Metformin revisited: A critical review of the benefit–risk balance in at-risk patients with type 2 diabetes

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Abstract

Metformin is unanimously considered a first-line glucose-lowering agent. Theoretically, however, it cannot be prescribed in a large proportion of patients with type 2 diabetes because of numerous contraindications that could lead to an increased risk of lactic acidosis. Various observational data from real-life have shown that many diabetic patients considered to be at risk still receive metformin and often without appropriate dose adjustment, yet apparently with no harm done and particularly no increased risk of lactic acidosis. More interestingly, recent data have suggested that type 2 diabetes patients considered at risk because of the presence of traditional contraindications may still derive benefit from metformin therapy with reductions in morbidity and mortality compared with other glucose-lowering agents, especially sulphonylureas. The present review analyzes the benefit–risk balance of metformin therapy in special populations, namely, patients with stable coronary artery disease, acute coronary syndrome or myocardial infarction, congestive heart failure, renal impairment or chronic kidney disease, hepatic dysfunction and chronic respiratory insufficiency, all conditions that could in theory increase the risk of lactic acidosis. Special attention is also paid to elderly patients with type 2 diabetes, a population that is growing rapidly, as older patients can accumulate several comorbidities classically considered contraindications to the use of metformin. A review of the recent scientific literature suggests that reassessment of the contraindications of metformin is now urgently needed to prevent physicians from prescribing the most popular glucose-lowering therapy in everyday clinical practice outside of the official recommendations.

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Keywords: Coronary artery disease; Elderly; Heart failure; Lactic acidosis; Metformin; Renal insufficiency; Type 2 diabetes

Résumé

La metformine revisitée : une revue critique de la balance bénéfice/risque chez les patients diabétiques de type 2 dits « à risque ».

La metformine est unanimement considérée comme le premier choix médicamenteux dans le traitement du diabète de type 2. Cependant, théoriquement, elle ne peut être prescrite dans une large proportion de patients avec un diabète de type 2 à cause de l’existence de nombreuses contre-indications correspondant aux situations susceptibles d’accroître le risque d’acidose lactique. Diverses données observationnelles issues de la vie réelle ont montré que bon nombre de patients diabétiques dits à risque reçoivent de la metformine, le plus souvent sans ajustement posologique approprié, et apparemment sans dommage, en particulier sans risque accru d’acidose lactique. De façon encore plus intéressante, des observations récentes suggèrent que les patients avec un diabète de type 2, considérés comme étant « à risque » à cause de la présence de contre-indications traditionnelles, tirent tout de même un bénéfice d’un traitement par metformine, avec mise en évidence d’une réduction de la morbidité et de la mortalité en comparaison avec d’autres agents anti-hyperglycémiant, plus particulièrement les sulfamides. La présente revue analyse la balance bénéfice–risque d’un traitement par metformine dans des populations spéciales, à savoir les patients avec une insuffisance coronarienne stable, un syndrome coronarien aigu ou un infarctus du myocarde, une insuffisance cardiaque, une insuffisance rénale chronique, une dysfonction hépatique et une insuffisance respiratoire chronique, toutes conditions qui théoriquement peuvent augmenter le risque d’acidose lactique. Une attention spéciale sera accordée aux patients âgés avec un diabète de type 2. En effet, cette population est en augmentation rapide et les patients âgés peuvent

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1. Introduction

Metformin is currently considered the first-line pharmacological therapy in type 2 diabetes mellitus (T2DM) [1,2], a recommendation that was recently confirmed in the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement [3]. The main reason is that the glucose-lowering activity of metformin as monotherapy is equal to or even better than that of any other oral agent without inducing either hypoglycaemia or weight gain. Also, metformin may be successfully combined with all other glucose-lowering agents, including insulin [2,3]. Metformin acts as a cellular AMP-activated protein kinase (AMPK) activator, a well-known cellular metabolic sensor [4]. Recent data also suggest that it suppresses hepatic gluconeogenesis by decreasing the production of cyclic AMP [5]. The antihyperglycaemic properties of metformin are mainly attributed to its suppression of hepatic glucose production, especially hepatic gluconeogenesis, and slightly increased peripheral tissue insulin sensitivity [6]. Although the precise biochemical mechanism of hypoglycaemic action of metformin remains unclear, it most probably interrupts mitochondrial oxidative processes in the liver [4] and corrects abnormalities of intracellular calcium metabolism in insulin-sensitive tissues (liver, skeletal muscle and adipocytes) as well as in cardiovascular tissue [7]. Adverse effects comprise gastrointestinal intolerance and, more rarely, lactic acidosis [8,9].

In the United Kingdom Prospective Diabetes Study (UKPDS), among patients allocated to intensive blood-glucose control, metformin showed a greater effect than sulphonylurea or insulin for any diabetes-related endpoint, all-cause mortality and stroke [10]. A significant reduction was also observed regarding myocardial infarction (MI) at the end of the trial in the metformin group compared with the conventional group [relative risk (RR): 0.61; P < 0.010], which persisted after a post-study follow-up of 10 years [RR: 0.67; 95% confidence interval (CI): 0.51–0.89] [11]. Soon after publication of the UKPDS, a risk–benefit assessment of metformin in T2DM was considered “very favorable” provided that contraindications were respected [12].

Nevertheless, although metformin has been considered the gold standard since the publication of that landmark study, its benefit–risk ratio has remained uncertain, including its cardiovascular efficacy according to a recent meta-analysis [13]. In addition, the UKPDS recruited individuals with newly diagnosed T2DM, while patients with cardiac or renal disease were excluded, as in most other clinical trials. Therefore, the risk–benefit ratio may be more open to question in a routine population with kidney and cardiovascular (CV) disease because of a higher risk of lactic acidosis [14].

Lactic acidosis associated with metformin treatment is a rare but important adverse event because it can be fatal. Several conditions have been described that may increase the risk of lactic acidosis associated with metformin [8]. These can be divided into circumstances:

- promote the formation of lactate by the peripheral tissues because of hypoxia (circulatory failure, severe respiratory insufficiency);
- impair lactate metabolism through the pathway of gluconeogenesis (primary or secondary hepatic failure);
- dramatically increase levels of metformin (renal impairment leads to metformin accumulation, thereby blocking liver gluconeogenesis) (Fig. 1).

In a recent Cochrane review, there was no evidence from 347 prospective comparative trials or observational cohort studies that metformin was associated with an increased risk of lactic acidosis or increased levels of lactate compared with other antihyperglycaemic treatments [15]. However, all clinical trials excluded at-risk patients and it is also plausible that published observational studies mainly included T2DM patients without the well-known contraindications. The scenario may therefore be rather different in real-life. Indeed, a population-based study showed that almost a quarter of patients prescribed metformin had contraindications to its use. Furthermore, the development of contraindications rarely resulted in discontinuation of metformin therapy [16]. These data have been confirmed in several other studies in various countries [17,18]. Despite this, lactic acidosis remains rare [8] even if case reports continue to be published regularly [9,19].
In the study sample of 19,691 T2DM patients with established atherothrombosis participating in the Reduction of Atherothrombosis for Continued Health (REACH) Registry, the 2-year mortality rate was significantly lower in patients treated with metformin than in those not treated with metformin [adjusted hazard ratio (HR): 0.76; 95% CI: 0.65–0.89]. Of major interest relevant to the topic of the present review, the metformin-related association with lower mortality was consistent among subgroups, most noticeably in patients aged > 65 years, those with a history of congestive heart failure (CHF) and those with moderate renal impairment [RI; estimated creatinine clearance or glomerular filtration rate (eGFR) of 30–60 mL/min/1.73 m²] [20].

The present review provides an updated evaluation of the use of metformin in patients who are considered at risk of lactic acidosis and for whom the use of metformin is contraindicated according to the official labeling. In particular, this review focuses on the following special populations:

- patients with stable coronary artery disease (CAD);
- patients with acute coronary syndrome or MI;
- patients with CHF;
- patients with RI or chronic kidney disease (CKD);
- patients with hepatic dysfunction;
- patients with chronic respiratory insufficiency;
- elderly patients, who may have accumulated several comorbidities (Table 1).

2. Methods

To identify the relevant studies, an extensive literature search of MEDLINE was performed of reports from January 1990 to February 2013, using the term “metformin” combined with “lactic acidosis”, and “metformin” combined with “coronary artery disease”, “acute coronary syndrome”, “myocardial infarction”, “congestive heart failure”, “renal insufficiency”, “chronic kidney disease”, “hepatic failure”, “respiratory insufficiency” and “elderly”. No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined.

3. Results

3.1. Metformin in patients with stable coronary artery disease

According to the ADA/EASD position statement, metformin may have some CV benefits and appears to be a useful drug in the setting of CAD, barring prevalent contraindications [3]. However, in a study from Israel of 2395 T2DM patients with CAD, those using metformin alone or in combination with sulphonylureas exhibited a significantly increased rate of mortality compared with T2DM patients not using oral glucose-lowering agents (Table 2). The conclusion was that, until the results of problem-orientated prospective studies of oral control of T2DM are available, alternative therapeutic approaches should be investigated in these patients [21]. However, these unfavorable results were not confirmed in other studies performed in various other countries.

In one nationwide Danish study, monotherapy with the most commonly used insulin secretagogues appeared to be associated with increased mortality and CV risk compared with metformin in 9607 T2DM patients with previous MI. Using multivariant Cox proportional-hazard analyses, including propensity analyses and compared with metformin monotherapy, the corresponding HR for all-cause mortality with various sulphonylureas were: glimepiride (the most prevalent sulphonylurea in this cohort): 1.30 (1.11–1.44); glibenclamide: 1.47 (1.22–1.76); glipizide: 1.53 (1.23–1.89); and tolbutamide: 1.47 (1.17–1.84). Results for gliclazide and repaglinide were not statistically different from that of metformin [22]. In a similar study in the US involving 2721 T2DM patients with documented CAD, a statistically significant increase in overall mortality risk was found with glipizide (HR: 1.41; 1.07–1.87) and glyburide (glibenclamide) (HR: 1.38; 1.04–1.83) vs. metformin [23].

The long-term effects of glipizide and metformin on major CV events were compared in 304 T2DM patients with a history of CAD. Treatment with metformin substantially reduced major CV events (composite of recurrent CV events, including death from a CV cause, death from any cause, non-fatal MI, non-fatal stroke and arterial revascularization) during a median follow-up period of 5.0 years compared with glipizide (HR: 0.54; 0.30–0.90). No difference was observed between the two groups regarding all-cause mortality, but the study had insufficient statistical power to specifically detect such a difference [24].

Optimal treatment for patients with both T2DM and stable ischaemic heart disease was investigated in the large prospective randomized BARI-2D trial, including 2368 T2DM patients. At 5 years, there was no significant difference in the rates of death and major CV events between patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization (metformin and/or thiazolidinedione) and insulin provision (insulin and/or sulphonylurea). Unfortunately the results could not distinguish between the effects of either insulin-sensitizing agent (metformin or thiazolidinedione), thereby making it impossible to specifically analyze the effects of metformin per se [25]. In a retrospective analysis of the Prevention of Restenosis with Tranilast and its Outcomes Trial (PRESTO), use of sensitizer therapy (metformin with or without additional therapy) in T2DM patients undergoing coronary interventions appeared to decrease adverse clinical events, especially death [odds ratio (OR): 0.39; 0.19–0.77] and MI (OR: 0.31; 0.15–0.66), compared with diabetic patients treated with non-sensitizer therapy (insulin and/or sulphonylureas) [26].

In patients with stable CAD, metformin is associated with a better CV prognosis than sulphonylureas. Stable CAD should not be considered a contraindication to the use of metformin in patients with T2DM.
Table 1
Comparison of risks and benefits associated with metformin use in special populations of patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Risk of lactic acidosis</th>
<th>Potential benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>Risk of myocardial infarction (hypoxia)</td>
<td>Decreased myocardial infarction, lower mortality</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>Risk of cardiogenic shock or acute congestive heart failure</td>
<td>Cardioprotection against ischaemia/reperfusion injury</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Hypoxia + functional renal insufficiency</td>
<td>Lower mortality</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Metformin accumulation, inhibition of gluconeogenesis</td>
<td>Lower mortality in cases of moderate renal impairment</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>Reduced gluconeogenesis</td>
<td>No data</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>Hypoxia</td>
<td>Lower mortality if no other contraindications</td>
</tr>
<tr>
<td>Elderly</td>
<td>Frailty, comorbidities</td>
<td></td>
</tr>
</tbody>
</table>

3.2. Metformin in patients following acute coronary syndrome

In a retrospective study evaluating the association of T2DM and glucose-lowering strategies with clinical outcomes after acute coronary syndrome, hypoglycaemic therapy with only insulin and/or sulphonylurea (insulin-providing; n = 1473) was associated with higher rates of 90-day death/MI/severe recurrent ischaemia compared with therapy using only biguanide and/or thiazolidinedione therapy (insulin-sensitizing; n = 100; adjusted OR: 2.1; 1.2–3.7). However, the study protocol again did not allow specific analysis of the effect of metformin [27].

In another retrospective cohort study of 24,953 Medicare beneficiaries with diabetes discharged after hospitalization with acute MI, after multivariable analysis there was only a trend for lower 1-year mortality rates in patients treated with metformin (HR: 0.92; 0.81–1.06) compared with patients prescribed an antihypoglycaemic regimen that included no insulin-sensitizer [28].

In a nationwide population-based follow-up study including all Danish patients hospitalized with first-time MI between 1996 and 2004, the overall cumulative 30-day and 1-year mortality rates were lower in patients treated with metformin than in patients receiving sulphonylureas, but the differences disappeared after multiple adjustments (Table 2) [29].

In patients with T2DM admitted with acute MI not treated with emergency percutaneous coronary intervention, monotherapy with sulphonylurea was associated with increased CV mortality (HR: 1.28; 1.14–1.44), CV death plus non-fatal MI (HR: 1.20; 1.08–1.33) and all-cause mortality (HR: 1.25; 1.13–1.40) compared with metformin as monotherapy [30]. The same group later confirmed a two- to threefold higher risk of CV mortality, CV mortality plus non-fatal MI and all-cause mortality, respectively, with glyburide (glibenclamide) compared with metformin [31].

In a post-hoc analysis using the total Diabetes Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) -2 cohorts as an epidemiological database, mortality and morbidity rates were assessed by glucose-lowering treatment during an extended period of follow-up (median 4.1 years, maximum 8.1 years) in 1145 patients with MI and T2DM. In contrast to sulphonylurea and insulin, metformin was associated with a lower mortality rate (HR: 0.65; 0.47–0.90), a lower risk of death due to malignancies (HR: 0.25; 0.08–0.83) and a trend towards a lower risk of CV death (HR: 0.72; 0.49–1.06). In this study, metformin appeared to be protective against the

Table 2
All-cause mortality in patients with type 2 diabetes and stable coronary artery disease (CAD), post-acute coronary syndrome (ACS) or myocardial infarction (MI) and congestive heart failure (CHF) with metformin therapy vs. oral glucose-lowering therapy without metformin (usually sulphonylureas).

<table>
<thead>
<tr>
<th>References</th>
<th>Comparator</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable CAD</td>
<td>Fisman et al., 1999 [21]</td>
<td>1.42</td>
<td>1.10–1.85</td>
</tr>
<tr>
<td></td>
<td>Schramm et al., 2011 [22]</td>
<td>0.77</td>
<td>0.64–0.93</td>
</tr>
<tr>
<td></td>
<td>Pantalone et al., 2012 [23]</td>
<td>0.72</td>
<td>0.54–0.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.71</td>
<td>0.53–0.93</td>
</tr>
<tr>
<td>Post-ACS or MI</td>
<td>Inzucchi et al., 2005 [28]</td>
<td>0.92</td>
<td>0.81–1.06</td>
</tr>
<tr>
<td></td>
<td>Horsdal et al., 2008 [29]</td>
<td>0.58&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.47–0.72</td>
</tr>
<tr>
<td></td>
<td>Jorgensen et al., 2010 [30]</td>
<td>0.80</td>
<td>0.71–0.88</td>
</tr>
<tr>
<td></td>
<td>Jorgensen et al., 2011 [31]</td>
<td>0.40</td>
<td>0.38–0.90</td>
</tr>
<tr>
<td></td>
<td>Mellblin et al., 2011 [32]</td>
<td>0.65</td>
<td>0.47–0.90</td>
</tr>
<tr>
<td>CHF</td>
<td>Masoudi et al., 2005 [39]</td>
<td>0.87</td>
<td>0.78–0.97</td>
</tr>
<tr>
<td></td>
<td>Eerich et al., 2005 [40]</td>
<td>0.70</td>
<td>0.54–0.91</td>
</tr>
<tr>
<td></td>
<td>Andersson et al., 2010 [41]</td>
<td>0.85</td>
<td>0.75–0.98</td>
</tr>
<tr>
<td></td>
<td>MacDonald et al., 2010 [42]</td>
<td>0.65</td>
<td>0.48–0.87</td>
</tr>
<tr>
<td></td>
<td>Aguilar et al., 2011 [43]</td>
<td>0.69</td>
<td>0.54–0.90</td>
</tr>
<tr>
<td></td>
<td>Roussel et al., 2010 [20]</td>
<td>0.76</td>
<td>0.63–0.92</td>
</tr>
</tbody>
</table>

<sup>a</sup> Compared with sulphonylurea, HR: 1.11 (0.90–1.36).

<sup>b</sup> 1-year mortality after multiple adjustments, HR: 0.96 (0.71–1.31).

<sup>c</sup> Compared with sulphonylurea, HR: 0.84 (0.67–1.06); HR: hazard ratio; 95% CI: 95% confidence interval.
risk of death, while insulin may have been associated with an increased risk of non-fatal cardiac events [32]. In yet another study involving chronic pretreatment with and without metformin, metformin pretreatment was shown to be associated with a reduction in the no-reflow phenomenon in 154 patients with T2DM after primary angioplasty for a first ST-segment elevation MI (4.2% and 14.6%, respectively; \( P < 0.05 \)) [33].

The finding that metformin limits MI size and remodeling in animal models of MI suggests that patients suffering from myocardial ischaemia could benefit from treatment with metformin even when patients do not have diabetes [34]. Currently, several clinical trials are ongoing to test this hypothesis. One percutaneous intervention as adjunct to primary intervention in ST elevation myocardial infarction (GIPS)-III trial, a prospective single-centre, double-blind, randomized placebo-controlled trial to assess the efficacy of metformin in preserving left ventricular ejection fraction in non-diabetic patients presenting with ST elevation MI (STEMI) [35].

In patients with acute coronary syndrome (MI or revascularization), metformin is associated with better short-term and long-term prognoses than other glucose-lowering agents. Acute coronary syndrome should not be considered a contraindication to the use of metformin in patients with T2DM provided there is no circulatory failure.

3.3. Metformin in patients with congestive heart failure

The use of metformin is widespread and has rapidly increased in Medicare beneficiaries with diabetes and CHF in direct contrast to explicit warnings against this practice by the US Food and Drug Administration (FDA) [36]. However, traditionally CHF was considered a contraindication to the use of metformin, more recent evidence has shown that this should no longer be the case [37,38].

In a retrospective cohort study of 16,417 Medicare beneficiaries with T2DM discharged after hospitalization with the principal discharge diagnosis of CHF, crude 1-year mortality rates were lower among the 1861 treated with metformin (24.7%) compared with the rates among the 12,069 not treated with an insulin-sensitizing drug (metformin or thiazolidinedione: 36.0%; \( P < 0.0001 \)). In multivariable models, treatment with metformin was associated with a significantly lower risk of death (HR: 0.87; 0.78–0.97), whereas there was no association between reduced mortality and treatment with sulphonylurea or insulin. There was also a lower risk of readmission for CHF with metformin treatment (HR: 0.92; 0.92–0.99) in contrast to a higher risk with thiazolidinedione. This observational study suggests that metformin is not associated with increased mortality and may improve outcomes in older patients with diabetes and CHF [39].

Using the Saskatchewan health databases, Canadian T2DM patients with incident CHF (\( n = 1833 \)) were grouped according to antidiabetic therapy: metformin monotherapy (\( n = 208 \)); sulphonylurea monotherapy (\( n = 773 \)); and the two in combination (\( n = 852 \)). After an average follow-up of 2.5 years and compared with sulphonylurea therapy, fewer deaths occurred in those receiving metformin: HR: 0.70 (0.54–0.91) as monotherapy; and HR: 0.61 (0.52–0.72) as a combination. A reduction in deaths or hospitalizations was also observed with metformin as monotherapy (HR: 0.83; 0.70–0.99) and combination therapy (HR: 0.86; 0.77–0.96). Thus, metformin alone or in combination in patients with T2DM and CHF was associated with lower morbidity and mortality compared with sulphonylurea monotherapy [40].

A nationwide retrospective cohort study investigated the risk of all-cause mortality associated with individual glucose-lowering treatment regimens used in the current clinical practice in Denmark. Again, treatment with metformin was associated with a lower risk of mortality in diabetic patients with CHF compared with sulphonylurea treatment (HR: 0.85; 0.75–0.98) or with insulin [41].

A case-control study nested within the UK’s General Practice Research Database showed that the current use of metformin monotherapy (adjusted OR: 0.65; 0.48–0.87) or metformin with or without other agents (OR: 0.72; 0.59–0.90) was associated with lower mortality compared with patients not exposed to antidiabetic drugs, whereas the use of other oral glucose-lowering agents or insulin was not associated with lower all-cause mortality [42].

The association between metformin use and the risk of death or hospitalization was also examined in a US national cohort of 6185 patients with CHF and diabetes treated in ambulatory clinics at Veteran Affairs Medical Centers. In the propensity score-matching analysis (\( n = 2874 \)) at 2 years of follow-up, death rates were 16.1% in patients receiving metformin compared with 19.8% in patients not receiving metformin (HR: 0.76; 0.63–0.92; \( P < 0.01 \)). Neither hospitalization related to CHF nor total hospitalization rates were significantly different between individuals treated with metformin compared with those not treated with the drug [43].

In patients with T2DM and established atherothrombosis participating in the REACH Registry, a significant reduction in 2-year death rates was associated with metformin therapy in patients with a history of CHF (HR: 0.69; 0.54–0.90) [20].

Despite uncertainty in the scientific literature because of the observational nature of the published data, there appears to be no clinical uncertainty as regards the safety and effectiveness of metformin in CHF, making a definitive randomized trial virtually impossible [44]. Metformin, previously contraindicated in CHF, may now be used if ventricular dysfunction is not severe, if the patient’s CV status is stable and if renal function is normal [3,45]. However, diabetic patients with elevated systolic blood pressure are at increased risk of developing acute decompensated CHF, a condition that is often associated with increased kidney function. During acute decompensated CHF, timely treatment may prevent the loss of kidney function to the threshold...
associated with an increased risk of metformin-associated lactic acidosis. Metformin should not be withheld in diabetic patients with stable CHF who do not have other risk factors for acute decompensated CHF or lactic acidosis [46].

3.4. Metformin in patients with renal insufficiency

Metformin undergoes renal excretion [47,48]. The population mean renal clearance [CL(R)] and apparent total clearance after oral administration [CL/F] of metformin were estimated to be 510 ± 130 mL/min and 1140 ± 330 mL/min in healthy subjects and T2DM patients with good renal function, respectively. Over a range of renal function, the population mean values of CL(R) and CL/F of metformin were 4.3 ± 1.5 and 10.7 ± 3.5 times as great, respectively, as the clearance of creatinine. As the CL(R) and CL/F decreased approximately in proportion to creatinine clearance, the dosage of metformin should be reduced in patients with RI in proportion to the reduced eGFR [48]. Prolonged elimination of metformin in patients with CKD, which is negatively correlated with creatinine clearance, may explain the risk of metformin accumulation in cases of RI [49].

Classically, CKD (creatinine clearance < 60 mL/min) represents a contraindication to the use of metformin in patients with T2DM [12]. In cases of RI, metformin may certainly accumulate, block gluconeogenesis and cause lactic acidosis, a serious complication that can be fatal [9,50]. Most cases reporting severe lactic acidosis involve patients with rather severe RI, although renal dysfunction may only be a prerequisite for metformin accumulation [8]. In any case, because of this contraindication, very few data are available in the literature regarding the use of metformin in patients with moderate RI. In contrast to what has been reported for other glucose-lowering agents, especially the new incretin-based therapies, no specific trials have been performed to assess the benefit-risk balance of metformin use in patients with moderate or severe RI [51]. In the various series reporting real-life data, however, patients receiving metformin despite the presence of RI as an official contraindication are not unusual and apparently not harmed [16–18]. In the US Fourth National Health and Nutrition Examination Survey (NHANES IV), the proportion of patients using metformin progressively decreased according to their severity of RI from 45.6% at stage 1 to 23.8% at stage 3, and 0% at stages 4 and 5 [52]. Also, the US retrospective database analysis of the GE centricity electronic medical records (EMR) for outpatients showed that, after eGFR calculation, almost no patients with orders for metformin received doses of the drug appropriate for their degree of RI [53]. Thus, although metformin is frequently used at inappropriate doses in patients with RI, the clinical consequences of such use remain poorly understood.

According to the results of REACH, metformin was prescribed worldwide in 1572 patients with moderate renal failure [Kidney Disease Outcomes Quality Initiative (KDOQI) stage 3] in contraindication to guidelines for its use [54]. In this subgroup, metformin use was associated with at least a similar reduction in mortality as in the overall population. The 2-year mortality rate associated with metformin (n = 1572) vs. other glucose-lowering agents (n = 3388) was significantly lower in patients with an eGFR of 30–60 mL/min/1.73 m² (adjusted HR: 0.64; 0.48–0.86; P = 0.003). The reduction was even greater than that observed in patients with an eGFR ≥ 60 mL/min/1.73 m² (metformin: n = 4442; no metformin: n = 6326; HR: 0.89; 0.71–1.11) [20].

These findings were confirmed in a cohort study from the Swedish National Diabetes Register involving 51,675 patients with T2DM and different levels of renal function. Metformin compared with any other treatment showed similar reduced risks for all-cause mortality in patients with an eGFR of 45–60 mL/min/1.73 m² and in those with an eGFR > 60 mL/min/1.73 m². No benefit, but no harm either, was observed with metformin therapy in patients with an eGFR of 30–45 mL/min/1.73 m² (Table 3) [55].

In patients with mild-to-moderate CKD, consistent observational data have shown that metformin is associated with a better overall prognosis (including all-cause mortality) than other glucose-lowering agents, and that the risk of lactic acidosis in the absence of acute concomitant events is very low. Stable mild-to-moderate (with appropriate dose reduction) CKD should not be considered an absolute contraindication to the use of metformin in patients with T2DM.

3.5. Metformin in patients with hepatic dysfunction

The liver plays a major role in gluconeogenesis, and hepatic failure can dramatically hamper lactate removal through this biochemical pathway (Fig. 1). Given the importance of the liver for lactate clearance, focusing on the severity of and prognosis for liver disease has been suggested. Indeed, in many cases, as already mentioned, renal dysfunction is only a prerequisite for metformin accumulation, which may only be dangerous when associated with liver failure [8]. Therefore, hepatic failure as seen in advanced cirrhosis or severe liver hypoperfusion is considered a contraindication to metformin in patients with T2DM. Nevertheless, no specific studies have been performed with metformin in patients with liver failure.

However, a recent observational prospective cohort of 100 consecutive diabetic patients with ongoing hepatitis C
Table 3
All-cause mortality in patients with type 2 diabetes receiving metformin therapy compared with any other glucose-lowering agent.

<table>
<thead>
<tr>
<th>CKD</th>
<th>Patients by eGFR (mL/min/1.73 m²)</th>
<th>Metformin vs. any other agent (n)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roussel et al., 2010 [20]</td>
<td>&gt;60</td>
<td>4442 vs. 6326</td>
<td>0.89</td>
<td>0.71–1.11</td>
</tr>
<tr>
<td></td>
<td>30–60</td>
<td>1572 vs. 3388</td>
<td>0.64</td>
<td>0.48–0.86</td>
</tr>
<tr>
<td>Ekstrom et al., 2012 [55]</td>
<td>&gt;60</td>
<td>28,015 vs. 31,614</td>
<td>0.87</td>
<td>0.81–0.94</td>
</tr>
<tr>
<td></td>
<td>45–60</td>
<td>4079 vs. 6176</td>
<td>0.87</td>
<td>0.77–0.99</td>
</tr>
<tr>
<td></td>
<td>30–45</td>
<td>715 vs. 2152</td>
<td>1.02</td>
<td>0.84–1.24</td>
</tr>
<tr>
<td>Elderly</td>
<td>Patients by age (years)</td>
<td>Metformin vs. any other agent (n)</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Roussel et al., 2010 [20]</td>
<td>40–65</td>
<td>2987 vs. 3859</td>
<td>0.63</td>
<td>0.45–0.89</td>
</tr>
<tr>
<td></td>
<td>65–80</td>
<td>3791 vs. 6768</td>
<td>0.77</td>
<td>0.62–0.95</td>
</tr>
<tr>
<td></td>
<td>&gt;80</td>
<td>598 vs. 1492</td>
<td>0.92</td>
<td>0.66–1.28</td>
</tr>
<tr>
<td>Tzoulaki et al., 2009 [74]</td>
<td>&lt;65</td>
<td>NA vs. 1114</td>
<td>0.56</td>
<td>0.49–0.625</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>NA vs. 8492</td>
<td>0.74</td>
<td>0.70–0.78</td>
</tr>
</tbody>
</table>

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HR: hazard ratio; 95% CI: 95% confidence interval; NA: not available.

a Compared with second-generation sulphonylureas.

virus (HCV) cirrhosis and no contraindication to metformin were included in a screening programme for hepatocellular carcinoma. After a median follow-up of 5.7 years, use of metformin was independently associated with reduced incidences of hepatocellular carcinoma (HR: 0.19; 0.04–0.79) and liver-related death/transplantation (HR: 0.22; 0.05–0.99) [56].

Thus, metformin may not be contraindicated in patients with compensated HCV cirrhosis, but may instead provide benefits [57]. Further studies are needed to confirm this observation.

Liver dysfunction associated with non-alcoholic fatty liver disease (NAFLD) and even non-alcoholic steatohepatitis (NASH) should be distinguished from true hepatic failure. Mild-to-moderate steatosis is a common finding in overweight/obese patients with T2DM, and metformin may be prescribed in such a population with no harmful effects [58]. In particular, no increased risk of lactic acidosis has been reported. Metformin may also have potentially beneficial effects in patients with NAFLD, although the evidence is rather scanty [59–61]. Conflicting results have been reported in young people with fatty liver, with a reduction in prevalence and severity after 6 months of metformin in one study [62], but no better results compared with lifestyle after 24 months of metformin in another [63]. In participants in the Edinburgh Type 2 Diabetes Study, the use of metformin was unexpectedly associated with the presence of hepatic steatosis (compared with those classed as normal/probable normal) on ultrasound scans independent of body mass index (BMI) and glycaemic control (OR: 2.19; 1.59–3.00) [64]. As previous studies of the use of metformin in NAFLD had shown a positive or neutral effect [65], a causative link between metformin use and NAFLD in that study is unlikely. A specific study compared the effects of metformin with those of thiazolidinedione in adult T2DM patients. While both agents increased hepatic insulin sensitivity, metformin, unlike rosiglitazone, did not decrease liver fat or increase insulin clearance [66]. In another study, metformin did not provide any specific beneficial effects in adult patients with NAFLD in contrast to pioglitazone [67]. According to the conclusions of some recent practical guidelines for the management of NAFLD based on an extensive review of the literature [59], metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH [68].

In patients with NAFLD, metformin may be used, but no substantial improvement in liver fat content should be expected (in contrast to what has been observed with thiazolidinediones). As the data supporting the use of metformin in patients with liver failure are limited, this remains a contraindication.

3.6. Metformin in patients with chronic respiratory insufficiency

Severe chronic respiratory insufficiency can lead to hypoxia and thereby enhance anaerobic glycolysis and promote lactic-acid formation (Fig. 1). That is why this medical condition is a traditional contraindication to the use of metformin. However, there is no specific study demonstrating the precise risk of metformin use in a population with chronic respiratory insufficiency or the level of severity that represents an absolute rather than relative contraindication to metformin use. Pulmonary diseases and respiratory insufficiency have been noted in some reports of inadequate use of metformin [17,18]. The risk of lactic acidosis associated with metformin therapy in T2DM patients with chronic respiratory disease is most probably very low, if still present, in the absence of concomitant hepatic failure and/or RI. Furthermore, as discussed by Lalau [8], the relationship between metformin and lactic acidosis is complex, as use of the drug may be causal, co-responsible or simply coincidental.
Surprisingly but of potential interest are the recent experimental data showing that metformin can reduce both airways inflammation and remodeling (at least partially) through the induction of AMPK activation while decreasing oxidative stress. These data provide insight into the beneficial role of metformin as a novel therapeutic drug for chronic asthma [69].

No data are available regarding the use of metformin in T2DM patients with chronic respiratory disease. Consequently, severe chronic respiratory insufficiency is a contraindication to the use of metformin because of the risk of hypoxia and lactic acidosis.

3.7. Metformin in elderly patients

Overall there is a scarcity of data regarding the use of pharmacological agents in general, and glucose-lowering agents in particular, in older adults with T2DM, and clinical guidance is largely based on data obtained in younger populations [70]. According to a recent position statement, strategies specifically minimizing the risk of low blood-glucose may be preferred in older people with T2DM, and this pharmacodynamic characteristic is shared by metformin [3].

A preliminary limited study of 24 elderly patients with T2DM (aged 70–88 years) concluded that, provided the dosage is adjusted to renal function, metabolic tolerance of metformin therapy is satisfactory [71]. A more recent study suggested that the efficacy of metformin in elderly Japanese patients with T2DM did not differ from that in non-elderly patients, and that its safety might be linked to specific and well-documented contraindications rather than to age itself [72]. Another recent study performed in Poland indicated relatively good tolerability of metformin by elderly patients (mean age: 67 years) despite the presence of the traditional contraindications to the drug [73].

Finally, and most interesting, in the above-mentioned REACH Registry, the overall lower 2-year mortality rate in T2DM patients with atherothrombosis treated with vs. without metformin was confirmed in the large cohort of subjects aged 65–80 years (n = 10,559; adjusted HR: 0.77; 0.62–0.95; P = 0.02) [20]. This reduction was only slightly lower than that observed in a younger age group (40–65 years; n = 6846; HR: 0.63; 0.45–0.89; P = 0.008). Few T2DM patients aged >80 years were included in the registry, and there was no mortality difference between those receiving metformin or not (n = 2090; HR: 0.92; 0.66–1.28). In this very elderly group, even if the benefit was not significant, no harm could be detected.

Similar reassuring findings were found in the 1990–2005 UK General Practice Research Database. Compared with second-generation sulphonylureas, metformin was associated with a significant reduction in all-cause mortality both in patients aged >65 years and in those aged ≤65 years at the time of their initial prescription (Table 3) [74].

Observational data have suggested that the use of metformin is not harmful in elderly T2DM patients, but may instead be associated with more favorable outcomes (including overall mortality) compared with other glucose-lowering agents, as previously observed in younger T2DM patients. Thus, old age per se should not be considered a contraindication to the use of metformin in the absence of any other absolute contraindications. However, despite the fact that metformin is widely prescribed in the elderly, no specific trial has been devoted to this special population with the aim of assessing the benefit–risk ratio.

3.8. General discussion

Given these observational data as recently published in the international literature, it may be easier to understand the somewhat provocative title of a paper published several years ago: “Contraindications can damage your health—is metformin a case in point?” [75]. What follows is a brief discussion of the benefit–risk balance of metformin in T2DM patients with CV disease, in patients with RI and in the elderly.

3.8.1. Metformin and cardiovascular disease

CV disease remains the main cause of mortality in patients with T2DM and tackling this common complication requires a multifactorial approach [76]. Diabetic patients with RI have an even greater risk of having and dying from CV disease. Therefore, CV protection in patients with T2DM represents a major objective in clinical practice. Although it remains a matter of controversy [13], metformin can offer CV protection in patients with newly diagnosed T2DM [10] and in insulin-treated patients at a later stage of the disease [77]. The putative beneficial actions exerted by metformin on arterial vessels may be explained by its effects on lipids, inflammation, haemostasis, endothelial and platelet function, and vessel-wall abnormalities [78].

Experimental studies have shown that AMPK activators (such as metformin) can attenuate cardiomyocytic apoptosis during cardioplegia-induced hypoxia/reoxygenation injury. Several mechanisms have been proposed to explain such cardioprotection by metformin, including reduction of endoplasmic reticulum stress, inhibition of cellular unfolded protein response, endothelial nitric-oxide synthase (eNOS) activation and increased expression of PGC-1α, a key controller of energy metabolism in muscle that is downregulated in diabetic conditions [79–81]. Chronic metformin treatment augments myocardial resistance to ischaemia/reperfusion injury by other mechanisms in addition to lowering blood-glucose. Thus, metformin prescribed chronically to T2DM patients may lead to a basal state of cardioprotection, thereby potentially limiting myocardial damage due to CV events [81].
3.8.2. Metformin and chronic kidney disease

The 2012 update of the KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease was intended to assist the practitioner caring for patients with diabetes and CKD [82].

Recent data have suggested that metformin may be administered with caution in patients with creatinine clearance at 45–60 mL/min or even lower (30–45 mL/min), provided that the daily dose is reduced by half and kidney function is regularly monitored [83]. In patients without comorbid conditions that predispose to lactic acidosis, elevated serum creatinine levels (or reduced GFR) should be considered a risk factor for the development of lactic acidosis, albeit not an absolute contraindication [84]. In daily clinical practice, the development of contraindications, including RI, rarely results in discontinuation of metformin therapy and yet, despite this, lactic acidosis remains a rare event [16,85]. In some studies, the prevalence of T2DM in those receiving metformin despite having a contraindication (including a GFR < 60 mL/min) was > 80%. Nevertheless, metformin use under such conditions does not appear to increase the risk of lactic acidosis, hospitalization or death [86]. Other than the possibility that creatinine levels may not be appropriately assessed by physicians both initially and during follow-up, another explanation for the common use of metformin in T2DM with RI may be that prescribers consider that the benefits of therapy outweigh the potential risks [87]. There are now more and more data to suggest that metformin can be used in stable mild-to-moderate CKD and that not prescribing metformin in these patients may cause more harm (no protection against CV disease, for instance) compared with the benefits of avoiding potentially rare complications (in this case, lactic acidosis) [75,88,89]. These observations led to a recent position statement in which metformin could be used down to a GFR of 30 mL/min, with dose reduction advised at 45 mL/min (Fig. 2) [3,82]. This would lead to being able to safely prescribe metformin in patients with an eGFR < 60 mL/min/1.73 m² and, more important in medical practice, legally and according to the law [90,91].

Nevertheless, the risk of lactic acidosis should not be neglected [9,89,92] and the drug should be immediately stopped in the presence of unstable RI, any acute event (such as high fever), gastrointestinal disorders (diarrhoea, vomiting) and dehydration, all conditions that can rapidly cause renal function to deteriorate [9,89]. Last but not least, the use of nephrotoxic agents (such as non-steroidal anti-inflammatory drugs) should also be avoided in any patient with renal dysfunction, especially in those with stage 3 CKD using metformin therapy.

3.8.3. Metformin and the elderly

The selection of appropriate drug regimens for older T2DM patients remains challenging. The substantial risk of hypoglycaemia with insulin secretagogues such as sulphphonylureas is well recognized in this population and, in this regard, metformin may offer substantial benefit [70]. However, no clinical trial has specifically been devoted to the risk–benefit balance of metformin in elderly patients with T2DM. Paradoxically, the best evidence can be found in clinical trials focusing on the effect of gliptins (dipeptidyl peptidase-4 inhibitors), as these new oral incretin-based glucose-lowering agents were either compared with metformin or combined with metformin as basal therapy [93,94]. These recent data have confirmed that metformin is effective and well tolerated in older patients with T2DM, although the older diabetic patients included in clinical trials may not be fully representative of the elderly population in real-life.

Because elderly patients with T2DM are exposed to multiple comorbidities, physicians caring for older adults with diabetes should be able to assess the patient’s health status and use this information to recommend a treatment plan consistent with the patient’s personal goals for care [95]. This means that older T2DM patients, who are frail, anorexic and/or underweight and those with CHF or renal or hepatic insufficiency, or dehydration, may not be appropriate candidates for metformin therapy [70].

In elderly patients with T2DM, beyond the CV risk, another leading cause of death is related to cancer. Growing recent data now support the protective effect of metformin against the development of most types of cancer (especially digestive system and breast cancers) and the associated mortality [96,97]. If these findings are confirmed, it would be a pity to have deprived older T2DM patients, just because of their age, of the use of a drug that may prove helpful.

4. Conclusion

Metformin represents the cornerstone of glucose-lowering therapy for T2DM. Despite its array of benefits that comparatively outweigh those of alternative oral antglycaemic agents, the ability of clinicians to prescribe metformin is restricted in many situations. There are numerous contraindications, reviewed in the present paper, and cautions concerning the putative risks of metformin-related side-effects that could necessitate cessation of metformin. Most notably, the often stated yet completely unsubstantiated heightened risk for the development...
of lactic acidosis in the context of RI or CHF is particularly contentious. Given its proven clinical benefit, restriction of metformin use based on creatinine cut-offs provided by the US FDA, or a GFR cut-off of ≤ 60 mL/min/1.73 m², has been called into question. Similarly, stable CHF or CAD can no longer be considered contraindications to the use of metformin. Considering the high prevalence of stable RI, CAD and/or CHF in the elderly population, the recently published observations on the potential benefit–risk balance of metformin therapy are of particular interest. Nevertheless, more valuable data relevant to the elderly population are still required because the evidence remains sparse. Individual benefit–risk ratios should be assessed so as not to deprive patients of a potentially beneficial drug and also to not expose T2DM individuals to unacceptable risk. For this reason, the patient-centred approach recommended by the ADA/EASD position statement is of major clinical value.

Disclosure of interest

A.J. Scheen has received lecturer/advisor fees from Abbott, AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, Glaxo-SmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi-Aventis.

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References


