The Burden of Cardiovascular Disease in Patients With Diabetes

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ABSTRACT

Adults with type 2 diabetes (T2D) have a 2-to-4–fold higher risk for cardiovascular morbidity and mortality than adults without diabetes, according to the American Heart Association (AHA). Furthermore, the AHA deems diabetes to be "1 of the 7 major controllable risk factors for cardiovascular disease (CVD)." Lack of glycemic control may lead to nerve and cardiac conduction impairments and CVD. However, glycemic control is not the only risk factor. Additional risk factors for CVD in T2D include hypertension, dyslipidemia, obesity, lack of physical activity, and smoking. Patients with T2D are also more likely to have risk factors that increase atherosclerotic cardiovascular disease (ASCVD) risk, including hypertension, dyslipidemia, and obesity. Control of these risk factors, as well as understanding the link between hyperglycemia and cardiovascular risk, is essential for the optimal management of T2D.

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Diabetes is a heterogenous group of metabolic disorders characterized by hyperglycemia resulting from insufficient insulin production, insulin resistance, or both.[1] According to the Centers for Disease Control and Prevention (CDC), approximately 30.3 million Americans (9.4% of the population) have diabetes, with 7.2 million of them undiagnosed.[2] In 2014, 14.2 million emergency department visits and 7.2 million hospital discharges involved diabetes and, in 2015, diabetes was the seventh leading cause of death in the United States.[2] The vast majority (90%-95%) of individuals with diabetes have type 2 diabetes (T2D); common comorbidities include obesity (87.5% of individuals with T2D), hypertension (73.6%), dyslipidemia (58.2%-66.9%), chronic kidney disease (CKD) (36.5%), and retinopathy (28.5%).[2,3]

The Incidence of Cardiovascular Disease With Diabetes and Economic Consequences

According to a recent global systematic review by Acs et al, 43.1% of patients with type 2 diabetes in North America and the Caribbean have cardiovascular disease (CVD).[4] Additional cardiovascular complications include heart failure (HF) (50.1%), coronary artery disease (CAD) (37.4%), myocardial infarction (MI) (18.2%), angina (17.3%), and stroke (10.5%).[4] The high prevalence of these cardiovascular comorbidities contributes to the already substantial morbidity and mortality of T2D.

Atherosclerotic cardiovascular disease (ASCVD) is defined as coronary heart disease, cerebrovascular disease, or peripheral arterial disease of atherosclerotic origin.[5] ASCVD is the leading cause of morbidity and mortality in T2D and is the largest contributor to both direct and indirect diabetes costs.[5] The risk for ASCVD is increased in the presence of uncontrolled risk factors such as hyperglycemia, hypertension, and dyslipidemia.[5] According to the National Health and Nutrition Examination Survey, more than 45% of patients with T2D are not at their glycemic goals, blood pressure goals, or lipid goals, and up to 75% of patients with T2D have not achieved their goals for all 3 risk factors, further increasing the risk for ASCVD.[6]

CVD Risk Factors in T2D

Traditional Risk Factors

Traditional risk factors for CVD in T2D include hypertension, dyslipidemia, obesity, lack of physical activity, poor glycemic control, and smoking.[5,7] Studies have demonstrated the value of controlling modifiable risk factors in T2D. A pooled analysis of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study demonstrated that patients with T2D who had optimal blood pressure, low-density lipoprotein cholesterol (LDL-C), and target glycated hemoglobin (A1C) levels had a substantially lower risk of coronary heart disease and CVD.[8] In the STENO-2 study, intensive multifactorial intervention targeting glucose, lipid, and blood pressure control had beneficial effects on vascular complications and cardiovascular death in at-risk patients with T2D.[9]

Multiple studies have also shown that patients with T2D are at the same risk for cardiovascular events as patients with a history of prior cardiovascular events and without diabetes.[10-13] Many of these risk factors are common for both T2D and CVD, suggesting that both disorders stem from a common source.[14,15]

Patients with T2D have higher prevalence of lipid abnormalities.[5] This is considered a triad of poor lipid count and often occurs in patients who have premature coronary heart disease. Atherogenic dyslipidemia/diabetic dyslipidemia is a lipid disorder that is associated with insulin resistance.[7] The 2018 American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) consensus statement for the treatment of T2D also identifies hypertension and dyslipidemia to be the 2 most important risk factors for ASCVD.[16]

Hypertension, which is common in T2D, is considered a major risk factor for ASCVD, HF, and microvascular complications, and it is also associated with insulin resistance (IR).[5] The prevalence of hypertension in T2D depends on the type and duration of diabetes, age, sex, race, ethnicity, body mass index, history of glycemic control, the presence of kidney disease, and other related factors.[17] Patients with both hypertension and diabetes double their risk for CVD.[7] Since 1990, it has been demonstrated that improvements in blood pressure control have led to decreased ASCVD mortality rates for T2D.[17-21] Numerous studies have demonstrated that antihypertensive therapy reduces ASCVD events, HF, and microvascular complications in patients with diabetes.[5,17,22-26] Even greater benefits are seen when multiple CVD risk factors are addressed together.[27]

There is a strong association between obesity and IR, leading to the increased risk of T2D and prediabetes.[28] People with prediabetes also are at an increased risk for cardiovascular disease and often have the presence of other cardiovascular disease risk factors such as IR, hypertension, and dyslipidemia. Some ASCVD risk factors may be improved with intensive lifestyle intervention focusing on weight loss through increased physical activity and reduced caloric intake, as evidenced in the Look AHEAD trial.[29] Weight loss can both improve CVD risk and increase insulin sensitivity.[7,16] Obesity and IR are also associated with hypertension.[7] Lack of physical activity is another risk factor that may lead to obesity. Increasing physical activity and weight loss are interventions that can prevent or delay the onset of T2D as well as reduce blood pressure and help reduce the risk of CVD.[7] Additionally, multiple studies demonstrate that smoking increases the risk of CVD in T2D.[30,31] The treatment of these traditional risk factors is very important for the reduction of CVD risk in patients with T2D.[32,33]

Nontraditional Risk Factors

In addition to the traditional risk factors for CVD in T2D, there are several nontraditional risk factors. Nontraditional risk factors for CVD in T2D include IR hyperinsulinemia, postprandial hyperglycemia, glucose variability, microalbuminuria, hematologic factors, thrombogenic factors, inflammation evidenced by elevated C-reactive protein, hyperhomocysteinemia and vitamin deficiencies, erectile dysfunction, genetics, and epigenetics.[14] In terms of thrombogenic factors, T2D is also associated with elevated plasminogen activator inhibitor-1 (PAI-1) levels, which contribute to a hypercoagulable state and can lead to an increased risk of cardiovascular complications.[34] There is an interaction and overlap between traditional risk factors and nontraditional risk factors that further increases the risk for CVD in patients with T2D. Many traditional and nontraditional risk factors occur simultaneously, thereby compounding the risk for CVD.[14] Martín-Timón et al further describe the delicate interplay between the risk factors and IR, lipids, proteins, and other factors that affect the development of CVD in patients with T2D.[14]

Most patients with T2D, and also many with prediabetes, are insulin resistant. IR is characterized by the presence of several ASCVD risk factors.[16] IR develops in several organs and muscles, such as the skeletal muscle, liver, adipose tissue, and heart. The pancreatic beta cell increases insulin secretion (hyperinsulinemia) in response to IR to maintain normoglycemia. When the beta cell can no longer keep up with the demand, hyperglycemia ensues. Thus, IR and hyperinsulinemia are key abnormalities of T2D. Obesity plays a major role in the development of IR.[14] The molecular mechanism by which IR causes T2D and increased CVD is not entirely understood; however, it has been shown that it may be linked to abnormalities in insulin signaling.[35] Increased concentrations of high-sensitivity C-reactive protein as a marker of inflammation are also associated with IR, T2D, and the development of T2D.[14] Inflammation has been strongly linked to endothelial dysfunction and plays a role in the development of the metabolic syndrome that leads to IR.[36,37]

Postprandial hyperglycemia and glucose variability have also been shown to increase the risk of CVD in patients with and without T2D.[14,38-42] These glucose excursions can be linked to postprandial elevated triglyceride levels and are related to augmented oxidative

stress, systemic inflammation, and endothelial dysfunctions that have been associated with atherosclerosis and cardiovascular events.[14,43,44]

Microalbuminuria describes a urinary albumin excretion between 30 mg and 300 mg per 24 hours. It is used to identify patients who are at an increased risk of CVD and progressive renal disease. In T2D, microalbuminuria is a sign of vascular damage to the glomerulus. Microalbuminuria has been identified as an important risk factor for diabetes and is identified by the American Diabetes Association (ADA) as a cardiovascular risk factor that should be screened annually in patients with T2D.[5,14]

There are several hematologic and thrombogenic factors, such as PAI-1, that are affected by T2D. These include increases in hypercoagulation that are more pronounced in the postprandial state as well as decreased fibrinolysis.[14,45] The increased platelet activity contributes to the increased incidence of cardiovascular events in T2D.[45] Increased plasma fibrinogen is also associated with T2D and is considered an additional CVD risk factor.[46,47]

The Relationship Between Elevated Glucose and CVD

Numerous studies have demonstrated the link between elevated glucose levels and ASCVD. Furthermore, the research shows that control of this risk factor positively impacts ASCVD. The Framingham Heart Study was the first study to show that patients with T2D are more susceptible to heart disease. The study reported a 2-to-3–fold increased risk of atherosclerotic disease in T2D.[48] In a retrospective look at the achieved A1Cs in the United Kingdom Prospective Diabetes Study (UKPDS), a 14% reduction in the risk of MI for each percentage point decrease in A1C in patients with recent-onset T2D was seen.[49] In the UKPDS, early intensive treatment with sulfonylureas or insulin versus diet alone showed that intensive therapy is associated with a 25% lower risk of developing macrovascular complications. There was a trend toward a reduction of MI in the intensive therapy group at 10 years after follow-up, but it was not statistically significant.[50] In another arm of the UKPDS, patients with obesity and T2D were randomized to receive either metformin or conventional therapy (primarily diet alone). In this arm, there was lower all-cause mortality in the metformin-treated group.[51] Although the median A1C level between the groups was 7.4% (metformin) versus 8.0% (control), metformin also lowered diabetes-related deaths and all-cause mortality at the 10-year follow-up with newly diagnosed patients.[51] Metformin was less effective in lowering A1C levels compared with intensive regimens with sulfonylurea or insulin. However, it was associated with a lower risk of death and stroke as well as lower risks for hypoglycemia.[51] Note that this was before statins, tighter hypertension control, and frequent aspirin use in patients with CAD.

In contrast to the UKPDS, the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) failed to show an overall reduction in cardiovascular events with aggressive glucose control.[52-55] The authors noted that this could be attributed to a longer mean duration of T2D or a shorter length of follow-up.[40] After 3.5 years, the ACCORD trial showed significant higher all-cause mortality in patients with T2D who received more intensive glycemic control compared with conventional controls. As a result, the glycemic control portion of the trial was stopped early.[52] A detailed scrutiny of the ACCORD data reveals that higher A1C levels predicted increased risks for death in the intensive arm of the trial. Most of the deaths occurred in the subgroup of patients whose A1C levels remained high despite intensive glycemic control.[56] Additionally, in a subgroup of patients who did not have documented CVD at baseline, a subanalysis showed that intensive glycemic control in this group was associated with a reduced risk for cardiovascular death as well as nonfatal cardiovascular events.[40,57]

The VADT compared intensive and standard treatment in patients with T2D. After a median follow-up of 5.6 years, the intensive control group achieved an A1C of 6.9% compared with 8.4% in the control group. There was no statistically significant difference in the incidence of major cardiovascular events.[53] However, in a subset analysis, patients without significant coronary atherosclerosis had a decrease in cardiovascular events with intensive therapy.[55] Both the VADT and ACCORD studies suggest that intensive glucose control may reduce cardiovascular events in patients who have a shorter duration of T2D as well as in those who do not have any significant preexisting CVD.[51,58]

The ADVANCE trial looked at patients after 5 years of intensive versus standard glycemic control. The results of the ADVANCE trial were similar to ACCORD and VADT. In patients who did not have established CVD, the rate of microvascular and macrovascular events was significantly lower in the intensive glucose control group.[59] ACCORD, ADVANCE, and VADT also had a shorter study duration than the UKPDS, and most of the patients had a longer duration of T2D.[60]

The benefits of early glycemic control may only be seen after several years.[40] Trials with longer durations, such as the UKPDS, Epidemiology of Diabetes Interventions and Complications (EDIC), and Steno-2, show greater benefit with aggressive glucose control than trials that have a shorter duration.[33,56] The cumulative data suggest that the benefits or harms from intensive glucose therapy may be determined by the presence of significant atherosclerosis at the time of therapy initiation.[40] A less aggressive A1C (7%-7.5%) may be preferred for patients with a limited life expectancy or those with established CVD or long-term T2D.[40] Pooled data from UKPDS, ACCORD, ADVANCE, VADT, and Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) studies demonstrate that there is an association between cardiovascular death in the intensive therapy arms and severe hypoglycemia.[40,61] Therefore, younger

patients with shorter durations of T2D and no established CVD may be better candidates for more intensive glycemic control.[40]

Retrospective data demonstrate that the risk of macrovascular complications increases with the severity of hyperglycemia, suggesting that there is a linear relationship between metabolic disturbance and vascular damage. With concerns of increased cardiovascular disease risk associated with some diabetes medications, the FDA issued guidance that all new medications for T2D must undergo cardiovascular outcomes trials. Since this time, several glucose-lowering agents have been tested for their efficacy and safety in lowering CVD in patients with T2D. Although some agents that carry risk for hypoglycemia have not been successful in lowering CVD, clinical trials have demonstrated improved ASCVD outcomes with empagliflozin, canagliflozin, and liraglutide, with potential benefit with metformin and pioglitazone.[40,51,60-68]

Healthcare professionals also need to balance the benefits of A1C lowering with the risk of hypoglycemia when considering glucose-lowering therapies. Hypoglycemia is proinflammatory and can increase the chances for plaque inflammation, rupture, and cardiovascular events.[40,69,70] Therefore, therapies that minimize hypoglycemia risk may be optimal, particularly in patients with preexisting CVD.

Screening and Treatment Recommendations for CVD Risk Factors in Patients With T2D

The current T2D treatment guidelines recommend a more comprehensive approach that includes the management of CVD risk factors, such as hypertension and dyslipidemia.[5,16] The 2018 ADA guidelines emphasize that CVD risk factors need to be assessed annually in all patients with T2D. These include both traditional and nontraditional risk factors, such as hypertension, dyslipidemia, smoking, a family history of premature coronary disease, CKD, and the presence of albuminuria. The ADA recommends that modifiable risk factors should subsequently be treated.[7] The ADA guidelines recommend that in patients with T2D and established ASCVD, antihyperglycemic therapy should begin with lifestyle therapy and metformin, with subsequent therapies including agents that have been proven to reduce major cardiovascular events and cardiovascular mortality, such as empagliflozin, canagliflozin, and liraglutide.[16,71]

The 2018 AACE/ACE consensus statement for the treatment of T2D algorithm also provides specific recommendations for blood pressure and lipid control, which the AACE/ACE deems to be the 2 most important risk factors for CVD.[16] The guidelines emphasize evaluating CVD risk and stratifying risk in patients. Lipid targets also must be stratified in patients with elevated blood glucose or T2D. The use of statins to treat dyslipidemia is emphasized by the ADA and the AACE/ACE.[5,16] The AACE/ACE guidelines also emphasize lifestyle therapy as well as the use of metformin and weight-loss therapies in patients with prediabetes to reduce ASCVD risk factors.[16] The AACE/ACE guidelines include algorithms to modify ASCVD risk factors as well as an algorithm to control hyperglycemia. A1C goals need to be individualized based on hypoglycemia risks.[16]

Conclusions

Numerous trials have demonstrated that, over time, poorly controlled diabetes leads to damage of the heart and blood vessels, and patients with T2D tend to develop CVD at a younger age than individuals without diabetes. Additionally, adults with T2D have a 2-to-4–fold higher risk of cardiovascular morbidity and mortality than adults without diabetes.[7] Managed care professionals need to acquire an understanding of and become familiar with the risk factors for CVD in T2D and the burden that diabetes inflicts on patients. Control of these risk factors, as well as an understanding of the link between hyperglycemia and CVD risk, is essential for the optimal management of T2D. Recent trials have demonstrated improved CVD outcomes with several novel glucose-lowering agents. Managed care professionals must evaluate these trials and results to provide optimal care to their patients with T2D. ■

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