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Metformin: Therapeutic profile in the treatment of type 2 diabetes

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Abstract

Metformin (dimethyl-biguanide) can claim its origins in the use of *Galega officinalis* as a plant treatment for symptoms ascribed to diabetes. Since the first clinical use of metformin as a glucose-lowering agent in 1957, this medicine has emerged as a first-line pharmacological option to support lifestyle interventions in the management of type 2 diabetes (T2D). It acts through multiple cellular pathways, principally in the gut, liver and muscle, to counter insulin resistance and lower blood glucose without weight gain or risk of overt hypoglycaemia. Other effects include improvements in lipid metabolism, decreased inflammation and lower long-term cardiovascular risk. Metformin is conveniently combined with other diabetes medications, can be prescribed in prediabetes to reduce the risk of progression to T2D, and is used in some regions to assist glycaemic control in pregnancy. Consistent with its diversity of actions, established safety profile and cost-effectiveness, metformin is being assessed for further possible clinical applications. The use of metformin requires adequate renal function for drug elimination, and may cause initial gastrointestinal side effects, which can be moderated by taking with meals or using an extended-release formulation. Thus, metformin serves as a valuable therapeutic resource for use throughout the natural history of T2D.

KEYWORDS
antidiabetic drug, glycaemic control, metformin, weight control

1 | INTRODUCTION

This overview examines the origins, landmarks in development and unique properties that have made metformin (dimethyl-biguanide) the most used pharmacological intervention for blood glucose control in the management of type 2 diabetes (T2D).

2 | ORIGINS OF METFORMIN

The history of metformin can be linked to the herbal use of *Galega officinalis* (goat's rue or French lilac), which was described in the 1700s as a traditional treatment for thirst and frequent urination (Figure 1).[1–4] In the mid-1800s, *G. officinalis* was shown to be rich in guanidine, and in 1918, guanidine was reported to lower blood glucose in animals (Figure 2).[5,6] Several mono-guanidine derivatives, notably galegine and synthalin, were introduced in the 1920s to treat diabetes. However, their limited efficacy and toxicity, plus the increasing availability of insulin, led to their disappearance during the 1930s and early 1940s.[7,8]

Dating from the 1870s, biguanides had been synthesized by linking two guanidine molecules, and various biguanide derivatives were synthesized in the 1920s.[9–11] Among these was dimethyl-biguanide, synthesized by Emil Werner and James Bell in 1922.[12] In 1929,

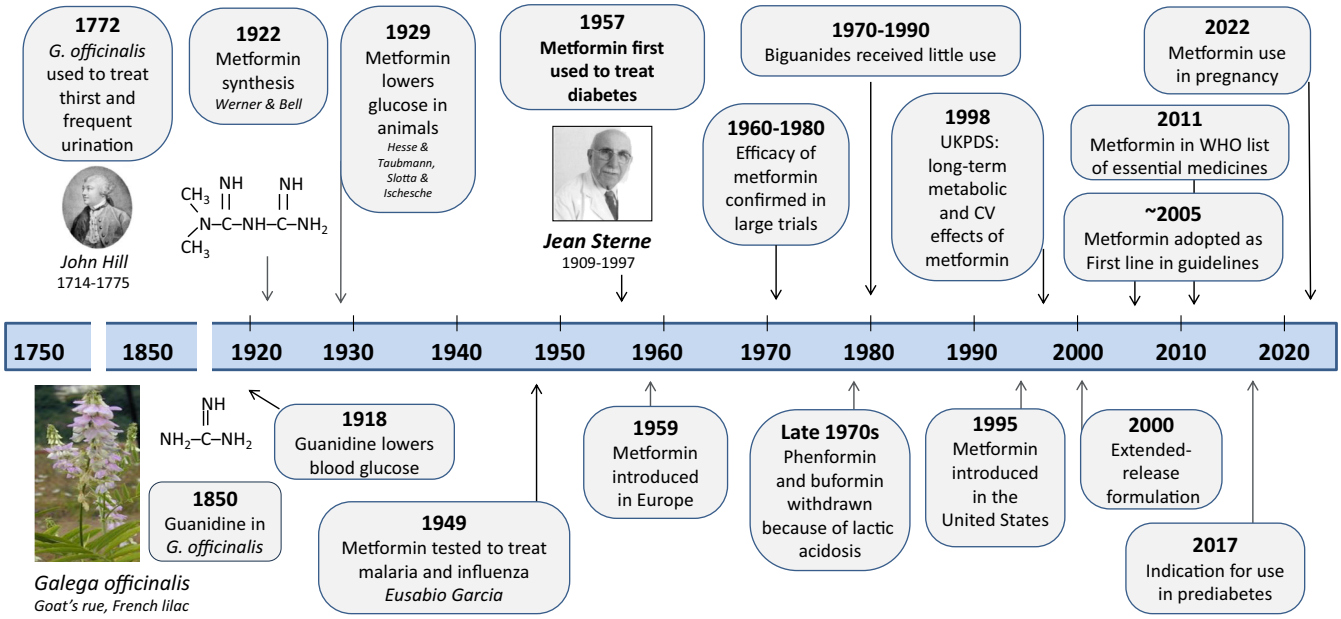

FIGURE 1 Timeline of the history of metformin. CV, cardiovascular; UKPDS, UK Prospective Diabetes Study; WHO, World Health Organization.

metformin and other biguanide derivatives, notably phenethyl-biguanide (phenformin) and butyl-biguanide (buformin), were shown to lower blood glucose in animals, but were not progressed as therapies for diabetes and appear to have been forgotten.[13,14]

Quite independently, in the 1940s, metformin was synthesized during the evaluation of guanidine-based antimalarial agents such as proguanil (paludrine). A clinical study in the Philippines by Eusebio Garcia found limited antimalarial value of metformin, but occasional glucose-lowering activity and general effectiveness against influenza were observed (the latter effect accounting for the introduction of the name Flumamine).[15] However, the antidiabetic potential of metformin was not taken forward.

2.1 | Metformin as a diabetes therapy

Key research that established metformin as a treatment for diabetes was conducted by Jean Sterne in 1956 and 1957 at the pharmaceutical laboratory set up by Jan Aron in Paris.[16] Sterne was a local physician Aron appointed and encouraged to investigate the potential of the biguanides. Many years earlier as an intern at l'Hopital de le Pitie, Sterne had been involved in a study of galegine and was aware of the work of Garcia. Sterne and his pharmacist colleague Denise Duval repeated much of the work on metformin and other biguanides from the 1920s, unaware of this previous research. They selected metformin for clinical investigation based on its glucose-lowering efficacy and tolerability in animal studies and the clinical experience with flumamine.[16]

Sterne took advantage of his position at l'Hopital Laennec in Paris and his collaboration with Dr Elie Azerad at Hopital Beaujon in Clichy to undertake clinical studies with metformin. They noted that metformin could reduce or eliminate the insulin requirement of adult-onset diabetes patients and reduce (but not eliminate) the insulin requirement of juvenile-onset diabetes patients.[16] They also observed that metformin was not associated with overt hypoglycaemia and exerted little or no glucose-lowering effect in individuals without diabetes. Sterne published an initial account of this work in 1957, with more detailed papers in the years to follow.[17–22] The name 'glucophage' (glucose eater) was proposed by Sterne, and the product was introduced into clinical practice in Europe as a diabetes treatment in 1959.

2.2 | Metformin enters clinical practice

The use of metformin was initially limited because sulphonylureas had recently become available (in 1956) to treat adult-onset diabetes, and two other biguanides were in contention: phenformin was introduced in the United States in 1957 and buformin in Germany in 1958.[10,23–25] These agents were considered to exert stronger glucose-lowering effects than metformin, and phenformin became the preferred biguanide.[26] Indeed, metformin and buformin were not introduced into the United States, and buformin was not introduced into the UK. However, interest in metformin was maintained by several large comparative studies that found metformin could deliver similar long-term metabolic control to sulphonylureas without serious hypoglycaemia or weight gain.[27–30] Nevertheless, metformin remained a minority

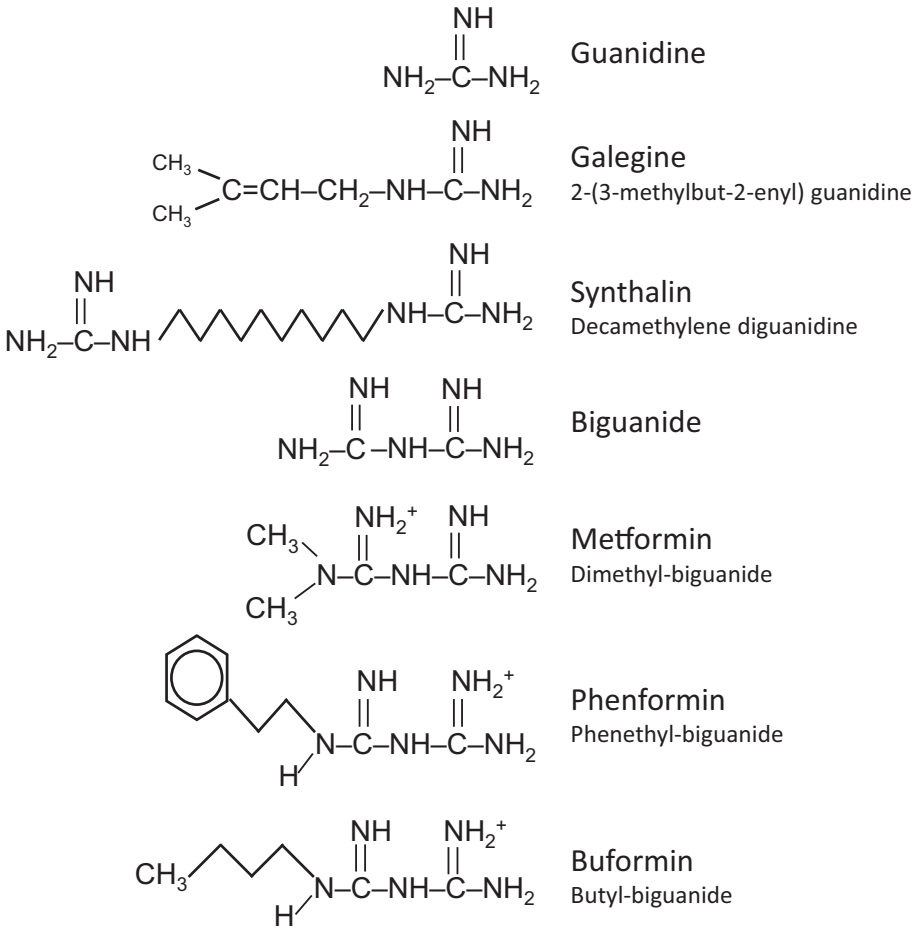

FIGURE 2 Structures of guanidine and guanidine-related compounds.

medication until the 1990s, constrained by uncertainty regarding its mode of action, concern about gastrointestinal (GI) side effects, and reticence through association with other biguanides.[30,31]

2.3 | The lactic acidosis issue

Suspicion about phenformin arose when it was withdrawn from the controversial University Group Diabetes Program trial in 1971 because of increased mortality.[32] However, a link with lactic acidosis in several studies was the main reason for phenformin and buformin being discontinued in most countries in the late 1970s.[33] The incidence of lactic acidosis with phenformin was estimated to be approximately 0.6 per 1000 patient years, whereas the incidence with metformin was much lower at approximately 0.03-0.08 per 1000 patient years.[25,34] Moreover, the incidence of metformin-associated lactic acidosis (MALA) was often indistinguishable from background for T2D.[35–37] The high incidence of phenformin-associated lactic acidosis has subsequently been attributed to reduced degradation of the drug by individuals with reduced function variants of CYP2D6.[38] Metformin is not metabolized and usually accumulates only when administration is continued for individuals with chronically impaired renal function or a serious acute renal event.[35,39,40]

2.4 | Metformin approved worldwide

Despite lingering concerns about lactic acidosis, modest use of metformin throughout the 1980s confirmed its favourable safety profile, and a growing appreciation of insulin resistance fostered interest in the therapeutic mechanism of metformin.[34,41–44] Although suppression of hepatic gluconeogenesis was established as the main glucose-lowering effect of metformin, its portfolio of therapeutically relevant insulin-dependent and insulin-independent actions generated confidence for approval by the US Food and Drug Administration (FDA) in 1994. So metformin was introduced in the United States in 1995 and soon after in other countries that take their lead from the FDA.[16,45,46] Key clinical trial data confirming the efficacy of metformin and a surge of interest in metformin followed.[47,48] Having begun at the small pharmaceutical company of Jon Aron, the production of Glucophage was transferred to Rona, a UK subsidiary of Aron, and was later acquired by Lipha and its affiliates and then Merck KGaA (Darmstadt, Germany). Bristol Myers Squibb acquired Glucophage in the United States and provided an extensive education programme to facilitate its use.[4,16] The US license was returned to Merck KGaA (operating as EMD Serono in the United States) in 2018.

2.5 | Metformin adopted by guidelines

Results of the UK Prospective Diabetes Study (UKPDS) in 1998 provided a landmark for the treatment of T2D and confirmed the long-term efficacy of metformin, including its apparent protection against atherosclerotic cardiovascular (CV) events.[49] This boost to the reputation of metformin encouraged the introduction of an extended-release formulation (in 2000) to improve GI tolerability, and further usage was assisted by fixed-dose combination (FDC) tablets with sulphonylureas and later with other glucose-lowering agents.[50–52] Post-2000 saw a plethora of national and international guidelines for the management of T2D that included metformin as a first-line pharmacological intervention for glycaemic control, a position that metformin has retained in most of the current versions.[53–55] The long-term advantages of metformin as an early intervention, particularly to reduce long-term adverse CV events, were consolidated by results of the 10-year post-trial follow-up of the UKPDS in 2008.[56]

2.6 | Therapeutic indications expanded

The ability of metformin to reduce the progression of prediabetes to T2D in the Diabetes Prevention Program and similar studies supported the approval in 2017 of an indication for metformin as an intervention in prediabetes.[57,58] Other large studies during the past two decades have supported further indications for metformin, including use in the elderly, children from the age of 10 years and people with mild to moderate chronic kidney disease (defined as an estimated glomerular filtration rate [eGFR] down to 30 mL/min/1.73m^2), all with suitable caution regarding dose and renal monitoring.[59,60] Experience with off-label use in pregnancy, plus several large controlled trials, supported approval in Europe (in 2022) for the use of metformin to assist glycaemic control during pregnancy and in the periconceptional period in T2D, and in some European countries in prediabetes and/or polycystic ovarian syndrome (PCOS).[59,61–63]

2.7 | Pharmacokinetics of metformin

The clinical applications of metformin take advantage of its pharmacokinetic features (Table 1). Metformin exists mostly as a cation at physiological pH (pKa ~11.5), and therapeutic doses (typically 1000-2000 mg/day) give peripheral plasma concentrations of 0.5-2.0 ug/mL (~10^{-5} mol/L).[64] Metformin enters (and leaves) cells via several organic cation transporters, principally OCT1, but including OCT2, OCT3 and the plasma membrane monoamine transporter (PMAT).[65] Metformin can also be taken up from the intestine via the serotonin re-uptake (SERT) transporter, while the multidrug and toxin extrusion transporters (MATE1/2) contribute to renal elimination. In consequence, individuals with reduced function variants of the intestinal transporters can incur reduced bioavailability of metformin and increased risk of GI side effects such as diarrhoea, as well as a reduced therapeutic effect.[64–66] Metformin is not metabolized and is eliminated unchanged in the urine: approximately 20% by filtration and 80% by tubular secretion.[67,68] Therefore, adequate renal function (Section 4) is a prerequisite to avoid excess drug accumulation.

TABLE 1 Pharmacokinetic properties of metformin.

Variable	Comment
Dosage (mg tablets)*	Standard IR, 500, 850, 1000
	Extended release (ER, SR, XR), 500, 750, 1000
Bioavailability	50%-60%; absorbed mainly from the small intestine
Plasma values	T_{max} 0.9-2.6 h for IR and 4-8 h for XR formulation
	C_{max} 1-2 ug/mL for IR, slightly lower for XR, but AUC extended
	Negligible plasma protein binding
	Volume of distribution 63-276 L
Metabolism	Not metabolized
Tissue distribution	Distributed into most tissues
	Tissue concentrations mostly similar to peripheral plasma
	High tissue concentrations in liver and kidney
	Very high concentrations in the intestinal wall and salivary glands
Elimination	Excreted unchanged in the urine
	Renal clearance typically > 400 mL/min (~20% filtered, ~80% secreted)
	$T_{1/2}$ ~ 6-7 h, multiexponential pattern
	~90% of absorbed drug is excreted in urine in 24 h

Abbreviations: AUC, area under curve of plasma concentration; C_{max}, maximum plasma concentration; IR, immediate release; $T_{1/2}$, plasma elimination half-life; T_{max}, time to maximum plasma concentration after a single 500-mg or 1000-mg oral dose.
*A liquid formulation of metformin (500 mg/mL) is available in some regions: not all dosage strengths of tablets are available in all regions. Fixed-dose combination tablets of metformin with a sulphonylurea (e.g. glyburide, glipizide), a dipeptidyl peptidase-4 inhibitor (e.g. sitagliptin, saxagliptin, linagliptin, alogliptin), a sodium-glucose co-transporter-2 inhibitor (e.g. dapagliflozin, canagliflozin, empagliflozin, ertugliflozin) or with pioglitazone, are also widely available (Table 5).

3 | CURRENT THERAPEUTIC INDICATIONS

Metformin is indicated to treat the hyperglycaemia of T2D, especially in overweight and obese patients, if lifestyle management by diet, exercise and health education does not achieve adequate glycaemic control (Table 2).[59,60] Metformin is typically included as an initial glucose-lowering pharmacotherapy in most treatment guidelines, and is conveniently used with additive efficacy in combination with any other glucose-lowering agents, including insulin, because of its different and complementary mode of action.[69,70] The key therapeutic properties of metformin reflect its ability to counter the effects of insulin resistance, such that it lowers blood glucose without causing clinically significant hypoglycaemia or weight gain, and without increasing basal insulin concentrations (Table 3).[27–31,34,47,48] Beyond

TABLE 2 Clinical use of metformin in the management of type 2 diabetes.

Category	Comment
Indications	Treatment of T2D, particularly in overweight patients, when dietary management, exercise and health education do not achieve adequate glycaemic control
Use	Monotherapy or combination with other glucose-lowering agents including insulin
Formulations and dosage strengths	Standard IR, 500, 850, 1000 mg
	Extended release (ER, SR, XR), 500, 750, 1000 mg
	Oral solution 500 mg/5 mL
	Powder for oral solution, sachets of 500 and 1000 mg available in some regions
Administration	Check renal function (e.g. eGFR) before starting therapy.
	IR: take before or with main meals starting with 500 mg once daily and increase dose slowly (e.g. weekly) based on fasting blood glucose. ER/SR/XR: take once daily before evening or morning meal starting with 500-1000 mg, increase dose slowly based on fasting blood glucose, consider dividing dose between morning and evening if gastrointestinal side effects
	Monitor glycaemic control; typical therapeutic dose 1500-2000 mg/day
	Maximum dose 2550 or 3000 mg/day depending on regional guidance
Children and elderly	Use in children aged ≥ 10 y (usual maximal dose 2000 mg/day)
	Use in elderly requires regular assessment of renal function and adjustment of dose accordingly
Check renal function	If eGFR < 45 mL/min/1.73m^2 initiate metformin with extra caution: consider factors that may increase the risk of lactic acidosis and increase the dose slowly. Suggested maintenance dose should be no more than one-half of the maximum dose
	If eGFR < 30 mL/min/1.73m^2 discontinue metformin and introduce an alternative treatment
	Check renal function at least yearly during metformin therapy and more frequently in patients considered to be at particular risk for renal impairment, such as the elderly
Contraindications and cautions	Renal disease (eGFR < 30 mL/min/1.73m^2), hepatic disease; decompensated heart failure or other serious cardiac condition (e.g. recent myocardial infarction); respiratory insufficiency; any hypoxic condition; severe infection; dehydration; alcohol abuse; history of lactic acidosis; temporarily discontinue during use of intravenous radiographic contrast agents; pregnancy (United States)
Side effects	Gastrointestinal symptoms: these usually improve with dose reduction or a switch to an extended-release formulation; metallic taste; reduced absorption of vitamin B12 and folic acid during long-term use
Adverse reactions	Risk of lactic acidosis in patients with a contraindication, notably unrecognized acutely or severely impaired renal function; hypoglycaemia can occur when used in combination with another glucose-lowering medication or in alcohol abuse
Precautions	Periodic checks of renal function; suggested occasional check of haemoglobin; possible interaction with cimetidine therapy

Abbreviations: eGFR, estimated glomerular filtration rate; IR, immediate release; T2D, type 2 diabetes.

glycaemic control, metformin offers several further clinical benefits that are highly relevant in T2D, notably an improved blood lipid profile, reduced blood coagulability and reduced inflammation, which support a reduction in CV risk.[47,71–73]

It is reminded that metformin cannot be used as a substitute for insulin in type 1 diabetes because metformin does not mimic the breadth of genetic and metabolic effects of insulin and requires the presence of insulin for its therapeutic glucose-lowering efficacy.[59,60] However, metformin has been used to potentiate the glucose-lowering efficacy of insulin and reduce the insulin dose in type 1 diabetes and insulin-treated T2D.[74–76] Consistent with the avoidance of overt hypoglycaemia, metformin has little effect on blood glucose concentrations in individuals with normal non-diabetic glycaemic control and exerts a substantially diminished glucose-lowering effect in prediabetes than T2D.[77]

3.1 | Glucose lowering

The glucose-lowering efficacy of metformin is mainly attributed to reduced hepatic glucose output, which serves predominantly to lower basal (fasting) glycaemia.[34,78–81] However, metformin also exerts glucose-lowering effects via increased anaerobic glucose metabolism by the intestine and increased insulin-stimulated peripheral glucose disposal (Figure 3).[82,83] Blood glucose concentrations decrease progressively during the first 1-2 weeks of metformin therapy, and thereafter with dose titration. Efficacy is dependent on many factors, including the severity of initial hyperglycaemia, degree of pancreatic beta-cell dysfunction, extent of insulin resistance and expression of transporters for cellular uptake of metformin.[52] In clinical trials with T2D patients, metformin has typically reduced HbA1c by 1%-2% (11-22 mmol/mol) and fasting blood glucose (FBG) by 2-3 mmol/L. In

patients with an average baseline HbA1c of 8.4% (68 mmol/mol) and fasting plasma glucose (FPG) of 13.5 mmol/L, treatment with metformin titrated to 2000 mg/day for 6 months reduced HbA1c by 1.5% (16 mmol/mol) and FPG by approximately 3.1 mmol/L.[48] In more severely hyperglycaemic patients (baseline HbA1c 9.9% [85 mmol/mol] and FPG 15.5 mmol/L), metformin titrated to 2000 mg/day for 3 months reduced HbA1c by approximately 2% (~22 mmol/mol) and FPG by approximately 4.5 mmol/L.[84] Long-term trials such as the UKPDS have confirmed the durability of the glucose-lowering efficacy of metformin.[30,49,52,70,85,86] However, this efficacy, like that of other glucose-lowering agents, is diminished by the variably progressive natural history of T2D, with rising hyperglycaemia and insulin resistance as beta-cell function deteriorates: hence the need for dose escalation and the introduction of additional agents with disease duration.[43,52] Because metformin offers a different and complementary mode of action with 'add-on' glucose-lowering agents, and provides further potentially beneficial effects, it is conveniently continued throughout the course of disease progression, provided that contraindications (especially renal function) are not breached.

TABLE 3 Key therapeutic effects of metformin in the management of type 2 diabetes.

Therapeutic effect	Comment
Glucose lowering by multiple mechanisms	↓ hepatic glucose output ↑ intestinal glucose utilization ↑ insulin-mediated peripheral glucose uptake
Not cause overt hypoglycaemia	Adequate counter-regulation is retained with metformin as monotherapy. There is a risk of hypoglycaemia when metformin is used in combination with other glucose-lowering agents
Not cause weight gain	Metformin may assist modest weight loss in overweight and obese patients
Not increase basal insulin concentration	Counter insulin resistance (not stimulate basal insulin secretion); can reduce basal hyperinsulinaemia
Improve lipid profile	↓ triglycerides, ↓ LDLc, ↑ HDLc in people with significant dyslipidaemia
Improve other vascular risk factors	↓ platelet aggregation, ↑ fibrinolysis, ↓ inflammatory markers
Reduce atherosclerotic events	↓ fatal and non-fatal myocardial infarction

Abbreviations: ↑, increase; ↓, decrease; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.

Metformin can be used to reduce the risk or delay the onset of T2D in individuals with prediabetes, particularly those who are younger, overweight or obese, and at high CV risk with worsening glycaemic control, despite intensive lifestyle management for 3-6 months.[58–60] Prediabetes is usually defined by HbA1c (e.g. 5.7%-6.4%; 39-47 mmol/mol) and/or impaired glucose tolerance (2-hour 75-g oral glucose tolerance test with a plasma glucose of 140-199 mg/dL; 7.8-11.0 mmol/L) or impaired FPG (e.g. 110-125 mg/dL; 6.1-6.9 mmol/L). Several large trials have shown that metformin (usually ≥ 1500 mg/day) can reduce the annual progression to T2D by approximately 30% and normalize glycaemia in some individuals. The extended Diabetes Prevention Program found that metformin remained effective throughout 21 years of follow-up (Diabetes Prevention Program Outcomes Study), and other studies have established that the effect of metformin is additive to that of intensive lifestyle management.[57,58,77,87–89]

In line with its glucose-lowering efficacy, protracted use of metformin is accompanied by reductions in the risk of microvascular complications.[49,90–92] The avoidance of overt hypoglycaemia is a valuable attribute of metformin monotherapy: the glucose-lowering effect diminishes as blood glucose levels approach normoglycaemia, and metformin does not interrupt the counter-regulatory response to subnormal glycaemia.[45,46,59,60,82,93]

Reduced hepatic glucose output with metformin (typically by 10%-30%) is mostly attributable to reduced gluconeogenesis, but

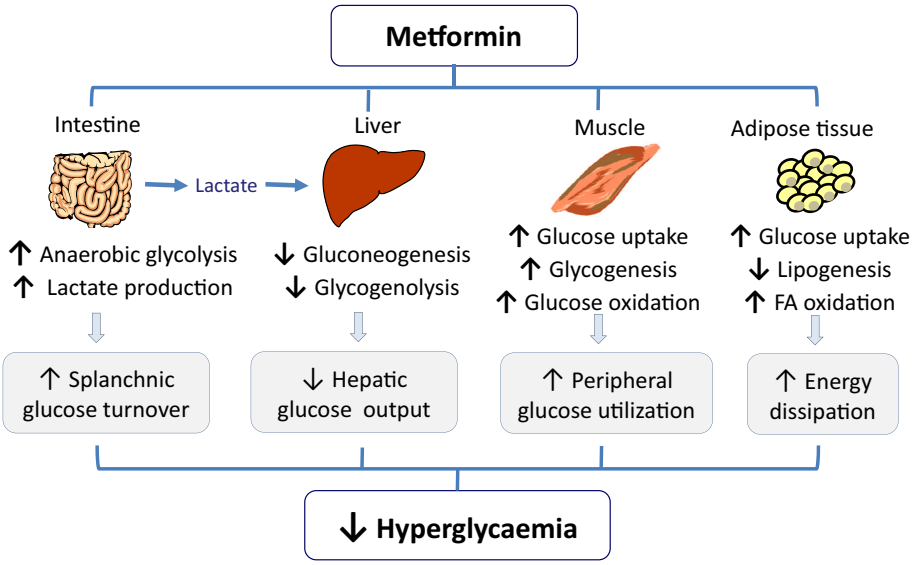

FIGURE 3 Key tissues contributing to the glucose-lowering effect of metformin. ↑, increase; ↓, decrease; FA, fatty acid.

glycogenolysis is also reduced.[80,81] Prandial glucose excursions, which start from a lower base through the effect of metformin, are usually only slightly reduced.[47,94] This is typically achieved with lesser insulin concentrations (consistent with reduced insulin resistance), and may partly reflect a reduced stimulatory effect on the pancreatic beta-cells because of the lower blood glucose, as well as increased utilization of glucose by the intestine, increased glucose uptake by peripheral tissues and reduced activity of glucagon. During euglycaemic-hyperinsulinaemic clamp studies in T2D patients, metformin increases glucose uptake by skeletal muscle: the magnitude of this effect is generally modest (e.g. ~10% increment) and associated with increased glycogenesis and aerobic glucose metabolism.[78,94] Although metformin is often accompanied by a rise in plasma lactate, this is typically still within the normal range, and the risk of excessively raised lactate is usually only through excessive metformin accumulation because of impaired renal elimination and co-existent morbidity (considered below).[31,35,82]

3.2 | Weight control

Limited weight gain or slight weight loss with metformin, despite reduced insulin resistance, has been attributed in part to increased intestinal secretion of growth differentiation factor-15 (GDF-15), which crosses the blood–brain barrier and provides a satiety signal.[95,96] It has been suggested that metformin may increase GDF-15 secretion by deferring glucose absorption more distally along the intestinal tract: a similar proposal has been advanced to account for the small increase in glucagon-like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY) from L-cells during metformin therapy.[97–99] GLP-1 and PYY provide further satiety effects and GLP-1 may assist with maintenance of the prandial insulin response and suppression of prandial glucagon release. Also, production of the anorexigenic metabolite *N*-lactoyl phenylalanine by muscle during exercise is increased by metformin.[100] The lowering of basal insulin concentrations, the energy-consuming glucose-lactate-glucose turnover, and increased expression of uncoupling protein-1 (UCP-1) in adipose tissue, are additional actions deemed to assist with weight control.[101–103] In routine clinical use some patients may lose weight through reduced appetite because of GI symptoms during metformin dose titration.[29]

3.3 | Lipid metabolism

There are various reports that metformin reduces visceral fat and total body adiposity, associated with increased fatty acid oxidation and reduced lipogenesis.[47,104–108] Although metformin has little effect on plasma lipid values within the normal ranges, it often improves the plasma lipid profile in individuals with dyslipidaemia.[109,110] This typically includes a reduction in plasma triglycerides (by > 10% in some studies), lower very-low-density lipoprotein and low-density lipoprotein cholesterol and a small rise in high-density lipoprotein cholesterol. A decrease in the rate of intestinal chylomicron production and an increase in extraction of fatty acids by adipose tissue have also been reported, consistent with a reduction in circulating free fatty acids.[47,72,109] Of particular relevance to the alleviation of insulin resistance, metformin has been shown to reduce ectopic triglycerides, diacylglycerol and ceramide.[111,112] An inhibitory effect of metformin on the active reabsorption of bile salts by the apical sodium-dependent bile acid transporter in the ileum reduces the enterohepatic circulation of bile salts, providing a further mechanism to reduce circulating cholesterol, and the overall improvements in the lipid profile offer potential advantages to reduce CV risk.[82,113]

3.4 | Cardiovascular effects

Considerable evidence indicates that metformin affords some long-term CV protection for individuals with T2D or prediabetes independently of the extent of glycaemic control and weight control.[49,73,90,114,115] Regarding prospective randomized trials, the UKPDS recorded relative risk reductions in myocardial infarction (MI; by 39%), diabetes-related deaths (by 42%) and all-cause deaths (by 36%) after 10 years of treatment with metformin in overweight and obese newly diagnosed T2D patients.[49] A 10-year follow-up noted that initial therapy with metformin was associated with continued CV protection (the so-called legacy benefit: relative risk reductions of 33%, 30% and 27%, respectively, for MI, diabetes-related deaths and all-cause deaths), and this benefit was still evident in the follow-up data collected 44 years after the start of the trial.[56,116] Other prospective randomized trials have confirmed reductions in a composite of CV events (CV death, all-cause deaths, non-fatal MI or stroke or arterial revascularization) by 46% after 5 years in metformin-treated compared with sulphonylurea-treated T2D.[117] Also, a study in insulin-treated T2D noted a 39% reduction in macrovascular morbidity and mortality after the addition of metformin for 4.3 years.[118]

These prospective trials have been criticized for limited numbers of participants receiving metformin (< 500 in each study) compared with the numbers randomized in present-day cardiovascular outcome trials (CVOTs), but many observational studies have affirmed the reductions in CV events with metformin.[46,119,120] A recent meta-analysis that included 16 studies and more than 1 million people with T2D reported a 27% decrease in the incidence of CV disease and a 56% decrease in CV mortality among those treated with metformin.[121] Another recent meta-analysis of 40 studies, with more than 1 million people with T2D and CV disease, reported a decrease by 29% in CV mortality among those receiving metformin.[122] As noted in the UKPDS, the CV benefits of metformin emerge gradually during several years of treatment, and while some short-term studies provide numerical reductions in CV events, these may not achieve statistical significance.[123] Although metformin can reduce long-term CV adverse events, it is reiterated that hypoxaemic conditions such as acute severe myocardial ischaemia are contraindications for metformin, and metformin should be discontinued during such episodes.[59,60]

Observational studies involving patients with T2D and heart failure (reduced or preserved ejection fraction) have reported that metformin can reduce mortality. A meta-analysis of nine studies with 34 504 T2D patients with heart failure found that metformin reduced mortality by 20%, and an analysis of 11 studies with 35 950 patients found a 22% reduction in mortality with metformin.[124,125] Metformin has also been shown to reduce the risk of onset of heart failure in T2D and to exert direct effects on the metabolic and bioenergetic status of cardiomyocytes.[126–129] However, recall that significantly decompensated hypoxaemic heart failure is a contraindication for metformin.

Various plethysmography studies have shown that metformin can improve endothelial-mediated vascular reactivity in T2D, and the addition of metformin to the insulin regimen of type 1 diabetes patients has reduced progression of the maximal carotid intima-media thickness over 3 years.[115,130,131] A succession of preclinical and clinical studies has noted that metformin can decrease atherosclerotic lesions, and this has been variously attributed, in part, to an improved lipid profile, reduced inflammation, reduced oxidative stress and reduced hyperinsulinaemia (Figure 4).[73,114,115,127,132–134] Indeed, metformin has been reported to improve endothelial function by decreasing endothelial production of adhesion and attractant molecules, reducing monocyte infiltration and foam cell formation.[73,114,115,135,136] Metformin has also been shown to improve the dynamics of the microvascular circulation.[73,90,114] Often forgotten are the effects of metformin on haemostasis and thrombolysis, notably to decrease platelet aggregation, alter fibrin polymerization and reduce plasminogen-activator inhibitor-1 (PAI-1).[45,46,73,114,115,137] Despite this catalogue of beneficial effects on the vasculature, most studies with metformin have noted little effect on blood pressure, beyond small reductions consistent with decreases in adiposity.[73,114,115]

Research studies continue to examine the CV effects of metformin, and several prospective trials with CV endpoints are ongoing for metformin, notably SMARTEST (NCT03982381), MIMET (NCT05182970), MetHeFT (NCT03514108) and VA-IMPACT (NCT02915198). However, it is unlikely that very large prospective randomized CVOTs will be conducted with this long-established drug for comparison with each new glucose-lowering agent.[113] It is noted that the majority of patients recruited into the CVOTs with new glucose-lowering agents are already receiving metformin, so the new agents are largely tested as add-on therapies to metformin.[138–140]

3.5 | Practicalities of starting metformin

All national and international guidelines for managing T2D have given priority to lifestyle measures (i.e. diet, exercise and behavioural interventions) as the primary therapeutic approach.[53–55,141] Lifestyle measures should be implemented immediately, optimized as far as possible and maintained throughout. Consistent with the product label, metformin is widely used as initial pharmacotherapy if lifestyle measures do not achieve adequate glycaemic control within a reasonable period of time (e.g. 3 months).[59,60] For patients who present with severely hyperglycaemic T2D, some guidelines advocate that consideration be given to the introduction of metformin at the same time as lifestyle measures, or to the introduction of lifestyle measures plus metformin plus another differently acting glucose-lowering agent.[54]

The introduction of metformin assumes respect for contraindications, in particular checking renal function (e.g. eGFR preferably > 45 mL/min/1.73m^2).[35,59,60] Standard (immediate release [IR]) metformin is taken before meals, starting with one 500-mg or 850-mg tablet (or 500-mg liquid formulation) before breakfast or other main meal (Table 2). Gradual dose escalation is suggested, guided by monitoring of glycaemic control, initially using FBG and subsequently HbA1c. Typically, dose escalation is by the addition of one tablet at a time at 4- to 14-day intervals, leading to two or three divided doses before the main meals, until the desired level of blood glucose control is achieved or the maximum tolerated dose is reached. A total dose of three or four 500-mg tablets (or equivalent dosage forms) or two to three 850-mg tablets is often required, and the full glucose-lowering effect is usually achieved with 2000 mg/day.[84] The maximum dose is 2550 or 3000 mg/day depending on the regional product label.[59,60]

Initiation of metformin therapy is often accompanied by GI side effects such as abdominal discomfort, diarrhoea, nausea, loss of appetite and a metallic taste. Symptoms are mostly transient and can be

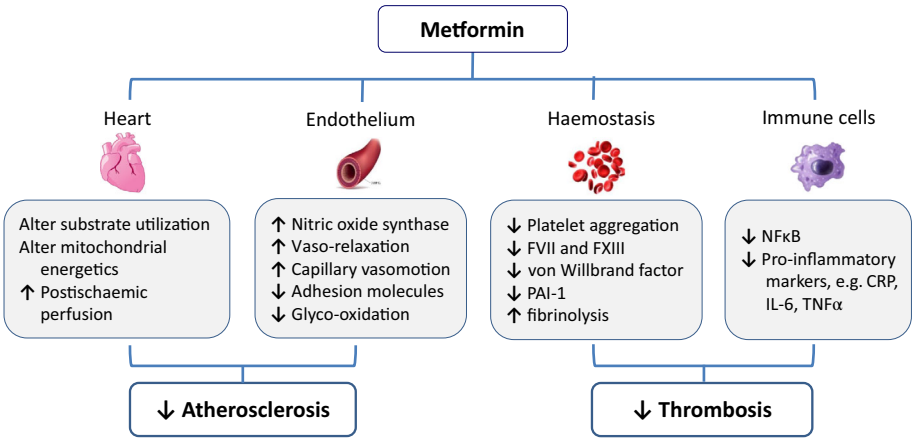

FIGURE 4 Cardiovascular effects of metformin contributing to reduced atherosclerosis and improved thrombolysis. ↑, increase; ↓, decrease; CRP, C-reactive protein; IL-6, interleukin-6; NFκB, nuclear factor kappa B; PAI-1, plasminogen-activator inhibitor-1; TNFα, tumour necrosis factor-alpha.

TABLE 4 Single-tablet fixed-dose combinations that contain metformin.[a]

Name	Constituents	Tablet strengths (mg)
Glucovance	Metformin + glyburide	250/1.25, 500/2.5, 500/5.0
Metaglip	Metformin + glipizide	250/2.5, 500/2.5, 500/5.0
Actoplus Met	Metformin + pioglitazone	500/15, 850/15
PrandiMet	Metformin + repaglinide	500/1, 500/2
Janumet	Metformin + sitagliptin	500/50, 000/50
Kombiglyze	Metformin + saxagliptin	500/5, 000/2.5, 1000/5.0
Jentadueto	Metformin + linagliptin	500/2.5, 850/2.5, 1000/2.5
Kazano	Metformin + alogliptin	500/12.5, 1000/12.5
Synjardy	Metformin + empagliflozin	500/5, 1000/5, 500/12.5, 1000/12.5
Invokamet	Metformin + canagliflozin	500/50, 1000/50, 500/150, 1000/150
Xigduo	Metformin + dapagliflozin	500/5, 1000/5, 500/10, 1000/10
Segluromet	Metformin + ertugliflozin	500/2.5, 500/7.5, 1000/2.5, 1000/7.5

[a]Metformin counters insulin resistance, and its mode of action is different to and complementary with other agents to provide additive glucose-lowering efficacy. Combinations of metformin with a sulphonylurea (e.g. Glucovance or Metaglip) or meglitinide (e.g. Prandimet) provide additional insulin secretion, while the combination of metformin with a thiazolidinedione (e.g. Actoplus Met) enables insulin resistance to be addressed through two different sets of cellular mechanisms. Combining metformin with a DPP-4 inhibitor (e.g. Janumet, Kombiglyze, Jentadueto or Kazano) is additive to the effects of endogenous incretin hormones (GLP-1 and GIP), notably to potentiate prandial insulin secretion, reduce glucagon secretion, delay gastric emptying and increase satiety. The combination of metformin with a SGLT-2 inhibitor (e.g. Synjardy, Invokamet, Xigduo or Segluromet) is additive to the glucose-lowering and weight-lowering glucosuric effects of the SGLT-2 inhibitor. A single-tablet triple combination of metformin with linagliptin and empagliflozin (Trijardy XR) is now available in some regions. The tablet strengths (mg) for the empagliflozin/linagliptin/metformin components are 5/2.5/1000, 12.5/2.5/1000, 10/5/1000 and 25/5/1000. GLP-1 receptor agonists or insulin (by subcutaneous injection) are administered separately from metformin (by tablets). Glyburide is known as glibenclamide in Europe.

reduced by taking IR tablets at the beginning of the meal, although prandial glucose-lowering efficacy is greater if tablets are taken 30-60 minutes before the meal. Symptoms are also reduced by gradual dose escalation and usually remit with temporary dose reduction, although a small proportion of patients (5%-10%) may not tolerate full dose titration or discontinue because of persistent GI effects. The extended-release (ER, SR, XR) formulations of metformin incur fewer GI side effects and may be preferred from the start or switching.[50,142,143] Extended-release tablets are generally taken once daily before the evening meal or sometimes twice daily before breakfast and the evening meal.[59,60] They are taken whole to preserve their inner- and outer-polymer compartments, which meter out metformin during passage through distal regions of the intestine over periods of up to 24 hours.[144]

4 | CONTRAINDICATIONS AND CAUTIONS

The need to check renal function before and at least annually during treatment with metformin is emphasized to reduce the risk of drug accumulation, which, in turn, reduces the risk of excessively raised lactate concentrations. Checks are suggested more frequently in the elderly or individuals considered to be at risk of a rapid decline in renal function.[59,60] The eGFR is conveniently calculated by Modification of Diet in Renal Disease or Chronic Kidney Disease-Epidemiology Collaboration equations. Initiation of metformin is not encouraged in patients with an eGFR of 30-45 mL/min/1.73m^2, and metformin is contraindicated in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73m^2). In Europe, patients in whom eGFR decreases to less than 45 mL/min/1.73m^2 are recommended to receive a lower than maximal dose, preferably 1000 mg/day or less, and reassessment of risk–benefit may be appropriate.

In addition to severe renal impairment, metformin is contraindicated in any clinically significant hypoxic state, notably chronic decompensated heart failure, acute heart failure, severe respiratory insufficiency, septicaemia and other conditions with hypoperfusion or hypoxaemia. Further suggested contraindications are significant liver disease, a history of lactic acidosis, any acute metabolic acidosis, alcohol abuse or other disturbances of liver function likely to prevent normal hepatic lactate metabolism.[59,60]

It is recommended that metformin is temporarily discontinued for approximately 48 hours during and after general surgery or use of intravascular contrast media, pending the return of normal renal function. Metformin should also be discontinued for approximately 48 hours before ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomographic imaging because metformin can increase the tissue uptake of ^{18}F-FDG, especially into the intestinal wall, thus interfering with image interpretation.[145]

Although MALA is rare (0.03-0.08 per 1000 patient years), it carries a mortality risk of approximately one in five. MALA is associated mostly with acute renal injury or unstable or unrecognized chronic renal insufficiency.[31,35,146,147] As a type B (of metabolic non-hypoxic causation) lactic acidosis, MALA is treated with a primary focus on restoration of acid–base balance and may require intravenous sodium bicarbonate and fluid if dehydrated. Haemodialysis is warranted if metformin concentrations are markedly raised (e.g. overdose), and/or renal insufficiency is severe, pH is particularly low or there is liver disease, sepsis or another limiting co-morbidity.[37,39,40] It is noted that lactic acidosis can occur in patients with diabetes unrelated to metformin therapy, and respiratory (type A) causes require different approaches to treatment.

Small decreases in the absorption of vitamin B12 and folate (vitamin B9) can occur during long-term use of metformin, but are rarely a cause of anaemia. A diet deficient in dairy products may be a contributory factor, so adequate dairy and/or appropriate vitamin supplementation will usually be corrective.[34,148]

The risk of significant hypoglycaemia, which is negligible with metformin monotherapy, should be appreciated if metformin is used in combination with other glucose-lowering agents, especially sulphonylureas or insulin, and adjustments to dose and timing of administration may be needed.[59,60] Also, introduction of treatments with a hyperglycaemic effect such as corticosteroids may require dose adjustment or the addition of further glucose-lowering therapy.[52] Because metformin is eliminated via the kidney, especial care is required when initiating therapies that affect renal function, such as antihypertensive agents, diuretics and non-steroidal anti-inflammatory drugs. Raised concentrations of metformin have been observed with cimetidine, and agents that share the same transporters in the renal tubules might compete for elimination, for example, furosemide and nifedipine.[59,60]

4.1 | Fixed-dose combinations

Combinations of glucose-lowering agents with different modes of action can achieve at least a partially additive effect ($2 + 2 = 3$) and sometimes a synergistic effect ($2 + 2 = 5$), and because metformin acts through different mechanisms to other glucose-lowering agents, it is suited to combination therapy.[51,52,149–152] Guidelines recognize that two or three differently acting glucose-lowering therapies may be required to maintain glycaemic control in advanced stages of T2D, and many single-tablet FDCs are available with metformin (Table 4).[52–55] FDCs provide bioequivalence with the separate tablets, while reducing the pill burden for patients. They can also simplify the administration regimen, improve patient adherence and may achieve greater efficacy gains than observed with separate tablets.[51] It is important, however, that FDCs receive the same cautions and contraindications as the separate tablets.

4.2 | Cellular mechanisms of action

A detailed description of the multiple cellular actions of metformin is beyond the scope of the current paper, and the reader is referred to several excellent recent reviews that plot the interactions of metformin with key signalling pathways and metabolic processes.[79–81,107,153,154] These actions are individually modest, but collectively substantial (Table 5): they vary between tissues because of different levels of drug exposure (e.g. differences in drug transporter expression) and to the different metabolic factors that operate within those tissues (e.g. differences in expression of insulin receptors and glucose transporters). Some effects of metformin appear to be independent of insulin, and some are dependent on insulin, although (Section 3) the blood glucose-lowering efficacy of metformin requires a presence of insulin. When interpreting mechanistic studies, it is noted that many preclinical and in vitro studies have exposed cells to much higher concentrations of metformin than during therapeutic use, resulting in claims of pharmacological mechanisms that do not equate with normal clinical use.[155,156]

Figure 5 offers a summary of key intracellular pathways involved in the glucose-lowering effects and some of the other effects of metformin. In the intestine, very high concentrations of metformin can alter the composition of the microbiome with an increase in the relative abundance of taxonomic groups capable of increasing the production of short-chain fatty acids.[82] Very high concentrations of

TABLE 5 Effects of metformin that contribute to glucose lowering, weight stability and an improved lipid profile.

Organ	Glucose lowering	Weight controlling	Affecting lipid profile
Intestine	↑ Anaerobic glycolysis	↑ Secretion of GDF-15, GLP-1, PYY	↓ Chylomicron production
	↑ Glucose utilization	↑ Splanchnic glucose-lactate-glucose turnover	↑ Short-chain fatty acid-producing bacteria
	(altered microbiome)	↑ Lac-Phe	
Liver	↓ Gluconeogenesis		↑ Fatty acid oxidation
	↓ Glycogenolysis		↓ VLDL triglycerides
	(↓ Glucagon action)		
Muscle	↑ Insulin-mediated peripheral glucose uptake and oxidation	↑ Lac-Phe during exercise	↑ Fatty acid oxidation
	↑ Glycogenesis		
Adipose	↑ Insulin-mediated peripheral glucose uptake and oxidation	↑ Fatty acid oxidation	↑ Uptake of fatty acids
		↓ Lipogenesis	↑ Fatty acid oxidation
		↑ Mitochondrial uncoupling (e.g. UCP-1)	

Abbreviations: ↑, increase; ↓, decrease; GDF-15, growth differentiation factor-15; GLP-1, glucagon-like peptide-1; Lac-Phe, *N*-lactoyl phenylalanine; PYY, peptide tyrosine tyrosine; UCP-1, uncoupling protein-1; VLDL, very-low-density lipoprotein.

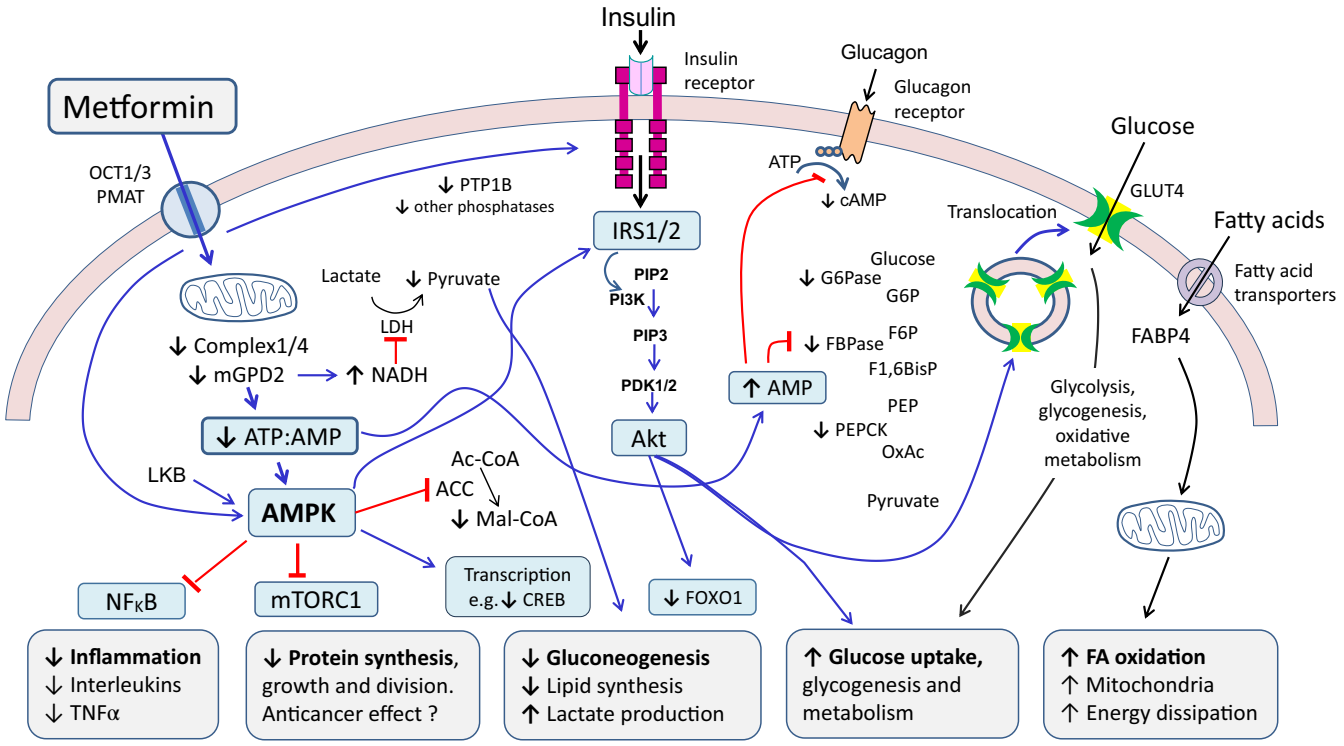

FIGURE 5 Summary of key cellular pathways involved in the glucose-lowering effects of metformin. Arrows indicate a positive effect; red bars indicate a negative effect. In intestinal enterocytes, very high metformin concentrations increase anaerobic glucose metabolism, principally via reduced activity of the mitochondrial respiratory chain. In liver, lesser concentrations of metformin reduce glucose production, principally gluconeogenesis, via AMPK-mediated mechanisms and accentuation of insulin signalling pathways. In muscle and adipose tissue, lower metformin concentrations increase insulin-stimulated glucose uptake and metabolism, with increased energy expenditure in adipose tissue associated with increased UCP-1 activity.[79,107,153–162] High concentrations of metformin exert an inhibitory effect on the mitochondrial respiratory chain at complex 1, decreasing cytosolic ATP and raising AMP, which activates AMPK. Lesser metformin concentrations can also reduce ATP synthesis by an inhibitory effect at complex 4. This restricts electron transfer and a backlog at complex 2/3 reduces the activity of mGPD, which impedes the glycerophosphate shuttle. The resulting increase in cytosolic redox state interrupts lactate conversion to pyruvate. Metformin can also activate AMPK directly, and increased AMPK modulates the activity of transcription factors (e.g. cAMP response element-binding protein [CREB]), controlling the expression of key gluconeogenic enzymes (PEPCK and G6Pase) and the activities of other enzymes involved in gluconeogenesis and lipid metabolism (e.g. ACC). Raised AMP directly reduces the activity of FBPase and reduces adenylate cyclase activity, which impairs glucagon signalling. Beyond nutrient metabolism, AMPK inhibits mTORC1, offering a potential mechanism for reduced cell growth and division, as well as inhibiting signalling of NF-κB, which then reduces the expression of several pro-inflammatory molecules. Metformin may improve insulin sensitivity by inhibiting phosphotyrosine phosphatases (e.g. PTP1B) that normally curtail activation of the insulin receptor, and inhibiting inositol phosphatases affecting nutrient metabolism. In peripheral tissues, insulin-stimulated glucose uptake is enhanced through increased translocation of GLUT4 glucose transporters into the plasma membrane. Increased fatty acid oxidation, mitochondrial biogenesis and uncoupling have also been observed. Effects of metformin on other cellular functions (e.g. affecting the endoplasmic reticulum and oxidative stress) are beyond the detail captured in this illustration.[79,107,153–162] ↑, increase; ↓, decrease; Ac-CoA, acetyl-coenzyme-A; ACC, acetyl-CoA carboxylase; Akt, protein kinase B (PKB); AMP, adenosine monophosphate; AMPK, 5′ AMP-activated protein kinase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CREB, cyclic adenosine monophosphate response element-binding protein; FA, fatty acid; FABP4, fatty acid binding protein-4; F6P, fructose 6-phosphate; FBPase, fructose-1,6-bisphosphatase; F1,6BisP, fructose 1,6-bisphosphate; FOXO1, forkhead box protein O1A; G6Pase, glucose-6-phosphatase; GLUT, glucose transporter isoform; IRS, insulin receptor substrate; LDH, lactate dehydrogenase; LKB1, serine/threonine–protein kinase STK11; Mal-CoA, malonyl-CoA; mGPD, mitochondrial glycerol-3-phosphate dehydrogenase; mTORC1, mammalian target of rapamycin complex-1; NADH, reduced nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa-B; OCT, organic cation transporter; OxAc, oxalacetate; PDK, 3-phosphoinositide-dependent protein kinase; PEP, phosphoenolpyruvate; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol-3,4-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PMAT, plasma membrane monoamine transporter; PTP1B, protein tyrosine phosphatase 1B; TNFα, tumour necrosis factor alpha; UCP-1, uncoupling protein-1.

metformin in enterocytes can suppress the mitochondrial respiratory chain, favouring anaerobic glucose metabolism and lactate production.[101,102] Interruptions of the mitochondrial respiratory chain by metformin decrease ATP production, which decreases the cytosolic ATP:AMP ratio and activates AMP-activated protein kinase (AMPK). Metformin may also interact directly with AMPK, and increased activity of AMPK in enterocytes has been implicated in the increased secretion of GLP-1, PYY and GDF-15, as well as triggering a vago-

vagal pathway to suppress hepatic glucose production.[82] AMPK exerts an inhibitory effect on the mammalian target of rapamycin (mTOR), providing a potential mechanism for reduced cell growth and division that could facilitate possible anticancer effects of metformin.

Lesser concentrations of metformin in the liver reduce the impact of mitochondrial actions and AMPK-mediated mechanisms and introduce interactions with insulin signalling pathways. Thus, although AMPK-mediated reductions in gluconeogenesis have been shown in many studies, therapeutically relevant metformin concentrations can also accentuate the antigluconeogenic effect of physiological concentrations of insulin with minimal changes in cytosolic ATP.[80,81,107,157] By contrast, increased fatty acid oxidation and reduced lipogenesis observed with metformin in liver and peripheral tissues appear to be independent of insulin and mediated at least in part via AMPK.[79,81,107,158]

In muscle, metformin concentrations are lower than in liver, but sufficient to act, in part, via AMPK, and by increased postreceptor insulin signalling to modestly increase insulin-stimulated glucose uptake, glycogenesis and aerobic glucose metabolism.[81,107,159] Low metformin concentrations in adipose tissue have also been reported to increase insulin-stimulated glucose uptake and to act via AMPK to increase mitochondrial biogenesis and to increase the activity of UCP-1, indicating a route to increase thermogenesis and energy expenditure.[81,160–162]

5 | FURTHER THERAPEUTIC PROSPECTS

Preclinical studies and off-label clinical use have identified potential additional therapeutic applications for metformin. Off-label use of metformin underpinned its evaluation in gestational diabetes, and there are anecdotal accounts of potential value in several non-diabetic insulin-resistant and/or hyperinsulinaemic conditions.[115,163] For example, metformin has provided clinical benefit in PCOS by reduced hirsutism and acne, improving menstrual cyclicity and supporting conception and the maintenance of pregnancy.[164–166] Metformin has also helped in the treatment of lipodystrophy in human immunodeficiency virus and to offset the hyperglycaemic effects of glucocorticoid therapy and some cancer chemotherapies.[167–169] Reductions in markers of chronic inflammation and reduced inflammatory responses to viral infections have been noted during metformin therapy independent of metabolic status: indeed, decreased susceptibility to SARS-CoV-2 (COVID-19) infection and its postacute symptoms have been reported with metformin.[15,170–173]

Optimistic anticipation surrounds evidence that metformin might reduce the incidence and mortality rates of certain cancers, and many trials (currently 437 randomized trials registered with ClinicalTrials.gov) are ongoing to investigate this more thoroughly and prospectively.[174–176] The association of metformin with reductions in fatty liver, vascular dementia, Alzheimer's and Parkinson's diseases, and possibly atrial fibrillation is also now under scrutiny, and intriguing evidence from animal studies suggests that metformin can increase the average (but not the maximum) lifespan and slow the onset of several features of the ageing process.[177–181] Extensive preclinical studies and observational clinical data provide encouraging support for further detailed investigation of possible therapeutic repurposing for metformin, particularly considering its much lower cost compared with current treatments for some of the conditions listed above.

6 | CONCLUSION

A wealth of clinical experience generated over more than 60 years corroborates the early introduction and continued use of metformin to support lifestyle interventions in the management of T2D. By countering insulin resistance through a diverse portfolio of cellular actions, metformin affords glucose-lowering efficacy without weight gain or risk of overt hypoglycaemia, and offers long-term CV protective effects. The broad therapeutic utility, safety profile and comparative cost-effectiveness of metformin prompted the World Health Organization in 2011 to add this agent to the list of essential medicines, and has encouraged ongoing evaluation of potential indications beyond diabetes.[182] With appropriate checks for contraindications, especially renal function, and dose titration aligned with meals, metformin provides a unique, effective and durable medicine with favourable safety credentials to address the varied and progressive pathophysiology of T2D.

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The author declares no conflict of interest.

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Data sharing not applicable and no new data generated.

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REFERENCES

1. Hill J. *The vegetable system, or the internal structure and the life of plants*. Vol XXI; 1772:54.
2. Bailey CJ, Day C. Metformin: its botanical background. *Pract Diabetes Int*. 2004;21:115-117.
3. Hadden DR. Goat's rue – French lilac – Italian fitch – Spanish sainfoin: gallega officinalis and metformin: The Edinburgh connection. *J R Coll Physicians Edinb*. 2005;35:258-260.
4. Bailey CJ. Metformin: historical overview. *Diabetologia*. 2017;60:1566-1576.
5. Strecker A. Untersuchungen über die chemischen Beziehungen zwischen Guanin, Xanthin, Theobromin. *Caffeïn und Kreatinin Liebigs Ann Chem*. 1861;118:151-177.
6. Watanabe CK. Studies in the metabolic changes induced by administration of guanidine bases. Influence of injected guanidine hydrochloride upon blood sugar content. *J Biol Chem*. 1918;33:253-265.

7. Frank E, Nothmann M, Wagner A. Über synthetisch dargestellte Korper mit Insulinartiger Wirkung auf den normallen und diabetischen Organismus. *Klin Wchnschr*. 1926;5:2100-2107.
8. Sterne J. Pharmacology and mode of action of the hypoglycemic guanidine derivatives. In: Campbell GD, ed. *Oral Hypoglycemic Agents*. Academic Press; 1969:193-245.
9. Rathke B. Uber Biguanid. *Berichte Deutschen Chemischen Gesellschaft*. 1879;12:776-784.
10. Beckmann R. Biguanide (Experimenteller Teil). *Handb Exp Pharmacol*. 1971;29:439-596.
11. Wiernsperger NF. Preclinical pharmacology of biguanides. *Handb Exp Pharmacol*. 1996;119:305-358.
12. Werner E, Bell J. The preparation of methylguanidine, and of ββ-dimethylguanidine by the interaction of dicyandiamide, and methylammonium and dimethylammonium chlorides respectively. *J Chem Soc Trans*. 1922;121:1790-1795.
13. Hesse G, Taubmann G. Die Wirkung des Biguanids und seiner Derivate auf den Zuckerstoffwechsel. *Arch Exp Path Pharmacol*. 1929; 142:290-308.
14. Slotta KH, Tschesche R. Uber Biguanide. Die blutzuckersenkende Wirkung der Biguanides. *Berichte Deutschen Chemischen Gesellschaft*. 1929;62:1398-1405.
15. Garcia EY. Flumamine, a new synthetic analgesic and anti-flu drug. *J Philipp Med Assoc*. 1950;26:287-293.
16. Pasik C, ed. *Glucophage 1957–1997: serving diabetology for 40 years*. Groupe Lipha; 1997:79.
17. Sterne J. Du nouveau dans les antidiabetiques. La NN dimetylamine guanyl guanidine (N.N.D.G.). *Maroc Med*. 1957;36:1295-1296.
18. Sterne J. Blood sugar-lowering effect of 1,1-dimethylbiguanide. *Therapie*. 1958;13:650-659.
19. Sterne J. Treatment of diabetes mellitus with N,N-dimethylguanylguanidine (LA. 6023, glucophage). *Therapie*. 1959;14:625-630.
20. Sterne J. Report on 5-years' experience with dimethyl biguanide (metformin, glucophage) in diabetic therapy. *Wien Med Wochenschr*. 1963;113:599-602.
21. Sterne J, Hirsch C. Experimental basis for combined treatment of diabetes with the biguanide-sulfonamide association. *Diabete*. 1964; 12:171-175.
22. Sterne J. Mechanism of action of antidiabetic biguanides. *Presse Med*. 1964;19:563-569.
23. Ungar G, Freedman L, Shapiro SL. Pharmacological studies of a new hypoglycaemic drug. *Proc Soc Exp Biol Med*. 1957;95:190-192.
24. Beringer A. Zur Behandlung der Zuckerkrankheit mit Biguaniden. *Wien Med Wschr*. 1958;108:880-882.
25. Bailey CJ. The origins of type 2 diabetes medications. *Br J Diabetes*. 2022;22:112-120.
26. Schafer G. Biguanides: a review of history, pharmacodynamics and therapy. *Diab Metab*. 1983;9:148-163.
27. Clarke BF, Duncan LJP. Comparison of chlorpropamide and metformin treatment on weight and blood glucose response of uncontrolled obese diabetics. *Lancet*. 1968;1:123-126.
28. Clarke B, Campbell IW. Comparison of metformin and chlorpropamide in non-obese maturity-onset diabetic uncontrolled on diet. *Br Med J*. 1977;275:1576-1578.
29. Hermann LS. Metformin: a review of its pharmacological properties and therapeutic use. *Diab Metab*. 1979;5:233-245.
30. Campbell IW, Howlett HC. Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. *Diabetes Metab Rev*. 1995;11(S1):S57-S62.
31. Bailey CJ. Biguanides and NIDDM. *Diabetes Care*. 1992;15:755-772.
32. University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. V. Evaluation of phenformin therapy. *Diabetes*. 1975;24(suppl 1):65-184.
33. Nattrass M, Alberti KGMM. Biguanides. *Diabetologia*. 1978;14: 71-74.
34. Bailey CJ, Turner RC. Metformin. *N Engl Med*. 1996;334:574-579.
35. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA*. 2014;312:2668-2675.
36. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care*. 2014; 37(8):2218-2224.
37. Lalau JD, Kajbaf F, Protti A, Christensen MM, de Broe ME, Wiernsperger N. Metformin-associated lactic acidosis (MALA): moving towards a new paradigm. *Diabetes Obes Metab*. 2017;19(11): 1502-1512.
38. Bosisio E, Kienle MG, Galli G, et al. Defective hydroxylation of phenformin as a determinant of drug toxicity. *Diabetes*. 1981;30: 644-649.
39. Lalau JD. Lactic acidosis induced by metformin: incidence, management and prevention. *Drug Saf*. 2010;33:727-740.
40. DeFronzo RA, Fleming GA, Chenc K, Bicsakc TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. *Metabolism*. 2016;65:20-29.
41. Howlett HCS, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Saf*. 1999;20:489-503.
42. Wiernsperger NF, Bailey CJ. The antihyperglycaemic effect of metformin: therapeutic and cellular mechanisms. *Drugs*. 1999;58(suppl 1):31-39.
43. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. *Nat Rev Dis Primers*. 2015;1(1):15019.
44. Bailey CJ. Insulin resistance: Impact on therapeutic developments in diabetes. *Diabetes Vasc Dis Res*. 2019;16(2):128-132.
45. Bailey CJ, Campbell IW, Chan JCN, et al., eds. *Metformin, the Gold Standard. A Scientific Handbook*. Wiley; 2007:288.
46. Campbell IW, Howlett HCS, Holman RR, Bailey CJ, eds. *Metformin; 60 Years of Clinical Experience*. Wiley; 2017:122.
47. Jeppesen J, Zhou M-Y, Chen Y-D, Reaven GM. Effect of metformin on postprandial lipemia in patients with fairly to poorly controlled NIDDM. *Diabetes Care*. 1994;17:1093-1099.
48. DeFronzo RA, Goodman AM, Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;333:541-549.
49. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352: 854-865.
50. Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets—results of a retrospective cohort study. *Curr Med Res Opin*. 2004;20:565-572.
51. Bailey CJ, Day C. Fixed-dose single tablet antidiabetic combinations. *Diabetes Obes Metab*. 2009;11:527-533.
52. Bailey CJ. Metformin. In: Umpierrez GE, ed. *Therapy for Diabetes Mellitus and Related Disorders*. 6th ed. American Diabetes Association; 2014:341-358.
53. Davies MJ, Aroda VR, Collins BS, et al. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2022;2022(65): 1925-1966.
54. Samson SL, Vellanki P, Blonde L, et al. American association of clinical endocrinology consensus statement: comprehensive type 2 diabetes management algorithm–2023 update. *Endocr Pract*. 2023;29: 305-340.
55. American Diabetes Association. Standards of care in diabetes–2024. *Diabetes Care*. 2024;47(Suppl 1):S1-S321.

56. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577-1589.
57. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
58. Hostalek U, Gwilt M, Hildemann S. Therapeutic use of metformin in prediabetes and diabetes prevention. *Drugs*. 2015;75:1071-1094.
59. Metformin, Electronic Medicines Compendium. Glucophage SR 500 mg prolonged release tablets. https://www.medicines.org.uk/emc/product/6298/smpc#gref
60. GLUCOPHAGE (metformin hydrochloride) Tablets. Access data, FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020357s037s039,021202s021s023lbl.pdf
61. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008;358:2003-2015.
62. Brand KMG, Saarelainen L, Sonajalg J, et al. Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study. *BMJ Open Diabetes Res Care*. 2022;10:e002363.
63. Dunne F, Newman C, Alvarez-Iglesias A, et al. Early metformin in gestational diabetes a randomized clinical trial. *JAMA*. 2023;330:1547-1556.
64. Tarasova L, Kalnina I, Geldnere K, et al. Association of genetic variation in the organic cation transporters OCT1, OCT2 and multidrug and toxin extrusion 1 transporter protein genes with the gastrointestinal side effects and lower BMI in metformin-treated type 2 diabetes patients. *Pharm Genom*. 2012;22:659-666.
65. Liang X, Giacomini KM. Transporters involved in metformin pharmacokinetics and treatment response. *J Pharm Sci*. 2017;106:2245-2250.
66. Samodelov SL, Kullak-Ublick GA, Gai Z, Visentin M. Organic cation transporters in human physiology, pharmacology, and toxicology. *Int J Mol Sci*. 2020;21(21):7890.
67. Scheen AJ. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet*. 1996;30(5):359-371.
68. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet*. 2011;50(2):81-98.
69. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA*. 2016;16:313-324.
70. Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. *Ann Intern Med*. 2020;173:278-286.
71. Solymár M, Ivic I, Pótó L, et al. Metformin induces significant reduction of body weight, total cholesterol and LDL levels in the elderly–a meta-analysis. *PLoS One*. 2018;13(11):e0207947.
72. Gillani SW, Ghayedi N, Roosta P. Effect of metformin on lipid profiles of type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *J Pharm Bioallied Sci*. 2021;13:76-82.
73. Schernthaner G, Brand K, Bailey CJ. Metformin and the heart: update on mechanisms of cardiovascular protection with special reference to comorbid type 2 diabetes and heart failure. *Metabolism*. 2022;130:155160.
74. Yki-Järvinen H, Nikkilä RK, Tulokas T, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1999;130(5):389-396.
75. Hemmingsen B, Lund SS, Wetterslev J, Vaag A. Oral hypoglycaemic agents, insulin resistance and cardiovascular disease in patients with type 2 diabetes. *Eur J Endocrinol*. 2009;161:1-9.
76. Bailey CJ. Insulin plus metformin for T2DM—are there benefits? *Nat Rev Endocrinol*. 2013;8:449-450.
77. Aroda VR, Knowler WC, Crandall JP, et al. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. *Diabetologia*. 2017;60:1601-1611.
78. Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. *Diabetes Rev*. 1998;6:89-131.
79. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia*. 2017;60(9):1577-1585.
80. LaMoia TE, Shulman GI. Cellular and molecular mechanisms of metformin action. *Endocr Rev*. 2021;42(1):77-96.
81. Foretz M, Guigas B, Viollet B. Metformin: update on mechanisms of action and repurposing potential. *Nat Rev Endocrinol*. 2023;19:460-476.
82. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. *Diabetologia*. 2016;59(3):426-435.
83. Herman R, Kravos NA, Jensterle M, Janež A, Dolžan V. Metformin and insulin resistance: a review of the underlying mechanisms behind changes in GLUT4-mediated glucose transport. *Int J Mol Sci*. 2022;23(3):1264.
84. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med*. 1997;103:491-497.
85. Johansen K. Efficacy of metformin in the treatment of NIDDM. Meta-analysis. *Diabetes Care*. 1999;22(1):33-37.
86. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355:2427-2443.
87. Aroda VR, Ratner RE. Metformin and type 2 diabetes prevention. *Diabetes Spectr*. 2018;31(4):336-342.
88. Goldberg RB, Orchard TJ, Crandall JP, et al. Effects of long-term metformin and lifestyle interventions on cardiovascular events in the Diabetes Prevention Program and its outcome study. *Circulation*. 2022;145:1632-1641.
89. Zhang L, Zhang Y, Shen S, et al. Safety and effectiveness of metformin plus lifestyle intervention compared with lifestyle intervention alone in preventing progression to diabetes in a Chinese population with impaired glucose regulation: a multicentre, open-label, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2023;11:567-577.
90. Bailey CJ. Metformin: effects on micro and macrovascular complications in type 2 diabetes. *Cardiovasc Drugs Ther*. 2008;22:215-224.
91. Eisenreich A, Leppert U. Update on the protective renal effects of metformin in diabetic nephropathy. *Curr Med Chem*. 2017;24:3397-3412.
92. Li Y, Ryu C, Munie M, et al. Association of metformin treatment with reduced severity of diabetic retinopathy in type 2 diabetic patients. *J Diabetes Res*. 2018;2018:2801450.
93. Gormsen LC, Søndergaard E, Christensen NL, Brøsen K, Jessen N, Nielsen S. Metformin increases endogenous glucose production in non-diabetic individuals and individuals with recent-onset type 2 diabetes. *Diabetologia*. 2019;62(7):1251-1256.
94. Jackson RA, Hawa MI, Jaspan JB, et al. Mechanism of metformin action in non-insulin-dependent diabetes. *Diabetes*. 1987;36:632-640.
95. Coll AP, Chen M, Taskar P, et al. GDF15 mediates the effects of metformin on body weight and energy balance. *Nature*. 2020;578:444-448.
96. Ouyang J, Isnard S, Lin J, et al. GDF-15 as a weight watcher for diabetic and non-diabetic people treated with metformin. *Front Endocrinol*. 2020;11:581839.
97. Mannucci E, Ognibene A, Cremasco F, et al. Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. *Diabetes Care*. 2001;24(3):489-494.
98. Napolitano A, Miller S, Nicholls AW, et al. Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus. *PLoS One*. 2014;9(7):e100778.

99. Bahne E, Sun EWL, Young RL, et al. Metformin-induced glucagon-like peptide-1 secretion contributes to the actions of metformin in type 2 diabetes. *JCI Insight*. 2018;3(23):e93936.
100. Scott B, Day EA, O'Brien KL, et al. Metformin and feeding increase levels of the appetite-suppressing metabolite Lac-Phe in humans. *Nat Metab*. 2024;6(4):651-658. doi:10.1038/s42255-024-01018-7
101. Bailey CJ, Wilcock C, Day C. Effect of metformin on glucose metabolism in the splanchnic bed. *Br J Pharmacol*. 1992;105:1009-1013.
102. Bailey CJ, Mynett KJ, Page T. Importance of the intestine as a site of metformin-stimulated glucose utilization. *Br J Pharmacol*. 1994;112:671-675.
103. Karise I, Bargut TC, del Sol M. Metformin enhances mitochondrial biogenesis and thermogenesis in brown adipocytes of mice. *Biomed Pharmacother*. 2019;111:1156-1165.
104. Sirtori CR, Tremoli E, Sirtori M, Conti F, Paoletti R. Treatment of hypertriglyceridemia with metformin: effectiveness and analysis of results. *Atherosclerosis*. 1977;26:583-592.
105. Xu T, Brandmaier S, Messias AC. Effects of metformin on metabolite profiles and LDL cholesterol in patients with type 2 diabetes. *Diabetes Care*. 2015;38(10):1858-1867.
106. Tokubuchi I, Tajiri Y, Iwata S, et al. Beneficial effects of metformin on energy metabolism and visceral fat volume through a possible mechanism of fatty acid oxidation in human subjects and rats. *PLoS One*. 2017;12(2):e0171293.
107. He L. Metformin and systemic metabolism. *Trends Pharmacol Sci*. 2020;41(11):868-881.
108. Green CJ, Marjot T, Walsby-Tickle J, et al. Metformin maintains intrahepatic triglyceride content through increased hepatic de novo lipogenesis. *Eur J Endocrinol*. 2022;186:367-377.
109. van Stee MF, de Graaf AA, Groen AK. Actions of metformin and statins on lipid and glucose metabolism and possible benefit of combination therapy. *Cardiovasc Diabetol*. 2018;17:94.
110. Kamenova P. Therapeutic potential of metformin in normal glucose tolerant persons with metabolic syndrome. *Biotechnol Biotechnological Equip*. 2020;34:30-37.
111. Bailey CJ. Treating insulin resistance: future prospects. *Diabetes Vasc Dis Res*. 2007;4:20-31.
112. Zabielski P, Chacinska M, Charkiewicz K. Effect of metformin on bioactive lipid metabolism in insulin-resistant muscle. *J Endocrinol*. 2017;233:329-340.
113. Carter D, Howlett HC, Wiernsperger NF, Bailey CJ. Differential effects of metformin on bile salt absorption from the jejunum and ileum. *Diabetes Obes Metab*. 2003;5(2):120-125.
114. Wiernsperger NF. Review: 50 years later: is metformin a vascular drug with antidiabetic properties? *Br J Diabetes Vasc*. 2007;7(5):204-210.
115. Triggle CR, Marei I, Ye K, et al. Repurposing metformin for vascular disease. *Curr Med Chem*. 2023;30(35):3955-3978.
116. UKPDS perspective, legacy effects and 44-year follow-up data. Session: S22, UKPDS 44-Year Follow-up Symposium, European Association for the Study of Diabetes. 2022 https://www.easd.org/media-centre/#!resources/ukpds-perspective-legacy-effects-and-44-year-follow-up-data Accessed 20 March 2024.
117. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care*. 2013;36:1304-1311.
118. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2009;169:616-625.
119. Monami M, Candido R, Pintaudi B, et al. Effect of metformin on all cause mortality and major adverse cardiovascular events: an updated meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2021;31:699-704.
120. Chen C, Yuan S, Zhao X, et al. Metformin protects cardiovascular health in people with diabetes. *Front Cardiovasc Med*. 2022;9:949113.
121. Zhang K, Yang W, Dai H, Deng Z. Cardiovascular risk following metformin treatment in patients with type 2 diabetes mellitus: results from meta-analysis. *Diabetes Res Clin Pract*. 2020;160:108001.
122. Han Y, Xie H, Liu Y, Gao P, Yang X, Shen Z. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. *Cardiovasc Diabetol*. 2019;18:96.
123. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia*. 2017;60:1620-1629.
124. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. *Circ Heart Fail*. 2013;6:395-402.
125. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. *Ann Intern Med*. 2017;166:191-200.
126. Tseng CH. Metformin use is associated with a lower risk of hospitalization for heart failure in patients with type 2 diabetes mellitus: a retrospective cohort analysis. *JAHA*. 2019;8:e011640.
127. Li JZ, Li YR. Cardiovascular protection by metformin: latest advances in basic and clinical research. *Cardiology*. 2023;148(4):374-384.
128. Nesti L, Natali A. Metformin effects on the heart and the cardiovascular system: a review of experimental and clinical data. *Nutr Metab Cardiovasc Dis*. 2017;27:657-669.
129. Salvatore T, Galiero R, Caturano A, et al. Effects of metformin in heart failure: from pathophysiological rationale to clinical evidence. *Biomolecules*. 2021;11(12):1834.
130. Ding Y, Zhou Y, Ling P, et al. Metformin in cardiovascular diabetology: a focused review of its impact on endothelial function. *Theranostics*. 2021;11:9376-9396.
131. Petrie JR, Rossing PR, Campbell IW. Metformin and cardiorenal outcomes in diabetes: a reappraisal. *Diabetes Obes Metab*. 2020;22:904-915.
132. Kheniser KG, Kashyap SR, Kasumov T. A systematic review: the appraisal of the effects of metformin on lipoprotein modification and function. *Obesity Sci Pract*. 2019;5:36-45.
133. Kim HS, Ren G, Kim T, et al. Metformin reduces saturated fatty acid-induced lipid accumulation and inflammatory response by restoration of autophagic flux in endothelial cells. *Scientific Reps*. 2020;10:13523.
134. Nafisa A, Gray SG, Cao Y. Endothelial function and dysfunction: impact of metformin. *Pharmacol Therap*. 2018;192:150-162.
135. Mather K, Verma S, Anderson T. Improved endothelial function with metformin in type 2 diabetes mellitus. *J Am Coll Cardiol*. 2001;37:1344-1350.
136. Agarwal N, Rice SPL, Bolusani H, et al. Metformin reduces arterial stiffness and improves endothelial function in young women with polycystic ovary syndrome: a randomized, placebo-controlled, crossover trial. *J Clin Endocrinol Metab*. 2010;95:722-730.
137. Grant PJ. Beneficial effects of metformin on haemostasis and vascular function in man. *Diabetes Metab*. 2003;29(6S):44-52.
138. Bailey CJ, Day C. The future of new drugs for diabetes management. *Diabetes Res Clin Pract*. 2019;155:107785.
139. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9:653-662.
140. Staplin N, Roddick AJ, Emberson J. Net effects of sodium-glucose co-transporter-2 inhibition in different patient groups: a meta-

analysis of large placebo-controlled randomized trials. *eClin Med*. 2021;41:101163.
141. Cosentino F, Grant PJ, Aboyans V, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2019;41(2):255-323.
142. Derosa G, D'Angelo A, Romano D, Maffioli P. Effects of metformin extended release compared to immediate release formula on glycemic control and glycemic variability in patients with type 2 diabetes. *Drug Des Devel Ther*. 2017;11:1481-1488.
143. Aggarwal N, Singla A, Mathieu C, et al. Metformin extended-release versus immediate-release: An international, randomized, double-blind, head-to-head trial in pharmacotherapy-naïve patients with type 2 diabetes. *Diabetes Obes Metab*. 2018;20:463-467.
144. Timmins P, Donahue S, Meeker J, Marathe P. Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clin Pharmacokinet*. 2005;44:721-729.
145. Zhang X, Ogihara T, Zhu M, et al. Effect of metformin on 18F-fluorodeoxyglucose uptake and positron emission tomographic imaging. *Br J Radiol*. 2022;95(1130):20200810.
146. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care*. 2011;34(6):1431-1437.
147. Brand KMG, Schlachter J, Foch C, Boutmy E. Quality and characteristics of 4241 case reports of lactic acidosis in metformin users reported to a large pharmacovigilance database. *Ther Clin Risk Manag*. 2022;18:1037-1047.
148. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: an association to bear in mind. *World J Diabetes*. 2021;12(7):916-931.
149. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2016;164:740-751.
150. Cai X, Gao X, Yang W, Han X, Ji L. Efficacy and safety of initial combination therapy in treatment-naïve type 2 diabetes patients: a systematic review and meta-analysis. *Diabetes Ther*. 2018;9(5):1995-2014.
151. Khan RA, Patel N, Folajimi A, et al. Comparison of the efficacy and safety of metformin-based combination therapy versus metformin alone in children and adolescents with type 2 diabetes mellitus: a meta-analysis. *Cureus*. 2023;15(2):e35014.
152. Hung WT, Chen YJ, Cheng CY, et al. Metformin plus a low hypoglycemic risk antidiabetic drug vs. metformin monotherapy for untreated type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract*. 2022;189:109937.
153. Agius L, Ford BE, Chachra SS. The metformin mechanism on gluconeogenesis and AMPK activation: the metabolite perspective. *Int J Mol Sci*. 2020;21(9):3240.
154. Kaneto H, Kimura T, Obata A, Shimoda M, Kaku K. Multifaceted mechanisms of action of metformin which have been unraveled one after another in the long history. *Int J Mol Sci*. 2021;22:2596.
155. He L, Wondisford FE. Metformin action: concentrations matter. *Cell Metab*. 2015;21(2):159-162.
156. Wilcock C, Bailey CJ. Accumulation of metformin by tissues of the normal and diabetic mouse. *Xenobiotica*. 1994;24(1):49-57.
157. Wollen N, Bailey CJ. Inhibition of hepatic gluconeogenesis by metformin: synergism with insulin. *Biochem Pharmacol*. 1988;37(22):4353-4358.
158. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest*. 2001;108(8):1167-1174.
159. Bailey CJ, Puah JA. Effect of metformin on glucose metabolism in mouse soleus muscle. *Diabete Metab*. 1986;12(4):212-218.
160. Matthaei S, Hamann A, Klein HH, et al. Association of metformin's effect to increase insulin-stimulated glucose transport with potentiation of insulin-induced translocation of glucose transporters from intracellular pool to plasma membrane in rat adipocytes. *Diabetes*. 1991;40(7):850-857.
161. Szymczak-Pajor I, Wenclewska S, Śliwińska A. Metabolic action of metformin. *Pharmaceuticals (Basel)*. 2022;15(7):810.
162. Ziqubu K, Mazibuko-Mbeje SE, Mthembu SXH, et al. Anti-obesity effects of metformin: a scoping review evaluating the feasibility of brown adipose tissue as a therapeutic target. *Int J Mol Sci*. 2023;24(3):2227.
163. Dutta S, Shah RB, Singhal S, et al. Metformin: a review of potential mechanism and therapeutic utility beyond diabetes. *Drug Des Devel Ther*. 2023;17:1907-1932.
164. Sam S, Ehrmann DA. Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome. *Diabetologia*. 2017;60:1656-1661.
165. Shpakov AO. Improvement effect of metformin on female and male reproduction in endocrine pathologies and its mechanisms. *Pharmaceuticals (Basel)*. 2021;14:42.
166. Attia GM, Almouteri MM, Alnakhli FT. Role of metformin in polycystic ovary syndrome (PCOS)-related infertility. *Cureus*. 2023;15(8):e44493.
167. Hadigan C, Rabe J, Grinspoon S. Sustained benefits of metformin therapy on markers of cardiovascular risk in human immunodeficiency virus-infected patients with fat redistribution and insulin resistance. *J Clin Endocrinol Metab*. 2002;87:4611-4615.
168. Landis D, Sutter A, Fernandez F, Nugent K. The effect of metformin on glucose metabolism in patients receiving glucocorticoids. *Am J Med Sci*. 2022;364:379-385.
169. Saraei P, Asadi I, Kakar MA, Moradi-Kor N. The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances. *Cancer Manag Res*. 2019;11:3295-3313.
170. Cameron AR, Morrison VL, Levin D, et al. Anti-Inflammatory effects of metformin irrespective of diabetes status. *Circ Res*. 2016;119:652-665.
171. Bharath LP, Nikolajczyk BS. The intersection of metformin and inflammation. *Am J Physiol Cell Physiol*. 2021;320:C873-C879.
172. Bailey CJ, Gwilt M. Diabetes, metformin and the clinical course of covid-19: outcomes, mechanisms and suggestions on the therapeutic use of metformin. *Front Pharmacol*. 2022;13:784459.
173. Bramante CT, Buse JB, Liebovitz DM, et al. Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. *Lancet Infect Dis*. 2023;23:1119-1129.
174. Heckman-Stoddard BM, DeCensi A, Sahasrabuddhe VV, Ford LG. Repurposing metformin for the prevention of cancer and cancer recurrence. *Diabetologia*. 2017;60(9):1639-1647.
175. Hua Y, Zheng Y, Yao Y, Jia R, Ge S, Zhuang A. Metformin and cancer hallmarks: shedding new lights on therapeutic repurposing. *J Transl Med*. 2023;21:403.
176. O'connor L, Bailey-Whyte M, Bhattacharya M, et al. Association of metformin use and cancer incidence: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2024;30:djae021.
177. Agostini F, Masato A, Bubacco L, Bisaglia M. Metformin repurposing for Parkinson disease therapy: opportunities and challenges. *Int J Mol Sci*. 2021;23(1):398.
178. Zheng B, Su B, Ahmadi-Abhari S, et al. Dementia risk in patients with type 2 diabetes: comparing metformin with no pharmacological treatment. *Alzheimers Dementia*. 2023;19:5681-5689.
179. Tahmi M, Luchsinger JA. Metformin in the prevention of Alzheimer's disease and Alzheimer's disease related dementias. *J Prev Alzheimers Dis*. 2023;10:706-717.

180. Chen S, Gan D, Lin S, et al. Metformin in aging and aging-related diseases: clinical applications and relevant mechanisms. *Theranostics*. 2022;12(6):2722-2740.
181. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. *Cell Metab*. 2020;32:15-30.
182. World Health Organization Model List of Essential Medicines-23rd List. 2023 https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

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