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REVIEW

Metformin: clinical use in type 2 diabetes

Elizabeth Sanchez-Rangel[1] · **Silvio E. Inzucchi**[1]

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Abstract Metformin is one of the most popular oral glucose-lowering medications, widely considered to be the optimal initial therapy for patients with type 2 diabetes mellitus. Interestingly, there still remains controversy regarding the drug's precise mechanism of action, which is thought to involve a reduction in hepatic glucose production. It is now recommended as first-line treatment in various guidelines, including that of the EASD and ADA. Its favoured status lies in its efficacy, low cost, weight neutrality and good safety profile. Other benefits have also been described, including improvements in certain lipids, inflammatory markers, and a reduction in cardiovascular events, apparently independent from the drug's glucose-lowering effect. Data have emerged questioning the previous reluctance to use this agent in those with mild to moderate chronic kidney disease. Regulations guiding its use in patients with stable, modest renal dysfunction have, as a result, become more lenient in recent years. With no long-term studies comparing it against newer glucose-lowering drugs, some of which have more robust evidence for cardioprotection, metformin's established role as 'foundation therapy' in type 2 diabetes may justifiably be challenged.

Keywords Biguanides · Glucose-lowering therapy · Metformin · Review · Type 2 diabetes mellitus

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✉ Silvio E. Inzucchi
silvio.inzucchi@yale.edu

[1] Section of Endocrinology, Yale School of Medicine and Yale-New Haven Hospital, Fitkin 106, 333 Cedar Street, New Haven, CT 06520-8020, USA

Abbreviations

DPP-4	Dipeptidyl peptidase-4
DPPOS	Diabetes Prevention Program Outcomes Study
eGFR	Estimated GFR
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
MALA	Metformin-associated lactic acidosis
Metformin XR	Extended-release metformin
SGLT2	Sodium–glucose cotransporter 2
UKPDS	UK Prospective Diabetes Study

Introduction

Metformin hydrochloride, a biguanide, is the most popular oral glucose-lowering medication in most countries, widely viewed as 'foundation therapy' for individuals with newly diagnosed type 2 diabetes mellitus. This reputation has resulted from its effective glucose-lowering abilities, low cost, weight neutrality, overall good safety profile (especially the lack of hypoglycaemia as an adverse effect), and modest evidence for cardioprotection [1]. A derivative of guanidine, which was initially extracted from the plant *Galega officinalis* or French lilac, metformin was first synthesised in 1922 and introduced as a medication in humans in 1957, after the studies of Jean Sterne [2]. Its popularity increased after eventual approval in the USA in 1994, although it was used extensively in Europe and other regions of the world prior to that [3]. The drug's efficacy has been demonstrated in monotherapy as well as in combination with other glucose-lowering medications for type 2 diabetes mellitus. Based on these important characteristics, there continues to be extensive interest in this compound, even now, many years after its

incorporation into the diabetes pharmacopeia. Interestingly, and despite this popularity, there still remains controversy about the drug's precise mechanism of action, although most data point to a reduction in hepatic glucose production being predominately involved (described further by Rena et al in this issue of *Diabetologia*) [4]; although, recent data suggests that some of the drug's effect may involve the stimulation of intestinal release of incretin hormones. Herein, we will review the most salient aspects of the clinical use of metformin in individuals with type 2 diabetes mellitus.

Use as first-line therapy

As noted, metformin is preferred by most guideline committees as the initial therapy in individuals not able to achieve glycaemic targets despite diet and other lifestyle interventions [5]. So widespread is its current use that virtually all diabetes drug development programmes include a series of studies involving the addition of the investigational compound to background metformin therapy. The drug's efficacy was best illustrated by DeFronzo et al, in a 1995 report. In 'protocol 1' of this study, 289 obese participants with uncontrolled diabetes, treated with diet alone, were assigned to receive metformin or placebo (forced titration from 850 mg daily to 850 mg thrice daily if fasting plasma glucose exceeded 7.8 mmol/l and side effects were tolerable). At 29 weeks, metformin resulted in a lower mean fasting plasma glucose of 10.6 vs 13.7 mmol/l with placebo ($p < 0.001$); compared with corresponding baseline values, fasting plasma glucose was reduced by 2.9 mmol/l in the metformin group and increased by 0.3 mmol/l in the placebo group. With metformin, mean HbA_{1c} decreased from 8.4% (68.3 mmol/mol) to 7.1% (54.1 mmol/mol), while, with placebo, it increased from 8.2% (66.1 mmol/mol) to 8.6% (70.5 mmol/mol; $p < 0.001$) (Fig. 1) [6].

The drug's efficacy is dose-dependent, as demonstrated by Garber and colleagues, who investigated the pharmacodynamic effects with different dosing regimens vs placebo, over 14 weeks in 451 individuals with type 2 diabetes. The minimal efficacious dose of metformin was 500 mg daily and maximal efficacy was achieved at a dose of 2000 mg daily. While some patients may benefit from doses as high as 2500 mg daily, in this study, overall, there were no major differences in fasting plasma glucose and HbA_{1c} when compared with the proximate lower daily dose of 2000 mg (Fig. 2). At 500 mg, metformin decreased fasting plasma glucose by an adjusted mean value of 1.1 mmol/l and HbA_{1c} by 0.9% (9.8 mmol/mol; placebo-subtracted); at 2000 mg, the corresponding reductions were 4.3 mmol/l and 2.0% (21.9 mmol/mol; $p \leq 0.01$) [7]. In both the studies by DeFronzo et al, and Garber et al, the drug was well tolerated with mild gastrointestinal (GI) side effects predominating and no increased risk of hypoglycaemia.

Since these original trials, follow-up and short-term studies (usually 3–6 months) using metformin have demonstrated mean HbA_{1c} reductions on the order of 1% (10.9 mmol/mol) to 1.5% (16.4 mmol/mol), depending, in part, on the baseline value. In head-to-head trials, the drug has been shown to be equipotent to sulfonylureas, thiazolidinediones and glucagon-like peptide-1 (GLP-1) receptor agonists, and, in general, more potent than dipeptidyl peptidase-4 (DPP-4) inhibitors [8, 9].

A Diabetes Outcome Progression Trial (ADOPT; 2006) was a long-term randomised, double-blind, controlled clinical trial comparing the durability of glycaemic-control efficacy of a sulfonylurea (glibenclamide, known as glyburide in the USA and Canada), metformin and a thiazolidinedione (rosiglitazone), as initial treatment for recently diagnosed type 2 diabetes. After 5 years, progression to monotherapy 'glycaemic failure' (liberally defined as fasting plasma glucose >10.0 mmol/l) was least with rosiglitazone (15% of participants), intermediate with metformin (21%) and greatest with glibenclamide (34%). Similar results were found when using the alternative and perhaps more conventional glycaemic failure definition of plasma glucose >7.8 mmol/l. As compared with glibenclamide, metformin was associated with a 46% ($p < 0.001$) relative reduction in the risk of monotherapy failure. However, the durability of glycaemic control with metformin was not as great as with rosiglitazone (63% less monotherapy failure than glibenclamide and 32% less than metformin; $p < 0.001$ for both). Optimal glucose control, as measured by the time mean HbA_{1c} was maintained at <7% (53.0 mmol/mol), was highest with rosiglitazone (57 months) intermediate for metformin (45 months) and lowest for glibenclamide (33 months) [10]. This landmark study once again illustrated the progressive nature of type 2 diabetes, as was initially reported by the UK Prospective Diabetes Study (UKPDS) in 1998 [11]. It also serves as a reminder that metformin, though seemingly better in attenuating this progression than insulin secretagogues, does not appear to substantially preserve beta cell function. This could also be considered as one conclusion of the Diabetes Prevention Program (DPP), which found that the transition from impaired glucose tolerance to type 2 diabetes was attenuated the most with lifestyle change, which had nearly twice as potent an effect as metformin [12].

Use in combination therapy

Metformin is also efficacious when used in various combination regimens. Such progressive therapy is now almost the rule in the management of type 2 diabetes because of the aforementioned decline in beta cell secretory capacity

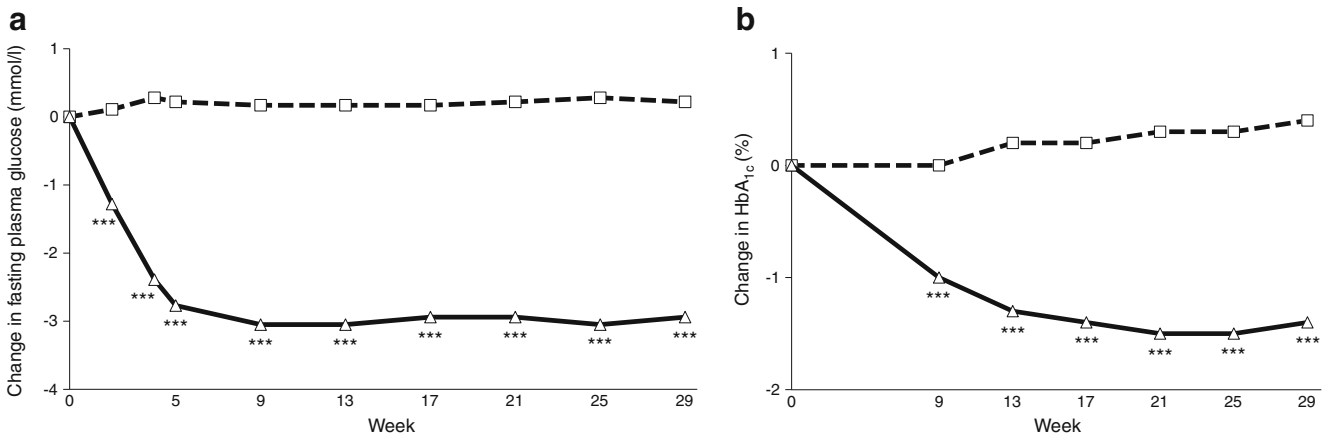

Fig. 1 Mean changes in (**a**) fasting plasma glucose and (**b**) HbA_{1c} in the Multicenter Metformin Study, Protocol 1. Participants (n = 143) with uncontrolled type 2 diabetes mellitus randomised metformin (triangles with solid line) experienced improved glycaemic control vs participants (n = 146) randomised to placebo (squares with dashed line.) ***$p < 0.001$ vs placebo. Figure adapted from The New England Journal of Medicine, DeFronzo et al, Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus, 333:541-549. Copyright © 1995 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society [6]. To convert values for HbA_{1c} in % into mmol/mol, multiply by 10.929

characterising this disease. As a result of its unique mechanism of action and lack of association with hypoglycaemia as an adverse effect, the drug pairs well with all other glucose-lowering medications. As noted, all type 2 diabetes drug development programmes incorporate extensive investigations of such joint therapies. Indeed, the most common agent incorporated into single-tablet fixed-dose combination formulations is metformin. In earlier studies involving sulfonylureas, thiazolidinediones and insulin, the efficacy of metformin was tested when added to these background therapies. However, as the biguanide's popularity as first-line therapy became established, studies involving more of the recently developed agents have tested their efficacy when added to a background of metformin therapy. We briefly review the most popular combinations below. Importantly, however, these trials have all been relatively short term, focusing predominately on variables of glycaemic efficacy for purposes of product labelling. More meaningful long-term microvascular or macrovascular outcomes have not been assessed.

Metformin and sulfonylureas The combination of metformin and a sulfonylurea is amongst the most commonly prescribed. In 'protocol 2' of the aforementioned study by DeFronzo et al, 632 individuals with uncontrolled blood glucose (defined as a fasting plasma glucose ≥7.8 mmol/l on two occasions) on the sulfonylurea glibenclamide were randomised to continued

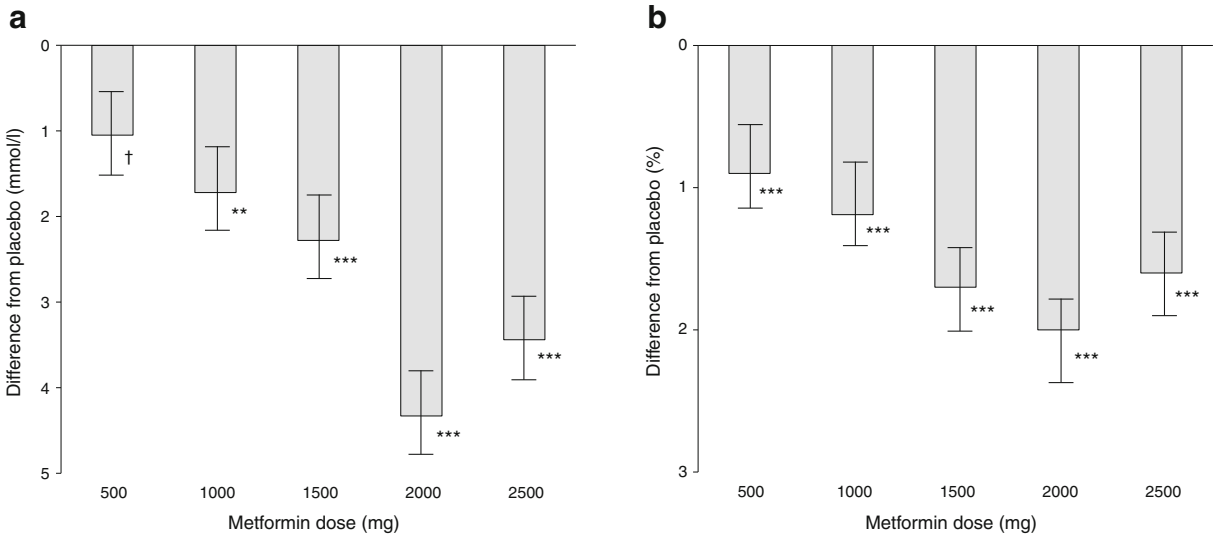

Fig. 2 Placebo-subtracted adjusted mean changes (± SE) in (**a**) fasting plasma glucose and (**b**) HbA_{1c} over 11 weeks in 451 patients with type 2 diabetes randomised to various metformin doses or placebo. †$p = 0.054$, **$p < 0.01$ and ***$p < 0.001$ vs placebo. Figure adapted from The American Journal of Medicine, 103, Garber et al, Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial, 491-497, Copyright 1997, with permission from Elsevier [7]. To convert values for HbA_{1c} in % into mmol/mol, multiply by 10.929

glibenclamide therapy, a switch from glibenclamide to metformin, or the addition of metformin to the sulfonylurea. Over the course of 29 weeks, better glycaemic outcomes were noted in the combination group vs glibenclamide alone (mean fasting plasma glucose, 10.5 vs 14.6 mmol/l [$p < 0.001$]; HbA_{1c} 7.1% [54.1 mmol/moL) vs 8.7% [71.6 mmol/mol; $p < 0.001$]). The effect of switching to metformin alone was ultimately similar to remaining on glibenclamide and, therefore, provided no glycaemic benefit. (Fig. 3) [6].

Similar results were found in another multicentre trial involving 372 participants on 2250 mg of metformin monotherapy with inadequately controlled type 2 diabetes. Herein, the addition of glimepiride to metformin resulted in superior glycaemic control compared with switching to glimepiride or remaining on the biguanide. The combination treatment was significantly more effective at reducing HbA_{1c} vs metformin alone (−0.74% vs +0.07% [−8.1 vs +0.8 mmol/mol]; $p < 0.001$) and vs glimepiride alone (−0.74% vs +0.27% [−8.1 vs +3.0 mmol/mol]; $p < 0.001$) [13].

Metformin and insulin In a 16-week randomised clinical trial involving 390 individuals with type 2 diabetes, compared with placebo, the addition of metformin to insulin therapy (basal/bolus regimens) resulted in superior glycaemic control, improved HbA_{1c} (6.9% [51.9 mmol/mol] vs 7.6% [59.6 mmol/mol], metformin+insulin vs placebo; both from baselines of approximately 7.9% [62.8 mmol/mol]; $p < 0.0001$), less weight gain (+0.4 vs +1.2 kg; $p = 0.01$) and reduced insulin requirements (63.8 vs 71.3 units/day; $p < 0.0001$) [14].

Another RCT evaluated the effects of the combination of bedtime insulin plus metformin. Ninety-six individuals with poorly controlled type 2 diabetes on sulfonylurea therapy were assigned to four groups: (1) bedtime NPH insulin plus glibenclamide and placebo; (2) bedtime NPH insulin plus metformin and placebo; (3) bedtime NPH insulin plus glibenclamide and metformin; or (4) NPH insulin twice daily. Participants were followed for 1 year and, at 1 year, body weight remained unchanged in those receiving bedtime insulin plus metformin (mean, +0.9 kg), while it increased by 3.9, 3.6 and 4.6 kg in individuals receiving NPH insulin plus glibenclamide, NPH insulin plus glibenclamide and metformin, and NPH insulin twice daily, respectively ($p < 0.001$ NPH insulin plus metformin vs all other groups). Moreover, a statistically significant, greater decrease in HbA_{1c} (from 9.7% [82.5 mmol/mol] to 7.2% [55.2 mmol/mol]) was observed in the bedtime insulin plus metformin group, as compared with the other groups, (ranging from 9.8–10.1% [83.6–86.9 mmol/mol] to 7.5–8.0% [58.5–63.9 mmol/mol]; $p < 0.01$ for all comparisons.) Hence, it can be concluded that the combination of bedtime NPH insulin with metformin is superior with regard to glycaemic control, weight gain and frequency of hypoglycaemia [15], and, as a result of this and similar trials, the drug is widely endorsed as an effective adjunct to insulin in those with more advanced type 2 diabetes.

Metformin and thiazolidinediones The first combination-therapy trial of metformin with a drug other than an insulin-providing agent involved the original thiazolidinedione, troglitazone. In the initial phase of this small but important trial, both drugs reduced fasting plasma glucose to an equivalent degree. Mechanistic studies incorporated into this trial revealed that the biguanide's main effect was to reduce hepatic glucose production, whereas the thiazolidinedione mainly improved peripheral glucose disposal. Thus, while

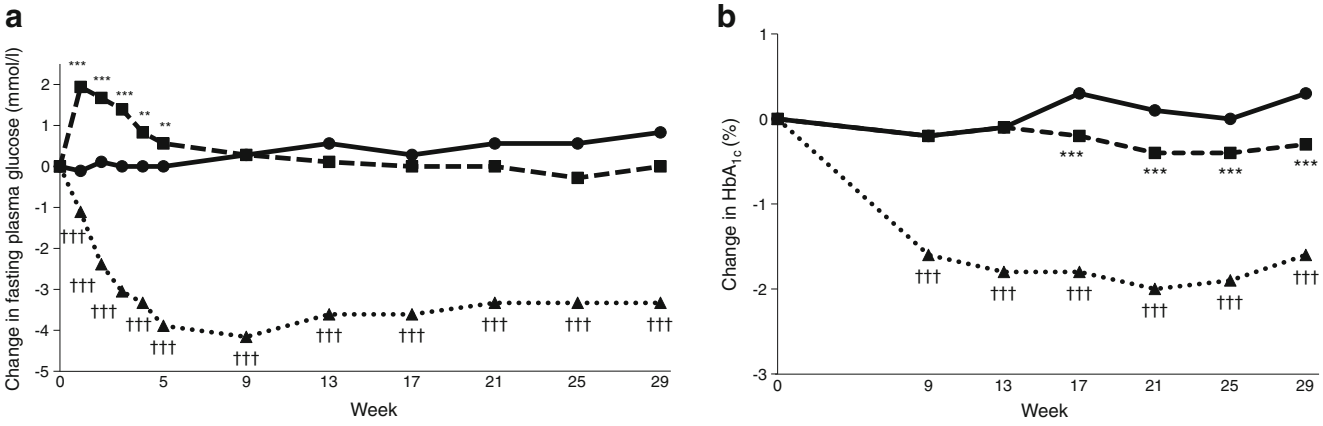

Fig. 3 Mean changes in (**a**) fasting plasma glucose and (**b**) HbA_{1c} in the Multicenter Metformin Study, Protocol 2. Participants ($n = 213$) with uncontrolled type 2 diabetes mellitus on glibenclamide monotherapy randomised to combination glibenclamide plus metformin therapy (triangles with dotted line) experienced improved glycaemic control vs the two monotherapy groups; the first of the monotherapy groups was comprised of 209 participants who remained on glibenclamide (circles with solid line) and the second was comprised of 210 participants who were switched from glibenclamide to metformin (squares with dashed line). $^{**}p < 0.01$, $^{***}p < 0.001$ metformin vs glibenclamide; †††$p < 0.001$ combination therapy vs glibenclamide. Figure adapted from The New England Journal of Medicine, DeFronzo et al, Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus, 333:541-549. Copyright © 1995 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society [6]. To convert values for HbA_{1c} in % into mmol/mol, multiply by 10.929

both drugs could be considered insulin sensitisers, they acted predominately in different organs (metformin in the liver, troglitazone in skeletal muscle). Next, when the drugs were combined for 3 months, both fasting plasma glucose and postprandial glucose were reduced further, reinforcing the notion that combined therapy using drugs with complementary mechanisms of action results in added glucose-lowering effect [16]. Similar glycaemic outcomes were subsequently found when pioglitazone and rosiglitazone were added to metformin [17, 18].

Metformin and DPP-4 inhibitors, GLP-1 receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors Most combination therapy studies involving metformin with members of newer glucose-lowering drug classes, DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors, have simply added the investigational compound (or placebo) to background metformin therapy. In general, the changes in HbA_{1c} changes recapitulated the approximate glucose-lowering effect of these drugs as monotherapy. Such studies, therefore, provide little insight into metformin itself, other than the observation that these respective combinations are effective, well tolerated and without any substantial added risk of hypoglycaemia [19–25]. Other investigations have examined initial combination therapy, mainly in treatment-naive individuals; these have further reinforced the concept that combining two drugs with distinct mechanisms of action leads to greater glucose-lowering potential than the constituents alone [23], allowing patients to better achieve HbA_{1c} targets.

Non-glycaemic effects

Once the cardiovascular benefits of metformin were suggested following clinical trials [26], interest into the pleiotropic effects of the drug arose. It has been proposed that its overall benefits are not solely the consequence of improved glucose control. This was evidenced in the UKPDS, where the biguanide was associated with reduced macrovascular complications, likely independent from glucose lowering since they were not observed with sulfonylureas or insulin treatment, which had, if anything, greater effects on blood glucose levels. In the 10-year follow-up of the UKPDS cohort, these cardiovascular benefits also appeared to be sustained [27]. Furthermore, in short-term studies, weight loss of up to 4 kg after 16–29 weeks of treatment with metformin has been reported [28, 29]. This effect may be mediated through carbohydrate malabsorption, enhanced carbohydrate utilization in the GI tract itself, or reduced calorie intake from mild anorexia [30]. In the longer-term UKPDS study, metformin was merely weight neutral, yet, this was in contrast to the predictable weight gain observed in those assigned to sulfonylureas or insulin. The effect of metformin on other cardiovascular risk markers and clinical events is discussed further by Griffin et al in this issue of *Diabetologia* [26].

Adverse effects

GI effects The most common side effects of metformin are GI in nature: diarrhoea, nausea and/or abdominal discomfort. They are usually mild, transient and dose-related, but can occur in up to 50% of patients taking the medication. About 5% of individuals cannot tolerate the drug, even at low doses [31]. Symptoms can be mitigated by gradual titration or reduction in dose [32]. These side effects may relate to drug accumulation in the enterocytes of the small intestine. Slow-release formulations (extended-release metformin [metformin XR]) are associated with fewer GI symptoms [33].

Lactic acidosis A much rarer but more concerning adverse consequence of biguanide therapy is lactic acidosis. In the 1970s, use of an earlier member of this class, phenformin was discontinued because of this association. A potentially lethal side effect, lactic acidosis has been ascribed to the promotion of anaerobic metabolism through interference with mitochondrial respiration, resulting in increased lactate generation. This is particularly the case when drug levels climb into the toxic range (> 5.0 mg/l [therapeutic levels, 0.5–2.0 mg/l]) [34], owing to decreased renal clearance, such as in advanced chronic kidney disease or acute kidney injury. Recognition of this risk substantially delayed the approval of metformin in the USA in the early 1990s [35]. Metformin-associated lactic acidosis (MALA) is actually rare, with an estimated incidence of 3–10 per 100,000 person-years. [36] Of note, the risk of developing lactic acidosis from metformin has been calculated to be 20 times less frequent than with phenformin [37]. Other risk factors for MALA include states that result in increased lactate production, such as sepsis, cardiogenic shock and alcoholism.

The US Food and Drug Administration (FDA) originally recommended against the use of metformin in individuals with renal impairment (i.e. serum creatinine ≥114 μmol/l in men, ≥ 107 μmol/l in women), or those over age 80 years with abnormal creatinine clearance, to minimise the likelihood of developing lactic acidosis. However, subsequent investigations have strongly suggested that the risk of lactic acidosis is extremely small and likely no different in users of metformin vs other glucose-lowering agents. In line with this, in an often-cited meta-analysis involving prospective and retrospective studies, the risk of MALA with metformin was found to be negligible. In fact, in most circumstances, so long as the estimated GFR (eGFR) was >30 ml min^{-1} [1.73 $m]^{-2}$, circulating drug levels remained within the safe range [38].

Based on these data and two citizen petitions, in April 2016, the FDA changed the labelling of all metformin-containing medications in the USA for use in individuals with mild and moderate impairment in kidney function [39]. The changes allowed for more widespread use of the drug, more akin to standards in place in the UK. Subsequently, the European Medicines Agency (EMA) also adopted these more liberal prescribing guidelines [40]. It is now recommended to use eGFR (which incorporates age, sex and race), instead of plasma creatinine concentration alone, in the assessment of renal function to determine whether the drug can be safely prescribed. Metformin use is now allowed when the eGFR falls below 60 ml min^{-1} [1.73 $m]^{-2}$; under 45 ml min^{-1} [1.73 $m]^{-2}$, a careful risk:benefit analysis should be conducted for each patient, but the medication may be cautiously continued (we advise a reduced dose at this juncture); metformin remains contraindicated when the eGFR falls under 30 ml min^{-1} [1.73 $m]^{-2}$ [41]. Of course, in individuals with labile renal disease, especially if frequent deteriorations in kidney function occur, this drug is a poor choice. The updated FDA guidelines also specify that metformin use should be withheld before iodinated contrast procedures if eGFR is 30–60 ml min^{-1} [1.73 $m]^{-2}$, in the setting of liver disease, alcoholism, or heart failure, or if intra-arterial contrast is used. The eGFR should then be checked 48 h later and the drug restarted if renal function remains stable.

B12 deficiency Vitamin B12 malabsorption is another potential side effect of metformin, now convincingly demonstrated through multiple case reports and cross-sectional and longitudinal studies. In one randomised trial involving 256 participants over 52 months, 19 individuals (9.9%) randomised to metformin therapy developed vitamin B12 deficiency (<150 pmol/l) vs five (2.7%) in the placebo group; another 35 individuals (18.2%) in the metformin group, compared with 13 individuals (7.0%) in the placebo group, developed a low vitamin B12 concentration (150–220 pmol/l) [42]. The Diabetes Prevention Program Outcomes Study (DPPOS) also reported an increased risk of low vitamin B12 levels with long-term treatment with the biguanide. Moreover, a higher prevalence of peripheral neuropathy (as assessed by monofilament testing) was reported in metformin-treated DPPOS participants who developed low vitamin B12 levels, but with very small numbers ($n = 13$). There is a paucity of other data showing that drug-associated changes in vitamin B12 concentrations result in any clinical symptoms. Nonetheless, based on the biochemical changes and given the potential irreversible neurological sequelae from unrecognised vitamin B12 deficiency, it is suggested that periodic testing of vitamin B12 levels be performed in patients on long-term metformin therapy, especially in those with anaemia or peripheral neuropathy [43]. Alternatively, prophylactic oral vitamin B12 supplements could simply be advised.

Dosing considerations

In order to minimise GI side effects, metformin should be taken with meals and initiated at a low dose, typically 500 mg once or twice daily with gradual increases (i.e. weekly) to the maximally tolerated dose, up to 2000 mg per day, given as 1000 mg twice daily [32]. As previously noted, more than 50% of the drug's efficacy is observed at 1000 mg [7]. Accordingly, in those patients having difficulty with higher doses, daily amounts of 1000–1500 mg should be considered substantially effective.

Various preparations of the drug exist, with immediate-release formulations being the most conventional, available in 500, 850 and 1000 mg tablets. The compound is absorbed largely in the proximal small intestine. This formulation requires twice- (or thrice-) daily dosing, which can compromise drug compliance. Metformin XR, and related products, is an extended-release formulation, available in 500, 750 and 1000 mg tablets. It has a dual polymer matrix, which slowly releases the active drug. It enables slower drug absorption in the upper GI tract, providing a once-daily dosing option, while also decreasing the frequency and severity of GI side effects [44]. In a randomised, double-blind trial involving 701 participants, the efficacy and safety of the extended-release formulation was found to be similar to the twice-daily immediate release drug [45].

Guidelines

Metformin is recommended as a first-line drug for the management of type 2 diabetes in most treatment guidelines [11], a position based on its efficacy, low cost, relative safety and the cardiovascular benefits shown by the UKPDS. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), in their joint

Summary of metformin use in type 2 diabetes

1. Effective glucose lowering as monotherapy and in combination with other agents, including insulin
2. Does not increase hypoglycaemia risk and is weight-neutral
3. Possible cardiovascular benefits
4. Maximally effective dose is usually 2000 mg daily
5. Major side effect is GI disturbance
6. Lactic acidosis risk is low; occurs mainly in those with advanced chronic kidney disease

position statement in 2012 and its update in 2015, recommend metformin as initial monotherapy to control HbA_{1c} levels in all individuals with type 2 diabetes unless there is demonstrated drug intolerance or any prevailing contraindication. These currently include advanced kidney or liver disease, acute unstable congestive heart failure, conditions marked by decreased perfusion or haemodynamic instability, major alcohol abuse, or conditions characterised by acidosis. If HbA_{1c} is not controlled, one of six other drug categories should then be added to the treatment regimen, such as a sulfonylurea, a thiazolidinedione, a DPP-4 inhibitor, an SGLT2 inhibitor, a GLP-1 receptor agonist or basal insulin, individualised to the patient and their disease features. If HbA_{1c} is greater than 9% (74.9 mmol/mol) at baseline, initiating dual combination therapy, i.e. metformin plus one of a member of these classes, is reasonable. Similar recommendations come from the National Institute of Health and Care Excellence (NICE) in the UK, the International Diabetes Federation (IDF) and the American College of Physicians [46–48]. However, beyond comparisons with sulfonlylureas and insulin, there are no long-term data comparing metformin as first-line treatment with other glucose-lowering agents (e.g. thiazolidinediones, SGLT2 inhibitors and GLP-1 receptor agonists) that also do not increase the risk of hypoglycaemia. Members of several of these drug classes have recently been demonstrated to have cardiovascular benefits [49]; how this biguanide would fare against these as monotherapy is unknown.

Future directions

Several recent, large cardiovascular outcome safety trials have found significant cardiovascular and, in some circumstances, renal benefits from non-biguanide therapies (e.g. specific thiazolidinediones, SGLT-2 inhibitors and GLP-1 receptor agonists) in individuals with type 2 diabetes at high cardiovascular disease risk. Therefore, an argument can now be made for a large outcomes trial to compare one or more of these agents with metformin as initial therapy.

Conclusions

With widespread use for more than two decades, metformin remains ensconced as an essential drug in the growing pharmacopeia for type 2 diabetes. It has established efficacy in both monotherapy and combination therapy regimens, is generally well tolerated and may have intrinsic cardiovascular benefits. Its role, however, as the optimal first-line glucose-lowering agent may now at least be legitimately challenged, since it has not yet been tested in long-term studies against newer drugs, some of which carry more robust proof of cardiovascular effectiveness, at least in individuals with established cardiovascular disease [49]. Until new evidence to the contrary is available, metformin will likely remain the ‘foundation therapy’ in type 2 diabetes.

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Contribution statement Both authors were responsible for drafting the article and revising it critically for important intellectual content. Both authors approved the version to be published.

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