REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

# Prevention of Cardiovascular Disease in Type 1 Diabetes

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Type 1 diabetes mellitus is a chronic metabolic disease resulting from autoimmune destruction of pancreatic beta cells. More than half the cases of type 1 diabetes are diagnosed in adulthood; 62% of new cases in 2021 were diagnosed in patients over the age of 20 years.[1] There are key genetic, immune, and metabolic differences between childhood- and adult-onset type 1 diabetes.[2] As a result of both a later age at diagnosis and longer life span, the mean age of a person living with type 1 diabetes is now 40 years.[1]

## Scope of the Problem

Despite remarkable advances in diabetes care, patients with type 1 diabetes continue to have a life expectancy that is approximately 13 years shorter than that of the general population.[3] Cardiovascular disease is the primary cause of this shortened life expectancy, and throughout their lifetime, persons with type 1 diabetes are at greater risk for cardiovascular disease than the general population.[4-12] In the Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, cardiovascular disease was the leading cause of death, and participants randomly assigned to a glycated hemoglobin goal of 9% (75 mmol per mole), the conventional goal, had a higher risk of death from cardiovascular causes at 20 years than those randomly assigned to the more stringent goal of 7% (53 mmol per mole).[13] Similarly, an analysis of data from the Swedish National Diabetes Register revealed the close association between levels of glycated hemoglobin and the risk of death from cardiovascular causes. Notably, in a 2014 study using data from the Swedish National Diabetes Register, even patients with a glycated hemoglobin level of 6.9% (52 mmol per mole) or lower had a risk of death from cardiovascular causes that was greater by a factor of 2 than that of nondiabetic controls.[14] A systematic review and meta-analysis of data from more than 214,000 patients with type 1 diabetes showed that the relative risk of cardiovascular events was twice as high for women as it was for men.[15]

## Biology of Cardiovascular Disease in Type 1 Diabetes

The mechanisms involved in the development of cardiovascular disease in persons with type 1 diabetes are similar to those that have been identified in persons with type 2 diabetes (Fig. 1; for more details, see the Supplementary Appendix, available with the full text of this article at NEJM.org).[16] However, in a study using multislice computed tomography to assess the plaque burden in 135 asymptomatic patients with type 1 or 2 diabetes, obstructive coronary heart disease was less extensive in persons with type 1 diabetes than in those with type 2 diabetes, even when the

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N Engl J Med 2024;390:1207-17.
DOI: 10.1056/NEJMra2311526
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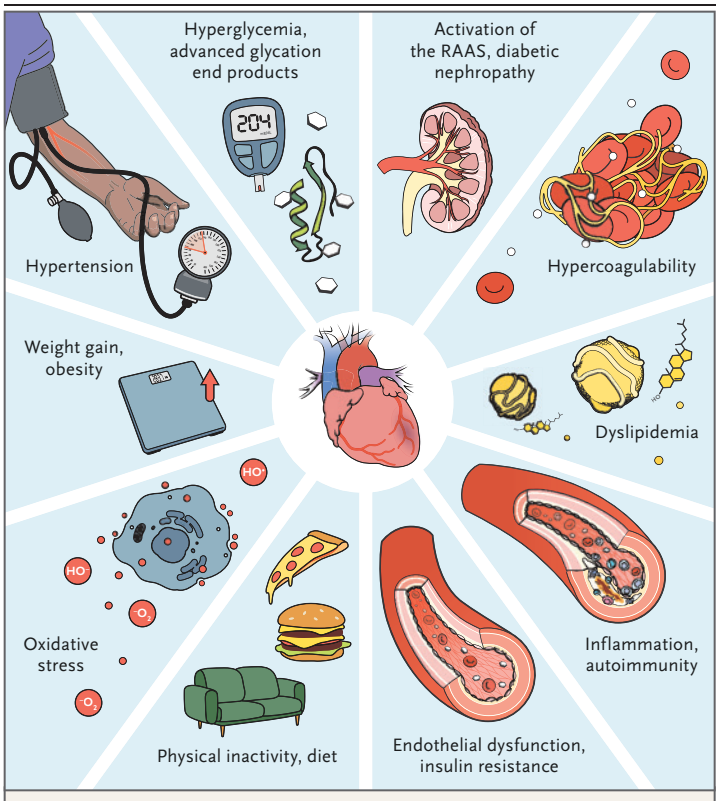


**Figure 1. Pathophysiology of Cardiovascular Disease in Patients with Type 1 Diabetes.**

The mechanisms involved in the development of cardiovascular disease in persons with type 1 diabetes are shown.

patients were matched for coronary-artery calcium scores.[17] Moreover, a potentially protective finding in the cohort with type 1 diabetes was a lower number of noncalcified plaques. A recent case–control study showed that the incidence of vascular-wall inflammation was higher among patients with type 1 diabetes than among persons without diabetes who were matched for age, sex, and body-mass index (BMI), an effect that was independent of glycemic control. This finding was associated with increased circulating inflammatory markers.[18] Confirmation of these results in future studies will prove helpful in understanding differences in the pathophysiology and treatment of atherosclerosis between patients with type 1 diabetes and those with type 2 diabetes.

Although insulin resistance, which clusters with various cardiovascular risk factors, is a distinctive feature of type 2 diabetes,[19] its presence in patients with type 1 diabetes is also associated with cardiovascular dysfunction,[20,21] an association that is independent of glycemia.[22] An examination of data from the Pittsburgh Epidemiology of Diabetes Complications Study revealed that the presence of the metabolic syndrome and some of its individual components in patients with type 1 diabetes was associated with worse cardiovascular and renal outcomes.[23]

## DIABETIC KIDNEY DISEASE

Albuminuria, a reduced glomerular filtration rate, or both are associated with an increased risk of cardiovascular events and death.[24,25] Antagonism of the renin–angiotensin–aldosterone system, in addition to strict glycemic control, is the most well-established strategy used to delay the progression of diabetic kidney disease. In one trial, captopril slowed the progression of kidney disease in patients with type 1 diabetes and nephropathy without affecting the risk of death from cardiovascular causes.[26] However, treatment with captopril was associated with a 50% reduction in the risk of a composite of death, dialysis, and renal transplantation. The more recent Heart Outcomes Prevention Evaluation (HOPE) study, which involved 3577 patients with diabetes, 81 of whom had type 1 diabetes, showed that ramipril reduced the incidence of cardiovascular events and overt nephropathy.[27] Clinical trials examining the effect of glucagon-like peptide 1 (GLP-1) receptor agonism and mineralocorticoid receptor antagonism in patients with type 1 diabetes and kidney disease, which are currently under way, offer hope for additional therapeutic strategies (Trial of Semaglutide for Diabetic Kidney Disease in Type 1 Diabetes (RT1D) [ClinicalTrials.gov number, NCT05822609] and A Study to Learn How Well the Study Treatment Finerenone Works and How Safe it is in People With Long-term Decrease in the Kidneys' Ability to Work Properly [Chronic Kidney Disease] Together With Type 1 Diabetes [FINE-ONE] [NCT05901831]).

## REDUCING THE CARDIOVASCULAR DISEASE BURDEN

### GLYCEMIC CONTROL

Levels of glycated hemoglobin are closely correlated with the risk of adverse cardiovascular outcomes and death among persons with type 1 diabetes.[28]



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The independent effects of hyperglycemia are multifactorial and include activation of the renin–angiotensin–aldosterone system and proinflammatory pathways, increased production of reactive oxygen species, and formation of advanced glycation end products and activation of their receptors (Fig. 1).[16,29,30] Most of the evidence supporting the importance of strict glycemic control comes from the DCCT/EDIC studies, which showed that intensive insulin therapy decreased the occurrence of microvascular complications.[31] Although the incidence of cardiovascular events did not differ significantly between the two study cohorts (patients assigned to intensive therapy and those assigned to usual care) during the initial 6.5 years of follow-up (DCCT), subsequent follow-up (EDIC) showed a 42% reduction in cardiovascular events at 17 years[32] and a 30% reduction after 30 years[33] in the intensive therapy cohort, despite similar baseline glycated hemoglobin levels in the two groups. These effects have been attributed to tighter glycemic control earlier in the course of the disease ("metabolic memory") and a lower incidence of diabetic kidney disease.[33] In addition, the intensive therapy group had a lower prevalence of hypertension.[34] Such effects, ascribed to metabolic memory, have led to further investigation.[34,35]

### TREATMENT OF HYPERCHOLESTEROLEMIA

Data from randomized, controlled trials examining the effect of statins on atherosclerotic cardiovascular disease in patients with type 1 diabetes are lacking. However, one of the most convincing lines of evidence supporting the benefit of statins in type 1 diabetes stems from the Swedish National Diabetes Register. A total of 24,230 patients with type 1 diabetes who did not have a history of cardiovascular disease were followed for the development of acute myocardial infarction, stroke, coronary heart disease, death from cardiovascular causes, and death from any cause.[35] Of these participants, 5387 were treated with lipid-lowering therapy (of whom 97% received statins) and 18,843 were untreated. After a mean follow-up of 6 years, the hazard ratios in the statin-treated group as compared with the untreated group were 0.56 (95% confidence interval [CI], 0.48 to 0.64) for death from any cause, 0.56 (95% CI, 0.46 to 0.70) for stroke, and 0.85 (95% CI, 0.74 to 0.97) for fatal or nonfatal coronary heart disease.

Given the lack of high-quality data from randomized, controlled trials, published guidelines from professional societies for cardiology, endocrinology, and nephrology have not consistently recommended statin use[36-40] (Table 1). An option for clinicians who would like to consider statin therapy for patients with type 1 diabetes would be to use a risk calculator (see a vignette for this scenario in the Supplementary Appendix).

Given the large number of children and adolescents who have type 1 diabetes, clinicians are often faced with the challenge of considering statin use in this population. In one study, youth with type 1 diabetes (mean age, 15 years) had higher levels of proprotein convertase subtilisin–kexin type 9 (PCSK9), which is positively correlated with glycated hemoglobin, triglyceride, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels, than age-matched controls.[42] In another study of youth with type 1 diabetes (mean ±SD age, 13.9±3.0 years), worsening glycemic control was associated with increased plasma PCSK9 and LDL cholesterol levels.[43] These findings have led to more aggressive use of statins in youth with type 1 diabetes.[44] The International Society for Pediatric and Adolescent Diabetes and the American Diabetes Association (ADA) differ in their recommendations for statin use in children with type 1 diabetes who are older than 10 years of age. Even though the Food and Drug Administration (FDA) recently requested removal of the "pregnancy category X" label for statins, the use of statins in women with type 1 diabetes who are pregnant or are lactating is not recommended.[45] Ezetimibe, bempedoic acid, and PCSK9 inhibitors also lower LDL cholesterol levels but do not have proven efficacy in patients with type 1 diabetes.

### HYPERTENSION AND BLOOD-PRESSURE CONTROL

Hypertension is common in type 1 diabetes. Its presence has been positively correlated with the duration of the disease and the age of the population examined. In the European Diabetes Insulin-Dependent Diabetes Mellitus (EURODIAB IDDM) study, the prevalence of hypertension was 24% (mean age, 32.7±10 years; mean diabetes duration, 14.7±9.3 years).[46] Maahs et al. reported an even higher prevalence of elevated blood pressure (43%) among a population-representative sample of patients (mean age, 37±9 years; mean



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**Table 1. Recommendations for Lipid-Lowering Therapy as Primary Prevention for Cardiovascular Disease in Patients with Type 1 Diabetes.***

| Source | Recommendations |
|---|---|
| American Diabetes Association[36,41] | For people 40 to 75 years of age without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle changes.<br>For people 40 to 75 years of age at higher cardiovascular risk, including those with ≥1 risk factor for atherosclerotic cardiovascular disease, use high-intensity statin therapy to reduce LDL cholesterol by ≥50% of baseline value and to target an LDL cholesterol goal of <70 mg/dl.<br>After the age of 10 years, addition of a statin can be considered in youth with type 1 diabetes who, despite medical nutrition therapy and lifestyle changes, continue to have LDL cholesterol >160 mg/dl or >130 mg/dl with ≥1 cardiovascular disease risk factor. |
| American College of Cardiology–American Heart Association[38] | In adults 40 to 75 years of age, regardless of estimated risk of atherosclerotic cardiovascular disease, moderate-intensity statin therapy is indicated.<br>For adults with multiple atherosclerotic cardiovascular disease risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL cholesterol by ≥50%. |
| European Society of Cardiology[37] | Statins should be considered in adults >40 years of age without a history of cardiovascular disease to reduce risk.<br>For younger patients, statins should be considered if the patient has other cardiovascular risk factors, microvascular disease, or a 10-year cardiovascular disease risk ≥10%. |
| International Society of Pediatric and Adolescent Diabetes | If the implementation of lifestyle interventions for 6 months does not lower LDL cholesterol to 130 mg/dl, statins should be considered in children >10 years of age, with an ideal LDL cholesterol target of <100 mg/dl.<br>Simvastatin, lovastatin, and pravastatin are effective and safe in children and adolescents. |

* Moderate-intensity statin doses are as follows: 10 to 20 mg of atorvastatin, 80 mg of fluvastatin, 40 mg of lovastatin, 40 to 80 mg of pravastatin, 5 to 10 mg of rosuvastatin, 20 to 40 mg of simvastatin, and 2 to 4 mg of pitavastatin. High-intensity statin doses are as follows: 40 to 80 mg of atorvastatin and 20 to 40 mg of rosuvastatin. To convert low-density lipoprotein (LDL) cholesterol values to millimoles per liter, multiply by 0.02586.

diabetes duration, 23.2±8.9 years), and only 42% of the patients had adequate blood-pressure control.[47] A more recent study, involving 4060 patients with type 1 diabetes, showed a hypertension prevalence of 66.2%, even though more than 60% of the participants were reportedly using renin–angiotensin–aldosterone system blockers.[48] As with statins, the evidence guiding blood-pressure targets for patients with type 1 diabetes originated from studies of patients with type 2 diabetes or adults without diabetes.[49,50] Although a clinical trial specifically examining the role of renin–angiotensin–aldosterone system blockade in preventing the progression of diabetic kidney disease in patients with type 1 diabetes was published 30 years ago, more recent data are lacking.[26] The ADA recommends that persons with diabetes and an office-based blood-pressure measurement of 130/80 mm Hg or higher should receive pharmacologic therapy to lower blood pressure.[36] An analysis of 25 years of data from 605 participants with type 1 diabetes and no known heart disease in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study showed that blood pressure above the threshold of 120/80 mm Hg predicted an increased risk of coronary heart disease.[51]

Pharmacologic treatment should include agents from a medication class with proven cardiovascular benefits in diabetes: thiazide-like diuretics, dihydropyridine calcium-channel blockers, angiotensin-converting–enzyme (ACE) inhibitors, or angiotensin-receptor blockers. Furthermore, the ADA noted that patients with hypertension and albuminuria would particularly benefit from renin–angiotensin–aldosterone system blockade.[49] Clinicians considering the use of beta-blockers in patients with type 1 diabetes who have established coronary artery disease or heart failure should take into account the potentially increased risk of severe hypoglycemia in this population.[52]



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### MANAGEMENT OF OBESITY

Obesity is a newly acknowledged coexisting condition in persons with type 1 diabetes. A report from the T1D Exchange noted that the body-mass index (BMI, calculated as the weight in kilograms divided by the square of the height in meters) for 22,697 patients with type 1 diabetes was similar to that for patients without diabetes and was also similar in all age groups (Fig. 2).[53,54] Overall, the prevalence of obesity in type 1 diabetes increased from 32.6% in 2004 to 36.8% in 2018.[48] In the DCCT, intensive insulin therapy was associated with increased body weight.[55] After 6.5 years of intensive therapy, 19% of patients had a BMI exceeding 30, as compared with 6% of patients receiving conventional therapy.[56] As expected, excess weight gain was associated with features of the metabolic syndrome and insulin resistance.[57] Surprisingly, the incidence of cardiovascular disease among patients in the intensive therapy group who had the greatest weight gain was similar to the incidence among those in the conventional therapy group.[57]

The pathogenesis of obesity in type 1 diabetes is more complex than simply a reduction in glycosuria that leads to a positive energy balance. Behavioral snacking to avoid hypoglycemia is common among patients, particularly those with long-standing diabetes, given the imperfections of older insulin formulations. Dysfunction and fibrosis of adipose tissue, changes in the microbiome, beta-cell dysfunction, mitochondrial dysfunction, and the differential metabolic effects of insulin in the systemic circulation as compared with the portal circulation have all been implicated in the genesis of obesity.[58] The DCCT also showed greater weight gain in participants randomly assigned to the intensive

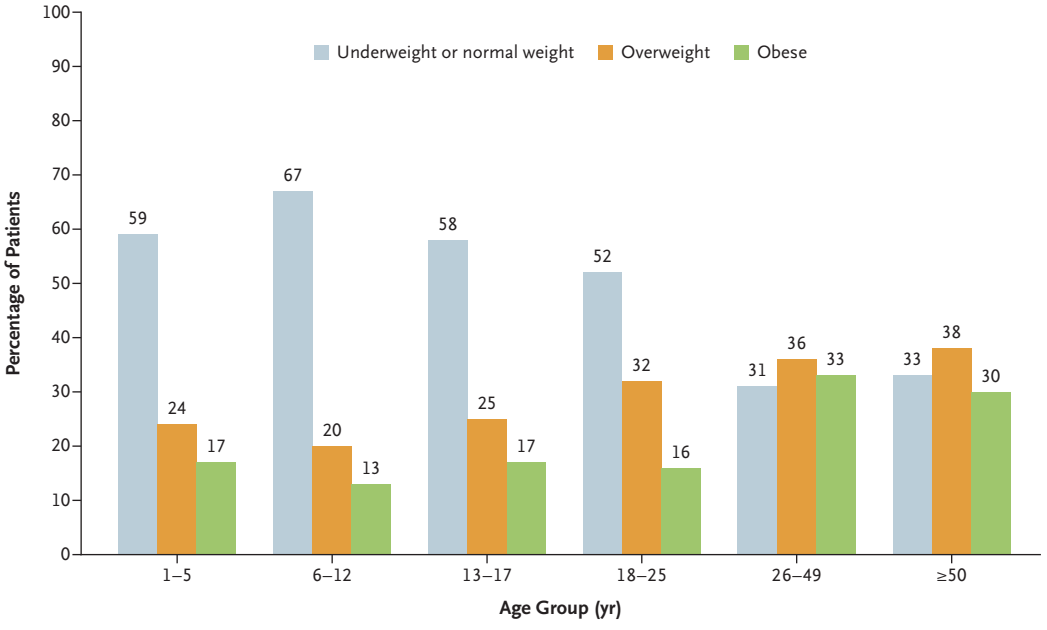


**Figure 2. Body-Mass Index (BMI) Range for Patients in the T1D Exchange Cohort.**

Data are from Foster et al.[53] The cohort comprised 22,697 patients with type 1 diabetes. BMI is the weight in kilograms divided by the square of the height in meters. Underweight or normal weight was defined as less than the 85th BMI percentile for participants younger than 20 years of age and a BMI of less than 25 for participants who were 20 years of age or older. Overweight was defined as the 85th to 94th BMI percentile for participants who were less than 20 years of age and a BMI of 25 to 29 for those who were 20 years of age or older, with obesity defined as the 95th BMI percentile or higher for the younger participants and a BMI of 30 or higher for the older participants. All BMI assessments were adjusted for sex and age. The data are similar to those for age-matched persons without diabetes in the general population.[54]



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therapy group who had a family history of type 2 diabetes than in those who did not have a family history, which suggests a genetic contribution.[59] A better understanding of all these likely mechanisms may lead to improved treatments in the future.

Current options for the treatment of obesity in patients with type 1 diabetes are limited, especially as compared with treatment options for patients who have type 2 diabetes. Lifestyle modification should be encouraged, yet defensive eating to avoid hypoglycemia makes this approach difficult and is associated with weight regain. Data in support of agents such as phentermine, phentermine–topiramate, or naltrexone–bupropion are limited, so these medications are rarely used in this population.

Bariatric surgery (also termed "metabolic surgery") has been shown to be an effective and relatively safe option for patients with type 1 diabetes and obesity. In a study involving 147 persons with type 1 diabetes who underwent Roux-en-Y gastric bypass or sleeve gastrectomy, weight reduction was similar regardless of which procedure was used, with parallel decreases in insulin requirements at 1 year.[60] Data from 17 studies involving a total of 107 persons with type 1 diabetes who underwent bariatric surgery showed a significant but modest reduction in glycated hemoglobin levels in conjunction with weight loss.[61]

Several clinical trials have examined the effect of incretin mimetics on glycemic control and body weight in persons with type 1 diabetes.[62-64] Although the trial results do not support an additive effect of incretin mimetics on glycemic control, patients consistently had weight loss, mainly as a result of appetite suppression.[65] Hyperglycemia with ketosis has been reported in some trials.[62,63,66] The GLP-1 receptor agonists liraglutide and semaglutide are currently approved by the FDA for the treatment of obesity but have not been specifically studied in patients with type 1 diabetes. Clinicians prescribing these agents for patients with type 1 diabetes should remain vigilant for potential postprandial hypoglycemia due to delayed gastric emptying. Studies are needed to assess the effects of longer-acting GLP-1 receptor agonists and combined GLP-1–glucose-dependent insulinotropic polypeptide receptor agonists on body weight and cardiovascular outcomes in patients with type 1 diabetes.

### ANTITHROMBOTIC THERAPY

The importance of antiplatelet therapy for the secondary prevention of atherosclerotic cardiovascular disease in all persons, whether or not they have diabetes, is well established.[36] Clinical trials examining the role of aspirin for primary prevention of cardiovascular disease in patients with type 1 diabetes have yielded conflicting results.[67-69] The ADA currently suggests the use of low-dose aspirin as primary prevention in patients who are over the age of 50 years and have diabetes (either type) and at least one additional risk factor (a family history of premature atherosclerotic cardiovascular disease, hypertension, dyslipidemia, smoking, or chronic kidney disease or albuminuria).[36] Careful consideration of the individual risk for bleeding is warranted before therapy is started.[36] Because persons with type 1 diabetes and elevated glycated hemoglobin levels have reduced inhibition of platelet aggregation with aspirin use,[70] improving glycemic control may be helpful for enhancing the effects of aspirin. Unfortunately, little information is available regarding the use of glycoprotein IIb/IIIa receptor inhibitors in patients with type 1 diabetes.

### ASSESSMENT OF CARDIOVASCULAR DISEASE RISK

Clinicians should perform a cardiovascular risk assessment annually for patients with type 1 diabetes and address modifiable risk factors.[36] Cardiac symptoms and abnormal findings on physical examination should then dictate the need for additional screening with electrocardiography or further cardiac testing.[36]

The coronary-artery calcium (CAC) score has emerged as a tool to guide initiation of pharmacologic therapies known to reduce the risk of cardiovascular disease. An analysis of CAC scores in DCCT/EDIC participants provided evidence of the score's predictive power.[71] A CAC score of 100 or higher was associated with an increased risk of cardiovascular disease among both persons with and those without type 1 diabetes. An analysis of data for the patients who did not have diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort showed that a CAC score of 100 or higher was associated with a



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favorable risk–benefit estimation for aspirin use, whereas a CAC score of 0 was estimated to confer net harm from aspirin.[72] These data were not from patients with type 1 diabetes but can reasonably be extrapolated to those with type 1 diabetes. Similarly, a CAC score of 0 in young adults (<40 years of age) without cardiovascular risk factors can be used to suggest delaying the start of statin therapy, with repeat CAC assessments at 5-year intervals.[73] After the initiation of statin therapy, there is no indication to reassess the CAC score, since statins can lead to increases in the score because of increased plaque density and stabilization.[74]

Evaluation of lipoprotein(a) levels is recommended as an additional tool for cardiovascular risk stratification. Several scientific societies endorse the measurement of lipoprotein(a) levels at least once in all adults and in youth with a family history of premature atherosclerotic cardiovascular disease, with consideration of earlier initiation of or more intensive statin therapy to reduce the risk of cardiovascular disease among patients with elevated levels of lipoprotein(a).[75,76] An observational analysis showed that in persons with type 1 diabetes, an elevated lipoprotein(a) level (>50 mg per deciliter) is a risk factor for the development of cardiovascular disease and albuminuria and is associated with poor glycemic control.[77]

### NONPHARMACOLOGIC MANAGEMENT OF CORONARY ARTERY DISEASE

The atherosclerotic process in the coronary arteries is diffuse. Although decisions about how to manage symptoms in patients with multivessel disease need to be individualized and the data are limited, outcomes after coronary-artery bypass grafting may be more favorable than those after percutaneous coronary intervention. In an observational study in Sweden, 683 patients with type 1 diabetes who underwent coronary-artery bypass grafting were compared over a mean period of 10.6 years with 1863 patients who underwent percutaneous coronary intervention. Although the risk of death from any cause was similar in the two groups, the risk of myocardial infarction, death from cardiovascular causes, or need for repeat revascularization was higher after percutaneous coronary intervention.[77]

## HEART FAILURE IN TYPE 1 DIABETES

Multiple mechanisms account for heart failure in patients with diabetes, including atherosclerotic disease, hypertension, and diabetic kidney disease, as well as diabetic cardiomyopathy, a term that may imply a role for microvascular injury.[78,79] In addition, cardiac autoimmunity has been described as a mechanism leading to cardiomyopathy in patients with type 1 diabetes.[80] A recent meta-analysis that included 61,885 patients with or without type 1 diabetes who were followed for 1 to 12 years showed an adjusted relative risk of heart failure of 3.4 (95% CI, 2.71 to 4.26) among patients with type 1 diabetes.[81] The risk was approximately 5 times as high for women and 3 times as high for men as the risk for sex-matched controls.

Though most of the data regarding biomarker testing to predict the onset of heart failure are for people with type 2 diabetes, the available information indicates that a similar prediction can be made for those with type 1 diabetes. For example, among 1093 adults with type 1 diabetes but no known heart disease, the rate of incident major adverse cardiovascular events after 6.3 years was 41 per 1000 person-years for an N-terminal pro–B-type natriuretic peptide (NT-ProBNP) level above 300 pg per milliliter versus 10 per 1000 person-years for an NT-proBNP level below 150 pg per milliliter.[82] Renin–angiotensin–aldosterone system blockers are the preferred agents in the management of stage A or B heart failure in persons with type 1 diabetes and hypertension, especially in the presence of albuminuria, coronary artery disease, or both.[83] An experienced cardiologist should be involved in the management of advanced heart failure in any given patient.

The use of sodium–glucose cotransporter 2 (SGLT2) inhibitors has revolutionized cardiovascular and kidney care for people with type 2 diabetes. Some clinical trials have also examined the glucose-lowering efficacy of these agents when used as an adjunct to insulin therapy in patients with type 1 diabetes. Overall, trials have shown a modest blood glucose–lowering effect in conjunction with an increased risk of ketoacidosis and hypoglycemia.[84] Real-world data have indicated that the side-effect profile of SGLT2 inhibitors in patients with type 1 diabetes is



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**Table 2. Recommendations for Glycemic Control, Blood-Pressure Control, Antithrombotic Therapy, and Obesity in Patients with Type 1 Diabetes.**

| Purpose | Recommendations |
|---|---|
| Glycemic control | Glycated hemoglobin <7%, if attainable without increased hypoglycemia[37] |
| Hypertension or blood-pressure control | Lifestyle interventions, with consideration of ambulatory blood-pressure monitoring[37]<br>Blood pressure of <130/80 mm Hg[36] (and ideally, <120/80 mm Hg[37,51]) is recommended as a goal of treatment in adults and adolescents >13 years of age[44]<br>Treatment should include blockade of renin–angiotensin–aldosterone system, unless patient is planning pregnancy or is pregnant or lactating[36,37] |
| Antithrombotic therapy | Aspirin (75–162 mg) can be considered as primary prevention in patients >50 years of age who have additional risk factors[36,37]<br>Aspirin (75–162 mg) is indicated as secondary prevention in patients with established atherosclerotic cardiovascular disease (clopidogrel indicated for aspirin intolerance)[36,37] |
| Obesity | Lifestyle modifications, including caloric restriction and increased physical activity, recommended to achieve minimal weight reduction of 5–10%<br>Consider referral to an intensive lifestyle modification program<br>Consider GLP-1 receptor agonist therapy, with shared decision making with the patient regarding potential side effects* |

* GLP-1 denotes glucagon-like peptide 1.

similar to that in patients with type 2 diabetes.[85,86] The FDA recently approved the dual SGLT1 and SGLT2 inhibitor sotagliflozin for the treatment of heart failure, without limiting its use in patients with type 1 diabetes. The package insert recommends ketone monitoring in this population. Similarly, strategies to mitigate the risk of ketoacidosis have been reported,[87,88] but additional studies are needed to better support the regular use of SGLT2 inhibitors in the clinical care of people who have type 1 diabetes and heart failure, with or without chronic kidney disease.

## CONCLUSIONS

There are many questions about approaches to mitigating the risk of cardiovascular disease among patients with type 1 diabetes, including the timing and dose of statins, specific blood-pressure targets, the use of aspirin for primary prevention, the comparative efficacy of incretin mimetic therapy and bariatric surgery, and the risks and benefits of SGLT2 inhibition. Which of these potential interventions require more rigorous study through a randomized clinical trial? Currently, cardiovascular disease prevention in persons with type 1 diabetes must depend on data from observational studies and, in some circumstances, data obtained from the small number of patients with type 1 diabetes who have been included in trials primarily involving patients with type 2 diabetes. Real-world data and artificial intelligence may help answer some questions. Cardiovascular disease is the leading cause of substantial illness and death in patients with type 1 diabetes, and observational data remain the basis for decisions about therapy, since evidence from randomized clinical trials is lacking (Table 2). Until such evidence is available, current recommendations from the many nonprofit professional organizations are useful but need to be compared and consolidated.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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