More Evidence for a Prevention-Related Indication for Metformin: Let the Arguments Resume!

William T. Cefalu[1] *and Matthew C. Riddle*[2]

Diabetes Care 2019;42:499–501 | https://doi.org/10.2337/dci18-0062

Global estimates of the number of individuals with diabetes are staggering, and the prevalence is reported to be increasing in most countries. In 2017, it was estimated that approximately 425 million adults (20–79 years of age) were living with diabetes and that half were undiagnosed (1). This number with diabetes is projected to increase to 629 million individuals by 2045 (1). An overwhelming majority of cases are attributable to type 2 diabetes. In the U.S., the latest projections identify over 30 million Americans living with diabetes (2). The numbers at risk for developing diabetes are also of great concern. Worldwide, 352 million people are thought to be at risk, with 84 million of those individuals in the U.S. (1,2).

The global diabetes burden imposes great personal costs to each individual and to society in general. Beyond the overall reduction of quality of life and productivity due to complications of diabetes, in 2017 diabetes was estimated to result in 4 million deaths worldwide (1). In addition, the International Diabetes Federation estimates that diabetes caused at least $727 billion (USD) in health expenditure in 2017—12% of total spending on adults (1). In the U.S., the estimated total costs of diagnosed diabetes have risen from $245 billion in 2012 to $327 billion in 2017, a 26% increase over a 5-year period (3). The growing personal burdens of diabetes are not acceptable given our research advances, and the costs of caring for diabetes are simply not sustainable! Thus, preventive strategies on a global scale remain a priority.

Clinical studies have provided extensive and growing evidence for the efficacy of preventive strategies (4–8). There is convincing support for using lifestyle modification (focused on healthy eating, weight loss, and enhanced physical activity) as the cornerstone of preventive therapy. We are encouraged by early results from lifestyle-based prevention strategies now being applied in real-world and community settings and in high-risk ethnic groups (9,10). However, it is clear that translation of lifestyle intervention is not always easy or effective. The results (notably, degree of weight loss and delay in diabetes development) achieved in clinical trials and in well-structured academic centers are not always replicated in real-world settings. Thus, key challenges for widespread implementation of preventive strategies remain despite considerable progress (8–14). A major and lingering concern is how to maintain lifestyle changes and their beneficial effects over extended periods of time on a community basis. Fortunately, additional evidence also supports the consideration of various pharmacologic therapies, in conjunction with lifestyle efforts, for preventing emergence of overt type 2 diabetes. In particular, there is clearly a need to develop evidence-based policies on the possible role of metformin in this setting.

The Diabetes Prevention Program (DPP) and its ongoing Diabetes Prevention Program Outcomes Study (DPPOS) has contributed greatly to this discussion. The DPP enrolled a population of 3,234 high-risk individuals, with randomized comparison of lifestyle modification, metformin, or placebo. The metformin group was assigned to take metformin 850 mg twice daily. An initial analysis after approximately 3 years of treatment demonstrated conclusively that both active interventions were effective in delaying the time to a new diagnosis of diabetes. At that time, progression to diabetes was reduced by 58% with lifestyle and 31% with metformin, relative to placebo. A large part of the DPP population has been followed subsequently in DPPOS, allowing refinement and extension of the early observations. Participants previously assigned to metformin were advised to continue taking it. Notably, later analyses have shown that metformin continues to protect against progression to overt diabetes over a long-term follow-up, especially in certain subgroups (15), and have demonstrated that the group randomized to metformin had reductions of some

[1]*American Diabetes Association, Arlington, VA*
[2]*Oregon Health & Science University, Portland, OR*

Corresponding author: William T. Cefalu, wcefalu@diabetes.org

See accompanying article, p. 601.

cardiovascular risk factors (16). A report after 10 years of follow-up showed that protection against progression from dysglycemia to overt diabetes was attained with both lifestyle modification and metformin when HbA_{1c} was used as a measure of outcome, as with fasting or postchallenge glucose in prior analyses (17).

Influenced in part by these findings, the American Diabetes Association (ADA) has been recommending (as outlined in its 2019 *Standards of Medical Care in Diabetes*) that "Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI $\geq$35 kg/m^2, those aged $<$60 years, and women with prior gestational diabetes mellitus" (18). In this issue of *Diabetes Care* is a new report from the DPP/DPPOS investigators that provides additional guidance on this clinical question, especially with regard to the most appropriate candidates for use of metformin to slow long-term progression to overt diabetes (19).

In this article, the Diabetes Prevention Program Research Group provides evidence that extends prior reports in several important ways. First, these analyses include data for an average follow-up of 15 years. Second, the separate analyses are done using both glucose measurements and also HbA_{1c} measurements (with individuals with HbA_{1c} $\geq$6.5% at baseline omitted from the analysis) for defining progression to diabetes. Third, statistical assessment of progression to diabetes was done both by a method describing relative risk (proportional hazard) and one based on rates (showing absolute differences). Fourth, subgroups by age, sex, ethnicity, BMI, prior history of gestational diabetes mellitus, and baseline fasting glucose and HbA_{1c} were systematically compared. A major strength of this comprehensive analysis is that the longer period of follow-up provides larger numbers of events and thus greater statistical power. Another is the inclusion of information about glycemic progression that is diagnosed by measurement of HbA_{1c}, a procedure now arguably more common, less burdensome, and less time-consuming than use of glucose tolerance testing.

Several findings are of particular interest. First, the analysis using HbA_{1c} $\geq$6.5% as a measure of outcome further supports the view that metformin compares favorably with lifestyle in its ability to delay progression of hyperglycemia. The initial report after 3 years of randomized treatment, using glucose values as the end point, found a 31% placebo-adjusted reduction of risk with metformin and 58% with lifestyle. The 10-year report using an HbA_{1c} end point measurement suggested incidence was reduced by 38% by metformin and 29% by lifestyle at this later time (17). The current analysis using HbA_{1c} suggests 36% lower risk with metformin versus placebo after 15 years (19). This was a post hoc analysis, by necessity using a subgroup of the overall DPP population, and therefore should be interpreted with caution as suggested by the authors. However, it offers reassurance that metformin can provide a quantitatively important reduction of risk of progression over this longer interval. It can be debated whether early therapeutic intervention in the DPP population should be regarded as "prevention" in the strict sense of this term or as an early intervention to limit dysglycemia over time, across a continuum of values. Nevertheless, metformin's ability to maintain HbA_{1c} below 6.5% for many individuals over 15 years must be considered a clinically relevant observation.

Other important observations concerned the subgroups of participants with greatest benefit from metformin. Metformin was more effective for participants whose fasting plasma glucose or HbA_{1c} was closer to diagnostic thresholds already. Confirmation that higher baseline glycemic measures suggest greater potential benefit from pharmacologic intervention comes as no surprise, as we recognize that there is a continuum of risk for values in the prediabetic range. Nevertheless, it provides a starting point for discussion regarding objective ways to identify individuals for whom pharmacologic intervention might be most desirable. The other subgroup with prominent benefit from metformin was, as in prior analyses, women with a history of gestational diabetes mellitus. The greatest advantage of using metformin in this subgroup was shown using glucose measurements as the measure of outcome. Unlike prior reports from the DPP, this analysis of 15-year data did not find that younger age and greater adiposity predict greater benefit from metformin. Instead, the present findings show substantial effectiveness of metformin in both women and men and over a wide range of age, adiposity, and ethnicity.

Overall, the current report from the DPP/DPPOS group provides strong support for further discussion of using metformin early in the evolution from dysglycemia to type 2 diabetes. It supports the view that HbA_{1c} values higher than 6.0% but not yet 6.5% or higher should prompt reconsideration of treatment strategies, potentially including pharmacotherapy. It also supports further discussion and heightened awareness of the need for postpartum screening of women with prior gestational diabetes mellitus. This very high-risk subgroup of women, typically in the 20–40 year age range, deserves special consideration for more vigorous preventive therapy to delay or prevent appearance of type 2 diabetes at an early age. While economic factors are beyond the scope of the present publication, these findings call for consideration of potential cost savings derived from using metformin for diabetes prevention (20).

It is also worth noting that, beyond the clinical trial results already discussed, our understanding of metformin has expanded in other ways. The remarkably improved cardiovascular outcomes among newly diagnosed patients in the UK Prospective Diabetes Study (UKPDS) who were assigned to metformin are well known and have led to study of its mechanisms of action. Although these are still not well understood, recent reports suggest that beyond effects on the liver there are direct effects on the intestinal epithelium leading to neural and hormonal signaling to the central nervous system and elsewhere (21,22). In the setting of dysglycemia or early type 2 diabetes, metformin treatment may be as effective as gastric banding with respect to effects on glycemic control and β-cell function (23). Data from the DPP/DPPOS cohort has provided evidence for certain microvascular and cardiac effects (16,24,25), but more information on these outcomes is needed. The risk of lactic acidosis as an adverse consequence of metformin therapy does not seem as great as has been feared, especially when dosage is reduced when renal impairment is present (26). Lower doses of metformin with delayed absorption may limit both blood levels and side

effects while retaining clinical actions (21,22).

This new information, too, deserves further consideration. Given the global burden of diabetes, it is clear we are at an important crossroad for diabetes prevention. There is a great need to evaluate all the lessons learned and to review all the incredible amount of data now available in order to take logical next steps as a society. We realize that lifestyle modification remains the cornerstone of diabetes prevention, yet long-term adherence is difficult and implementation can be labor intensive and costly and may face obstacles in real-world settings. Therefore, in order to be successful for diabetes prevention efforts, we need to continue to address these hurdles for successful lifestyle modification in a real-world setting. However, there is continued interest in preventive pharmacotherapy as an adjunct to lifestyle modification, and metformin continues to be the leading candidate. Its long-term efficacy and safety are well established. Although the ADA guidelines have, since 2008, endorsed consideration of metformin for individuals who are at very high risk for diabetes, further evolution of these guidelines may be needed. The latest report from the DPP/DPPOS investigators further supports the rationale for metformin as the most likely candidate for preventive strategies. More importantly, the data reported in this issue of *Diabetes Care* help to identify those individuals who would benefit most from this intervention. It is important to note that ADA's Standards of Care does not recommend use of other medications for diabetes prevention aside from metformin.

Despite a clear need for better means of preventing diabetes, the lack of a formal prevention-related indication for metformin is and will remain a significant barrier to more widespread use. Perhaps we are now ready to surmount this hurdle. We fully expect that, in the near future, discussion will resume as to when, for whom, and how metformin should be deployed as preventive therapy. Let the arguments begin!

Funding and Duality of Interest. No commercial sponsors contributed support. W.T.C. is an employee of the ADA. M.C.R. reports receiving research grant support through Oregon Health & Science University from Novo Nordisk and AstraZeneca and honoraria for consulting from Adocia, AstraZeneca, Dance, Elcelyx, Eli Lilly, GlaxoSmithKline, Novo Nordisk, Sanofi, and Theracos. These potential dualities of interest have been reviewed and managed by Oregon Health & Science University. No other potential conflicts of interest relevant to this article were reported.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 8th edition [Internet], 2017. Available from www.diabetesatlas.org. Accessed 18 January 2019
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017: Estimates of Diabetes and Its Burden in the United States [Internet]. U.S. Department of Health and Human Services, 2017. Available from https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed 18 January 2019
3. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917–928
4. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537–544
5. Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
6. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
7. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevention type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289–297
8. Cefalu WT, Buse JB, Tuomilehto J, et al. Update and next steps for real-world translation of interventions for type 2 diabetes prevention: reflections from a *Diabetes Care* Editors' Expert Forum. Diabetes Care 2016;39:1186–1201
9. Hall DL, Lattie EG, McCalla JR, Saab PG. Translation of the Diabetes Prevention Program to ethnic communities in the United States. J Immigr Minor Health 2016;18:479–489
10. Jiang L, Manson SM, Beals J, et al.; Special Diabetes Program for Indians Diabetes Prevention Demonstration Project. Translating the Diabetes Prevention Program into American Indian and Alaska Native communities: results from the Special Diabetes Program for Indians Diabetes Prevention demonstration project. Diabetes Care 2013;36:2027–2034
11. Albright AL, Gregg EW. Preventing type 2 diabetes in communities across the U.S.: the National Diabetes Prevention Program. Am J Prev Med 2013;44(Suppl. 4):S346–S351
12. U.S. Department of Health and Human Service. Independent experts confirm that diabetes prevention model supported by the Affordable Care Act saves money and improves health [Internet], 2016. Available from http://www.hhs.gov/about/news/2016/03/23/independent-experts-confirm-diabetes-prevention-model-supported-affordable-care-act-saves-money.html. Accessed 19 January 2019
13. Fradkin JE, Roberts BT, Rodgers GP. What's preventing us from preventing type 2 diabetes? N Engl J Med 2012;367:1177–1179
14. Kahn R, Davidson MB. The reality of type 2 diabetes prevention. Diabetes Care 2014;37:943–949
15. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program 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
16. Aroda VR, Knowler WC, Crandall JP, et al.; Diabetes Prevention Program Research Group. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. Diabetologia 2017;60:1601–1611
17. Diabetes Prevention Program Research Group. HbA_{1c} as a predictor of diabetes and as an outcome in the diabetes prevention program: a randomized clinical trial. Diabetes Care 2015;38:51–58
18. American Diabetes Association. 3. Prevention or delay of type 2 diabetes: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S29–S33
19. Diabetes Prevention Progam Research Group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. Diabetes Care 2019;42:601–608
20. Herman WH. The cost-effectiveness of diabetes prevention: results from the Diabetes Prevention Program and the Diabetes Prevention Program Outcomes Study. Clin Diabetes Endocrinol 2015;1:9
21. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia 2017;60:1577–1585
22. Buse JB, DeFronzo RA, Rosenstock J, et al. The primary glucose-lowering effect of metformin resides in the gut, not the circulation: results from short-term pharmacokinetic and 12-week dose-ranging studies. Diabetes Care 2016;39:198–205
23. Xiang AH, Trigo E, Martinez M, et al.; RISE Consortium. Impact of gastric banding versus metformin on β-cell function in adults with impaired glucose tolerance or mild type 2 diabetes. Diabetes Care 2018;41:2544–2551
24. Diabetes Prevention Program 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
25. Goldberg RB, Aroda VR, Bluemke DA, et al.; Diabetes Prevention Program 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
26. Lalau J-D, Kajbaf F, Bennis Y, Hurtel-Lemaire A-S, Belpaire F, De Broe ME. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. Diabetes Care 2018;41:547–553