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 as the first-line glucose-lowering agent. Theoretically, however, it cannot be prescribed in a large proportion of patients with type 2 diabetes because of the presence of numerous contraindications corresponding to situations that may increase the risk of lactic acidosis. Various observational data from real life showed that many diabetic patients considered as "at risk" still receive metformin, often without appropriate dose adjustment, apparently without any harm, especially no increased risk of lactic acidosis. More interestingly, recent data suggest that type 2 diabetes patients who are considered as being "at risk" because of the presence of traditional contraindications still take benefit from metformin therapy, with a reduction of morbidity and mortality compared with other glucose-lowering agents, more particularly sulfonylureas. 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 may theoretically increase the risk of lactic acidosis. A special attention will be devoted to elderly patients with type 2 diabetes. Indeed, this population is growing rapidly and older patients may cumulate several comorbidities classically considered as contraindications to the use of metformin. The recent scientific literature suggests that reconsidering the contraindications of metformin is urgently needed in order to avoid physicians prescribe the most popular glucose-lowering therapy in daily clinical practice outside the official recommendations.

Key-words : Coronary artery disease – Elderly – Heart failure – Lactic acidosis – Metformin – Renal insufficiency – Type 2 diabetes

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

RESUME

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-hyperglycémiants, 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 cumuler plusieurs comorbidités classiquement considérées comme des contre-indications à l'utilisation de la metformine. Au vu de l'analyse de la littérature récente, il est urgent de reconsidérer les contre-indications de la metformine pour éviter que les médecins, dans leur pratique clinique au quotidien, continuent à prescrire la thérapie anti-hyperglycémiante la plus populaire en dehors des recommandations officielles.

Mots-clé : Acidose lactique – Diabète de type 2 – Metformine – Insuffisance cardiaque – Insuffisance rénale – Insuffisance hépatique – Insuffisance coronaire – Patient âgé

Introduction

Type 2 diabetes (T2DM) is currently considered as the first line pharmacological therapy in T2DM [1, 2], a recommendation that has been confirmed in the recent ADA (American Diabetes Association)-EASD (European Association for the Study of Diabetes) position statement [3]. The main reason is that the glucose-lowering activity of metformin as monotherapy is equal or even better than that of any other oral agent, without inducing hypoglycaemia or weight gain. Furthermore, 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 suggested that it also suppresses hepatic glucagon signalling by decreasing production of cyclic AMP [5]. The antihyperglycaemic properties of metformin are mainly attributed to suppressed 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 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) and also in cardiovascular tissue [7]. Adverse effects comprise gastrointestinal intolerance and, more exceptionally, lactic acidosis [8, 9].

In the United Kingdom Prospective Diabetes Study (UKPDS), among patients allocated intensive blood-glucose control, metformin showed a greater effect than sulfonylureas 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 or RR=0,61; 95% confidence interval or CI ; P< 0,010), which persisted after a post-study follow-up of 10 years (RR=0.67 ; 0.51–0.89) [11]. Soon after the publication of the UKPDS, a risk-benefit assessment of metformin in T2DM was considered as "very favourable" provided that contraindications were respected [12].

Nevertheless, although metformin is considered the gold standard since the publication of this landmark study, its benefit/risk ratio remains uncertain, including its cardiovascular efficacy according to a recent meta-analysis [13]. In addition, the UKPDS recruited individuals with newly diagnosed T2DM, and patients with cardiac or renal disease were excluded, as in most other clinical trials. Therefore, the risk-benefit ratio may be more

questionable 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 that may be fatal. Several conditions have been depicted, which may increase the risk of lactic acidosis associated with metformin [8]. Schematically, they may be divided into circumstances that can (1) promote the formation of lactate by the peripheral tissues because of hypoxia (circulatory failure, severe respiratory insufficiency); (2) impair lactate metabolism through the pathway of gluconeogenesis (primary or secondary hepatic failure); and (3) dramatically increase the levels of metformin ((renal impairment leading to metformin accumulation, thereby blocking liver gluconeogenesis) (Figure 1). In a recent Cochrane review, there was no evidence from 347 prospective comparative trials or observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other anti-hyperglycaemic treatments [15]. However, all clinical trials excluded at risk patients and it is also plausible that published observational studies mainly included T2DM patients without well-known contraindications. The scene might be rather different in real life. Indeed, a population-based study shows that almost a quarter of patients prescribed metformin have contraindications to its use. Furthermore, development of contraindications rarely results 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 still 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 without metformin (adjusted hazard ratio or HR=0.76 ; 0.65-0.89). Of major interest regarding the topic of the present review, the metformin-related association with lower mortality was consistent among subgroups, noticeably in patients older than 65 years, patients with a history of congestive heart failure (CHF), and patients with moderate renal impairment (RI) (estimated creatinine clearance or glomerular filtration rate - eGFR - between 30 and 60 mL/min/1.73 m²) [20].

The present review provides an updated evaluation of the use of metformin in patients who are considered as at risk of lactic acidosis and for whom the use of metformin is contraindicated according to the official label. We will more particularly focus our attention

on the following special populations: 1) patients with stable coronary artery disease (CAD); 2) patients with acute coronary syndrome or MI; 3) patients with CHF; 4) patients with RI or chronic kidney disease (CKD); 5) patients with hepatic dysfunction; 6) patients with chronic respiratory insufficiency; and finally 7) elderly patients, who may cumulate several comorbidities (Table 1).

Methods

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

Results

1. Metformin in patients with stable coronary artery disease

According to the ADA-EASD position statement, metformin may have some CV benefits and would appear to be a useful drug in the setting of CAD, barring prevalent contraindications [3].

However, in a first study performed in Israel on 2,395 T2DM patients with CAD, those using metformin, alone or in combination with sulfonylureas, exhibited a significantly increased mortality compared with T2DM patients without oral glucose-lowering agents (Table 1). The conclusion was that until the results of problem-oriented prospective studies on oral control of T2DM will be available, alternative therapeutic approaches should be investigated in these patients [21]. However, these unfavourable results were not confirmed in further studies performed in various countries.

In a Danish nation-wide study, monotherapy with the most used insulin secretagogues seems to be associated with increased mortality and CV risk compared with metformin among 9,607 T2DM patients with previous MI. By multivariable Cox proportional-hazard analyses including propensity analyses and compared with metformin monotherapy, the corresponding HR of all-cause mortality were as follows for various sulfonylureas:

glimepiride (the most prevalent sulfonylurea in this cohort): 1.30 (1.11-1.44), glibenclamide: 1.47 (1.22-1.76), and glipizide: 1.53 (1.23-1.89). Results for gliclazide and repaglinide were not statistically different from metformin[22]. In another similar study in the US, in 2,721 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) versus metformin [23].

The long-term effects of glipizide and metformin on the major CV events were compared in 304 T2DM patients who had 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, nonfatal MI, nonfatal stroke, or arterial revascularization) in a median follow-up 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 no sufficient statistical power to detect specifically such a difference[24].

Optimal treatment for patients with both T2DM and stable ischemic heart disease has been investigated in the large prospective randomized trial BARI-2D with 2,368 T2DM patients. At 5 years, there was no significant difference in the rates of death and major CVevents 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 sulfonylurea). Unfortunately, the results cannot distinguish between the effect of either insulin-sensitizer agent (metformin or thiazolidinedione) and thus it is impossible to analyze specifically the effect of metformin per se [25]. In a retrospective analysis of the Prevention of Restenosis with Tranilast and its Outcomes Trial, use of sensitizer therapy (here metformin with or without additional therapy) in T2DM patients undergoing coronary interventions appeared to decrease adverse clinical events, especially death (odds ratio or OR=0.39 ; 0.19-0.77) and MI (OR=0.31 ; 0.15-0.66), compared with diabetic patients treated with nonsensitizer therapy (insulin and/or sulfonylureas) [26].

BOX : In patients with stable CAD, metformin is associated with a better CV prognosis than sulfonylureas. Stable CAD should not be considered as a contraindication to the use of metformin in patients with T2DM.

2. Metformin in patients following acute coronary syndrome

In a retrospective study evaluating the associations of T2DM and glucose-lowering strategies with clinical outcomes after acute coronary syndrome, hypoglycaemic therapy including only insulin and/or sulfonylurea (insulin-providing; n = 1,473) was associated with higher 90-day death/MI/severe recurrent ischaemia compared with therapy that included only biguanide and/or thiazolidinedione therapy (insulin-sensitizing; n = 100) (adjusted OR or OR=2.1 ; 1.2-3.7). Again, the study protocol did not allow analyze specifically 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 antihyperglycaemic regimen that included no insulin sensitizer [28].

In a nationwide population-based follow-up study among all Danish patients hospitalised with first-time MI from 1996 to 2004, the overall cumulative 30 day and 1 year mortality rates were lower in patients treated with metformin compared with patients receiving sulfonylureas, but the differences vanished after multiple adjustments (Table 2) [29].

In patients with T2DM admitted with acute MI not treated with emergent percutaneous coronary intervention, monotherapy treatment with sulfonylureas was associated with increased CV mortality (HR=1.28; 1.14-1.44), composite of CV death and non-fatal MI (HR=1.20; 1.08-1.33) and all-cause mortality (HR=1.25; 1.13-1.40) compared with metformin monotherapy [30]. Later on, the same group confirmed a 2 to 3 increased risk of CV mortality, CV mortality and nonfatal MI and all-cause mortality, respectively, with glyburide (glibenclamide) compared to metformin [31].

In a post hoc analysis of the total Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 cohort as an epidemiological database, mortality and morbidity rates were assessed by glucose-lowering treatment during an extended period of follow-up (median 4.1 and max 8.1 years) in 1,145 patients with MI and T2DM. In contrast to sulfonylureas and insulin, metformin was associated with a lower mortality rate (HR=0.65; 0.47-0.90), a lower risk of death from malignancies (HR=0.25 ; 0.08-0.83) and a trend for a lower risk of CV deaths (HR 0.72 ; 0.49-1.06). In that study, metformin seems to be protective against risk of death, while insulin may be associated with an increased risk of non-fatal cardiac events [32].

In another dedicated study, chronic pretreatment with metformin has been shown to be associated with the reduction of the no-reflow phenomenon in 154 patients with T2DM after primary angioplasty for a first ST-segment elevation MI (4.2 and 14.6%, 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 these patients do not have diabetes [34]. Currently, several clinical trials are being performed to test this hypothesis. As an example, the Glycometabolic Intervention as adjunct to Primary percutaneous intervention in ST elevation myocardial infarction (GIPS)-III trial is a prospective, single center, double blind, randomized, placebo-controlled trial, which is currently studying the efficacy of metformin with the aim to preserve left ventricular ejection fraction in non-diabetic patients presenting with ST elevation MI (STEMI) [35].

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

3. Metformin in patients with congestive heart failure

The use of metformin is common and has increased rapidly in Medicare beneficiaries with diabetes and CHF in direct contrast with explicit warnings against this practice by the Food and Drug Administration [36]. However, whereas, 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 1,861 treated with metformin (24.7%) compared with that among the 12,069 treated with no insulin-sensitizing drug (metformin or thiazolidinedione : 36.0%, P <0.0001). In multivariable models, treatment with metformin was associated with significantly lower risks of death (HR=0.87 ; 0.78-0.97), while there was no association between reduced mortality and treatment with sulfonylureas or insulin. There was a lower risk of readmission for CHF with metformin treatment (HR=0.92 ; 0.86-0.99), contrasting with a

higher risk for thiazolidinedione. This observational study suggested 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 in the US, T2DM patients with incident CHF (n=1,833) were grouped according to antidiabetic therapy: metformin monotherapy (n=208), sulfonylurea monotherapy (n=773), or combination therapy (n=852). After an average follow-up 2.5 years and compared with sulfonylurea therapy, fewer deaths occurred in subjects receiving metformin: HR=0.70; 0.54-0.91 for monotherapy and HR=0.61; 0.52-0.72 for combination therapy. A reduction in deaths or hospitalizations was also observed: for metformin monotherapy HR=0.83 ; 0.70-0.99 and for combination therapy HR=0.86 ; 0.77-0.96). Thus, metformin, alone or in combination, in subjects with T2DM and CHF was associated with lower morbidity and mortality compared with sulfonylurea monotherapy [40].

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

A case-control study nested within the U.K. General Practice Research Database cohort 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 who were not exposed to antidiabetic drugs whereas use of other oral glucose-lowering agents drugs or insulin was not associated with all-cause mortality [42].

The association between metformin use and the risk of death or risk of hospitalization was examined in a national cohort of 6,185 patients with CHF and diabetes treated in ambulatory clinics at Veteran Affairs medical centers. In the propensity score-matched analysis (n=2,874) at 2 years of follow-up, death occurred in 16.1% of patients receiving metformin compared with 19.8% of patients not receiving metformin (HR=0.76; 0.63-0.92; P<0.01). Hospitalization related to CHF or total hospitalization rates were not significantly different between individuals treated with metformin compared with those not treated with metformin [43].

In patients having T2DM with established atherothrombosis participating in the REACH Registry, a significant reduction of 2-year death 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 does not appear to be clinical uncertainty with regards to the safety or effectiveness of metformin in CHF making a definitive randomized trial virtually impossible [44]. Metformin, previously contraindicated in CHF, can now be used if the ventricular dysfunction is not severe, if 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 for developing acute decompensated CHF, which is often associated with decreased kidney function. During acute decompensated CHF, timely treatment may prevent the decrease in 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].

BOX : In patients with stable CHF, consistent observational data showed that metformin is associated with a better overall prognosis than other glucose-lowering agents. Stable CHF should not be considered as a contraindication to the use of metformin in patients with T2DM.

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, respectively, in healthy subjects and T2DM patients with good renal function. Over a range of renal function, the population mean values of CL(R) and CL/F of metformin are 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 decrease approximately in proportion to the clearance of creatinine, the dosage of metformin should be reduced in patients with RI in proportion to the reduced eGFR [48]. The prolonged elimination of metformin in patients with CKD, inversely correlated with creatinine clearance, explain the risk of metformin accumulation in case of RI [49].

Classically, CKD (creatinine clearance < 60 mL/min) represents a contraindication to the use of metformin in patients with T2DM [12]. In case of RI, metformin may, indeed, accumulate, block gluconeogenesis and cause lactic acidosis, a harmful complication that may be fatal [9, 50]. Most cases reporting severe lactic acidosis concern patients with quite severe RI, although, renal dysfunction may only be a prerequisite for metformin accumulation [8].What so ever, 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 assessing the benefit-risk balance of metformin use in patients with moderate or severe RI [51]. In the various series reporting real-life data, patients receiving metformin despite the presence of RI as official contraindication are not rare, apparently without any harm [16-18]. In the fourth National Health and Nutrition Examination Survey (NHANES IV), the proportion of patients using metformin progressively decreases according to the severity of RI, from 45.6 % at stage 1 to 23.8 at stage 3 and 0 % at stages 4 and 5 [52]. Retrospective database analysis using GE Centricity Outpatient Electronic Medical Records in the US showed that after the eGFR calculation, almost no patients with orders for metformin received doses of the drug appropriate for their degree of RI [53]. While metformin is frequently used at inappropriate doses in patients with RI, the clinical consequences of these findings remain poorly understood.

According to the results of REACH, metformin was prescribed worldwide in 1,572 patients with moderate renal failure (KDOQI stage 3) in contraindication to guidelines for its use [54]. Among this subgroup, metformin use was associated with at least a similar reduction in mortality as among the overall population. The 2-year mortality rate associated with metformin versus other glucose-lowering agents was significantly lower in patients with an eGFR of 30 to 60 mL/min/1.73 m². The reduction was even greater than that observed in patients with an eGFR $\geq$ 60 mL/min/1.73 m² (Table 3) [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 of all-cause mortality in patients with eGFR 45-60 ml/min/1.73 m² and in patients with eGFR > 60 ml/min/1.73 m². No benefit, but not harm, was observed with metformin therapy in patients with eGFR 30-45 ml/min/1.73 m² (Table 3) [55].

BOX : In patients with mild to moderate CKD, consistent observational data showed 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 absence of acute

intercurrent event is very low. Stable mild to moderate (with appropriate dose reduction)
CKD should not be considered as an absolute contraindication to the use of metformin in
patients with T2DM.

5. Metformin in patients with hepatic dysfunction

Liver plays a major role in gluconeogenesis and hepatic failure may dramatically hamper lactate removal through this biochemical pathway (Figure 1). Given the importance of the liver in lactate clearance, it has been suggested focusing on the severity of and prognosis for liver disease. Indeed, in many cases, as already mentioned, renal dysfunction is only a prerequisite for metformin accumulation, which may only be dangerous per se when associated with liver failure [8].Therefore hepatic failure, such as in advanced cirrhosis or severe liver hypoperfusion, is considered as a contraindication for using 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 HCV cirrhosis and no contraindication for metformin were included in a screening program for hepatocellular carcinoma. After a median follow-up of 5.7 years, use of metformin was independently associated with reduced incidence 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 hepatitis C cirrhosis but rather may provide benefits [57]. Further studies are needed to confirm this observation.

Liver dysfunction associated with non-alcoholic fatty liver disease (NAFLD) or 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. Metformin may be prescribed in that population without any harm [58]. Especially no increased risk of lactic acidosis has been reported. Metformin may potentially exert beneficial effects in patients with NAFLD, although the evidence remains rather scarce [59-61]. Contrasting results were reported in young individuals with fatty liver, with a reduction in prevalence and severity after 6 months of metformin in one study [62], but no better results compared to lifestyle after 24 months of metformin in another study [63]. In participants from the Edinburgh Type 2 Diabetes Study, unexpectedly, the use of metformin was associated

with the presence of hepatic steatosis (compared with those classed as normal/probable normal) on ultrasound scan, independently of BMI and glycemic control (OR=2.19 ; 1.59–3.00) [64]. Because previous studies of the use of metformin in NAFLD have shown a positive or neutral effect in individuals [65], it seems unlikely that there is a causative link between metformin use and NAFLD in that study. A specific study compared the effects of metformin with that of a thiazolidinedione in adult T2DM patients. Both agents increased hepatic insulin sensitivity. However, metformin did not decrease liver fat or increase insulin clearance, in contrast to rosiglitazone [66]. In another study, metformin does not provide specific beneficial effects in adult patients with NAFLD, in contrast to pioglitazone [67]. According to the conclusion of 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].

BOX : In patients with NAFLD, metformin may be used but no substantial improvement in liver fat content should be expected (in contrast to what was observed with thiazolidinediones). Limited data are available supporting the use of metformin in patients with liver failure, which remains a contraindication.

6. Metformin in patients with chronic respiratory insufficiency

Severe chronic respiratory insufficiency may lead to hypoxia and thereby enhance anaerobic glycolysis and promote lactic acid formation (Figure 1). It is the reason why such medical condition is a traditional contraindication for the use of metformin. However, there is no specific study demonstrating the precise risk of using metformin in such a population with chronic respiratory insufficiency, neither the level of severity that represents an absolute rather than a relative contraindication for metformin use. Pulmonary diseases and respiratory insufficiency are noticed in some reports on 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 existing, in absence of concomitant hepatic failure and/or RI. Furthermore, as discussed by Lalau, the relationship between metformin and lactic acidosis is complex, since use of the drug may be causal, co-responsible or simply coincidental [8].

Quite surprisingly, but of potential interest, recent experimental data showed that metformin reduces both airway inflammation and remodeling at least partially through the induction of AMPK activation and decreases oxidative stress. These data provide insight into the beneficial role of metformin as a novel therapeutic drug for chronic asthma [69].

BOX : 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.

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 from younger populations [70]. According to a recent position statement, strategies specifically minimising the risk of low blood glucose may be preferred in older people with T2DM, a pharmacodynamic characteristic shared by metformin [3].

In a preliminary limited study of 24 elderly patients with T2DM (aged between 70-88 years), the conclusion was that provided the dosage is adjusted to renal function, the metabolic tolerance of metformin therapy is satisfactory [71]. A more recent study suggested that the efficacy of metformin in Japanese elderly patients with T2DM is not different from that in non-elderly patients, and that its safety might be linked to specific and well-documented contraindications rather than age itself [72]. Another recent study performed in Poland indicated a relatively good tolerability of metformin by elderly patients (mean age = 67 years) despite the presence of the traditional contraindications to this 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 metformin versus without metformin was confirmed in the large cohort of subjects aged 65-80 years (Table 3) [20]. This reduction was only slightly lower than that observed in the younger age group. Less T2DM patients above 80 years were included in this registry, with no mortality difference between those receiving metformin or not. In this very old 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 to sulfonylureas of

second generation, metformin was associated with a significant reduction in all-cause mortality both in patients older than 65 years and in patients 65 years old and younger at initial prescription (Table 3) [74].

BOX : *Observational data suggested that the use of metformin is not harmful in elderly T2DM patients but rather that metformin may be associated with more favourable outcomes (including overall mortality) compared to other glucose-lowering agents, as previously observed in younger T2DM patients. Thus, old age per se should not be considered as a contraindication to the use of metformin, in absence of 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.*

8. General discussion

Considering all these observational data recently published in the international literature, one may better understand the rather provocative title of a paper already published several years ago *"Contraindications can damage your health - is metformin a case in point ?"* [75]. We will briefly discuss the benefit/risk balance of metformin in T2DM patients with CV disease, in patients with RI and in the elderly population.

8.1.Metformin and CV disease

CV disease still 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 suffering 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 may offer CV protection, both in patients with newly diagnosed T2DM [10] and at a later stage of the disease in insulin-treated patients [77]. Putative CV beneficial action 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 showed that AMPK activators (like metformin) attenuate cardiomyocytic apoptosis during cardioplegia-induced hypoxia/reoxygenation injury. Several

mechanisms have been proposed to explain such cardioprotection by metformin, including lessening endoplasmic reticulum stress, inhibition of cellular unfolded protein response, eNOS activation and increased expression of PGC-1α, a key controller of energy metabolism in muscle, which is down-regulated in diabetic conditions [79-81]. Chronic metformin treatment augments myocardial resistance to ischemia-reperfusion injury, by alternative mechanisms in addition to the lowering of blood glucose. Thus, metformin prescribed chronically to T2DM patients may lead to a basal state of cardioprotection, thereby potentially limiting the occurrence of myocardial damage by cardiovascular events [81].

8.2. Metformin and CKD

The 2012 update of the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Diabetes and Chronic Kidney Disease (CKD) is intended to assist the practitioner caring for patients with diabetes and CKD [82].

Recent data suggested that metformin may be administered with caution in patients with creatinine clearance 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 would predispose them to lactic acidosis, elevated serum creatinine levels (or reduced GFR) should be considered a risk factor for the development of lactic acidosis but not an absolute contraindication [84]. In daily clinical practice, development of contraindications, including RI, rarely results in discontinuation of metformin therapy and, despite this, lactic acidosis remains a rare event [16, 85]. In some studies, the prevalence of T2DM receiving metformin despite having a contraindication (including a GFR < 60 mL/min) was over 80%. Nevertheless, metformin use in such conditions did not appear to increase the risks of lactic acidosis, hospitalization and death [86]. Besides the possibility that creatinine levels are not appropriately assessed by physicians initially and during follow-up, another explanation for the common use of metformin in T2DM with RI may be that prescribers judge that benefits of therapy outweigh potential risks [87]. There are more and more data suggesting that meformin can be used in stable mild to moderate CKD and that not prescribing metformin in these patients may cause more harm (no optimal protection against CV disease, for instance) compared to 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 may be used down to a GFR of 30 mL/min, with dose reduction advised at 45 mL/min (Figure 2) [3, 82]. This would lead to safely prescribing metformin in patients with an eGFR < 60 mL/min/1.73 m², and more importantly in medical practice, according to the law [90, 91].

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

8.3. Metformin and elderly

The selection of appropriate drug regimens for older T2DM patients remains challenging. The substantial risk of hypoglycaemia with insulin secretagogues such as sulfonylureas is well recognized in this population. In this regard, metformin may offer a substantial benefit [70]. However, no clinical trial was specifically 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) because these new oral incretin-based glucose-lowering agents were either compared to metformin or combined with metformin as basal therapy [93, 94]. These recent data confirmed that metformin is effective and well tolerated in older patients with T2DM, although old 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 must be able to assess the patient's health status and use this information to recommend a treatment plan that is consistent with the patient's personal goals for care [95]. In this regard, older T2DM patients who are frail, anorexic, or underweight and those with CHF, 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. Increasing recent data now support a protective effect of metformin against the development of most types of cancer (especially, digestive cancers and breast cancer) and its associated mortality [96]. If this concept is confirmed, it would be a pity to deprive T2DM patients, only because the problem of old age, from a drug that may be helpful.

9. Conclusion

Metformin represents the cornerstone of glucose-lowering therapy for T2DM. Despite its array of benefits that comparatively outweigh alternative oral anti-glycaemic agents, the ability of clinicians to prescribe metformin is restricted in many conditions. There are numerous contra-indications, reviewed in the present paper, and cautions concerning the putative risks of metformin-related side effects that necessitate cessation of metformin. Notably the often stated, yet completely unsubstantiated, heightened risk for 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 the creatinine cutoffs provided by the FDA, or a GFR cutoff of ≤ 60 mL/min/1.73 m², has been called into question. Similarly, stable CHF or CAD cannot be considered anymore as a contraindication to the use of metformin. Considering the high prevalence of stable RI, CAD and/or CHF in the elderly population, the recent published observations regarding the potential benefit/risk balance of metformin therapy are of major interest. Nevertheless, more valuable data in the elderly population is still required because the evidence is still sparse. Individual benefit/risk ratio should be assessed in order not to deprive patients from a potentially beneficial drug but also not to expose T2DM individuals to an unacceptable risk. In this regard, the patient-centered approach recommended by the ADA-EASD position statement is of major clinical value.

Figure 1 : Illustration of the occurrence of lactic acidosis in special circumstances that may increase the risk associated to metformin therapy.

Figure 2 : Proposed recommendations for use of metformin according to renal function estimated by glomerular filtration rate(eGFR). (*) Caution : Increase monitoring of renal function (every 3-6 months), avoid any nephrotoxic drugs, stop metformin in case of dehydration.

Table 1 : Comparison of benefits and risks associated with metformin use in special populations of patients with type 2 diabetes

Patient's characteristics	Risk of lactic acidosis	Potential benefits
Coronary artery disease	Risk of myocardial infarction (hypoxia)	Decreased myocardial infarction Decreased mortality
Acute coronary syndrome	Risk of cardiogenic shock or acute congestive heart failure	Cardioprotection against ischemia/reperfusion injury
Congestive heart failure	Hypoxia + functional renal insufficiency	Decreased mortality
Renal insufficiency	Metformin accumulation Inhibition of gluconeogenesis	Possibly decreased mortality in case of moderate renal impairment
Hepatic failure	Reduced gluconeogenesis	No data
Chronic respiratory disease	Hypoxia	No data
Elderly	Frailty, comorbidities	Possibly decreased mortality if no other contraindications

Table 2 : All-cause-mortality in patients with T2DM and stable coronary artery disease (CAD), post-acute coronary syndrome (ACS) or myocardial infarction (MI), or congestive heart failure (CHF) receiving metformin therapy compared to oral glucose-lowering therapy without metformin (usually sulfonylurea). HR : hazard ratio. 95% CI : 95 % confidence interval.

	Reference	Comparator	HR	95% CI
Stable CAD	Fishman et al 1999 [21]	No antidiabetic agent (*)	1.42	1.10-1.85
	Schramm et al 2011 [22]	Glimepiride	0.77	0.64-0.93
	Pantalone et al 2012 [23]	Glibenclamide Glipizide	0.72 0.71	0.54-0.96 0.53-0.93
Post-ACS or MI	Inzucchi et al 2005 [28]	Any except insulin-sensitizing agent	0.92	0.81-1.06
	Horsdal et al 2008 [29]	Any sulfonylurea	0.58 (***)	0.47-0.72
	Jorgensen et al 2010 [30]	Any sulfonylurea	0.80	0.71-0.88
	Jorgensen et al 2011 [31]	Glyburide (glibenclamide)	0.40	0.18-0.90
	Mellbin et al 2011 [32]	Any agent except metformin	0.65	0.47-0.90
CHF	Masoudi et al 2005 [39]	Any except insulin-sensitizing agent	0.87	0.78-0.97
	Eurich et al 2005 [40]	Any sulfonylurea	0.70	0.54-0.91
	Andersson et al 2010 [41]	Any sulfonylurea	0.85	0.75-0.98
	McDonald et al 2010 [42]	No antidiabetic agent (**)	0.65	0.48-0.87
	Aguilar et al 2011 [43]	Any agent except metformin	0.69	0.54-0.90
	Roussel et al 2010 [20]	Any agent except metformin	0.76	0.63-0.92

(*) Compared with sulfonylurea versus no antidiabetic agent : HR=1.11 (0.90-1.36)

(**) Compared with sulfonylurea versus no antidiabetic agent : HR=0.84 (0.67–1.06)

(***) 1 year-mortality after multiple adjustments : HR=0.96 (0.71-1.31)

Table 3 : All-cause-mortality in patients with T2DM receiving metformin therapy compared to any other glucose-lowering agent. The T2DM population is divided in subgroups according to estimated glomerular filtration rate (eGFR), a marker of chronic kidney disease (CKD) (top panel) or according to age (bottom panel). HR : hazard ratio. 95% CI : 95 % confidence interval.

CKD	Subgroup eGFR ml/min/m²	Metformin vs any other agent n	HR	95% CI
Roussel et al 2010 [20]	>60	4442 vs 6326	0.89	0.71-1.11
	30-60	1572 vs 3388	0.64	0.48-0.86
Ekström et al 2012 [55]	>60	28015 vs 31614	0.87	0.81-0.94
	45-60	4079 vs 6176	0.87	0.77-0.99
	30-45	715 vs 2152	1.02	0.84-1.24
ELDERLY	Subgroup Age (years)	Metformin vs any other agent n	HR	95% CI
Roussel et al 2010 [20]	40-65	2987 vs 3859	0.63	0.45-0.89
	65-80	3791 vs 6768	0.77	0.62-0.95
	>80	598 vs 1492	0.92	0.66-1.28
Tzoulaki et al 2009 [74]	<65	NA vs 1114(*)	0.56	0.49-0.625
	>65	NA vs 8492(*)	0.74	0.70-0.78

NA : not available. (*) Compared with sulfonylureas of second generation.

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