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The right place for metformin today

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ABSTRACT

Metformin is the most widely used glucose lowering drug worldwide in the treatment of patients with type 2 diabetes, since we have experience with this drug for more than 60 years about the efficacy and safety. Metformin is very effective in HbA1c lowering associated with some weight loss, but does not increase risk for hypoglycemia. At the moment all guidelines in the world recommend to use metformin in monotherapy in patients with newly diagnosed diabetes or in combination with other antidiabetic drugs with documented CV (and renal) benefit in cardiovascular outcome trials (CVOT). Although a randomized placebo controlled CVOT with metformin is lacking, many observational studies in patients with coronary heart disease, heart failure and chronic kidney disease have demonstrated consistent beneficial effects. A recent metanalysis of 26 observational studies including 815 839 patients showed that metformin use was associated with a significantly lower rate of all-cause mortality (HR: 0.74; 95% CI: 0.68–0.81). Whether this very consistent reduction of all-cause mortality is related to the incidence/outcome of several cancers has still to be investigated. In the future early combination therapy of metformin e.g. with SGLT-2 inhibitors should be more often used.

Contents

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1. Introduction

Diabetes mellitus affects over 450 million people worldwide, is associated with a high cardiovascular morbidity/mortality and is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Metformin has been used in the treatment of type 2 diabetes mellitus (T2DM) since 1957 [1], and is recommended as the first-line agent in the management of hyperglycaemia by most of the international and national guidelines including the American Diabetes Association guidelines, the European Association for the Study of Diabetes guidelines, and the British NICE (National Institute for Health and Care Excellence) guidelines. Over 50 years ago various biguanides (e.g. metformin, phenformin, buformin) were used in different countries for the treatment of T2DM. All but metformin were removed from the international market in the 1970 s because of the associated high risk of lactate acidosis [2]. In the late 1970 s and early 1980 s of the last century, papers about this drug were rejected from leading journals, since it was felt that metformin is already historical. Since metformin had not been marketed in the USA at that time, it was only in 1995 that it was approved for use there, after safety concerns were satisfied by decades of experience in Canada, Europe and Asia. It is astonishing that metformin could only be used in Germany for decades in the late phase of T2DM in combination with sulfonylureas, when most patients had already contraindications. Remarkably, in the last 20 years the role of metformin changed from devil to angel, in particular after the publication of UKPDS 34 [2,3].

According to a recent analysis 77% of all newly diagnosed patients with T2DM in the US are using metformin as first line therapy [4]. In the global DISCOVER study [5] first-line treatments were also mostly metformin (in 70% of the patients) either as monotherapy (55.6%) or in combinations of metformin with a sulfonylurea (14.4%). The most commonly prescribed second-line therapies were combinations of metformin with a DPP-4 inhibitor (23.5%) or a sulfonylurea (20.9%). Thus, it can be assumed that about 200 million diabetic patients are taking metformin everyday as monotherapy or in combination with sulfonylureas or DPP-4 inhibitors. Information about the benefit-risk ratio is therefore very relevant for about half of all diabetic patients worldwide.

2. Metabolic effects of metformin

Metformin is highly efficacious in improving glycaemic management, with significant reductions in glycated haemoglobin (HbA1c) of up to 2.0% [6-8] and is very affordable, costing about 15 cents per tablet. In head-to-head trials, the drug has been shown to be equipotent to sulfonylureas, thiazo-

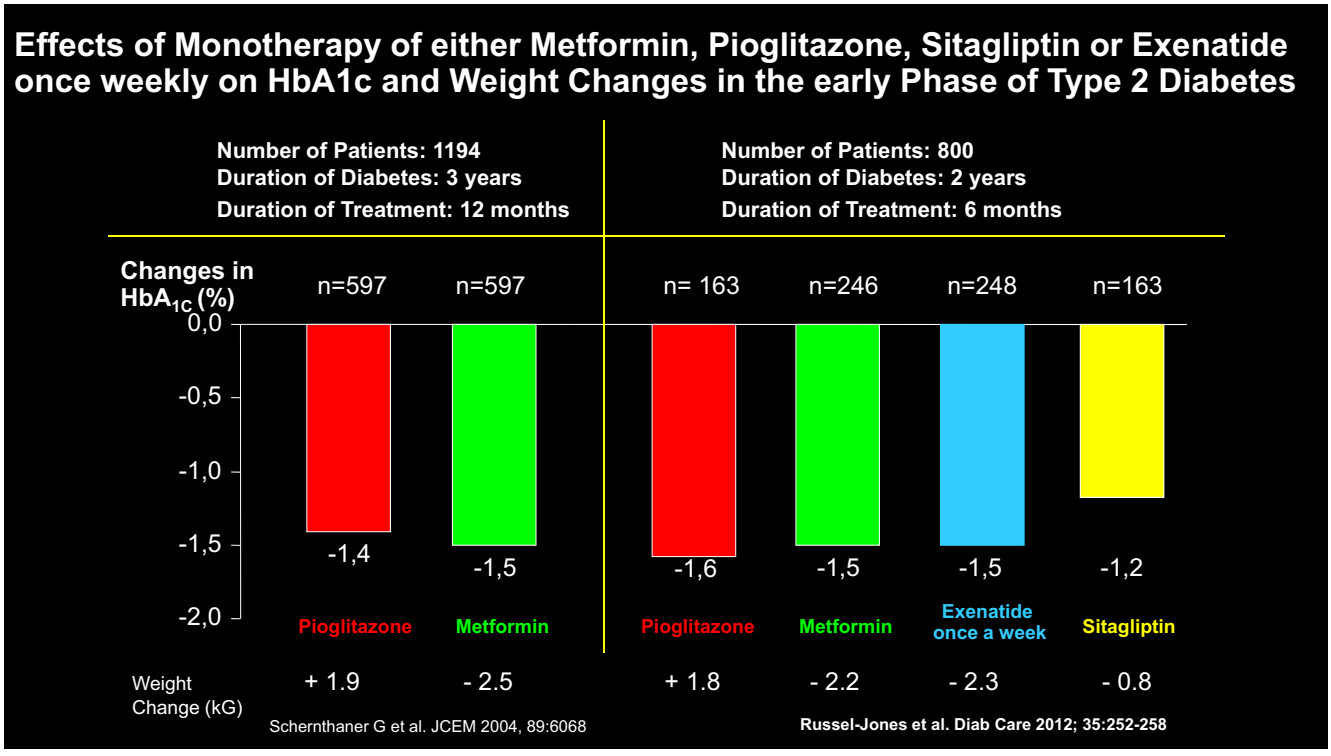

Fig. 1 – Metformin and diabetes.

lidinediones and glucagon-like peptide-1 (GLP-1) receptor agonists, and, in general, more potent than DPP-4 inhibitors and SGLT-2 inhibitors [8,9]. Fig. 1 shows the effects of metformin versus other glucose lowering drugs on HbA1c lowering and weight reduction in 2 large prospective randomized trials [7,8]. It works primarily by reducing hepatic glucose production and, to a lesser effect, by enhancing insulin-mediated glucose uptake and utilisation in peripheral tissues [10-13]. Although metformin is generally considered to mediate its antihyperglycemic effects by suppressing hepatic glucose output through the activation of AMP-activated protein kinase dependent in the liver, accumulating evidence indicates that it might also act through pathways in the gut [14]. Recently, metformin was reported to alter the gut microbiota community in humans, suggesting that the hyperglycemia-lowering action of the drug could be the result of modulating the population of gut microbiota [15]. Although gastrointestinal adverse effects such as nausea and diarrhoea are common, metformin is generally well tolerated and serious (life- threatening) adverse events are rare.

2.1. *Metformin in the UKPDS and ADOPT study*

In 1998, the publications of the results of the United Kingdom Prospective Diabetes Study (UKPDS) totally changed the position of metformin in the treatment of patients with T2DM [16,17]. Among 3,867 newly diagnosed diabetic patients, those randomized to sulfonylureas and insulin had superior glucose control and fewer microvascular outcomes compared to diet, but surprisingly, diabetes-related and all-cause mortality at 10 years was similar in those randomized to sulfonylurea, insulin, and diet only [16]. Nevertheless, in a sub-study of overweight patients [17], those randomized to metformin experienced 42% fewer diabetes-related deaths and 36% fewer all-cause deaths compared to the diet alone arm. Compared to overweight patients randomized to sulfonylureas or insulin, there was also an advantage of metformin on mortality. However, this sub-analysis included only 342 patients on metformin and all patients were overweight [17]. Nevertheless, in the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, $p = 0.01$), myocardial infarction (33%, $p = 0.005$), and death from any cause (27%, $p = 0.002$) after a 10-year follow up [18]. The ADOPT trial (A Diabetes Outcome Prevention Trial), randomized 4,360 patients to metformin, rosiglitazone, or glyburide [19]. Cardiovascular events (fatal/non fatal acute myocardial infarction and stroke) were a secondary (adverse) outcome, and after a median of 4 years were low overall, with no differences between the 3 arms (2.9% metformin vs. 2.9% rosiglitazone vs. 2.4% glyburide).

3. Observational studies showing beneficial effects of metformin

After publication of the UKPDS study results a number of observational studies were reported comparing the effect of metformin versus sulfonylureas as first line therapy in patients with type 2 diabetes. In 2012 Roumie et al [20] have analyzed the comparative effectiveness of sulfonylurea and metformin monotherapy on risk of cardiovascular events in type 2 diabetes mellitus using large data from the National Veterans Health Administration. Among 253,690 patients – 98,665 sulfonylurea and 155,025 metformin initiators - the crude outcome rates were 18.2 and 10.4 per 1000 person-years in sulfonylurea and metformin users, respectively ([adjusted Hazard Ratio (aHR)] 1.21, 95% confidence interval (CI): 1.13, 1.30). A recent review of observational metformin users [21] involving 34,000 patients also showed a lower incidence of CV death and all-cause mortality observed among metformin-treated patients (aHR: 0.80; 95% CI: 0.74–0.87; $p < 0.001$). No increased risk was observed for metformin in those with reduced left ventricular ejection fraction, nor in those with heart failure (HF) and chronic kidney disease (CKD).

4. Metformin in patients with cardiovascular disease (CVD)

The REACH (Reduction of Atherothrombosis for Continued Health) registry analysis [22] including 16,691 patients having diabetes with established atherothrombosis showed a lower rate of CV death and all-cause mortality among patients with HF treated with metformin (HR: 0.69; 95% CI: 0.54–0.90; $p = 0.006$). Association with lower mortality was consistent among subgroups, noticeably in patients older than 65 years (HR: 0.77; 95% CI: 0.62–0.95; $p = 0.02$), and patients with an estimated creatinine clearance of 30 to 60 mL/min/1.73 m(2) (HR: 0.64; 95% CI: 0.48–0.86; $p = 0.003$).

In a recent metaanalysis by Han et al [23] the potential effect of metformin in patients with coronary artery disease (CAD) using data from 40 studies comprising 1,066,408 patients. The CV mortality, all-cause mortality and incidence of CV events were lowered to aHR: 0.81, aHR: 0.67 and aHR: 0.83 respectively, after the patients with CAD were given metformin. Subgroup analysis showed that metformin reduced all-cause mortality in myocardial infarction (aHR = 0.79) and heart failure patients (aHR = 0.84). Based on their data the authors concluded that metformin reduces CV mortality, all-cause mortality and CV events in CAD patients. In a recent analysis from the SAVOR-TIMI 53 trial [24] comparing CV outcomes among patients with T2DM and high CV risk, metformin use was associated with a significantly lower rate of all cause mortality (HR: 0.75; 95% CI: 0.59–0.95), even after adjustment for clinical variables and biomarkers. However, metformin was not associated with lower rates of the composite andpoint of CV Death, MI or ischemic stroke. However, these associations are based on observational data in a relatively small subgroup and lack adequate statistical power. Based on their data the authors have made a metaanalysis of 26 observational studies including 815 839 patients reporting the outcome of all-cause mortality based on metformin exposure [24]. Using a random effects model, metformin use was associated with a significantly lower rate of all-cause mortality (HR: 0.74; 95% CI: 0.68–0.81).

5. Metformin in patients with heart failure

It was proposed that metformin might be safe and efficacious in patients with T2DM and HF. This was based on large obser-

vational studies where metformin was associated with lower mortality and HF hospitalization rates compared with other anti-diabetic therapies [25,26]. In Canadian patients with a new diagnosis of HF, metformin monotherapy was associated with a reduced 1-year mortality [25] when compared with sulfonylurea treatment: HR: 0.66 (95% CI: 0.44–0.97). One-year mortality was also lower in patients taking metformin and sulfonylurea combination therapy than in patients taking sulfonylurea monotherapy: HR: 0.54 (95% CI: 0.42–0.70). In Americans admitted to the hospital with HF [26], metformin use was associated with a lower 1-year mortality when compared to treatment with insulin or sulfonylurea (24.7 vs. 36%, $p < 0.0001$). All-cause re-admission and HF hospitalization were also less common in patients treated with metformin than in those not treated with an insulin-sensitizing drug. However, these two studies were not prospective, randomized, or designed to address the safety or efficacy of metformin in this population. In a retrospective study of a large British database, metformin significantly decreased mortality by 28% compared with a 45% reduction with ACE inhibitor/ARB treatment and 24% with β-blocker treatment [27]. In a retrospective study of patients with diabetes with low ventricular ejection fraction, metformin improved 1-year survival [28]. A comprehensive search for controlled studies, evaluating the association between metformin and morbidity and mortality in people with diabetes mellitus and HF revealed nine cohort studies [21]. Metformin was associated with a 20% lower mortality, compared mostly with sulphonylureas (HR 0.80, 95%CI 0.74–0.87; $P < 0.001$). In 2006, the US Food and Drug Administration (FDA) removed CHF as a contraindication for metformin use. Unfortunately, there are no RCTs of metformin in patients with T2DM and HF. Whether or not metformin is efficacious or safe is inconclusive. Nevertheless, previous concerns that metformin may cause metabolic acidosis are no longer justified. Recently [29], utilizing the Taiwan's nationwide administrative database, it was shown by a large population-based retrospective cohort study, that metformin use in patients with T2DM is associated with a lower risk of hospitalization for HF (HR: 0.57; 95% CI: 0.53–0.62) in a dose-response pattern, when compared with patients who have never been treated with metformin. In a position statement from the Heart Failure Association of the European Society of Cardiology [30] it was stated that metformin should be recommended as first-line treatment for patients with T2DM and HF who have preserved or moderately reduced renal function (i.e. eGFR > 30 mL/min).

6. Metformin in patients with CKD

Recent observational studies suggest metformin use may be associated with reduced cardiovascular events, morbidity and mortality in people with T2DM and renal impairment. This was first described in a study analysing data from 19,691 people with T2DM and established atherosclerotic disease [22]. Among the 5,031 people with an eGFR of 30–60 mL/min/1.73 m 2, the mortality rate was lower in metformin users compared with non-users (HR: 0.64; 95% CI: 0.48–0.86; $p = 0.003$), with the greatest effect observed in people with an eGFR of 30–44 mL/min/1.73 m2 (HR: 0.57; 95% CI: 0.35–0.92; $p = 0.02$). Compared with sulfonylureas and other hypoglycaemic agents, metformin has been associated with a statistically significant lower risk of all-cause mortality in people with T2DM and various stages of CKD, in both a Swedish population-based [31] longitudinal study (n = 51,675) and a large cohort study [32] of veterans with diabetes and CKD (n = 175,296).

In a very recent retrospective cohort study of the US Veterans Health Administration [33], there were 174 882 persistent new users of metformin and sulfonylureas who reached a reduced kidney function threshold (eGFR < 60 mL/min/1.73 m2 or creatinine ≥ 1.4 mg/dL for women or ≥ 1.5 mg/dL for men). During follow-up (1.1 years) of 67 749 metformin and 28 976 sulfonylurea persistent monotherapy users (median age 70 years, median eGRF 55.8 mL/min/1.73 m2 and median HbA1c level 6.6%) there were 1048 MACE outcomes (23.0 per 1000 person-years) among metformin users and 1394 events (29.2 per 1000 person-years) among sulfonylurea users. The cause-specific adjusted hazard ratio of MACE for metformin was 0.80 (95% CI, 0.75–0.86) compared with sulfonylureas, yielding an adjusted rate difference of 5.8 (95% CI, 4.1–7.3) fewer events per 1000 person-years of metformin use compared with sulfonylurea use.

These results are in line with a newly published retrospective observational study [34] that analysed data on survival, cardiovascular and kidney disease outcomes in metformin users (n = 591) and non-users (n = 3,447) with T2DM, CKD and anaemia (haemoglobin < 130 g/L) enrolled in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT). In that study metformin use was independently associated with a reduced risk of all-cause mortality (HR: 0.49; 95% CI: 0.36–0.69), CV death (HR: 0.49; 95% CI: 0.32–0.74), the CV composite (H: 0.67, 95% CI: 0.51–0.88) and the kidney disease composite (HR: 0.77; 95% CI: 0.61–0.98). Based on their data the authors concluded that metformin may be safer for use in CKD than previously considered and may lower the risk of death and cardiovascular events in individuals with stage 3 CKD. A population-based study of 144,252 older adults with diabetes and chronic kidney disease in Canada/Ontario showed that up to 27.6% of patients with CKD stage 4–5 disease or receiving chronic dialysis were prescribed metformin [35]. Metformin should not be used in patients with stage 5 CKD [36], since diabetic patients from Taiwan presenting with high serum creatinine values > 6 mg (>530 μmol/l) had an increased mortality (aHR: 1.35; 95% CI: 1.20–1.51; $p < 0.0001$) when they used metformin [37].

7. Metformin and lactic acidosis

Despite its multiple benefits, metformin use in patients with kidney disease remains limited by the perceived, albeit rare, risk of lactic acidosis. Lactic acidosis associated with metformin use is a complex issue and the causal relationship, which is often related to the presence of coexisting medical conditions, remains open to debate. The data on the safety of metformin in mild to moderate renal impairment (eGFR 30–60 mL/min/1.73 m2) have been limited until recently and sometimes conflicting, despite increased laxity in prescribing guidelines. A recent study by Lazarus et al [38] provide further evidence that metformin does not appear to increase the risk

of lactic acidosis in mild to moderate renal impairment. In the analyzed cohort (n = 75,413) there were 2,335 hospitalizations with acidosis over a median follow-up of 5.7 years. Compared with alternative diabetes management, time-dependent metformin use was not associated with incident acidosis overall (aHR: 0.98; 95% CI: 0.89–1.08) or in patients with eGFR 45–59 mL/min/1.73 m2 (aHR: 1.16; 95% CI: 0.95–1.41) and eGFR 3044 mL/min/1.73 m2 (aHR: 1.09; 95% CI: 0.83–1.44). By contrast, metformin use was associated with an increased risk of acidosis in patients presenting eGFR less than 30 mL/min/1.73 m2 (aHR: 2.07; 95% CI: 1.33–3.22). Based on a dose finding study Lalau et al [39] recommend using the following metformin dosis in patients with impaired kidney function: 1.500 mg/day for CKD stage 3a and 1.000 mg/day for stage 3b; eGFR should be assessed every 6 months in CKD stage 3. Metformin should be withdrawn in patients likely to experience acute kidney injury in the context of severe pathologies.

8. Metformin improves prognosis after kidney and heart transplantation

A retrospective US cohort study from the Scientific Registry of Transplant Recipients [40] linked data for all incident kidney transplants (2001–2012) with national pharmacy claims (n = 46,914). Recipients having one or more pharmacy claims for a metformin-containing product (n = 4,609) were compared with those having one or more claims for a non-metformin glucose-lowering agent (n = 42,305) [40]. Metformin was associated with lower aHRs at three years post-transplant for living donor (0.55, 95% Ci: 0.38–0.80; p = 0.002) and deceased donor allograft survival (0.55, 95% CI: 0.44–0.70; p < 0.0001), and with a significantly lower mortality of the patients with kidney transplantation (0.60, 95% CI: 0.46–0.79; p = 0.0003).

A recently published study from Israel [41] prospectively following up diabetic patients after heart transplantions from 1994 to 2018 showed that metformin therapy was independently associated with a significant 90% reduction (95% CI: 0.02–0.46, p = 0.003) in the risk for the development of cardiac allograft vasculopathy (CAV), and a 91% reduction (95% CI: 0.02–0.42; p = 0.003) in the risk for CAV or cardiovascular mortality. The same group [42] previously reported that diabetic patients DM patients who were treated with metformin had a markedly lower risk (65%; p = 0.001) for the development of a malignancy or death after heart transplantation as compared with non-DM patients.

9. Association of use of metformin with reduced cancer incidence and mortality

The increased mortality risk associated with T2DM is well established. However, the mortality caused by CVD, which was the leading cause of death among diabetes patients in the USA, declined by 32% every 10 years among people with type 2 diabetes [43]. Interestingly, the rate of decline of CVD death was significantly greater among those with T2DM than those without [43].

A recently published *meta*-analysis, including 20 million individuals, showed that diabetes is a risk factor for all-site cancer for both men and women and the excess risk of cancer is greater for women than men [44]. T2DM and cancer have many modifiable risk factors in common, including obesity, physical activity, diet, alcohol, smoking and long latency periods before clinically manifesting. T2DM appears to be an independent risk factor for pancreatic, endometrial, liver, colorectal, bladder and breast cancer [44]. Possible mechanisms linking diabetes with cancer include hyperglycemia and hyperinsulinemia (endogenous or exogenous), plus alterations of the insulin-like growth factor system, chronic subclinical inflammation, abnormalities in sex hormone metabolism, adipokines and possibly antidiabetes medication used in the management of T2DM[45].

A recently published population-based study [45] demonstrated that cancer has overtaken CVD as the commonest cause of death in T2DM patients in Scotland. Within the study period (2009–2014), 12.7% of people with T2DM died, the most common cause of death was cancer (27.8%), followed by heart disease (24.1%). This study showed that cancer is the major contributing cause of the increase in all-cause mortality seen in T2DM in the UK. Likewise, in Japan the proportion of total deaths from cancer in patients with T2DM exceeds that from vascular causes, the proportion of deaths in patients with T2DM in 2001–2010 was 14.9% for vascular disease 14.9% and 38,3% for cancer [46]. These studies highlight the continued need for greater cancer risk-factor mitigation in adults with diabetes to prevent premature death from cancer. A recent study [47] showed that diabetes medication use is associated with survival among patients of breast, colorectal, lung, or gastric cancer. After adjustment for clinical characteristics and treatment factors, use of metformin was associated with better overall survival among colorectal cancer patients (HR: 0.55; 95% CI: 0.34 to 0.88) and for all four types of cancer combined (HR: 0.75; 95% CI: 0.57 to 0.98). By contrast, ever use of insulin was associated with worse survival for all cancer types combined (HR: 1.89; 95% CI: 1.57 to 2.29) and sulfonylureas use was associated with worse overall survival for breast or gastric cancer (HR: 2.87; 95% CI: 1.22 to 6.80 and HR: 2.05; 95% CI: 1.09 to 3.84, respectively).

A large population-based cohort study during 2009–2011 in Korea including 223,530 diabetic patients investigated the association between different glucose-lowering treatments and new-onset metastatic cancer among T2DM patients with comorbid incident cancer [48]. Metastatic risk was lower with metformin with or without combination of DPP-4 inhibitors (HR: 0.84, 95% CI: 0.79–0.90 and 0.87, 95% CI: 0.80–0.95), but not significantly associated with DPP-4 inhibitors alone (0.99, 0.77–1.29) and significantly higher with insulin therapy (1.81, 1.46–2.24) compared to no-antidiabetic drug use for all cancers combined. Other modern glucose lowering drugs such as GLP-1 receptor agonists [49] or SGLT-2 inhibitors [50] did not yet show a significant effect on the risk of cancers in patients with diabetes.

Multiple *meta*-analyses of case–control and cohort studies have reported a decrease in overall cancer incidence of approximately 10 to 40% with metformin use, along with a decrease in mortality by a similar range [51-53]. In contrast, *meta*-analyses of RCTs have shown a non-significant change in cancer incidence [52]; however, the randomised trials

included were conducted to treat diabetes or reduce cardiovascular events and had baseline median ages ranging from 47 to 60 and short follow-up time, making them underpowered to detect an effect on cancer incidence. There is a long history and much clinical experience with metformin that makes it a very attractive candidate for drug repurposing for cancer prevention [53]. An analysis of clinical trials registered on ClinicalTrials.gov (clinicaltrials.gov/, accessed 15 October 2019) revealed an additional 23 trials examining the effect of metformin in participants at risk of cancer, 30 presurgical studies and 30 studies in the adjuvant setting. Based on the available data it seems very unlikely that the use of metformin has no effect on cancer incidence or cancer mortality. Since all the other available glucose lowering drugs have no beneficial on the cancer outcome in diabetic patients, recommendation to use of metformin with other glucose lowering drugs, when available in fixed dosed combination drugs makes sense [54].

10. Metformin in the cardiovascular outcome trials (CVOTs)

During the last decade, the spectrum for glucose-lowering drugs has increased enormously by the development of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors, allowing individualization of antidiabetic therapy for patients with T2DM. Many combinations can now be used without an increased risk for severe hypoglycemia and weight gain. Following a request of the US Food and Drug Administration, many large cardiovascular outcome trials (CVOTs) have been performed in patients with longstanding disease and established CVD. In the majority of CVOTs, CV risk factors were well controlled and a high number of patients were already treated with ACE inhibitors/angiotensin receptor blockers, statins and anti-platelet drugs [55]. To date, only members of 2 drug classes, GLP1-Receptor agonists and SGLT2 inhibitors have been shown to reduce significantly the risk of major CV events [56,57] in the CVOTs, such as the composite of myocardial infarction, stroke, and CV death (MACE). Both drug classes reduced MACE in a similar magnitude with GLP1-RA reducing the risk by 12% (HR: 0.88; 95% CI: 0.84–0.94; $p < 0.001$) and SGLT2i by 11% (HR: 0.89; 95% CI: 0.83–0.96; $p = 0.001$, however this treatment effect was restricted to a 14% reduction in those with established atherosclerotic CVD (HR: 0.86; 95% CI: 0.80–0.93; $p = 0.002$), whereas no effect [58] was seen in patients without established atherosclerotic CVD (HR: 1.01; 95% CI: 0.87–1.19; $p = 0.81$; p interaction = 0.028). Both GLP1-RA (HR: 0.82; 95% CI: 0.75–0.89; $p < 0.001$) and SGLT2i (HR: 0.62; 95% CI: 0.58–0.67; $p < 0.001$) reduced the risk of progression of kidney disease including macroalbuminuria, but only SGLT2i reduced the risk of worsening estimated glomerular filtration rate, end-stage kidney disease, or renal death (HR: 0.55; 95% CI: 0.48–0.64; $p < 0.001$) [58].

Based on the positive CV outcome data in the CVOTs with empagliflozin [56] and liraglutide [57] it was discussed whether metformin should be replaced by these drugs not only in secondary but also in the primary prevention in patients without a previous CV history. We and others [59] do not share this view, since many positive data were reported for metformin in patients with CVD, heart failure, CKD and cancer as summarized in this review. In addition, 75–81% of patients included in EMPA REG Outcome, LEADER and CANVAS trials [56,57,60] had metfomin therapy at baseline. Unfortunately, we have very limited information about a potential interaction of the tested drugs with metformin. The 4 DPP-4 inhibitors (saxagliptin, alogliptin, sitagliptin, linagliptin) did not show CV or renal protection in the CVOTs [55], but the results were different in patients with or without concomitant metformin therapy when the data of 3 CVOTs (SAVOR, EXAMINE, TECOS) were pooled [61]. While prevalent metformin users experienced a trend toward improved CV outcomes with DPP-4i (summary HR: 0.92, 95% CI: 0.84–1.01), baseline metformin nonusers showed a trend toward harm (HR: 1.10, 95% CI 0.97, 1.26). The difference in overall DPP-4i effect between metformin user and nonuser subgroups was statistically significant ($p = 0.036$) [61]. In the EMPA REG Outcome study [56] empagliflozin in patients not on metformin (n = 1,840) showed a strong reduction of the 3-point MACE (HR: 0,72; 95% CI: 0.56–0.94), whereas in patients on metformin (n = 5,180) the effect was less impressive (HR 0,92; 95% CI: 0.77–1.10). Although the p-value for interaction did not reach significance, based on these data we cannot exclude someinteraction between metformin and SGLT-2 inhibitors. The data could be interpreted that metformin itself had a strong effect on 3-point MACE, since the addition of empagliflozin in that large group of patients reduced MACE by only 8%. However, reduction of CV death with empagliflozin was similar in patients with metformin (HR 0.71, 95%CI 0.54, 0.94) or without metformin (HR = 0.46; 95% CI 0.32, 0.68).

Most patients included in the CVOTs had a previous CV event and were in the secondary prevention [62]- only 2 studies allowed to analyze the effect of SGLT-inhibitors (DECLARE) or GLP1-receptor agonists (REWIND) in the primary prevention [62], since about 60% in the DECLARE [63] and 69% of patients in the REWIND [64] study had only CV risk factors, but not an established CVD. Use of dapaglifozin in DECLARE [63] was not associated with a reduction of MACE or mortality, but treated patients had a lower rate of hospitalisation for heart failure. By contrast use of dulaglutide in REWIND [64] was associated with lower rate of MACE (0.88, 95% CI: 0.79–0.99; $p = 0.026$), but all-cause mortality did not differ between groups in the dulaglutide group vs in the placebo group. In both DECLARE [63] and REWIND [64] the majority of all patients were treated with metformin at baseline (82% and 81.7%) and we have no information whether the findings were similiar or different in metformin users and metformin nonusers.

11. Changes in the algorithm for the management of patients with type 2 diabetes from 2006 to 2019

During the last 13 years the recommendation for the glucose lowering management of patients with T2DM has changed many times, which induced some confusion in particular for doctors with limited experience in the diabetes treatment. In 2006 either basal insulin, sulfonylureas or thiazolidinediones (TZDs) were recommended if lifestyle intervention and maxi-

mal tolerated dose of metformin failed to achieve or sustain glycaemic goals [65]. In 2008 greater caution in using the TZDs, especially in patients at risk of, or with, congestive HF was recommended [66]. In 2009 the consensus regarding the second medication added to metformin was to choose either insulin or a sulfonylurea [67]. In this version GLP-1 receptor agonists were classified as less validated therapies. Remarkably, DPP-4 inhibitors were not recommended at all, since the authors had concerns about the potential for this class of compounds to interfere with immune function and low glucose lowering efficacy [67]. In 2010 a debate article was published by an international expert group critizing that these recommendations were not evidence based [68]. Consequently, a patient-entered approach was in the focus of the 2012 ADA-EASD consensus paper with the concept of individualizing the therapy [69]. However, all 5 classes of glucose lowering drugs (sulfonylureas, pioglitazone, DPP-4i, GLP-1RA and insulin) were offered as a therapeutic option after metformin not giving a preference for any of the five options. In 2015 an updated position statement was published included fort he first time SGLT-2i as a new class for antidiabetic treatment [70].

In 2018 the management of hyperglycemia in type 2 diabetes has become extraordinarily complex with the number of glucose-lowering medications now available [71]. The positive outcome data in the several CVOTs [56,57,60] resulted in a change of the paradigm in the treatment recommendations. For patients who have established ASCVD, SGLT2i or GLP-1RA with proven CV benefit in the CVOTs were recommended as part of glycemic management after metformin [71]. Remarkably, metformin was always recommended as first-line treatment in all consensus papers from 2006 to 2019. In patients without CVD, renal disease or heart failure metformin can still be used in the primary prevention, but in the presence of CVD GLP-1RA or SGLT-1i should be prescribed together with metformin, whereas in patients with HF SGLT-2i and not GLP-1RA may be the drug of choice in combination with metformin. In patients with renal impairment metformin should be used in combination with either SGLT-2i or GLP1RA, whereby SGLT-2i have demonstrated a stronger effect on hard endpoints such as ESRD or doubling of serum creatinine [72]. The recently published guidelines from the European Society of Cardiology (ESC) recommend using SGLT-2i or GLP-1RA as monotherapy in drug-naive patients presenting either with ASCVD, or only with high/very high CV risk [73]. Since we do not have any evidence from published studies for this provocative recommendation, it seems very unlikely that the ADA-EASD consensus group will agree with this statement in the awaited updated version published at the end of this year. However, early combination use of metformin with SGLT-2 inhibitors instead of metformin monotherapy makes sense for most of the patients, since glycemic control reducing glucotoxicity would be better and all patients with subclinical silent ischemia, heart failure or early kidney disease would have benefit [74].

12. Conclusions

Metformin is used for 60 years, has beneficial effects on glucose lowering and weight control, is inexpensive and is used in monotherapy or fixed-dose combination therapy in > 200 million diabetic patients worldwide. Metformin has demonstrated many positive effects in observational studies in patients with coronary artery disease, heart failure and chronic kidney disease. A recent metaanalyis of of 26 observational studies including 815 839 patients showed that metformin use was associated with a 26% reduction of all-cause mortality [24]. Thus, metformin should not be replaced my monotherapies with SGLT-2 inhibitors or GLP-1 receptor agonists, but should be combined with these drugs (in particular with SGLT-2 inhibitors) in the very early phase of type 2 diabetes to protect patients from deterioration of glucose control and to offer broad protective effects for heart failure and renal disease.

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Declaration of Competing Interest

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