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Prevention of Diabetes Mellitus in Patients with Prediabetes

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Abstract

Cardiovascular disease is a leading cause of death among 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/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 stakeholders.

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Keywords

Cardiology; Prediabetes; Lifestyle; Metformin

Introduction

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. While 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, 8, 9, 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 deemphasized its importance relative to American Diabetes Association (ADA) and American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) 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 1960s²³ and recent reports have described significantly increased microvascular and

macrovascular risks among 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/risk, and implement all necessary preventive interventions, many of which are certainly already being addressed (i.e., antihypertensive, antihyperlipidemic, antihyperglycemic, 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 to standard care/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, 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. While 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 While 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 among adults aged 20–74, 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 While 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 While 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 to usual care, which results in delayed diagnosis. At the very least, patients with prediabetes require close followup 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 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

While 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/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 prior, potentially prodiabetic interventions (i.e., thiazide-type diuretics, beta-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 While 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 While 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 Program showed that men and those of working age were underrepresented 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, 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, other guideline recommended medication for diabetes prevention).

Emerging Evidence

While high-intensity lifestyle intervention and metformin have become the standards to prevent diabetes, 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 prevention 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 Nondiabetic hyperglycaemia Trial (GLINT) (ISRCTN34875079) which is assessing the cardiovascular outcomes of metformin treatment versus placebo in patients with non-diabetic 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 100-125 mg/dL or their 2 hour post prandial glucose during 75 gram oral glucose tolerance test of 140-199 mg/dL.^{10, 30} The ADA guideline also includes HbA1c 5.7-6.4% 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 relationships 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 m² – 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. While 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.

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References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;373:2117–2128. [PubMed: 26378978]
2. Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. How Low to Go With Glucose, Cholesterol, and Blood Pressure in Primary Prevention of CVD. *J Am Coll Cardiol* 2017;70:2171–2185. [PubMed: 29050566]
3. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, Ortiz RV, Wilding JPH, Skjoth TV, Manning LS, Pi-Sunyer X. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017;389:1399–1409. [PubMed: 28237263]
4. Ligthart S, van Herpt TT, Leening MJ, Kavousi M, Hofman A, Stricker BH, van Hoek M, Sijbrands EJ, Franco OH, Dehghan A. Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study. *Lancet Diabetes Endocrinol* 2016;4:44–51. [PubMed: 26575606]
5. Spencer Bonilla G, Rodriguez-Gutierrez R, V MM. What We Don't Talk About When We Talk About Preventing Type 2 Diabetes-Addressing Socioeconomic Disadvantage. *JAMA Intern Med* 2016;176:1053–1054. [PubMed: 27367180]
6. Mainous AG, 3rd, Tanner RJ, Baker R. Prediabetes Diagnosis and Treatment in Primary Care. *J Am Board Fam Med* 2016;29:283–285. [PubMed: 26957387]
7. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.
8. Tseng E, Yeh HC, Maruthur NM. Metformin Use in Prediabetes Among U.S. Adults, 2005-2012. *Diabetes Care* 2017;40:887–893. [PubMed: 28373205]
9. American Diabetes Association. 5. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018;41:S51–S54. [PubMed: 29222376]
10. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, DeFronzo RA, Einhorn D, Fonseca VA, Garber JR, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez GE. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2018 EXECUTIVE SUMMARY. *Endocr Pract* 2018;24:91–120. [PubMed: 29368965]
11. Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, Burgess S, Freitag DF, Pennells L, Peters SA, Hart CL, Haheim LL, Gillum RF, Nordestgaard BG, Psaty BM, Yeap BB, Knuiman MW, Nietert PJ, Kauhanen J, Salonen JT, Kuller LH, Simons LA, van der Schouw YT, Barrett-Connor E, Selmer R, Crespo CJ, Rodriguez B, Verschuren WM, Salomaa V, Svardsudd K, van der Harst P, Bjorkelund C, Wilhelmsen L, Wallace RB, Brenner H, Amouyel P, Barr EL, Iso H, Onat A, Trevisan M, D'Agostino RB, Sr., Cooper C, Kavousi M, Welin L, Roussel R, Hu FB, Sato S, Davidson KW, Howard BV, Leening MJ, Rosengren A, Dorr M, Deeg DJ, Kiechl S, Stehouwer CD, Nissinen A, Giampaoli S, Donfrancesco C, Kromhout D, Price JF, Peters A, Meade TW, Casiglia E, Lawlor DA, Gallacher J, Nagel D, Franco OH, Assmann G, Dagenais GR, Jukema JW, Sundstrom J, Woodward M, Brunner EJ, Khaw KT, Wareham NJ, Whitsel EA, Njolstad I, Hedblad B, Wassertheil-Smoller S, Engstrom G, Rosamond WD, Selvin E, Sattar N, Thompson SG, Danesh J. Association of Cardiometabolic Multimorbidity With Mortality. *JAMA* 2015;314:52–60. [PubMed: 26151266]
12. Cefalu WT, Buse JB, Tuomilehto J, Fleming GA, Ferrannini E, Gerstein HC, Bennett PH, Ramachandran A, Raz I, Rosenstock J, Kahn SE. 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. [PubMed: 27631469]
13. Moin T, Li J, Duru OK, Ettner S, Turk N, Keckhafer A, Ho S, Mangione CM. Metformin prescription for insured adults with prediabetes from 2010 to 2012: a retrospective cohort study. *Ann Intern Med* 2015;162:542–8. [PubMed: 25894024]

14. Wu J, Ward E, Threatt T, Lu ZK. Metformin prescribing in low-income and insured patients with prediabetes. *J Am Pharm Assoc* 2017;57:483–487.
15. Mainous AG, 3rd, Tanner RJ, Scuderi CB, Porter M, Carek PJ. Prediabetes Screening and Treatment in Diabetes Prevention: The Impact of Physician Attitudes. *J Am Board Fam Med* 2016;29:663–671. [PubMed: 28076248]
16. Tseng E, Greer RC, O'Rourke P, Yeh HC, McGuire MM, Clark JM, Maruthur NM. Survey of primary care providers' knowledge of screening for, diagnosing and managing prediabetes. *J Gen Intern Med* 2017;32:1172–1178. [PubMed: 28730532]
17. Herman WHES, Ratner RE, Montez MG, Ackermann RT, Orchard TJ, Foulkes MA, Zhang P, Saudek CD, Brown MB. 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. [PubMed: 22442395]
18. Ely EK, Gruss SM, Luman ET, Gregg EW, Ali MK, Nhim K, Rolka DB, Albright AL. A National Effort to Prevent Type 2 Diabetes: Participant-Level Evaluation of CDC's National Diabetes Prevention Program. *Diabetes Care* 2017;40:1331–1341. [PubMed: 28500215]
19. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:S1–45. [PubMed: 24222016]
20. Redberg RF. The Medicalization of Common Conditions. *JAMA Intern Med* 2016;176:1863.
21. Shahraz S, Pittas AG, Kent DM. Prediabetes Risk in Adult Americans According to a Risk Test. *JAMA Intern Med* 2016;176:1861–1863. [PubMed: 27695825]
22. Farr OM, Mantzoros CS. Treating prediabetes in the obese: are GLP-1 analogues the answer? *Lancet* 2017;389:1371–1372. [PubMed: 28237265]
23. Medical News. Prediabetes' Research - A means to Eventual Prevention of Diabetes. *JAMA* 1963;185:32–33.
24. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014. *Lancet Diabetes Endocrinol* 2018;6:392–403. [PubMed: 29500121]
25. 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. [PubMed: 26377054]
26. Siu AL. Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2015;163:861–868. [PubMed: 26501513]
27. American Diabetes Association. 10. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018;41:S105–S118. [PubMed: 29222381]
28. Goldberg RB, Aroda VR, Bluemke DA, Barrett-Connor E, Budoff M, Crandall JP, Dabelea D, Horton ES, Mather KJ, Orchard TJ, Schade D, Watson K, Temprosa M. 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. [PubMed: 28476766]
29. Svensson E, Baggesen LM, Johnsen SP, Pedersen L, Norrelund H, Buhl ES, Haase CL, Thomsen RW. Early Glycemic Control and Magnitude of HbA1c Reduction Predict Cardiovascular Events and Mortality: Population-Based Cohort Study of 24,752 Metformin Initiators. *Diabetes Care* 2017;40:800–807. [PubMed: 28404659]
30. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018;41:S13–S27. [PubMed: 29222373]
31. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589. [PubMed: 18784090]

32. Centers for Medicare & Medicaid Services (CMS), HHS. Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule and Other Revisions to Part B for CY 2018; Medicare Shared Savings Program Requirements; and Medicare Diabetes Prevention Program. Federal Register 2017;82:52976–53371. [PubMed: 29231695]
33. Mancia G Preventing new-onset diabetes in thiazide-treated patients. Lancet Diabetes Endocrinol 2016;4:90–92. [PubMed: 26489807]
34. DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, Clement SC, Henry RR, Hodis HN, Kitabchi AE, Mack WJ, Mudaliar S, Ratner RE, Williams K, Stentz FB, Musi N, Reaven PD. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104–1115. [PubMed: 21428766]
35. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP, Jr., Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med 2016;374:1321–1331. [PubMed: 26886418]

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}

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, 2005–2012	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 national recommendations