscle, with a lesser effect in adipose tissue.¹ Within the liver, the principal effect of metformin is a reduction in hepatic glucose output, largely due to a reduction in the rate of gluconeogenesis and a small effect upon glycogenolysis (figure 1).^{1–4} The increase in peripheral glucose disposal of about 20–30% observed after metformin administration arises largely through increased non-oxidative glucose disposal into skeletal muscle.^{1,3,5} Since improved insulin sensitivity can indirectly enhance β -cell function through reduced glucotoxicity, metformin has been shown to improve β -cell function in some type 2 diabetic patients.⁶

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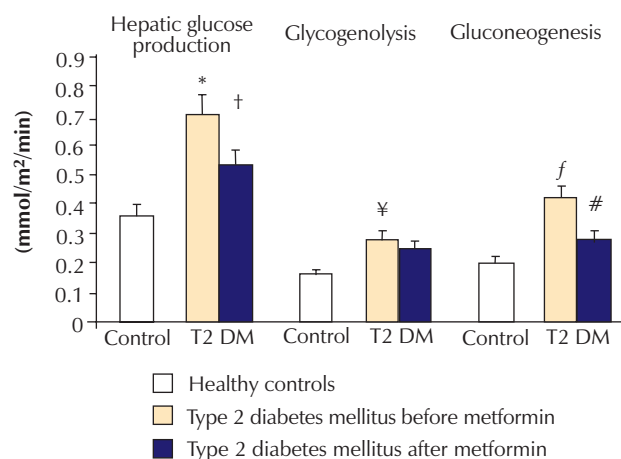
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Figure 1. Effects of three months of treatment with metformin on hepatic glucose output in seven subjects with type 2 diabetes and in seven healthy control subjects matched for gender, age and body mass index



Key: * $p < 0.0001$ vs. controls; † $p = 0.0009$ vs. pre-metformin; ‡ $p = 0.0002$ vs. controls; ^f $p = 0.0005$ vs. controls; [#] $p = 0.0002$ vs. pre-metformin

Adapted with permission from Giannarelli R, Aragona M, Coppelli A, Del Prato S. Reducing insulin resistance with metformin: the evidence today. *Diabetes Metab* 2003;29:6S28–6S35

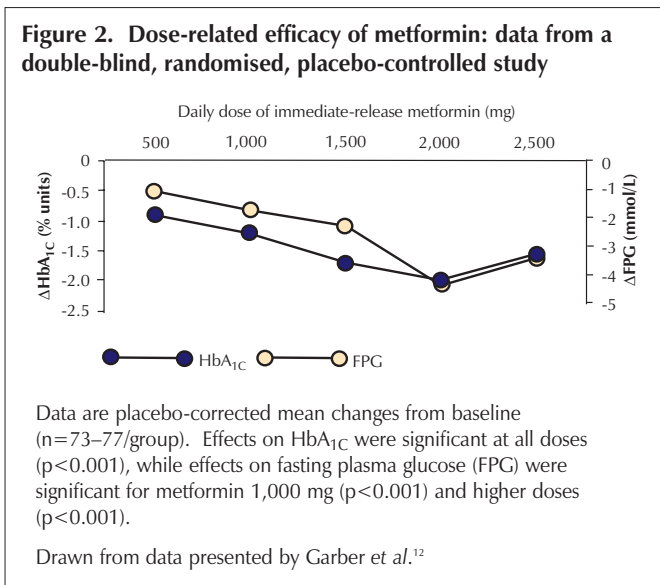
Beneficial effects of metformin have also been observed in adipose tissue (reduced fatty acid oxidation),⁷ and in the activation of the enzyme adenosine monophosphate (AMP) kinase to increase glucose transporter (GLUT4) translocation in muscle and fat, and reduce gluconeogenesis in liver.^{8,9}

Recent reports suggest that increases in the circulating concentration of glucagon-like peptide-1 (GLP-1) may contribute to the metabolic effects of metformin.^{10,11} This might arise from increased secretion of GLP-1, possibly due to greater glucose absorption in more distal segments of the small intestine where the GLP-1 secreting L-cells are more abundant. Metformin does not appear to inhibit the enzyme dipeptidyl peptidase-4 (DPP-4).¹¹

Antihyperglycaemic efficacy of metformin

Dose-related efficacy

Since metformin has little effect upon blood glucose in normoglycaemic states, metformin is better termed 'antihyperglycaemic' rather than 'hypoglycaemic'. The glucose-lowering efficacy of metformin in type 2 diabetes is dose-related across most of its dosage range (up to 2,500–3,000 mg/day).^{12–15} About 2,000 mg/day may represent the optimal dose for many patients (figure 2).¹² The beneficial cardiovascular effects of metformin observed in the UK Prospective



Diabetes Study (UKPDS; see below) were obtained at a median daily metformin dosage of 2,550 mg, as this study set out to determine the benefits of intensive glycaemic management.¹⁶ However, patients receiving lower doses of metformin appeared to derive cardiovascular benefit.¹⁷

Comparison with other oral antidiabetic agents

The long-term glucose-lowering efficacy of metformin is comparable to that of other first-line antidiabetic therapies, as illustrated in the UKPDS and other studies.^{18–19} Metformin has shown greater antihyperglycaemic efficacy than α -glucosidase inhibitors^{20–22} and DPP-4 inhibitors^{23–24} when given as monotherapy.

Metformin may have similar or greater antihyperglycaemic efficacy compared to a thiazolidinedione in drug-naïve type 2 patients during the first 1–2 years of therapy.²⁵ Longer-term follow-up in the ADOPT (A Diabetes Outcomes Progression Trial) trial showed a lower fasting plasma glucose (FPG) and lower mean glycosylated haemoglobin (HbA_{1c}) in patients receiving rosiglitazone, although the proportion of patients achieving a glycaemic target of HbA_{1c} < 7.0% was similar in the metformin- and rosiglitazone-treated groups.^{26,27} A likely factor contributing to glycaemic control in this study was the differential weight change between the two treatments, with a net difference of 6.9 kg in favour of metformin.

Metformin in combination

The glucose-lowering extent of metformin is additive when used in combination with a sulphonylurea,^{28–34} a meglitinide,³⁵ a thiazolidinedione^{36–45} or an α -glucosidase inhibitor.^{20,46–48} A one-year study demonstrated equivalent antihyperglycaemic efficacy with a metformin-sulphonylurea combination compared with a pioglitazone-sulphonylurea combination in patients inadequately controlled on a sulphonylurea alone.⁴⁹ The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study demonstrated a greater reduction of HbA_{1c} with metformin (n=272) compared with rosiglitazone (n=301), when added

to maximal sulphonylurea therapy for 18 months (mean treatment difference 0.06% [95% CI -0.09 to 0.20]).⁵⁰ Improved glycaemic control has been observed with regimens involving combinations of metformin and the GLP-1 analogues, exenatide^{51–58} and liraglutide,^{59,60} or the DPP-4 inhibitors, vildagliptin^{61,62} or sitagliptin.^{26,63–66} The additive antihyperglycaemic efficacy of these combinations relates to different cellular modes of action of metformin compared with each of the other classes of agents.

Consistent with the insulin-sparing effects of metformin, the addition of metformin to insulin-based regimens improved glycaemic control, reduced insulin requirements, limited increases in body weight, and reduced the incidence of hypoglycaemia.^{67,68}

Efficacy in special populations

Weight

Metformin is widely recognised to have either little effect on body weight or to facilitate modest weight loss in type 2 diabetes.⁶⁹ There is no major effect of obesity status on the antihyperglycaemic effect of metformin but a slightly larger glucose-lowering effect of metformin has been observed as body mass index (BMI) decreases.⁷⁰ The magnitude of the reduction in HbA_{1c} following metformin decreased by 0.08% units for each increase in BMI of 5 kg/m². A post-hoc analysis of an evaluation of metformin in patients who were hyperglycaemic despite diet and exercise showed that the effect of metformin was similar in patients with BMI values ≥ 28 kg/m² or < 28 kg/m², whether given alone (mean changes -1.1% and -1.0%, respectively) or added to a sulphonylurea (mean changes 1.4–1.6% and 1.5–1.7%, respectively).⁷¹ Thus, body weight should not unduly influence the decision whether to prescribe metformin.

Age

Increasing age does not appear to modify the therapeutic profile of metformin in adult type 2 diabetes patients but the normal decline in renal function in the elderly can affect their suitability for treatment with metformin.^{71,72} Regarding type 2 diabetes in children and adolescents, double-blind, randomised studies have shown that the efficacy and tolerability of metformin in paediatric type 2 diabetes patients (aged 10–16 years) are similar to adults.^{73,74} Thus, metformin is indicated as monotherapy or in combination with insulin in patients aged 10 years or above in Europe, and as monotherapy in type 2 diabetic patients aged ≥ 10 years, or in combination with a sulphonylurea or insulin in type 2 diabetic patients aged ≥ 17 years of age in the US.

Cardiovascular benefits with metformin

Vascular protection

In newly-diagnosed type 2 diabetic patients followed for a median of 11 years in the UKPDS,¹⁶ patients who received metformin benefited from clinically and statistically significant improvements in the risk of all-cause death, diabetes-related death, myocardial infarction, and in a composite measure of 21 diabetes-related complications (table 1). Since other intensive therapies delivered a similar level of glycaemic control without those CV benefits, UKPDS

Table 1. Selected clinical outcomes in patients randomised to intensive glycaemic management with metformin, or with a sulphonylurea or insulin, in the UK Prospective Diabetes Study^{16,75}

	Metformin		Sulphonylurea/insulin	
	Mean change in risk ^a	P value	Mean change in risk ^a	P value
Diabetes-related death	↓ 42%	0.017	↓ 20%	0.19
All-cause mortality	↓ 36%	0.011	↓ 8%	0.49
Any diabetes-related end point	↓ 32%	0.0023	↓ 7%	0.46
Myocardial infarction	↓ 39%	0.01	↓ 21%	0.11
Stroke	↓ 41%	0.13	↑ 14%	0.6

Key: ^aCompared with conventional therapy based on diet/exercise in overweight patients

Reproduced with permission from Scarpello JH. Improving survival with metformin: the evidence base today. *Diabetes Metab* 2003;**29**:6S36-6S43

outcomes have indicated that metformin affords protection from macrovascular diabetic complications independently of glycaemic lowering.⁷⁵

A sub-study of the UKPDS evaluated addition of metformin to sulphonylurea monotherapy and suggested an excess of mortality in the combination group vs. sulphonylurea alone.¹⁶ Further analysis has shown that these data resulted from fewer than expected deaths occurring in the sulphonylurea monotherapy group, with no absolute increase of deaths above that expected in the combination group.⁷⁶

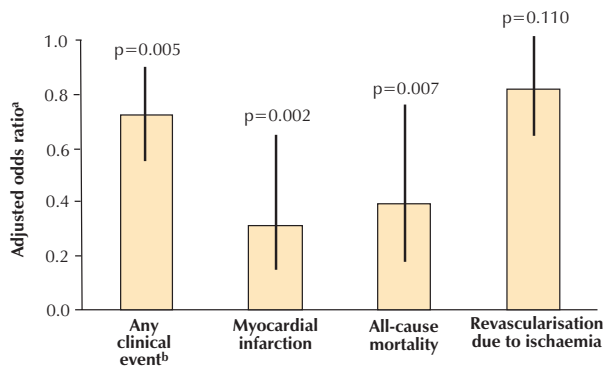
The UKPDS recruited a newly-diagnosed type 2 diabetic population largely free of prior major vascular events (only 1% of the overall UKPDS population had a history of myocardial infarction).⁷⁷ Several observational analyses have suggested significant cardioprotective benefits with metformin in patient populations with more severe cardiovascular disease at baseline (table 2).⁷⁸⁻⁸³ Principal results from one of these studies, the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial, are shown in figure 3.⁷⁸ Metformin was associated with significant improvements in cardiovascular outcomes, compared with those observed in patients not receiving this agent.

Table 2. Observational analyses of the effects of metformin on clinical cardiovascular outcomes

Ref number	Patients	N	Treatments compared	Main findings
78	Diabetic subgroup of a large randomised trial	1,997	Metformin Any other OAD (no metformin or TZD)	Significantly lower rates of any clinical event, myocardial infarction and all-cause mortality in the metformin group
79	New prescriptions of oral antidiabetic agents in Saskatchewan, Canada	12,272	Metformin SU Metformin + SU	Significantly lower risk of all-cause mortality vs. SU monotherapy with metformin (-40%) or metformin + SU (-34%)
80	New prescriptions of oral antidiabetic agents in Saskatchewan, Canada	4,142	Metformin SU Metformin + SU	Lower risk of composite of hospitalisation + CV death (-19%) or mortality (-25%) with metformin monotherapy vs. SU monotherapy Lower risk of CV death with metformin + SU (-39%) vs. SU monotherapy Similar risk of hospitalisation with metformin + SU vs. SU monotherapy
81	Developed incident heart failure on metformin in Saskatchewan, Canada	1,833	Metformin SU Metformin + SU	Significantly lower risk of mortality (-30%) or combined risk of mortality or hospitalisation (-17%) for metformin monotherapy vs. SU monotherapy Significantly lower risk of mortality (-39%) or combined risk of mortality or hospitalisation (-14%) for metformin + SU vs. SU monotherapy
82	New prescriptions of oral antidiabetic agents in UK	5,730	Metformin SU Metformin + SU	3-4-fold lower risk of mortality for metformin vs. SU monotherapy Increased mortality of metformin + SU vs. metformin monotherapy
83	Ischaemic cardiomyopathy 301 (survivors of MI)		Metformin No metformin	Reduced risk of recurrent MI with metformin (-82% vs. no metformin)

Key: N = total number of patients in the analysis; OAD = oral antidiabetic drug; SU = sulphonylurea; MI = myocardial infarction; CV = cardiovascular; TZD = thiazolidinedione

Figure 3. Odds ratios (95% CI) for adverse cardiovascular outcomes in metformin-treated diabetic patients with established coronary disease in the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial



Bars show 95% CI.

Key: ^aAdjusted for risk factors including age, gender, trial centre, percent stenosis after percutaneous coronary intervention, drug treatments, previous percutaneous coronary angioplasty, extent of coronary atherosclerosis, peripheral vascular disease, smoking and body weight; ^bdefined as death, myocardial infarction or revascularisation due to ischaemia.

Drawn from data presented by Kao *et al.*⁷⁶

Mechanisms of vascular protection

Table 3 summarises a number of potential vasculoprotective mechanisms attributed to metformin in clinical and/or experimental studies. In addition to the reduced incidence of macrovascular events noted during the UKPDS, several

studies have demonstrated improved vascular reactivity in patients receiving metformin.

Insulin resistance

Metformin counters insulin resistance and consequently reduces the atherogenic effects of insulin resistance. The association between insulin resistance and atherothrombotic disease is beyond the scope of this review and the reader is referred to definitive articles on the subject.^{84,85}

Improved lipid profiles

Numerous studies have demonstrated improved lipid profiles in dyslipidaemic patients receiving metformin, and these are reviewed extensively elsewhere.⁸⁶ Modest improvements in levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides are often observed, though little or no change in high-density lipoprotein (HDL)-cholesterol is usually seen. Figure 4 shows an example of the effects of metformin on the lipid profile, from a double-blind, randomised, placebo-controlled crossover study in 27 type 2 diabetic patients treated with metformin for 12 weeks.⁸⁷

Adiposity

The modest reductions in body weight often observed with metformin⁶⁹ are associated with redistribution of fat from visceral depots to subcutaneous depots, which carry lesser cardiovascular (CV) risk.⁸⁸

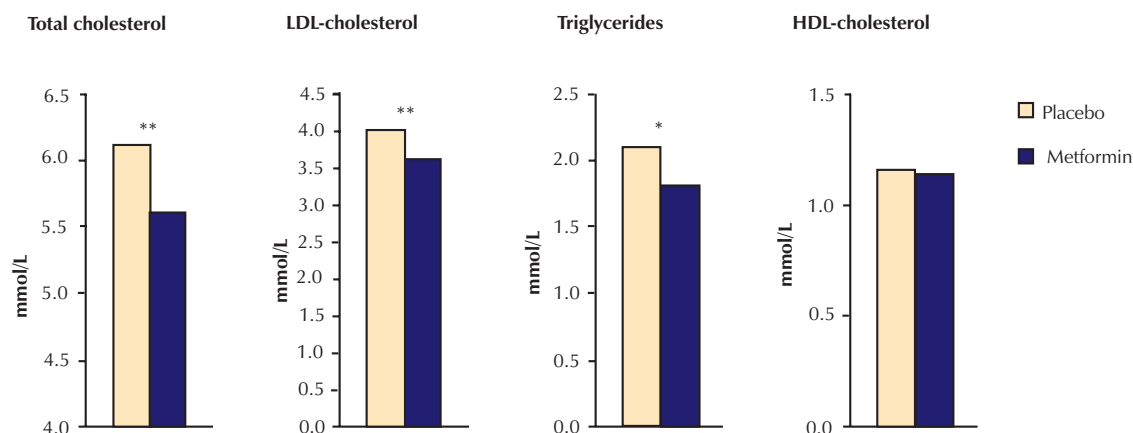
Improved haemostasis

Randomised studies have shown that treatment with

Table 3. Proposed cardiovascular protective mechanisms of metformin

Action	Proposed consequence
Improved insulin sensitivity (amelioration of insulin resistance)	↓ Cardiovascular risk factors associated with the metabolic syndrome ↓ Reduced hyperinsulinaemia and glucotoxicity
Improved lipid profiles	↓ Atherogenesis
Reduced body weight and central obesity	↓ Visceral fat associated with improved insulin sensitivity
Improved fibrinolysis	↓ Risk of intravascular thrombus
Antioxidant effects	↓ Apoptosis of endothelial cells ↓ Oxidative damage to cellular components
Neutralisation of advanced glycation end-products	↓ Potential for damage to key enzymes and tissues ↓ Oxidative stress/apoptosis
Reduced expression of endothelial adhesion molecules	↓ Adhesion of inflammatory cells to the endothelium ↓ Atherogenesis
Reduced differentiation of inflammatory cells into macrophages	↓ Atherogenesis
Reduced lipid uptake into macrophages	↓ Atherogenesis
Improved microcirculation	↑ Nutritive blood flow to tissues

Figure 4. Effect of metformin on lipid profiles: data from a randomised, double-blind, placebo-controlled, crossover study in 27 patients with type 2 diabetes



Columns show levels of lipids after 12 weeks' treatment with metformin or placebo.

Key: LDL = low-density lipoprotein; HDL = high-density lipoprotein

Differences between treatments: * $p < 0.05$; ** $p < 0.01$. To convert cholesterol values to mg/dL, divide by 0.02586; for triglycerides, divide by 0.01129. Drawn from data presented by Nagi *et al.*⁸⁷

metformin reduces levels or activity of plasminogen activator inhibitor-1 (PAI-1),^{13,87,89-90} and sometimes increases the activity of tissue plasminogen activator (tPA).⁹⁰ Other antithrombotic mechanisms of metformin include stabilisation of reduced aggregation of platelets in response to stimuli⁹⁰ and reduction of the activity of clotting Factor VII⁹¹ and Factor XIII,⁹² which are involved in thrombus formation and stabilisation, respectively.

Inhibition of glycooxidation

Metformin inhibits the formation of advanced glycation end-products (AGE) through improved glycaemia, like other oral antidiabetic agents.⁹³ However, metformin molecules also react directly with, and neutralise, highly reactive α -dicarbonyl intermediates involved in AGE formation (e.g. methylglyoxal) in the plasma of type 2 diabetic patients treated with metformin.^{94,95} Metformin treatment also increases the activity of glyoxalase, an enzyme which deactivates methylglyoxal to D-lactate.⁹⁶ Oxidative stress, generation of free radicals and apoptosis often co-exist, and are an important cause of adverse myocardial remodelling post-myocardial infarction.^{97,98} Improvement of cellular antioxidant defences provides a further mechanism by which metformin may diminish damage caused by oxidative stress.⁹⁹

Cellular anti-atherogenic mechanisms

Exposing endothelial cells to metformin inhibits the expression of endothelial adhesion molecules, including intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and E-selectin. This is consistent with an anti-atherogenic action of the drug.^{100,101}

Improved microcirculation

A number of microcirculatory abnormalities are associated with type 2 diabetes, including inappropriate dilatation and

contractility of arterioles and venules, and disturbances of blood rheology. Experimental data suggest beneficial effects of metformin in increasing arteriolar and venular vasomotion, in reducing capillary permeability, and in increasing post-ischaemic capillary density.¹⁰¹ In these ways, metformin appears to improve blood flow in the diabetic microcirculation.

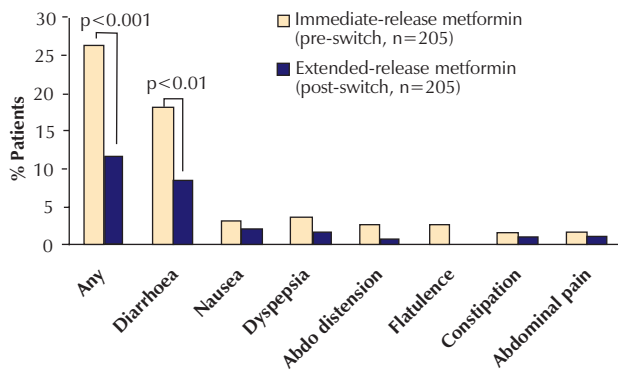
Metformin was evaluated in a randomised study in patients with 'cardiac syndrome X', in whom microvascular dysfunction contributes to the development of the classic symptoms of myocardial ischaemia.¹⁰² Metformin improved endothelium-dependent microvascular blood flow and ameliorated symptoms of myocardial ischaemia, including a 38% reduction in maximal ST-segment depression and a 30% reduction in the incidence of chest pain during an exercise test.

Safety and tolerability

Gastrointestinal tolerability

The gastrointestinal intolerance often associated with rapid titration and high-dose initiation of metformin therapy remains a practical issue to be addressed by taking the agent with meals, reducing the rate of dose escalation, or transferring to a prolonged-release formulation.¹⁰³ The causes of gastro-intestinal intolerance are probably a high concentration of metformin in the upper gastrointestinal (GI) tract and alteration of glucose metabolism in enterocytes, leading to local irritation.¹⁰⁴ More distally, metformin can cause bile salt malabsorption, which increases fluid retention in the large bowel, leading to loose stools and diarrhoea in some patients.¹⁰⁵ Symptoms rarely lead to drug withdrawal, however, and a discontinuation rate of 5% of patients is often quoted.¹⁰⁶ A prolonged-release form of metformin, offering a slower absorption rate, has been associated with improved tolerability (figure 5).¹⁰⁷⁻¹⁰⁹

Figure 5. Gastrointestinal side-effects before and after a switch from immediate-release metformin to extended-release metformin in a retrospective chart review



Reproduced with permission from: Howlett H, Davidson J. New extended-release metformin improves gastrointestinal tolerability. *Br J Diabetes Vasc Dis* 2004;4(4):273-7¹⁰⁷

Lactic acidosis

The reported incidence of lactic acidosis in patients receiving metformin is approximately 3/100,000 patient-years of treatment, though many cases described as 'metformin-associated lactic acidosis' arise from concomitant pathological disorders rather than administration of metformin.¹¹⁰⁻¹¹³ A systematic review of 194 trials involving > 60,000 patient-years of treatment concluded that the risk of lactic acidosis with metformin was no greater than that with other oral antidiabetic medications, when contra-indications were respected.¹¹⁴ Thus, the incidence of lactic acidosis with metformin is extremely low or negligible when the contra-indications and precautions to its use are respected.¹¹⁵

Hypoglycaemia

Since metformin does not stimulate insulin secretion and does not modulate the glucose counter-regulatory mechanism, hypoglycaemia is seldom an issue when the drug is prescribed alone in patients who are suitable for therapy.¹¹⁶

Contra-indications and precautions

Metformin is contra-indicated in patients with diabetic ketoacidosis or diabetic pre-coma, renal failure or renal dysfunction (e.g. serum creatinine $\geq 135 \mu\text{mol/L}$ in males and $> 110 \mu\text{mol/L}$ in females, or creatinine clearance $\leq 60 \text{ mL/min}$), acute conditions with the potential to alter renal function (such as dehydration, severe infection, shock or intravascular administration of iodinated contrast agents), acute or chronic disease which may cause tissue hypoxia (such as cardiac or respiratory failure, recent myocardial infarction or shock), hepatic insufficiency, acute alcohol intoxication, in alcoholism and in lactating women. Renal function should be monitored during treatment with metformin as part of routine patient care.

In clinical practice, about 25–50% of patients receiving metformin may have concomitant conditions included in the list of precautions or contra-indications to treatment

with metformin.^{117,118} Renal impairment or cardiovascular morbidity signifies excess cardiovascular risk in diabetic patients,¹¹⁹ and such patients are likely to benefit from the proven cardioprotective properties of metformin.¹²⁰ The list of contra-indications for metformin has arisen largely from a perceived need to minimise the risk of lactic acidosis. However, available clinical evidence suggests that metformin can be given to patients with mild renal dysfunction or other co-morbidities.^{120,121} Observations of improved clinical outcomes and/or maintained safety during treatment with metformin of patients with contra-indications to this agent have led to calls for the relaxation of the contra-indications for metformin.¹²⁰⁻¹²⁴ The contra-indications and precautions as presently listed should be adhered to until this debate is resolved.

Estimated glomerular filtration rate (eGFR)¹²⁵ is rapidly replacing serum creatinine as the measure of renal function used routinely to allow or deny the use of metformin.¹²⁶ There is no absolute standard for use of eGFR as yet, although provisional recommendations relating to the use of eGFR have appeared. Concern over underestimation of renal dysfunction in elderly patients and in women is driving the transition to eGFR, but this has important potential implications for the use of metformin that are as yet unclear. In particular, this may lead to fewer patients qualifying for treatment with metformin and more being denied this therapy. Two analyses in large cohorts of patients in the UK showed that adoption of a threshold level of eGFR somewhere within the range of values corresponding to chronic kidney disease (CKD) stage 3 (eGFR 30–59 mL/min/1.73 m²) would leave the number of patients eligible to receive metformin unchanged.^{127,128} Initial recommendations suggest a cut-off value for eGFR of $< 30 \text{ mL/min/1.73 m}^2$ (CKD stage 4 or greater) as an absolute contra-indication to the use of metformin, with CKD stage 3 as reason to adopt caution.^{128,129}

Potential clinical uses beyond type 2 diabetes

Metformin and diabetes prevention

The most compelling evidence for a potential role for metformin in the prevention of type 2 diabetes comes from the US Diabetes Prevention Program (DPP).¹³⁰ This trial compared intensive lifestyle intervention, standard lifestyle advice plus placebo, or standard lifestyle advice plus metformin in patients with combined IFG (Impaired Fasting Glucose) and IGT (Impaired Glucose Tolerance). Compared with standard lifestyle advice + placebo, metformin and intensive lifestyle advice reduced the risk of developing type 2 diabetes by 31% and 58%, respectively ($p < 0.001$ for each, and for between the two). The intensive lifestyle intervention was similarly effective in all patient sub-groups, while metformin was most effective in younger, more obese subjects, and in subjects with FPG values near the diagnostic threshold for diabetes. Metformin also significantly reduced the risk of developing diabetes in an Indian population of subjects with IGT,¹³¹ and in a further study carried out in China.¹³² These benefits of metformin in reducing the progression of IGT to type 2 diabetes are likely to reflect the ability of metformin to counter the progressive development

Table 4. Initiation of treatment according to principal guidelines for the management of type 2 diabetes or pre-diabetes

Sponsor	Glycaemic target	Try lifestyle first?	Application of pharmacological therapy	
			Initiation	Intensification
<i>Type 2 diabetes</i>				
IDF ^{157,158}	HbA _{1C} < 6.5% if possible Capillary glucose < 6 mmol/L before meals and < 8 mmol/L 1–2 hours after meals	Yes	Begin with metformin where no evidence or risk of renal impairment	Add sulphonylurea, thiazolidinedione or α -glucosidase inhibitor as needed Consider early use of insulin
ADA/EASD ¹⁰³	General goal < 7% < 6% if possible	No	Metformin + lifestyle from diagnosis of type 2 diabetes	Add insulin or one or two other oral antidiabetic agents as required End with metformin + insulin with or without a thiazolidinedione
<i>Pre-diabetes</i>				
IDF ¹⁵⁹	–	Yes	Metformin	–
ADA ¹⁶⁰	–	Yes for isolated IGT or IFG	Lifestyle and/or metformin for younger subjects with IFG + IGT complicated by obesity or other risk factors	–
Key: IDF = International Diabetes Federation; ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes; IGT = impaired glucose tolerance; IFG = impaired fasting glucose				
Recommendations for use of metformin assume no contra-indications. See text for further explanation of recommendations				

of insulin resistance which characterises the worsening of IGT.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is associated with insulin resistance. A Cochrane review reported that metformin significantly improved ovulation rates and pregnancy rates, especially in patients with clomifene-resistant PCOS.¹³³ Another recent review noted that these meta-analyses may have been unduly influenced by smaller trials, and concluded that metformin does not have a role in the routine management of PCOS.¹³⁴ Although metformin is not currently indicated for PCOS, new guidelines from the UK National Institute for Health and Clinical Excellence (NICE) recommend metformin for clomifene-resistant PCOS¹³⁵ and a position statement from the American Association of Clinical Endocrinologists recommends metformin for most women with PCOS.¹³⁶

Other conditions associated with insulin resistance

Non-alcoholic fatty liver disease (NAFLD) and the related non-alcoholic steatohepatitis (NASH) are associated with insulin resistance and cardiometabolic risk factors reminiscent of the metabolic syndrome.^{137–139} Improved liver function has been observed with metformin in this population.^{140–144} Patients receiving highly active antiretroviral therapy (HAART) for HIV are at risk of lipodystrophy syndrome, also characterised by insulin resistance,^{145–147} and demonstrated

improved cardiometabolic risk factor status with metformin.^{148–150}

Cancer

Metformin acts partly by activating the enzyme AMPK, as described above. The tumour suppressor, LKB1, is an upstream regulator of AMPK and increased activity of this pathway may exert an anti-tumour effect.^{151–153} *In vitro*, metformin can suppress the growth of cancer cell lines that express LKB1, but not cell lines that do not express LKB1.¹⁵⁴ Two observational studies in patients with type 2 diabetes have demonstrated a significantly lower risk of cancer in patients receiving metformin relative to other treatments.^{155,156}

Conclusions

The metabolic and vasculo-protective profiles of metformin have been recognised in treatment guidelines for type 2 diabetes; the recommendations of the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), International Diabetes Federation (IDF) place metformin as first-line therapy (table 4).^{103,157,158} The drug is suitable irrespective of age, body weight and severity of hyperglycaemia (except patients with symptoms necessitating insulin). Metformin complements lifestyle management throughout the treatment of type 2 diabetes and forms a convenient pharmacological foundation for combined therapy with other antidiabetic therapies, including insulin.

Metformin is recommended as a strong candidate therapy by the ADA and IDF for the treatment of pre-diabetes, particularly those with combined IFG and IGT.^{159,160} There is growing interest in the use of metformin in insulin resistance states such as PCOS, NASH and HIV lipodystrophy syndrome. Finally, preliminary reports claiming that metformin expresses anti-tumour activity have opened up new research possibilities in the field of cancer therapy.

Conflicts of interest statement

JHBS has received honoraria and assistance to attend conferences from various pharmaceutical companies including Merck Serono.

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