Metformin and Type 2 Diabetes Prevention

Vanita R. Aroda[1] and Robert E. Ratner[2]

■ **IN BRIEF** Metformin, an established therapy for the treatment of type 2 diabetes, has demonstrated safety and effectiveness in the prevention or delay of type 2 diabetes in people at high risk. The Diabetes Prevention Program randomized clinical trial demonstrated that intensive lifestyle intervention and metformin therapy reduced progression to diabetes by 58 and 31%, respectively, compared to placebo in people at risk of type 2 diabetes. Although lifestyle intervention was beneficial in all groups, metformin had a selectively greater effect in those who were more obese, had a higher fasting glucose, had a history of gestational diabetes, or were younger. Long-term effects included an 18% diabetes reduction with metformin compared to placebo over 15 years, a reduction in microvascular complications among those who did not progress to diabetes (without difference among treatment arms), and suggestion by coronary calcium assessment of a possible impact on atherosclerosis in men. Although long-term follow-up to assess later-stage outcomes is underway, current efforts to address gaps in evidence and translation remain of significant public health interest.

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

[1]Brigham and Women's Hospital, Boston, MA

[2]Georgetown University School of Medicine, Washington, DC

Corresponding author: Vanita R. Aroda, varoda@bwh.harvard.edu

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-

TABLE 1. Randomized Clinical Trials Evaluating Metformin for the Prevention of Type 2 Diabetes in High-Risk Individuals

Study (Country, Year of Publication, n)	Key Glycemic Eligibility Criteria	Duration of Follow-Up	Intervention (n)	Diabetes Incidence, by Events (Per 100 Person-Years) or by Cumulative Incidence at Study End (%)	Relative Risk Reduction in Diabetes Incidence Compared to Control/Placebo (%)
DPP (United States, 2002, n = 3,234) (3)	• FPG 95–125 mg/dL (≤125 mg/dL in American Indian clinics) • 2-hour glucose after 75 g oral glucose load: 140–199 mg/dL	2.8 years	Metformin 850 mg BID (n = 1,073)	7.8*	31*
			Intensive lifestyle intervention (n = 1,079)	4.8*	58*
			Placebo (n = 1,082)	11.0	—
IDPP (India, 2006, n = 531) (11)	• IGT on two occasions (persistent IGT)	30 months	Metformin 250 mg BID (n = 133)	40.5%*	26*
			Lifestyle modification (n = 133)	39.3%*	29*
			Lifestyle modification plus metformin (n = 129)	39.5%*	28*
			Control (standard health advice) (n = 136)	55.0%	—
CANOE (Canada, 2010, n = 207) (12)	• At least one risk factor for type 2 diabetes • IGT	3.9 years	Rosiglitazone + metformin (2 mg/500 mg combination capsule BID) (n = 103)	13.6%*	66*
			Placebo (n = 104)	39.4%	—

*P <0.05 compared to placebo or control. BID, twice daily.

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 and the combination of lifestyle with metformin. Despite 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 55% in the control group at 3 years, was 6.9, on par with the 6.4 with lifestyle modification (11).

Finally, the CANOE (Canadian Normoglycemia Outcomes Evaluation) trial, involving 207 people, evaluated metformin as part of a low-dose combination approach with rosiglitazone in the prevention of diabetes in 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 relative risk reduction in incidence of diabetes of 66%—an absolute

risk reduction of 26%—providing a number needed to treat of 4 (12).

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 β-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 β-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 2. Clinical Practice Recommendations Commenting on the Use of Metformin for the Prevention of Type 2 Diabetes, 2013–2018, Listed From Most Recent

Organization, Year	Name of Recommendation or Guideline	Recommendations Related to Metformin
American Diabetes Association, 2018 (23)	5. Prevention or Delay of Type 2 Diabetes: *Standards of Medical Care in Diabetes—2018*	Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially those with BMI ≥35 kg/m², those aged <60 years, and women with prior gestational diabetes.
International Diabetes Federation, 2016 (25)	Cost-Effective Solutions for the Prevention of Type 2 Diabetes	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.
Canadian Diabetes Association, 2013 (29)	2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Reducing the Risk of Developing Diabetes	In individuals with IGT, pharmacological therapy with metformin may be used to reduce the risk of type 2 diabetes.
IMAGE Project (European multidisciplinary consortium), 2010 (30)	A European Evidence-Based Guideline for the Prevention of Type 2 Diabetes	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.
Diabetes Australia, 2009 (31)	National Evidence Based Guideline for the Primary Prevention of Type 2 Diabetes	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.

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

Author Contributions

References

1. Bailey CJ. Metformin: historical overview. Diabetologia 2017;60:1566–1576

2. DPP Research Group. Design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care 1999;22:623–634

3. Knowler WC, Barrett-Connor E, Fowler SE, et al.; DPP Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403

4. Aroda VR, Knowler WC, Crandall JP, et al.; DPP Research Group. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. Diabetologia 2017;60:1601–1611

5. Ratner RE, Christophi CA, Metzger BE, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008;93:4774–4779

6. Aroda VR, Christophi CA, Edelstein SL, et al.; DPP Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program Outcomes Study 10-year follow-up. J Clin Endocrinol Metab 2015;100:1646–1653.

7. DPP Research Group. HbA1c as a predictor of diabetes and as an outcome in the Diabetes Prevention Program: a randomized clinical trial. Diabetes Care 2015;38:51–58

8. DPP Research Group; Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677–1686

9. DPP Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015;3:866–875

10. DPP Research Group; Hamman RF, Horton E, Barrett-Connor E, et al. Factors affecting the decline in incidence of diabetes in the Diabetes Prevention Program Outcomes Study (DPPOS). Diabetes 2015;64:989–998

11. Ramachandran A, Snehalatha C, Mary S, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289–297

12. Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. Lancet 2010;376:103–111

13. DPP Research Group. Effects of withdrawal from metformin on the development of diabetes in the Diabetes Prevention Program. Diabetes Care 2003;26:977–980

14. Retnakaran R, Qi Y, Harris SB, Hanley AJ, Zinman B. Changes over time in glycemic control, insulin sensitivity, and beta-cell function in response to low-dose metformin and thiazolidinedione combination therapy in patients with impaired glucose tolerance. Diabetes Care 2011;34:1601–1604

15. Ratner R, Goldberg R, Haffner S, et al. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. Diabetes Care 2005;28:888–894

16. Goldberg R, Temprosa M, Otvos J, et al. Lifestyle and metformin treatment favorably influence lipoprotein subfraction distribution in the Diabetes Prevention Program. J Clin Endocrinol Metab 2013;98:3989–3998

17. Goldberg RB, Temprosa MG, Mather KJ, et al. Lifestyle and metformin interventions have a durable effect to lower CRP and tPA levels in the diabetes prevention program except in those who develop diabetes. Diabetes Care 2014;37:2253–2260

18. Orchard TJ, Temprosa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med 2005;142:611–619

19. Goldberg RB, Aroda VR, Bluemke DA, et al.; DPP Research Group. Effect of long-term metformin and lifestyle in the Diabetes Prevention Program and its outcome study on coronary artery calcium. Circulation 2017;136:52–64

20. Lachin JM, Christophi CA, Edelstein SL, et al.; DPP Research Group Factors associated with diabetes onset during metformin versus placebo therapy in the Diabetes Prevention Program. Diabetes 2007;56:1153–1159

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

with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care 2012;35:731–737

22. Aroda VR, Edelstein SL, Goldberg RB, et al.; DPP Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016;101:1754–1761

23. American Diabetes Association. 5. Prevention or delay of type 2 diabetes: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S51–S54

24. U.S. Food and Drug Administration. Glucophage® (metformin hydrochloride) tablets; Glucophage® XR (metformin hydrochloride) extended-release tablets: description. Available from www.access data.fda.gov/drugsatfda_docs/label/201

7/020357s037s039,021202s021s023lbl.pdf. Accessed 8 May 2018

25. International Diabetes Federation. Cost-effective solutions for the prevention of type 2 diabetes. Available from www. idf.org/e-library/epidemiology-research/ diabetes-atlas/126-cost-effective- solutions-for-the-prevention-of-type-2- diabetes.html. Accessed 2 March 2018

26. DPP Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care 2012;35:723–730

27. Tseng E, Yeh HC, Maruthur NM. Metformin use in prediabetes among U.S. adults, 2005–2012. Diabetes Care 2017;40:887–893

28. Moin T, Li J, Duru OK, et al. Metformin prescription for insured adults with

prediabetes from 2010 to 2012: a retro- specive cohort study. Ann Intern Med 2015;162:542–548

29. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee; Ransom T, Goldenberg R, Mikalachki A, Prebtani AP, Punthakee Z. Reducing the risk of developing diabetes. Can J Diabetes 2013;37(Suppl. 1):S16–S19

30. Paulweber B, Valensi P, Lindstrom J, et al. A European evidence-based guideline for the prevention of type 2 diabetes. Horm Metab Res 2010;42(Suppl. 1):S3–S36

31. Colagiuri R, Girgis S, Gomez M, Walker K, Colagiuri S, O'Dea K. National evidence based guideline for the primary prevention of type 2 diabetes. Available from static. diabetesaustralia.com.au/s/fileassets/ diabetes-australia/b1126d58-2763-403a- bd2d-44a241bb9189.pdf. Accessed 2 March 2018