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Review

Metformin and the heart: Update on mechanisms of cardiovascular protection with special reference to comorbid type 2 diabetes and heart failure

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ABSTRACT

Metformin has been in clinical use for the management of type 2 diabetes for more than 60 years and is supported by a vast database of clinical experience: this includes evidence for cardioprotection from randomised trials and real-world studies. Recently, the position of metformin as first choice glucose-lowering agent has been supplanted to some extent by the emergence of newer classes of antidiabetic therapy, namely the sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. These agents have benefitted through support from large cardiovascular outcomes trials with more modern trial designs than earlier studies conducted to assess metformin. Nevertheless, clinical research on metformin continues to further assess its many potentially advantageous effects. Here, we review the evidence for improved cardiovascular outcomes with metformin in the context of the current era of diabetes outcomes trials. Focus is directed towards the potentially cardioprotective actions of metformin in patients with type 2 diabetes and heart failure (HF), now recognised as the most common complication of diabetes.

1. Introduction: a brief history of the therapeutic use of metformin

Metformin was introduced into the clinical management of diabetes in 1957 [1]. The place of metformin in medicine faced a number of serious challenges in its early years of use, not least the unacceptable risk of lactic acidosis with other biguanides, phenformin and buformin, and a suggestion of increased mortality with phenformin in the University Group Diabetes Program trial in 1970 [1,2]. Metformin is now prescribed as the primary glucose-lowering agent for type 2 diabetes in most countries, taking account of important cautions and contraindications (Box 1). These are designed to avoid its use in settings that could increase the risk of lactic acidosis (principally states of acute or chronic renal dysfunction that could cause accumulation of metformin, and conditions associated with tissue hypoxia such as decompensated heart failure [HF]), noting that metformin-associated lactic acidosis is a rare event.

Metformin is as effective in lowering blood glucose as other antidiabetes agents, can be combined with any other treatment for diabetes (including insulin), does not cause hypoglycaemia or weight gain, and is inexpensive [3]. The demonstration of improved cardiovascular outcomes with metformin in the randomised UK Prospective Diabetes Study (UKPDS) in 1998 cemented its place at the head of almost all algorithms for the pharmacological management of type 2 diabetes and as the most used antidiabetes drug worldwide for the following two decades [4].

The current status of metformin within the management of type 2 diabetes is informed by its history, especially regarding the evidence base for its safety profile and its effects on cardiovascular outcomes. The latest challenge to the place of metformin has come from the recent demonstration of substantial cardiovascular outcomes benefits with glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors. We review the current state-of-the-art on the therapeutic profile of metformin, and where this veritable survivor of a treatment stands within this new era of type 2 diabetes management. We focus on the use of metformin in people with diabetes and HF, the latest frontier in the management of type 2 diabetes and its complications [5].

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2. Search strategy

This is a narrative review based on a structured literature search (PubMed) for studies that evaluated clinical outcomes in people with type 2 diabetes treated with metformin: *metformin [ti] AND (macrovascular OR "myocardial infarction" OR stroke OR cerebrovascular OR "heart failure" OR "cardiovascular event" OR MACE OR microvascular)*. A subsidiary search explored possible anti-atherogenic mechanisms of action of metformin: *metformin [ti] AND cardiovascular AND (mechanism OR atherogenesis OR atherosclerosis)*. Literature cited in these articles, and authors' knowledge and literature collections provided further references for review here. Preference was given to randomised trials for consideration of clinical outcomes, although observational studies are also reviewed briefly here.

3. The evidence for improved cardiovascular outcomes with metformin in people with diabetes

3.1. Atherosclerotic cardiovascular disease

3.1.1. Randomised trials in populations with type 2 diabetes

Three randomised trials evaluated the effects of metformin on cardiovascular outcomes in populations with type 2 diabetes. The principal source of evidence is the UKPDS, a randomised comparison of intensive blood glucose control (oral pharmacotherapy or insulin) with the "conventional" treatment of the time (essentially diet advice) in patients with newly-diagnosed type 2 diabetes. Metformin was a late addition to the treatments evaluated, and was given to overweight subjects only (>120% ideal weight), as expert opinion at the time considered that metformin was likely to be more effective in this insulin resistant population. A total of 1704 such patients were randomised to receive metformin, sulfonylurea, insulin or "conventional" treatment (753 patients were included in the comparison of metformin with the control intervention) in 15/23 UKPDS centres [4,6]. It is important to note that metformin was included within the primary randomisation, and was not evaluated in a sub-study, as is often claimed.

Randomised treatment continued for about ten years. Allocation to metformin was associated with clinically and statistically significant reductions in the risk of pre-specified clinical outcomes, including mortality, myocardial infarction (MI), any endpoint related to diabetes, diabetes-related mortality, and all-cause mortality (Table 1a) [4,7]. Patients returned to the care of their own physicians when randomised treatment concluded, and most who had received metformin elected to continue. An epidemiological follow-up ten years after the end of randomised treatment (20 years post-randomisation) showed that the cardiovascular and mortality benefits of prior randomisation to metformin had been maintained during this time (Table 1a) [4–9].

Such a "legacy benefit" has been seen after intensive multifactorial risk factor intervention in the Steno-2 study in patients with type 2 diabetes and macroalbuminuria [10], and following treatment of non-diabetic hyperglycaemia ("prediabetes") with intensive lifestyle intervention in the Da Qing diabetes prevention study [11]. These legacy benefits appear to arise from a long-term amelioration of macrovascular disease progression by early, intensive improvement in glycaemia. There were no such long-term macrovascular legacy benefits in the VADT [12], ACCORD [13] or ADVANCE [14] trials that compared more versus less intensive glucose control in populations who already had advanced type 2 diabetes (other than reduced retinopathy progression post-ACCORD). Thus, early intervention to control glycaemia in diabetes is necessary to reduce micro- and macro-vascular complications in type 2 diabetes [15].

Two smaller randomised outcomes trials evaluated metformin. One

Box 1
Safety, tolerability and contraindications relating to the therapeutic use of metformin in the management of type 2 diabetes.

Therapeutic indication: Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone do not result in adequate glycaemic control (monotherapy or with other glucose-lowering agents, including insulin).

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin as first-line therapy after diet failure

Contraindications: Any acute metabolic acidosis (e.g. lactic acidosis, DKA)

Diabetic pre-coma

Severe renal failure (e.g. GFR <30 mL/min), noting that dose reduction should be considered in relation to declining renal function

Acute conditions with the potential to alter renal function

Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) e.g. decompensated HF, respiratory failure, recent MI, shock

Hepatic insufficiency, acute alcohol intoxication, alcoholism Hypersensitivity to metformin or excipients

Most common side-effects: Gastrointestinal adverse events (nausea, vomiting, diarrhoea, abdominal pain, loss of appetite) occur usually at the beginning of therapy, and resolve spontaneously in most cases

Compiled from information contained in the EU Summary of Product Characteristics. Wording has been updated and abbreviated for conciseness, always read the full document relevant to your location before prescribing. DKA: diabetic ketoacidosis; GFR: glomerular filtration rate; MI: myocardial infarction.

Table 1
Randomised, controlled cardiovascular outcomes trials that evaluated metformin in populations with type 2 diabetes.

a) UK Prospective Diabetes Study (UKPDS): 753 overweight (>120% ideal weight) people with newly diagnosed type 2 diabetes randomised to metformin (n = 342) or to diet intervention (n = 411).

Outcome	Randomised phase (median 10.7 y) [4]		10 y post-trial follow-up [7]	
	RR (95% CI)[a]	p[a]	RR (95% CI)[a]	p[a]
Any diabetes-related endpoint	0.68 (0.53, 0.87)	0.0023	0.79 (0.66 to 0.95)	0.01
Myocardial infarction	0.61 (0.41, 0.89)	0.01	0.67 (0.51 to 0.89)	0.005
Diabetes-related death	0.58 (0.37, 0.91)	0.017	0.70 (0.53 to 0.92)	0.01
All-cause death	0.64 (0.45, 0.91)	0.011	0.73 (0.59 to 0.89)	0.002
Stroke, peripheral vascular disease, microvascular disease	No significant reduction associated with metformin vs. control (diet) for any of these endpoints			

b) Hong et al, metformin versus glipizide [8]: 304 type 2 diabetes patients with coronary artery disease randomised to metformin 1500 mg/day or glipizide 30 mg/day; median follow-up 5 years.

Outcome	RR (95% CI)[a]	p[a]
Primary cardiovascular composite[b]	0.54 (0.30 to 0.90)	0.026

c) Kooy et al, metformin versus placebo in insulin-treated people with diabetes [9]: 390 insulin-treated type 2 diabetes patients with diabetes duration >13 years were randomised to additional metformin (up to 2550 mg/day) or placebo for median 4.3 y

Outcome	RR (95% CI)[a]	p[a]
Primary composite[c]	0.92 (0.72 to 1.18)	$p = 0.33$
Cardiovascular composite[d]	0.60 (0.40 to 0.92)	0.04
Microvascular composite[d]	1.04 (0.75 to 1.44)	$p = 0.43$

[a] HRs and p values are for metformin vs. non-metformin control, as specified (values <1 favour metformin).
[b] Non-fatal myocardial infarction or stroke, revascularisation, cardiovascular death or all-cause death).
[c] Myocardial infarction; heart failure; prespecified ECG changes; acute coronary syndrome; diabetic foot; stroke; transient ischemic attack; peripheral arterial disease; peripheral arterial reconstruction; percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass graft (CABG); non-traumatic amputation; sudden death; progression of retinopathy, nephropathy, or neuropathy; death by any other cause; myocardial infarction, stroke, PTCA, CABG, cardiovascular death, all-cause death. HR: hazard ratio; RR: relative risk.
[d] Microvascular and microvascular components of the primary endpoint.
Adapted from ref. [1].

study, which involved 304 type 2 diabetes patients, demonstrated a significant reduction in a cardiovascular composite for metformin compared with a sulfonylurea after 5 years of randomised treatment (Table 1b) [8]. The other trial randomised 390 participants with insulin-treated type 2 diabetes to metformin versus placebo for an average of 4.3 years (Table 1c) [9]. The primary endpoint (a mixture of macrovascular and microvascular endpoints) was not affected significantly, although there was a significant reduction in the secondary macrovascular composite.

3.1.2. Randomised trials in populations with type 1 diabetes

The REMOVAL trial randomised 428 middle-aged people with type 1 diabetes, suboptimally controlled glycaemia and cardiovascular risk factors to 3 years of metformin or placebo, each added to standard of care [16]. Randomisation to metformin did not affect the primary endpoint significantly (mean change versus placebo in far wall carotid intima-media thickness [cIMT] was −0.005 mm/year [−0.012, 0.002], $p = 0.1664$). Metformin was associated with a significant effect on a prespecified tertiary endpoint (the mean reduction in maximal cIMT versus placebo was −0.013 mm/year [−0.024 to −0.003], $p = 0.0093$). Interestingly, there was a significant reduction of cIMT progression (the original primary endpoint) with metformin in never-smokers, but not in ever- or current smokers, suggesting that a cardiovascular benefit of metformin in this population was negated by tobacco use [17].

3.1.3. Observational studies and meta-analyses

Many observational studies and meta-analyses of the effects of metformin have been published, and a review of the largest has been published elsewhere [18]. These included demonstrations of reduced risk of mortality and/or cardiovascular events in comparison with no metformin or (most commonly) sulfonylurea treatment, and in populations with type 2 diabetes and HF (see also below). Meta-analyses of randomised, controlled trials have [19–21] or have not [22–24] demonstrated a reduced frequency of cardiovascular events or death in the metformin versus non-metformin group (Table 2). The meta-analytic approach to analysing randomised trials is problematic in the case of metformin, however, because duration of treatment appears to be an important factor: the effect of metformin on cardiovascular outcomes took about 6 years to become apparent in the UKPDS [4], and few other trials of comparable duration to this are available. The extent to which concurrent or prior sulfonylurea treatment may confound or oppose the effects of metformin on cardiovascular clinical outcomes is also difficult to establish [25,26].

A recent (2020) comprehensive meta-analysis that included 701,843 people with type 2 diabetes who had received metformin and 1,160,254 controls noted reduced risks of mortality (OR 0.44 [0.34, 0.57]) or adverse cardiovascular outcomes (OR 0.73 [0.59, 0.90]) for metformin versus no metformin [27]. A meta-analysis from 2019 that included data from >1 million subjects with type 2 diabetes and coronary artery disease reported similar results [28]. A database study of 4030 patients with type 2 diabetes with incident MI showed that receipt of metformin at hospital admission was associated with an increased risk of major adverse cardiovascular events (MACE) in survivors after discharge [29]. Accordingly, metformin may be harmful in the setting of acute myocardial ischaemia, consistent with its contraindications (Box 1). However, the risk of subsequent MACE was reduced in patients who received metformin after the period of acute ischaemia.

3.2. Clinical outcomes following metformin treatment in people with type 2 diabetes and HF

HF is a common complication of type 2 diabetes, with a prevalence about 4-fold higher versus the general population [30]. A diagnosis of diabetes at age <40 years confers a 4.8-fold risk of developing HF later on [31]. Conversely, HF markedly increases the risk of developing type 2 diabetes [32]. The presence of diabetes (or prediabetes) and HF together substantially increases the risk of adverse cardiovascular outcomes compared with either alone [30,33].

Metformin can be prescribed for patients with stable HF, but is contraindicated for patients with decompensated HF (Box 1). Randomised evaluations of metformin are not available in populations recruited for having HF at baseline. A meta-analysis of 9 observational studies included 34,504 patients with type 2 diabetes and HF (6624 were receiving metformin) [34]. Compared with non-metformin controls (mostly sulfonylurea), metformin was associated with reduced risk of mortality (relative risk 0.80 [0.74, 0.87], $p < 0.001$). Findings were similar in a meta-analysis of 11 observational studies ($N = 35,950$ with diabetes and HF), where treatment with versus without metformin was associated with a 22% reduction in mortality (HR 0.78 [0.71, 0.87], $p = 0.003$]) [35]. Risk reductions became non-significant in two studies in patients with severely reduced left ventricular ejection fraction (LVEF <30% or <40%) or in two studies in patients with comorbid chronic kidney disease (CKD), but there was no adverse safety signal in these sub-populations. Cohort studies in populations with HF and type 2

Table 2
Systematic reviews/meta-analyses of the effects of metformin on clinical cardiovascular outcomes in populations with type 2 diabetes.

Ref	Year published	Objective	No. of studies	Overview of main outcomes
[19]	2021	RCTs ≥1 y duration, metformin monotherapy vs. no intervention or active comparators	13	No significant effect on all-cause mortality vs. comparators: OR 0.80 (0.60, 1.07) Significant reduction with metformin in all-cause mortality after excluding RCTs comparing metformin with SU, SGLT2i or GLP-1RA: OR 0.71 (0.51, 0.99) Significant reduction with metformin for MACE vs. comparators: OR 0.52 (0.37, 0.73)
[20]	2005	RCTs comparing metformin with any oral intervention	29	Significant benefit for metformin in all-cause mortality for metformin vs. SU or insulin: RR 0.73 (0.55 to 0.97) based on outcomes from the UKPDS No significant differences between treatments for MACE pooled from four studies involving treatment with metformin, SU or TZDs.
[21]	2011	RCTs ≥52 w duration that evaluated morbidity or mortality on metformin vs. comparators	35	No significant difference for CV events (all trials): OR 0.94 (0.82, 1.07) Significant benefit for metformin vs. placebo on CV events: OR 0.79 (0.64, 0.98] No benefit for metformin vs. active comparators on CV events: OR 1.03 (0.72, 1.77)
[22]	2020	RCTs ≥1 y duration, metformin monotherapy vs. no intervention, behavioural or pharmacologic interventions	18	"No clear evidence for a difference in outcomes between metformin and comparators"
[23]	2016	RCTs ≥24 y duration evaluating glucose lowering therapies	301	"No significant differences in associations between any drug class as monotherapy, dual therapy, or triple therapy with odds of cardiovascular or all-cause mortality"
[24]	2017	All RCTs of metformin vs. no intervention, placebo or lifestyle intervention with data on CV events and/or mortality	13	No significant benefit for metformin for all cause mortality (OR 0.96 [0.84, 1.09]), CV death (OR 0.97 [0.80, 1.16]); MI (OR 0.89 [0.75, 1.06]), stroke (OR 1.04 [0.73, 1.48]); peripheral vascular disease (OR 0.81 [0.50, 1.31])

CV: cardiovascular; HR: hazard ratio; GLP-1RA: glucagon-like polypeptide-1-1 receptor agonists; MACE: major adverse cardiovascular events; MI: myocardial infarction; OR: odds ratio; RCT: randomised, controlled trial; SGLT2i: sodium-glucose transporter-2 inhibitors; SU: sulfonylurea; TZD: thiazolidinedione; UKPDS: UK Prospective Diabetes Study.

diabetes published since the appearance of this meta-analysis (2017) support its findings, with reduced mortality versus non-metformin treatment [36,37], reduced hospitalisation versus non-metformin treatment [38], or reduced hospitalisation versus sulfonylurea treatment in patients with comorbid CKD [39]. Another cohort study suggested that metformin versus sulfonylurea as initial pharmacologic antihyperglycaemic treatment was associated with a lower risk of hospitalisation for HF in a population with a low prevalence of HF at baseline [40].

Strong pathogenic links have emerged between diabetes and HF with preserved ejection fraction (HFpEF) [41]. A meta-analysis of four studies in patients with T2D and HFpEF demonstrated a significant reduction in mortality with metformin, especially for those with LVEF > 50% [42]. A recent retrospective study of patients with type 2 diabetes and HFpEF demonstrated reduced mortality associated with metformin only in patients with sub-optimal glycaemic control (HbA1c ≥ 7%) [43]. A further study reported a substantial reduction in the risk of new-onset HFpEF associated with use versus non-use of metformin (HR 0.351 [0.145, 0.846], $p = 0.020$) [44].

4. Potentially cardioprotective mechanisms of metformin

Multiple pharmacologic mechanisms have been proposed to account for the observations of cardiovascular protection with metformin described above (Table 3, Fig. 1) and are considered here briefly. The pathogenesis of atherosclerotic cardiovascular disease and HF are considered separately here.

4.1. Mechanisms of potential relevance to atherosclerotic cardiovascular disease

Table 3 summarises a number of potentially atheroprotective mechanisms that have been reported for metformin. Firstly, improved glycaemia *per se* likely makes a modest contribution to improved cardiovascular outcomes in type 2 diabetes, especially when applied early ("legacy benefits"), which would apply to any glucose-lowering agent [45,46]. However, inhibition of mitochondrial Complex I by metformin (the principal mechanism of its antihyperglycaemic effect [47,48]) has been associated with reduced reperfusion injury in a rodent model of myocardial ischaemia [49].

Effects on classical cardiovascular risk factors (lipids, blood pressure, weight) are mostly consistent with reduced cardiovascular risk, but are modest in magnitude [50–56], and are unlikely to contribute substantially to improved cardiovascular outcomes with metformin. Endothelial dysfunction is an early event in atherogenesis, and its reversal may be considered to be cardioprotective [57]. Most studies (including randomised clinical trials) that have measured endothelial dysfunction in type 2 diabetes patients have noted an improvement in this parameter with metformin [58–75].

The final event in the onset of a myocardial infarction is the development of an intravascular thrombus. A number of studies have described potentially beneficial effects of metformin on haemostasis, including reduced platelet aggregation and blood viscosity [76], reduced levels of clotting factors FVII, FXIII and von Willbrand factor [63,77,78], reduced stability of thrombi [78], and improved fibrinolysis in randomised trials [59,62,63,79–85].

Atherosclerosis in type 2 diabetes is an inflammatory process characterised by systemic oxidative stress [86]. Randomised trials have reported reductions in markers of systemic oxidative stress in metformin-treated type 2 diabetes patients [87–93]. Metformin has been shown to

Table 3
Overview of reported anti-atherothrombotic mechanisms of metformin.

Mechanism	Summary of effects and potential relevance
Reduced blood glucose [47,48]	Intensive blood glucose reduces the risk of adverse cardiovascular outcomes by about 15% Intensive, early blood glucose control provides longer-term improvements in clinical outcomes (legacy benefits[a]) In principle, these benefits would apply to any glucose lowering intervention
Classical cardiovascular risk factors [50–56]	Metformin induces modest improvements in total and LDL-cholesterol and triglycerides in most studies Little or no effect on HDL-cholesterol (although a shift to more atheroprotective HDL species has been observed) Effects of metformin on blood pressure have been inconsistent Weigh neutrality or weight loss usually occurs with metformin (and metformin opposes insulin-induced weight gain) Overall, effects on classical cardiovascular risk factors are unlikely to contribute markedly to effects of metformin on the cardiovascular outcomes
Vascular function [58–75]	Metformin improved endothelial function in most (but not all) studies in people with T2D or other insulin resistant states (prediabetes or polycystic ovary syndrome) Metformin reduced the risk of the no-reflow phenomenon following percutaneous revascularisation of people with diabetes (retrospective study) Improved production of endothelial progenitor cells may underlie effects of metformin on endothelial function Endothelial dysfunction is an early event in atherogenesis, and its reversal may be considered to be cardioprotective; however, no randomised trial has yet demonstrated improved cardiovascular outcomes following improvement in endothelial function per se
Haemostasis [59,62,63,76–85]	Reduced platelet aggregation and blood viscosity following intravenous infusion of L-arginine in type 2 diabetes patients Reduced levels of clotting factors FVII, FXIII and von Willbrand factor Reduced structural rigidity of fibrin clots Improvements in fibrinolysis (increased secretion or activity of tPA and/or reduced PAI-1) These effects are consistent with reduced atherothrombotic risk but the extent to which they contribute to improved clinical outcomes with metformin has not been determined conclusively
Oxidative stress and inflammation [87–97]	Metformin reduced markers of oxidative stress in randomised trials in people with type 2 diabetes Suppression of glyco-oxidation (a source of systemic inflammation) via an AMPK-dependent mechanism and direct neutralisation by the metformin molecule of a dicarbonyl intermediate of advanced glycation end-products Reduced glycol-oxidative damage to lipoproteins Oxidative stress and inflammation are believed to play a role in atherogenesis, and their reversal may be considered to be cardioprotective; however, no randomised trial has yet demonstrated improved cardiovascular outcomes following improvement in endothelial function per se
Cellular antiatherogenic effects [98–101]	Reduced uptake of lipids into the arterial wall (animals) Reduced the production of adhesion molecules by endothelial cells (cultured cells) Decreased adhesion of monocytes to the activated endothelium (cultured cells) Reduced the production of foam cells and neointima in preclinical atherosclerosis models
Gut microbiome [104–109]	These experimental findings are consistent with an antiatherogenic effect but have not yet been observed clinically Metformin alters the balance of bacterial species in the gut, with modulation of metabolites potentially associated with insulin resistance or dysglycaemia (randomised controlled trials in populations with type 2 diabetes or prediabetes) Interactions between metformin and the microbiome may influence the gastrointestinal tolerability of metformin Further research will be needed to understand the contribution of alterations of the gut microbiome to the cardiovascular protective actions of metformin

[a] See Section 3.1.1 for further discussion. AMPK: AMP-dependent protein kinase; PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator.

reduce glyco-oxidation caused by advanced glycation end products (AGEs) in the setting of hyperglycaemia, both via an AMPK-dependent mechanism, and via direct chemical neutralisation of an intermediate in the formation of AGEs [92,94–97]. A range of cellular antiatherogenic effects of metformin have been described in experimental studies [98–101].

Finally, the gut microbiome is a powerful, if incompletely understood, modulator of health and disease, including diabetes and prediabetes (reviewed elsewhere [102,103]). Randomised, controlled trials in populations with prediabetes or diabetes have shown that treatment with metformin alters the balance of bacterial species in the gut, with consequences that included modulation of metabolites potentially associated with insulin resistance, dysglycaemia or HF (see below) [104–109]. Interactions between metformin and the microbiome may influence the gastrointestinal tolerability of metformin [107]. Further research will be needed to understand the precise contribution of alterations of the gut microbiome to cardiovascular disease in general, and the cardiovascular protective actions of metformin in particular.

Thus, numerous mechanisms have been proposed to explain the effects on cardiovascular outcomes seen in the UKPDS and elsewhere. Many of these mechanisms have been demonstrated in humans, often in the setting of randomised trials, while others have been described in experimental settings. It is not possible at this time to identify any single mechanism, or combination of mechanisms, to account for cardioprotective effects of metformin. Nevertheless, these observations add mechanistic plausibility to metformin as a potentially cardioprotective agent.

4.2. *Mechanisms of potential relevance to heart failure*

The healthy heart derives 60–90% of its energy from fatty acid oxidation, with the remainder mostly from glycolysis and metabolism of lactate from the circulation [110]. The failing heart has a deficient energy supply, involving reduced activity of the mitochondrial respiratory/electron transport chain, reduced utilisation of fatty acids and glucose, and increased production of mitochondrial uncoupling proteins: these lead to impaired production of ATP and phosphocreatine and reduced oxygen consumption [111–113].

Several aspects of the metabolism of the failing heart could in principle be amenable to intervention with metformin [114,115]. Activation of AMPK by metformin may enhance mitochondrial β-oxidation of fatty acids via enhanced expression of carnitine palmitoyl transferase 1, reduced apoptosis of cardiomyocytes, and reduced formation of myocardial AGEs [114–115]. Experimental evidence from dogs with cardiac pacing-induced HF [116] and mice subjected to coronary artery ligation [117] support a role for metformin-induced activation of AMP kinase in this setting. Other experimental studies found that metformin

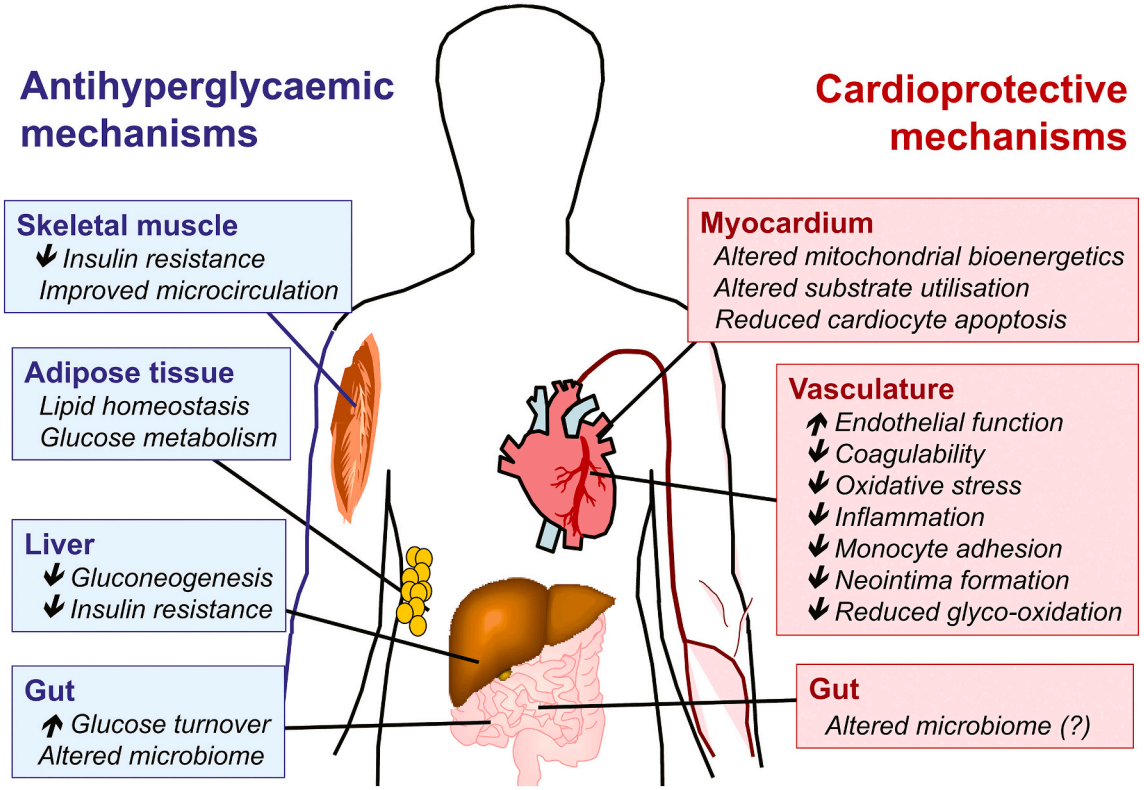

Fig. 1. Overview of mechanisms for the antihyperglycaemic and cardioprotective mechanisms for metformin that have been presented in the literature.

reduced the development of HF in spontaneously hypertensive, insulin-resistant rats [118], prevented progression of cardiac dysfunction in a model of adult congenital heart disease [119], and improved myocardial function in a rat model of post-MI HF [120]. Finally, changes in the gut microbiome that may be specific to the pathogenesis of HF (including HFpEF) have been described during treatment with metformin, especially involving bacteria that produce short chain fatty acids [108,109].

Two small, randomised clinical studies may shed light on the mechanisms of metformin in the failing human heart. In one study, 62 insulin resistant patients with HFrEF received metformin or placebo for 4 months [121]. There was no significant effect on the primary endpoint (maximal VO_2), but metformin increased the slope of the ratio of minute ventilation to CO_2 production (a prespecified secondary endpoint), consistent with improved myocardial mechanical efficiency. The second study randomised 36 non-diabetic patients with HFrEF to metformin or placebo for 3 months [122]. Metformin (versus placebo) significantly increased the work metabolic index (WMI) and reduced myocardial oxygen consumption without reducing stroke work, also signifying improved myocardial mechanical efficiency, without changes in LVEF or exercise capacity. Moreover, changes in WMI were larger in patients with higher versus lower plasma metformin. *Post-hoc* analyses indicated that the magnitude of the clinical response to metformin depended on the genotype of MATE-1 (a multidrug transmembrane carrier which transports metformin into cells). Finally, metformin was associated with reduced body weight, but there were no changes in measures of whole-body insulin sensitivity, or glucose production, disposal or oxidation, in a recent, small ($N = 18$), short (3 months) randomised, placebo-controlled trial in patients with HFrEF without diabetes [123].

These proof-of-concept studies that demonstrated changes in cardiac dynamics following treatment with metformin are encouraging, but further randomised trials are needed. The ongoing DANHEART trial (NCT03514108) is evaluating the effects of metformin or hydralazine isosorbide dinitrate, each versus placebo in a 2×2 factorial design) on clinical outcomes in 1500 patients with type 2 diabetes and HF with HFrEF [124]. Metformin is being administered at a dose of 2000 mg/day (1000 mg/day for eGFR 35–60 mL/min/1.73 m^2) over an expected duration of 4 years. The primary endpoint will be a composite of death or hospitalisation with worsening HF, MI or stroke, and results are expected by about mid-2023.

5. How do we interpret the evidence base for metformin today?

The literature on metformin is vast – a PubMed search for metformin yields more than 25,000 hits at the time of writing – and goes back for decades. Standards of trial design have evolved, especially since the US Food and Drug Administration (FDA) mandated in 2008 that nearly all new therapies for type 2 diabetes required a pre- and or post-marketing CV outcomes trial (CVOT). Newer classes of glucose-lowering medications – the dipeptidyl peptidase-4 (DPP4) inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists – benefitted from a series of recent CVOTs, usually recruiting several thousands of patients, and designed to specifically explore cardiovascular endpoints independently of glucose-lowering effects, while metformin did not. This complicates comparison of clinical data gathered before and after these distinct eras of trial design, whether conducted in a narrative fashion (as here), or via a future systematic review.

The FDA-mandated CVOTs have confirmed their cardiovascular safety (with some lingering debate about the effect of some DPP4 inhibitors on HF), and have demonstrated improved cardiovascular outcomes with SGLT2 inhibitors and GLP-1 receptor agonists [125]. Although a majority of participants (67–82%) in these trials received metformin before and throughout addition of the other agents, an analysis of participants not taking metformin has noted that GLP-1 receptor agonists still reduced the risk of MACE and SGLT2 inhibitors still reduced the risk of HF-related endpoints. However, the authors suggest that metformin may assist the CV effects of other agents [126]. Accordingly, recent guidelines for the management of type 2 diabetes have suggested that the intensification of glucose-lowering therapy as

add-on to metformin should focus on cardio-renal risk, and GLP-1 receptor agonists and SGLT2 inhibitors with demonstrated cardiovascular disease benefits should be considered first-line for patients at high risk or already exhibiting atherosclerotic cardiovascular disease or HF [127,128].

In contrast, UKPDS 34, reported in 1998 with 753 patients randomised to metformin or the control intervention, is seen as small by current CVOT standards. We should note that the UKPDS was also a 10-year randomisation, which is much longer than the CVOTs for the newer agents. Interestingly, in consequence, the number of MIs in the UKPDS 34 (112) was very similar to the number in the SUSTAIN-6 CVOT that evaluated semaglutide (111) [4,129]. Moreover, there was no prespecified distinction between primary and secondary endpoints in UKPDS 34, and no hierarchical statistical evaluation, unlike modern CVOTs. Also, the decision to limit the use of metformin to overweight patients was rational at the time, but is often cited as limiting its generalisability to diabetes patients today, despite much subsequent evidence to show similar effects of metformin irrespective of body mass index.

How then do we interpret the UKPDS today? The cardiovascular benefits of metformin were substantial, and have been supported by other small (but randomised) trials, meta-analyses and many observational studies. Because observational data are subject to a greater risk of bias than prospective randomised trials they are appropriately treated with more caution, but these real world studies have demonstrated apparent outcomes benefits in multiple studies with different designs and across multiple patient phenotypes. Additionally, a range of systemic and cellular mechanisms support the concept of cardiovascular protection with metformin.

The potential to improve myocardial function in chronic HF is perhaps the next chapter in metformin's long story, and the results of the DANHEART study are awaited with great interest. HFpEF, in particular, is regarded increasingly as a hitherto under recognised cardiovascular complication of diabetes, and is associated with a severely adverse prognosis [41]. The EMPEROR Preserved trial [130] recently identified a SGLT2 inhibitor as the first pharmacologic intervention to improve hard clinical outcomes in this population – the suggestion of improved outcomes in metformin-treated patients with HFpEF from a meta-analysis [42] and retrospective studies [43,44], described above, merits further study.

Elsewhere, VA-IMPACT (Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular Outcomes; NCT02915198) is a large (>7000 participants) multicentre, prospective, randomised, double blind, secondary prevention study to investigate whether metformin reduces mortality and cardiovascular morbidity in people with pre-diabetes and established atherosclerotic cardiovascular disease. The primary outcome of this trial is the time to first occurrence of death, non-fatal myocardial infarction or stroke, hospitalisation for unstable angina with evidence of acute myocardial ischemia, or coronary revascularization driven by acute or progressive symptoms. Recruitment to this trial is on temporary hold during the coronavirus pandemic: it was due to complete late 2024 but will now be later. Several other studies are assessing related conditions, including LIMIT (NCT04500756) in abdominal aortic aneurism. Current diabetes management guidelines emphasise the potential of SGLT2 inhibitors to reduce the risk of adverse HF outcomes, and of GLP-1RA to reduce the risk of atherosclerotic CVD, taking account of varying guidance for their introduction as first-line or second-line glucose-lowering agents [127,128]. The ongoing SMARTEST study (NCT03982381) will be the first head-to-head comparison between metformin and an SGLT2 inhibitor in an extended rage of cardiovascular outcomes, and this study is also due for 2024.

These ongoing studies will extend the clinical database on metformin with respect to effects on clinical cardiovascular outcomes, and will clarify the extent to which metformin protects the cardiovascular system in people with type 2 diabetes. It is unlikely that metformin will benefit in future from the kind of modern, event-driven outcomes trials that have been conducted recently by the sponsors of the newer classes of antidiabetes treatments. As we stand today, we have evidence for cardiovascular protection with metformin, including from randomised trials, many observational studies, and substantial experimental data, which we have summarised above. However, the nature of the clinical trial evidence has been overtaken by the new constellation of outcomes trials that were designed to address questions of clinical safety that were formulated long after the randomised evaluations of metformin were conducted. Interpreting the current evidence base for metformin is undoubtedly a challenging task, but no less important for that.

Declaration of competing interest

KB is a full-time employee of Merck Healthcare KGaA, Darmstadt, Germany, the originator of metformin and pharmaceutical sponsor of several formulations of metformin. GS and CJB declared there to be no conflicts of interest relevant to this article.

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