Metformin and Type 2 Diabetes Prevention
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The herbal ancestry of metformin dates back to 1772 in medieval Europe, when the herb Galega officinalis was first used to treat symptoms of diabetes, including thirst and frequent urination (1). It was later recognized that this herb was rich in guanidine, which was shown to lower blood glucose in 1918. Metformin, a guanidine derivative, was ultimately introduced as an agent to treat diabetes in the 1950s in Europe and in the 1990s in the United States (1).

Metformin has multiple pharmacodynamic effects that have made it an agent of interest in many areas, including the prevention of type 2 diabetes. Recognizing that diabetes is a significant risk factor for both micro- and macrovascular complications and that cardiovascular (CV) disease risk is already heightened in those at high risk of type 2 diabetes, efforts have targeted the prevention of type 2 diabetes in people at high risk to minimize long-term complications (2).

The largest study evaluating metformin for the prevention of diabetes in high-risk individuals was the Diabetes Prevention Program (DPP) (3). Metformin was chosen given its record of efficacy in lowering glycemia, established safety profile, and years of use and the likelihood of adherence and retention in an otherwise generally healthy population. Furthermore, several of its known mechanisms and effects were consistent with the goal of prevention of type 2 diabetes, including suppression of hepatic glucose production, delay or inhibition of glucose absorption from the gastrointestinal tract, and evidence of improvement in insulin sensitivity and in CV risk factors (2).

This review highlights the clinical trials that have evaluated metformin...
for the prevention of type 2 diabetes and delves into findings from the DPP and its longer-term outcomes study, the Diabetes Prevention Program Outcomes Study (DPPOS), as the largest and longest controlled clinical trial of metformin used for the prevention of diabetes in people at high risk of type 2 diabetes (4). Finally, we provide an overview of current clinical practice guidance and recommendations on the use of metformin for the prevention of type 2 diabetes, concluding with a brief discussion of current gaps and areas of interest in the efforts to affect the rising prevalence of type 2 diabetes.

**Metformin and the Prevention or Delay of Type 2 Diabetes: What Is the Evidence?**

Several prospective randomized clinical trials have evaluated metformin in the prevention of type 2 diabetes, with the DPP being the largest (Table 1).

The DPP randomized 3,234 participants ≥25 years of age with a high risk of diabetes (i.e., elevated fasting plasma glucose [FPG], impaired glucose tolerance [IGT], and overweight/obesity) to 850 mg metformin twice daily, intensive lifestyle intervention, or a placebo control. There were numerous exclusions, including the presence of medical conditions that could limit life span and/or increase risk from the intervention, conditions or behaviors likely to affect the conduct of the trial, and medications or medical conditions likely to confound assessment for diabetes (2).

The intensive lifestyle intervention aimed for a 7% weight loss through a low-energy, low-fat diet and ≥150 minutes/week of moderate-intensity physical activity. Both the metformin and placebo groups also received standard lifestyle recommendations in the form of written information and an annual individual session emphasizing the importance of a healthy lifestyle. Metformin was initiated at a dose of 850 mg orally once daily and increased to 850 mg twice daily at 1 month, with the option to initiate treatment with half a tablet daily or to extend the titration period for tolerability. Participants in the metformin and placebo arms were followed quarterly, during which time pill counts and adherence were assessed. The intensive lifestyle arm underwent a one-on-one individualized lifestyle intervention consisting of a 16-lesson curriculum over 24 weeks, followed by both group and individual reinforcement. The primary outcome of the DPP was diabetes, based either on an annual oral glucose tolerance test or semiannual FPG test, with diagnosis requiring confirmation with a repeat test within 6 weeks.

After an average follow-up of 2.8 years, the study was stopped early given the clear efficacy of both the metformin and lifestyle intervention treatment groups in preventing or delaying diabetes. Metformin significantly reduced the incidence of diabetes by 31% compared to placebo (95% CI 17–43%), whereas lifestyle intervention reduced the incidence by 58% (95% CI 48–66%). The number needed to treat with metformin to prevent one case of diabetes over 3 years was 13.9 (6.9 with lifestyle intervention) (2,3).

Although lifestyle intervention had a significantly greater effect on progression to diabetes than metformin in the overall study, the DPP identified subgroups with comparable efficacy between the two interventions. Namely, metformin was comparable to intensive lifestyle intervention in obese individuals with a BMI ≥35 kg/m², demonstrating a 53% reduction in progression to diabetes (compared to 51% for lifestyle); in younger individuals aged 25–44 years, with a 44% reduction compared to 48% with lifestyle (3); and in women with a history of gestational diabetes, showing a reduction in incidence of diabetes of ~50% with either lifestyle or metformin therapy (5), a benefit that persisted at the 10-year follow-up (6). Metformin also demonstrated a greater effect compared to placebo in individuals with an elevated FPG of 110–125 mg/dL (48% reduction) compared to those with an FPG of 95–109 mg/dL (15% reduction) (3), likely reflecting its mechanism of suppression of fasting hepatic glucose production.

Equally informative, the DPP identified subgroups in which metformin was not as effective compared to placebo, including those with a BMI of 22 to <30 kg/m² (3% reduction compared to placebo, 95% CI −36 to 30%) and older individuals ≥60 years (11% reduction compared to placebo, 95% CI −33 to 41%) (3). Of interest, post-hoc analyses evaluating outcomes from the DPP based on currently accepted A1C-based criteria for the diagnosis of diabetes showed that metformin and lifestyle were similarly effective in preventing diabetes based on A1C (44% reduction with metformin and 49% with lifestyle) (7).

At the end of the DPP, 88% of the participants continued in the DPPOS. In the bridge period to the DPPOS, all participants received group-based lifestyle instruction based on the DPP. In the DPPOS, those originally assigned to metformin continued metformin, now unmasked, and placebo was discontinued, while those in the lifestyle intervention group received intermittent lifestyle reinforcement (8). Overall, those in the metformin group had an 18% risk reduction in incidence of diabetes at 15 years compared to a 27% risk reduction seen in the original lifestyle group, both compared to placebo (9). Incidence rates during the DPPOS period, however, were no different between the original groups, and overall incidence of diabetes was lower during the DPPOS compared to DPP, with further analyses suggesting that this may be because those at highest risk of diabetes developed diabetes during the DPP, and the remaining participants in DPPOS have been less susceptible (4,10).

The Indian Diabetes Prevention Programme (IDPP) addressed whe-
ther lifestyle intervention, metformin, or a combination of both could influence progression to diabetes in native Asian Indians with IGT. Here, 531 participants were assigned to lifestyle modification, metformin, metformin in combination with lifestyle modification, or a control group. This study was not blinded. A metformin dose of 250 mg twice daily was used. Efforts to increase the dose of metformin to 500 mg twice daily in the first 50 participants resulted in significant intolerability, with 45% reporting symptoms of hypoglycemia, including excess hunger, sweating, and giddiness; thus, the dose of metformin reverted to 250 mg twice daily for the remainder of the participants and the length of the study.

In the IDDP, all intervention groups showed a significant reduction in progression to diabetes, with a 28.5% reduction in the lifestyle group (95% CI 20.5–37.3%), a 26.4% reduction with metformin (95% CI 19.1–35.1%), and a 28.2% reduction with lifestyle modification plus metformin (95% CI 20.3–37.0%) compared to control, with no difference between lifestyle modification plus metformin and the low dose of metformin used in this study, the number needed to treat for metformin in this high-risk population, which saw a cumulative incidence of 3.9 years resulted in a significant relative risk reduction of 66%—an absolute difference of 21%—in the low-dose combination approach with rosiglitazone in the prevention of diabetes by modifying lifestyle and the combination of rosiglitazone with metformin. Finally, the CANOE (Canadian Normoglycemia Outcomes Evaluation) trial involving 207 people with IGT. Compared to placebo, the combination capsule of rosiglitazone (2 mg) with metformin (500 mg) given twice daily over a median of 3.9 years resulted in a significant 66% reduction in diabetes incidence compared to placebo (95% CI 61.6–70.4%). This study was blinded. A metformin dose of 250 mg twice daily was used. Efforts to increase the dose of metformin to 500 mg twice daily in the first 50 participants resulted in significant intolerability, with 45% reporting symptoms of hypoglycemia, including excess hunger, sweating, and giddiness. In the IDDP, all intervention groups showed a significant reduction in progression to diabetes, with a 28.5% reduction in the lifestyle group (95% CI 20.5–37.3%), a 26.4% reduction with metformin (95% CI 19.1–35.1%), and a 28.2% reduction with lifestyle modification plus metformin (95% CI 20.3–37.0%) compared to control, with no difference between lifestyle modification plus metformin and the low dose of metformin used in this study, the number needed to treat for metformin in this high-risk population, which saw a cumulative incidence of 3.9 years resulted in a significant relative risk reduction of 66%—an absolute difference of 21%—in the low-dose combination approach with rosiglitazone in the prevention of diabetes by modifying lifestyle and the combination of rosiglitazone with metformin.
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Metformin and Prevention of Type 2 Diabetes: Additional Insights From Long-Term Follow-Up

**Does Metformin Alter the Underlying Pathophysiology of Prediabetes?**

To address whether metformin alters the course of disease or merely pharmacologically masks its onset, the DPP reassessed participants who had not yet developed diabetes after a 1- to 2-week washout period and found that the odds of diabetes increased by 50% in the metformin group compared to placebo during the washout ($P = 0.098$), but when looking at the combined period of the DPP plus the washout, the odds of diabetes were still reduced by 25% compared to placebo (13). A longer washout of metformin/placebo would have been more definitive. In the CANOE trial, despite improvement at 1 year in glycemic parameters and insulin sensitivity (Matsuda index) in the rosiglitazone/metformin arm, these subsequently deteriorated as in the placebo arm, with no significant difference in $\beta$-cell function (insulin secretion-sensitivity index-2) and insulin sensitivity, suggesting that drug intervention did not modify the natural history of worsening insulin resistance and $\beta$-cell dysfunction in this population (14). Thus, the mechanism of type 2 diabetes prevention with metformin appears to involve both pharmacological and possibly downstream physiological effects.

**Does Metformin Prevent Type 2 Diabetes–Related Microvascular Complications?**

The DPPOS assessed an aggregate microvascular outcome consisting of retinopathy, nephropathy, and neuropathy 15 years after initial randomization and found a 28% reduction in prevalence of the microvascular complications in those who did not develop diabetes compared to those who did. No difference between treatment arms was seen with microvascular outcomes, which was possibly related to the small difference in glycemia between the treatment groups, limited power, and length of follow-up. Nonetheless, regardless of approach, the findings support the importance of preventing diabetes to reduce long-term microvascular complications (9).

**Does Metformin Alter CV Risk?**

Early effects of metformin on CV risk factors emerged in the DPP. Although no significant differences in blood pressure or lipids were seen compared to placebo during the DPP (15), metformin improved lipoprotein subfractions (16), $C$-reactive protein (CRP) (17), and tissue plasminogen activator (tPA) (17) and reduced the incidence of metabolic syndrome by 17% (18). Moreover, reductions in CRP and tPA levels were not seen in those who developed diabetes (17), highlighting the importance of preventing diabetes regardless of intervention. Coronary artery calcification (CAC) at 14 years suggests a decreased presence and severity of CAC in men assigned to metformin compared to placebo (19), with hard CV outcomes being explored in the DPP’s ongoing follow-up. Finally, early analyses from the DPP suggest that weight loss is an important contributor to metformin’s diabetes preventive effect (20). Over 15 years, the metformin group has continued to maintain a lower weight compared to placebo (89.5 vs. 91.0 kg, not significant) (9). It remains to be seen whether these long-term effects on weight translate to improved CV outcomes.

**What Are the Long-Term Tolerability and Effects of Metformin When Used for Diabetes Prevention?**

Metformin for prevention of diabetes in those at high risk of type 2 diabetes was shown to be safe and well tolerated in the DPP. Seventy-two percent of participants in the metformin group took at least 80% of the prescribed dose (3), but this fell to an average of 49% during the DPPOS (2002–2013) (4,9). Over 10 years, metformin participants reported study medication-related gastrointestinal symptoms more frequently than those in the placebo group (9.5 vs. 1.1%, $P<0.0001$), with rates waning over time and becoming similar by years 6–9 (21). No reported cases of lactic acidosis have been seen in >15,000 person-years of exposure to metformin in the DPP/DPPOS, interpretable within the context of not having enrolled patients with medical conditions that would increase the risk of lactic acidosis, such as renal disease or advanced heart failure (2,4). At 5 years, biochemical vitamin B12 deficiency levels (<150 pmol/L) were seen more often in the metformin group than in the placebo group (4.3 vs. 2.3%, $P = 0.02$), with a nonsignificant difference seen at 13 years (7.4 vs. 5.4%, $P = 0.12$). Prevalence of anemia was also higher in the metformin group but did not differ by B12 level (22). With these findings, the current standards recommend periodic measurement of vitamin B12 levels and supplementation as needed in patients treated with metformin (23).

Although metformin is not indicated by the U.S. Food and Drug Administration (FDA) for diabetes prevention, its label encompasses these general safety precautions for metformin. Special attention is given to reduce the risk of lactic acidosis, including educating patients and families about symptoms of lactic acidosis and about discontinuing metformin and reporting to their health care provider should these symptoms occur.

In addition, monitoring estimated glomerular filtration rate (eGFR) is recommended, with a contraindication to using metformin in patients with an eGFR <30 mL/min/1.73 m² or initiating it in those with an eGFR between 30 and 45 mL/min/1.73 m². Furthermore, it is recommended that eGFR be monitored at least annually.
and more often in those at risk of developing renal impairment (e.g., the elderly) and to reassess the benefit and risk of continuing therapy in those whose eGFR falls to <45 mL/min/1.73 m². The label suggests stopping metformin at the time of or before iodinated contrast studies in those with an eGFR between 30 and 60 mL/min/1.73 m², with re-evaluation of eGFR in 48 hours and restarting of metformin if renal function is stable.

Metformin should also be temporarily discontinued during times of restricted food and fluid intake, such as surgery or other procedures, or during hypoxic states such as acute congestive heart failure. Excessive alcohol intake is also advised against, as it may potentiate the effect of metformin on lactate metabolism, and metformin should be avoided in those with evidence of hepatic disease. Finally, the label suggests annual screening for B12-associated anemia and measurement of vitamin B12 at 2- to 3-year intervals in those predisposed to developing subnormal B12 levels (24).

**Clinical Practice Recommendations for Using Metformin for the Prevention or Delay of Type 2 Diabetes**

With both short- and long-term evidence available on the use of metformin for the prevention or delay of type 2 diabetes, several organizations have incorporated recommendations on when and in whom metformin may be considered for this purpose. Recent guidelines (2009–2018) that address metformin for the prevention of type 2 diabetes are summarized in Table 2. The American Diabetes Association draws its recommendations from the subgroups in the DPP in which metformin was as effective as lifestyle intervention, sharing that metformin should be considered in those with prediabetes, especially those with a BMI ≥35 kg/m², younger individuals, and women with a history of gestational diabetes (23). Several guidelines, including those from the International Diabetes Federation, have recognized that metformin is a cost-effective pharmacological intervention in people at high risk of developing diabetes (25). This is supported by data from the DPP and DPPOS suggesting that over 10 years, metformin treatment is cost-saving, decreasing the cumulative costs of medical care received outside the DPP and DPPOS compared with placebo (26).

**Concluding Discussion: Gaps in Evidence and Translation and Next Steps**

The short- and long-term effects of metformin on the prevention of type 2 diabetes have been extremely well characterized, with much of the evidence coming from the DPP and DPPOS. Despite this wealth of data, the uptake of metformin for the prevention of type 2 diabetes has been extremely low. In an evaluation of

<table>
<thead>
<tr>
<th>Organization, Year</th>
<th>Name of Recommendation or Guideline</th>
<th>Recommendations Related to Metformin</th>
</tr>
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<tbody>
<tr>
<td>American Diabetes Association, 2018 (23)</td>
<td>5. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes—2018</td>
<td>Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially those with BMI ≥35 kg/m², those aged &lt;60 years, and women with prior gestational diabetes.</td>
</tr>
<tr>
<td>International Diabetes Federation, 2016 (25)</td>
<td>Cost-Effective Solutions for the Prevention of Type 2 Diabetes</td>
<td>Metformin is an inexpensive drug for the management of type 2 diabetes and can provide sustainable health gains. It could be considered as a cost-effective strategy for type 2 diabetes prevention, alongside comprehensive lifestyle programs.</td>
</tr>
<tr>
<td>Canadian Diabetes Association, 2013 (29)</td>
<td>2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Reducing the Risk of Developing Diabetes</td>
<td>In individuals with IGT, pharmacological therapy with metformin may be used to reduce the risk of type 2 diabetes.</td>
</tr>
<tr>
<td>IMAGE Project (European multidisciplinary consortium), 2010 (30)</td>
<td>A European Evidence-Based Guideline for the Prevention of Type 2 Diabetes</td>
<td>In people with IGT, metformin can be used as a second-line strategy for prevention of type 2 diabetes, provided that the drug’s tolerability (gastrointestinal side effects) and contraindications (kidney, liver diseases, hypoxic conditions) are considered.</td>
</tr>
<tr>
<td>Diabetes Australia, 2009 (31)</td>
<td>National Evidence Based Guideline for the Primary Prevention of Type 2 Diabetes</td>
<td>Pharmacological interventions are effective in preventing/delaying the onset of type 2 diabetes in high-risk individuals. Pharmacological interventions could be considered in people at high risk of developing type 2 diabetes. Metformin is a cost-effective pharmacological intervention in people at high-risk of developing diabetes.</td>
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the National Health and Nutrition Examination Survey 2005–2012, the age-adjusted prevalence of metformin use among adults with prediabetes was 0.7% (27), and in a national sample of insured adults, only 3.7% of patients with prediabetes were prescribed metformin over a 3-year period (28).

There are several possible barriers and reasons for this lack of uptake, including lack of translatability of clinical trial evidence to real-world settings, differing recommendations from professional societies, and lack of a formal FDA-approved indication for the treatment of prediabetes or prevention of type 2 diabetes (28). Furthermore, it remains to be seen whether early intervention in this population with pharmacotherapy affects later-stage hard outcomes such as CV disease and mortality; early indicators of effect (effects on glycemia, weight, and CV risk factors) may not be compelling enough for some providers and patients. In addition, although intensive lifestyle intervention programs based on the DPP have been widely supported and disseminated, this is not the case for metformin. In general, many consider lifestyle intervention to be the first-line intervention for the prevention of type 2 diabetes. Greater understanding of when one should choose or escalate to pharmacotherapy is needed. Further study should be done to address these existing gaps in evidence and translation.

In summary, metformin is safe and effective in preventing or delaying type 2 diabetes in adults at high risk of diabetes, with a comparable effect to lifestyle intervention seen in specific subgroups (i.e., those who are more obese, younger, or have a history of gestational diabetes). With the growing impact of prediabetes and diabetes worldwide, a greater systematic effort to address the remaining gaps and translate the current evidence is essential and perhaps overdue.

Duality of Interest
V.R.A. has served as a consultant for AstraZeneca, Novo Nordisk, and Sanofi; received research contracts (clinical trials) from AstraZeneca, Calibra, Eisai, Eli Lilly, Janssen, Novo Nordisk, and Sanofi; and has a spouse who is an employee of Merck Research Laboratories. No other potential conflicts of interest relevant to this article were reported.

Author Contributions
V.R.A. researched data, wrote the manuscript, contributed to the discussion, and reviewed/edited the manuscript. R.E.R. contributed to the discussion and reviewed/edited the manuscript. V.R.A. is the guarantor of this work, and as such, takes responsibility for the integrity and accuracy of the information presented.

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21. DPP Research Group. Long-term safety, tolerability, and weight loss associated...


