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Metformin beyond type 2 diabetes: Emerging and potential new indications

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Abstract

Metformin is best known as a foundational therapy for type 2 diabetes but is also used in other contexts in clinical medicine with a number of emerging and potential indications. Many of its beneficial effects may be mediated by modest effects on weight loss and insulin sensitivity, but it has multiple other known mechanisms of action. Current clinical uses beyond type 2 diabetes include: polycystic ovarian syndrome; diabetes in pregnancy/gestational diabetes; prevention of type 2 diabetes in prediabetes; and adjunct therapy in type 1 diabetes. As metformin has been in clinical use for almost 70 years, much of the underpinning evidence for its use in these conditions is, by definition, based on trials conducted before the advent of contemporary evidence-based medicine. As a result, some of the above-established uses are 'off-label' in many regulatory territories and their use varies accordingly in different countries. Going forward, several current 'repurposing' investigational uses of metformin are also being investigated: prevention of cancer (including in Li Fraumeni syndrome), renal protection, Alzheimer's disease, metabolic dysfunction-associated steatotic liver disease and promotion of healthy ageing. Despite the longevity of metformin and its important current roles beyond type 2 diabetes in clinical medicine, it has further potential and much research is ongoing.

KEYWORDS
antidiabetic drug, glycaemic control, metformin, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Metformin (1,1-dimethylbiguanide) is a simple and inexpensive molecule that has been in therapeutic use for nearly 70 years. As discussed elsewhere in this Supplement, it is recommended in current international clinical guidelines as a first-line oral agent for glucose-lowering in type 2 diabetes.[1,2]

Metformin lowers blood glucose concentration by inhibiting hepatic glucose production (mainly gluconeogenesis), reducing glucose absorption, opposing glucagon action and enhancing whole-body insulin sensitivity. It enhances hepatic insulin sensitivity and reduces hepatocyte lipid stores by activating AMP-activated protein kinase (AMPK), a cellular energy sensor that maintains energy homeostasis by activating catabolic pathways and inhibiting anabolic pathways. This inhibits fat synthesis and activates hepatic fat oxidation by direct phosphorylation of the two isoforms of acetyl-CoA carboxylase (ACC1/ACC2). In addition to glucose-lowering, metformin is associated with modest weight reduction and reduces visceral fat loss and waist circumference, improving several metabolic risk factors.[3]

At the cellular level, metformin is concentrated in mitochondria, where it inhibits complex 1 of the respiratory chain, inhibiting ATP production, increasing the AMP/ATP ratio and (indirectly) activating AMPK.[4]

In addition, it inhibits the mitochondrial isoform of glycerophosphate dehydrogenase, contributing to its effect on gluconeogenesis by altering the NAD/NADH+ ratio.[4] Metformin is concentrated in the gut, where it promotes the production of glucagon-like peptide 1, leading to an increase in prandial insulin secretion.[5] In addition, it has recently been discovered that it increases circulating levels of growth differentiation factor 15, accounting for suppression of appetite and lowering of body weight with associated improvements in energy balance.[6] There may also be positive effects on the microbiome.[5]

A number of clinically important effects beyond glucose-lowering have also been postulated via other mechanisms, including direct and indirect effects on multiple other pathways involved in the aetiopathogenesis of diabetes complications, including inflammation, thrombosis and oxidative stress ('pleiotropic' effects).[7,8]

Metformin has an excellent long-term safety profile; however, it is associated with appreciable rates of gastrointestinal upset even when taken at meal-times (rates are lower with extended-release preparations).[3] Long-term use is associated with reduced absorption of vitamin B12, but this is currently thought to have only marginal clinical relevance in terms of the risk of clinical neuropathy.[3] Metformin is excreted unchanged by the kidneys; hence, there is a risk of accumulation when renal function is impaired (see discussion of lactic acidosis in Section 3.3). For safety, prescribing guidelines recommend dose reduction in chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) of <45 ml/min/1.72 m^2 and stopping when the eGFR is <30 ml/min/1.73 m^2.[9,10]

2 | CURRENT CLINICAL USES OF METFORMIN BEYOND TYPE 2 DIABETES

2.1 | Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a common but complex disorder affecting 10%-13% of women of reproductive age. The key features are an irregular menstrual cycle, hirsutism, hyperandrogenism and subfertility; these are often associated with metabolic features such as obesity, dysglycaemia, dyslipidaemia and insulin resistance.[11] Women with the condition are at increased risk of cardiovascular events.[12]

An influential 2003 review focusing on the role of metformin identified 13 trials that included 543 women with PCOS (diagnosed either by biochemical or ultrasound criteria). Meta-analysis showed metformin versus placebo to reduce fasting insulin concentrations, blood pressure and low-density lipoprotein cholesterol and to be effective in promoting ovulation [odds ratios 3.88 (95% confidence interval, CI: 2.25-6.69)]. In addition, the combination of metformin with clomiphene was more effective than clomiphene alone in this regard [odds ratio 4.41 (95% CI: 2.37-8.22)]. Pregnancy rates were also improved.[13]

As a result, metformin is commonly used in the management of PCOS, to the extent that many recent trials assessing the role of other anti-obesity agents in PCOS (e.g. glucagon-like peptide-1 agonists) have included metformin in the comparator arm or assessed the role of combination therapy.[14] However, a 2023 evidence-based international guideline makes a 'conditional' (as opposed to 'strong') recommendation for the use of metformin in PCOS alongside lifestyle intervention for women with a body mass index (BMI) >25 kg/m^2 for its effect on weight/adiposity and cardiometabolic features (insulin resistance, glucose and lipid profiles) of the condition; other treatments (combined oral contraceptive pill, laser hair removal) are recommended to treat androgenic features.[11]

Several systematic reviews were conducted to underpin these guidelines. One review focusing on obesity concluded that evidence for the use of anti-obesity agents (including metformin) for this indication was 'very limited,' identifying only 11 relevant trials (including a total of 996 participants with PCOS) with only four included in the meta-analysis.[15] Another review focusing on the treatment of hirsutism based on 36 relevant trials concluded that the combined oral contraceptive pill was superior to metformin for women with a BMI <25 kg/m^2, but that the evidence for this outcome in other BMI groups was of very low quality.[16] Another review focusing on lowering weight and testosterone levels with insulin sensitizers (metformin vs. PPARγ agonists) based on 13 randomized controlled trials (RCTs) involving 787 women concluded that metformin was superior to rosiglitazone and non-inferior to pioglitazone.[17] The international guideline referenced above[11] emphasizes that the quality of the evidence reviewed was in general low for all agents reviewed (not just metformin) and that evidence-practice gaps persist—a situation that reflects a more general problem in medical research into women's health.[18] Despite the above-mentioned apparently favourable cardiometabolic effects of metformin in PCOS, no trials have been conducted to date on its potential long-term effects to reduce rates of cardiovascular disease in women affected by the condition.

Despite widespread use, metformin is currently licensed for PCOS in only a few countries, but it is probable that the present situation of clinical use 'off-label' for its apparent benefits will continue in many other countries unless evidence emerges of a more effective treatment of equivalent safety for the metabolic features of PCOS.

2.2 | Gestational diabetes/type 2 diabetes in pregnancy

As metformin crosses the placenta, foetal levels are similar to maternal concentrations. Concerns regarding safety in pregnancy thus date back to the earliest days of metformin clinical use, particularly given that the foetal circulation is relatively hypoxic (potentially increasing the risk of lactic acidosis). The field of drug safety in diabetes and pregnancy is complex given that maternal hyperglycaemia is known to increase rates of congenital malformation; that is, there are risks as well as benefits from withholding therapies. Use of metformin was avoided in pregnancy in the United Kingdom and many other countries for decades, and there were few systematic data on safety.[19] However, during this time, it was used widely in this context in some other countries (including South Africa).[19]

The 2008 Metformin in Gestational Diabetes (MiG) trial was a relatively small study that changed clinical practice in many countries by providing some reassurance on the safety of metformin in pregnancy[20]: 751 women with gestational diabetes (20-33 weeks gestation) in New Zealand and Australia were randomized on an intention-to-treat basis to either metformin or usual treatment, that is, insulin therapy (of note, 46% in the metformin group required supplemental insulin). The rate of the primary outcome—a composite of neonatal hypoglycaemia (<2.6 mmol/L), respiratory distress, need for phototherapy, a 5 min Apgar score (<7) or premature birth (before 37 weeks)—was similar with metformin (32.0%) and insulin (32.2%) [relative risk 0.99 (95% CI: 0.80 to 1.23)]. Secondary outcomes, including birthweight, neonatal anthropometrics and rates of large for gestational age (>90th centile), were also equivalent between the groups. Importantly, women preferred metformin to insulin and tolerability was acceptable (discontinuation because of gastrointestinal side effects in 1.9% of women and dose reduction in 8.8%). The rates of more severe neonatal hypoglycaemia (<1.6 mmol/L) were lower in the metformin group.

The more recent EMERGE trial examined earlier use of metformin versus placebo in gestational diabetes, that is, from the time of diagnosis.[21] The trial did not meet its primary outcome (reduction in a composite outcome of insulin initiation or a fasting glucose level of ≥5.1 mmol/L or greater at 32 or 38 weeks of gestation), but secondary outcomes, including time to insulin initiation and gestational weight gain, were reduced. Moreover, allocation to metformin resulted in a lower proportion of infants weighing >4 kg with metformin (albeit with an increase in the proportion of infants weighing <2500 g or small for gestational age).

In addition to MiG and EMERGE, the clinical experience of using metformin as a component of treatment of subfertility in PCOS (see Section 2.1 above) has provided greater confidence for its use in the first trimester of pregnancy. A 2014 meta-analysis in which a total of 351 women with PCOS had metformin during pregnancy did not suggest an increase in risk of congenital anomaly [odds ratio of a major birth defect 0.86 (95% CI: 0.18, 4.08)].[22] This estimate was based on a small sample size; hence, CIs were wide. In a more recent meta-analysis, including two randomized trials and five observational studies, the odds ratio was 1.05 (95% CI: 0.50 to 2.18), that is, with somewhat narrower CIs.[23]

Several meta-analyses have since further supported the safe use of metformin in terms of the long-term outcomes of the offspring of women with gestational diabetes. The most recent at the time of writing included seven high-quality studies with a combined cohort of 14 042 children (7641 exposed during pregnancy) who were followed for up to 14 years of age.[24] Metformin was not associated with neurodevelopmental delay in infancy or at ages 3-5 years. When compared with unexposed peers, metformin use during pregnancy was not associated with altered motor or cognitive scores. However, it is not clear whether metformin exposure in utero may still affect other outcome measures: 5-10-year post-randomization follow-up data from the Norwegian PregMet clinical trial suggested that such children have a higher BMI than non-exposed children,[25] but follow-up of two randomized trials of metformin in Finland found no difference.[26]

With increasing evidence for the safety of metformin in pregnancy, a group of UK investigators investigated the hypothesis that metformin treatment (by improving insulin sensitivity) might actually be of benefit for the neonatal outcomes of pregnancies of non-diabetic obese women by reducing the incidence of high birthweight.[27] In a double-blind, placebo-controlled RCT in which 449 women were randomized to either placebo ($n = 223$) or metformin ($n = 226$), mean birthweight at delivery was almost identical between the two groups. Children born to participants in the trial are currently being followed up for further information on any longer-term effects of maternal metformin treatment on offspring (including measurements of weight, fat mass and other aspects of metabolism).

As discussed above, safety is always difficult to show definitively in this context and differences in approach continue between countries to the present day. In accordance with the extent of data on exposed pregnancies available, the licence for metformin in the United Kingdom supports 'consideration' of use of metformin during pregnancy 'if clinically needed … during and in the periconceptional phase as an addition or an alternative to insulin'.[7,8] However, the 2024 American Diabetes Association (ADA) 2024 Standards of Care explicitly state that metformin should not be used as first-line therapy for gestational diabetes, continuing to recommend insulin as the first-line therapy.[28]

Regarding women with existing type 2 diabetes before pregnancy (rather than gestational diabetes), the MiTy randomized trial (conducted in Canada and Australia) recently showed that metformin resulted in better glycaemic control, a lower insulin requirement and fewer Caesarean births compared with placebo. Similar to the EMERGE trial in gestational diabetes,[29] infants of mothers taking metformin were less likely to weigh >4 kg at birth and had reduced adiposity measures, but more infants were small for gestational age.

In many countries, a clinical consensus has emerged that prior metformin treatment should be continued in pregnancy, as discontinuation at this point would potentially result in later maternal complications associated with poor glycaemic control.[19] However, in other countries, including the United States, a switch to insulin treatment would usually be favoured (as for gestational diabetes as described above); this is mainly driven by residual concerns for the longer-term outcomes of offspring, which may only be abated by further long-term surveillance.

2.3 | Prediabetes

Prediabetes is present when an individual meets criteria for impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), or has glycated haemoglobin (HbA1c) above a specific threshold value lower than required for the diagnosis of diabetes.[30] Unlike diabetes, prediabetes is not associated with a substantial risk of microvascular disease. However, it is associated with an increased risk of conversion to full-blown diabetes (predominantly driven by IFG)—with a consequent risk of microvascular complications in the long term—and an increased risk of cardiovascular disease (predominantly driven by IGT).

Over 20 years ago, the Diabetes Prevention Programme showed that metformin therapy can reduce progression from the IGT form of prediabetes to type 2 diabetes.[31] In total, 3324 overweight or obese individuals with abnormalities of glucose tolerance (predominantly IGT) were randomized 1:1:1 to an intensive lifestyle intervention (exercise and diet), metformin or placebo (allocation to medication was double-blind) for a planned duration of 3 years. Compared with placebo, the intensive lifestyle intervention reduced the incidence of type 2 diabetes by 58% (95% CI: 48%-66%), while metformin reduced it by 31% (95% CI: 17%-43%); however, in a direct comparison, the intensive lifestyle intervention was significantly more effective than metformin. The investigators estimated that to prevent one case of diabetes over 3 years, 6.9 persons would have to participate in the DPP lifestyle-intervention programme or 13.9 would have to be allocated to metformin therapy. The effects of this lifestyle intervention and metformin were durable over time post-randomization, with point estimates for prevention of diabetes, respectively, as follows: −18 and −34% at 10 years, −18 and −27% at 15 years, and −18 and −25% at 22 years.[32] Long-term weight loss and other benefits were seen in both groups,[33] and meta-analyses have provided pooled effect sizes based on these and other studies.[34]

Based on cost-effectiveness (i.e. lower acquisition costs of metformin vs. effective lifestyle intervention programmes), it can be argued from these data that metformin should be widely prescribed to prevent type 2 diabetes.[35] However, it can be counterargued that a pharmacological approach over-medicalizes what is essentially a public health problem and exposes relatively healthy people to lifelong medication (and associated potential adverse effects) when they could be participating instead in a healthy lifestyle programme.[36]

The former viewpoint has generally prevailed, and prediabetes is now a licensed indication for metformin therapy in at least 66 countries.[33] In the United Kingdom, slow-release (but not standard-release) metformin is licensed for delaying the onset of type 2 diabetes, specifically in overweight individuals with IGT and/or IFG who are at high cardiovascular risk and who are at high risk of progressing to frank diabetes despite lifestyle change.[9,10] Metformin is not licensed for prediabetes in the United States, but current ADA treatment guidelines do recommend that metformin 'should be considered' for the prevention of type 2 diabetes in adults <60 years of age with a BMI ≥35 kg/m^2 and higher levels of fasting hyperglycaemia and in women with previous gestational diabetes.[37]

In an era of cardiovascular outcome trials, a prediabetes indication for metformin would likely be even more universally accepted if there were evidence that it prevented long-term complications, including myocardial infarction and stroke, in a prediabetes population. There are quite strong data to support metformin's effectiveness in reducing rates of cardiovascular events in type 2 diabetes, but, as argued elsewhere,[38] the trials on which contemporary guidelines are based were relatively small and conducted to different standards than those that have been conducted with more recently introduced agents. The idea of conducting a cardiovascular outcomes trial with metformin in prediabetes therefore emerged with twin aims, i.e. (a) establishing whether the benefits of metformin in prediabetes extend beyond prevention of diabetes to reducing rates of cardiovascular outcomes, and (b) indirectly testing in a contemporary large-scale clinical trial whether the position of metformin as a first-line therapy in type 2 diabetes is justified in a way that is not possible in type 2 diabetes itself given that it is widely accepted as a standard of care, that is, randomization to placebo would be considered unethical.

The GLINT study (Glucose Lowering In Non-diabetic hyperglycaemia Trial) was therefore designed as a clinical outcomes study of slow-release metformin (metformin XR up to 1500 mg/day) versus placebo in people with prediabetes and risk factors for cardiovascular disease.[39] A feasibility study was initiated at two sites in the United Kingdom, but the full trial did not ultimately progress as the systems adopted for recruitment did not accrue sufficient numbers of participants in a realistic timeframe. The VA-IMPACT trial (Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes) study was initiated more recently with a similar aim, targeting 8000 people with any form of non-diabetic hyperglycaemia and elevated cardiovascular risk for randomization to metformin XR or placebo (NCT02915198) and following up for a composite cardiovascular primary endpoint.[40] It can be speculated that a positive result would support metformin gaining prediabetes as a licensed indication in further territories (including the United States).

In the meantime, a clinical question that can arise—particularly in countries in which metformin is not licensed for use in prediabetes—is whether to continue metformin in individuals whose type 2 diabetes has gone into remission (e.g. after successful weight loss) and in whom it is well-tolerated. Much of the evidence at present supports continuation, but best practice would be for the choice to be guided by shared and informed decision-making, including consideration of long-term cardiovascular risk.

2.4 | Adjunct therapy in type 1 diabetes

Overweight (BMI 25-29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) are increasingly prevalent in people living with type 1 diabetes.[41] A key mechanism is peripheral hyperinsulinaemia because of the therapeutic subcutaneous (rather than physiological portal) delivery of insulin, which promotes fat synthesis and inhibits hepatic fat oxidation.[42] Another key factor is that people with type 1 diabetes often need to take additional snacks (i.e. beyond those required to achieve satiety) to prevent or treat hypoglycaemia. Matching the time-action profiles of currently-marketed insulins to daily (and hourly) changes in carbohydrate ingestion and levels of physical activity is always a difficult balance.

Reliable data on absolute rates of overweight and obesity in type 1 diabetes versus the general population across different geographical territories and age groups are scarce. In adults with type 1 diabetes, followed in the Pittsburgh Epidemiology of Diabetes Complications study until 2007, the prevalence of obesity increased from the mid-1980s to the mid-2000s from 4% to 23%.[43] In Scotland, where nationwide population-based figures are published annually based on measurements made in routine care (and where there is reliable

recording of type 1 vs. type 2 diabetes), the overall prevalences of overweight and obesity in >30 000 adults with type 1 diabetes in 2022 were 36% and 31%, respectively.[44] Available data for children and youth in the United States also indicates disturbing absolute levels and trends.[45]

One strategy for achieving glycaemic control without causing or aggravating obesity is adding non-insulin glucose-lowering agents (including metformin) 'off-label' as adjunct therapy. Anecdotally, practice varies widely among clinicians across and within territories. In a 2016 extract of population data from Scotland, 15% of adults with type 1 diabetes had received at least one prescription for metformin at any time, and 8% were using it currently.[46] A systematic review and meta-analysis led by the present author in 2010 highlighted the paucity of evidence for the use of metformin in type 1 diabetes. Only nine small randomized, double-blind trials were identified and a single trial contributed more than half of the 192.8 patient-years available for analysis.[47] When metformin was added to insulin therapy, there was no consistent reduction in HbA1c but a significant reduction in insulin dose requirement (6.6 U/day, $p < .001$), while body weight and low-density lipoprotein were reduced in some trials. There was no information on cardiovascular outcomes, whether clinical or surrogate.

Later that year, having repeated this meta-analysis, the UK National Institute for Health and Care Excellence (NICE) went on to recommend metformin for adults with type 1 diabetes and a BMI ≥25 kg/m^2 who 'want to improve glucose control while minimizing their effective insulin dose'.[48] The ADA followed, stating that 'adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/obese patients with poorly controlled type 1 diabetes'.[49] Based on the above estimates of the prevalence of overweight and obesity, full implementation of such recommendations would have resulted in a sharp rise in metformin prescribing in type 1 diabetes.

Given supportive data with continuing uncertainty, two major clinical trials of metformin as adjunct therapy in type 1 diabetes have since been conducted. The US Type 1 Diabetes Exchange study was a double-blind, placebo-controlled randomized trial in 140 overweight and obese adolescents with poor glycaemic control [mean HbA1c, 8.8% (73 mmol/mol)] and high insulin dose requirements.[50] HbA1c was reduced at 3 months with metformin [by 0.3% (3.3 mmol/mol)], but this was not sustained at 6 months. Insulin dose requirement was reduced by 25% from baseline (a pre-specified outcome) by metformin versus placebo in 23% versus 1% of participants; BMI was reduced by 10% or more (also pre-specified) in 24% versus 7%. No changes were observed in cholesterol levels.

The REMOVAL study, led by the present author, was an international multicentre trial that attempted to address the lack of cardiovascular data for metformin use in type 1 diabetes by conducting a 3-year double-blind, placebo-controlled trial of metformin treatment (1000 mg twice daily) in adults aged ≥40 years with three or more cardiovascular risk factors.[51] Key outcome measures were based on carotid artery intima-media thickness (cIMT) as a validated surrogate marker of atherosclerotic cardiovascular disease.[52] The main result was that the primary outcome measure (mean far wall cIMT) was not significantly reduced by metformin; however, the tertiary cIMT outcome measure (maximal far wall cIMT, also pre-specified) was reduced, and both cIMT outcomes were reduced in a subsequent pre-specified subgroup analysis excluding cigarette smokers.[53] Secondary outcomes included a sustained reduction in weight with metformin (by 1.2 kg), as well as modest reductions in insulin dose requirement (by about 2 U/day from the 6-month time point onwards) and low-density lipoprotein cholesterol (by 0.13 mmol/L), despite a high prevalence of statin use. There was no increase in hypoglycaemia. About a quarter of individuals (twice the rate of those taking placebo) discontinued metformin over 3 years, suggesting that about one in eight had genuine intolerance (predominantly gastrointestinal adverse effects). Longer-term data on the effects of metformin on cardiovascular outcomes in type 1 diabetes are still required.

In many respects, the results of these two more recent metformin trials in type 1 diabetes confirmed the evidence provided by smaller previous studies that metformin has a variety of modestly-sized beneficial effects in type 1 diabetes (as summarized in an updated meta-analysis[54]). However, enthusiasm for the use of metformin in type 1 diabetes in international recommendations has since diminished. For example, the current ADA 2024 Standards of Care state that 'the addition of metformin in adults with type 1 diabetes was associated with small reductions in body weight, insulin dose, and lipid levels but did not sustainably improve A1c'.[55]

3 | INVESTIGATIONAL 'REPURPOSING' USES OF METFORMIN BEYOND TYPE 2 DIABETES

3.1 | Prevention of cancer

Metformin has the potential to inhibit tumour cell proliferation and consequently reduce cancer development and progression via direct and indirect mechanisms.[56] The former include activation of AMP-activated protein kinase and inhibition of mammalian target of rapamycin; the latter include reduction of overstimulation of insulin and insulin-like growth factor-1 receptors by hyperinsulinaemia.

Numerous observational studies have reported that individuals with obesity and diabetes treated with metformin have a lower incidence of cancer, and when pooled in meta-analyses, mean effect sizes of about 15% are reported.[57] However, reduced rates of cancer have not generally been observed in participants randomized to metformin in controlled trials.[58] A recent meta-analysis involving the present author and including seven randomized trials not included in previous meta-analyses used the technique of trial sequential analysis to address whether this discrepancy is because of either biases in observational studies (favouring a positive result) or insufficient statistical power because of smaller sample sizes in RCTs (i.e. type II statistical error)[56]; 27 trials were included, providing a total of 10 717 subjects in the metformin group and 10 003 in the control group.

The conclusion was that the cumulative sample size was large enough to exclude a significant effect of metformin on overall cancer incidence (in either direction). Based on this, any effect of metformin on overall cancer incidence would probably be too small to be clinically significant, although this does not exclude an effect on specific cancers. For example, a specific action of metformin has been hypothesized in treating hepatocellular carcinoma: reprogramming immune T-cell function via AMPK-dependent upregulation of Krüppel-like factor 6 expression, leading to downstream cell cycle arrest and inhibition of cell proliferation.[59] However, as with overall cancer incidence, positive studies to date have mainly been observational.

3.2 | Li Fraumeni syndrome

Another cancer-related condition in which metformin could plausibly have a clinically important effect is Li Fraumeni syndrome (LFS), a rare autosomal dominant syndrome that causes predisposition to cancer because of variants in the tumour suppressor gene TP53. These include (more commonly) bone and soft-tissue sarcomas, breast, brain and adrenocortical cancers, and less commonly, lung, colon, haematological, skin, stomach and ovarian cancers. Approximately 50% of males and females with LFS develop cancer before the age of 46 years and 31 years, respectively. Experimental work has implicated abnormalities in mitochondrial metabolism as a mechanism for tumorigenesis, and there is an experimental proof of concept that these can be reversed with metformin. A large open-label clinical trial in LFS (MILI) has recently been initiated in the United Kingdom [funded by the National Institute for Health and Care Research (NIHR)] with a primary outcome of cancer-free survival at 5 years.[60] Because of the low prevalence of the condition, parallel studies are planned in Canada, Germany and the United States with a prespecified individual patient meta-analysis to ensure adequate statistical power.

3.3 | Renal protection

A treatment strategy for achieving target glycaemic control is considered (principally based on the ADVANCE trial[61]) to reduce the risk of renal disease in type 2 diabetes; however, the effects of individual glucose-lowering agents, including metformin, on the kidney are not well explored. Metformin therapy is associated with a small but predictable rise in serum lactate (usually within the normal range); given widespread use, there is a potential for hyperlactataemia (serum lactate >5 mmol/L) to be detected if lactate is measured incidentally. More seriously, metformin can be implicated as having a causal role in cases of lactic acidosis (hyperlactataemia associated with arterial blood low pH <7.35) during severe intercurrent illness—hence current regulatory restrictions on use by the CKD category as outlined above.[9,10] This was the concern that led to the non-availability of metformin on the US market until 1995, despite widespread use in Europe, and to the permanent demise or withdrawal from the development of more potent antecedent biguanide compounds such as phenformin and buformin.

At present, despite restrictions on the use of metformin in later stages of CKD, a number of lines of evidence suggest that it may be associated with benefit rather than harm. For example, in a rat model of CKD, metformin (vs. vehicle) prevented the rise in serum creatinine levels (and fall in eGFR) induced by chronic adenine dosing; this was associated with reduced interstitial inflammation and a specific proteomic signature associated with activation of the Hippo signalling pathway (which is involved in tissue development, organ size, cell proliferation and apoptosis).[62] In an observational study of patients with CKD that were propensity score matched (mean eGFR at baseline 33 ml/min/1.73 m^2) and followed up within an RCT of darbepoetin alfa, use ($n = 591$) versus non-use ($n = 3447$) of metformin was associated with a reduction in a composite renal outcome (HR, 0.77; 95% CI: 0.61-0.98).[63] In keeping with these findings, in the REMOVAL trial in type 1 diabetes, eGFR was better maintained over 3 years in the metformin group versus placebo, with a between-group difference of 4.0 ml/min/1.73 m^2 (2.19 to 5.81, $p < .001$) in favour of metformin.[51]

In addition to the potentially beneficial effects on renal outcomes, metformin may have cardiovascular benefits in individuals with renal disease. In a retrospective cohort study of US veterans, rates of major adverse cardiovascular events were lower in 28 976 people with diabetes receiving metformin propensity matched with 67 749 patients receiving sulphonylureas [adjusted HR 0.80 (95% CI: 0.75 to 0.86)].[64] Moreover, in the above-mentioned observational study within a trial of darbepoetin alfa, cardiovascular outcomes were reduced with metformin versus sulphonylurea treatment [HR, 0.67 (95% CI: 0.51-0.88)].[63] Indeed, a systematic review and meta-analysis of observational studies (including the above study and two other post hoc analyses of clinical trials) showed that metformin was associated with significant reductions in all-cause mortality [pooled RR = 0.71 (95% CI: 0.61-0.84)] and cardiovascular death [pooled RR = 0.76 (95% CI: 0.60-0.97)] in patients with CKD stage 1-3.[65]

These lines of evidence and others supported the commissioning of the Metformin as RenoProtector of Progressive Kidney Disease trial (RenoMet, NCT038314), which is evaluating metformin versus placebo in non-diabetic individuals with proteinuria, CKD 2-3B (eGFR 30-90 ml/min/1.73 m^2) and an annual decline in eGFR of 2-15 ml/min/1.73 m^2.[66] The primary outcome is time to 30% decline in eGFR, with all-cause mortality as a secondary outcome. RenoMet was originally expected to report by 2021 but is now expected to be completed by the end of 2024; alongside analysis of data from other previous trials, it is expected to provide useful information on the effects of metformin on cardiorenal outcomes.

In addition to the effects in CKD, metformin may also have protective effects in acute kidney injury. In a rat model of acute injury (ablation/infarction), metformin treatment led to preservation of both eGFR and renal histological appearances via an AMPK-dependent mechanism.[67] These findings are in keeping with observational evidence from a population-based study (involving the present author): in patients with diabetes admitted to a hospital with acute kidney

injury in Scotland, treatment with metformin on admission was associated with a higher rate of survival at 28 days (after adjustment for age, sex, pre-admission eGFR, HbA1c and diabetes duration).[68]

3.4 | Alzheimer's disease

Resistance to insulin action in type 2 diabetes is classically described in liver, muscle and adipose tissue, but other tissues are also affected. A current hypothesis for the aetiopathogenesis of Alzheimer's disease is that impaired insulin signalling in neural tissues induces overactivation of GSK-3 kinase, increases tau phosphorylation, alters tau modification and promotes neurofibrillary degeneration.[69] Experimental studies have provided proof-of-concept for metformin; for example, a study in which it stimulated microglial-induced phagocytosis of amyloid deposits and tau proteins, thereby reducing amyloidogenesis in a mouse model (APP/PS1).[70] Repurposing of various agents used in type 2 diabetes has therefore been proposed as a viable therapeutic strategy for Alzheimer's disease.

Focusing on metformin, a Mendelian randomization analysis of over half a million individuals found a robust effect on Alzheimer's disease for one AMPK-independent metformin target (mitochondrial complex 1).[71] However, a meta-analysis of 10 observational studies did not support a reduction in the risk of Alzheimer's disease with metformin.[72]

Three relevant clinical trials are currently under way based on the above experimental proof of concept; each is expected to report in 2027. Metformin in Alzheimer's Dementia Prevention (MAP) is a double-blind multicentre RCT of metformin versus placebo (NCT04098666) being conducted in the United States in 326 non-diabetic overweight or obese men and women aged 55-90 years with mild cognitive impairment. The primary outcome is based on neuropsychological testing; 50% of participants will also undergo magnetic resonance imaging and positron emission tomography brain imaging.[73]

Second, MET-FINGER is a double-blind, parallel-group, placebo-controlled clinical trial being conducted in 600 older adults (60-79 years), including participants genetically at increased risk of Alzheimer's Disease (APOE ε4) in Finland, Sweden and the United Kingdom. It involves a multimodal lifestyle and metformin intervention for the prevention of cognitive impairment (NCT05109169). The primary outcome is the composite z-score of an extensive neuropsychological test battery.[74] Finally, MET-MEMORY (NCT04511416) is a trial of metformin versus placebo over 3 years in 242 non-diabetic obese participants with mild cognitive impairment with a similar primary outcome.[75]

3.5 | Metabolic dysfunction-associated steatotic liver disease

Anti-inflammatory effects of metformin, including AMPK-mediated inhibition of tumour necrosis factor-alpha/nuclear factor-kappaB and mammalian target of rapamycin signalling pathways and AMPK-independent suppression of proinflammatory cytokines such as interleukin-6 have been shown in vitro and ex vivo, including in adipose-derived mesenchymal cells, mouse perivascular tissue and human umbilical vein cells.[8] As proinflammatory hepatic cytokine production plays an important role in metabolic dysfunction-associated steatotic liver disease (MASLD; which was formerly known as non-alcoholic fatty liver disease), metformin is considered a candidate molecule for the treatment of MASLD.

In a recent analysis of the clinicaltrials.gov database, metformin was an investigational agent (or a component of a combination investigational therapy) in four of 19 evaluable trials of medical therapies aimed at treating MASLD.[76] Studies of metformin monotherapy in MASLD to date have not, however, shown consistent benefits and a systematic review concluded that despite effects on weight and glucose control, there was no difference from placebo in measures of steatosis or fibrosis.[77] Further experimental and mechanistic work to determine whether the anti-inflammatory effects of metformin can be shown at relevant concentrations in hepatocytes would help inform the design of future studies. In the meantime, there is clearly still considerable interest in the potential efficacy of metformin in MASLD when used in combination with other therapies.

3.6 | Healthy ageing

Interest in metformin as a method of promoting healthy ageing was sparked by a 2013 study that showed long-term treatment with metformin (0.1% w/w in diet) starting at middle age extended lifespan (and 'healthspan') in male mice.[78] Small studies in human tissues [including the Metformin in Longevity Study (MILES, NCT02432287)] have since reported preliminary results that metformin may induce anti-ageing transcriptional changes.[79] However, a critical review of studies investigating the effect of metformin on overall lifespan in mice and nematodes found that metformin was not significantly associated with an overall lifespan-prolonging effect in either species.[80] The prevailing current opinion is that any beneficial effects of metformin on ageing are indirect via its effects on cellular metabolism (increasing insulin sensitivity, reducing oxidative stress and enhancing vascular endothelial function), thereby reducing the risk of one or more of the individual conditions mentioned above (type 2 diabetes, cardiovascular disease, Alzheimer's disease, cancer).[81] A trial protocol entitled Targeting Aging with Metformin (TAME) has been designed with input from the US Food and Drug Administration with the aim of creating a regulatory framework that recognizes ageing as an indication for treatment.[82]

4 | CONCLUSION

Beyond its use in type 2 diabetes, metformin is routinely used 'off-label' in the management of PCOS and in many countries as a glucose-lowering therapy in gestational diabetes/type 2 diabetes in pregnancy. Use in prediabetes to prevent progression to frank diabetes is approved and/or supported by guidelines in many countries.

TABLE 1 Summary of the current clinical uses of metformin beyond type 2 diabetes.

Condition (section of manuscript)	Supported by evidence from RCTs with surrogate endpoints	Supported by evidence from RCTs with clinical endpoints	Supported by evidence from meta-analysis of RCTs	Supported by ADA standards of care	Widely used	Licensed therapy[b]	Key RCTs or other research in progress[b]
Polycystic ovarian disease (Section 2.1)	Yes (e.g. fasting insulin concentrations, blood pressure and low-density lipoprotein cholesterol)[13]	Yes (promoting ovulation)[13] No evidence available of effects on CV outcomes	'Limited'[15–17] (as per evidence for other agents used in this condition)	Yes (but not after first trimester of pregnancy)	Yes	Label supports use in some territories (e.g. France, Japan and Brazil) but not the United Kingdom or the United States	No
Gestational diabetes/type 2 diabetes in pregnancy (Section 2.2)	Yes (e.g. glucose-lowering, maternal preference, reduced neonatal hypoglycaemia)[20,21]	Yes (e.g. fewer infants weighing >4 kg)[20,21] Long-term safety concerns for offspring remain in some countries	Yes[24]	No	Yes (with exception of the United States and some other countries)	Label supports use in many territories (including Europe and the United Kingdom)	Post-randomization long-term surveillance of neonatal and childhood outcomes ongoing
Prediabetes (Section 2.3)	Not applicable	Yes, prevention of new-onset diabetes, but no evidence available on effects on CV outcomes[31,32]	Yes[34]	Yes[37]	Yes	Label supports use for high-risk subgroups in more than 66 countries (including the United Kingdom but not in the United States)	VA-IMPACT cardiovascular outcome trial in progress (NCT02915198)[40]
Adjunct therapy in type 1 diabetes (Section 2.4)	Yes (e.g. LDL cholesterol, weight, maximal carotid IMT)[38]	No (and no evidence available on effects on CV outcomes)	Yes[47] (but surrogate outcomes only)	No	No	Label supports use, for example, in France[a] and Brazil but not, for example, in the United Kingdom or the United States	No

Note: For summary of evidence see the relevant sections of the manuscript (Sections 2.1-2.4) and associated references.

Abbreviations: ADA, American Diabetes Association; CV, cardiovascular; IMT, intima-media thickness; LDL, low-density lipoprotein; RCTs, randomized controlled trials.

[a]As metformin embonate. [b]Up to the end of May 2024.

TABLE 2 Summary of proof of concept for current 'repurposing' investigational indications of metformin.

Condition (section of manuscript)	Supported by experimental evidence[a]	Supported by longitudinal observational evidence[a]	Supported by evidence from RCTs[a]	Supported by evidence from meta-analysis of RCTs	RCTs in progress likely to significantly extend evidence base
Prevention of cancer (Section 3.1)	Yes	Yes	Trials mostly negative	No (for overall cancer)[56]	Yes (targeting tissue-specific tumours)
Li Fraumeni syndrome (Section 3.2)	Yes	Yes	Insufficient evidence	Insufficient evidence	MILI trial initiated in the United Kingdom; other national trials in set-up
Renal protection (Section 3.3)	Yes	Yes	Insufficient evidence	Insufficient evidence	Yes (RenoMet, NCT03831[66])
Alzheimer's disease (Section 3.4)	Yes	Conflicting results	Insufficient evidence	Insufficient evidence	Yes (MET-FINGER,[73] NCT05109169,[74] NCT04511416)[75]
Metabolic dysfunction-associated liver disease (Section 3.5)	Yes	Yes	Trials mostly negative	No (clinically important effect of metformin monotherapy unlikely)[77]	Yes (mostly on combination therapy with GLP-1 analogues and DPP-4 inhibitors)
Healthy ageing (Section 3.6)	Yes	Yes	Anti-ageing transcriptional changes in a small trial	Insufficient evidence	Yes (TAME[82])

Note: For summary of evidence see the relevant sections of the manuscript and associated references.
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; RCTs, randomized controlled trials.
[a]NB In the opinion of the author.

Use as adjunct therapy in type 1 diabetes is less well-established. Further RCTs conducted to contemporary standards are needed in all these domains, and some are in progress (Table 1), with those relating to women's health particularly neglected to date. Despite metformin's longevity, it still inspires intense enthusiasm for ongoing investigation of potential 'repurposing' indications, including in cancer (particularly LFS), renal disease, Alzheimer's disease, liver disease (MASLD) and healthy ageing (Table 2). By the time metformin is an octogenarian and several of the above-mentioned trials have been reported, there may still be more solid evidence to support its use in further clinical contexts beyond type 2 diabetes.

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DATA AVAILABILITY STATEMENT

All data used in the preparation of this article are publicly available.

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