Received: 30 October 2018 | Revised: 1 April 2019 | Accepted: 18 April 2019

DOI: 10.1002/dmrr.3173

REVIEW ARTICLE

WILEY

Mechanisms of action of metformin with special reference to cardiovascular protection

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Funding information
Merck

Summary

Management guidelines continue to identify metformin as initial pharmacologic antidiabetic therapy of choice for people with type 2 diabetes without contraindications, despite recent randomized trials that have demonstrated significant improvements in cardiovascular outcomes with newer classes of antidiabetic therapies. The purpose of this review is to summarize the current state of knowledge of metformin's therapeutic actions on blood glucose and cardiovascular clinical evidence and to consider the mechanisms that underlie them. The effects of metformin on glycaemia occur mainly in the liver, but metformin-stimulated glucose disposal by the gut has emerged as an increasingly import site of action of metformin. Additionally, metformin induces increased secretion of GLP-1 from intestinal L-cells. Clinical cardiovascular protection with metformin is supported by three randomized outcomes trials (in newly diagnosed and late stage insulin-treated type 2 diabetes patients) and a wealth of observational data. Initial evidence suggests that cotreatment with metformin may enhance the impact of newer incretin-based therapies on cardiovascular outcomes, an important observation as metformin can be combined with any other antidiabetic agent. Multiple potential mechanisms support the concept of cardiovascular protection with

metformin beyond those provided by reduced blood glucose, including weight loss, improvements in haemostatic function, reduced inflammation, and oxidative stress, and inhibition of key steps in the process of atherosclerosis. Accordingly, metformin remains well placed to support improvements in cardiovascular outcomes, from diagnosis and throughout the course of type 2 diabetes, even in this new age of improved outcomes in type 2 diabetes.

KEYWORDS

cardiovascular outcomes, hyperglycaemia, metformin, type 2 diabetes

1 | INTRODUCTION

The choice of treatments for type 2 diabetes is wider than ever before, and several drugs have now been shown to significantly reduce the risk of major adverse cardiovascular events (MACEs) and/or the risk of premature mortality in this population. Nevertheless, at the time of writing, influential diabetes management guidelines continue to identify metformin as initial antidiabetic pharmacotherapy of choice (in the absence of contraindications) more than 60 years after its first therapeutic administration to a person with diabetes.[1] It is important to place our knowledge of the actions of metformin within the current context of increased emphasis on the need to protect the cardiovascular system in type 2 diabetes. In this review, we provide a concise snapshot of current knowledge concerning the effects of metformin on glycaemia and clinical cardiovascular outcomes, together with a review of the diverse range of proposed mechanisms of action that underlie such effects.

2 | SEARCH STRATEGY

For this narrative review, we searched PubMed for articles on "metformin" and "cardiovascular," limited to "randomized controlled trial," in order to locate articles describing the effects of metformin on cardiovascular outcomes. Additional specific searches (eg, "microbiome") were conducted to explore new data on the antihyperglycaemic mechanisms and potential cardiovascular mechanisms of metformin to capture latest findings. Review articles and authors' experience provided additional material.

3 | ANTIHYPERGLYCAEMIC MECHANISMS

3.1 | Systemic actions

The main systemic antihyperglycaemic action of metformin is a reduction of hepatic glucose production, due to a reduction in gluconeogenesis, although some (but not all) studies have identified enhanced insulin-mediated glucose uptake in muscle during treatment with metformin (see also Table 1).[2-10] The net result is a clinically significant

TABLE 1 Summary of therapeutic mechanisms of metformin discussed in this review

Glycaemia
Liver—reduction of hepatic glucose production
Activation of AMP kinase secondary to shift in cellular energy balance due to mild inhibition of mitochondrial respiratory complex I
Functional inhibition of glucagon-induced hepatic gluconeogenesis due to reduction in cellular cAMP
Muscle—increased glucose uptake
Enhanced action of insulin-induced glucose uptake and disposal in muscle (probably less important than effects on the liver)
Intestine—increased glucose disposal within the gut wall
Accumulation of metformin in intestinal tissues leads to increased insulin-independent anaerobic glucose metabolism
Intestine—enhanced GLP-1 secretion
Stimulates glucose-sensitive insulin release in the pancreas
Cardiovascular protection
Weight loss
Mechanism unclear may involve redistribution of fat from central to less metabolically active visceral depots
Effects on classic cardiovascular risk factors
Modest improvement in lipid parameters (LDL cholesterol and triglycerides)
Variable effects on blood pressures have been observed.
Improved haemostatic function
Shift toward more efficient fibrinolysis consistent with reduced tendency to intravascular clot formation
Reduced inflammation/oxidative stress
Reduced formation of free radicals in mitochondria
Enhanced antioxidant defences, direct, insulin-independent neutralization of key intermediates in the formation of advanced glycation end products
Direct antiatherogenic effects
Improved endothelial function (in some studies)
Inhibition of conversion of monocytes to macrophages, reduced invasion of the arterial wall by inflammatory cells, and reduced lipid uptake by activated macrophages within the atherosclerotic plaque
Results of clinical studies measuring atherosclerosis have provided variable results.

Note. See text for references.

reduction in fasting plasma glucose (FPG) that is similar to that seen with other agents.[1]

At a cellular level, in both liver and muscle, the actions of metformin have been associated with activation of the enzyme, AMP kinase (AMPK), a sensor of energy homoeostasis.[11] Activation of AMPK results in a shift from energy-consuming activities (eg, lipid production and gluconeogenesis) to energy-sparing/generating activities (eg, glucose uptake and lipid oxidation).[12] The activation of AMPK is indirect: an increase in the ration of AMP and ADP to ATP within the cell, in turn caused by a mild inhibition by metformin of oxidative phosphorylation, particularly respiratory complex I.[13]

Most people with type 2 diabetes display a paradoxical increase in glucagon levels during the postprandial state, rather than the decrease seen in normoglycaemic individuals.[14] Another cellular action described for metformin is an inhibition of cAMP accumulation, which leads to reduced activity of adenylate cyclase and a functional inhibition of the stimulatory effect of glucagon on hepatic glucose production.[15] Incretin-based therapies and glucagon antagonists (currently in clinical development for the treatment of type 2 diabetes) improve glucose homoeostasis at least in part by suppression of glucagon signalling pathways: this action of metformin may therefore have important functional significance.[14]

3.2 | The intestine as a site of action of metformin

3.2.1 | Intestinal disposal of glucose

Observations on increased uptake of metformin into the intestines of rodents were made first in the early 1990s.[16-18] More recently, a randomized trial in newly diagnosed type 2 diabetes patients showed that metformin increased glucose uptake into the intestine by twofold to threefold (depending on the part of the intestine studied), while rosiglitazone had limited effect.[19] Experimental data from the same publication confirmed that the uptake occurred in the mucosal layer, as described previously.[19] A retrospective evaluation of patients who underwent ^{18}F-fluorodeoxyglucose (FDG) PET-CT scans for diagnostic purposes also showed that metformin but not insulin or sulphonylurea increased FDG uptake into all parts of the intestine.[20] Finally, a recent pilot study in 12 people with diabetes or metabolic syndrome showed that the uptake of metformin into the colon was 150-fold greater than into the plasma.[21] The intestinal uptake of metformin appears to be mediated by a range of cation transporters (reviewed elsewhere[22]). Genetic variations in these proteins have been associated with altered tissue uptake of metformin, but this effect may be more important for modulating the gastrointestinal side effects of metformin than altering its effects on plasma glucose.[22,23] Metformin may also alter glucose uptake into the gut via effects on glucose transporters, including SGLT1 and GLUT transporters.[24,25]

Increased intestinal glucose uptake during treatment with metformin appears to be functionally significant, as it is accompanied by an increase in anaerobic glucose metabolism, sufficient in magnitude to account for a clinically significant proportion of the overall antihyperglycaemic action of metformin.[16-18] It has been suggested that this anaerobic metabolism, which generates relatively little ATP, effectively amounts to a futile cycle of glucose metabolism that may contribute to weight loss commonly observed during metformin treatment.[22,26] Conversely, prospective data from nondiabetic subjects showed that uptake of metformin into the gut was not associated with increased energy expenditure and thus may not contribute to the weight loss that has been observed during treatment with metformin.[27]

Clinical studies have confirmed that the antihyperglycaemic action of immediate-release[28] or prolonged-release[29] metformin on blood glucose is dose-dependent but not related clearly to systemic exposure to metformin, as measured by plasma concentration-time curves.[30] This is especially so at higher metformin doses, consistent with a local antihyperglycaemic effect of unabsorbed metformin within the intestine.[30] In addition, metformin is known to accumulate in intestinal tissues after dosing, as described above. These observations are consistent with a clinically significant antihyperglycaemic action of metformin in the gut. Finally, a delayed-release formulation of metformin has been developed. This preparation delivers metformin to the distal intestine, mostly avoiding absorption of the drug, which occurs in a restricted portion of the upper intestine. Delayed-release metformin has been shown to induce clinically significant effects on blood glucose and enhanced secretion of incretin peptide hormones, despite minimal systemic exposure.[31]

3.2.2 | Enhanced GLP-1 secretion

A number of studies have demonstrated increased secretion of GLP-1 (including the active form of the peptide), following administration of metformin to people with or without type 2 diabetes.[32-35] The increased GLP-1 secretion may arise in part from reduced glucose absorption in the gut during metformin treatment, so that more glucose reaches the L-cells in the distal intestine that secrete GLP-1.[36] Such a mechanism would be consistent with the observed reduction in SGLT1 activity described above.[25] However, clinical observations of increased GLP-1 secretion with a delayed-release formulation of metformin (associated with very limited systemic exposure) suggest a direct action of metformin in the distal exposure unrelated to effects on glucose.[31] One study showed that metformin enhanced GLP-1 secretion induced by bile acids, without an effect of metformin alone on GLP-1 secretion.[37] A synergistic[38] or additive[39] effect of metformin coadministered with a DPP4 inhibitor in increasing GLP-1 levels has also been shown in people with type 2 diabetes.

Importantly, effects of metformin on GLP-1 secretion appear well maintained, as shown by the 18-month CAMERA study, where placebo-subtracted total GLP-1 was increased during metformin treatment, by 21% at 6 months, 27% at 12 months, and 19% at 18 months.[32] These changes were independent of changes in glycaemia or weight and independent of other cardiometabolic confounders.

3.2.3 | The intestinal microbiome

The gut microbiome contains more than 1000-fold more genes than the human genome,[40] and new research is elucidating its role in health and disease. Alterations in gut microbiota have been associated with dysglycaemia, including on people with prediabetes.[41] Treatment with type 2 diabetes patients with metformin has been shown to alter the relative abundance of individual microbial species within the gut, particularly increasing the number of bacteria that produce short-chain fatty acids[42-45] or reduce the abundance of bacteria producing branched amino acids associated with insulin resistance.[46] A recent randomized trial demonstrated altered gut microbiota during metformin treatment of antidiabetic drug-naïve type 2 diabetes patients.[47] Interestingly, this study confirmed the effect on microbiota by reproducing the effect in patients switched from placebo to metformin and confirmed an association with effects on glycaemia by demonstrating improved glucose tolerance in rodents that received transfers of faecal samples from patients at baseline and after treatment. Addition of a commercially available modulator of the microbiome to metformin (claimed to increase the provision of short-chain fatty acids by gut bacteria) improved the gastrointestinal tolerability of metformin in a randomized placebo-controlled trial.[48] Experimental data suggest that alterations to the gut microbiome in rodents by metformin treatment modulate a glucose-sensing glucoregulatory system mediated via expression of the sodium-glucose transporter, SGLT1, in the upper intestine.[49]

Accordingly, the gut microbiome appears to be an important, if currently incompletely understood, site of action of metformin. This action of metformin may be relevant not only to its antihyperglycaemia effects but also to other pathologies including disorders of the immune system and cancer.[50]

4 | CARDIOVASCULAR PROTECTION WITH METFORMIN

4.1 | Overview of evidence for cardiovascular protection

Table 2 summarizes details of the three randomized controlled trials that provide the most important evidence for cardiovascular protection with metformin.[51-53] The principal evidence for cardiovascular protection by metformin arises from the UK Prospective Diabetes Study (UKPDS 34).[51] In this study, 1704 overweight patients (>120% ideal body weight) within the overall UKPDS population of 4075 patients were randomized to a diet control intervention (the "conventional" treatment policy of the time) or to intensive blood glucose control with metformin, glibenclamide (glyburide), chlorpropamide, or

TABLE 2 Randomized controlled parallel-group cardiovascular outcomes trials that evaluated metformin in populations with type 2 diabetes

Trial	UKPDS 34 (main analysis[a])[51]	Kooy et al[52]	Hong et al[53]
Patients	Overweight (>120% ideal weight), newly diagnosed T2D patients	Insulin-treated T2D (diabetes duration >13 y)	T2D patients with CAD (history of MI or at least 50% stenosis of one coronary artery)
Treatment allocation	342 randomized to metformin, 411 randomized to diet-based treatment for median 10.7 y	390 randomized to additional metformin (≤2550 mg/d) or placebo for median 4.3 y	304 randomized to metformin 1500 mg/d or glipizide 30 mg/d for median 5 y
Key outcomes	RRR vs control for the following: • Any diabetes-related endpoint (0.68 [0.53-0.87]; *P* = .0023) • MI (0.61 [0.41-0.89]; *P* = .01) • Diabetes-related mortality (0.58 [0.37-0.91]; *P* = .017) • All-cause mortality (0.64 [0.45-0.91]; *P* = .011)	Significant benefit for metformin on secondary macrovascular composite endpoint[b] (HR 0.60 [0.40-0.92]; *P* = .04) No significant effect on primary composite of macrovascular + microvascular[c] endpoints (plus death by other cause) or on composite of microvascular endpoints[c]	Significant benefit for metformin on primary CV composite endpoint[d]: HR 0.54 [0.30-0.90]; *P* = .026)

Note. Figures in square brackets are 95% CI.

Abbreviations: CAD, coronary artery disease; CV, cardiovascular; HR, hazard ratio; RRR, relative risk reduction; T2D, type 2 diabetes; UKPDS, UK Prospective Diabetes Study.

[a]CV benefits persisted after 10 years posttrial follow-up ("legacy" effect; see text).

[b]The composite macrovascular endpoint contained myocardial infarction[e]; heart failure[e]; ECG changes (Minnesota scores 1.1-1.3, 4.1-4.3, 5.1-5.3, and 7.1); admission for acute coronary syndrom[e]; admission for diabetic foot[e]; stroke[e]; transient ischaemic attack[e]; peripheral arterial disease on angiography; peripheral arterial reconstruction[f]; coronary revascularisation[f]; nontraumatic amputation[f]; sudden death.

[c]The composite microvascular endpoint contained progression of retinopathy, nephropathy, and neuropathy.

[d]The composite macrovascular endpoint contained recurrent cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, death from a cardiovascular cause, and death from any cause.

[e]Diagnoses documented by appropriately competent physician (cardiologist, internist, surgeon, or neurologist, as appropriate).

[f]Determined by a physician and well documented in the original medical record and in the case record form.

insulin. The comparison between metformin and control included 753 patients. There were clinically and statistically significant reductions for metformin vs the control treatment for any diabetes-related endpoint (relative risk reduction [RRR] −32%), diabetes-related death (RRR −42%), myocardial infarction (RRR −39%), and all-cause death (RRR −36%).[51] Observational/epidemiologic follow-up of the UKPDS 10 years after the end of randomized treatment (20 y of treatment in all) showed that significant benefits persisted in terms of reduced risk of any diabetes-related endpoint (RRR 21%), myocardial infarction (RRR 33%), and death from any cause (RRR 27%).[54]

This main analysis of the study reported 20 years ago,[51] yet some myths about the trial persist.[55] For example, some contend that the evaluation of metformin was conducted in a substudy (eg, in this article,[56] from 2017) but metformin was included within the primary randomization of the trial, although restricted to overweight participants. Second, the trial is regarded as small and has been so described in a transatlantic management guideline for type 2 diabetes.[57] This is true, compared with the current generation of outcomes trials for new antidiabetes agents, which mostly have trial populations of several thousand patients.[1] Nevertheless, it is worth noting that, while the population of 342 patients randomized to metformin is often cited in this context, the number of patients randomized increases to 753 when the diet-treated control group is included, as it should be.[51]

Two other prospective randomized trials (Table 2) have also demonstrated improved cardiovascular outcomes with metformin. One study randomized 390 insulin-treated type 2 diabetes patients to additional metformin or placebo for a mean[52] of 4.3 years. Here, the other compared metformin with glipizide on patients with type 2 diabetes and coronary artery disease.[53]

Many observational studies have also reported cardiovascular benefits of metformin, and these have been reviewed elsewhere.[58,59] Of note, receipt of metformin vs no metformin has been associated in observational studies or systematic reviews with reduced risk of adverse cardiovascular outcomes or death in the primary care setting,[60] in cohorts with elevated cardiovascular risk indicated by the presence of established atherosclerosis,[61] coronary heart disease,[62,63] and elevated cardiac biomarkers[64] or smoking,[65] and in populations with congestive heart failure (CHF),[61,66-71] chronic kidney disease (CKD),[61,66] or chronic liver disease.[66] Analysis of cardiovascular outcomes trials of dipeptidyl peptidase-4 inhibitors has suggested that coadministration of metformin may mitigate the observed increase in the risk of developing CHF associated with the agents (reviewed by Packer elsewhere[72]).

Observational studies also demonstrated improved clinical outcomes in patients receiving metformin compared with sulphonylurea,[66,68,73-78] acarbose,[79] or lifestyle intervention[80] in people with type 2 diabetes. And metformin also reduced the risk of stroke in one large database study.[81] Post hoc analyses of cardiovascular outcomes trials with DPP4 inhibitors have also suggested improved clinical outcomes in metformin- vs nonmetformin-treated patients,[82] including in subgroups with CHF or CKD, consistent with the studies described above.[83]

The current transatlantic guideline for the management of type 2 diabetes[1] notes that a meta-analysis of randomized trials that evaluated metformin[84] did not demonstrate a reduction in cardiovascular disease. Overall, the results of meta-analyses of the effects of metformin vs other diabetes medications on clinical outcomes have been conflicting.[84-86] These meta-analyses included mostly short-term studies, while the cardiovascular benefit for metformin vs the control population in the UKPDS did not emerge until after several years of treatment.

Finally, metformin did not significantly reduce the incidence of microvascular complications in the randomized or posttrial phases of the UKPDS.[51,54]

4.2 | Mechanisms of metformin proposed to protect the cardiovascular system

Table 1 provides an overview of mechanisms of action that have been reported to explain the effects of metformin on glycaemia and on the cardiovascular system. These mechanisms are explained briefly below.

4.2.1 | Endothelial function and haemostasis

The vascular endothelium is intimately involved in the regulation of cardiovascular function, with a central role in regulating vascular tone and haemostasis. Alterations in haemostasis, such as decreased activity of tissue plasminogen activator (tPA), cluster with cardiovascular risk factors associated with the metabolic syndrome and signify an increased risk of intravascular thrombus. Randomized controlled studies have demonstrated reduced plasminogen activator inhibitor-1 (PAI-1) following administration of metformin to people with type 2 diabetes.[87-92] Other studies have demonstrated potentially beneficial effects of metformin on other components of the haemostatic system, such as factors VII and XIII.[93,94] It has been suggested that an overall improvement in thrombolysis may underlie the reduction of ischaemia-reperfusion injury by metformin in animal models or myocardial infarction and that prospective clinical study of this phenomenon is warranted.[95,96]

Metformin also reduced the expression of markers of activation of the endothelium (an early step in atherogenesis)[87] and improved the vascular response to endothelium-dependent vasodilators in controlled trials in type 2 diabetes patients, suggesting improved vascular function.[97,98] Not all randomized controlled trials have shown improvement in endothelial function with metformin however.[99]

4.2.2 | Body weight, fat distribution, and other classical cardiovascular risk factors

Many studies have reported weight loss with metformin, although this has not been seen reliably in placebo-controlled trials.[100] Also, significant weight loss for metformin vs placebo was found to be an important factor in reducing the risk of type 2 diabetes in metformin-treated patients in the Diabetes Prevention Program (where weight loss accounted for 64% of the overall effect of metformin in preventing

conversion of impaired glucose tolerance to clinical diabetes).[101] Recent meta-analyses have demonstrated clinically significant weight loss with metformin in nondiabetic populations with conditions associated with weight gain, ie, women with gestational diabetes,[102] women with polycystic ovary syndrome,[103] and in people receiving atypical antipsychotic medications.[104,105] Decreased food intake has been proposed as the main mechanisms for metformin-associated weight loss, arising from numerous mechanisms operating in the brain and periphery.[105]

Regional fat deposition has emerged as an important driver of cardiovascular risk, with deposition of central (visceral) adiposity associated strongly with insulin resistance and adverse cardiovascular risk. Studies reported in abstract form have associated metformin treatment with redistribution of fat from central to subcutaneous depots[106] and with a reduction in the thickness of epicardial adipose tissue in people with type 2 diabetes.[107]

Metformin treatment also modestly improves the lipid profile where, typically, small reductions in LDL cholesterol and triglycerides are seen, with little effect on HDL cholesterol.[108-110] A meta-analysis concluded that blood pressure was essentially unaffected by metformin in people with diabetes,[110] although a second meta-analysis demonstrated an average reduction in systolic blood pressure of about 2 mmHg, with larger effects seen in subjects with impaired glucose tolerance or obesity.[111]

4.2.3 | Cellular antiatherogenic effects

The binding of monocytes to the activated endothelium is an early event in the development of atherosclerosis. The subsequent infiltration of monocytes into the vascular wall, and their differentiation into macrophages, sets the scene for the development of the mature atherosclerotic plaque. Recent experimental data have shown that metformin inhibited the conversion of monocytes to macrophages and inhibited angiotensin II-induced atherosclerotic plaque formation, in a strain of genetically engineered mice prone to atherosclerosis.[112] Reduced infiltration of macrophages into the vascular wall, with reduced secretion of inflammatory cytokines, was also observed in a rabbit model of atherogenesis.[113] The effect on angiogenesis in one of these studies[114] and in and in other experimental studies[115,116] was associated with stimulation of the AMPK/inhibition of mTOR by metformin, which suggests that such a mechanism may be of relevance to the clinical therapeutic action of metformin. Other potentially vascular protective mechanisms described for metformin in experimental studies include reduced cholesterol uptake[117] or enhanced cholesterol efflux from macrophages,[118] inhibition of fission of mitochondria in endothelial cells,[119] protection of mitochondrial function during and after myocardial ischaemia,[120] and reduced formation of foam cells[121] or neointima[122] in the developing plaque.

These mechanisms have been studied in experimental systems, and their clinical relevance remains to be determined. To date, some but not all studies have demonstrated evidence of reduced atherosclerotic burden in type 2 diabetes patients receiving metformin.[123-125] One of these, the REducing With MetfOrmin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) study, demonstrated a minor and transient reduction for metformin vs placebo of one measure of carotid atherosclerosis in people with type 1 diabetes with cardiovascular risk factors during 3 years of randomized treatment.[125]

4.2.4 | Glycoxidation

Chronic exposure to hyperglycaemia causes sugar moieties to become attached to proteins, which can impair their function, and is believed to represent an important cellular mechanism for the development of long-term complications of diabetes.[126] The formation of these advanced glycation end products (AGE) activates a specific receptor (RAGE), which in turn promotes a toxic combination of oxidative stress and inflammation, a process that has been termed "glycoxidation." Metformin interacts chemically with key α-dicarbonyl intermediates in the formation of AGE (to form triazepinone compounds) and neutralizes them, thus inhibiting the formation of AGE.[127]

Two studies suggest that this phenomenon may be clinically relevant. First, dose-dependent reductions in the levels of two of these dicarbonyls (glyoxal and methylglyoxal) were seen during metformin treatment in people with type 2 diabetes.[128] Second, the presence of triazepinones has been demonstrated in the urine of metformin-treated type 2 diabetes patients, suggesting that metformin does indeed neutralize these toxic metabolites in the therapeutic setting.[129]

Other clinical evidence further suggests a potentially beneficial effect of metformin on parameters related to oxidative stress and inflammation in people with type 2 diabetes. This includes improvements in the levels of metabolites believed to act as antioxidant defence mechanisms,[130] reduced peroxidation of circulating lipids (oxidization of lipids increases their atherogenicity),[131] and reduced production superoxide free radicals, which is likely related to the mild inhibition by metformin of respiratory complex I (see above).[132]

4.2.5 | Glycaemia

The so-called mega-trials, such as ACCORD, VADT, ADVANCE, etc, did not demonstrate a cardiovascular benefit for intensive vs moderate glycaemic control; however, a large meta-analyses of these and other studies showed that tight glycaemic control (difference in HbA1c for active comparators vs controls of 0.9%) reduced the relative risk of coronary heart disease events by 15% and of nonfatal myocardial infarction by 17%.[133] An observational study in a cohort of metformin initiators for type 2 diabetes showed that a larger initial fall in HbA1c and maintenance of lower HbA1c levels for the first 6 months of therapy were associated with improved cardiovascular outcomes.[134] Such a benefit may, in principle, apply to any antihyperglycaemic agent, as long as it did not bring side effects deleterious to the cardiovascular system.

Indeed, observational/epidemiologic follow-up studies to the UKPDS (sulphonylurea/insulin vs diet in people with type 2 diabetes)[54] and the Diabetes Control and Complications Trial (more vs less intensive application of insulin in people with type 1 diabetes)[135] showed that initial randomization to more vs less intensive glycaemic

control was associated with reduced risk of adverse cardiovascular outcomes many years after the end of randomized treatment. This was despite the fact that average HbA1c levels had become similar for the groups previously randomized to each treatment arm. These "legacy effects" in populations with relatively early diabetes suggest that hyperglycaemia at this time sets in motion long-term adverse effects on cardiovascular tissues and that achievement of glycaemic control is especially important for cardiovascular protection in this population, as long as this can be achieved safely and without excessive hypoglycaemia.[1]

5 | CURRENT AND FUTURE PERSPECTIVES

Improvements in cardiovascular outcomes in type 2 diabetes patients randomized to SGLT2 inhibitors and some members of the GLP-1 agonist class (reviewed elsewhere[136-138]) have been received with considerable (and justified) excitement. This review has sought to review outcomes and mechanisms for metformin, a much older antidiabetes medication, and indeed one that has been clinically available for 60 years.[59]

The key to a successful outcome in type 2 diabetes is successful individualization of therapy, matching the right regimen to the patient. In addition, type 2 diabetes is a lifelong disease, and the needs of the patient change, from the newly diagnosed setting where the risk of a cardiovascular event is rather low to the late, perhaps insulin-requiring stage, where cardiovascular risk is much higher. The evidence that metformin improves cardiovascular outcomes in people with diabetes is substantial and has been seen in randomized trials and observational studies in people with early- and late-stage diabetes, as described above. In addition, metformin can be combined with any other antidiabetic agent, and this therapy can be continued for patients without contraindications as newer medications are added on. In this way, adequate glycaemic control can be maintained using a metformin-based regimen over the long-term, maintaining protection from microvascular complications in addition to the cardiovascular benefits of metformin. In the opinion of the authors, this evidence base justifies the retention of metformin as initial pharmacologic antidiabetes therapy.

The era of regulator-mandated cardiovascular outcomes trials is a recent phenomenon, and the randomized outcomes trials with metformin described above predate this era. Modern cardiovascular outcomes trials usually employ a primary outcome of three-point MACEs, with hierarchical statistical analysis protocols, rather than the more complex designs (with a larger number of endpoints) used by the UKPDS and other studies. Thus, it is difficult to compare side by side the outcomes trials with metformin with the studies of the modern era in diabetes research, and we lack a truly definitive randomized outcomes trial with metformin that employs a modern design. A review of experience from trials in heart failure has also emphasized the importance of the use of a definitive trial design to assess important clinical outcomes,[139] and the changing nature of trials in diabetes tends to favour newer agents over older generic agents such as metformin. Accordingly, further evaluation of the cardiovascular benefits of metformin in randomized trials will be welcome, as called for by expert societies.[1] Another recent review has noted the evidence for diverse potentially cardioprotective effects of metformin in people with and without type 2 diabetes, arising from various antiatherosclerotic mechanisms.[140] These authors echo the call for further rigorous study of the effects of metformin on hard clinical outcomes, including in people without type 2 diabetes at risk of cardiovascular events.

Ideally, active-controlled studies are called for as metformin represents the standard of care for initial antidiabetic pharmacotherapy (in the absence of contraindications), withholding this treatment in favour of a placebo presents ethical difficulties. A placebo-controlled study is being planned to evaluate the effects of metformin on clinical cardiovascular outcomes in prediabetic subjects: the Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes study (VA-IMPACT, NCT02915198) is currently recruiting patients in the United States and will evaluate metformin XR on clinical cardiovascular outcomes in people with prediabetes. VA-IMPACT and perhaps other trials will help in future to define the potential of metformin to improve clinical cardiovascular outcomes. Only new clinical data can provide definitive answer to the ongoing debate on the place of metformin within the management algorithm for type 2 diabetes.

ACKNOWLEDGEMENTS

A medical writer (Dr Mike Gwilt, GT Communications, funded by Merck) provided editorial assistance in the development of the manuscript. The authors retained full control over the content of the manuscript.

Dr Salim Mihson Alruba, a leading diabetes physician in Iraq, contributed importantly to the ideas behind this article but sadly passed away before its preparation. We, the authors, acknowledge his contribution, and our thoughts and prayers are with his family.

AUTHOR CONTRIBUTIONS

All authors (Alexey V Zilov, Sulaf Ibrahim Abdelaziz, Afaf AlShammary, Ali Ashraf Amir , Samir Helmy Assaad Khalil, Kerstin Brand, Nabil Elkafrawy, Ahmed AK Hassoun, Adel Jahed, Nadim Jarrah, Sanaa Mrabeti, and Imran Paruk) participated in a meeting to discuss the proposed scope and content of the article before drafting. Alexey V Zilov chaired this meeting. Additionally, Sanaa Mrabeti (corresponding author), supported by Samir Helmy Assaad Khalil, oversaw production of the first draft and coordinated contacts between authors during manuscript development. Kerstin Brand provided information on the status of ongoing studies on metformin for consideration of inclusion. All authors reviewed and commented on the manuscript, and all approved the final version.

DUALITY OF INTEREST

This review arose from a meeting funded by Merck (all co-authors thus acted as honorary consultants to Merck). K.B. and S.M. are employees of Merck.

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How to cite this article: Zilov AV, Abdelaziz SI, AlShammary A, et al. Mechanisms of action of metformin with special reference to cardiovascular protection. *Diabetes Metab Res Rev*. 2019;35:e3173. https://doi.org/10.1002/dmrr.3173