AMA
AMERICAN MEDICAL ASSOCIATION

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February 11, 2021

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Chief Medical Officer and Director
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Dear Dr. Fleischer:

The American Medical Association (AMA) is following up on the recent review by the Measure Application Partnership (MAP) on the Centers for Medicare & Medicaid Services (CMS) 2020-2021 Measure Under Consideration (MUC) list. Specifically, we are following up on the review of measure, *MUC20-0040 Intervention for Prediabetes eCQM*, which the AMA developed through a multi-stakeholder technical expert panel (TEP) that included representatives from the Centers for Disease Control and Prevention (CDC), American Academy of Family Physicians (AAFP), and the Endocrine Society. The AMA closely followed the MAP deliberations and believes that there was a great misunderstanding of the evidence base supporting the measure and the National Quality Forum (NQF) review of the measure did not consistently adhere to the NQF endorsement process and measure evaluation criteria.

Prevention of type 2 diabetes is imperative to bending the cost curve and the COVID-19 pandemic has further shined a spotlight on the importance and need for preventing diabetes. In a recent retrospective review of commercial administrative claims, researchers identified that within at least five years prior to the initial diabetes diagnosis, health care costs begin to rise and continue to increase once the diagnosis is confirmed.[1] This finding supports efforts to identify and address prediabetes before it progresses to type 2 diabetes, and why the AMA prioritized activating health care organizations across the U.S. to help them in identifying and managing more people at risk for type 2 diabetes. Therefore, we offer the following specific feedback to address concerns raised by the MAP Clinician Workgroup/Coordinating Committee and public comments:

1. Expansion of the numerator to include physician or physical therapist counseling: The evidence-base and clinical recommendations support intensive behavioral counseling, which is typically delivered by a qualified non-physician health coach.[2,3] Brief counseling to prevent type 2 diabetes does not have an equivalent evidence base demonstrating effectiveness.[4,5,6]

2. Inclusion of Metformin in the numerator will encourage over prescribing of medication: Metformin has a Level A rec from American Diabetes Association (ADA), and it is also recommended by the American Association of Clinical Endocrinology (AACE).[7,8] Including Metformin in the numerator does not assume that Metformin is a "first-line treatment," but rather a safe and effective preventive *option* to offer to patients who may not be willing or able to access intensive lifestyle therapy due to their personal preferences and circumstances **(see attached for literature).** The AMA multi-stakeholder TEP also considered this concern and

there was agreement that there should be more than one option, including the option to meet the numerator by prescribing Metformin, which is well supported by evidence.[9]

3. Prediabetes as a diagnosis vs. risk factor: Prediabetes is a condition recognized by numerous public health and health care organizations including the CDC, ADA, and AACE.[7,8,10] Debate regarding whether it is a disease, condition, or risk factor should not detract from the fact that prediabetes is a state with clear elevated risk for subsequent development of type 2 diabetes and cardiovascular disease.[11] Moreover, effective preventive interventions are available to prevent type 2 diabetes—interventions which are already supported by the CDC's National Diabetes Prevention Program and the Medicare Diabetes Prevention Program. Prediabetes identification and prevention of type 2 diabetes is a recognized priority by the National Clinical Care Commission.

4. Referral and follow-up by the patient to a Diabetes Prevention Program (DPP) or Nutrition Counseling is expensive and could increase the costs that patients must cover themselves: Medicare covers CDC-recognized Diabetes Prevention Programs through the Medicare DPP benefit as part of Medicare Part B without cost-sharing.

5. The measure did not receive NQF endorsement: The measure passed all the NQF "must pass" measure evaluation criteria (Importance to Measure and Report and Scientific Acceptability of the Measure Properties), yet the Standing Committee did not vote to endorse the measure. There also was a general inconsistency in committee deliberations across the three measures under review and the AMA never received a clear response from NQF staff or the Standing Committee on why a measure that passed all of the criteria was not endorsed.

We also would like to once again reiterate our disappointment with CMS' decision to not move forward and place on the 2020-2021 MUC list the two other measures (*Screening for Abnormal Blood Glucose eCQM* and *Retesting of Abnormal Blood Glucose in Patients with Prediabetes eCQM*) the AMA developed and proposed to address diabetes prevention. We believe that a fairer assessment would have been made by the MAP had all three measures moved forward for consideration in the Merit-based Incentive Program (MIPS). The three measures were developed as a suite and are a direct response to feedback we received from the healthcare institutions with whom the AMA has partnered, including the CDC. The Intervention measure is intended to be driven by the numerator of the Screening measure, so if only the Intervention measure is approved, we lose out on the critical screening component.

These measures address clear gaps in care. A study examining National Health and Nutrition Examination Survey (NHANES) data estimated that only 46 percent of adults meeting abnormal glucose screening criteria have received a laboratory test.[12] Even more strikingly, a study using National Health Interview Survey data found that only four percent of people with prediabetes reported being referred to a DPP lifestyle change program, and another systematic review estimated that between one and eight percent of people with prediabetes have received Metformin.[9,13] Additionally, the National Health Interview Survey asked people who had a diagnosis of prediabetes whether they had recent laboratory re-testing and 81 percent reported that they had a glucose test within the past year.[14] It is important to note that the methodology involved analyzing people who knew they had a diagnosis of prediabetes, which is estimated to be 15 percent of the prediabetes population.[10] So, the actual percentage of people with prediabetes who do receive annual laboratory re-testing is likely lower.

The AMA appreciates CMS' desire to focus on an outcome measure, such as reduced population incidence of type 2 diabetes. While we agree that an outcome measure should be the ultimate goal, we must allow and encourage physicians and health care systems to put processes in place first to address these significant care gaps. The AMA has heard from clinical champions that there is a need for enhanced quality improvement processes for prediabetes screening, management, and re-testing in order to provide clinical teams with a population approach for reaching clinical outcomes. That is the impetus behind the Screening and Re-testing measures. Without improving screening and laboratory monitoring for people with prediabetes, health systems will not be able to accurately estimate patient or population outcomes like changes in glycemic status or type 2 diabetes incidence. In addition, there is great interest in the measures by state government agencies, including Medicaid, as well as the Center for Medicare and Medicaid Innovation (CMMI) and including the measures as part of the MIPS program would better align the program with what is going on at the local level and APM adoption and allow physicians to more uniformly adopt measures across programs. Furthermore, the measures are eCQMs so supports CMS' goal of full digital measure adoption by 2025.

We remind CMS that section 1848(q)(2)(D)(viii) of MACRA does not require CMS to utilize the Measure Application Partnership (MAP) to provide guidance into the pre-rulemaking process on the selection of MIPS quality measures, but requires the Secretary to consult with relevant eligible clinician organizations, including state and national medical societies. Therefore, CMS has the flexibility regardless of the MAP review.

The AMA appreciates CMS' consideration of our concerns and welcomes the opportunity to clarify or discuss anything further. We are happy to coordinate a call with CMS to walk through and explain the challenges with the recommendations made by the MAP. To schedule a call or if you have any follow-up questions please contact Koryn Rubin, Assistant Director, Federal Affairs at koryn.rubin@ama-assn.org.

Sincerely,

James L. Madara, MD

Attachment

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HHS Public Access

Author manuscript

Am J Prev Med. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Am J Prev Med. 2018 October ; 55(4): 565–574. doi:10.1016/j.amepre.2018.04.038.

Review of Metformin Use for Type 2 Diabetes Prevention

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Abstract

Context: Prediabetes is prevalent and significantly increases lifetime risk of progression to type 2 diabetes. This review summarizes the evidence surrounding metformin use for type 2 diabetes prevention.

Evidence acquisition: Articles published between 1998 and 2017 examining metformin use for the primary indication of diabetes prevention available on MEDLINE.

Evidence synthesis: Forty articles met inclusion criteria and were summarized into four general categories: (1) RCTs of metformin use for diabetes prevention (n=7 and n=2 follow-up analyses), (2) observational analyses examining metformin use in heterogeneous subgroups of patients with prediabetes (n=9 from the Diabetes Prevention Program, n=1 from the biguanides and the prevention of the risk of obesity [BIGPRO] trial), (3) observational analyses examining cost effectiveness of metformin use for diabetes prevention (n=11 from the Diabetes Prevention

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All authors made substantial contributions to conception and design or analysis and interpretation of data and drafting of the article or critical revision for important intellectual content. TM wrote the first draft of the manuscript. TM, JAS, JF, JY, LD, WH, and EW analyzed the data. All authors reviewed and edited the manuscript. TM is the guarantor of this article.

TM, JAS, JHF, LK, JHY, CMM, WHH, EAW have no financial disclosures. AJK receives funding from AstraZeneca, Co. for an unrelated independent investigator study.

CM is a member of the U.S. Preventive Services Task Force. This article does not necessarily represent the views and policies of the U.S. Preventive Services Task Force.

Program, *n*=1 from the Indian Diabetes Prevention Program), and (4) real-world assessments of metformin eligibility or use for diabetes prevention (*n*=9). Metformin was associated with reduced relative risk of incident diabetes, with the strongest evidence for use in those at highest risk (i.e., aged <60 years, BMI ≥35 kg/m^2, and women with histories of gestational diabetes). Metformin was also deemed cost effective in 11 economic analyses. Recent studies highlighted low rates of metformin use for diabetes prevention in real-world settings.

Conclusions: Two decades of evidence support metformin use for diabetes prevention among higher-risk patients. However, metformin is not widely used in real-world practice and enhancing the translation of this evidence to real-world practice has important implications for patients, providers, and payers.

CONTEXT

More than 30 million U.S. adults have type 2 diabetes and diabetes-related healthcare costs account for 20% of healthcare spending.[1-3] Despite recent decreases in rates of diabetes-associated complications, the high prevalence of type 2 diabetes (referred to as diabetes throughout this manuscript) creates a significant societal burden.[2] Prediabetes is an intermediate metabolic state between normoglycemia and diabetes,[4] including either impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or both conditions. The risk of progression to diabetes is greater for individuals with IGT and IFG close to the diagnostic boundary for diabetes. On average, about 15%–30% of adults with prediabetes are expected to progress to diabetes in 5 years.[5] From a population perspective, this risk is substantial given the high prevalence of prediabetes.

Accordingly, numerous studies have examined the efficacy of behavioral/lifestyle and pharmacologic interventions in preventing or delaying incident diabetes among individuals with prediabetes. Metformin is not approved by the Food and Drug Administration (FDA) for use in prediabetes, but several studies have examined its use for diabetes prevention over the past two decades. The objective of this study is to review the literature to better understand the current state of evidence surrounding metformin use for diabetes prevention.

EVIDENCE ACQUISITION

Data Sources and Searches

Standard strategies for literature reviews were used to identify studies, determine eligibility, and summarize findings as described below. A MEDLINE search was conducted using the following Medical Subject Heading terms and text words (*prediabetes* AND *metformin*). Searches were limited to literature published in English.

Study Selection

To be eligible, studies had to address metformin use for diabetes prevention or diabetes risk reduction as the primary outcome. Studies had to be published between January 1, 1998 and December 31, 2017. Randomized clinical trials and associated analyses (i.e., reports of longitudinal follow-up and subgroup analyses) were included. Trial protocols, reviews, commentaries/opinion pieces, and animal studies (i.e., non-human subjects) were excluded.

Studies that examined metformin use in combination with other antihyperglycemic agents were also excluded.

Data Extraction and Quality Assessment

Studies were reviewed by one or more independent co-authors to assess initial eligibility. Data were extracted using a standardized template with no masking to author lists or journals. A multidisciplinary team with diverse expertise in both clinical and research disciplines including internal medicine, endocrinology, health services, epidemiology, and health economics contributed to this review. Two independent team members reviewed all eligible studies to confirm eligibility and accuracy of data extraction. Reference lists were also reviewed in detail, cited reference searches for included manuscripts were conducted, and discussions with topic experts also yielded additional studies for review. The Cochrane Risk of Bias Tool was used for quality assessment of RCTs.[6,7]

Data Synthesis and Analysis

Forty articles met inclusion criteria (a Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow diagram[8] is presented in Figure 1). After detailed review, manuscripts were further divided into four broad categories, as summarized in more detail below; (1) RCTs of metformin use for diabetes prevention (n=7 RCTs and n=2 follow-up analyses), (2) analyses examining metformin use in heterogenous subgroups of patients with prediabetes (n=9 subgroup analyses from the Diabetes Prevention Program [DPP], n=1 from the Biguanides and the Prevention of the Risk of Obesity [BIGPRO] trial), (3) analyses examining cost effectiveness of metformin use for diabetes prevention (n=11 analyses from the DPP, n=1 analysis from the Indian DPP), and (4) real-world assessments of metformin eligibility or use for diabetes prevention (n=9).

EVIDENCE SYNTHESIS

RCTs of Metformin Use for Diabetes Prevention

The DPP is the largest RCT examining metformin use for diabetes prevention.[9] Eligible participants from 27 U.S. medical centers were randomized to metformin (850 mg twice per day [bid], n=1,073), or an intensive lifestyle intervention (16 weekly, one-on-one lifestyle intervention sessions with a health coach and monthly follow-up thereafter, n=1,079), or placebo (n=1,082). Over 2.8 years of follow-up, diabetes incidence was significantly reduced by 31% (95% CI=17%, 43%) in the metformin arm and by 58% (95% CI=48%, 66%) in the intensive lifestyle intervention arm as compared with placebo. The intensive lifestyle intervention arm provided 39% (95% CI=24%, 51%) relative risk reduction of incident diabetes compared with metformin across the pooled sample and was also effective for individuals aged >60 years (where metformin was not significantly better than placebo). However, relative risk reduction for incident diabetes was comparable between the metformin and lifestyle intervention arms for participants with a BMI ≥35 kg/m^2 and women with histories of gestational diabetes.

About 88% (n=2,776) of the DPP cohort enrolled in a long-term follow-up study known as the DPP Outcomes Study (DPPOS).[10,11] Over a total of 10 years of combined follow-up,

diabetes incidence was reduced by 18% (95% CI=7%, 28%) in the metformin arm and by 34% (95% CI=24%, 42%) in the intensive lifestyle intervention arm, compared with placebo.[10] In the 15-year follow-up report, participant data was analyzed by intervention arm using an intent-to-treat analytic approach and diabetes incidence was reduced by 18% in the metformin arm (hazard ratio [HR]=0.82, 95% CI=0.72, 0.93) and by 27% in the intensive lifestyle intervention arm (HR=0.73, 95% CI=0.65, 0.83), compared with placebo.[11]

Six additional randomized trials have examined metformin for diabetes prevention. As compared to the DPP, these were much smaller studies, with a total of 2,513 participants, from China,[12] India,[13,14] Pakistan,[15] Greece,[16] and the United Kingdom.[17] Eligibility criteria varied (i.e., IGT, or IFG, or BMI), as did metformin dosing (ranging between 250 mg and 500 mg, bid or three times a day [tid]). In 1999, prior to the DPP, Li and colleagues[12] had randomized 90 participants between age 30 and 60 years with IGT to placebo versus metformin 250 mg tid in Beijing, China. As treated analyses of data from 70 participants at 12 months follow-up showed significantly lower rates of incident diabetes in the metformin arm (3.0% vs 16.2%, p=0.001). In 2003, Holman et al.[17] randomized 631 participants with IFG from nine United Kingdom centers to metformin 500 mg tid, or acarbose 50 mg tid, or placebo, or combination therapy. The authors reported no difference in relative risk reduction of incident diabetes in the metformin arm compared with placebo over 6 years of follow-up (of note, these results were published in a brief abstract, not a complete publication).[17]

In the Indian DPP, Ramchandran and colleagues[13] randomized 531 participants with IGT to standard lifestyle (control), intensive lifestyle (personal sessions every 6 months and monthly telephone calls focused on individualized lifestyle change goals), metformin 250 mg–500 mg bid, or intensive lifestyle and metformin 250 mg–500 mg bid (almost all patients only ever received 250mg bid). Over 30 months of follow-up, the relative risk reduction for incident diabetes was 26.4% (95% CI=19.1, 35.1, p=0.029) with metformin alone, 28.2% (95% CI=20.3, 37.0, p=0.022) with intensive lifestyle and metformin and 28.5% with lifestyle alone (95% CI=20.5, 37.3, p=0.018), as compared with placebo. Thus, both lifestyle and metformin significantly reduced diabetes incidence but there was no additive benefit when they were combined.[13]

Iqbal et al.[15] also examined metformin in combination with lifestyle intervention. They randomized 317 participants with IGT to control, or intensive lifestyle (one-on-one counselling sessions every 2 months with specific goals including ≥5% weight loss), or intensive lifestyle and metformin 500 mg bid. Relative risk reduction of incident diabetes was 71% for lifestyle alone (95% CI=13.7, 90.3) and 76.5% (95% CI=19.7, 93.1) for lifestyle and metformin compared with control. The 5.5% difference in risk reduction between the two interventions arms was not statistically significant.[15]

In the Greek study by Andreadis and colleagues,[16] 366 participants with BMI>27 kg/m^2 were randomized to standard lifestyle and cardiovascular risk factor management or standard lifestyle and cardiovascular risk factor management and metformin 850 mg once daily. Diabetes incidence was reduced by 7% (95% CI=12.7%, 1.4%, p=0.012) in the metformin

arm across all participants. The degree of relative risk reduction was 18.5% (95% CI=33.1%, 3.9%, p=0.010) among the subset of participants with IFG or IGT at baseline (n=110).[16] A 2016 RCT by Weber et al.[14] randomized 578 overweight/obese Asian Indians with IGT, IFG, or IGT and IFG to lifestyle intervention and stepwise addition of metformin 500 mg bid at ≥4 months if at high risk of converting to diabetes (IFG and IGT or IFG and glycosylated hemoglobin [HbA1c] ≥5.7%) versus control. At 3 years follow-up, significantly fewer intervention participants developed incident diabetes (25.7% vs 34.9%, p=0.014). Relative risk reduction was 32% (95% CI=7, 50), and the number needed to treat to prevent one case of diabetes was 9.8.

All but one[17] of the RCTs included in this review found metformin to be an effective means of lowering risk of incident diabetes among individuals with prediabetes, although the degree of relative risk reduction varied widely. Some of this variability may be attributable to differences in eligibility criteria and hence risk of diabetes, dosages of metformin and length of follow-up. The study by Holman and colleagues[17] was the only RCT that did not find a significant reduction in risk of incident diabetes, but the authors reported that ≅14% of participants were lost to follow-up and that among those who had not developed diabetes, only 39% were taking metformin. Overall, risk of bias was high among RCTs except the DPP. Thus, the strongest and highest quality RCT evidence comes from the DPP.

Analyses Examining Metformin Use in Heterogenous Subgroups of Patients With Prediabetes

Data from the DPP was used to conduct nine subanalyses examining metformin use in heterogeneous subgroups of patients with prediabetes (Appendix Table 2). These subgroup analyses have assessed the influence of metformin withdrawal,[18] body size,[19,20] body shape, [19, 20] autonomic nervous system function,[21] age,[22,23] genetic diabetes risk scores,[24] diabetes risk,[25] and race[26] on development of diabetes among the DPP cohort.

Data from these subgroup analyses suggest that metformin may be more effective among individuals with higher diabetes risk, younger age, higher BMI, higher fasting glucose levels, and possibly African American race. In addition, withdrawal from metformin over 1–2 weeks after the DPP (i.e., a per protocol analysis during the bridge between DPP and DPPOS) decreased the magnitude of relative diabetes risk reduction associated with metformin use from 31% to 25%, suggesting at least partial direct pharmacological benefits (i.e., diabetes was prevented or delayed, not just masked).[18] In a few instances, findings appear somewhat contradictory, prompting the need for caution when interpreting findings. For example, Hivert et al.[24] concluded there is no definitive evidence that the efficacy of metformin is influenced by genetic loci associated with diabetes risk, which differs markedly from the post-hoc non-genetic risk stratification analysis by Sussman and colleagues.[25] Also, an analysis using an HbA1c-defined outcome of incident diabetes for DPP participants showed that treatment interactions with age were not statistically significant,[23] contrasting the significant age and treatment interactions observed in the DPP with a glucose-defined diabetes outcome. In fact, metformin and lifestyle intervention were equally effective when HbA1c was used to define the outcome of incident diabetes.[23] In another example, Fujimoto et al.[20] reported that relative risk reductions of incident diabetes

in the DPP metformin arm appear to be independent of changes in adiposity whereas the DPP Research Group has shown metformin to be as effective as lifestyle intervention in preventing diabetes in individuals with a baseline BMI ≥35 kg/m^2 or a waist circumference ≥98.0 cm.

One subgroup analyses was based on BIGPRO1, which randomized 457 participants with high waist-to-hip ratios to metformin versus placebo. The original trial findings, published in 1996, showed improvements in weight, total cholesterol, as well as glucose and insulin levels in the metformin arm.[27] A 2009 post-hoc analysis examined the effects of metformin on the subset of patients that would have met criteria for prediabetes showing significant reductions in fasting plasma glucose, systolic blood pressure, and total and low-density lipoprotein cholesterol, as compared with placebo after adjustment for age and gender.[28]

Overall, these subgroup analyses may be underpowered for some comparisons and results should be interpreted with caution because evidence from post-hoc analyses is less strong for establishing causal inference. Data from these subgroups and post-hoc analyses should ideally be confirmed using prospective, hypothesis-driven study designs with adequate controls.

Analyses Examining Cost Effectiveness of Metformin Use for Diabetes Prevention

Twelve analyses have focused on the cost effectiveness (i.e., <$50,000 per quality-adjusted life year cut off) of metformin use for diabetes prevention (Appendix Table 3). Eleven of these are based on data from the DPP[29-39] and one was based on data from the Indian DPP.[40] All but one economic analysis[33] concluded that metformin use for diabetes prevention is cost effective. There is also some evidence to suggest that metformin may even be cost saving.[37] Several analyses have also shown metformin as a cost-effective strategy for diabetes prevention or delay when DPP data are extrapolated to other countries.[34-36,39,41,42] Data from the Indian DPP demonstrated metformin to be a cost-effective intervention for preventing diabetes in India.[40]

The majority of these analyses were based on the original DPP design and were applicable to the healthcare settings and funding circumstances at the time the analyses were conducted. The results of economic analyses are driven by the cost of both interventions and outcomes, and these do vary widely across settings. However, the analyses presented reflect a variety of settings across both high- and middle-income countries and in each instance, metformin was cost effective.

Real-World Assessments of Metformin Eligibility or Use for Diabetes Prevention

Nine analyses have assessed metformin eligibility or use for diabetes prevention (Appendix Table 4). The first was a 2010 cross-sectional analysis using National Health and Nutrition Examination Survey data to assess the proportion of U.S. adults with prediabetes meeting American Diabetes Association (ADA) consensus panel recommendations for metformin eligibility for prevention or delay of diabetes.[43] The ADA consensus panel criteria for metformin use included the presence of both IFG and IGT, with more than one additional diabetes risk factor: age<60 years, BMI>35 kg/m^2, family history of diabetes, elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, or HbA1c >6.0%.

[44] The authors concluded that >96% of adults with IFG and IGT were likely to meet ADA consensus panel recommendations for metformin use. Thus, if this sample were representative of the U.S. population, it would equate to approximately one in 12 U.S. adults meeting ADA consensus panel criteria for metformin use.

The remaining real-world assessments are retrospective cohort analyses examining metformin use for diabetes prevention/prediabetes. These studies either used data from electronic health records,[45-48] insurance claims,[49,50] and national surveys.[51,52] These real-world assessments have been predominantly focused on commercially insured adults but one claims-based analysis focused on Medicaid beneficiaries.[50] Overall, the rates of metformin use ranged from <1% to 8.1% but there were important differences in the populations (i.e., age, gender, region of care, prediabetes diagnostic criteria, study windows) that may have explained some of this variation.

Rates of metformin use among higher risk groups, such as women with gestational diabetes, age <60 years, and elevated BMI, were estimated by three studies and ranged between 0% and 17.5%, depending on the subgroups and data source.[53] In three studies where predictors of metformin use were also examined, obesity or higher BMI was associated with higher likelihood of metformin use.[49,50,52] Other predictors of metformin use reported by at least one study included female sex,[49] African American race,[50] presence of other comorbidities,[49,50] older age,[50] and higher glucose levels.[52]

DISCUSSION

This review provides a comprehensive summary of the literature on metformin use for diabetes prevention published between 1998 and 2017. The DPP is the largest RCT conducted to date, therefore much of the evidence to support metformin use for diabetes prevention is derived from this one trial. However, the DPP was also the most rigorously designed study with the longest follow-up, providing the highest quality evidence from which to draw conclusions. The evidence accumulated from the DPP, as well as other analyses over the last two decades included in this review, strongly suggest that metformin is effective, particularly among subsets of higher-risk patients. A prior meta-analysis of data from the DPP,[9] Indian DPP,[13] and a 1999 trial by Li and colleagues[12] showed metformin use was associated with an absolute risk reduction for diabetes progression ranging from 4.4% to 14.3% and a number needed to treat between seven and 14 over a 3 year period.[54] As noted by the Lily et al.,[54] these effect sizes are quite meaningful on a population level and comparable with other treatments routinely used in clinical care. These data also demonstrate that metformin is safe, tolerable, cost effective, and possibly even cost saving. However, recent assessments show that metformin is rarely used in real-world settings, highlighting an important gap that needs further study.[45,46,49]

Amidst intensive national efforts to curb the growing diabetes epidemic and reduce healthcare expenditures, researchers and policy makers should examine ways in which the evidence supporting metformin use can be translated into real-world settings for patients at highest risk. The lack of clear “eligibility” criteria for metformin use in routine care is an important translational barrier. In most studies, the oral glucose tolerance test (OGTT) has

been used to identify individuals with IGT as potential candidates (Table 1). However, OGTT is not commonly used in practice and the definition of prediabetes has now been expanded to include IGT, IFG, and abnormal HbA1c. Because no trials have examined the effectiveness of metformin using these broader prediabetes definitions, there is no evidence to support metformin use for all 84 million U.S. adults currently estimated[1] to have prediabetes. Thus, additional studies discerning clear real-world criteria for eligibility for metformin use for diabetes prevention may be helpful in deciphering which patients should be considered for metformin therapy.[55]

Studies to date demonstrate that metformin use may be beneficial in subsets of the patients who are at higher risk of progression to diabetes. For example, when HbA1c was used to define the outcome of incident diabetes in a DPP post-hoc analysis, metformin and lifestyle interventions were equally effective, contrasting the OGTT-based outcome showing lifestyle interventions as the most effective therapy.[23] Therefore, there may be some evidence to suggest that patients with abnormal HbA1c, particularly those with HbA1c values in the upper end of the prediabetes range (i.e., 6.0%–6.4%), may benefit from metformin therapy. Examination of treatment effects within the DPP and DPPOS demonstrate significant heterogeneity, such that obese participants (BMI 35 or more kg/m^2), those with higher fasting glucose levels, and women with a history of gestational diabetes had greater risk reduction with metformin.[10,11,56] Sussman and colleagues[25] also showed that DPP participants in the highest risk quarter averaged an absolute risk reduction of 21% over 3 years, with number needed to treat close to five. Similarly, Herman et al.[57] showed an absolute risk reduction of 25% among DPP participants at highest risk of developing diabetes who adhered to metformin. Thus, there is evidence to suggest that metformin use would be reasonable to consider in certain subsets of patients with prediabetes at higher risk.

Because patients with prediabetes have varying risk levels, understanding which patients are most likely to benefit from metformin use for diabetes prevention is critical to informing discussions regarding the risks versus benefits of this potential therapy. The DPP Research Group recently developed multivariate models to predict individual risk of progression to diabetes and reversion to normal glucose regulation using clinical variables routinely collected in practice.[57] The DPP Research Group plans to make these risk prediction models accessible on the DPPOS website to guide prediabetes care decisions.

Even in higher risk patients where metformin use should be considered, safety considerations may also be a barrier. Common side effects related to metformin include mild gastrointestinal effects (e.g., diarrhea, nausea, abdominal pain) and vitamin B12 deficiency.[58] To mitigate against these side effects, the metformin dose can be titrated slowly[59] and routine testing of vitamin B12 can also be considered.[58] The most worrisome side effect of metformin is lactic acidosis, but this is extremely rare. A 2010 Cochrane review, examining the risk of fatal and nonfatal lactic acidosis among 70,490 patient-years of metformin use, concluded that “there is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other antihyperglycemic treatments.”[60] Impaired renal function is an important risk factor for lactic acidosis but the FDA has revised warnings to expand metformin use in certain patients with diabetes and

reduced renal function.[61] However, there is no FDA indication for metformin use in prediabetes. This may present another barrier[62] because FDA labeling can play an important role in medication prescription patterns.[63] Other potential barriers to metformin use include possible lack of marketing to providers and patients, related to both lack of FDA approval and the limited potential for financial gain by manufacturers because of the availability of many inexpensive generic preparations; reluctance to "medicalize" prediabetes; limited awareness of prediabetes; and advocates against metformin use.[46,62,64] In a recent study, only 6% of primary providers surveyed were able to correctly identify risk factors that warrant prediabetes/diabetes screening and only 17% correctly identified the laboratory parameters for diagnosing prediabetes.[53] Studies have also shown that physician attitudes toward prediabetes can vary significantly and this variation impacts prediabetes care, including recommendations for treatment that patients may or may not receive. [65]

Although evidence over the last two decades suggests metformin may be a safe, effective, and potentially cost-saving therapy, intensive lifestyle programs must be reinforced as first line treatment for all patients with prediabetes. Thus, national efforts are underway to translate intensive lifestyle programs and make them more readily available across the U.S. [66,67] In recent years, national care guidelines have begun to endorse metformin use for diabetes prevention, particularly for higher risk patients, while still recognizing that lifestyle interventions are first-line and provide the greatest overall relative risk reduction (Table 1).[68] Intensive lifestyle intervention was associated with the largest relative risk reduction overall in the DPP and also the greatest weight reduction in one of the first comparative effectiveness trials of intensive lifestyle intervention, metformin versus standard care in Hispanic women with prediabetes.[69] Outside of study settings, however, the majority of patients with prediabetes do not receive any recommendation for treatment (lifestyle or metformin)[48,46,51,65] and most patients are not even aware of their prediabetes diagnosis.[64] Thus, it is more important than ever to address the many existing gaps in prediabetes care to ensure patients are informed and empowered to reduce their diabetes risk.

CONCLUSIONS

The current evidence suggests that metformin is an effective, safe, tolerable, cost effective, and possibly even cost-saving intervention to prevent or delay incident diabetes. Evidence for metformin use is strongest in those with IGT and IFG at higher risk; age 60 or less years, BMI 35 or more kg/m^2, and in women with histories of gestational diabetes. Despite growing evidence, recent studies show metformin is rarely used in real-world settings, even among the highest risk patients. This is an important gap in knowledge patients, providers, payers, and policy makers should be aware of. Stakeholders should work together to understand the barriers to meaningful translation of nearly two decades of evidence supporting metformin use for diabetes prevention into the real world. Lifestyle intervention remains the first-line treatment, but metformin is an evidence-based treatment option that can also be considered for higher-risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors would like to thank Ms. Karen R. Estacio of Kaiser Permanente Northern California Division of Research for her editorial support.

TM received support from the Department of Veterans Affairs (QUE 15-272, 15-286), Centers for Disease Control and Prevention (CDC; U18DP006140), and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; R18DK105464). JAS and AJK received support for this work from the Health Delivery Systems Center for Diabetes Translational Research (P30 DK092924). JHF was partially supported by Agency for Healthcare Research and Quality (K08 HS023898-01). HCY was partially supported by NIH grant P30DK079637. CMM received support from the University of California at Los Angeles (UCLA), Resource Centers for Minority Aging Research Center for Health Improvement of Minority Elderly under NIH/National Institute of Aging under Grant P30AG021684, by the NIDDK of NIH under Grant R18DK105464, the CDC under Grant U18DP006140 and from NIH/National Center for Advancing Translational Sciences UCLA Clinical and Translational Science Institute under Grant UL1TR000124. CM holds the Barbara A. Levey and Gerald S. Levey Endowed Chair in Medicine, which partially supported her work. WHH was partially support by NIH grant DK092926. EAW received support from NIH grant DK020541 and DK111022.

Funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs, CDC, or NIH.

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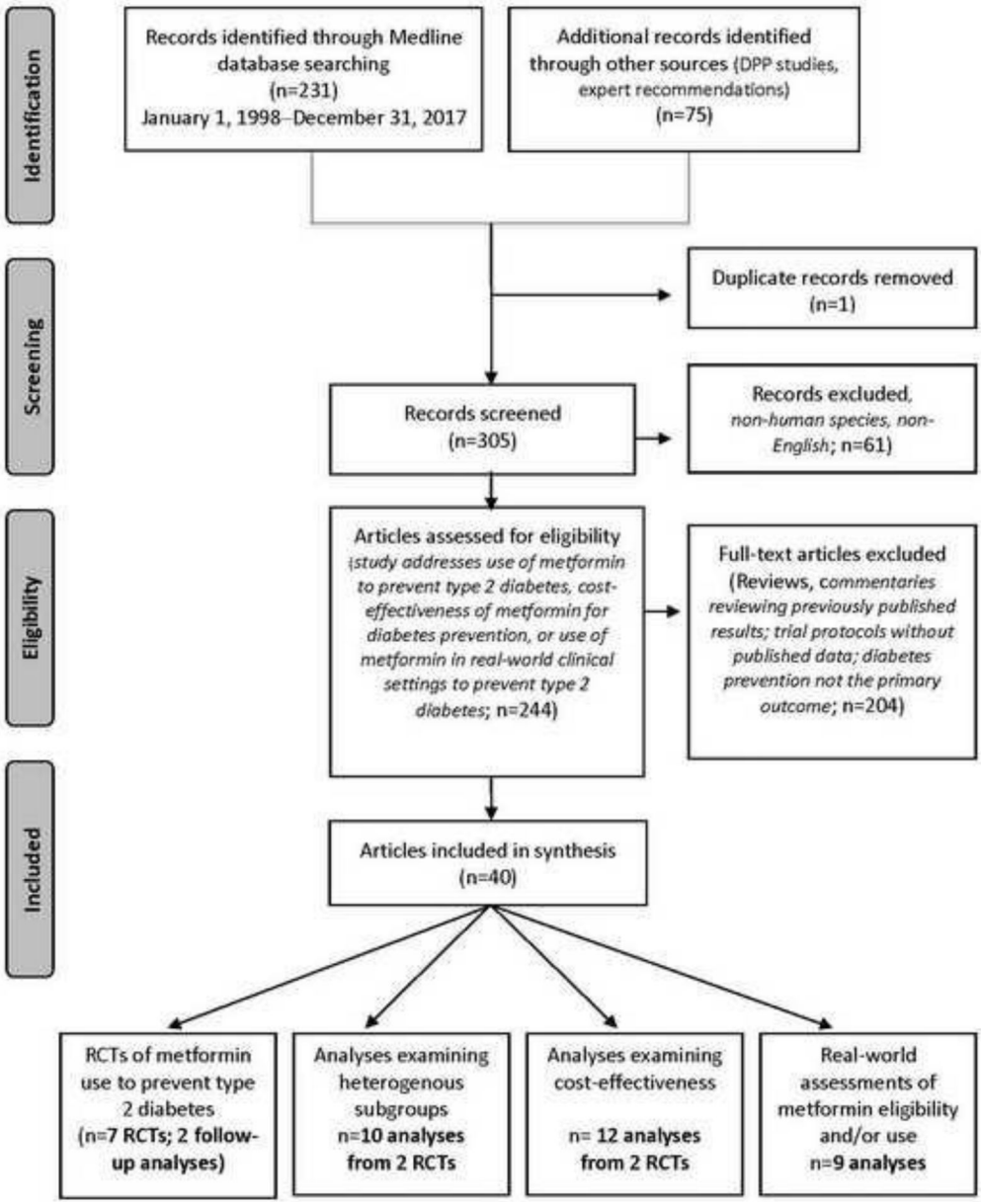

Figure 1. PRISMA 2009 flow diagram from Moher et al.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1.

National Care Guidelines

Guideline, Year	Wording regarding metformin use in prediabetes
ADA, 2018[70]	"Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years, and women with prior gestational diabetes mellitus"
ISCI, 2014[71]	"Metformin therapy for prevention of T2DM may be considered in those with IGT, IFG or an A1c, especially for those with BMI >35 kg/m^2, aged <60 years, and women with prior GDM"
AACE/ACE, 2015[72]	"In addition to lifestyle modification, medications including metformin, acarbose, or thiazolidinediones (TZDs) should be considered for patients who are at moderate-to-high risk for developing DM, such as those with a first-degree relative with DM"
VA/DoD, 2010[73]	"When lifestyle modifications have been ineffective at preventing a sustained rise in glucose, the patient may be offered pharmacologic therapy with a metformin or an alpha-glucosidase inhibitor (e.g., acarbose) to delay progression from pre-diabetes to a diagnosis of diabetes" The 2017 VA/DoD Guidelines for Management of Diabetes in Primary Care does not cover diabetes prevention.

ADA, American Diabetes Association; ISCI, Institute for Clinical Systems Improvement, AACE/ACE, American Association of Clinical Endocrinologists; VA/DoD, Veteran's Health Administration/Department of Defense; DPP, Diabetes Prevention Program; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.