Diabetes is one of the largest global health emergencies of the 21st century, with the number of people with diabetes growing rapidly worldwide. In 2017, 424.9 million adults were estimated to live with diabetes around the world. This number is predicted to increase to 628.6 million by 2045.1 Cardiovascular disease (CVD) is a major cause of death and disability among people with diabetes. Cardiovascular disease includes stroke, coronary artery disease and peripheral artery disease. People with diabetes are at increased risk of CVD, and these events generally occur at an earlier age compared to people without diabetes.1 Because of the increasing number of aging population and an increasing prevalence of obesity and sedentary life habits the prevalence of diabetes is increasing. Thus, diabetes must take its place alongside the other major risk factors as important causes of CVD. According to American Heart Association, “In fact, from the point of view of cardiovascular medicine, ‘diabetes is a cardiovascular disease.’”2

**Epidemiology of Diabetes and Concomitant CVD**

Cardiovascular disease is the leading cause of morbidity and mortality. Type 2 diabetes mellitus (T2DM) is a major risk factor for developing macrovascular events, including atherosclerosis, myocardial infarction (MI), stroke and peripheral vascular disease.5 According to International Diabetes Federation (IDF), it is difficult to estimate the global burden of heart disease in people with diabetes, due to lack of data and standardization. Only 41 countries worldwide have high-quality data on heart disease in people with diabetes, and even in these countries there are diverse definitions and classifications of heart and vascular disease. Overall, of studies of middle-aged people (mean age 50 to 69 years) with diabetes living in high- and middle-income countries, 14 to 47 per 1,000 had a CVD event each year, of which 2 to 26 per 1,000 were a coronary artery disease event each year and 2 to 18 per 1,000 were a stroke each year. Among them, 41% had a prior CVD event, approximately 20% had coronary artery disease and 6% had a history of stroke. Middle-aged people with type 2 and unspecified diabetes, 2 to 27 people out of 1,000 died from CVD each year. Of these, 2 to 7 deaths were from coronary artery disease and 1 to 9 deaths were from stroke. In general, in younger people with T1DM living in high- and middle-income countries (mean age of 25 to 44 years), 7% had a prior CVD event. Up to 16% of younger people with T1DM had a history of CVD, which included stroke, coronary artery disease, and peripheral artery disease. Further studies of younger people with T1DM, 0.3 to 5 people out of 1,000 died from CVD each year and there was a lack of data for people with diabetes living in low-income countries. The prevalence increased with age, and there was substantial variation between regions.1 However, age is a determining factor for cardiovascular event, and the risk of death from CVD is 2 to 4 times higher than in adults without diabetes.5
Metabolic Changes: Impact on CVD in Diabetic Patient

Clustered metabolic disorders i.e, the metabolic syndrome (hyperglycemia, dyslipidemia, and hypertension) contribute to the development and progression of CVD. Genetic susceptibility and environmental factors, including poor nutrition, obesity, and lack of physical activity, also play a significant role in developing CVD. Mature adipocytes produce several adipokines (proinflammatory mediators), including C-reactive protein (CRP), interleukin-6, tumor necrosis factor-\(\alpha\), visfatin, leptin, resistin, angiotensinogen, and plasminogen activator inhibitor-1 (PAI-1), that are associated with developing CVD. Endothelial dysfunction is one of the earliest events in the pathogenesis of CVD. The endothelium is an active organ that regulates multiple vascular functions. The proinflammatory state has been directly linked to insulin resistance and atherogenesis. A number of studies have shown that CRP is a strong predictor of cardiovascular events. Insulin resistance and several other factors related to central adiposity have been implicated in endothelial dysfunction. Hyperglycemia induces free radical production and increases superoxide production and oxidative stress, which contributes to atherogenesis. Hyperglycemia also augments the expression of adipokines, further inducing adipokine-related endothelial dysfunction. Emerging data continue to support the proposal that abdominal obesity increases CVD risk via production of adipokines, which appear to play a central role and may serve as the cellular link mediating both the metabolic syndrome of insulin resistance and the endothelial dysfunction present in the obese state. Treatment that is focused on reducing total body and visceral fat may help reverse the metabolic and vascular abnormalities. Studies have shown that lifestyle interventions resulting in weight loss and increased physical activity lead to decreased inflammatory proteins and reduced insulin resistance.5

Diabetic Cardiomyopathy

One reason for the poor prognosis in patients with both diabetes and ischemic heart disease seems to be an enhanced myocardial dysfunction leading to accelerated heart failure. Thus, patients with diabetes are unusually prone to congestive heart failure. Several factors probably underlie diabetic cardiomyopathy: severe coronary atherosclerosis, prolonged hypertension, chronic hyperglycemia, microvascular disease, glycosylation of myocardial proteins, and autonomic neuropathy. Improved glycemic control, better control of hypertension, and prevention of atherosclerosis with cholesterol-lowering therapy may prevent or mitigate diabetic cardiomyopathy.

Stroke

Mortality from stroke is increased almost 3-fold when patients with diabetes are matched to those without diabetes. The most common site of cerebrovascular disease in patients with diabetes is occlusion of small paramedial penetrating arteries. Diabetes also increases the likelihood of severe carotid atherosclerosis. Patients with diabetes, moreover, are likely to suffer irreversible brain damage with carotid emboli that otherwise would produce only transient ischemic attacks in persons without diabetes. Approximately 13% of diabetic patients >65 years old have had a stroke.

Renal Disease

Renal disease is a common and often severe complication of diabetes. Approximately 35% of patients with type 1 diabetes of 18 years’ duration will have signs of diabetic renal involvement. Up to 35% of new patients beginning dialysis have T2DM. For patients with diabetes who are on renal dialysis, mortality rates probably exceed 20% per year. When diabetes is present, CVD is the leading cause of death among patients with ESRD (End-stage renal disease).

Diabetes and Specific CVD

Atherosclerotic Coronary Heart Disease

Both T1DM and T2DM are independent risk factors for Coronary Heart Disease (CHD). Moreover, myocardial ischemia due to coronary atherosclerosis commonly occurs without symptoms in patients with diabetes. As a result, multivessel atherosclerosis often is present before ischemic symptoms occur and before treatment is instituted. A delayed recognition of various forms of CHD undoubtedly worsens the prognosis for survival for many diabetic patients.2

Risk Factors for Concomitant Diabetes and CVD

Obesity

Obesity is common in patients with diabetes mellitus (DM), particularly T2DM, and is associated with an increased risk of CVD. One possible mechanism linking DM and obesity with subsequent CVD is low-grade inflammation. Diabetes mellitus and insulin resistance are associated with the overexpression of many cytokines by adipose tissue.
including tumor necrosis factor-α, interleukin (IL)-1, IL-6, leptin, resistin MCP-1, PAI-1, fibrinogen and angiotensin. The over expression of these cytokines contributes to increased inflammation and lipid accumulation, which have a deleterious effect on blood vessels and can lead to the development of endothelial dysfunction, MI and cardiomyopathy.4

**Hypertension**

Hypertension is very common among patients with T1DM and T2DM, with prevalence rates of 30% and 60%, respectively.4 Hypertension among diabetic patients is closely tied to the development of diabetic nephropathy (DN). With DN, renal cells are stimulated by hyperglycemia, leading to the production of humoral mediators, cytokines, and growth factors. The production of these factors is often responsible for structural alterations seen in the glomeruli of diabetic patients including hyaline arteriolosclerosis (primarily of the efferent arteriole), increased collagen deposition of the extracellular matrix, and increased permeability of the glomerular basement membrane.

**Dyslipidemia**

Diabetic patients are at increased risk of developing dyslipidemia. One mechanism underlying this connection is increased free fatty-acid release present in insulin-resistant fat cells. High levels of free-fatty acids promote triglyceride production, which in turn stimulates the secretion of apolipoprotein B (ApoB) and very LDL (VLDL) cholesterol. High levels of ApoB and VLDL have both been tied to increased risk of CVD.

**Cigarette Smoking**

Cigarette smoking is a leading risk factor for CVD. Patients with diabetes who are smokers are doubly at risk. Nicotine decreases insulin sensitivity, directly or indirectly. Also smoking increases circulating free fatty acid levels, and this is an additional negative factor for the insulin-mediated glucose uptake. Diabetic patients who are current smokers should be proposed a planned smoking cessation program that includes pharmacological treatment if it is necessary.3

**Cardiovascular Disease Risk Reduction**

Type 2 diabetes mellitus can be viewed as the end product of years of metabolic stress accompanying a state of insulin resistance. It seems that in patients with insulin resistance, the “clock starts ticking” for acceleration of atherosclerosis long before the onset of hyperglycemia. Thus, early detection of the risk factors associated with the metabolic syndrome is needed for institution of appropriate primary prevention measures in patients at risk for diabetes. Clinical evidence of insulin resistance includes abdominal obesity (or borderline abdominal obesity), high-normal blood pressure (or mild hypertension), high-normal triglycerides, reduced HDL cholesterol, borderline high-risk LDL cholesterol, and in some patients, impaired fasting glucose (IFG). The detection of IFG seems particularly significant; it usually signifies long-standing insulin resistance and is a strong risk factor for type 2 diabetes mellitus.2 Some large randomized control trials such as the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Post Trial Observational Study) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) trials reported that tight glycemic control may not provide any reduction in subsequent CVD and may actually be harmful in patients who were slightly older and with a longer duration of diabetes. This might reveal that treating hyperglycemia aggressively in high risk patients with longer-standing DM is too late to have a clinically significant impact, and that earlier, aggressive treatment among patients shortly after DM diagnosis may be more beneficial.4 The American Heart Association and the American Diabetes Association issued a combined set of key specific recommendations (table 1.1), which is very much focused on cardiovascular risk reduction in diabetic patient.

**Empagliflozin- New Hope for CV Risk Reduction**

Empagliflozin is a SGLT-2 inhibitor (Sodium glucose co-transporter 2) that has been approved for type 2 diabetes mellitus by US FDA in August 2014. Given as either monotherapy or as an add-on therapy, the drug is reported to reduce glycated hemoglobin levels in patients with T2DM. It reduces rates of hyperglycemia in patients with T2DM by decreasing renal glucose reabsorption, thereby increasing urinary glucose excretion. Furthermore, empagliflozin is associated with weight loss and reductions in blood pressure without increases in heart rate. Empagliflozin also has favorable effects on markers of arterial stiffness and vascular resistance, visceral adiposity, albuminuria, and plasma urate. A recent trial of EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in T2DM Patients-Removing Excess Glucose) showed a convincing effect of empagliflozin on CVD outcomes. The trial examined the effects of empagliflozin, as compared with placebo, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care. A total of 7020
Table 1.1: Current Recommendations for CVD Risk Factor Management in Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relevant Statement or Guideline</th>
<th>Specific Recommendation</th>
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<tbody>
<tr>
<td>Nutrition</td>
<td>Nutrition Therapy Recommendations for the Management of Adults With Diabetes</td>
<td>Reduction of energy intake for overweight or obese patients. Individualized medical nutrition therapy for all patients with diabetes mellitus. Carbohydrate monitoring as an important strategy for glycomic control. Consumption of fruits, legumes, vegetables, whole grains, and dairy products in place of other carbohydrate sources. Mediterranean-style dietary pattern may improve glycomic control and CVD risk factors. Limit of sodium to &lt;2300 mg/d, similar to recommendations for the general population.</td>
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<tr>
<td>Obesity</td>
<td>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</td>
<td>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. For patients with BMI ≥40 kg/m² or BMI ≥35 kg/m² 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.</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>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) Standards of Medical Care in Diabetes—2015</td>
<td>Lower A1c to ≤7.0% in most patients to reduce the incidence of microvascular disease; this can be achieved with a mean plasma glucose of 8.3–8.9 mmol/L (&lt;150–160 mg/dL); ideally, fasting and premeal glucose should be maintained at &lt;7.2 mmol/L (&lt;130 mg/dL) and postprandial glucose at &lt;10 mmol/L (&lt;180 mg/dL). More stringent A1c targets (eg, &lt;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. Less stringent A1c goals (eg, &lt;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.</td>
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<tr>
<td>Blood pressure</td>
<td>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 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) Standards of Medical Care in Diabetes—2015</td>
<td>For most individuals with diabetes mellitus, achieve a goal of &lt;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. Pharmacological therapy should include a regimen with either an ACEI or an ARB; if 1 class is not tolerated, the other should be substituted. For patients with CKD, antihypertension treatment should include an ACEI or ARB. 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 &lt;140 mm Hg but that lower systolic targets (eg, &lt;130 mm Hg) may be appropriate for certain individuals such as younger patients if it can be achieved without undue treatment burden.</td>
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<tr>
<td>Cholesterol</td>
<td>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 Standards of Medical Care in Diabetes—2015</td>
<td>Patients with diabetes mellitus between 40 and 75 y of age with LDL-C &gt;70 and 189 mg/dL should be treated with a moderate-intensity statin†. 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. Among individuals with diabetes mellitus who are &lt;40 or &gt;75 y of age, practitioners should evaluate the benefit of statin treatment. Evaluate and treat patients with fasting triglycerides &gt;500 mg/dL.</td>
</tr>
</tbody>
</table>

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; A1c, 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%.
patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; \( P = 0.04 \) for superiority). There were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). Over the last decade many glucose-lowering agents have been tested for their safety and efficacy in T2DM with CVD. Noteworthy, most of these studies failed to show a significant benefit in terms of CV morbidity and mortality, despite intensive glycemic control. From the cardiologists’ perspective, empagliflozin could be viewed as a CV drug that also has a beneficial effect on reducing hyperglycemia in diabetes patient.8

**Future Directions**

While there have been many trials that have helped further the understanding of DM as it relates to CVD, further research is required to better identify and quantify CV risk in patients with DM. Determining how glycemic control relates to CVD is another area where additional research is needed. There is some evidence that improved glycemic control does in fact improve CV outcomes in patients with DM. One study even found that HbA1c in non-diabetic patients is an independent predictor of coronary artery disease and its severity which would suggest that glycemic control is critical to managing CV health in all patient populations. More studies are needed to better understand the relationship between glycemic control and development of CVD and determine if the onset and duration of treatment matters in the reduction of CV events in patients with DM. It is also necessary to determine what the best treatment is to decrease the risk and severity of cardiomyopathy in patients with DM. It is also needed to better understand how CV risk factors including dyslipidemia, obesity and blood pressure should be monitored and managed in diabetic patients. In addition, the role of HDL on CV health is complicated, and it is necessary to determine if pharmacological agents designed to increase HDL can provide clinical benefit in diabetic patients. The effect of weight loss in patients with DM is also somewhat unclear as to if, and how much, weight loss is necessary to achieve clinically significant improvements in CV outcomes and what the best treatment method is to reach that weight loss goal.4

**Conclusion**

Diabetes mellitus has reached epidemic proportions, resulting in increased morbidity and mortality due to concomitant CVD. In fact, on the basis of the data from the IDF, the global prevalence of type 2 diabetes mellitus has continued to increase at a rapid pace. Cardiovascular disease can be prevented or delayed by controlling blood glucose, blood pressure and cholesterol, as well as by smoking cessation, eating healthily and increasing physical activity. Drug therapy that is safe and effective, tolerable and acceptable to the patient should be selected. Empagliflozin that has been shown to demonstrate beneficial CV outcomes in patients with T2DM, should be considered as a promising drug.

**References**

2. American Heart Association (1999). Diabetes and Cardiovascular Care, A Statement for Healthcare Professionals From the American Heart Association. (CIR.100.10.1134). Retrieved from: http://circ.ahajournals.org/content/100/10/1134.long