Review article

J Atherosclerosis Prev Treat. 2022 May-Aug;13(2):67–73
doi.: 10.53590/japt.02.1035

Metformin and type 2 diabetes in the era of cardiovascular outcome trials; A narrative review

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ABSTRACT

Metformin has been for many years the first-line pharmaceutic treatment for most patients with type 2 diabetes. However, new classes of antidiabetic agents with proven cardiorenal benefits beyond glycemic control challenge metformin's predominance. The hypoglycemic effect of metformin is mediated in liver by inhibiting gluconeogenesis and improving insulin sensitivity and in intestines by reducing glucose absorption, increasing incretins and altering intestinal microbiome. After decades of use metformin has been proved to be one of the most potent, safe and cost-effective medications for the treatment of type 2 diabetes. Several other pleiotropic actions of metformin in inflammation pathways suggest a potential cardioprotective role. This hypothesis has been tested in a few randomized trials and in more observational studies and metanalyses with controversial results. Given the lack of robust evidence for the cardioprotective effect of metformin compared to the newer antidiabetic agents, current treatment algorithms are under scrutiny. Ongoing randomized clinical trials comparing metformin to placebo are expected to elucidate the effect of metformin on specific cardiovascular and renal outcomes.

KEY WORDS: *Metformin, type 2 diabetes, cardiovascular risk, cardiovascular outcome, renal outcome, CVOTs*

INTRODUCTION

Metformin has been for decades the first-line treatment for most of the drug naïve patients with type 2 diabetes not achieving their glycemic target with diet and lifestyle modification alone. However, within the recent years, new classes of antidiabetic drugs with proven cardiorenal benefits beyond their hypoglycemic effect have emerged. Tested extensively in Cardiovascular Outcome randomized placebo-controlled Trials (CVOTs) these new factors challenge metformin's predominance in the treatment of diabetes[1]. The aim of this review is a critical reappraisal of current data for the cardiovascular and renal safety of metformin and for potential additional cardiovascular benefits from its use.

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Submission: 19.07.2022, Acceptance: 11.08.2022

The antidiabetic mechanisms of metformin

Metformin is a synthetic derivative of galegine, a natural product from the plant *Galega officinalis* used in herbal medicine for many years. Unlike the newer antidiabetic agents, metformin was introduced in clinical practice in late 50s, without preceding mechanistic studies and with many molecular pathways of its hypoglycemic action still not well defined[2]. After oral administration of metformin 70% of the given dose is absorbed from the small intestine and the remainder is excreted in feces passing unchanged the colon. Metformin is also excreted unchanged in urine. Pharmacokinetic studies and use of Positron Emission Tomography (PET) reveal up to 5fold increased concentration of oral administered metformin in the liver and in the intestines compared to plasma[3]. On the contrary, the accumulation of the drug in muscles is low. Therefore, it seems that most of the hypoglycemic effect of metformin is mediated by molecular pathways mainly in the liver and in the intestine.

Endogenous glucose production by the hepatocytes is an energy consuming chemical reaction demanding the degradation of six ATP equivalents for each newly synthesized glucose molecule. ATP production takes place mainly in mitochondria. Metformin carries a positive charge and as a result achieves high concentrations in mitochondria inhibiting gluconeogenesis through two main pathways: It inhibits the Complex I of the respiratory chain thus suppressing ATP production and it also inhibits mitochondrial glycerophosphate dehydrogenase (mGPD), a key enzyme for mitochondrial transportation and re-oxidation of molecules reduced in cytoplasm[4,5]. Metformin seems, also, to activate AMP-activated protein kinase (AMPK). AMPK is activated by increases in AMP:ATP and ADP:ATP ratios acting as a cellular energy sensor. Once activated, AMPK is switching on catabolic pathways, namely lipolysis and fatty acids oxidation suppressing at the same time processes consuming energy, such as gluconeogenesis and lipogenesis. Metformin's act as insulin sensitizer for hepatocytes may be mediated predominantly by AMPK activation[8,9].

Recent genetic and clinical studies underscore the importance of the intestines as target-organ for metformin through several mechanisms[10-12]. Metformin increases the anaerobic glucose metabolism in enterocytes thus reducing glucose uptake. It, also, seems to increase Glucagon-Like Peptide-1 (GLP-1) secretion from enterocytes. Finally, alteration of the intestinal microbiome related to the use of metformin may contribute to the total glucose-lowering effect.

The aforementioned high concentrations of metformin in the enterocytes, the alteration of intestinal microbiome and an increase in serotonin release from enterochromaffin cells potentially explain the gastrointestinal side effects of this antidiabetic agent. In addition, alteration of intestinal microbiome may be associated with vitamin B12 deficiency observed after long term use of metformin. At the initiation of treatment with metformin gastrointestinal side effects may affect up to 20-30% of patients. Low start dose and slow titration may prevent many of these side effects. However, only 5% of patients discontinue metformin due to serious gastrointestinal side effects[14,15].

Although many of the mechanisms underlying its glucose-lowering effect remain unclear, metformin is one of the most potent, safe and cost-effective antidiabetic agent with an anticipated decrease in HbA1c from its use up to 1.5-2.0 percentage units.

Metformin and cardiovascular risk

UKPDS is the first clinical trial to suggest a potential cardioprotective effect from the use of metformin[17]. In this cornerstone, open-label, randomized, polycentric trial 1,709 overweight, newly diagnosed patients with type 2 diabetes from 15 out of 23 participating diabetes centers were randomized to receive intensive diabetes treatment with metformin (342 patients), sulphonylurea or insulin (961 patients) or conventional treatment with diet without use of placebo. After median follow-up of 10.6 years patients assigned to metformin had a significant decrease in the risk for every outcome related to diabetes by 36% and in the risk for death related to diabetes by 42%. Moreover, the risk for myocardial infarction was reduced significantly by 39% and there was a 30% decrease in the risk for the composite outcome of myocardial infarction, sudden death, angina, stroke and peripheral vascular disease. Participants in UKPDS were epidemiologically followed for ten more years after the end of the randomized trial under the surveillance of their personal physicians[18]. Although the difference in HbA1c between the two initial groups rapidly diminished after the end of the randomized trial, patients assigned to metformin had still significantly lower risk for the aforementioned cardiovascular outcomes ten years after the initial intervention.

In the double-blind HOME Trial 390 insulin treated patients with type 2 diabetes and mean disease duration 13 years were randomized to receive metformin or placebo as add on treatment to insulin[19]. The primary endpoint was a composite of 3 microvascular and 13 macrovascular outcomes, while each micro and macrovascular outcome was separately analyzed as secondary outcome. After 4.3 years median follow-up the two groups did not differentiate in the primary outcome. However, patients assigned to metformin had 39% lower risk for macrovascular com-

plications [HR 0.61 (95% CI 0.40-0.94), P=0.02]. Part of this favorable effect could be attributed to a 3Kg weight loss and a 0.4% lower HbA1c achieved with metformin treatment. The estimated Number of patients Needed to Treat (NNT) with metformin for 4 years to prevent one cardiovascular event was estimated to be 16.

In another double-blind, secondary prevention clinical trial with equally small number of participants 304 type 2 diabetics with mean disease duration 6 years and history of Coronary Artery Disease (CAD) were randomly assigned to receive metformin1.5gr daily or glipizide 30mg daily for 3 years[20]. After median follow up of 5 years patients on metformin had significantly lower risk for the primary composite outcome of death from cardiovascular cause, death from any cause, non-fatal myocardial infarction, non-fatal stroke, or arterial revascularization compared to those on glipizide [HR 0.61 (95% CI 0.40-0.94), P=0.02].

In Diabetes Prevention Program (DPP), a randomized trial for the prevention of type 2 diabetes in individuals with impaired glucose tolerance, metformin significantly reduced the incidence of type 2 diabetes in overweight participants. However, in the following the end of DPP observational Diabetes Prevention Program Outcomes Study (DPPOS) metformin showed no effect on the composite primary endpoint of non-fatal Acute Myocardial Infarction (AMI), non-fatal stroke or cardiovascular death [HR:1.03 (95% CI, 0.78-1.37; P=0.81)][21].

Three recent meta-analyses of randomized clinical trials investigated the effect of metformin on cardiovascular risk (CVR). Griffin et al analyzed data from 13 randomized clinical trials with more than 2,000 participants with Type 2 diabetes assigned to metformin and a similar number of patients assigned to lifestyle modification, placebo or no intervention at all[22]. In only four of the above studies metformin was compared to placebo and cardiovascular outcomes were included in the endpoints. Treatment with metformin had no effect on the risk for death from cardiovascular or from any cause, for non-fatal AMI or stroke and for peripheral vascular disease. The population of these studies was overweight patients with suboptimal glycemic control, the heterogeneity was low and the risk of bias high or undetermined for most of them. In another meta-analysis Monami et al analyzed data from 13 randomized clinical trials with at least 52 weeks duration comparing metformin to placebo, to other antidiabetic agent or to no intervention[23]. Data for Major Adverse Cardiovascular Events (MACE) were extracted and analyzed from the studies that included MACE in their outcomes, while data for death from any cause were analyzed from all the trials included in meta-analysis. Similarly to Griffin's meta-analysis, metformin had no effect on MACE or on mortality from any cause. However, in an analysis excluding trials where metformin was compared to other active agents such as sulphonylureas, SGLT-2 inh and GLP-1RA mortality from any cause seemed to be lower with metformin [OR 0.71(95% CI 0.51-0.99)]. Finally, Tsapas et al in a systematic review and network meta-analysis of 453 randomized clinical trials compared the efficacy of treatment with 9 classes of anidiabetic agents. They reported that in newly diagnosed, low CVR patients with type 2 diabetes treatment with metformin or with any other agent has no significant effect on CVR[24].

Numerous retrospective and prospective cohort studies in type 2 diabetics with or without history of Cardiovascular Disease(CVD) or Heart Failure (HF) with preserved Ejection Fraction co-relate treatment with metformin to significantly reduced risk for death from any cause, death from CVD, hospitalization for HF or non-fatal cardiovascular events[25-27]. Recently, in a prospective cohort study in drug-naïve patients with type 2 diabetes initiation of treatment with metformin was compared to that of an SGLT-2 inh (empagliflozin, canagliflozin or dapagliflozin)[28]. The primary endpoint of the study was a composite of cardiovascular outcomes (death from any cause, AMI, or stroke). After median follow-up of 12 months there was no difference between the two interventions in the incidence of the primary endpoint. However, patients that initiated an SGLT-2 inh had significantly lower risk for hospitalization due to HF [HR, 0.78 (95%CI 0.63-0.97)].

Several pathophysiologic mechanisms have been proposed to mediate the putative cardioprotective effect of metformin. Randomised clinical trials, observational studies and mechanistic studies consistently report anti-inflammatory actions of metformin such as suppression of monocyte differentiation into macrophage, suppression of proinflammatory cytokine secretion, decrease of the Neutrophil to Lymphocyte Ratio (NLR), a marker recently proposed as predictor of all-cause mortality and cardiac events, oxidative stress reduction and improvements in endothelial function and in fibrinolysis mechanisms[2]. Intestine microbiome changes and increased GLP-1 levels may also play role in the potent cardioprotective actions of metformin[29-31].

Metformin and diabetic kidney disease

Clinical data on renal outcomes in metformin treated patients with type 2 diabetes are limited. No significant effect of metformin on renal death or renal failure was reported in UKPDS. However, in this population of newly diagnosed type 2 diabetics only six renal events were recorded[17]. In a post hoc subgroup analysis of data from the EMPA-REG randomized placebo controlled trial, the incidence of new or the deterioration of preexisting renal

disease were lower in patients on baseline treatment with metformin (12.4% with empagliflozin vs 16.9% with placebo) compared to those not receiving metformin (13.7% with empagliflozin vs 24.6% with placebo)[32]. These data suggest a background renoprotection with metformin.

Real-World and observational studies report cardiorenal benefit from the use of metformin in patients with Chronic Kidney Disease (CKD). In a retrospective cohort study patients with type 2 diabetes and CKD treated with metformin had 20% lower risk for MACE compared to those treated with sulphonylureas [HR 0.80 (95% CI 0.75-0.86)][33]. Similarly, in a post hoc subgroup analysis of data from a randomized interventional study with darbepoetin alfa in patients with type 2 diabetes, anemia and CKD (mean eGFR: 33ml/min/1.73^2) participants receiving metformin had significantly lower risk for cardiovascular or any cause mortality, for a composite endpoint of death, HF hospitalization, AMI, stroke and myocardial ischemia and for a composite end point of End Stage Renal Disease (ESRD) or death. There was no difference between users and non-users of metformin in the incidence of ESRD[34]. On the contrary, Lee et al analyzing data from insurance database suggested a small but significant increase in the risk of ESRD among metformin users[35].

Metformin increases plasma lactate levels by inhibiting Complex I of the mitochondrial respiratory chain predominantly in the hepatocytes[2]. As plasma metformin concentrations remain within the therapeutic range, below 2μg/ml, the observed increase in plasma lactate is of non-clinical significance. However, since metformin is excreted unchanged via the kidney acute elevations of its plasma concentrations, usually above 5μg/ml, in the course of comorbidities such as renal function impairment, liver failure, HF, sepsis, or shock of any cause predispose to elevated levels of lactate and substantially increase the risk of lactic acidosis. Metformin-Associated Lactic Acidosis (MALA) is the most serious adverse event related to metformin[36]. Although the reported incidence of MALA in clinical practice has proved to be very low (<10 cases per 100,000 patient-years), mortality rates remain as high as 30-50%. The fear of MALA historically restricted the use of metformin in patients with eGFR>60ml/min/1.73^2 excluding a large number of patients that could possibly benefit from its use. Recently, pharmacokinetic studies in patients with Stage 3-4 CKD and observational studies from large registries suggest that treatment with metformin is safe and effective with appropriate dose adjustment for patients with CKD[37,38]. According to the current prescription guidelines, metformin is contraindicated in patients with eGFR <30ml/min/1.73^2 while the daily dose should not exceed 1000mg in patients with eGFR: 30-45ml/min/1.73^2 and 2000mg in patients with eGFR: 45-60ml/min/1.73^2 [39].

Conclusions and Perspectives

The results of large CVOTs of newer glucose-lowering agents, GLP-1RA and SGLT-2 inh have recently changed the algorithm for the pharmacologic management of type 2 diabetes. Moreover, the traditional glucocentric way of treatment focused on the achievement of glycemic targets tends to be replaced by a therapeutic approach targeting mainly the prevention of "hard outcomes" related to diabetes such as cardiovascular or any cause mortality, AMI, stroke, HF and CKD[40]. GLP-1RA semaglutide, liraglutide and dulaglutide, and SGLT-2inh empagliflozin, dapagliflozin and canagliflozin have shown in large CVOTs cardiorenal protection beyond their hypoglycemic effect in patients with type 2 diabetes and established, or high risk for, CVD. Remarkably, 75% of the participants in these CVOTs were on baseline treatment with metformin.

The suggestive cardiovascular benefit of metformin is based mainly on data from three randomized trials with relatively small number of participants. Compared to the newer drugs' CVOTs these trials have certain weaknesses such as absence of comparison to placebo, differences in glycemic control between the interventions group and not prespecified primary cardiovascular outcomes[17-20]. Thus, the results of these trials should be cautiously interpreted. Meta-analyses of randomized clinical trials have failed to show cardiovascular benefit from the use of metformin[22,23]. In newly diagnosed drug-naive patients with type 2 diabetes without history of CVD, or low CVR initiation of treatment with metformin or any other antidiabetic agent including GLP-1RA and SGLT-2 inh has no effect on CVR[24]. However, the risk for hospitalization due to HF and for renal outcomes is significantly lower with initiation of SGLT-2inh in patients with history of HF and CKD with or without diabetes[42-45]. The latest data have modified the algorithms for the pharmaceutic treatment of type 2 diabetes. Since 2019 the European Society of Cardiology (ESC) suggests the use of SGLT-2 inh and GLP-1RA as first-line treatment in drug-naïve patients with type 2 diabetes and CVD or HF[46]. The European Association for the Study of Diabetes (EASD) in consensus with the American Diabetes Association(ADA) encourages the use of a GLP-1RA or an SGLT-2inh with proven cardiovascular benefit in patients with established, or high risk for, CVD or with HF or CKD independently from the achievement of their glycemic target with their baseline treatment. In these guidelines metformin remains first-line pharmaceutic treatment for the majority of patients with type 2 diabetes[1].

Two ongoing randomized clinical trials are expected to further elucidate the effect of metformin on cardiorenal outcomes. In the secondary prevention trial VA-IMPACT individuals with prediabetes and CVD are randomized to

receive metformin 2000mg daily or placebo. The primary outcome of the trial is a composite of death, non-fatal AMI, non-fatal stroke, hospitalization for unstable angina or need for coronary artery revascularization[47]. In RenoMet trial patients with stage 2-3B CKD without history of diabetes with eGFR 30-90ml/min/1.73^2, proteinuria <2gr/24h, and annual decline in eGFR of 2-15ml/min/1.73^2 over the preceding 3 years are randomized to receive metformin or placebo. The primary endpoint of the trial is a 30% decline of eGFR[48]. In addition to these studies, subgroup metanalyses of participants not receiving metformin in CVOTs and in other randomized trials are expected to give more definitive answers regarding the position of metformin in contemporary algorithms of pharmaceutic treatment of type 2 diabetes.

Conflict of interest

None to declare.

ΠΕΡΙΛΗΨΗ

Μετφορμίνη και Διαβήτης τύπου 2 στην εποχή των μελετών καρδιαγγειακής ασφάλειας: αφηγηματική ανασκόπηση

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Η μετφορμίνη αποτελεί εδώ και πολλά την φαρμακευτική θεραπεία πρώτης γραμμής για τους περισσότερους ασθενείς με Σακχαρώδη Διαβήτη Τύπου 2. Ωστόσο, η πρωτοκαθεδρία της αμφισβητείται από νεότερους αντιδιαβητικούς παράγοντες με αποδεδειγμένα καρδιονεφρικά οφέλη επιπλέον του υπογλυκαιμικού τους αποτελέσματος. Η αντιδιαβητική δράση της μετφορμίνης ασκείται στο ήπαρ με την αναστολή της γλυκονεογένεσης και τη βελτίωση της ευαισθησίας στην ινσουλίνη καθώς και στον εντερικό σωλήνα με τη μείωση της απορρόφησης της γλυκόζης, την αύξηση των επιπέδων των ινκρετινών και τη μεταβολή στη σύσταση του εντερικού μικροβιώματος. Μετά από δεκαετίες χρήσης της στην θεραπεία του Σακχαρώδη Διαβήτη τύπου 2 η μετφορμίνη έχει αποδειχθεί ένας ισχυρό, ασφαλές και οικονομικά προσιτό αντιδιαβητικό φάρμακο. Πλειοτροπικές δράσεις της μετφορμίνης σε μεταβολικές οδούς που αφορούν τη συστηματική φλεγμονή και αθηρογένεση, πιθανολογούν επιπλέον του υπογλυκαιμικού της αποτελέσματος καρδιοπροστατευτικό ρόλο. Η υπόθεση αυτή έχει ελεγχθεί, ως τώρα, σε λίγες μόνο τυχαιοποιημένες κλινικές δοκιμές και σε περισσότερες μελέτες παρατήρησης και μετα αναλύσεις με αντικρουόμενα αποτελέσματα. Δεδομένης της έλλειψης ισχυρής τεκμηρίωσης για την καρδιοπροστατευτική δράση της μετφορμίνης σε σύγκριση με τους νεότερους αντιδιαβητικούς παράγοντες οι τρέχοντες θεραπευτικοί αλγόριθμοι τίθενται σε διαδικασία αναθεώρησης. Υπό εξέλιξη τυχαιοποιημένες κλινικές δοκιμές που συγκρίνουν τη μετφορμίνη με εικονικό φάρμακο αναμένεται να δώσουν περισσότερα δεδομένα για την επίδραση της μετφορμίνης σε συγκεκριμένες καρδιαγγειακές και νεφρικές εκβάσεις. .

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Μετφορμίνη, διαβήτης τύπου 2, καρδιαγγειακός κίνδυνος, καρδιαγγειακές εκβάσεις, νεφρικές εκβάσεις, μελέτες καρδιαγγειακής ασφάλειας*

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