Title

Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence

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Type 2 Diabetes Mellitus in Light of Recent Evidence:

A Scientific Statement From the American Heart Association and the American Diabetes Association

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Abstract

Cardiovascular disease risk factor control as primary prevention in patients with type 2 diabetes mellitus has changed substantially in the past few years. The purpose of this scientific statement is to review the current literature and key clinical trials pertaining to blood pressure and blood glucose control, cholesterol management, aspirin therapy, and lifestyle modification. We present a synthesis of the recent literature, new guidelines, and clinical targets, including screening for kidney and subclinical cardiovascular disease for the contemporary management of patients with type 2 diabetes mellitus.

Keywords

AHA Scientific Statements; cardiovascular disease; diabetes; primary prevention

Diabetes mellitus, defined by elevated glycemic markers, is a major risk factor for cardiovascular disease (CVD), which is the most common cause of death among adults with diabetes mellitus,[1] underscoring the need for aggressive CVD risk factor management. In 1999, the American Heart Association (AHA) and the American Diabetes Association (ADA) published a joint statement focused on CVD prevention in diabetes mellitus.[2] In

2007, the AHA and ADA again issued a combined set of recommendations focused on the primary prevention of CVD in diabetes mellitus.[3] Since then, several new clinical trials have emerged that have changed the clinical practice of CVD risk management in diabetes mellitus.

Since the earlier scientific statement, diabetes mellitus screening and diagnosis have changed, with the inclusion of glycated hemoglobin (A_{1c}) of at least 6.5% in the diagnostic criteria of type 2 diabetes mellitus.[4] This change in criteria has identified separate subsets of newly diagnosed patients with diabetes mellitus while the overall diabetes mellitus epidemic continues, with a 75% increase in the number of affected individuals with diabetes mellitus across all age groups from 1988 to 2010.[5] Fewer than half of US adults meet recommended guidelines for diabetes mellitus care,[6] underscoring the magnitude of the public health burden of type 2 diabetes mellitus.

Given the changes in the diabetes mellitus landscape over the past 5 years, the purpose of this scientific statement is to summarize key clinical trials pertaining to lifestyle, blood glucose, blood pressure, and cholesterol management for the primary prevention of CVD. We have synthesized the established clinical guidelines and clinical targets for the contemporary management of patients with type 2 diabetes mellitus to reduce CVD risk. When possible, we have included the AHA/American College of Cardiology (ACC) Class of Recommendation/Level of Evidence grading system (Table 1) or the ADA evidence grading system for clinical practice recommendations (Table 2).[4]

Specifically, we start with the updated diagnostic criteria for diabetes mellitus. Next, we focus on lifestyle management in diabetes mellitus, including physical activity and nutrition. Then, we focus on CVD risk factor management in diabetes mellitus, including weight management, aspirin use, glucose control, blood pressure management, and lipid management. Next, we move to screening for renal and CVD complications of diabetes mellitus. Finally, we close with a list of selected areas of controversy requiring further research. Throughout, we emphasize that this document is not a comprehensive review of the literature but rather a focus on the major new trials that have led to recent guideline changes in the area of primary prevention of CVD in type 2 diabetes mellitus.

New Diagnostic Criteria for Diabetes Mellitus and Prediabetes

In 2010, the ADA included A_{1c} for the first time among the tests recommended for the diagnosis of diabetes mellitus. This recommendation has also been adopted by the European Association for the Study of Diabetes, the World Health Organization, and other professional groups in the United States. Clinical practice recommendations from the ADA now state that an A_{1c} value of ≥6.5% or previous criteria for fasting glucose (≥126 mg/dL) or 2-hour glucose (≥200 mg/dL) can be used for the diagnosis of diabetes mellitus (Table 3).[4] In 2010, the ADA also added A_{1c} to the tests used to identify people with prediabetes, who are at increased risk for type 2 diabetes mellitus. Thus, along with fasting glucose of 100 to 125 mg/dL or 2-hour glucose of 140 to 199 mg/dL, individuals with A_{1c} in the range of 5.7% to 6.4% are classified as having an increased risk for diabetes mellitus (Table 3).[4]

A_{1c} and Diabetes Mellitus

A major strength of using A_{1c} for the diagnosis of diabetes mellitus is the evidence linking A_{1c} to clinical outcomes. Randomized, clinical trials have demonstrated that improvements in glycemic control reduce the risk of microvascular complications.[8–11] Evidence for current diagnostic cut points also includes epidemiological studies demonstrating strong, graded, cross-sectional associations for fasting glucose, 2-hour glucose, and A_{1c} with prevalent retinopathy.[11–15] In one of the few prospective studies of retinopathy, an analysis of data from a large Japanese population showed that individuals with an A_{1c} of ≥6.5% had an elevated risk of newly developed retinopathy during 3 years of follow-up compared with those with A_{1c} values in the range of 5.0% to 5.4%.[16] Recent studies have also established robust relationships of A_{1c} with future risk of diabetes mellitus, chronic kidney disease (CKD), CVD, and all-cause mortality in initially nondiabetic populations.[17–20] These data linking A_{1c} to both microvascular and macrovascular outcomes provide further evidence to support the new A_{1c} criteria.

A_{1c} and Prediabetes

Epidemiological studies have shown that individuals with A_{1c} in the range of 5.7% to 6.4% have a high risk of future diabetes mellitus,[20–22] supporting the use of this range to define prediabetes. However, the A_{1c} threshold for increased diabetes mellitus risk is less clearly defined than that for a diagnosis of diabetes mellitus. There is a strong risk gradient between 5.7% and 6.4%, with no obvious threshold. Elevated A_{1c}, even below the threshold for diagnosis of diabetes mellitus, is also associated with cardiovascular outcomes after adjustment for traditional cardiovascular risk factors.[19,20,23,24] The evidence for an association of impaired fasting glucose (100–125 mg/dL) with cardiovascular outcomes is less robust,[25] possibly because of the higher variability in fasting glucose levels compared with A_{1c}.[26,27] Indeed, in a recent very large study that pooled data from >50 separate epidemiological cohorts, greatly enhancing the power to detect a modest association, fasting glucose levels in the nondiabetes range were moderately but significantly associated with risk of vascular death.[28] The high risk of both diabetes mellitus and CVD among people with an A_{1c} of 5.7% to 6.4% highlights the need for cardiovascular and diabetes mellitus prevention efforts in this population.

Strengths and Limitations of Using A_{1c} for Diabetes Mellitus Diagnosis

There are a number of advantages of using A_{1c} for diagnosing diabetes mellitus; however, there are also some limitations to consider[18,20,26,29–33] that are summarized in Table 4.

Some A_{1c} measurement methods are known to give falsely high or low values in the presence of hemoglobin variants, although modern assays are mostly unaffected by common variants.[29] However, other nonglycemic determinants of A_{1c}, that is, hemoglobin characteristics (other than hemoglobinopathies), red cell turnover, and the tendency of hemoglobin to undergo glycation, may contribute to variability in the population.[30]

In summary, updated diagnostic criteria for diabetes mellitus are well aligned with the current evidence linking A_{1c} to long-term complications. Because the same tests identify diabetes mellitus and prediabetes, current guidelines represent a convenient approach to

identifying individuals with either condition, so individuals with prediabetes can be targeted for diabetes mellitus risk reduction and patients with diabetes mellitus can receive aggressive cardiovascular risk prevention.

Lifestyle Management of Type 2 Diabetes Mellitus

Once type 2 diabetes mellitus is diagnosed, lifestyle management is a cornerstone of clinical care. This section reviews some of the evidence from large clinical trials that focus on lifestyle management in type 2 diabetes mellitus.

Physical Activity

The Look AHEAD (Action for Health in Diabetes) study, conducted from 2001 to 2012, provided extensive longitudinal data on the effect of an intensive lifestyle intervention, targeting weight reduction through caloric restriction and increased physical activity, on CVD rates (the primary outcome) and CVD risk factors among adults with type 2 diabetes mellitus. In this trial, 2575 participants were randomized to a control group and 2570 to an intervention that consisted of a weekly goal for physical activity of 50 min/wk initially, increasing to ≥175 min/wk of moderately intense activity by week 26.[34] The second component of the physical activity intervention included a focus on lifestyle activity (eg, using the stairs instead of elevators, walking instead of riding), which is equally as effective as aerobic activity in leading to weight loss and improvement in CVD risk factors.[35] Participants were provided a pedometer in the seventh week and instructed to increase their daily steps by 250 each week until they reached the goal of ≥10 000 a day. One-year results revealed that participants in the intensive lifestyle intervention achieved an average of 136.7±110.4 min/wk of physical activity; moreover, there was a significant association between the minutes of physical activity and weight loss at 12 months.[36]

The primary results of Look AHEAD were published in 2013.[37] At 1 year, greater weight loss was observed in the intervention arm (8.6%) compared with the usual care arm (0.7%), which was attenuated but still sustained by the end of the study (6.0% versus 3.5%). In addition to weight loss, the patients in the intervention arm had improved physical fitness and high-density lipoprotein (HDL) cholesterol (HDL-C) levels, had greater reductions in A_{1c} and waist circumference, and required less medication for glucose, blood pressure, and lipid control. However, after a median follow-up of 9.6 years, the trial was stopped early because of futility: There were 403 CVD events in the intervention arm compared with 418 CVD events in the usual care arm (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.83–1.09; P=0.51). The reasons for this are not clear[38] but may be the result of decreased use of cardioprotective drugs, particularly statins, in the intervention group resulting from an improvement in risk factors with the lifestyle intervention. At a minimum, the study informs clinicians that increased physical activity and improvements in diet can safely lead to weight loss and reduced requirement for medication to control CVD risk factors without a concomitant increase in the risk of cardiovascular events.

In addition to absolute amounts of exercise, the type of exercise in patients with diabetes mellitus might make a difference. A recent randomized, controlled trial (RCT) of 262 sedentary patients with diabetes mellitus randomized to the nonexercise control group or to

a resistance training alone, an aerobic training alone, or a combined resistance and aerobic training group showed that only the combined exercise was associated with lower A_{1c} levels (mean decline, 0.34%; P=0.03).[39] These findings highlight how exercise type may be as important as exercise quantity in type 2 diabetes mellitus.

Nutrition

In addition to physical activity, nutrition plays an important role in the treatment of type 2 diabetes mellitus and CVD risk prevention. Published recommendations for the treatment of people with diabetes mellitus assert the continued importance of diet, exercise, and education as a cornerstone of optimal diabetes mellitus treatment.[4,40–43]

Current nutrition recommendations for individuals with type 2 diabetes mellitus center around a dietary pattern that emphasizes intake of fruits, vegetables, reduced saturated fat, and low-fat dairy products. The recommendations also consist of individualized modification of macronutrient intake to accommodate individual needs for the distribution of calories and carbohydrates over the course of the day. Eating patterns such as the Dietary Approaches to Stop Hypertension (DASH), Mediterranean, low-fat, or monitored carbohydrate diet are effective for controlling glycemia and lowering CVD risk factors.[44] The Prevención con Dieta Mediterránea (PREDIMED) trial was an RCT looking at the effect of a Mediterranean diet on CVD outcomes. Those patients randomized to the Mediterranean diet had a 30% reduced risk of CVD events.[45] The prespecified diabetes mellitus subgroup demonstrated similar results, suggesting that a Mediterranean diet may promote CVD risk reduction in patients with diabetes mellitus.

Some data suggest that eating patterns with low glycemic index may be effective in achieving glycemic control (ie, positive effects on postprandial blood glucose and insulin) and in lowering triglyceride levels,[46–48] whereas other studies have shown no effect of low–glycemic index diets on triglycerides.[49–51] The importance of the glycemic index needs further investigation.

Given that individuals with diabetes mellitus commonly have elevated triglycerides and reduced HDL-C levels, it is important to optimize nutrition-related practices, including moderate alcohol intake, substituting healthy fats (eg, monounsaturated fatty acids, polyunsaturated fatty acids) for saturated and *trans* fats, limiting added sugars, engaging in regular physical activity, and losing excess weight. These changes can reduce triglycerides by 20% to 50%.[52]

Dietary Supplements

With regard to dietary supplements, no consistent findings have emerged from large-scale, randomized trials in individuals with diabetes mellitus.[53,54] In individuals without diabetes mellitus, some studies have demonstrated an association with lower CVD risk when a healthful diet is supplemented with antioxidant vitamins, B vitamins, or specific fatty acids (eg, omega-3 fatty acids).[54–57] However, there are no conclusive studies in patients with diabetes mellitus. Whether vitamin D supplementation will ultimately be important in preventing diabetes mellitus remains to be determined.

Nutritional Recommendations

The ADA recently issued a position statement on nutritional recommendations for adults living with diabetes mellitus.[43] The stated goals of nutrition therapy for adults with diabetes mellitus are to attain individualized glycemic, lipid, and blood pressure goals; to achieve and maintain healthy body weight; to prevent or delay diabetes mellitus complications; and to provide those living with diabetes mellitus tools for meal planning. Key specific recommendations[43] can be found in Table 5.

Weight Management

The next section of this update focuses on weight management through lifestyle, pharmacological, and surgical approaches in type 2 diabetes mellitus.

Lifestyle

The primary approach to weight management is lifestyle, which includes 3 components: dietary change that is focused on caloric restriction, increased energy expenditure through increased daily physical activity and regular aerobic activity 3 to 5 d/wk, and behavior changes related to lifestyle. Numerous clinical trials have established the efficacy of this approach.[64,65] In type 2 diabetes mellitus, a landmark trial is the recent Look AHEAD study. In terms of the specific intervention, the Look AHEAD trial intensive intervention diverged from that of the Diabetes Prevention Program (DPP) in that there were more counseling sessions extending over a longer duration with both individual and group treatment in addition to the meal replacements that were provided.[34] Meal replacements are an approach that addresses portion control and the difficulty individuals have in estimating calorie content of consumed foods.[66,67] The dietary component of the trial included an energy goal of 1200 to 1500 kcal/d for those weighing <114 kg and 1500 to 1800 for those weighing ≥114 kg. Additional goals included restricting fat to <30% of total calories and <10% from saturated fat. The physical activity component is described in detail in the previous section.

The third component was focused on behavior modification and included group sessions during the first year; in subsequent years, contact was achieved by monthly individual sessions and by telephone. Of all the behavioral strategies taught in these sessions, self-monitoring or recording one’s food intake and physical activity was likely the most important strategy for success. There is extensive empirical evidence on the association between self-monitoring and successful outcomes in weight loss treatment.[68,69] Individuals were weighed before each session and were provided feedback; they were also encouraged to weigh themselves more often because there is evidence that more frequent weighing is associated with improved weight loss and maintenance.[70,71]

The final component of the lifestyle program was the use of a toolbox, a strategy also used in the DPP. The purpose of the toolbox was to have an array of strategies to use with an individual who was not achieving adequate adherence to the protocol or who had lost <1% of baseline weight. Treatment options included the use of motivational interviewing strategies to assist an individual in goal setting and improved adherence to written contracts with the lifestyle counselor. Other techniques used over the subsequent years to keep

participants engaged and motivated and to promote weight loss maintenance included refresher courses, campaigns, and incentives such as prizes for campaign winners.[72]

At 4 years, participants in the intensive lifestyle arm of Look AHEAD lost 4.7% of initial weight compared with 1.1% in the usual care group. Consistent with the DPP findings, older individuals had greater adherence to session attendance, greater participation in the intervention, and lower self-reported energy intake and lost more weight than their younger counterparts. However, it is important to reflect on the primary results of Look AHEAD, reviewed above, which, despite weight loss and concomitant improvement in CVD risk factors, did not demonstrate reduced CVD events in the intensive lifestyle arm. Thus, further work in type 2 diabetes mellitus is needed to elucidate the role of physical activity and weight loss in reducing clinical CVD end points.[37]

Another study examining the role of intensive lifestyle management on CVD risk factors was the Italian Diabetes and Exercise Study (IDES). The IDES was an RCT designed to examine the effects of an intensive exercise intervention strategy on modifiable CVD risk factors in 606 sedentary subjects with type 2 diabetes mellitus enrolled in 22 outpatient diabetes mellitus clinics across Italy.[73] The subjects were randomized by center, age, and diabetes mellitus treatment to 150 minutes of twice-a-week supervised aerobic and resistance training plus structured exercise counseling (exercise group) or to structured individualized counseling alone (control group) for 12 months. In the structured individualized counseling sessions, which occurred every 3 months, participants were encouraged to meet the current physical activity recommendations through increasing energy expenditure during commuting, occupational, home, and leisure time. Subjects in both groups received dietary counseling, which included caloric intake (55% complex carbohydrates, 30% fat, and 15% protein) designed to obtain a negative balance of 500 kcal/d against energy expended. Compared with the control group, supervised exercise produced significant improvements in physical fitness, A_{1c}, systolic and diastolic blood pressures, HDL-C and low-density lipoprotein (LDL) cholesterol (LDL-C) levels, waist circumference, body mass index (BMI), insulin resistance, inflammation, and coronary heart disease (CHD) risk scores.[74]

The association of smoking cessation, an important CVD prevention strategy, with weight gain deserves specific mention. A previously unanswered question was whether the weight gain of 3 to 6 kg that occurs after smoking cessation would be associated with an increased cardiovascular risk in those with diabetes mellitus. A recent observational study found that, despite a mean weight increase of 3.6 kg for recent (<4 years) quitters, smoking cessation was still associated with a decreased risk of CHD.[75]

Pharmacological Therapy

When lifestyle interventions for weight loss fail to achieve the desired goals, the physician and patient may wish to consider alternatives, including medications or surgery. In clinical trials, medications and surgery almost always produce more weight loss than the lifestyle/placebo interventions against which they are compared. In accordance with the new AHA/ACC/The Obesity Society guidelines for weight loss,[58] pharmacological therapy is indicated for individuals with a BMI of 25 to 30 kg/m^2 with comorbidities or a BMI >30

kg/m^2 with or without comorbidities. The new guidelines for obesity are briefly summarized in Table 5, although they contain no specific recommendation for the use of medications.

The weight loss achieved with an intensive lifestyle intervention usually wanes over time. The first step in evaluating medications for the obese patient is to make sure that the patient is not taking drugs that produce weight gain. These potentially include certain antidiabetes drugs, antidepressants, and antiepileptics.[76–78] If such agents are identified and if there are acceptable alternatives that are weight neutral or produce weight loss, the healthcare provider should consider changing to the drugs that produce weight loss.[78]

Several drugs are approved by the US Food and Drug Administration for treatment of the patient with obesity (Table 6),[76,79,80] several for short-term use (usually considered <12 weeks) and 3, orlistat,[81] lorcaserin,[82] and extended-release topiramate/phentermine, for longer-term use.[83] Bupropion/naltrexone is currently under review while a cardiovascular outcome trial is being conducted.[84] In addition, 4 pharmacological agents (phentermine, diethylpropion, benzphetamine, and phendimetrazine) are approved for short-term use. All agents except orlistat are classified by the US Drug Enforcement Administration as having the potential for abuse and are schedule III or IV drugs. Several guiding principles should be followed when weight loss agents are prescribed. First, the patient should be familiarized with the drugs and their potential side effects. Second, the patient should receive effective lifestyle support for weight loss along with the pharmacological agent. Third, because response to medications is variable, patients should be re-evaluated regularly, and if they have not lost 5% of their body weight after 3 months of treatment, a new plan should be implemented.[85,86]

Many overweight and obese patients also have type 2 diabetes mellitus, and there are several hypoglycemic therapies to choose from,[76] some that increase weight and others reduce weight. For example, thiazolidinediones, insulin, glinides, and sulfonylureas produce weight gain; dipeptidyl peptidase-4 inhibitors are weight neutral; and metformin, pramlintide, exenatide, liraglutide, and sodium-glucose cotransporter-2 inhibitors produce weight loss.[76] Exenatide and liraglutide are both glucagon-like peptide-1 agonists and produce modest weight loss of 5% at doses recommended for the treatment of diabetes mellitus. In clinical trials, a higher dose of liraglutide is being investigated as a long-term treatment for obesity.[87] The sodium-glucose cotransporter-2 inhibitors block the sodium-glucose cotransporter in the renal tubule and can produce modest weight loss, although long-term safety data are not yet available.[88] If all other things are equal, the healthcare provider may wish to use antidiabetes drugs that produce weight loss. However, there are many selection factors to consider in the choice of glucose-lowering agents for patients with diabetes mellitus, including cost.

Surgical Procedures for Severe Obesity and Metabolic Disease

Bariatric surgery (ie, weight loss surgery) is the most effective treatment for attaining significant and durable weight loss in severely obese patients. Because metabolic and weight-related comorbidities are often improved or resolved through weight loss or neuroendocrine mechanisms, the term metabolic surgery is rapidly replacing bariatric surgery. In general, metabolic operations alter the gastrointestinal tract by reducing stomach

capacity (gastric restrictive operations); rerouting nutrient flow, leading to some degree of malabsorption (bypass procedures); or combining both concepts. Metabolic procedures have evolved since the abandoned jejunoileal bypass of the early 1950s and 1960s. Commonly performed procedures (frequency of use) include the Roux-en-Y gastric bypass (49%), sleeve gastrectomy (30%), adjustable gastric banding (19%), and biliopancreatic diversion (2%). The development of laparoscopic approaches to all these metabolic procedures in the mid-1990s was a major advance resulting in a significant reduction in perioperative morbidity and mortality.

The indications for weight loss surgery have evolved since the seminal National Institutes of Health guidelines from 1991, which recommended surgical intervention for weight loss in patients with a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 with significant obesity-related comorbidities.[89] The most recent guidelines for bariatric surgery pertaining to patients with type 2 diabetes mellitus came from the International Diabetes Federation in 2011. This group recommended considering surgery for obese individuals (BMI >30 kg/m^2) with type 2 diabetes mellitus who had not achieved the International Diabetes Federation treatment targets with an optimal medical regimen, especially if other cardiovascular risk factors were present.[90] The new AHA/ACC/The Obesity Society guidelines recommend that adults with BMI ≥35 kg/m^2 and an obesity-related comorbidity such as diabetes mellitus who are motivated to lose weight should be considered for referral to a bariatric surgeon.[58]

Effect of Surgery on Weight Loss—The primary intent of bariatric procedures is a reduction of excess body fat and comorbidity improvement or resolution. A meta-analysis (136 studies) of mostly short-term (<5 years) weight loss outcomes after > 22 000 bariatric procedures demonstrated an overall mean excess weight loss (defined as follows: initial body weight in kilograms minus current weight in kilograms divided by initial body weight in kilograms minus ideal body weight times 100%) of 61.2 % (95% CI, 58.1–64.4), 47.5% (95% CI, 40.7–54.2) for patients who underwent gastric banding, 61.6% (95% CI, 56.7–66.5) for those who had gastric bypass, 68.2% (95% CI, 61.5–74.8) for patients with gastroplasty, and 70.1% (95% CI, 66.3–73.9) for patients with biliopancreatic diversion or duodenal switch.[91]

The best long-term surgical weight loss data come from the Swedish Obese Subjects (SOS) study, a prospective study (>90% follow-up rate) evaluating the long-term effects of bariatric surgery compared with nonsurgical weight management of severely obese patients in a community setting.[92] At 15 years, weight loss (percent of total body weight) was 27±12% for gastric bypass, 18±11% for vertical-banded gastroplasty, and 13±14% for gastric banding compared with a slight weight gain for control subjects. In contrast, long-term medical (nonsurgical) weight loss rarely exceeded 8%.[37]

Effect of Surgery on Glycemic Control, CVD Risk Factors, and CVD Outcomes

Observational Data: Multiple observational studies demonstrate significant, sustained improvements in glycemia in type 2 diabetes mellitus among patients with severe obesity (BMI ≥35 kg/m^2) after weight loss procedures. A meta-analysis involving 19 studies (mostly observational) and 4070 patients reported an overall type 2 diabetes mellitus resolution rate

of 78% after bariatric surgery.[93] Resolution was typically defined as becoming nondiabetic with normal A_{1c} without medications. Most of these studies, however, were retrospective, with follow-up of only 1 to 3 years on average, and varied by type of procedure. A_{1c} typically improved from baseline by a minimum of 1% up to 3% after surgery, an effect rarely equaled by medical treatment alone. In the SOS study, the remission rate for type 2 diabetes mellitus was 72% at 2 years and 36% at 10 years compared with 21% and 13%, respectively, for the nonsurgical control subjects ($P<0.001$).[95] Bariatric surgery was also markedly more effective than nonsurgical treatment in the prevention of type 2 diabetes mellitus, with a relative risk reduction of 78%.[96] A systematic review of long-term cardiovascular risk factor reduction after bariatric surgery involved 73 studies and 19 543 patients.[93] At a mean follow-up of 57.8 months, the average excess weight loss for all procedures was 54%, and remission/improvement was 63% for hypertension, 73% for type 2 diabetes mellitus, and 65% for hyperlipidemia.

Few, mostly retrospective, studies have evaluated the effect of metabolic surgery on the progression of microvascular disease such as retinopathy, nephropathy, and neuropathy in type 2 diabetes mellitus. The results are far from conclusive but suggest a potential reversal in or reduced development of nephropathy after bariatric surgery.[97,98] Recently, 12 cohort-matched studies comparing bariatric surgery with nonsurgical controls were reviewed.[99] Collectively, all but 2 of these studies support a lower CVD event rate and all-cause mortality rate among patients who had undergone bariatric surgery. Of these studies, the SOS study has the longest outcomes follow-up (median, 14.7 years). CVD mortality in the surgical group was lower than for control patients (adjusted HR, 0.47; 95% CI, 0.29–0.76; $P=0.002$) despite a greater prevalence of smoking and higher baseline weights and blood pressures in the surgical cohort.[92]

RCT Data: Four short-term (1–2 years) RCTs have compared bariatric surgery with medical treatment of type 2 diabetes mellitus. Among 60 patients with mild type 2 diabetes mellitus and a BMI of 30 to 40 kg/m^2, adjustable gastric banding produced larger reductions in weight, fasting blood glucose, A_{1c}, and diabetes mellitus medication use compared with medical treatment and achieved remission (defined as A_{1c} <6.3% without medications) rates of 73% compared with only 13% for medical management ($P<0.05$).[100] A larger RCT of 150 patients with mild to moderate obesity (BMI, 27–43 kg/m^2) and poorly controlled type 2 diabetes mellitus (mean A_{1c}, 9%)[101] demonstrated better glycemic control (defined as A_{1c} <6% with or without medications) after Roux-en-Y gastric bypass (42%) or sleeve gastrectomy (37%) compared with intensive medical therapy (12%) at 1 year ($P<0.001$). Both surgical procedures resulted in greater improvement in other CVD risk factors, including triglycerides and HDL-C, compared with intensive medical therapy. Two other RCTs in patients with obesity and type 2 diabetes mellitus consisting of 60[102] and 120[103] patients demonstrated similar results. All 4 RCTs showed that surgery in the short term (1–2 years) was well tolerated, with few major complications, and resulted in both superior glycemic control and greater improvements in CVD risk factors compared with medical treatment alone in up to 24 months of follow-up. The longer-term durability of these findings remains unknown, as well as whether improvements in CVD risk factors will

ultimately translate into CVD event reduction. These issues represent important future areas of research.

Complications of Surgery: The safety of bariatric surgery is of primary concern in the determination of whether the potential benefits outweigh the surgical risks. A meta-analysis of published mortality data after bariatric surgery reported an overall 30-day postoperative mortality of 0.28% (n=84 931) and total mortality from 30 days to 2 years of 0.35% (n=19 928).[104] The Longitudinal Assessment of Bariatric Surgery (LABS) study subsequently reported a similarly low 30-day mortality rate (0.3 %) among 4776 patients.[105] Immediate- and long-term perioperative morbidity rates for bariatric surgery are lower than might be expected for this medically comorbid population; the LABS Consortium reported a 4.3% incidence of major adverse events in the early postoperative period. Although these reports are encouraging, a number of complications associated with bariatric surgery are potentially fatal and merit careful consideration. The most common complications are summarized in Table 7.[105]

Bariatric surgery can reverse or improve many obesity-related disease processes, including type 2 diabetes mellitus. There is now evidence supporting decreases in short- and medium-term CVD, although these data are derived from observational studies only. Benefits should be weighed against short- and long-term complications, which are best managed by a long-term multidisciplinary effort. Bariatric surgery may be particularly suitable for patients with type 2 diabetes mellitus and severe obesity (BMI ≥35 kg/m^2) because these patients may benefit from obesity comorbidity improvement and significantly improved glycemic control compared with medical therapy alone. Taken together, these data highlight how bariatric surgery can result in weight loss, A_{1c} improvement, and CVD risk factor improvement. The durability of these metabolic improvements, particularly from the RCT literature, over time remains to be determined and represents an important future area of research.

Aspirin Therapy

Whether to use aspirin for the primary prevention of CVD events in patients with diabetes mellitus remains controversial. Aspirin reduces CVD events in patients with known CVD (secondary prevention).[106] In the general primary prevention population, aspirin is effective in preventing nonfatal myocardial infarction (MI) in men[106]; for women, the evidence is less clear, but aspirin appears to reduce the risk of stroke.[107]

Trials examining the effect of aspirin for primary prevention in patients with diabetes mellitus are summarized: 6 trials[108–113] were conducted in the general population that also included patients with diabetes mellitus, and 3 other trials[114–116] specifically examined patients with diabetes mellitus. Trials ranged from 3 to 10 years in duration and have examined a wide range of aspirin doses. Participants were mainly late middle-aged adults; 3 trials[108,109,112] included only men. The range of underlying CVD risk varied widely across trials. Participants in the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial were at very low risk (0.25% annual CHD risk), whereas earlier trials had control group CHD risks exceeding 2%/y.

Through 2012, 7 meta-analyses have synthesized data on the effects of aspirin for patients with diabetes mellitus.[106,117–122] The available analyses differ somewhat in the trials they included. Overall, the 7 analyses suggest at best a modest effect of aspirin, with statistically nonsignificant risk reductions of ≈10% each for the key individual outcomes of stroke and MI. When analyses examined total CVD events (MI and stroke together), CIs were narrower and sometimes statistically significant.

Some analyses found evidence for sex-related differences in outcomes,[117,121,122] with larger reductions in CHD events for men and larger reductions in stroke for women. Zhang et al[117] found that for trials with >50% women, the risk of MI was 1.10 and the risk of stroke 0.67 with aspirin use compared with nonuse. Conversely, trials with ≥50% men had a relative risk for CHD events of 0.71 and a relative risk for stroke of 1.05 with aspirin use compared with nonuse.[117] Risk of bleeding appeared to be increased ≥2-fold but was not statistically significant in any meta-analysis.

Taken as a whole, these results suggest a modest (≈9%) relative reduction in risk for CVD events and ≥2-fold relative risk of bleeding, mainly from the gastrointestinal system. The net effect of aspirin therefore depends on the baseline risks of CVD events and (gastrointestinal) bleeding. Modeling using data from studies of general middle-aged adults suggests that aspirin is highly beneficial when the 10-year risk of CVD events is >10% and the baseline risk of gastrointestinal bleeding is not increased.[124,125] It is likely that such a benefit also accrues to patients with diabetes mellitus, but further modeling work and better data on sex-specific effects of aspirin are needed. A separate meta-analysis of both primary and secondary prevention trials did not find a difference in the efficacy of aspirin in diabetes mellitus according to dose.[119] Specific recommendations based on current clinical guidelines for aspirin administration in adults with diabetes mellitus and no pre-existing CVD are summarized.[120]

Recommendations

1. Low-dose aspirin (75–162 mg/d) is reasonable among those with a 10-year CVD risk of at least 10% and without an increased risk of bleeding (*ACC/AHA Class IIa; Level of Evidence B*) (*ADA Level of Evidence C*).
2. Low-dose aspirin is reasonable in adults with diabetes mellitus at intermediate risk (10-year CVD risk, 5%–10%) (*ACC/AHA Class IIb; Level of Evidence C*) (*ADA Level of Evidence E*).

A_{1c} Targets in Type 2 Diabetes Mellitus

Observational Data

Type 2 diabetes mellitus is associated with a 2- to 4-fold increased risk of CVD, with event rates correlating with the degree of hyperglycemia.[126,127] In a large multiethnic cohort, every 1-mmol/l (18-mg/dL) increase in fasting plasma glucose predicted a 17% increase in the risk of future cardiovascular events or death.[128] After adjustment for other CVD risk factors, an increase of 1% in A_{1c} was associated with an increased risk of 18% in CVD events,[129] 19% in MI,[129] and 12% to 14% in all-cause mortality.[130,131] However, the

correlation between hyperglycemia and microvascular disease is much stronger than that for macrovascular disease, with a 37% increase in the risk of retinopathy or renal failure associated with a similar 1% increase in A_{1c}.[132]

Randomized, Clinical Trials Looking at A_{1c} Level and Incident CVD

Despite the strong link between hyperglycemia and CVD risk, the evidence that intensive glycemic control reduces this risk is limited compared with the well-proven risk reduction in microvascular and neuropathic complications.[8,133] For example, the Diabetes Control and Complications Trial (DCCT; made up of individuals with type 1 diabetes mellitus) and the United Kingdom Prospective Diabetes Study (UKPDS) found highly significant reductions, ranging from 25% to 70%, in various measures of microvascular and neuropathic complications from more intensive control of glycemia in type 1 and type 2 diabetes mellitus, respectively.[8,133] However, neither study could demonstrate significant CVD risk reduction during the period of randomized intervention. In the DCCT, the number of CVD cases was fewer in the intensive group (mean achieved hemoglobin A_{1c}, ≈7%) compared with standard control (≈9%) after a mean treatment duration of 6.5 years, but the numbers of events were small and not significantly different.[8] Significant reductions in CVD events emerged nearly 10 years after the study ended despite subsequent similar mean A_{1c} levels (≈8%) in both groups during follow-up of the DCCT cohort (the Epidemiology of Diabetes Interventions and Complications [EDIC] study). Participants previously randomized to the intensive arm experienced a 42% reduction (P=0.02) in CVD outcomes and a 57% reduction (P=0.02) in nonfatal MI, stroke, or CVD death compared with those in the standard arm.[134] The UKPDS randomized participants newly diagnosed with type 2 diabetes mellitus to intensive (with sulfonylureas or insulin) compared with conventional therapy. The overall A_{1c} achieved was 0.9% lower in the intensive group (7.0% versus 7.9%). The study found a nonsignificant trend (16% risk reduction; P=0.052) toward reduced MI with the more intensive strategy after 10 years.[133] As in the DCCT/EDIC, this approximate risk (15%; P=0.01) reduction in MI became significant only after 10 years of observational follow-up of the UKPDS population, despite the convergence of mean A_{1c} soon after the randomized component of the study ended.[135]

Three large trials in type 2 diabetes mellitus were designed to address continuing uncertainty[136] about the effects of even more intensive glycemic control on CVD outcomes and reported results in 2008: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[137] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial,[138] and the Veterans Affairs Diabetes Trial (VADT).[139] All 3 studied middle-aged or older (mean age, 60–68 years) participants with established type 2 diabetes mellitus (mean duration, 8–11 years) and either known CVD or multiple major CVD risk factors. They compared the effects of 2 levels of glycemic control (median A_{1c}, 6.4%–6.9% in the intensive arms compared with 7.0%–8.4% in the standard arms) on macrovascular outcomes. None of the trials could demonstrate any significant reduction in the primary combined cardiovascular end points. ACCORD was stopped early as a result of increased mortality in the intensive group. The study results and post hoc analyses have been comprehensively reviewed and analyzed in a scientific statement of the ACC Foundation and AHA/position statement of the ADA.[140]

The increased mortality in the ACCORD intensive arm compared with the standard arm (1.41%/y versus 1.14%/y; HR, 1.22; 95% CI, 1.01–1.46) was predominantly cardiovascular in nature and occurred in all prespecified subgroups. Exploratory analyses were unable to link the increased deaths to weight gain, hypoglycemia, rapid lowering of A_{1c}, or use of any specific drug or drug combination. Although hypoglycemia was more frequent in the intensive arm, the association of severe hypoglycemia with mortality was stronger in the standard control arm.[141] Within the intensive arm, participants with the highest A_{1c} levels during the trial actually had the highest risk for mortality. Thus, increased mortality in ACCORD was associated with individuals who were assigned to the intensive glycemic control group but ultimately failed to achieve intensive glycemic control.[142]

There was no difference in overall or CVD mortality between the intensive and standard glycemic control arms in ADVANCE, although the median A_{1c} level achieved in intensively treated patients was similar (6.4%) to those in ACCORD. However, compared with ACCORD subjects, ADVANCE participants at entry had a shorter duration of diabetes mellitus, a lower A_{1c}, and less use of insulin; glucose was lowered less rapidly in ADVANCE; and there was less hypoglycemia. In ADVANCE, intensive glycemic control significantly reduced the primary outcome, a combination of microvascular events (nephropathy and retinopathy) and major adverse CVD events (MI, stroke, and CVD death). However, this was attributable solely to a significant reduction in the microvascular outcome, primarily the development of macroalbuminuria, with no reduction in the macrovascular outcome.[138]

VADT randomized participants with poorly controlled type 2 diabetes mellitus (median A_{1c} at entry, 9.4%) to a strategy of intensive glycemic control (achieved A_{1c}, 6.9%) or standard glycemic control (achieved A_{1c}, 8.4%). After 5.6 years, there was no significant difference in the cumulative primary outcome, a composite of CVD events. A post hoc analysis found that VADT participants with a duration of diabetes mellitus of <15 years had a mortality benefit in the intensive arm, whereas those with a duration of >20 years had higher mortality with the more intensive strategy.[143]

A meta-analysis of trials of intensive glycemic control suggests that glucose lowering may have a modest but statistically significant reduction in major CVD outcomes, primarily nonfatal MI, but no significant effect on mortality.[144–147] However, any such benefit of glucose lowering on CVD in type 2 diabetes mellitus is slight compared with the treatment of other CVD risk factors.

The Outcome Reduction With an Initial Glargine Intervention (ORIGIN) trial studied glucose lowering earlier in the course of type 2 diabetes mellitus. This study assessed CVD outcomes from the provision of sufficient basal insulin to normalize fasting plasma glucose levels in people ≥50 years of age with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes mellitus and other CVD risk factors. Early use of basal insulin achieved normal fasting plasma glucose levels in the trial but had no effect on CVD outcomes compared with guideline-suggested glycemic control.[148]

Recommendations for A_{1c} Targets for CVD Event Reduction

Recommendations for individualization of therapeutic targets have drawn from considerations of the time required for microvascular risk reduction to alter rates of clinically significant vision loss or kidney dysfunction, comparison of the mortality findings in ACCORD and ADVANCE, subgroup analyses of VADT, and other post hoc analyses. These analyses suggest that the potential risks of intensive glycemic control may outweigh its benefits in certain individuals such as those with a long duration of diabetes mellitus, a known history of severe hypoglycemia, advanced atherosclerosis, and a limited life span because of advanced age, frailty, or comorbid conditions.[59,149] Current recommendations for glucose-lowering and A_{1c} targets can be found in Table 5.

Glucose-Lowering Agent Selection for CVD Risk Reduction

Metformin is widely accepted as the first-choice agent for glycemic lowering because it does not cause weight gain or hypoglycemia and may improve CVD outcomes.[59] The first evidence for a CVD benefit of metformin came from a small UKPDS substudy involving 753 overweight patients, which found a relative risk reduction of 39% in MI in the group assigned to metformin versus conventional therapy.[10] Meta-analyses also found evidence of reduced CVD with metformin therapy.[150,151] Another small study found an adjusted HR of 0.54 (P=0.026) for a composite CVD outcome in patients with type 2 diabetes mellitus and coronary artery disease (CAD) who received metformin compared with glipizide.[152]

Beyond metformin, there are limited data on the comparative effectiveness of the many other effective antihyperglycemic drugs; most studies are of short duration and focus on glycemic lowering and side effects rather than CVD outcomes. Two exceptions deserve mention. When added to baseline antihyperglycemic therapy regimens in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), pioglitazone had no apparent benefit on the primary end point, which was a broad cardiovascular composite that include peripheral vascular events.[153] However, a secondary outcome (MI, stroke, and cardiovascular mortality) was modestly reduced by 16% (HR, 0.84; 95% CI, 0.72–0.98; P=0.027), although an increase in heart failure has been observed.[154] Another thiazolidinedione, rosiglitazone, has been shown to have no such effect.[155] Indeed, there is lingering controversy as to whether rosiglitazone may actually increase the risk of MI,[156,157] and this has clouded the issue concerning the potential benefits of this insulin-sensitizer drug class in atherosclerosis. Finally, in a diabetes mellitus prevention trial, Study To Prevent Non-insulin-Dependent Diabetes Mellitus (STOP-NIDDM), the α-glucosidase inhibitor acarbose was associated with a 49% relative reduction in cardiovascular events (HR, 0.51; 95% CI, 0.28–0.95; P=0.03) in patients with impaired glucose tolerance.[158] An acarbose trial (Acarbose Cardiovascular Evaluation [ACE]) is currently being conducted in China to determine whether this apparent benefit can be replicated in patients with already established type 2 diabetes mellitus.

New Glucose-Lowering Medications and CVD Risk

US Food and Drug Administration guidance now requests evidence that new glucose-lowering therapies are not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus[159] (www.fda.gov/downloads/Drugs/

GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf). As a result, several large trials are currently underway to test the cardiovascular safety and efficacy of newer antihyperglycemic therapies, including incretin-based drugs (glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors) and the sodium-glucose cotransporter-2 inhibitors. Two publications on the cardiovascular safety of dipeptidyl peptidase-4 inhibitors are the result of this US Food and Drug Administration mandate. Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) randomized 16 492 patients. At a median follow-up of 2.1 years, rates of ischemic events were similar with saxagliptin and placebo, but hospitalization for heart failure was significantly higher with saxagliptin (3.5% versus 2.8%; HR, 1.27; P=0.007).[160] Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE) randomized 5380 patients with a mean duration of follow-up of 18 months.[161] As in SAVOR-TIMI 53, the rates of CVD events were similar in the treatment and placebo arms. Of note, both studies were designed to demonstrate non-inferiority of the study drugs and enrolled patients with established CHD to achieve adequate event rates with a relatively short duration of follow-up.

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)[162] will compare glycemic lowering of 4 commonly used classes of diabetes mellitus medications (sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and insulin) in combination with metformin in 5000 subjects with an anticipated observation period of 4 to 7 years. The 4 drugs will also be compared with respect to durability, selected microvascular complications, CVD risk factors, adverse effects, tolerability, quality of life, and cost-effectiveness. To date, there are no convincing data to suggest that any single type of antihyperglycemic therapy in type 2 diabetes mellitus has a CVD advantage over another other than perhaps metformin.[159] Therefore, in choosing among available therapies, providers should consider not only efficacy in glycemic control but also safety, adverse effects such as weight gain and hypoglycemia, and outcomes that matter most to patients, including cost and quality of life.

Hypoglycemia as a CVD Risk Factor in Type 2 Diabetes Mellitus

Incidence of Hypoglycemia

Hypoglycemia is the most common adverse effect of insulin therapy and a major factor limiting glucose control in many patients with type 2 diabetes mellitus, particularly those with long-standing disease.[163] Severe hypoglycemia is defined as an event requiring external assistance for recovery, whereas milder episodes may be self-treated. The incidence of hypoglycemia increases with the duration of insulin therapy. Prospective, population-based data indicate that the overall incidence of hypoglycemia in insulin-treated type 2 diabetes mellitus is approximately one third of that in type 1 diabetes mellitus.[164] The UK Hypoglycemia Study Group found that patients with type 1 diabetes mellitus with an insulin therapy duration <5 or >15 years had 110 and 320 episodes of severe hypoglycemia per 100 patient-years, respectively.[165] Patients with type 2 diabetes mellitus treated with insulin for <2 or >5 years had incidences of 10 and 70 episodes per 100 patient-years, respectively.[165]

However, the occurrence of hypoglycemia unawareness limits the determination of the true incidence of this self-reported condition. Although most commonly associated with insulin therapy, hypoglycemia is also a side effect of insulin secretagogs such as sulfonylurea and glinides.

Mechanisms of Hypoglycemia and CVD

Although the lower range of normal postprandial glucose is ≈70 mg/dL, as glucose approaches this level, endogenous insulin secretion stops. When glucose falls below 70 mg/dL, counterregulatory hormones are released, and autonomic neural activation occurs. These may produce symptoms such as tremor, diaphoresis, tachycardia, anxiety, hunger, and headache. In most circumstances, these warning symptoms prompt patients to ingest glucose or other carbohydrates to protect against neuroglycopenia, which may alter behavior and impair cognition, judgment, and performance of physical tasks. Patients with repeated episodes of hypoglycemia are at increased risk of deficient counterregulation and loss of self-awareness of hypoglycemia, putting them at increased risk for seizures, coma, or even death.[166,167]

There are several mechanisms by which hypoglycemia might promote adverse cardiovascular outcomes in high-risk individuals.[168,169] Hemodynamic changes after autonomic activation induced by hypoglycemia include increases in heart rate, systolic blood pressure, myocardial contractility, and cardiac output. These effects may exacerbate ischemia in individuals with occlusive CAD. Small studies have shown that hypoglycemia induces ischemic and other ECG changes, and arrhythmias have been reported during severe episodes.[170] Hypoglycemia has also been associated with prolongation of the QT interval. An interaction of hypoglycemia-induced abnormalities of cardiac repolarization with autonomic neuropathy, a complication of long-standing diabetes mellitus, may contribute to arrhythmias and the risk of sudden death in individuals with diabetes mellitus. Finally, hypoglycemia has additionally been reported to have deleterious effects on endothelial function, platelet reactivity, and coagulation while increasing inflammatory mediators and blood viscosity and lowering potassium levels.[171,172]

Hypoglycemia and CVD Events

Clinical trials in patients with type 2 diabetes mellitus with or at high risk of CVD have raised concern about the risks of hypoglycemia in this population.[140] Together, ACCORD,[137] ADVANCE,[138] and VADT[139] randomized nearly 24 000 patients to intensive versus standard control with follow-up periods from 3.4 to 5.6 years. Although the A_{1c} goals for intensive and standard therapy differed among the trials, rates of severe hypoglycemia were substantially higher with intensive compared with standard therapy in all 3 trials: 16.2% versus 5.1% in ACCORD, 2.7% versus 1.5% in ADVANCE, and 21.2% versus 9.7% in VADT. Shorter duration of diabetes mellitus, younger age of participants, and less use of insulin likely contributed to the lower rates of hypoglycemia in ADVANCE.

In ACCORD, rates of severe hypoglycemia and death were increased with intensive treatment; however, secondary analyses did not establish hypoglycemia as the cause of the increased mortality in the intensive group.[141,173] In ADVANCE and VADT, intensive

glucose control was not associated with excess mortality. In both ADVANCE and ACCORD, severe hypoglycemia was a risk factor for mortality, but annual mortality among patients who reported severe hypoglycemia was actually higher in the group receiving standard treatment than in the group receiving intensive treatment.[141,174] In addition, more frequent hypoglycemia (<70 mg/dL) identified by self-monitoring of blood glucose was associated with a small but statistically significant reduction in mortality in the intensive but not the standard group.[175] In ADVANCE, severe hypoglycemia was associated not only with an increased risk of cardiovascular events and death but also with a wide range of other adverse outcomes, including major microvascular events, death resulting from any cause, and nonvascular outcomes such as respiratory, digestive, and skin conditions.[174] Although secondary analyses could not exclude the possibility that severe hypoglycemia had a direct causal link with death, the investigators have concluded that hypoglycemia was likely serving as a marker of inherent vulnerability to adverse clinical outcomes.

Two studies of intensive glycemic control earlier in the course of type 2 diabetes mellitus were also associated with an increased risk of hypoglycemia compared with standard therapy, although the absolute rates were low. In ORIGIN,[148] the incidence of a first episode of severe hypoglycemia was 1.00 per 100 person-years in the insulin-glargine group and 0.31 per 100 person-years in the standard care group, the majority of whom used no insulin (P<0.001), with no difference in CVD events between the groups. The UKPDS[133] had a severe hypoglycemia rate of 1.8%/y in the intensive control versus 0.7%/y in the standard control group, with a modest and nearly significant reduction in CVD event rate (P=0.052) in the intensive group. Thus, early in the course of type 2 diabetes mellitus, glycemic control therapies that increased the risk of hypoglycemia do not appear to be associated with an increased risk of cardiovascular events.

In summary, hypoglycemia is a serious and common complication of diabetes mellitus management and is associated with CVD events and mortality. Although causality is unproven, avoidance of hypoglycemia is a key goal of diabetes mellitus management. Patients treated with insulin or insulin secretagogs should be queried regularly about the occurrence of hypoglycemia, and therapy should be adjusted to mitigate its risk. Whether the use of drugs in type 2 diabetes mellitus associated with lower hypoglycemia risk improves clinical outcomes remains controversial.

Blood Pressure Lowering in Type 2 Diabetes Mellitus

Increased blood pressure is a major contributor to higher risk of CVD events in diabetes mellitus. A vast majority (70%–80%) of patients with type 2 diabetes mellitus have hypertension. The presence of hypertension in patients with type 2 diabetes mellitus increases the risk of MI, stroke, and all-cause mortality. Additionally, the coexistence of both conditions increases the risk of developing heart failure, nephropathy, and other microvascular events.[176] Epidemiological observations from landmark studies such as the Multiple Risk Factor Intervention Trial (MRFIT), UKPDS, and others have demonstrated that there is a progressive increase in the risk of macrovascular and microvascular events with increasing levels of systolic blood pressure, starting as low as 115 mm Hg.[176–178] In addition, some of the earlier interventional RCTs (UKPDS and Hypertension Optimal

Treatment [HOT]) have demonstrated the benefit of aggressive blood pressure reduction in lowering the risk of both macrovascular and microvascular events.[113,177,178] It is important to recognize, however, that in both studies the achieved systolic blood pressure in the aggressive intervention arm was 144 mm Hg,[113,178] and older studies did not address the more contemporary questions of usual compared with intensive blood pressure lowering on CVD risk.

Data from Recent RCTs on Intensive Blood Pressure Lowering in Type 2 Diabetes Mellitus

Several recent RCTs have specifically examined the role of an intensive blood pressure–lowering strategy to achieve systolic blood pressure <130 mm Hg (in patients with diabetes mellitus and hypertension) on various outcomes, including CVD mortality, nonfatal MI, fatal and nonfatal stroke, all-cause mortality, and various microvascular events, including nephropathy.[179,180] These studies did not find any substantive benefit of intensive blood pressure control (systolic blood pressure <130 mm Hg) in reducing the risk of coronary events defined as fatal or nonfatal MI. The ACCORD study randomized 4733 patients with type 2 diabetes mellitus to either intensive blood pressure lowering (defined as systolic blood pressure <120 mm Hg) or usual therapy (systolic blood pressure <140 mm Hg)[179]; the primary study outcome was a composite end point of nonfatal MI, nonfatal stroke, or CVD death. After 12 months, systolic blood pressure was 119 mm Hg in the intensive blood pressure–lowering arm compared with 133 mm Hg in the usual care arm. However, there was no difference in the primary end point (HR, 0.88; 95% CI, 0.73–1.06; P=0.20); similar results were observed for death resulting from all causes. The only significant finding was observed for stroke, a prespecified secondary end point, for which the HR was 0.59 (95% CI, 0.39–0.89; P=0.01). Similarly, the ADVANCE trial tested the effect of a fixed combination of perindopril and indapamide[180]; 11 140 patients with type 2 diabetes mellitus were randomized to the fixed combination compared with placebo. After 4.3 years of follow-up, patients in the intervention arm had lower blood pressure (systolic blood pressure, 5.6 mm Hg). Overall, the result of the combined primary end point (composite of macrovascular and microvascular outcomes) was significant (HR, 0.91; 95% CI, 0.83–1.00; P=0.04). However, when stratified by macrovascular or microvascular outcomes, neither was significant (macrovascular: HR, 0.92; 95% CI, 0.81–1.04; P=0.16; microvascular: HR, 0.91; 95% CI, 0.80–1.04; P=0.16).

These findings are further corroborated by the results of a meta-analysis of 37 736 patients from 13 trials that similarly failed to identify benefit of an intensive blood pressure–lowering strategy over standard blood pressure–control strategy on macrovascular and microvascular (cardiac, renal, and retinal) events[181] in patients with type 2 diabetes mellitus or impaired fasting glucose. However, an association with stroke reduction in the intensive versus usual group was noted (17% reduction in risk).

There are additional safety concerns for intensive blood pressure lowering in type 2 diabetes mellitus. Most patients with type 2 diabetes mellitus and hypertension require multiple pharmacological agents to obtain adequate blood pressure control. ACCORD and the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) demonstrated that the use of multiple antihypertensive drugs was associated

with an increased incidence of serious adverse effects, including hypotension, syncope, and worsening renal function.[179,182] Specifically, the ACCORD blood pressure trial found that serious adverse events occurred in 3.3% of the intensive blood pressure–lowering arm compared with 1.3% in the usual care arm.[179]

The Seventh Joint National Committee guidelines recommend that, in patients with type 2 diabetes mellitus and hypertension, the target blood pressure should be <130/80 mm Hg (and even lower to 120/75 mm Hg in those with renal impairment).[177] The updated report from the panel members appointed to the Eighth Joint National Committee now recommends that target blood pressure be <140/90 mm Hg.[61] However, on the basis of newer evidence from RCTs that explicitly tested the benefit of usual versus more intensive blood pressure lowering, it is difficult to define a universal target blood pressure goal for all patients with type 2 diabetes mellitus and hypertension.[183] Given the appearance of heterogeneity of the effects of intensive blood pressure lowering on coronary compared with cerebral events, the effects may also vary on the basis of the presence or absence of comorbid conditions in a given individual and the subsequent risk of events.[183] In patients at higher risk of stroke who do not have pre-existing CHD, it may be beneficial to reduce systolic blood pressure to targets lower than recommended for the general diabetes mellitus population, if this can be accomplished safely.[181,183,184] We note that the ADA recommends blood pressure targets of <130/80 mm Hg in certain individuals if these targets can be achieved safely.[4] Overall, RCTs are needed to prospectively examine and demonstrate appropriate target blood pressure levels that can be achieved safely and are beneficial in such patients. Taken together, data from recent trials do not suggest that intensive lowering of blood pressure in type 2 diabetes mellitus should be implemented as a universal recommendation. Further studies are necessary to identify the at-risk populations and their appropriate targets.

Current clinical recommendations for blood pressure targets in diabetes mellitus can be found in Table 5, along with the new recommendations from the panel members appointed to the Eighth Joint National Committee and the ADA.[4,60,61] Currently, most individuals with diabetes mellitus are recommended to achieve a blood pressure goal of <140/90 mm Hg.

Cholesterol and Lipoproteins and CVD Risk in Type 2 Diabetes Mellitus

Lipoprotein Abnormalities in Type 2 Diabetes Mellitus

In patients with type 2 diabetes mellitus, triglycerides are often elevated, HDL-C is often decreased, and LDL-C may be elevated, borderline, or normal. LDL particles are small and dense. Thus, the LDL-C concentration may be misleading because there will be more LDL particles for any cholesterol concentration. Additionally, these small, dense LDL particles may be more atherogenic than would be suspected by their concentration alone because in vitro and cell culture studies suggest that they may be more readily oxidized and glycated.[185] Nevertheless, the relationship between LDL particle size and CVD is confounded by many other CVD risk factors. Thus, targeting changes in LDL size to reduce CVD risk is not indicated.[186] Moreover, although an elevated LDL-C level generally is not recognized as the major lipid abnormality in patients with type 2 diabetes mellitus, clinical trials amply demonstrate that statin treatment will reduce the risk for major coronary events.[187]

LDL-C Lowering in Type 2 Diabetes Mellitus

LDL-C is identified as the primary target of lipid-lowering therapy. The focus on LDL-C is supported by results of controlled, clinical trials that have shown that LDL-C lowering with statins will reduce the risk of major CVD events in patients with or without diabetes mellitus. In addition, data from 18 686 individuals with diabetes mellitus (1466 with type 1 and 17 220 with type 2) during a mean follow-up of 4.3 years demonstrated a 21% proportional reduction in major vascular events per 1-mmol/L (39-mg/dL) reduction in LDL-C in people with diabetes mellitus (relative risk, 0.79; 99% CI, 0.72–0.86; $P<0.0001$) and a 9% proportional reduction in all-cause mortality per 1-mmol/L reduction in LDL-C (relative risk, 0.91; 99% CI, 0.82–1.01; $P=0.02$).[187] These outcomes were similar to those achieved in patients without diabetes mellitus. It is also important to recognize that the results of statin interventions in patients with diabetes mellitus have demonstrated that the observed benefits were independent of baseline LDL-C and other lipid values.

Triglyceride Lowering in Type 2 Diabetes Mellitus

Triglyceride-rich lipoproteins, especially very-low-density lipoproteins, are often elevated in patients with diabetes mellitus, appear to be atherogenic, and represent a secondary target of lipid-lowering therapy. According to the National Cholesterol Education Program Adult Treatment Panel III, this goal is non–HDL-C.[40] Although the ADA recognizes serum triglycerides as a surrogate for atherogenic triglyceride-rich lipoproteins and suggests a target of <150 mg/dL,[4] the 2013 ACC/AHA guidelines on the treatment of cholesterol to reduce atherosclerotic cardiovascular risk in adults provide no evidence-based recommendations for the evaluation or treatment of hypertriglyceridemia to reduce of CVD risk.[62] However, consistent with the National Cholesterol Education Program Adult Treatment Panel III guidelines, the panel continued to endorse the evaluation and treatment of patients with fasting triglycerides >500 mg/dL to prevent more severe hypertriglyceridemia and pancreatitis.[62]

Clinical trials conducted to date do not support triglyceride reduction in the presence or absence of diabetes mellitus as a means to reduce CVD risk. Unfortunately, such trials have suffered from inadequate experimental design and are few in number, and the overall findings are hypothesis generating at best. The most selective of the triglyceride-reducing drugs are the fibrates. Four major fibrate trials in which patients with CHD or diabetes mellitus have been included have been completed. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) was carried out in men with known CVD and low levels of HDL-C (<40 mg/dL), and gemfibrozil was the fibrate chosen. VA-HIT was the only fibrate study to demonstrate a significant benefit of a fibrate on CVD, an effect mostly demonstrated in the 25% of patients with diabetes mellitus.[188] The Bezafibrate Infarction Prevention (BIP) had a minority of patients with diabetes mellitus, and as in VA-HIT, no patients were on statins,[189] whereas the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was conducted exclusively in patients with diabetes mellitus with a statin drop-in rate of 23% in the placebo group and 14% in the fenofibrate group.[190] In the Action to Control Cardiovascular Risk in Diabetes Lipid Trial (ACCORD-LIPID), all patients had diabetes mellitus and were on simvastatin.[191] Despite the lack of benefit of a fibrate in patients with diabetes mellitus in BIP, FIELD, and ACCORD-LIPID, post

hoc analyses of all 3 trials suggested that those patients with hypertriglyceridemia with (FIELD, ACCORD-LIPID) or without (BIP) low levels of HDL-C appeared to benefit. At best, we are left with post hoc analyses that could potentially help guide the design of the optimal trial to follow, that is, in hypertriglyceridemic patients with diabetes mellitus with or without statin therapy. We note that ADA clinical practice guidelines indicate that "combination therapy (statin/fibrate and statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended" (*Level of Evidence A*).[4]

HDL Raising in Type 2 Diabetes Mellitus

Currently, HDL-C is not a target for therapy according to the ACC/AHA cholesterol treatment guidelines.[62] However, the ADA considers levels of HDL-C >40 mg/dL in men and >50 mg/dL in women desirable.[4] Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH), a trial of niacin in statin-treated patients with known CVD, included 34% of patients with diabetes mellitus.[192] A total of 3414 patients were randomly assigned to receive niacin or placebo. The trial was stopped after a mean follow-up period of 3 years because of a lack of efficacy. At 2 years, niacin increased the median HDL-C from 35 to 42 mg/dL, lowered triglycerides from 164 to 122 mg/dL, and lowered LDL-C from 74 to 62 mg/dL; however, the primary end point of CVD events or hospitalization for unstable angina was no different in the niacin versus the placebo group. Moreover, outcomes in patients with diabetes mellitus appeared to be similar to those in patients without diabetes mellitus. Another HDL-C–raising trial, which used the cholesterol ester transfer protein inhibitor dalcetrapib, was carried out in 15 871 patients who had experienced a recent acute coronary syndrome, and 25% had diabetes mellitus.[193] The primary end point was a composite of death resulting from CHD, nonfatal MI, ischemic stroke, unstable angina, or cardiac arrest with resuscitation. On dalcetrapib, HDL-C increased from a baseline of 42 mg/dL by 31% to 40% and by 4% to 11% in the placebo group without LDL-C lowering in either group. As in AIM-HIGH, this trial was terminated for futility with no evidence of CVD risk reduction in the entire cohort, including patients with diabetes mellitus.

Recommendations for Lipid Management in Type 2 Diabetes Mellitus

In adult patients with diabetes mellitus, lipid levels should be measured at least annually for compliance with recommended treatment. Lifestyle modification deserves primary emphasis in all patients with diabetes mellitus with a focus on the reduction of saturated and *trans* fat intake, weight loss (if indicated), and increases in dietary fiber and physical activity. These lifestyle changes, especially weight reduction, have been shown to improve most components of the lipid profile in patients with diabetes mellitus.[194] In patients with diabetes mellitus who are >40 years of age without overt CVD, the new ACC/AHA cholesterol guidelines indicate that there is strong evidence that moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age or high-intensity statin should be started if the individual calculated risk is high. This and additional guidelines for statin therapy are summarized in Table 5. Briefly, between 40 and 75 years of age, all patients with diabetes mellitus and LDL-C levels between 70 and 189 mg/dL should

be treated with a statin. The ADA 2015 practice guidelines are now concordant with the AHA guidelines.[4]

Presently, the data do not support a recommendation that patients with diabetes mellitus on a statin with fasting plasma triglycerides >200 mg/dL have reduced CVD risk with the addition of a fibrate.

Screening for Renal and Cardiovascular Complications

This section provides the evidence base for screening for CVD and renal complications in type 2 diabetes mellitus.

Kidney Disease in Diabetes Mellitus

In type 2 diabetes mellitus, CKD is common and is associated with adverse health outcomes. Although CKD in most patients with diabetes mellitus is attributable to diabetes mellitus, other causes of CKD should be considered when the clinical presentation is atypical because the prognosis and treatment of these diseases may differ from those of diabetic kidney disease (DKD).[195] Clinical manifestations of DKD include elevated urine albumin excretion (albuminuria) and impaired glomerular filtration rate (GFR).[4,195,196] Among adults with diabetes mellitus in the United States, the prevalence of DKD is ≈34.5%: 16.8% with albuminuria (ratio of urine albumin to creatinine ≥30 mg/g), 10.8% with impaired GFR (estimated GFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), and 6.9% with both albuminuria and impaired GFR.[197] Among people with or without diabetes mellitus, albuminuria and impaired GFR are independently and additively associated with increased risks of end-stage renal disease, acute kidney injury, cardiovascular events, and death.[198] Recent evidence suggests that the presence of DKD identifies a subset of people with type 2 diabetes mellitus who are at markedly increased mortality risk.[199]

Although RCTs of screening versus not screening have not been conducted,[200] the ADA and National Kidney Foundation recommend yearly DKD screening for all patients with type 2 diabetes mellitus, beginning at diabetes mellitus diagnosis, on the basis of the considerations above.[4,195] This recommendation includes measurement of both urine albumin excretion, most conveniently measured as the ratio of albumin to creatinine in a single-voided urine sample, and GFR, calculated from serum creatinine concentration with a validated formula. The staging of DKD according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline links severity of DKD with risks of adverse outcomes, including CVD.[196]

Goals of care for patients with DKD include preventing progression to end-stage renal disease and reducing the risks of cardiovascular events and death. Randomized, clinical trials provide compelling evidence that people with type 2 diabetes mellitus and substantially elevated urine albumin excretion (ie, ≥300 mg/g creatinine) or impaired GFR (estimated GFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) should be treated with an inhibitor of the renin-angiotensin system. In this population, renin-angiotensin system inhibitors reduce the risks of progression to end-stage renal disease, CVD events, and death.[195,200–202] A head-to-head comparison of an angiotensin-converting enzyme inhibitor and an angiotensin receptor

blocker in type 2 diabetes mellitus with elevated urine albumin excretion suggested that the effects on CKD progression were clinically equivalent,[203] whereas a recent meta-analysis reported that evidence for cardiovascular benefit was strongest for angiotensin-converting enzyme inhibitors.[204] A combination of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is not recommended because it increases the risk of impaired kidney function and hyperkalemia compared with either agent alone.[205–207]

Renin-angiotensin system inhibitors are also appropriate first-line antihypertensive agents for patients with milder DKD (urine albumin excretion ≥30 mg/g and <300 mg/g creatinine with normal estimated GFR) or without evidence of DKD, but clinical trials conducted among such patients have not demonstrated improvements in hard renal or cardiovascular outcomes. On the basis of the strong relationship of blood pressure with kidney disease progression, the presence of DKD may also be a factor favoring control of blood pressure to low target levels (eg, 130/80 mmHg) in select patients. However, as reviewed earlier, the ACCORD trial did not demonstrate that a lower blood pressure target significantly improved renal or cardiovascular outcomes overall.[179]

The presence of DKD may modify the safety or efficacy of common diabetes mellitus therapies. In particular, with DKD, the toxicity of some medications may be increased by impaired drug clearance and the presence of more frequent and severe comorbidities. For example, in the ACCORD trial, the risk of severe hypoglycemia associated with intensive glucose control was increased among participants with greater urine albumin excretion or higher serum creatinine concentration measured at baseline.[173] Patients with DKD may also have reduced longevity, so they may not reap the long-term benefits of tight glucose control. As a result, in individualized plans for glycemic control, the presence of more advanced DKD may favor less aggressive intervention.[205] Additional studies are required to define the impact of DKD on other common diabetes mellitus–related interventions.

Subclinical CAD Assessment

Identification of asymptomatic CAD may allow the opportunity for more aggressive lifestyle or pharmacological interventions to prevent clinical events or, when disease is advanced, the pursuit of revascularization. Because CAD may present in a silent fashion and symptomatic disease is associated with worse clinical outcomes in diabetes mellitus, the detection of disease before acute coronary syndrome events may improve morbidity and mortality. However, because there is a paucity of data suggesting any specific benefits of invasive interventions over medical therapy alone, CAD screening in the asymptomatic patient with diabetes mellitus remains highly controversial.[209,210] Although it is important to individualize clinical decision making, widespread screening for silent CAD in diabetes mellitus cannot be recommended at this time.[209]

A variety of CAD screening tests[211–229] are available (Table 8). These include the simple, inexpensive, and noninvasive resting ECG, which may detect evidence of prior myocardial injury or ischemia. Several prior studies have demonstrated that baseline ECG abnormalities are common in asymptomatic patients with diabetes mellitus and no history of CAD. In the UKPDS, 1 in 6 patients with newly diagnosed type 2 diabetes mellitus had evidence of silent MI on the baseline surface ECG.[211] In older studies, the prevalence of ECG abnormalities

in patients with diabetes mellitus and no known CAD was even higher, approaching 20%.[212] Although the sensitivity and specificity of ECG abnormalities in patients with diabetes mellitus have been questioned[230] and their additive discriminating value on top of known CAD risk factors is marginal, data from UKPDS indicate that an abnormal ECG is an independent risk factor for all-cause mortality and fatal MI in patients with diabetes mellitus.[211] Given the wide availability and low cost of ECGs, the high prevalence of abnormal ECG findings in patients with type 2 diabetes mellitus, and their association with morbid outcomes, the use of ECGs in the risk stratification of patients with type 2 diabetes mellitus appears reasonable.[213] Further testing of patients with diabetes mellitus and abnormal ECG findings for inducible ischemia is currently endorsed by the professional societies.[210] Whether such a strategy improves patient outcomes remains unknown. This test is not currently recommended by the ADA or the US Preventive Services Task Force during the initial or follow-up evaluation of patients with diabetes mellitus because data are lacking that adding an ECG improves risk stratification, although the AHA states that it is reasonable to obtain a resting ECG in asymptomatic adults with diabetes mellitus (Table 8).

Other screening tests include ECG exercise tolerance testing, exercise (or pharmacological) myocardial perfusion imaging (nuclear scintigraphy), and exercise (or pharmacological) stress echocardiography. The ankle-brachial index and coronary artery calcium (CAC) scoring by electron-beam computed tomography (CT) are used to detect evidence of atherosclerosis, although these methods cannot assess for active or inducible ischemia. Emerging techniques include CT angiography, cardiac magnetic resonance imaging, and cardiac positron emission tomography, but none have had widespread application in asymptomatic patients. Table 8 provides a summary overview of several additional screening tests, along with guideline recommendations from the AHA or ADA.

Of these, CAC, a marker of intracoronary atherosclerosis, can be measured with CT. Patients are typically stratified by Agatston units, yielding CAC scores of <100 (low risk), 100 to 400 (moderate risk), and >400 (high risk). Extensive data indicate a linear relationship between CAC and clinical CHD events among individuals with and without diabetes mellitus.[220–224]

However, patients with diabetes mellitus have a greater prevalence and extent of coronary calcification than those without diabetes mellitus. In fact, several studies suggest that majority of asymptomatic patients with type 2 diabetes mellitus have coronary calcification, and nearly 20% have markedly elevated CAC.[225–228] Furthermore, the prognostic significance of elevated CAC in predicting adverse events appears to be greater in patients with diabetes mellitus than in those without diabetes mellitus.[229]

Several studies show that abnormal CAC is correlated with demonstrable myocardial ischemia and predicts future CVD events. Anand et al[232] measured CAC in 520 asymptomatic patients with type 2 diabetes mellitus; moderate to large perfusion defects were seen in 31.5% of patients with CAC >100. The entire cohort was then followed up for a mean of 2.2 years, during which time 20 major adverse cardiovascular events occurred, with myocardial perfusion imaging results available in 18 of these individuals, 16 of whom had abnormal studies. In Cox models, CAC and extent of myocardial ischemia by myocardial perfusion imaging were the only independent predictors of adverse outcomes. The authors

suggested that a 2-staged approach of first identifying the highest-risk patients by CT and then proceeding to screen those individuals with the highest CAC scores with stress scintigraphy would be a more efficient approach than initial myocardial perfusion imaging alone. Importantly, however, the design of this study does not allow an assessment of the ability of this screening paradigm to reduce future coronary events.

The rates of death and MI rise incrementally with higher CAC score among patients with diabetes mellitus, as demonstrated in several prospective studies.[223,232] As importantly, the absence of coronary calcium portends a remarkably favorable prognosis despite the presence of diabetes mellitus, with 0% of patients experiencing adverse cardiac events during ≈5 years of follow-up.[229] Furthermore, CAC not only is an independent predictor of adverse cardiovascular events but also is superior to both the UKPDS risk engine and the Framingham Risk Score in this patient population.[229,232] For these reasons, current ACC/AHA guidelines consider CAC reasonable for cardiovascular risk assessment in asymptomatic patients with diabetes mellitus who are ≥40 years of age (Table 8).[213]

There are currently no convincing data to suggest that performing CAC motivates patients to better adhere to lifestyle modifications or medical therapy for CVD prevention. Limited data suggest that CAC influences physicians' management of CAD risk factors.[233] Although an exploratory subgroup analysis from a single randomized, clinical trial suggests that statin therapy in asymptomatic patients with CAC >400 may improve outcomes,[234] no dedicated, prospective studies have been performed to suggest that the detection of subclinical CAD by CAC leads to improvement in clinical events.

In addition to CAC, there is a large published experience in screening patients with diabetes mellitus for subclinical CAD with nuclear scintigraphy, and the results of key studies are summarized in Table 8. The Milan Study on Atherosclerosis and Diabetes (MiSAD) could not provide an overall estimate of myocardial perfusion defects in asymptomatic patients with diabetes mellitus because only 112 actually had stress-induced ischemic ECG changes qualifying them to proceed to myocardial perfusion imaging. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study is the only prospective, randomized, controlled investigation to rigorously assess the clinical value of screening asymptomatic diabetic patients for CAD.[219] DIAD was able to demonstrate that such a screening strategy is not likely to improve actual clinical outcomes. This conclusion is likely due in part to the very low overall cardiac event rate in DIAD, which may reflect widespread use of modern CVD risk reduction strategies. The neutral results of the DIAD study appeared to be buttressed by those of the Do You Need to Assess Myocardial Ischemia in Type 2 Diabetes (DYNAMIT) trial (Table 8), although the latter study was dis-continued prematurely because of recruitment difficulties and a lower-than-expected event rate. Taken together, however, the findings from these randomized trials do not support the routine use of nuclear imaging in patients with type 2 diabetes mellitus for subclinical disease CAD screening.

Other Modalities

A number of other noninvasive or semi-invasive tests are currently under study, including coronary CT angiography (CCTA), cardiac magnetic resonance imaging, and cardiac positron emission tomography. Although more elaborate, as with other more traditional

tests, these tests appear to demonstrate disease and even to predict CHD events across a population of patients. The FACTOR 64 trial randomized 900 patients without symptomatic CAD with either type 1 or type 2 diabetes mellitus to CCTA followed by CCTA-directed therapy versus control (standard guideline-based diabetes mellitus management).[235] Over a mean of 4 years of follow-up, there was no difference in the primary outcome of fatal or nonfatal coronary disease (6.2% in the CCTA group versus 7.6% in the control group; P=0.38). These findings support the concept that CCTA should not be used for CAD screening in asymptomatic patients with diabetes mellitus. Thus, even with more sensitive modalities, the lack of benefit remains consistent.

Selected Areas of Controversy and Future Research

Several important key areas of controversy require further research. Below, we highlight areas that we consider important in advancing CVD prevention in type 2 diabetes mellitus over the next few years:

1. Antihyperglycemic therapy: The specific role of antihyperglycemic therapy (in terms of both intensity and specific drug strategy) in reducing cardiovascular events in type 2 diabetes mellitus remains poorly understood. Whether any specific drug class will ever emerge as presenting a clear advantage in this regard is unknown.

2. Bariatric surgery: Bariatric surgery is currently an effective treatment for weight loss. It is critical to understand the durability of the remission of diabetes mellitus and other CVD risk factors in longer-term follow-up in the setting of rigorously designed RCTs.

3. Hypoglycemia: Hypoglycemia is a frequent complication of blood sugar lowering in type 2 diabetes mellitus. However, because hypoglycemia is difficult to identify comprehensively, its true prevalence is likely markedly underestimated. Future studies are necessary to more fully characterize the burden of hypoglycemia and its attendant risks, particularly on the cardiovascular system.

4. Blood pressure lowering: Recent blood pressure trials of tight compared with usual blood pressure targets have failed to identify a cardiovascular benefit. However, prespecified secondary analyses have identified a possible protective signal for stroke.[179] Further work in high-risk stroke populations is necessary to validate these findings and to determine whether a lower blood pressure target is beneficial in this subpopulation of patients with diabetes mellitus.

5. Cholesterol lowering: Most lipid guidelines indicate efficacy with statin treatment in patients with type 2 diabetes mellitus. However, the definitive trial of triglyceride lowering among patients with type 2 diabetes mellitus and elevated triglycerides, with or without low HDL-C, with a statin background remains to be conducted. Further research is necessary to determine whether triglyceride lowering in this subpopulation can reduce CVD events in patients with type 2 diabetes mellitus. Furthermore, the current cholesterol-lowering

guidelines focus on individuals between 40 and 75 years of age. Further research is necessary to best elucidate treatment recommendations on those falling outside this age range.

6. Imaging for subclinical CVD assessment: Although the prevalence of CAD in patients with diabetes mellitus is substantial and associated with increased morbidity and mortality, to date, it has been difficult to demonstrate that detecting disease in its preclinical or subclinical state will actually reduce event rates or improve overall patient outcomes, especially in an era when aggressive CVD risk factor reduction is widely endorsed for this population. Future large, randomized trials are needed to determine whether screening for subclinical CAD, particularly with newer modalities that may have improved detection of functional CAD or biomarkers such as high-sensitivity troponin, can reduce CVD event rates in patients with diabetes mellitus. Such studies would need to be adequately powered to assess the potential of additive impact of screening results and subsequent interventions on actual patient outcomes.

Summary

After reaching a peak in the 1960s, mortality rates from CAD have been declining steadily in the United States. Improvements in CVD risk factors such as lowering smoking prevalence and total cholesterol and blood pressure levels have been major drivers for these improvements in CVD outcomes.[236] Although these improvements also occurred in patients with type 2 diabetes mellitus, the incremental CVD risks associated with type 2 diabetes mellitus persist.[237] As a result, considerable work remains to be done to enhance our understanding of how to more effectively prevent CVD in patients with type 2 diabetes mellitus. The purpose of this scientific statement was to update the state of the science with respect to CVD risk factor control and renal and subclinical CAD screening. We have also summarized the current relevant CVD prevention guidelines as they pertain to type 2 diabetes mellitus. Finally, we have highlighted key areas of controversy that require further study to allow us to make greater strides in lowering clinical CVD in this high-risk patient population. As a scientific community, our goal is better primary prevention of CVD in all patients with diabetes mellitus.

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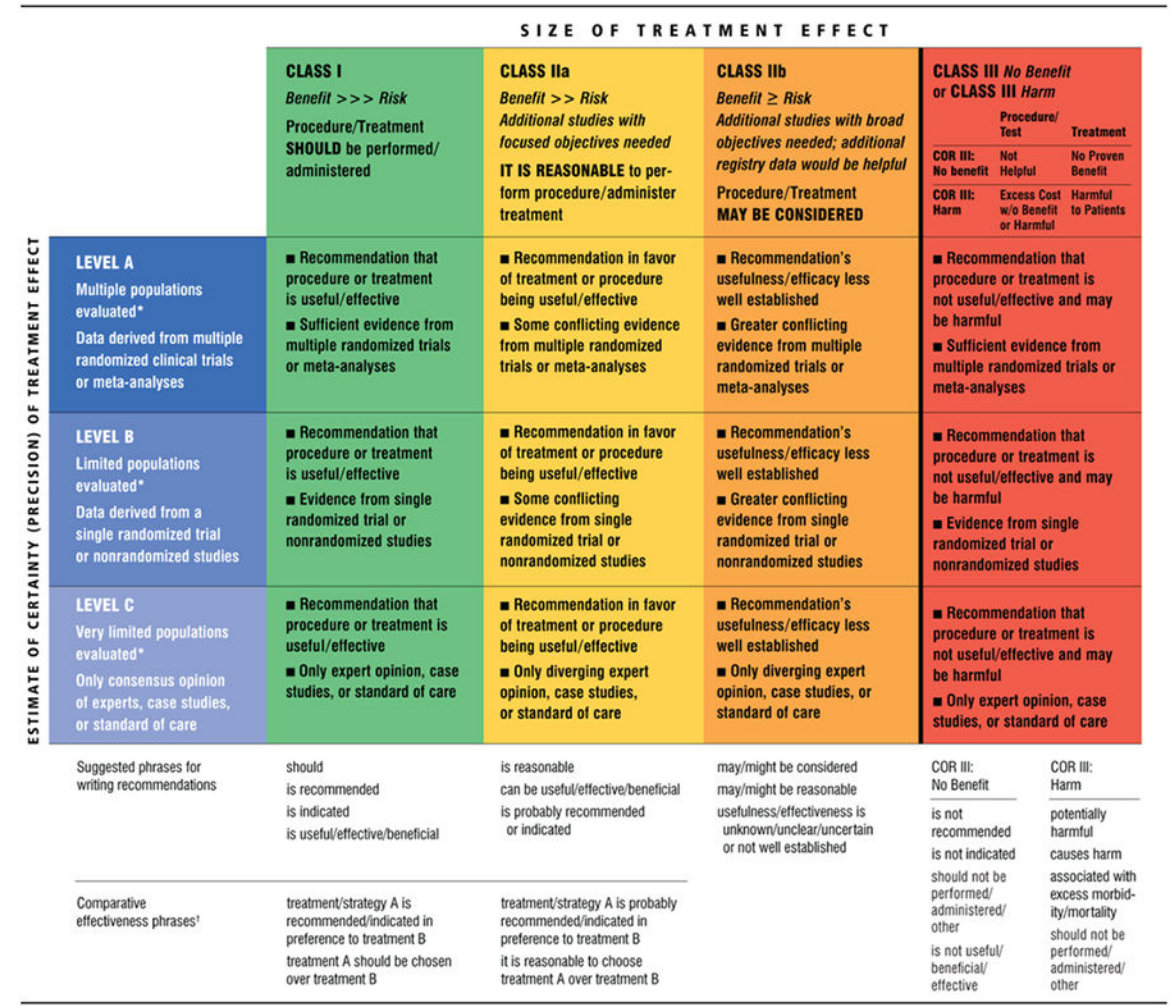
Table 1.

Applying Classification of Recommendations and Level of Evidence



ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* COR III: No benefit — Procedure/Test: Not Helpful — Treatment: No Proven Benefit COR III: Harm — Procedure/Test: Excess Cost w/o Benefit or Harmful — Treatment: Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

[*] Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

[†] For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Table 2.

ADA Evidence Grading System for Clinical Practice Recommendations[4]

Level of Evidence	Description
A	Clear evidence from well-conducted, generalizable RCTs that are adequately powered, including the following: Evidence from a well-conducted multicenter trial Evidence from a meta-analysis that incorporated quality ratings into the analysis
	Compelling nonexperimental evidence (ie, “all or none” rule developed by the Centre for Evidence-Based Medicine at the University of Oxford)
	Supportive evidence from well-conducted RCTs that are adequately powered, including the following: Evidence from a well-conducted trial at ≥1 institutions Evidence from a meta-analysis that incorporated quality ratings into the analysis
B	Supportive evidence from well-conducted cohort studies Evidence from a well-conducted prospective, cohort study or registry Evidence from a well-conducted meta-analysis of cohort studies
	Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies Evidence from randomized clinical trials with ≥1 major or ≥3 minor methodological flaws that could invalidate the results Evidence from observational studies with a high potential for bias (eg, case series with comparison with historical control subjects) Evidence from case series or case reports
	Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

ADA indicates American Diabetes Association; and RCT, randomized, controlled trial.

Table 3.

Diagnostic Criteria for Diabetes Mellitus and Categories of Increased Risk for Diabetes Mellitus and Prediabetes

	Diabetes Mellitus	Prediabetes
A_{1c}, %	≥6.5	5.7–6.4
Fasting glucose, mg/dL	≥126	100–125
2-h glucose, mg/dL	≥200	140–199
Random glucose in patients with classic symptoms of diabetes mellitus, mg/dL	≥200	N/A

A_{1c} indicates glycated hemoglobin. Modified from “Standards of Medical Care in Diabetes–2015.”[4]

Table 4.

Strengths and Limitations of Using A_{1c} for Diabetes Mellitus Diagnosis

Strengths	Limitations
Reflects chronic hyperglycemia, providing global index of glycemic exposure (tracks well over time)	Certain conditions interfere with the interpretation of results[18,29,33] (www.ngsp.org), including hemoglobin traits and alterations in red cell turnover (eg, hemolytic anemia, recent transfusion, pregnancy, loss of blood)
Less biological (day-to-day) variability compared with single fasting or 2-h glucose[26,31,32]	Lack of assay standardization in many parts of the world
Eliminates need for fasting or timed samples	Cost and lack of availability in resource-poor areas
Unaffected by acute illness or recent activity (eg, physical activity)[30]	
Already used as a guide to adjust diabetes mellitus treatment[33]	
Laboratory methods are well standardized in the US and some other countries[33]	
More robust predictor of complications than fasting blood glucose[18,20]	

A_{1c} indicates glycated hemoglobin.

Table 5.

Current Recommendations for CVD Risk Factor Management in Type 2 Diabetes Mellitus

Risk Factor	Relevant Statement or Guideline	Specific Recommendation and Level of Evidence
Nutrition	"Nutrition Therapy Recommendations for the Management of Adults With Diabetes"[43]	Reduction of energy intake for overweight or obese patients (*ADA Level of Evidence A*). Individualized medical nutrition therapy for all patients with diabetes mellitus (*ADA Level of Evidence A*). Carbohydrate monitoring as an important strategy for glycemic control (*ADA Level of Evidence B*). Consumption of fruits, legumes, vegetables, whole grains, and dairy products in place of other carbohydrate sources (*ADA Level of Evidence B*). Mediterranean-style dietary pattern may improve glycemic control and CVD risk factors (*ADA Level of Evidence B*). Limit of sodium to <2300 mg/d, similar to recommendations for the general population (*ADA Level of Evidence B*; note that the AHA differs and recommends sodium <1500 mg/d).
Obesity	"2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society"[58]	Overweight and obese patients should be counseled that lifestyle changes can produce a 3%−5% rate of weight loss that can be sustained over time and that this can be associated with clinically meaningful health benefits (*ACC/AHA Class I; Level of Evidence A*). For patients with BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with an obesity-related comorbidity who want to lose weight but have not responded to behavioral treatment with or without pharmacological treatment, bariatric surgery may improve health (*ACC/AHA Class IIa; Level of Evidence A*).
Blood glucose	"Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)"[59] "Standards of Medical Care in Diabetes-2015"[4]	Lower A_{1c} to ≤7.0% in most patients to reduce the incidence of microvascular disease (*ADA Level of Evidence B*); this can be achieved with a mean plasma glucose of ≈8.3–8.9 mmol/L (≈150–160 mg/dL); ideally, fasting and premeal glucose should be maintained at <7.2 mmol/L (<130 mg/dL) and postprandial glucose at <10 mmol/L (<180 mg/dL). More stringent A_{1c} targets (eg, <6.5%) might be considered in selected patients (with short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycemia or other adverse effects of treatment (*ADA Level of Evidence C*). Less stringent A_{1c} goals (eg, <8.0% or even slightly higher) are appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, cognitive impairment, and extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counseling, and effective doses of multiple glucose-lowering agents, including insulin (*ADA Level of Evidence B*).
Blood pressure	"An Effective Approach to High Blood Pressure Control: A Science Advisory From the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention"[60] "2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)"[61] "Standards of Medical Care in Diabetes-2015"[4]	For most individuals with diabetes mellitus, achieve a goal of <140/90 mm Hg; lower targets may be appropriate for some individuals, although the guidelines have not yet been formally updated to incorporate this new information (*Expert Opinion, Grade E*).[60,61] Pharmacological therapy should include a regimen with either an ACEI or an ARB (*ADA Level of Evidence B*); if 1 class is not tolerated, the other should be substituted (*ADA Level of Evidence C*).[4] For patients with CKD, antihypertension treatment should include an ACEI or ARB (*Expert Opinion, Grade E*). Hypertension/blood pressure control has been revised to suggest that the systolic blood pressure goal for many people with diabetes mellitus and hypertension should be <140 mm Hg (*ADA Level of Evidence A*) but that lower systolic targets (eg, <130 mm Hg) may be appropriate for certain individuals such as younger patients if it can be achieved without undue treatment burden (*ADA Level of Evidence C*).[4]
Cholesterol	"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"[62] "Standards of Medical Care in Diabetes-2015"[4]	Patients with diabetes mellitus between 40 and 75 y of age with LDL-C between 70 and 189 mg/dL should be treated with a moderate-intensity statin *† (*ACC/AHA Class I; Level of Evidence A*) (*ADA Level of Evidence A*). Statin therapy of high intensity‡ should be given to individuals with diabetes mellitus between 40 and 75 y of age with a ≥7.5% estimated risk of ASCVD (*ACC/AHA Class IIa; Level of Evidence B*) Among individuals with diabetes mellitus who are <40 or >75 y of age, practitioners should evaluate the benefit of statin treatment (*ACC/AHA Class IIa; Level of Evidence C*) Evaluate and treat patients with fasting triglycerides >500 mg/dL

ACC indicates American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; A_{1C}, glycated hemoglobin; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and TOS, The Obesity Society.

[*] Moderate-intensity statin therapy lowers LDL-C on average by 30% to 50%.

[†] We note that these recommendations do not replace clinical judgment, including consideration of potential risks, benefits, drug interactions, and adverse events.

[‡] High-intensity statin lowers LDL-C on average by >50%.

Table 6.

Drugs Approved by the FDA for Weight Loss*

Generic Name, Year of Approval	Trade Name(s)	Dose	DEA Schedule
Pancreatic lipase inhibitor approved by the FDA for long-term use (≥12 mo)			
Orlistat,1999	Xenical	120 mg 3 times daily before meals	Not scheduled
Orlistat, 2007	Alli (over the counter)	60 mg 3 times daily before meals	Not scheduled
Serotinin-2C receptor agonist approved by the FDA for long-term use (12 mo)			
Lorcaserin, 2012	Belviq	10 mg twice daily	IV
Combination of phentermine-topiramate approved by the FDA for long-term use (12 mo)			
Phentermine-topiramate, 2012	Qsymia	3.75/23 mg 7.5/46 mg 15/92 mg	IV
Noradrenergic drugs approved for short-term use (usually <12 wk)			
Diethylpropion, 1959	Tenuate Tenuate Dospan	25 mg 3 times a day 75 mg every morning	IV
Phentermine, 1959	Adipex and many others	15–30 mg/d	IV
Benzphetamine, 1960	Didrex	25–50 mg 3 times daily	III
Phendimetrazine, 1959	Bontril Prelu-2	17.5–70 mg 3 times daily 105 mg daily	III

DEA indicates US Drug Enforcement Administration; and FDA, US Food and Drug Administration.

*Side effect profiles can be found in the package inserts for each agent.

Table 7.

Complications of Bariatric Surgery

Complications	Frequency, %, and Outcomes
Sepsis from anastomotic leak[105]	1–2
Hemorrhage[105]	1–4
Cardiopulmonary events[105]	…
Thromboembolic disease[105]	0.34
Late complications for AGB	Surgical revision required in as many as 20 within 5 y
Band slippage	15
Leakage	2–5
Erosion	1–2
Late complications of bypass procedures	
Anastomotic strictures	1–5
Marginal ulcers	1–5
Bowel obstructions	1–2
Micronutrient and macronutrient deficiencies from RYGB 2–3 y after surgery[105]	
Iron deficiency	45–52
Vitamin B_{12} deficiency	8–37
Calcium deficiency	10
Vitamin D deficiency	51
Fat-soluble vitamin deficiencies (A, D, E, K) and protein calorie malnutrition from BPD and DS procedures	1–5

AGB indicates adjustable gastric banding; BPD, biliopancreatic diversion; DS, duodenal switch; and RYGB, Roux-en-Y gastric bypass.

Table 8.

Screening Tests for Asymptomatic CAD in Patients With Diabetes Mellitus

Test	Description	Key Results	Inclusion in a Recent AHA Guideline?
ECG	Resting electric activity through the cardiac cycle	In the UKPDS study, 1 in 6 patients with newly diagnosed type 2 diabetes mellitus had evidence of silent MI on the baseline surface ECG.[211] Prevalence of ECG abnormalities in patients with diabetes mellitus and no known CAD was even higher in older studies, approaching 20%.[212] UKPDS data indicate that an abnormal ECG is an independent risk factor for all-cause mortality and fatal MI in patients with diabetes mellitus.[211] Specific ECG abnormalities associated with increased risk of CVD events in cohort studies include pathological Q waves, LVH (particularly if accompanied by repolarization abnormalities), QRS prolongation, ST-segment depressions, and pathological T-wave inversions.[213] Abnormal ECG findings have been demonstrated to predict inducible ischemia.[214]	Class IIa: A resting ECG is reasonable for cardiovascular risk assessment in asymptomatic adults with hypertension or diabetes mellitus (*Level of Evidence C*).[213]
ABI	Ratio of systolic blood pressure at the ankle and arm. Used as an indicator of underlying peripheral arterial disease	A systematic review of ABI as a predictor of future CVD events demonstrated high specificity (≈93%) but very low sensitivity (16%),[215] thus limiting its utility as a screening test for CAD.	Class IIa: Measurement of ABI is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (*Level of Evidence B*).[213]
Stress MPI	Radioactive tracer (eg, thallium-201, Tc^{99m} sestamibi, or Tc^{99m} tetrofosmin) uptake within the myocardium is assessed before and after stress with scintigraphy. Option for pharmacological stress (dipyridamole, adenosine, or regadenoson) in those not able to exercise	MiSAD[216]: • A total of 925 asymptomatic patients with type 2 diabetes mellitus underwent an ECG stress testing, which, if positive or equivocal, led to stress thallium MPI. • Silent CAD prevalence 12.5% for abnormal exercise ECG and 6.4% for both abnormal ECG and MPI. • Abnormal scintigraphy predicted cardiac events at 5 y (HR, 5.5; 95% CI, 2.4–12.3; *P*<0.001). DIAD[217,219]: • In total, 1123 patients with type 2 diabetes mellitus were enrolled from multiple centers (mean duration of diabetes mellitus, 8.5 y); 522 patients were randomized to adenosine sestamibi SPECT MPI, and 561 served as the control group and were randomized to follow-up alone. • Silent ischemia prevalence=21.5%. • At 5 y of follow-up, there was no difference in the primary end point, nonfatal MI and cardiac death, between the screened and unscreened cohorts (overall annual rate, 0.6%; 15 vs 17 events; HR, 0.88; 95% CI, 0.44–1.80; *P*=0.73). • No differences in any secondary end points (unstable angina, heart failure, stroke, coronary revascularization). DYNAMIT trial[218]: • Prospective, randomized, double-blind, multicenter study conducted in France. • In total, 631 patients were randomized to either CAD screening with either a stress ETT or dipyridamole SPECT MPI vs follow-up only (without screening).	Class IIb: Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes mellitus or asymptomatic adults with a strong family history of CHD or when previous risk assessment testing suggests a high risk of CHD (eg, a CAC score of ≥400) (*Level of Evidence C*).[213] Class III: No benefit. Stress MPI is not indicated for cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults (*Level of Evidence C*).[213]

Test	Description	Key Results	Inclusion in a Recent AHA Guideline?
		• Study was stopped prematurely; no difference in cardiac outcomes was seen between screened and unscreened groups (HR, 1.00; 95% CI, 0.59–1.71).	
CAC scoring	Quantitative assessment of calcium deposited within the coronary arteries (as a marker of atherosclerosis) via EBCT or multidetector CT, stratified by Agatston units, yielding CAC scores of <100 (low risk), 100–400 (moderate risk), and >400 (high risk)	Linear relationship between CAC and clinical CHD events among individuals with and without diabetes mellitus.[220–225] Patients with diabetes mellitus have a greater prevalence and extent of CAC than those without diabetes mellitus.[225–228] Prognostic significance of elevated CAC in predicting adverse events is greater in patients with diabetes mellitus than in those without diabetes mellitus.[229] No dedicated randomized trials have suggested that the detection of subclinical CAD by CAC leads to improvement in clinical events. This represents an important area of future research.	In asymptomatic adults with diabetes mellitus ≥40 y of age, measurement of CAC is reasonable for cardiovascular risk assessment (*Level of Evidence B*).[213]

ABI indicates ankle-brachial index; AHA, American Heart Association; CAC, coronary artery calcium; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CT, computed tomography; CVD, cardiovascular disease; DIAD, Detection of Ischemia in Asymptomatic Diabetics; DYNAMIT, Do You Need to Assess Myocardial Ischemia in Type 2 Diabetes; EBCT, electron-beam computed tomography; ETT, exercise tolerance testing; HR, hazard ratio; LVH, left ventricular hypertrophy; MI, myocardial infarction; MiSAD, Milan Study on Atherosclerosis and Diabetes; MPI, myocardial perfusion imaging; SPECT, single-photon emission computed tomography; and UKPDS, United Kingdom Prospective Diabetes Study.