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REVIEW

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Metformin: evidence from preclinical and clinical studies for potential novel applications in cardiovascular disease

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ABSTRACT

Introduction: For a long time, metformin has been the first-line treatment for glycemic control in type 2 diabetes; however, the results of recent cardiovascular outcome trials of sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists have caused many to question metformin's position in the guidelines. Although there are several plausible mechanisms by which metformin might have beneficial cardiovascular effects, for example, its anti-inflammatory effects and metabolic properties, and numerous observational data suggesting improved cardiovascular outcomes with metformin use, the main randomized clinical trial data for metformin was published over 20 years ago. Nevertheless, the overwhelming majority of participants in contemporary type 2 diabetes trials were prescribed metformin.

Areas covered: In this review, we will summarize the potential mechanisms of cardiovascular benefit with metformin, before discussing clinical data in individuals with or without diabetes.

Expert opinion: Metformin may have some cardiovascular benefit in patients with and without diabetes, however the majority of clinical trials were small and are before the use SGLT2 inhibitors and GLP1-RAs. Larger contemporary randomized trials, with metformin evaluating its cardiovascular benefit are warranted.

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1. Introduction

Metformin, an oral antidiabetic drug of the biguanide class, is often the first medication for people with type 2 diabetes [1]. Its mechanism of action is complex, but simply, it lowers blood glucose levels by reducing the amount of glucose produced and released by the liver, and by increasing insulin sensitivity. This results in clear benefits for glucose metabolism and improved glycemic control [2]. Recently, there has been an increasing recognition that management of individuals with type 2 diabetes should simply not just be targeted at reducing blood glucose but should also taken into consideration reducing complications of diabetes, in particular, major adverse cardiovascular events. Metformin has cardioprotective effects [3–5], although its overall effect on cardiovascular outcomes is uncertain [6,7]. This uncertainty has become increasingly important as recent randomized trials have demonstrated significant improvements in cardiovascular outcomes with newer classes of antidiabetic therapies, such as sodium-glucose co-transporter 2 inhibitors (SGLT2i) [8] and glucagon-like peptide 1-receptor agonists (GLP1-RA) [9]. Nevertheless, metformin remains the first-line treatment for type 2 diabetes in many guidelines (Table 1) [10–13]. Given that cardiovascular disease (CVD) remains the major cause of morbidity and mortality in diabetic individuals, it is important to reappraise the cardiovascular benefits of metformin and place these in the context of modern diabetes treatment. The purpose of this review is to summarize the current state of knowledge of metformin's effects on cardiovascular disease.

2. Mechanisms of action of metformin

The mechanisms of action of metformin are complex and have not been elucidated fully. In hepatocytes, metformin uptake is catalyzed by the organic cation transporter-1 (OCT1) [7]. This results in the rise of cytoplasmic AMP:ATP and ADP:ATP ratios, which promote the activation of AMPK by inhibition of the mitochondrial respiratory-chain complex I that reduces production of ATP (Figure 1) [14]. Metformin also activates the AMPK through the lysosomal pathway [15]. Metformin may form a complex with v-ATPase-regulator by directly acting on v-ATPase and promoting the translocation of AXIN/LKB1 onto the surface of lysosome, resulting in AMPK activation [15]. It is also suggested that metformin can dissociate mTORC1 from v-ATPase/Regulator, resulting in a direct inactivation mTORC1. Metformin acts directly on v-ATPase and promotes the occupation of ATPase-Regulator complex by AXIN [8], resulting in dissociation of the complex from Raptor and mTOR and direct inactivation of mTORC1, a master regulator for anabolic pathways [16]. Moreover, metformin can mediate mTORC1 inhibition through AMPK/TSC2/mTORC1 signaling pathway, as

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Article highlights

- Metformin is currently still recommended as the first-line pharmacological treatment for management of hyperglycemia in type 2 diabetes despite recent trials showing the cardiovascular benefits of newer agents, such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists.
- The main randomized trial evidence showing clinical outcome benefit with metformin in type 2 diabetes comes from an older, comparatively small trial.
- Metformin has a number of plausible potential mechanisms of cardiovascular benefit beyond its glycemic effects including anti-inflammatory effects and reductions in oxidative stress, body weight and blood pressure.
- Metformin may also have beneficial effects in individuals without type 2 diabetes.
- There is a need for contemporary evidence from large randomized trials to ascertain the cardiovascular benefits of metformin and clarify its position in clinical guidelines.

AMPK inhibits mTORC1 by direct phosphorylation of TSC2 and Raptor [17].

These multiple mechanisms may contribute to some cardiovascular benefits. Long-term treatment with metformin has been shown to significantly attenuate ventricular hypertrophy induced by transaortic constriction through activation of AMPK and downstream signaling pathways involving eNOS-NO [18]. In cardiomyocytes, metformin has also shown to inhibit Angiotensin II-induced protein synthesis by enhancing phosphorylation of AMPK and eNOS and increased NO production [18].

There is also evidence that metformin inhibits hepatic glucose production via its inhibitory effect on the Kruppel-like factor 15 (KLF15) protein and gene expression, an important regulator of gluconeogenesis. In hepatocytes, KLF-15 plays a critical role in the regulation of gene expression for gluconeogenesis and amino acid-degrading enzymes [19]. Metformin, however, induces the proteasomal degradation of KLF15 by promoting its ubiquitination [19]. This has raised the possibility that the inhibitory effect of metformin on gluconeogenesis is mediated at least in part, by downregulation of KLF-15 and subsequent attenuation of expression of such genes [19].

In the failed heart, metformin improves mitochondrial function and metabolism in cardiomyocytes. In a pre-clinical study in mice with ischemic myocardium, small doses of metformin had been shown to improve left ventricular structure and function, leading to improved survival. This was attributed to an increase in AMPK phosphorylation, up-regulation in endothelial nitric oxide synthase (eNOS) expression and PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), master regulators of biogenesis and function of mitochondria [20]. Activation of both eNOS and PGC-1α elevates ATP synthesis and restores the normal ratio of ATP synthesis/oxygen use, therefore improving cardiomyocyte metabolism [21]. Metformin also inhibits collagen synthesis in myocardium and therefore contributes to a significant reduction in left ventricular dimensions and reduces LV diastolic pressure via reduction of the activity of transforming growth factor beta 1 (TGF-β1) which is the basic pro-fibrotic growth factor in myocardium [22]. Therefore, the inhibition of TGF-β1 activity may play a role in the favorable effect of metformin in cardiovascular disease. It is, however, unclear how much of metformin's effects are directly on the myocardium. A study using positron emission tomography found that the majority of the uptake of radiolabelled metformin was in the liver and intestines with relatively little in the myocardium [23]. Whether the potential cardiovascular protective effects of metformin are due to any direct effects on the heart or are rather due to beneficial systemic effects (Figure 1) remains to be determined, particularly as mechanisms demonstrated in pre-clinical animal studies are often not replicated in clinical studies.

3. Anti-inflammatory effects of metformin

There is an increasing recognition of the importance of inflammation in the pathophysiology of CVD, and recent trials have

Table 1. Evolution of the position of metformin in recent international diabetes guidelines/consensus statements.

Guideline	Year	Reference	Recommendation	Comments
ADA/ EASD	2018	[10]	Metformin first-line pharmacological therapy including in those with established ASCVD or CKD.	'Metformin remains the preferred option for initiating glucose-lowering medication in type 2 diabetes and should be added to lifestyle measures in newly diagnosed patients.'
ESC/ EASD	2019	[11]	Drug-naïve T2D patients: If established ASCVD or high/very high CV risk then SGLT2i or GLP1RA monotherapy. If HbA1c above target then add metformin.	'Observational and database studies provide supporting evidence that long-term use of metformin improves CV prognosis. Still, there have been no large-scale randomized CV outcome trials (CVOTs) designed to assess the effect of metformin on CV events.'
ADA/ EASD	2022	[12]	'Overall, for treatment of hyperglycemia, metformin remains the agent of choice in most people with diabetes, based on its glucose-lowering efficacy, minimal risk of hypoglycemia, lack of weight increase, and affordability.' 'In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin.'	' … metformin has traditionally been recommended as first-line glucose-lowering therapy for the management of type 2 diabetes. However, there is ongoing acceptance that other approaches may be appropriate.'

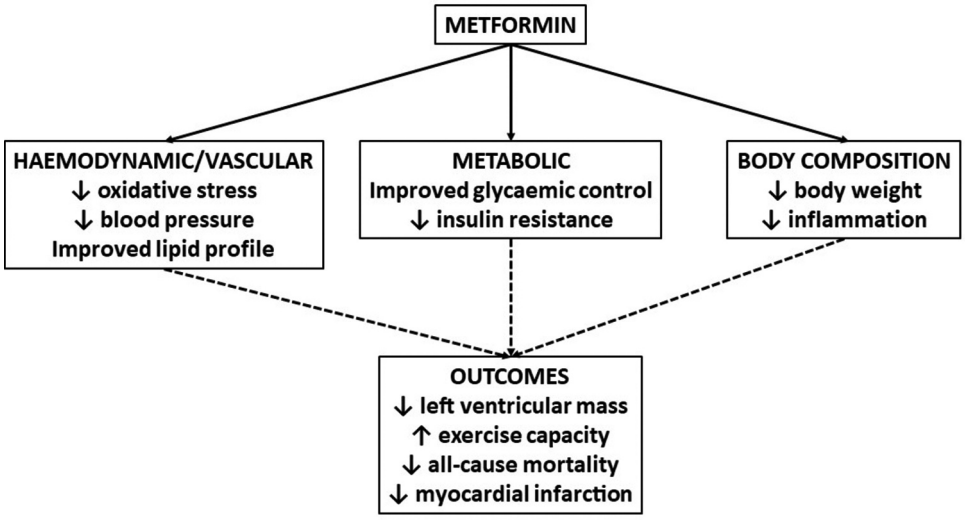

Figure 1. Summary of potential mechanisms of cardiovascular benefit caused by metformin. metformin has a number of potential mechanisms of cardiovascular benefit that include its effects on the vasculature, metabolism and body composition.

suggested that anti-inflammatory therapies may improve cardiovascular outcomes in at-risk individuals with cardiovascular disease [24–26]. Work by our research group has found that metformin has anti-inflammatory effects, regardless of diabetes status [27]. Our study investigated the effect of metformin and inhibitor of kappa B kinase (IKKB) inhibitor BI605906 on primary mouse hepatocytes [27]. It found both compounds inhibited TNF-α–dependent expression of CINC-1/CXCL1, CXCL2, IL-1β, and IL-6 [27]. The study also measured the effect of metformin on lipogenesis and found that metformin reduced mRNA expression and prevented TNF-α–lipogenic inducing increases. We also found that metformin affected cytokine secretion from activated macrophages and reduced IL-12p40 and IL-6 secretion without any effect on IL-10 secretion. Translating this to a clinical study using plasma from patients who took part in a placebo clinical control trial on metformin, we found that metformin reduced cytokines such as CCL22 and CXCL12 as well as being associated with a reduction in systemic inflammation compared to sulfonylureas measured by neutrophil-to-lymphocyte ratio.

These anti-inflammatory effects may lead to cardiovascular benefit. In an animal study, metformin caused inhibition of STAT3, reducing inflammation and monocyte to macrophage differentiation. This reduction attenuated atheromatous plaque formation by a reduction in monocyte infiltration [28]. Metformin was also shown to markedly suppress Angiotensin II (Ang II)-induced atherogenesis, an Ang II-mediated increase in LDL and triglyceride levels, which have pro-atherosclerotic effects, but increased HDL and IL-10, which is anti-inflammatory cytokine and inversely related to atherosclerosis [28].

Metformin, furthermore, may prevent oxidative stress-induced atherosclerosis by regulating the sterol regulatory element-binding protein 2-Low Density Lipoprotein receptor axis (SERBP2-LDLR axis). A study which investigated the effects of metformin on lipid hemostasis found that metformin-mediated activation of AMPK was able to reduce cholesterol uptake via low-density lipoprotein receptor (LDLR) by inhibiting sterol regulatory element-binding protein 2-M (SEREBP2-M), which is a mature form of SEREBP2 and is associated with the inhibition of AMPK activation during oxidative stress [29]. Furthermore, evidence showed that anti-atherosclerotic effects of metformin are likely mediated in part by disrupted macrophage infiltration and proinflammatory cytokine production [30]. Investigating the possible effects on the progression of atherosclerosis, metformin was shown to significantly inhibit mRNA expression levels of monocyte chemoattract protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which are involved in plaque formation and progression in atherosclerosis in arterial blood vessels. These data suggest that if metformin does have cardiovascular benefit, the mechanism may be at least in part due to its anti-inflammatory effects.

4. Clinical studies of metformin in cardiovascular disease

In this section, we will review the literature regarding clinical studies of metformin in CVD.

4.1. Metformin in atherosclerotic cardiovascular disease

The UKPDS trial is the key source of evidence demonstrating the cardiovascular benefits of metformin in individuals with type 2 diabetes [31]. This was a randomized trial of intensive blood glucose control (i.e. drugs) vs. standard treatment (i.e. diet). Metformin was one of the drug therapies evaluated (in addition to sulfonylureas and insulin) and only prescribed to overweight individuals. Metformin caused a significant reduction in all-cause death, diabetes-related death and myocardial infarction. While this trial was small by modern standards, it provides the main support for metformin's current position in diabetes guidelines.

Metformin has multiple pharmacological mechanisms that have a beneficial effect on atherosclerosis [32]. Metformin regulates blood glucose and contributes to better cardiovascular outcomes in type 2 diabetes, especially when applied early and

intensively [33,34]. Via inhibition of mitochondrial complex I [35] metformin has been shown to reduce infarction size and reperfusion injury. Metformin also reduces the classical risk factors of atherosclerotic cardiovascular diseases through modest improvements in total and LDL-cholesterol and triglycerides [36], weight loss, and opposing insulin-induced weight gain [37]. Metformin is associated with improvement in endothelial dysfunction, an early event in atherogenesis and leading cause of accelerated atherosclerosis that is also implicated in cognitive impairment [38,39]. In a non-randomized clinical study including prediabetic patients with nonobstructive coronary artery diseases, metformin use was found to be associated with a lower likelihood of coronary artery endothelial dysfunction and reduced risk of adverse cardiovascular events [40]. Another recent study reported that metformin use was associated with a lower prevalence of features of plaque vulnerability using optical coherence tomography imaging in individuals with type 2 diabetes and coronary artery disease who had undergone percutaneous coronary intervention [41]. Finally, the anti-inflammatory effects described earlier may also play an important role in metformin's anti-atherosclerotic effects.

Despite these numerous potential mechanisms of benefit, there is still a lack of clinical trial evidence confirming that these pathophysiological mechanisms actually translate into improved atherosclerotic CVD benefits. In the REMOVAL trial of 428 individuals with type 1 diabetes, there was no effect of metformin on the primary endpoint of mean far wall carotid intimal media thickness (although there was a significant reduction in maximal carotid intimal media thickness) [42]. These results were similar after 18 months of treatment in a randomized trial in non-diabetics [43]. In the GIPS-III trial, 380 patients without diabetes post-ST-elevation myocardial infarction were randomized to metformin or placebo for 4 months [44]. Metformin did not cause a significant improvement in the primary outcome of left ventricular ejection fraction compared to placebo, although ejection fraction was preserved in the study population. There was also no significant difference in NT-proBNP between the two groups. Interestingly, metformin does not appear to reduce levels of subclinical cardiac damage measured by NT-proBNP or troponin [45,46]. The dose of metformin used was modest however (1 g/day). The duration of treatment with metformin may be important, as the benefit seen in UKPDS took 6 years to appear, and several meta-analyses have reported that any cardiovascular benefit with metformin appears to require a long duration of treatment [47]. A recent long-term follow-up of the Diabetes Prevention Program found, however, that after a median of 21 years metformin use was not associated with a reduction in major adverse cardiovascular events in over 3,000 individuals with pre-diabetes, despite a reduction in incidence of new-onset diabetes, although the study had several limitations that may have masked any significant effect of metformin [48].

Another question is whether any benefits of metformin in individuals with type 2 diabetes are present in the modern era with novel glycemic therapies. A post-hoc analysis of the SAVOR-TIMI 53 trial (saxagliptin vs. placebo) did suggest that metformin exposure was associated with lower rates of all-cause mortality but not of the composite cardiovascular outcome (CV death, myocardial infarction, and stroke) [49]. Whether these results would be replicated in the SGLT2i or GLP1-RA trials, where these drug classes improved CV outcomes, is unknown.

4.2. Metformin in left ventricular hypertrophy (LVH) and heart failure

Left ventricular hypertrophy is a key risk factor for development of heart failure and is associated with an increased risk of adverse cardiovascular outcome [50]. Regression of LVH using antihypertensive therapy is associated with a reduction in adverse cardiovascular events [51,52]. Metformin may reduce cardiac remodeling and hypertrophy via different mechanisms. Metformin reduces myocardial fibrosis and collagen synthesis, which is an important pathophysiological process that increases myocardial stiffness, reducing pumping capacity, and contributes to heart failure [19]. Metformin can inhibit the TGF-β1–Smad3 signaling pathway [53], which plays a critical role in the fibrotic remodeling of the infarcted ventricle [54]. Metformin's effects on KLF-15 may also play an important role in its effects on LVH [55].

In a randomized controlled trial of metformin vs. placebo in individuals with LVH, coronary artery and insulin resistance or pre-diabetes (but excluding diabetics), we found that metformin 2 g daily for 12 months significantly reduced LV mass compared to placebo [56]. Interestingly, the regression in LVH was independent of any changes in insulin resistance. Metformin did, however, cause other potentially beneficial changes, including reductions in body weight, blood pressure and oxidative stress. These data were supported by a meta-analysis of nine randomized trials in patients without diabetes, finding that metformin use caused a significant reduction in left ventricular mass after 12 months of treatment (approximately 10 g/m^2) [57].

Metformin may also have beneficial effects in established heart failure. As metformin is first-line for glycemic control in individuals with type 2 diabetes, there is little trial data for the use of metformin in diabetics with HF. Observational data does, however, suggest that there may be some cardiovascular benefit from metformin in diabetics with HFrEF and HFpEF [58–60]. A large randomized trial of metformin vs. placebo in individuals with heart failure and diabetes or pre-diabetes is underway [61]. In the meta-analysis by Kamel et al., metformin use was associated with ~ 3% improvement in left ventricular ejection fraction in patients with heart failure [57]. Data from recent SGLT2i trials have shown that the cardiovascular benefits of SGLT2i are maintained regardless of background glucose lowering therapy [62]. In a recent small trial of 36 patients with HF with reduced ejection fraction and insulin resistance found that metformin improved myocardial efficiency compared to placebo, mediated by a reduction in myocardial oxygen consumption without improvements in insulin sensitivity [63,64]. In an earlier study in 62 HF patients with insulin resistance 4 months of treatment with metformin resulted in an improvement of VE/VCO_2 slope (a prognostic measure of exercise capacity) on cardiopulmonary exercise testing compared to placebo [65]. With the use of SGLT2i in heart failure now established regardless of diabetes status, there may be an

opportunity to consider the repurposing of metformin for use in non-diabetic heart failure.

4.3. Metformin in other cardiovascular diseases

Stroke and peripheral vascular disease are also common causes of cardiovascular morbidity in individuals with diabetes. Some observational data suggests that metformin use at the time of an ischemic stroke may be associated with improved functional recovery in people with type 2 diabetes [66,67]. These results are in line with data from UKPDS [31], however it is unclear if they would be replicable in the era of GLP1-RAs, which cause significant reductions in incident stroke [68].

Metformin use may also be associated with improved peripheral vascular flow and reduced vessel calcification [69,70]. Although metformin use may be associated with a reduced incidence of major adverse cardiovascular events in individuals undergoing limb revascularisation, it may not improve limb patency or limb salvage [71]. In these areas, there is limited data in non-diabetics, and very little randomized trial data to confirm any benefit.

Atrial fibrillation (AF) is the most common abnormal heart rhythm in clinical practice and is an independent risk factor for stroke [72]. In preclinical studies, AF has been shown to be associated with AMPK activation. In paroxysmal AF, AMPK expression was upregulated while in persistent AF the phosphorylation of AMPK was reduced [73]. There is some observational evidence suggesting that metformin use might be associated with a reduction in incident atrial fibrillation, as well as ventricular arrhythmias [74–77]. Clinical trials are ongoing to prospectively assess whether metformin may be useful in the prevention of AF (NCT03603912).

Metformin may also have a beneficial effect on cholesterol profile, with some studies finding an association between metformin use and lower low-density lipoprotein (LDL) cholesterol and increased high-density lipoprotein cholesterol, although these changes are unlikely to be wholly responsible for any cardiovascular benefit caused by metformin [78,79]. Indeed, other randomized trial data have not found any improvements in cholesterol profile (in particular lower LDL-cholesterol) with metformin [43,80,81].

Metformin may have some benefit in cardiac microvascular function. In a randomized trial of 33 non-diabetic women with normal diagnostic coronary angiography, but electrically positive exercise tolerance tests, metformin caused improvements in endothelial function and ST change during exercise [82].

Observational data suggests that metformin may also be beneficial in individuals with abdominal aortic aneurysms, with reduced rate of expansion and lower incidence of adverse events [83]. This hypothesis is now being tested in a multicentre randomized placebo-controlled trial [84].

5. Future directions and conclusions

Metformin has many potentially plausible methods of action that could provide cardiovascular benefit and a plethora of observational data suggesting its association with improved cardiovascular outcomes. Nevertheless, there is a relative lack of randomized clinical trial data, particularly in the contemporary era, which has led some to question its place as a first-line treatment for type 2 diabetes. Given this position and the high use of metformin in type 2 diabetes, it is unlikely that there will be many large cardiovascular outcome trials of metformin in type 2 diabetes, though the ongoing SMARTEST trial of metformin vs. dapagliflozin will be extremely informative (NCT03982381) [85]. We must also remember that the majority of individuals in the SGLT2i and GLP1-RA trials were on background metformin therapy, so there is no clear evidence to support downgrading of metformin's position in current guidelines.

The pleotropic effects of metformin beyond glucose-lowering have, however, led to interest in the potential for metformin to be used in type 1 diabetes or in individuals without diabetes [7]. Several trials are underway that might further elucidate the benefits of metformin (Table 2) [61,84,85]. Metformin may still have an important role to play in cardiovascular disease, and further well-designed trials are needed to evaluate its benefits in individuals with and without diabetes.

6. Expert opinion

Metformin remains the first-line drug for glycemic control in type 2 diabetes with a well-established efficacy and safety profile and is inexpensive. Some clinical studies have suggested that metformin may have some cardiovascular benefit, however they are limited by small sample size and were predominantly conducted prior to the use of SGLT2 inhibitors and GLP-1 receptor agonists, both of which have demonstrated cardiovascular benefit.

Larger, well-designed contemporary studies evaluating the cardiovascular effects of metformin in diabetic and non-diabetic populations are required in order to provide evidence for metformin's current position in guidelines. The large cardiovascular benefit seen in the SGLT2 inhibitor and GLP-1RA trials has called into question whether metformin should remain first-line for glycemic control in type 2 diabetes. The anti-hyperglycemic effects of metformin are not as potent as other options, though given the prevalence of obesity in type 2 diabetes, other aspects of its profile such as weight loss and avoidance of hypoglycemia still make it an attractive option.

The UKPDS trial is the main randomized trial providing underpinning evidence for the use of metformin in type 2 diabetes. The trial, conducted over 20 years ago, randomized type 2 diabetics to diet or intensive glucose control, predominantly with insulin or sulfonylureas. In the intensive control arm, overweight patients could also be given metformin, however only 342 individuals were randomized to metformin. Metformin caused a significant reduction in mortality, unlike insulin or sulfonylureas, and since then has been first-line therapy in type 2 diabetes. The UKPDS trial does, however, seem small in comparison to contemporary cardiovascular outcome trials, such as EMPA-REG, DECLARE-TIMI 58, LEADER and SUSTAIN-6. Nevertheless, the majority of patients in these trials were taking metformin and so the majority of guidelines have retained metformin as initial therapy for type 2 diabetes,

Table 2. Ongoing phase 3 randomised trials of metformin.

Trial Name	Reference (if available)	Intervention	Number of Participants	Patient Population	Primary Outcome	Estimated Study Completion
DANHEART (NCT03514108)	[61]	Metformin 2 g daily vs. hydralazine/nitrate vs. placebo (2×2 factorial)	1500	HFrEF (LVEF<40%) and prediabtes or diabetes	Death, HF hospitalization, acute myocardial infarction or stroke	2026
VA-IMPACT (NCT02916198)		Metformin 2 g daily vs. placebo	7410	Pre-diabetes and established atherosclerotic cardiovascular disease	Death, non-fatal MI, stroke, hospitalized unstable angina or symptom driven coronary revascularisation	2028
MIMET (NCT05182970)		Metformin 2 g daily vs. placebo	5160	Pre-diabetes, acute myocardial infarction	All-cause death, MI, heart failure or stroke	2026
MAT	[84]	Metformin 1500 mg daily vs. placebo	1954	Infrarenal abdominal aortic aneurysm (≥35 mm)	AAA repair or mortality due to AAA rupture.	2025
SMARTEST (NCT03982381)	[85]	Metformin up to 3 g daily vs. dapagliflozin	4300	Type 2 diabetes (treatment-naïve or on monotherapy)	Death, myocardial infarction, stroke, heart failure, diabetic nephropathy, retinopathy or foot ulcer	2025

although the most recent consensus document from the ADA and EASD has, for the first time, separated cardiovascular risk management and glycemic control in the overall management of type 2 diabetes.

There is also some evidence that metformin may have beneficial cardiovascular effects in individuals without diabetes, for example, in reducing adverse cardiac remodeling. Given its other effects (such as its anti-inflammatory action), metformin could be a potential treatment option for conditions characterized by systemic inflammation such as heart failure with preserved ejection fraction.

The mechanisms by which metformin might lead to cardiovascular benefit remain unclear. While there may be some direct cardiac effects, metformin use may also provide indirect benefits such as reductions in body weight, blood pressure and systemic inflammation that could also improve cardiovascular outcomes.

Several large phase 3 trials involving metformin in individuals with and without diabetes are underway. The results of these trials are highly anticipated and should provide a large amount of clarity regarding the role of metformin in the contemporary era. We now have consistent evidence from several large, randomized trials showing that SGLT2i and GLP1-RA improve cardiovascular outcomes in individuals with type 2 diabetes. It is possible that the results of these trials will either lead to the downgrading of metformin to second-line treatment for type 2 diabetes or alternatively cement its position as first-line and even see it recommended for individuals without diabetes in specific conditions.

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Declaration of interest

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