

25 June 2023. Sections 2 and 3 have been updated based on U.S. Food and Drug Administration approval of a new drug to delay the incidence of type 1 diabetes. The changes are described in detail in: Addendum. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes—2023. *Diabetes Care* 2023;46(Suppl. 1):S19–S40 (<https://doi.org/10.2337/dc23-ad08>) and Addendum. 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Care in Diabetes—2023. *Diabetes Care* 2023;46(Suppl. 1):S41–S48 (<https://doi.org/10.2337/dc23-ad08a>).

3. Prevention or Delay of Diabetes and Associated Comorbidities: *Standards of Care in Diabetes—2023*

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Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Jason L. Gaglia, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, and Robert A. Gabbay, on behalf of the American Diabetes Association

The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For guidelines related to screening for increased risk for type 1 and type 2 diabetes (prediabetes), please refer to Section 2, “Classification and Diagnosis of Diabetes.” For guidelines related to screening, diagnosis, and management of type 2 diabetes in youth, please refer to Section 14, “Children and Adolescents.”

Recommendation

3.1 Monitor for the development of type 2 diabetes in those with prediabetes at least annually; modify based on individual risk/benefit assessment. **E**

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (Table 2.3) or with an assessment tool, such as the American Diabetes Association risk test (Fig. 2.1), is recommended to guide health care professionals on whether performing a diagnostic test for prediabetes (Table 2.5) and previously undiagnosed type 2 diabetes (Table 2.2) is appropriate (see Section 2, “Classification and Diagnosis of Diabetes”). Testing high-risk adults for prediabetes is warranted because the laboratory assessment is safe and reasonable in cost, substantial time exists before the development of type 2 diabetes and its complications during which one can intervene, and there is an effective means of preventing or delaying type 2 diabetes in those determined to have prediabetes with an A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance, or impaired fasting glucose. The utility of A1C screening for prediabetes and diabetes may be limited in the presence of hemoglobinopathies and conditions that affect red blood cell turnover. See Section 2, “Classification and Diagnosis of Diabetes,” and Section 6, “Glycemic Targets,” for additional details on the appropriate use and limitations of A1C testing.

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LIFESTYLE BEHAVIOR CHANGE FOR DIABETES PREVENTION

Recommendations

- 3.2** Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥ 150 min/week of moderate-intensity physical activity. **A**
- 3.3** A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. **B**
- 3.4** Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. **A** Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed.
- 3.5** Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

The Diabetes Prevention Program

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial (1), the Finnish Diabetes Prevention Study (DPS) (2), and the Da Qing Diabetes Prevention Study (Da Qing study) (3), demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic markers (such as blood pressure, lipids, and inflammation) (4). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial (1). The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to

type 2 diabetes: 39% reduction at 30 years in the Da Qing study (5), 43% reduction at 7 years in the Finnish DPS (2), and 34% reduction at 10 years (6) and 27% reduction at 15 years (7) in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min moderate-intensity physical activity per week, such as brisk walking. The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals (8). Although weight loss was the most important factor in reducing the risk of incident diabetes, it was also found that achieving the target behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44% (9).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes. Participants were encouraged to achieve the $\geq 7\%$ weight loss during the first 6 months of the intervention. Further analysis suggests maximal prevention of diabetes with at least 7–10% weight loss (9). The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the dietary intervention was on reducing total fat rather than calories. After several weeks, the concept of calorie balance and the need to restrict calories and fat was introduced (8).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (8).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for the tailoring of interventions to reflect the diversity of the population (8).

The DPP intervention was administered as a structured core curriculum followed by a flexible maintenance program of individual counseling, group sessions, motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program. It included sessions on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors, and guidance on managing psychological, social, and motivational challenges. Further details are available regarding the core curriculum sessions (8).

Nutrition

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total dietary fat and calories (1,8,9). However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals (10). Based on other intervention trials, a variety of eating patterns characterized by the totality of food and beverages habitually consumed (10,11) may also be appropriate for individuals with prediabetes (10), including Mediterranean-style and low-carbohydrate eating plans (12–15). Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes (16–19). Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes (18,20–22). As is

the case for those with diabetes, individualized medical nutrition therapy (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes,” for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (23).

Physical Activity

Just as 150 min/week of moderate-intensity physical activity, such as brisk walking, showed beneficial effects in those with prediabetes (1), moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (24,25). Based on these findings, health care professionals are encouraged to promote a DPP-style program, including a focus on physical activity, to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training (8,26,27). Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels (28,29). The preventive effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM) (30).

Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention

Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes among those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payers ensued (31–35). Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (36–40).

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities (cdc.gov/diabetes/prevention/index.htm). This online resource includes

locations of CDC-recognized diabetes prevention lifestyle change programs (cdc.gov/diabetes/prevention/find-a-program.html). To be eligible for this program, individuals must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing, a previous diagnosis of GDM, or a positive risk test (cdc.gov/prediabetes/takethetest/). During the first 4 years of implementation of the CDC’s National DPP, 35.5% achieved the 5% weight loss goal (41). The CDC has also developed the Diabetes Prevention Impact Tool Kit (nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP lifestyle change program (42). In an effort to expand preventive services using a cost-effective model, the Centers for Medicare & Medicaid Services expanded Medicare reimbursement coverage for the National DPP lifestyle intervention to organizations recognized by the CDC that become Medicare suppliers for this service (innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program). The locations of Medicare DPPs are available online at innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program/mdpp-map. To qualify for Medicare coverage, individuals must have BMI >25 kg/m² (or BMI >23 kg/m² if self-identified as Asian) and laboratory testing consistent with prediabetes in the last year. Medicaid coverage of the DPP lifestyle intervention is also expanding on a state-by-state basis.

While CDC-recognized behavioral counseling programs, including Medicare DPP services, have met minimum quality standards and are reimbursed by many payers, lower retention rates have been reported for younger adults and racial/ethnic minority populations (43). Therefore, other programs and modalities of behavioral counseling for diabetes prevention may also be appropriate and efficacious based on individual preferences and availability. The use of community health workers to support DPP efforts has been shown to be effective and cost-effective (44,45) (see Section 1, “Improving Care and Promoting Health in Populations,” for more information). The use of community health workers may facilitate the adoption of behavior changes for diabetes prevention while bridging barriers related to social determinants of health. However, coverage

by third-party payers remains problematic. Counseling by a registered dietitian nutritionist (RDN) has been shown to help individuals with prediabetes improve eating habits, increase physical activity, and achieve 7–10% weight loss (10,46–48). Individualized medical nutrition therapy (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes,” for more detailed information) is also effective in improving glycemia in individuals diagnosed with prediabetes (23,46). Furthermore, trials involving medical nutrition therapy for adults with prediabetes found significant reductions in weight, waist circumference, and glycemia. Individuals with prediabetes can benefit from referral to an RDN for individualized medical nutrition therapy upon diagnosis and at regular intervals throughout their treatment plan (47,49). Other health care professionals, such as pharmacists and diabetes care and education specialists, may be considered for diabetes prevention efforts (50,51).

Technology-assisted programs may effectively deliver the DPP program (52–57). Such technology-assisted programs may deliver content through smartphones, web-based applications, and telehealth and may be an acceptable and efficacious option to bridge barriers, particularly for low-income individuals and people residing in rural locations; however, not all programs are effective in helping people reach targets for diabetes prevention (52,58–60). The CDC Diabetes Prevention Recognition Program (DPRP) (cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based programs; such programs must use an approved curriculum, include interaction with a coach, and attain the DPP outcomes of participation, physical activity reporting, and weight loss. Therefore, health care professionals should consider referring adults with prediabetes to certified technology-assisted DPP programs based on their preferences.

PHARMACOLOGIC INTERVENTIONS

Recommendations

3.6 Metformin therapy for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the Diabetes Prevention

Program, especially those aged 25–59 years with BMI ≥ 35 kg/m², higher fasting plasma glucose (e.g., ≥ 110 mg/dL), and higher A1C (e.g., $\geq 6.0\%$), and in individuals with prior gestational diabetes mellitus. **A**

3.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. **B**

Because weight loss through behavior changes in diet and physical activity alone can be difficult to maintain long term (6), people at high risk of diabetes may benefit from support and additional pharmacotherapeutic options, if needed. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α -glucosidase inhibitors, glucagon-like peptide 1 receptor agonists (liraglutide, semaglutide), thiazolidinediones, testosterone (61), and insulin have been shown to lower the incidence of diabetes in specific populations (62–67), whereas diabetes prevention was not seen with nateglinide (68).

In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years (9). In postpartum individuals with GDM, the risk of type 2 diabetes increased by 18% for every 1 unit BMI above the preconception baseline (69). Several medications evaluated for weight loss (e.g., orlistat, phentermine/topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of diabetes to various degrees in those with prediabetes (67,70–72).

Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan but no efficacy in preventing diabetes with ramipril or anti-inflammatory drugs (73–76). Although the Vitamin D and Type 2 Diabetes (D2d) prospective randomized controlled trial showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk (77), post hoc analyses and meta-analyses suggest a

potential benefit in specific populations (77–80). Further research is needed to define characteristics and clinical indicators where vitamin D supplementation may be of benefit (61).

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for a specific indication of type 2 diabetes prevention. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost, side effects, and efficacy considerations. Metformin has the longest history of safety data as a pharmacologic therapy for diabetes prevention (81).

Metformin was overall less effective than lifestyle modification in the DPP, though group differences declined over time in the DPP0S (7), and metformin may be cost-saving over a 10-year period (33). In the DPP, metformin was as effective as lifestyle modification in participants with BMI ≥ 35 kg/m² and in younger participants aged 25–44 years (1). In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (82). Both interventions remained highly effective during a 10-year follow-up period (83). By the time of the 15-year follow-up (DPP0S), exploratory analyses demonstrated that participants with a higher baseline fasting glucose (≥ 110 mg/dL vs. 95–109 mg/dL), those with a higher A1C (6.0–6.4% vs. $< 6.0\%$), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that benefitted the most from metformin (84). In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; of note, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP (85). Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., those with a history of GDM or those with BMI ≥ 35 kg/m²). Consider periodic monitoring of vitamin B12 levels in those taking metformin chronically to check for possible deficiency (86,87) (see Section 9, “Pharmacologic Approaches to Glycemic Treatment,” for more details). While there is not a universally accepted recommended periodicity of monitoring, it is notable that the lowering effect of metformin on vitamin B12

increases with time (88), with a significantly higher risk for vitamin B12 deficiency (< 150 pmol/L) noted at 4.3 years in the HOME (Hyperinsulinaemia: the Outcome of its Metabolic Effects) study (88) and significantly greater risk of low B12 levels (≤ 203 pg/mL) at 5 years in the DPP (87). It has been suggested that a person who has been on metformin for more than 4 years or is at risk for vitamin B12 deficiency should be monitored for vitamin B12 deficiency annually (89).

PREVENTION OF VASCULAR DISEASE AND MORTALITY

Recommendations

3.8 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**

3.9 Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be discontinued. **B**

3.10 In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fracture. **A** Lower doses may mitigate the risk of adverse effects. **C**

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia (90), and are at increased risk for cardiovascular disease (91,92). If indicated, evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes (93–95), a time when individuals should be monitored for diabetes development and receive concurrent evidence-based lifestyle behavior change for diabetes prevention described in this section. See Section 5, “Facilitating Positive Health

Behaviors and Well-being to Improve Health Outcomes,” for more detailed information. The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors (96,97). In longer-term follow-up, lifestyle interventions for diabetes prevention also prevented the development of microvascular complications among women enrolled in the DPPOS and in the study population enrolled in the China Da Qing Diabetes Prevention Outcome Study (7,98). The lifestyle intervention in the latter study was also efficacious in preventing cardiovascular disease and mortality at 23 and 30 years of follow-up (3,5). Treatment goals and therapies for hypertension and dyslipidemia in the primary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular diseases risk factors (99). Statins have been associated with a modestly increased risk of diabetes (100–104). In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled hazard ratio [95% CI] for incident diabetes 1.36 [1.17–1.58]) (102). In studies of primary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes (105,106), suggesting a favorable benefit-to-harm balance with statin therapy. Hence, discontinuation of statins is not recommended in this population due to concerns of diabetes risk.

Cardiovascular outcome trials in people without diabetes also inform risk reduction potential in people without diabetes at increased cardiometabolic risk (see Section 10, “Cardiovascular Disease and Risk Management,” for more details). The IRIS (Insulin Resistance Intervention after Stroke) trial was a dedicated study of people with a recent (<6 months) stroke or transient ischemic attack, without diabetes but with insulin resistance, as defined by a HOMA of insulin resistance index of ≥ 3.0 , evaluating pioglitazone (target dose of 45 mg daily) compared with placebo. At 4.8 years, the risk of stroke or myocardial infarction, as well as the risk of diabetes, was lower within the pioglitazone group than with placebo,

though risks of weight gain, edema, and fracture were higher in the pioglitazone treatment group (107–109). Lower doses may mitigate the adverse effects, though further study is needed to confirm the benefit at lower doses (110).

PERSON-CENTERED CARE GOALS

Recommendations

- 3.11** In adults with overweight/obesity at high risk of type 2 diabetes, care goals should include weight loss or prevention of weight gain, minimizing the progression of hyperglycemia, and attention to cardiovascular risk and associated comorbidities. **B**
- 3.12** Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, cardiovascular risk reduction) may be considered to support person-centered care goals. **B**
- 3.13** More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥ 35 kg/m², those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, A1C $\geq 6.0\%$), and individuals with a history of gestational diabetes mellitus. **A**

Individualized risk/benefit should be considered in screening, intervention, and monitoring to prevent or delay type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications (111,112). In the DPP, which enrolled high-risk individuals with impaired glucose tolerance, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo arm was 11.0 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 28.9% (1). Characteristics of individuals in the DPP/DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases/100 person-years) included BMI ≥ 35 kg/m², those at higher glucose levels (e.g., fasting plasma

glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, and A1C $\geq 6.0\%$), and individuals with a history of gestational diabetes (1,82,83). In contrast, in the community-based Atherosclerosis Risk in Communities (ARIC) study, observational follow-up of older adults (mean age 75 years) with laboratory evidence of prediabetes (based on A1C 5.7–6.4% and/or fasting glucose 100–125 mg/dL), but not meeting specific BMI criteria, found much lower progression to diabetes over 6 years: 9% of those with A1C-defined prediabetes, 8% with impaired fasting glucose (112).

Thus, it is important to individualize the risk/benefit of intervention and consider person-centered goals. Risk models have explored risk-based benefit, generally finding higher benefit of the intervention in those at highest risk (9). Diabetes prevention and observational studies highlight key principles that may guide person-centered goals. In the DPP, which enrolled a high-risk population meeting criteria for overweight/obesity, weight loss was an important mediator of diabetes prevention or delay, with greater metabolic benefit generally seen with greater weight loss (9,113). In the DPP/DPPOS, progression to diabetes, duration of diabetes, and mean level of glycemia were important determinants of the development of microvascular complications (7). Furthermore, the ability to achieve normal glucose regulation, even once, during the DPP was associated with a lower risk of diabetes and lower risk of microvascular complications (114). Observational follow-up of the Da Qing study also showed that regression from impaired glucose tolerance to normal glucose tolerance or remaining with impaired glucose tolerance rather than progressing to type 2 diabetes at the end of the 6-year intervention trial resulted in significantly lower risk of cardiovascular disease and microvascular disease over 30 years (115). Prediabetes is associated with increased cardiovascular disease and mortality (92), emphasizing the importance of attending to cardiovascular risk in this population.

Pharmacotherapy for weight management (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes,” for more details), minimizing the progression of hyperglycemia (see Section 9, “Pharmacologic Approaches to Glycemic Treatment,” for more details), and cardiovascular risk reduction (see Section 10, “Cardiovascular

Disease and Risk Management,” for more details) are important tools that can be considered to support individualized person-centered goals, with more intensive preventive approaches considered in individuals at high risk of progression.

PHARMACOLOGIC INTERVENTIONS FOR TYPE 1 DIABETES

Recommendation

3.14 Teplizumab-mzww infusion to delay the onset of symptomatic type 1 diabetes should be considered in selected individuals aged ≥ 8 years with stage 2 type 1 diabetes. Management should be in a specialized setting with appropriately trained personnel. **B**

Teplizumab was approved to delay the onset of stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with stage 2 type 1 diabetes based in part upon the efficacy results of a single study in relatives at risk for type 1 diabetes (116). In this study, 44 individuals were randomized to a 14-day course of teplizumab and 32 to placebo. Based on a Cox proportional hazards model, stratified by age and oral glucose tolerance test status at randomization, median time to stage 3 type 1 diabetes diagnosis was 50 months in the teplizumab group and 25 months in the placebo group, for a difference of 25 months at a median follow-up time of 51 months. In prespecified analyses, the presence of HLA-DR4 and absence of HLA-DR3 were associated with more robust responses to teplizumab (hazard ratio 0.20 [95% CI 0.09–0.45] and 0.18 [95% CI 0.07–0.45], respectively). The most common adverse reactions were lymphopenia (73%) followed by rash (36%).

Numerous clinical studies are being conducted to test methods of preventing or delaying the onset of stage 3 type 1 diabetes in those with evidence of autoimmunity without symptoms, or delaying loss of insulin secretory capacity after onset of stage 3, some with promising results (see ClinicalTrials.gov and trialnet.org).

References

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

2. Lindström J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006;368:1673–1679

3. Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol* 2014;2:474–480

4. Nathan DM, Bennett PH, Crandall JP, et al.; DPP Research Group. Does diabetes prevention translate into reduced long-term vascular complications of diabetes? *Diabetologia* 2019;62:1319–1328

5. Gong Q, Zhang P, Wang J, et al.; Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019;7:452–461

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

7. Diabetes Prevention Program Research Group; Nathan DM, Barrett-Connor E, Crandall JP, et al. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications: the DPP Outcomes Study. *Lancet Diabetes Endocrinol* 2015;3:866–875

8. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care* 2002;25:2165–2171

9. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006;29:2102–2107

10. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care* 2019;42:731–754

11. Department of Health and Human Services and Department of Agriculture. Dietary Guidelines for Americans 2015–2020, Eighth Edition. Accessed 12 October 2022. Available from <https://www.health.gov/dietaryguidelines/2015/guidelines>

12. Salas-Salvadó J, Guasch-Ferré M, Lee C-H, Estruch R, Clish CB, Ros E. Protective effects of the Mediterranean diet on type 2 diabetes and metabolic syndrome. *J Nutr* 2016;146:920S–927S

13. Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on health outcomes of a Mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. *Ann Intern Med* 2016;165:491–500

14. Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;378:e34

15. Stentz FB, Brewer A, Wan J, et al. Remission of pre-diabetes to normal glucose tolerance in obese adults with high protein versus high carbohydrate diet: randomized control trial. *BMJ Open Diabetes Res Care* 2016;4:e000258

16. Chiu THT, Pan W-H, Lin M-N, Lin C-L. Vegetarian diet, change in dietary patterns, and

diabetes risk: a prospective study. *Nutr Diabetes* 2018;8:12

17. Lee Y, Park K. Adherence to a vegetarian diet and diabetes risk: a systematic review and meta-analysis of observational studies. *Nutrients* 2017;9:E603

18. Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA Intern Med* 2019;179:1335–1344

19. Esposito K, Chiodini P, Maiorino MI, Bellastella G, Panagiotakos D, Giugliano D. Which diet for prevention of type 2 diabetes? A meta-analysis of prospective studies. *Endocrine* 2014;47:107–116

20. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *Lancet* 2014;383:1999–2007

21. Jacobs S, Harmon BE, Boushey CJ, et al. A priori-defined diet quality indexes and risk of type 2 diabetes: the Multiethnic Cohort. *Diabetologia* 2015;58:98–112

22. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr* 2012;142:1009–1018

23. Parker AR, Byham-Gray L, Denmark R, Winkle PJ. The effect of medical nutrition therapy by a registered dietitian nutritionist in patients with prediabetes participating in a randomized controlled clinical research trial. *J Acad Nutr Diet* 2014;14:1739–1748

24. Fedewa MV, Gist NH, Evans EM, Dishman RK. Exercise and insulin resistance in youth: a meta-analysis. *Pediatrics* 2014;133:e163–e174

25. Davis CL, Pollock NK, Waller JL, et al. Exercise dose and diabetes risk in overweight and obese children: a randomized controlled trial. *JAMA* 2012;308:1103–1112

26. Sigal RJ, Alberga AS, Goldfield GS, et al. Effects of aerobic training, resistance training, or both on percentage body fat and cardiometabolic risk markers in obese adolescents: the Healthy Eating Aerobic and Resistance Training in Youth randomized clinical trial. *JAMA Pediatr* 2014;168:1006–1014

27. Dai X, Zhai L, Chen Q, et al. Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes: a randomized control trial. *Diabetes Metab Res Rev* 2019;35:e3143

28. Thorp AA, Kingwell BA, Sethi P, Hammond L, Owen N, Dunstan DW. Alternating bouts of sitting and standing attenuate postprandial glucose responses. *Med Sci Sports Exerc* 2014;46:2053–2061

29. Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time: beneficial associations with metabolic risk. *Diabetes Care* 2008;31:661–666

30. Russo LM, Nobles C, Ertel KA, Chasan-Taber L, Whitcomb BW. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. *Obstet Gynecol* 2015;125:576–582

31. Herman WH, Hoerger TJ, Brande M, et al.; Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 2005;142:323–332

32. Chen F, Su W, Becker SH, et al. Clinical and economic impact of a digital, remotely-delivered

- intensive behavioral counseling program on Medicare beneficiaries at risk for diabetes and cardiovascular disease. *PLoS One* 2016;11:e0163627
33. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care* 2012;35:723–730
34. Alva ML, Hoerger TJ, Jeyaraman R, Amico P, Rojas-Smith L. Impact of the YMCA of the USA Diabetes Prevention Program on Medicare spending and utilization. *Health Aff (Millwood)* 2017;36:417–424
35. Zhou X, Siegel KR, Ng BP, et al. Cost-effectiveness of diabetes prevention interventions targeting high-risk individuals and whole populations: a systematic review. *Diabetes Care* 2020;43:1593–1616
36. Ackermann RT, Finch EA, Brizendine E, Zhou H, Marrero DG. Translating the Diabetes Prevention Program into the community. The DEPLOY Pilot Study. *Am J Prev Med* 2008;35:357–363
37. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. *Ann Intern Med* 2015;163:437–451
38. Li R, Qu S, Zhang P, et al. Economic evaluation of combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. *Ann Intern Med* 2015;163:452–460
39. Gilmer T, O'Connor PJ, Schiff JS, et al. Cost-effectiveness of a community-based Diabetes Prevention Program with participation incentives for Medicaid beneficiaries. *Health Serv Res* 2018;53:4704–4724
40. Ackermann RT, Kang R, Cooper AJ, et al. Effect on health care expenditures during nationwide implementation of the Diabetes Prevention Program as a health insurance benefit. *Diabetes Care* 2019;42:1776–1783
41. Ely EK, Gruss SM, Luman ET, et 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
42. Lanza A, Soler R, Smith B, Hoerger T, Neuwahl S, Zhang P. The Diabetes Prevention Impact Tool Kit: an online tool kit to assess the cost-effectiveness of preventing type 2 diabetes. *J Public Health Manag Pract* 2019;25:E1–E5
43. Cannon MJ, Masalovich S, Ng BP, et al. Retention among participants in the National Diabetes Prevention Program lifestyle change program, 2012–2017. *Diabetes Care* 2020;43:2042–2049
44. The Community Guide. Diabetes Prevention: Interventions Engaging Community Health Workers, 2016. Accessed 12 October 2022. Available from <https://www.thecommunityguide.org/findings/diabetes-prevention-interventions-engaging-community-health-workers>
45. Jacob V, Chattopadhyay SK, Hopkins DP, et al. Economics of community health workers for chronic disease: findings from Community Guide systematic reviews. *Am J Prev Med* 2019;56:e95–e106
46. Raynor HA, Davidson PG, Burns H, et al. Medical nutrition therapy and weight loss questions for the Evidence Analysis Library prevention of type 2 diabetes project: systematic reviews. *J Acad Nutr Diet* 2017;117:1578–1611
47. Sun Y, You W, Almeida F, Estabrooks P, Davy B. The effectiveness and cost of lifestyle interventions including nutrition education for diabetes prevention: a systematic review and meta-analysis. *J Acad Nutr Diet* 2017;117:404–421.e36
48. Briggs Early K, Stanley K. Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. *J Acad Nutr Diet* 2018;118:343–353
49. Powers MA, Bardsley JK, Cypress M, et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. *Diabetes Care* 2020;43:1636–1649
50. Hudspeth BD. Power of prevention: the pharmacist's role in prediabetes management. *Diabetes Spectr* 2018;31:320–323
51. Butcher MK, Vanderwood KK, Hall TO, Gohdes D, Helgersson SD, Harwell TS. Capacity of diabetes education programs to provide both diabetes self-management education and to implement diabetes prevention services. *J Public Health Manag Pract* 2011;17:242–247
52. Grock S, Ku J-H, Kim J, Moin T. A review of technology-assisted interventions for diabetes prevention. *Curr Diab Rep* 2017;17:107
53. Sepah SC, Jiang L, Peters AL. Translating the Diabetes Prevention Program into an online social network: validation against CDC standards. *Diabetes Educ* 2014;40:435–443
54. Bian RR, Piatt GA, Sen A, et al. The effect of technology-mediated diabetes prevention interventions on weight: a meta-analysis. *J Med Internet Res* 2017;19:e76
55. Sepah SC, Jiang L, Peters AL. Long-term outcomes of a web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. *J Med Internet Res* 2015;17:e92
56. Moin T, Damschroder LJ, AuYoung M, et al. Results from a trial of an online Diabetes Prevention Program intervention. *Am J Prev Med* 2018;55:583–591
57. Michaelides A, Major J, Pienkosz E Jr, Wood M, Kim Y, Toro-Ramos T. Usefulness of a novel mobile Diabetes Prevention Program delivery platform with human coaching: 65-week observational follow-up. *JMIR Mhealth Uhealth* 2018;6:e93
58. Kim SE, Castro Sweet CM, Cho E, Tsai J, Cousineau MR. Evaluation of a digital diabetes prevention program adapted for low-income patients, 2016–2018. *Prev Chronic Dis* 2019;16:E155
59. Vadheim LM, Patch K, Brokaw SM, et al. Telehealth delivery of the Diabetes Prevention Program to rural communities. *Transl Behav Med* 2017;7:286–291
60. Fischer HH, Durfee MJ, Raghunath SG, Ritchie ND. Short message service text message support for weight loss in patients with prediabetes: pragmatic trial. *JMIR Diabetes* 2019;4:e12985
61. Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. *Lancet Diabetes Endocrinol* 2021;9:32–45
62. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319–328
63. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011;364:1104–1115
64. Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–1105
65. le Roux CW, Astrup A, Fujioka K, et al.; SCALE Obesity Prediabetes NN8022-1839 Study Group. 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
66. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072–2077
67. Wilding JPH, Batterham RL, Calanna S, et al.; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384:989–1002
68. Holman RR, Haffner SM, McMurray JJ, et al.; NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010;362:1463–1476
69. Dennison RA, Chen ES, Green ME, et al. The absolute and relative risk of type 2 diabetes after gestational diabetes: a systematic review and meta-analysis of 129 studies. *Diabetes Res Clin Pract* 2021;171:108625
70. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27:155–161
71. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care* 2014;37:912–921
72. Jastreboff AM, Aronne LJ, Ahmad NN, et al.; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;387:205–216
73. McMurray JJ, Holman RR, Haffner SM, et al.; NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010;362:1477–1490
74. Bosch J, Yusuf S, Gerstein HC, et al.; DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006;355:1551–1562
75. Everett BM, Donath MY, Pradhan AD, Thuren T, Pais P, Nicolau JC, et al. Anti-inflammatory

- therapy with canakinumab for the prevention and management of diabetes. *J Am Coll Cardiol* 2018;71:2392–2401.
76. Ray KK, Colhoun HM, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;7:618–628
77. Pittas AG, Dawson-Hughes B, Sheehan P, et al.; D2d Research Group. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med* 2019;381:520–530
78. Dawson-Hughes B, Staten MA, Knowler WC, et al.; D2d Research Group. Intratrial exposure to vitamin D and new-onset diabetes among adults with prediabetes: a secondary analysis from the vitamin D and type 2 diabetes (D2d) study. *Diabetes Care* 2020;43:2916–2922
79. Zhang Y, Tan H, Tang J, et al. Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes: a systematic review and meta-analysis. *Diabetes Care* 2020;43:1650–1658
80. Barbarawi M, Zayed Y, Barbarawi O, Bala A, Alabdouh A, Gakhal I, et al. Effect of vitamin D supplementation on the incidence of diabetes mellitus. *J Clin Endocrinol Metab* 2020;105:dgaa335.
81. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2012;35:731–737
82. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774–4779
83. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. *J Clin Endocrinol Metab* 2015;100:1646–1653
84. Diabetes Prevention Program Research Group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2019;42:601–608
85. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006;49:289–297
86. Griffin SJ, Bethel MA, Holman RR, et al. Metformin in non-diabetic hyperglycaemia: the GLINT feasibility RCT. *Health Technol Assess* 2018;22:1–64
87. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab* 2016;101:1754–1761
88. de Jager J, Kooy A, Leher P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ* 2010;340:c2181
89. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020;98(4S):S1–S115
90. 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
91. Pan Y, Chen W, Wang Y. Prediabetes and outcome of ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2019;28:683–692
92. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ* 2016;355:i5953
93. Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. *Ann Intern Med* 2010;152:10–17
94. Oba S, Noda M, Waki K, et al.; Japan Public Health Center-Based Prospective Study Group. Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study. *PLoS One* 2012;7:e17061
95. Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, et al. Smoking cessation, weight change, type 2 diabetes, and mortality. *N Engl J Med* 2018;379:623–632
96. Orchard TJ, Temprosa M, Barrett-Connor E, et al.; Diabetes Prevention Program Outcomes Study Research Group. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. *Diabet Med* 2013;30:46–55
97. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, et al.; PREDIMED-Plus investigators. Effect of a lifestyle intervention program with energy-restricted mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus Trial. *Diabetes Care* 2019;42:777–788
98. Gong Q, Gregg EW, Wang J, et al. Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. *Diabetologia* 2011;54:300–307
99. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596–e646
100. Thakker D, Nair S, Pagada A, Jamdade V, Malik A. Statin use and the risk of developing diabetes: a network meta-analysis. *Pharmacoepidemiol Drug Saf* 2016;25:1131–1149
101. Macedo AF, Douglas I, Smeeth L, Forbes H, Ebrahim S. Statins and the risk of type 2 diabetes mellitus: cohort study using the UK Clinical Practice Research Datalink. *BMC Cardiovasc Disord* 2014;14:85
102. Crandall JP, Mather K, Rajpathak SN, et al. Statin use and risk of developing diabetes: results from the Diabetes Prevention Program. *BMJ Open Diabetes Res Care* 2017;5:e000438
103. Preiss D, Seshasai SRK, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305:2556–2564
104. Mansi IA, Chansard M, Lingvay I, Zhang S, Halm EA, Alvarez CA. Association of statin therapy initiation with diabetes progression: a retrospective matched-cohort study. *JAMA Intern Med* 2021;181:1562–1574
105. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012;380:565–571
106. Cai T, Abel L, Langford O, et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. *BMJ* 2021;374:n1537
107. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016;374:1321–1331
108. Inzucchi SE, Viscoli CM, Young LH, et al.; IRIS Trial Investigators. Pioglitazone prevents diabetes in patients with insulin resistance and cerebrovascular disease. *Diabetes Care* 2016;39:1684–1692
109. Spence JD, Viscoli CM, Inzucchi SE, et al.; IRIS Investigators. Pioglitazone therapy in patients with stroke and prediabetes: a post hoc analysis of the IRIS randomized clinical trial. *JAMA Neurol* 2019;76:526–535
110. Spence JD, Viscoli C, Kernan WN, et al. Efficacy of lower doses of pioglitazone after stroke or transient ischaemic attack in patients with insulin resistance. *Diabetes Obes Metab* 2022;24:1150–1158
111. Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-onset type 2 diabetes consensus report: current status, challenges, and priorities. *Diabetes Care* 2016;39:1635–1642
112. Rooney MR, Rawlings AM, Pankow JS, et al. Risk of progression to diabetes among older adults with prediabetes. *JAMA Intern Med* 2021;181:511–519
113. Lachin JM, Christophi CA, Edelstein SL, et al.; DPP Research Group. Factors associated with diabetes onset during metformin versus placebo therapy in the diabetes prevention program. *Diabetes* 2007;56:1153–1159
114. Perreault L, Pan Q, Schroeder EB, et al.; Diabetes Prevention Program Research Group. Regression from prediabetes to normal glucose regulation and prevalence of microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPPOS). *Diabetes Care* 2019;42:1809–1815
115. Chen Y, Zhang P, Wang J, et al. Associations of progression to diabetes and regression to normal glucose tolerance with development of cardiovascular and microvascular disease among people with impaired glucose tolerance: a secondary analysis of the 30 year Da Qing Diabetes Prevention Outcome Study. *Diabetologia* 2021;64:1279–1287
116. Herold KC, Bundy BN, Long SA, et al.; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med* 2019;381:603–613