Prevention of Diabetes Mellitus in Patients With Prediabetes

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Cardiovascular disease is a leading cause of death in patients with diabetes. Consequently, as antidiabetic medications have demonstrated cardiovascular benefit, cardiologists have been asked to weigh in regarding antidiabetic therapy. The cardiologist's role will continue to grow as antidiabetic agents with cardiovascular benefit are being studied in prediabetes as part of an evolving clinical environment. Still, current guidelines primarily recommend high-intensity lifestyle intervention or metformin for diabetes prevention. Considering that many patients cared for by a cardiologist will have prediabetes, we propose herein that cardiologists can also facilitate diabetes prevention through direct intervention, referring patients to community-based high-intensity lifestyle interventions, and through advocacy, policy, and additional guideline development. The most important messaging for a patient is that avoiding new-onset diabetes can reduce microvascular disease, reduce healthcare cost, and improve health-related quality of life. Moreover, as the mortality risk of patients with a history of myocardial infarction and diabetes is almost double that of patients with a history of myocardial infarction who are free of diabetes, there is even more potential benefit in delaying and/or avoiding diabetes in patients with cardiovascular disease. Despite these important health advantages, the implementation of diabetes prevention strategies is lagging. The under implementation may be exaggerated by published opinions conflicting major guidelines in addition to conflicting guideline recommendations. In conclusion, we propose cardiologists can play a key role in preventing diabetes and aligning practice patterns with guideline recommendations among endocrinology, cardiology, and primary care stake holders. **(Am J Cardiol 2019;123:507−512)**

Cardiologists are increasingly being asked to weigh in on diabetes management as select agents demonstrate cardiovascular benefit.[1] Such input is warranted as cardiovascular disease remains a leading cause of death in patients with diabetes,[2] and cardiologists' impact will grow as the same antidiabetic medications with cardiovascular benefit in diabetes are being studied for preventing diabetes.[3] Eighty-four million patients in the United States have prediabetes and at least 70% will develop diabetes unless they receive an intervention.[4] Additionally, most of these patients have or are at risk for cardiovascular disease. Although societal and economic factors are primary culprits contributing to the extensive expansion of diabetes,[5] these factors do not explain the observed clinical inertia related to prediabetes (Table 1).[6] Therefore, cardiologists have another opportunity to play a key role in improving human health, as cardiologists are centrally positioned to help patients through facilitating the adoption of a healthier lifestyle, prescribing therapeutic and preventive medications when appropriate, and by being on the front line of advocacy, policy, and guideline development.[7−10] The objective of this *Review Article* is to describe and critique factors contributing to clinical inertia, propose a straightforward approach to the patient with prediabetes, engage cardiologists in the prevention of diabetes, thus reaching their patients at considerable cardiometabolic risk.[11]

Does Everyone Agree that Diabetes is a Global Emergency?

Observational and epidemiologic data demonstrate that diabetes is associated with increased mortality, morbidity, and cost.[11,12] Though as described in Table 1, interventions to prevent diabetes are underused,[6,8,13,14] which may be related to varied physician and health-system factors.[15,16] We propose that the current state of practice related to prediabetes reflects a division in how the outcomes of diabetes prevention studies are interpreted. The division primarily follows the randomized controlled trial (RCT) data of high-intensity lifestyle intervention and metformin which demonstrate potent effect in preventing diabetes, through only a small or no effect in preventing stroke, myocardial infarction, cardiovascular death, or mortality.[12,17,18] Subsequently, some researchers, guidelines, and editors have omitted guidance on diabetes prevention or de-emphasized its importance relative to American Diabetes Association (ADA) and American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE)

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Table 1
State of practice in prediabetes

Study	Study sample/population	Key finding
Mainous AG 3rd et al[6]	National Ambulatory Medical Care Survey, 2012; ~1.2 million survey weighted office-based ambulatory medical care visits	Prediabetes treatment (lifestyle modification counseling and/or metformin) found in 23% of patients with prediabetes
Moin T et al[13]	Insured cohort of ~17,000 working-age adults with prediabetes, 2010 to 2012	Metformin prescriptions identified for 647 (3.7%) of patients with prediabetes
Wu J et al[14]	~7100 patients with South Carolina Medicaid, aged 18 to 60 years, with prediabetes, 2009 to 2013	520 (~7%) were prescribed metformin for prediabetes
Tseng E et al[8]	~7700 patients with prediabetes, National Health and Nutrition Examination Survey, 2005 to 2012	91 taking metformin (age-adjusted prevalence ~1%)
Tseng E et al[16]	Primary care providers, 140 respondents (response rate 90%), 2015	9 (6%) identified all risk factors that should prompt prediabetes screening
Mainous AG 3rd et al[15]	Electronic survey ~1200 respondent academic family physicians (response rate 35%), 2016	594 (47.6%) report not following or not knowing if they are follow national recommendations regarding prediabetes

guidelines.[9,10,19–22] We propose 5 positions frequented in the literature are key contributors to clinical inertia and address each individually in the sections below.

Normalization of Prediabetes

It has been asserted that prediabetes has only been a consideration for ~10 years and that the term medicalizes common conditions.[20] However, articles regarding prediabetes date back to the 1960s[23] and recent reports have described significantly increased microvascular and macrovascular risks in patients with prediabetes.[24] As 84 million patients in the United States have prediabetes, we propose cardiologists could identify intermediately elevated measures of glycemia, consider a patients' overall cardiometabolic health and/or risk, and implement all necessary preventive interventions, many of which are certainly already being addressed (i.e., antihypertensive, antihyperlipidemic, antihyperglycemic, and antiplatelet).

Lack of Effect

It has been asserted that diabetes prevention interventions do not alter the course of diabetes-related complications.[21] When this assertion is made, it is used to dissuade providers and health-systems from implementing robust diabetes prevention initiatives. Therefore, it fails to consider some types of data and some outcomes of interest. Primarily, it cannot be ignored that avoiding diabetes is in of itself an outcome of interest, at the very least from a humanistic perspective.[12,17] The Diabetes Prevention Program study and its extensions demonstrated that intensive lifestyle intervention and metformin reduced the incidence of diabetes compared with standard care and/or placebo with much of the effect being maintained long term (~15 years; lifestyle, 27% reduction; metformin, 18% reduction).[25] In line with the humanistic consideration, lifestyle intervention has been shown to significantly improve health-related quality of life, and metformin to not have a negative impact on health-related quality of life, even having a minimal nonsignificant benefit.[17] The safety and efficacy of lifestyle intervention and metformin for preventing diabetes, as an outcome alone, makes them worthy interventions.[9,10,26] Lifestyle intervention has garnered the most widespread support, though implementation should be improved.[6,9,26] Additionally, metformin has received a Grade A recommendation from the ADA for preventing diabetes, despite its known side effects including gastrointestinal adverse effects and potential to decrease vitamin B12 levels.[9]

Returning to diabetes-related complications and the impact of diabetes prevention interventions, there are 2 broad categories of interest, microvascular disease (i.e., retinopathy, neuropathy, and nephropathy) and macrovascular disease (i.e., coronary artery disease, stroke, and peripheral arterial disease). We note that no RCT has demonstrated a conclusive improvement in these outcomes with either lifestyle intervention or metformin, although quality of life is expected to be improved. However, as it pertains to the care of a patient, cardiologists can ask, is there a benefit to my patient if they do not develop diabetes? To address this question, observational data can be reviewed to illuminate areas in which RCT data are not definitive. Although no arm of the Diabetes Prevention Program significantly reduced microvascular disease, a key finding was a 28% reduction in microvascular disease in patients that did not develop diabetes, portending a benefit to patients who avoid new-onset diabetes.[25] Although not conclusive, this finding is important as up to 40% of patients with diabetes will develop related kidney disease, diabetic retinopathy is the most common cause of incident blindness in adults aged 20 to 74 in developed countries, and peripheral neuropathy and loss of protective sensations contributes to amputation risk.[27]

As diabetes prevention interventions relate to macrovascular disease, or more importantly, "major adverse cardiovascular events" (MACE, i.e., stroke, myocardial infarction, cardiovascular death) it is again correct to assert that these outcomes are not typically reduced in RCTs. However, failure to prevent MACE in an RCT does not assess if patients who avoid new-onset diabetes have a reduced risk of cardiovascular disease. Based on emerging data we suggest a cardiovascular benefit may be achieved by the patient avoiding or delaying the onset of diabetes.[28,29] First, the Diabetes Prevention Program demonstrated that metformin treatment reduced coronary artery calcium in men.[28] Although this is a surrogate outcome in a

subgroup of patients, it highlights that working age men, who are the least represented in real-world diabetes prevention lifestyle interventions,[18] may benefit most from metformin treatment.[9,25,28] Second, a recent cohort study of ~25,000 patients in Denmark demonstrated that achieving glycemic control in the first 6 months reduced cardiovascular events over a median 2.6 years of follow-up.[29] Although the cohort data does not speak to diabetes prevention, it highlights that cardiovascular risk may progress quickly in new-onset diabetes. As type 2 diabetes can go undiagnosed for many years,[30] we propose there is a cardiovascular benefit in attempting to prevent type 2 diabetes compared with usual care, which results in delayed diagnosis. At the very least, patients with prediabetes require close follow-up to minimize the delay between diabetes' onset and treatment to minimize microvascular and macrovascular risk. Moreover, RCT data of tight versus standard diabetes control suggests a decade is required to demonstrate any cardiovascular benefit.[31] Therefore, progression to diabetes, longer duration of diabetes, and longer duration of poorly controlled diabetes portend less reversibility of cardiovascular risk. As such, we suggest there is a cardiovascular benefit from engaging patients early. In line with this, we highlight that it is incongruent to recommend medications to achieve a HbA1c <6.5% in new-onset diabetes,[2] yet recommend against medication use to not allow HbA1c to rise above 6.5% in the first place.[2]

Although suggestive data should not dictate policy, avoiding and delaying diabetes' onset and improving health-related quality of life are the outcomes that compel the use of diabetes prevention interventions.[9,10,17] Therefore, it is incomplete to focus diabetes prevention solely in scope of cardiovascular disease,[2] and cardiologists could consider an individual patient's cardiovascular health, health-related quality of life, and preferences (e.g., avoiding and/or delaying diabetes' onset) when deciding whether a diabetes prevention intervention is appropriate. However, health-systems must also consider cost.

Cost

It is proper to consider the cost of diabetes prevention initiatives given the prevalence of prediabetes. In United States alone there are estimated to be 84 million patients with prediabetes.[7] Certainly, providing low-value care to a large number of patients would detract from other aspects of healthcare. However, diabetes prevention programs have become increasingly efficient through the use of group interventions.[17,18,32] Coupled with the increasing cost of diabetes care,[12] evidence-based diabetes prevention interventions (i.e., group high-intensity lifestyle intervention, metformin) are expected to be cost-saving.[17,18,32] As interventions with established health benefit and expected cost-savings are highly desirable, cardiologists (and health-systems) might consider it low-value care when diabetes prevention interventions are not offered to a patient with prediabetes.

No Prevention Recommendation

With research into statin-related diabetes burgeoning, guidelines took proper notice of the large overall net clinical benefit from statin therapy.[19] The overall benefit of statins in patients with prediabetes (and cardiovascular risk) is certain to outweigh the risk of new-onset diabetes. Indeed, this has remained true through previous, potentially prodiabetic interventions (i.e., thiazide-type diuretics, β-blockers).[33] However, a patient-centered care model cannot ignore the negative outcomes associated with new-onset diabetes, regardless of the expected net clinical benefit. Moreover, the use of potentially prodiabetic agents negates any argument that preventing diabetes is outside the scope of cardiology practice, as clinicians are responsible for and "take ownership" of the side effects of medications they prescribe. Therefore, cardiologists could attempt to implement evidence-based methods of diabetes prevention for their patients with prediabetes for 4 reasons: (1) multiple cardiovascular medications may increase risk for new-onset diabetes; (2) improved health-related quality of life; (3) decreased health-system cost; and (4) potentially decreased cardiovascular risk.[17,19]

Single Intervention

The debate of preferred diabetes prevention intervention can be found in almost all related literature.[22] Although the 2 most accepted interventions are high-intensity lifestyle intervention and metformin,[9,10] the debate has resulted in some guidelines only recommending high-intensity lifestyle intervention, as the clearly superior intervention.[26] Although the general superiority of high-intensity lifestyle intervention is established, it may not be suitable for all patients.[5,18] Indeed, the initial report from the Centers for Disease Control and Prevention's National Diabetes Prevention Programed showed that men and those of working age were under-represented or less able to engage in the intervention.[18] Cardiologists might identify patients who are unable to invest time in behavior modification classes or who lack access to mobile devices, safe locations for exercise, or healthy food choices.[5] Therefore, we the authors favor a patient-centered pathway (Figure 1) we developed based on ADA and AACE/ACE guideline recommendations.[9,10] Certainly all patients should have their cardiovascular risk assessed and addressed overall (e.g., antihypertensives, antihyperlipidemic, and antiplatelets), and almost all patients have room to improve their lifestyle habits. However, greater action is needed to advance general lifestyle counseling to an evidence-based high-intensity lifestyle intervention. Additionally, though lifestyle intervention is highly effective, some patients will not engage in the intervention or will have progression toward diabetes despite engaging in the intervention. Therefore, all patients with prediabetes should be continually assessed, for both effectiveness of any intervention they are using and for new-onset diabetes. Other interventions should be considered in patients continuing to progress toward diabetes (e.g., metformin, alternative lifestyle intervention program, and other guideline recommended medication for diabetes prevention).

Emerging Evidence

Although high-intensity lifestyle intervention and metformin have become the standards to prevent diabetes,

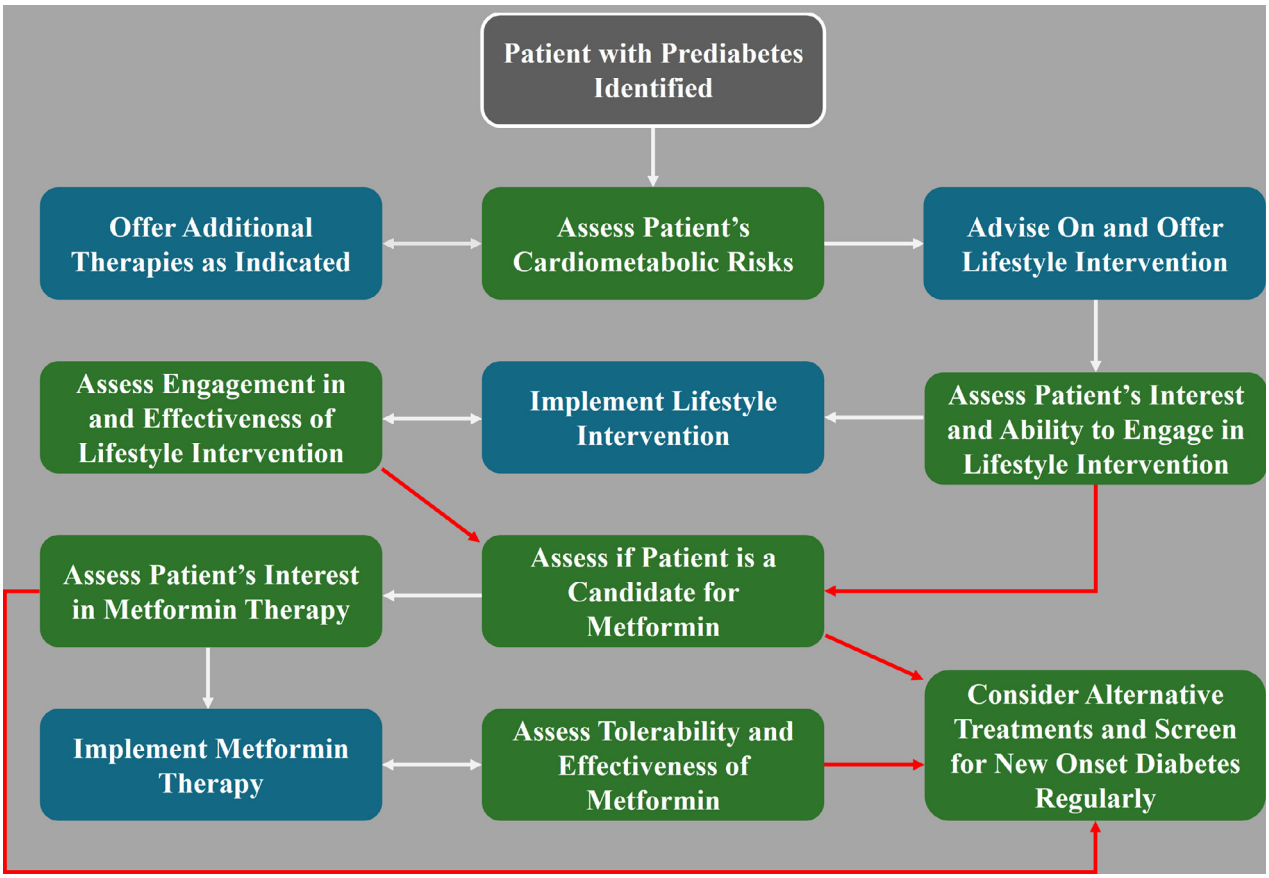

Figure 1. A prediabetes pathway*.
Gray arrows indicate the standard pathway
Bi-directional *gray arrows* indicate continued treatment with reassessment
Red arrows indicate alternative approach is required
*Pathway based on recommendations from the American Diabetes Association Standards of Medical Care in Diabetes and American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Statement.[9,10]

newer antidiabetic agents with established cardiovascular benefit in diabetes are being studied in prediabetes. In patients with prediabetes, versus placebo, liraglutide resulted in an additional 1 patient reverting to normoglycemia for every 3 patients treated and significantly reduced new-onset diabetes.[3] Empagliflozin is currently being studied in a Phase 2 trial of patients with prediabetes (NCT03227484), and is highly anticipated based on its cardiovascular benefit in patients with diabetes.[1] Pioglitazone, with known ability to prevent diabetes,[34] has now demonstrated cardiovascular benefit in patients with recent ischemic stroke or transient ischemic attack and insulin resistance (without diabetes).[35] In light of pioglitazone's demonstrated effect, we enthusiastically await the results of the Glucose Lowering in Non-diabetic hyperglycemia Trial (GLINT) (ISRCTN34875079) which is assessing the cardiovascular outcomes of metformin treatment versus placebo in patients with nondiabetic hyperglycemia who are at high cardiovascular risk. We expect metformin to demonstrate a cardiovascular benefit in the GLINT trial based on metformin's general track record of safety, its impact on coronary artery calcium in men with prediabetes,[28] and the cardiovascular benefit expected from early glycemic control.[29] However, regardless of the outcome of the GLINT trial, metformin has established benefit in preventing diabetes and reducing health-system cost, even being called by the *Diabetes Care* Editor's Expert Form the, "most likely candidate for widespread use in diabetes prevention."[9,12,17] Overall, high-intensity lifestyle intervention and metformin can prevent diabetes and decrease health-system cost, can reduce microvascular disease in patients avoiding diabetes, and may offer cardiovascular benefit.[17,32] Therefore, cardiologists could consider beginning to implement evidence-based methods of diabetes prevention today.

Conclusion

There is agreement between the ADA and AACE/ACE guidelines that patients have prediabetes if their fasting plasma glucose is 100 to 125 mg/dl or their 2 hour postprandial glucose during 75 g oral glucose tolerance test of 140 to 199 mg/dl.[10,30] The ADA guideline also includes HbA1c 5.7% to 6.4% as indicative of prediabetes.[30] Through the course of standard care, cardiologists will invariably identify patients with dysglycemia. We strongly

advocate for cardiologists to increase action on abnormal results. To facilitate clinical action, cardiologists should consider solidifying relations with health-system and community partners to simplify patient referral to programs which deliver high-intensity lifestyle interventions. Additionally, cardiologist should consider initiating metformin in select patients (e.g., eGFR ≥45 ml/minute/1.73 m^2−for safe use, and age <60 years−for better diabetes prevention effect)[9] with communication to patients' primary care providers to optimize continuity of care. Finally, we suggest cardiologist consider exhorting others through policy, advocacy, and guideline to do likewise. Although cardiovascular outcomes in RCTs of diabetes prevention interventions are equivocal; attempting to prevent diabetes has demonstrated clear unambiguous benefits to patients with prediabetes and to the health-systems in which they reside.

Disclosures

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