REVIEW

Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research

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Abstract
The incidence of diabetes mellitus (DM) continues to rise and has quickly become one of the most prevalent and costly chronic diseases worldwide. A close link exists between DM and cardiovascular disease (CVD), which is the most prevalent cause of morbidity and mortality in diabetic patients. Cardiovascular (CV) risk factors such as obesity, hypertension and dyslipidemia are common in patients with DM, placing them at increased risk for cardiac events. In addition, many studies have found biological mechanisms associated with DM that independently increase the risk of CVD in diabetic patients. Therefore, targeting CV risk factors in patients with DM is critical to minimize the long-term CV complications of the disease. This paper summarizes the relationship between diabetes and CVD, examines possible mechanisms of disease progression, discusses current treatment recommendations, and outlines future research directions.

Key words: Diabetes mellitus; Cardiovascular disease; Mechanism; Treatment

Core tip: The link between diabetes and cardiovascular disease (CVD) is summarized and discussed in detail with a focus on growing prevalence, mechanisms of disease progression and current treatment of CVD in diabetic patients. Directions of future research are also examined.

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INTRODUCTION

The incidence of diabetes mellitus (DM) is increasing substantially worldwide. Over the past three decades, the global burden of DM has swelled from 30 million in 1985 to 382 million in 2014, with current trends indicating that these rates will only continue to rise[1]. The latest estimates by the international diabetes federation project that 592 million (1 in 10 persons) worldwide will have DM by 2035[2]. While the rates of both type 1 DM (T1DM) and T2DM are growing, T2DM has a disproportionately greater contribution to the rising prevalence of DM globally compared to T1DM[1]. One consequence of the growing rates of DM is a considerable economic burden both for the patient and the healthcare system. In the United States, the total cost of DM averages $2108/patient per year, which is nearly twice that of non-diabetic patients[3]. The economic burden associated with DM is substantial both in terms of the direct costs of medical care as well as indirect costs of diminished productivity tied to diabetes related morbidity and mortality[4]. The direct costs of DM are primarily attributed to both macrovascular and microvascular complications such as coronary artery disease, myocardial infarction, hypertension, peripheral vascular disease, retinopathy, end-stage renal disease and neuropathy[3,4].

A close link exists between DM and cardiovascular disease (CVD). CVD is the most prevalent cause of mortality and morbidity in diabetic populations[5]. CVD death rates in the United States are 1.7 times higher among adults (> 18 years) with DM than those without diagnosed DM, largely due to an increased risk of stroke and myocardial infarction (MI)[6]. This increased risk of CVD mortality in diabetic patients is found in both men and women. The relative risk for CVD morbidity and mortality in adults with diabetes ranges from 1 to 3 in men and from 2 to 5 in women compared to those those without DM[7].

Proper control and treatment of DM is critical as both the prevalence and economic burden of the disease continue to mount. As CVD is the most prevalent cause of mortality and morbidity in patients with DM, a primary goal of diabetes treatment should be to improve the cardiovascular (CV) risk of diabetic patients. However, one challenge associated with treating DM and reducing CV events is the complex and multifaceted nature of the relationship linking DM to CVD. CV risk factors including obesity, hypertension and dyslipidemia are common in patients with DM, particularly those with T2DM. In addition, studies have reported that several factors including increased oxidative stress, increased coagulability, endothelial dysfunction and autonomic neuropathy are often present in patients with DM and

may directly contribute to the development of CVD[5]. Collectively, the high rates of CV risk factors and direct biological effects of diabetes on the CV system place diabetic patients at increased risk of developing CVD, and contribute to the increased prevalence of MI, revascularization, stroke and CHF[5,8]. Due to the complexity and numerous mechanisms linking DM to CVD, it is crucial to focus treatment to what will have the greatest clinical impact on improving CV outcomes. This paper examines the mechanisms linking DM to CVD as well as current treatment recommendations and future research in diabetes management.

CV RISK FACTORS AND CVD

Obesity

Obesity is common in patients with 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[9]. DM 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[10]. The overexpression 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 (CMP)[5,11-14]. Diabetic patients also have increased amounts of C-reactive protein (CRP), which may contribute to endothelial dysfunction. Many studies have demonstrated that CRP impairs endothelial production of nitric oxide (NO) and prostacyclin, which are vital to vessel compliance. CRP has also been shown to increase the uptake of oxidized low-density lipoprotein (LDL) in coronary vasculature walls, which can contribute to endothelial dysfunction as well as the development of atherosclerotic plaques[14]. Patients with DM also have decreased adiponectin production, which may result in diminished endothelial function[10]. Adiponectin helps limit endothelial dysfunction by increasing NO production and reducing the expression of adhesion molecules. Adiponectin is also protective in the atherosclerotic process by inhibiting LDL oxidation[15]. This increase in atherosclerotic plaque can place diabetic patients at a heightened risk of MI. In particular, increased levels in the inflammatory cytokine IL-1, as seen in patients with DM, can contribute to the destabilization of atheromatous plaques and subsequent MI[11]. Insulin resistance is also associated with an elevation of plasma free fatty acids, leading to increases in muscular triglycerides stores, hepatic glucose production, and increased insulin production in patients with T2DM[16]. Insulin resistance has also been linked to CMP in diabetics *via* cardiomyocyte hypertrophy and contractile dysfunction[16,17].

Hypertension

Hypertension is very common among patients with

T1DM and T2DM, with prevalence rates of 30% and 60%, respectively[5]. Hypertension among diabetic patients is closely tied to the development of diabetic nephropathy (DN)[18]. 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[19]. These structural changes increase filtration pressure and often lead to microalbuminemia with a compensatory activation of the renin-angiotensin system (RAAS). Chronic activation of the RAAS often progresses to hypertension, placing added stress on the glomeruli and causing additional damage to the nephrons of diabetic patients. If left untreated, DN can progress to a nephrotic syndrome, characterized by proteinuria, a hypercoagulable state (due to loss of ATIII) and hyperlipidemia, which may contribute to the increased risk of CVD seen in diabetic patients with renal dysfunction[20,21].

Dyslipidemia

Diabetic patients are at increased risk of developing dyslipidemia[22]. 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[23-26]. In addition to high ApoB and VLDL, hyperinsulinemia is associated with low high-density lipoprotein (HDL) cholesterol levels[27]. Hyperglycemia may also negatively impact lipoproteins (particularly LDL and VLDL) through increased glycosylation and oxidation, decreasing vascular compliance and facilitating the development of aggressive atherosclerosis[28]. High circulating FFA's and triglycerides, increased stimulation of ApoB and VLDL cholesterol, decreased HDL levels and lipoprotein modification have all been appreciated in patients with DM and likely contributes to the high prevalence of CVD in diabetic patients.

Diabetic cardiomyopathy

DM appears to contribute directly to the development of CMP, rather than solely *via* coronary atherosclerosis and hypertension[29]. This diabetic CMP has been described in many noninvasive studies and includes changes that occur in LV structure and cardiac function of diabetics. Specifically, diabetics tend to have greater cardiac mass, particularly LV mass, than those without DM[30,31]. This may be related to an increased adipocyte release of cytokines such as leptin and resistin which have hypertrophic effects on cardiomyocytes[12,13]. One study looking at a multi-ethnic population found that the likelihood of having LV mass that exceeds the 75th

percentile is greater in patients with T2DM, even after adjusting for covariates[32]. Patients with DM also tend to have a slightly diminished diastolic function compared to nondiabetics[33-35]. One possible mechanism could be that increased triglyceride synthesis in patients with DM leads to increased myocardial triglyceride content[36]. Increased cardiac triglyceride accumulation is associated with lipotoxicity and altered calcium hemostasis in myocardium, both of which negatively impact diastolic function[37-39]. This could help explain the finding that 40%-75% of individuals with DM and no signs of overt coronary artery disease (CAD) suffer from diastolic dysfunction[34,35]. Subtle abnormalities in systolic function have also been observed in patients with DM using tissue Doppler imaging and Doppler strain analysis of peak systolic velocity[40-44]. This systolic dysfunction may be related to impaired myocardial sympathetic innervation and impaired contractile reserve[45]. In addition, interstitial fibrosis with increased collagen deposition has been observed in patients with DM and may negatively contribute to the diminished cardiac function seen in diabetics[46]. It is likely that many of the mechanisms that contribute to reductions in systolic and diastolic function seen in diabetic patients also place them at an increased risk of heart failure (HF)[47,48]. The prevalence of HF, particularly heart failure and preserved ejection fraction, is higher in diabetic patients (16%-31%) than the general population (4%-6%)[49]. While some of the difference may be accounted for by traditional CV risk factors, DM may independently alter cardiac structure and function by promoting hypertrophy and fibrosis[50].

Cardiovascular autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN) is common among patients with DM and is correlated with an increased 5-year mortality rate from CVD[51]. The clinical manifestations of CAN are resting tachycardia, postural hypotension, exercise intolerance, abnormal coronary vasomotor regulation, increased QT interval, and perioperative instability. Collectively, the clinical manifestations of CAN are related to an increased risk of renal disease, stroke, CVD and sudden death[52]. The development and progression of CAN is likely related to dysregulation of the autonomic nervous system (ANS) with increased sympathetic activity and elevated inflammatory markers. As the ANS is responsible for maintaining the activity of the sinus node, end diastolic volume, end systolic volume and systemic vascular resistance, ANS dysfunction can lead to arterial stiffness, left ventricular hypertrophy and ventricular diastolic dysfunction[53]. Incidence of CAN increases with age and inadequate glycemic control, which places patients with DM at higher risk of developing both CAN and CVD[54].

Myocardial infarction and DM

Diabetes is a major risk factor for the development of CAD with a higher incidence of MI in patients with DM than those without[55,56]. In addition, following a MI, diabetic patients have higher rates of morbidity,

mortality and re-infarction than non-diabetics, with one-year mortality rates of nearly 50%[57]. Although the exact pathophysiology of CAD progression in patients with DM has not yet been determined, the most recent studies postulate that the underlying atherosclerotic process is similar between those with and without DM. It is thought that the higher incidence of myocardial infarction in patients with DM is attributable to increased coagulability[58]. Many studies have found that diabetics have increased expression of glycoprotein ⅡB/ⅢA receptors and vWF, which are responsible for platelet activation[59,60]. Patients with DM also have increased plasminogen activator inhibitor type 1 which could decrease fibrinolysis, increase thrombus formation and accelerate plaque formation[61]. Finally, diabetic patients also tend to have decreased circulating anti-coagulants such as protein c and antithrombin Ⅲ due in a large part to the proteinuria present with DN[62]. Collectively, these factors place patients with DM in a prothrombotic and procoagulant state, which may account for the higher rates of MI seen in diabetic patients.

Silent myocardial ischemia may also contribute to the higher rates of MI seen in diabetic patients. Ischemia and subsequent angina often serves as an early warning system to patients developing obstructive CAD[63]. However, those with silent ischemia are often asymptomatic and diagnosed later into the progression of CAD, which is associated with higher rates of MI-related mortality and morbidity[64]. Silent ischemia is far more prevalent in patients with DM (10%-20%) than those without DM (1%-4%). This disparity may be responsible for the observation seen in some angiographic studies where CAD was usually more advanced at the time of diagnosis in diabetic patients[65,66]. Diabetic neuropathy is one factor that may explain the increased incidence of silent ischemia in patients with DM[67,68].

TREATMENT

As CVD is the most prevalent cause of mortality and morbidity in patients with DM, effective treatment is critical to lower the subsequent risk of CV events, particularly MI, CAD, stroke and CHF in diabetics. Suboptimal glycemic control, obesity, hypertension, dyslipidemia and autonomic dysfunction are common CV risk factors among diabetic patients, placing them at heightened risk of CV complications. Therapy that is targeted to modify these risk factors can improve CV outcomes, but this can be a challenging to achieve. The guidelines pertaining to these risk factors typically vary from the guidelines for non-diabetic patients and the recommendations often change or differ depending on what organization publishes them. In addition, the research on how these different risk factors affect the CV risk profile of diabetics can be unclear, and at times, contradictory. The purpose of this section is to provide the most recent guidelines for the treatment of glycemic control, hypertension, dyslipidemia and autonomic dysfunction in patients with DM, and also describe the

research that pertains to each of these topics.

GLYCEMIC CONTROL

As many studies have linked poor glycemic control to worse CV outcomes, current treatment recommendations for patients with DM place a heavy emphasis on closely monitoring and controlling glycemic levels in an effort to improve cardiac outcomes. The exact glycemic level that should be targeted for diabetics, however, is controversial and varies depending on which organization is making the guideline. For example, the current recommendation by the American Association of Clinical Endocrinologists Guidelines has a goal hemoglobin A1c (HbA1c) of less than or equal to 6.5%, and encourages providers to treat patients with an A1c value greater than 6.5% with a combination of lifestyle modification, weight loss and pharmacological agents[69]. The ACC/AHA have a slightly more relaxed A1c goal of less than 7% for non-pregnant patients with T1DM or T2DM in order to reduce the risk of microvascular or macrovascular complications. In addition, ACC/AHA also qualifies their recommendation by including a recommendation that an A1c goal of greater than 7 may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbidities, or for those with long-standing diabetes. The recommendation also states that an A1c goal lower than the general goal of less than 7.0% may be beneficial for certain diabetic patient populations including those with a short duration of diabetes, long life expectancy, and no CVD[70]. The VA/DoD guidelines use a more individualized algorithm for determining an appropriate A1c goal for diabetic patients. This guideline range from a target A1c of < 7 to < 9 depending on the patient's current health status, comorbid conditions, life expectancy, risk of hypoglycemia and duration of diabetes status[71].

CV OUTCOMES

There have been many studies that have investigated the effect of intensive treatment of hyperglycemia on CV outcomes in patients with diabetes. The UKPDS trial was one of the first multi-center, randomized control trials to investigate the effect of intensive glycemic control in patients with recently diagnosed T2DM. Patients were either randomized to "conventional" or "intensive" glycemia-lowering therapy and were followed for 10 years. The intensive glycemic group reduced HbA1c by 11% over 10 years (median 7.0%) as compared to the group treated with conventional therapy who did not have a significant change in their HbA1c (median 7.9%). The primary effect seen in the group with tighter glycemic control was a 12% reduction in all diabetes-related endpoints and a 25% reduction in microvascular disease (primarily through decreased retinopathy). In addition, the intensive therapy group trended towards a

decrease in macrovascular disease although it was not statistically significant[72].

Another large study that investigated the effect of tight glycemic control in patients with T2DM was the VADT trial. The population for this study consisted primarily of older (mean age 60.4 years) adult men with poorly controlled T2DM (average HbA1c of 9.4%) and an average duration of disease of 11.5 years. The subjects were randomized to either "intensive" or "conventional" glycemia-lowering therapy and were followed for 5.6 years. The group with the tighter glycemic control did have a significantly greater decrease in A1c levels over the course of the study (6.9% *vs* 8.4%), but there was no significant decrease in MI or all cause mortality in the "intensive" therapy group as compared to the "conventional" therapy group[73].

The ADVANCE trial placed a focus on the vascular effects of intensive glycemic therapy in adults with T2DM. This large multi-center randomized control trial recruited T2DM patients with a history of major macrovascular or microvascular disease from 215 collaborating centers in 20 countries. Subjects were randomized to either an "intensive" or "standard" glycemia-lowering strategy and followed for 5 years. The intensive glycemic therapy group was treated to an HbA1c of less than or equal to 6.5%. The group randomized to the tighter glycemic control did have a significantly greater reduction in HbA1c (6.5% *vs* 7.3%) and experienced a 23% reduction in microvascular events (primarily nephropathy). However, there was no difference between the groups in MI or all cause mortality and the group with 'intensive' therapy had increased rates of severe hypoglycemia hospitalization[74].

The ACCORD trial was conducted concurrently to the ADVANCE trial and focused primarily on whether intensive glycemic control reduced to risk of CV events. This multi-center randomized control trial investigated if very tight glycemic control (less than or equal to an HbA1c of 6%) had lower rates of nonfatal MI, nonfatal stroke and CV death than standard glycemic control (HbA1c of 7%-7.9%) in older adults. The subjects were followed for an average of 3.4 years and the group with the tighter glycemic control did achieve a significantly lower HbA1c than those with standard treatment (7.3% *vs* 6.5%). The intensive glycemic control group had slightly lower rates of nonfatal MI, but after 3.7 years the trial was stopped early because the intensive treatment group had increased rates of all-cause and CV mortality. The group with tight glycemic control also had increased weight gain, and risk of hypoglycemia as seen in the ADVANCE trial[75].

DCCT and the long-term follow-up trial EDIC investigated how strict glycemic control with intensive therapy effected CV outcomes in patients with T1DM. These trials randomized young (ages 13-39 years) patients with T1DM to either "intensive" or "conventional" glycemic therapy with an HbA1c goal of 7% in the group for those in the "intensive" treatment group. The primary finding of the DCCT trial was that after 10 years of follow-up, the group with strict glycemic control had a 70% decrease in the number of microvascular complications, particularly retinopathy. In addition, the long-term follow-up study, EDIC, found a 42% reduction in CV events in the group with intensive glycemic treatment as compared to the conventional glycemic therapy[18,76].

While it does appear that a link exists between glycemic control and CV outcomes in diabetic patients, the findings thus far on the effect of tight glycemic control on CVD are conflicting. Current studies fail to show that intensive glycemic control (HbA1c $\leqslant$ 6.5%) has a significant CV benefit compared to standard glycemic control targets (HbA1c of 7%-7.9%) in patients with T2DM. While there may be a small reduction in the number of microvascular events in T2D patients with the tighter glycemic control, there does not seem to be a sizeable benefit in the rates of all-cause and CV-specific mortality. Furthermore, very tight glycemic control (HbA1c $\leqslant$ 6%), as seen in the ACCORD trial, may place patients at additional risk of hypoglycemia, weight gain and all cause mortality[75]. In patients with T1DM, tighter glycemic control does appear to be beneficial. The DCCT and EDIC trials do suggest that intensive glycemic therapy (goal HbA1c $\geqslant$ 7%) can help reduce rates of microvascular and macrovascular disease in T1D[18,76].

One potential interpretation of the studies thus far is that the concurrent CV risk factors present in diabetics may overwhelm any benefit that intensive treatment of hyperglycemia can provide in reducing risk. Thus, diabetic patients who achieve tighter glycemic control earlier during their disease course and prior to the development of other CV risk factors may see the greatest benefit from more intensive therapy in terms of CV outcomes. For this reason, many of the new recommendations look to tailor A1c goals to the individual patient as opposed to a single A1c cutoff for all diabetic patients. The ACC/AHA and VA/DoD, for example, adjust their glycemic goals based on factors such as age, years with the disease and CV risk[70,71]. While further studies are needed to determine what the best glycemic treatment goal is for these different patient populations, adjusting the target A1c depending on the individual's current level of CVD risk may provide benefit to diabetic patients.

Obesity

Obesity is a common comorbidity of DM, particularly T2DM, and is linked with higher rates of CV morbidity and mortality. Thus, current treatment recommendations encourage weight loss in overweight and obese patients with DM to improve their CV risk profile and decrease the risk of CVD. The recommendation is for 5% weight loss over 4 years in diabetic patients that are overweight or obese. A "moderate" amount of evidence suggests that 5% weight loss by lifestyle intervention is associated with an increase in HDL-c, a reduction in triglycerides and a decrease in newly prescribed lipid lowering medications in diabetic patients. In addition, there is a "high" level of evidence suggesting that orlistat results in

2-3 kg of weight loss in overweight and obese diabetic patients at 1 and 2 years, and is associated with greater reductions in fasting blood glucose and HbA1c. These recommendations were graded as high, moderate, or low on the basis of scientific methodology, scientific strength, and consistency of results[77].

As obesity is a major risk factor both for CVD and T2DM, many studies have investigated the efficacy of weight loss in reducing the development and severity of DM. Some studies have focused on body weight reduction in pre-diabetic patients in order to decrease the incidence of subsequent DM. Of note, the diabetes prevention program (DPP) and finnish diabetes pre-vention studies evaluated the effect of behavior modification on weight loss and consequent risk of developing diabetes in pre-diabetic adults. Both studies yielded similar results in that those randomized to the lifestyle intervention group had significantly greater weight loss and reduced risk of developing diabetes as compared to the control group[78,79]. Other studies have looked at methods for attaining weight loss and improving the CV risk profile of patients who are already diabetic. A variety of techniques including intensive lifestyle intervention, weight loss medications and bariatric surgery were effective in achieving weight loss and improving the CV risk profile of diabetic patients through improved glycemic control, blood pressure and cholesterol levels[80-82].

Although many studies have shown that weight loss can be achieved in diabetic patients, there is mixed evidence as to whether weight loss in these patients actually reduces subsequent CV morbidity and mortality. Thus far, there has been mixed evidence if modest weight loss in patients with DM does improve their CV risk. While the SCOUT trial found that modest weight loss could improve 5-year CV mortality rates among diabetic patients, the Look AHEAD trial did not find that weight loss had any effect on CV mortality, MI, stroke, or angina hospitalization after 9.6 years of follow-up[83,84].

The current recommendation for overweight and obese patients with DM is a goal weight loss of 5%[77]. Studies thus far have demonstrated that this goal is attainable both in pre-diabetic and diabetic patients through a variety of techniques including intensive behavioral modification therapy, pharmacological agents and bariatric surgery. In addition, all of these methods of weight loss appear to either decrease the rates of incident DM in pre-diabetic patients, or improve the CV risk profile of diabetic patients[78-82]. However, it is unclear whether modest weight loss in diabetic patients translates to a decrease in CVD[83,84].

It is possible that the CV risk profile is too high in older adults with DM for modest weight loss to make a significant improvement in CV outcomes. It might be more advantageous to focus obesity treatment efforts on pre-diabetics before they develop DM. Programs such as the DPP have demonstrated that weight loss can decrease the rate of incident diabetes, but further research is needed to determine if modest weight loss in pre-diabetic patients results in improved CV morbidity and mortality[78]. It is also possible that while modest weight loss does seem to improve the CV risk profile of patients with DM, even greater weight loss is necessary to see more definitive improvements in the rates of CV events. Further investigation into the effects of weight loss greater than 5% on CVD in diabetic patients may help identify the existence of a dose effect with weight loss and CV health.

Hypertension

Since hypertension is a common comorbidity of patients with DM and a major risk factor for CVD, the current treatment recommendations strongly encourage pro-viders to lower BP in hypertensive diabetics. There are many studies that have investigated the effect of lowering blood pressure in patients with diabetes on CV outcomes. The UKPDS 38 trial examined the effect of tight control of blood pressure control (< 150/85) compared to less tight control (< 180/105) on macro-vascular and microvascular complications in patients with T2DM. After 9 years follow-up, mean blood pressure was significantly lower in the tightly controlled BP group (144/82 mmHg) compared to the patients in the less tightly controlled group (154/87 mmHg). In addition, the group with tighter BP control had a 34% reduction in macrovascular disease risk (myocardial infarction, sudden death, stroke, and peripheral vascular disease) and a 37% reduction in risk of microvascular disease (retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure) compared with the less tightly controlled BP group[85].

While many studies have shown that lowering BP in diabetics does improve CV outcomes, the ACCORD-BP trial investigated the effect of intensive BP control (systolic BP < 120 mmHg) compared to standard BP control (systolic BP < 140 mmHg) on the risk of fatal or nonfatal major CV events in patients with T2DM. After 4.7 years of follow-up, the group with intensive BP control did not have a reduction in fatal and nonfatal major CV events as compared to the standard BP control group (1.87% *vs* 2.09% per year). In addition, the intensive BP group had increased adverse events including hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema and renal failure[86].

Given the results of these trials, recent treatment recommendations indicate that, pharmacologic treat-ment should be initiated at a SBP of > 140 mmHg or a DBP of > 90 mmHg for diabetic adults between 18 and 60 years of age. For patients older than 60, the threshold to initiate treatment is a SBP of < 150 mmHg or a DBP of < 90 mmHg. The recommendation on the type of pharmacological therapy that should be used varies in the general nonblack *vs* black population. For nonblack patients with DM and hypertension, initial treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker

(ARB). For black patients with DM and hypertension, the initial treatment should include a thiazide-type diuretic or a CCB. In addition, hypertensive patients with DM and CKD should be treated with an ACE inhibitor or an ARB to improve kidney outcomes[87]. While different antihypertensive agents used to treat hypertension have varying metabolic effects, many studies, including the ALLHAT trail, found no significant difference in the risk of coronary heart disease, nonfatal myocardial infarction, total mortality, or other clinical complications attributable to the initial antihypertensive drug therapy used to treat diabetic patients[88,89]. This would suggest that metabolic differences between the various antihypertensive agents do not play a major role in the subsequent development of CVD in patients with DM. It should be noted that these recommendations have been controversial and several authors have argued that the guideline is too relaxed in the treatment of certain at-risk groups including African Americans, women and the elderly based on previous studies evaluating blood pressure control and subsequent CVD in these populations[90]. There is likely a therapeutic BP range that provides diabetic patients with a lower CV risk but also protects them from adverse events associated with hypotension. Whether the new guidelines, particularly with the increased systolic BP threshold in adults over 60 years, match this therapeutic BP range is yet to be determined. There is also little evidence as to what the proper treatment range should be for different age groups. In addition, hypertension in different racial subgroups may have different effects on CV health. Further research is needed to investigate the ideal BP range for adults of different age groups as well as different racial groups.

Dyslipidemia

Dyslipidemia is both common in patients with DM and associated with increased risk of CVD[91,92]. Health providers are encouraged to identify and aggressively treat patients with dyslipidemia to help diminish their risk of subsequent CV events. The current recommendation for treating dyslipidemia in diabetic patients varies by age and is in line with recognition that treatment with fixed-dose statins, rather to specific LDL target levels, is the validated approach from clinical trials. Accordingly, diabetic patients who are under the age of 40 are recommended to take a high-intensity statin if they have clinical evidence of atherosclerotic CVD or a LDL-c greater than 189 mg/dL. All diabetic patients over the age of 40 are encouraged to begin statin therapy. Patients over 40 with an estimated 10-year ASCVD risk greater than 7.5% are treated with a high-intensity statin, and patients with a 10-year ASCVD risk less than 7.5% are treated with a moderate-intensity statin[93].

There have been many studies conducted to determine the effect of treating dyslipidemia in diabetic patients as a means to lower CV risk. The CARDS study was the first multicenter randomized controlled trial to evaluate statin therapy prospectively in patients with T2DM. Adult patients with T2DM were randomized to either receive a placebo or 10 mg/d of atorvastatin. The median follow-up time was 3.9 years and the group treated with atorvastatin had an average 26% reduction in total cholesterol and a 40% reduction in LDL-c. In addition, the statin therapy group had a 37% reduction in CV events, a 27% reduction in all-cause mortality and a 48% reduction in stroke as compared to the group treated with the placebo. The CARDS trial was stopped early to due the significant benefit demonstrated with statin therapy[94].

After the CARDS trial found that statin therapy provided a significant CV benefit to diabetic patients, the TNT trial examined the effect of high-dose statins on CAD mortality, non-fatal MI, and fatal or nonfatal stroke in diabetic patients with T2DM. Adult patients with T2DM were randomized to receive either a high dose (80 mg/d) or low dose (10 mg/d) statin and followed on average for 4.9 years. The high dose stain group achieved a greater reduction in LDL-c (77 mg/dL *vs* 101 mg/dL) and had a greater reduction in combined CAD mortality, non-fatal MI, or fatal or nonfatal stroke (8.7% *vs* 10.9%) compared to the lower dose group. However, it was noted that the higher dose group did have a higher rate of adverse events (myalgia, persistent elevation in alanine aminotransferase, aspartate aminotransferase, or rhabdomyolysis)[95].

As many studies had demonstrated that statins, particularly high-dose statins, had CV benefit in diabetic patients, the 4D study examined the effect of statins in diabetic patients receiving hemodialysis. In the 4D trial, diabetic patients receiving hemodialysis were randomly assigned either 20 mg of atorvastatin per day or a placebo. The purpose of the study was to determine if a low-dose statin in diabetic patients with end stage renal disease lowered the rates of death from cardiac causes, nonfatal myocardial infarction, and stroke as compared to the placebo group. The group randomized to the statin therapy did have a significant reduction in their LDL-c compared to the placebo group (-42.0% *vs* -1.3%), but there was no significant difference between the groups in CV outcomes after 3.96 years of follow-up. In addition, there were significantly more cases of fatal stroke in the statin therapy group than those treated with a placebo[96].

While the previous studies had focused on reducing cholesterol in diabetic patients using statin therapy, other research groups have investigated the effect of non-statin lipid-lowering therapies on CVD in diabetic patients. For example, the FIELD trial evaluated if lowering cholesterol *via* fenofibrate therapy could improve CV outcomes in patients with DM. In the FIELD trial, diabetic patients (mean age 62 years; 63% men) were randomized to either receive a fenofibrate (200 mg/d) or a placebo and then assessed for subsequent rates of fatal coronary heart disease (CHD) or nonfatal MIs. While the group randomized to the fenofibrate therapy did reduce their cholesterol compared to the placebo group at 4 mo (total cholesterol, LDL-cholesterol, and triglycerides by 11%, 12%, and 29%, respectively),

the differences decreased between the groups as the trial continued due in a large part to patients starting additional cholesterol lowering therapies outside of the study. After a median of 5 years, the group randomized to the fenofibrate group had a combined 11% reduction in fatal CHD or nonfatal MIs, but this difference was non-significant. The fenofibrate group did however have a statistically significant reduction (24%) in nonfatal MI's compared to the placebo group[97]. In addition, since HDL has been identified in many large prospective studies to be associated with improved CV health, some research groups have investigated whether raising HDL through pharmaceutical agents reduces the risk of CV events. The HATS trial was the first to investigate the effect of increasing HDL with Niacin therapy and generated promising results on improving CV outcomes in adult patients (16% with DM). After 38 mo of follow-up, the group randomized to the niacin therapy did have a significant increase in HDL and patients with T2DM had a 13% decrease in absolute risk of CV disease[98]. Recently however, the AIM-HIGH trial found no significant clinical benefit in adding Niacin therapy to patients with atherosclerotic CVD as compared to a placebo. The trial was stopped after 3 years due to lack of efficacy; the group randomized to the niacin therapy (34% with DM) did not have a significant reduction in composite coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization (16.4% *vs* 16.2%) despite significant improvements in HDL (25% *vs* 11.8%). These findings were similar between diabetics and nondiabetics[99].

Dyslipidemia is prevalent among diabetic patients and a major risk factor for CVD[91,92]. Current treatment recommendations encourage providers to lower lipid levels in diabetic patients, primarily through the use of statins, with a dose dependent on the patient's level of risk. Some trials have also investigated if additional CV benefit can be achieved in patients with DM by combining a statin with other lipid-lowering therapies. For example, the IMPROVE-IT trial found that the combination of ezetimibe (a cholesterol absorption inhibitor) with simvastatin was superior to simvastatin alone in reducing CV events for diabetic patients with acute coronary syndrome[100]. The evidence thus far suggests that statin therapy in patients with DM is advantageous for CV health and that higher doses, as well as combined lipid-lowering therapy, can provide additional CV protection[93]. While some meta-analyses have suggested that statin therapy could be associated with increased incidence of DM, the absolute benefit of the therapy in diabetic patients largely outweighs the risk[101]. Other lipid lowering agents, such as fen-ofibrates, have not demonstrated the same level of efficacy and reductions in CV events as statins[97]. Pharmacological agents that raise HDL also appear to provide minimal, if any, CV benefit[98,99]. Further studies are necessary to better understand the role of HDL in CV health.

CAN

CAN is a common complication of diabetes and places patients with DM at increased risk of CV related morbidity and mortality. The autonomic dysfunction commonly found in diabetic patients is associated with a high risk of cardiac arrhythmias and sudden death, as well as other serious CV sequelae including silent myocardial ischemia, diabetic cardiomyopathy, stroke, and both intraoperative and perioperative CV instability. Some of the most common clinical manifestations of CAN include heart rate variability (variability in the instantaneous beat-to-beat intervals), resting tachycardia, exercise intolerance, orthostatic hypotension and abnormal blood pressure regulation[102].

Early treatment of autonomic dysfunction can slow the pathogenesis and complications of CAN[102]. Some studies have shown that tight glycemic control may play an important role in reducing the incidence of CAN in patients with DM. For example, the DCCT demonstrated that patients with better glycemic control, as measured by Hba1c, had significantly lower risk of developing autonomic dysfunction according to a CAN index[103]. While the effect of glycemic control on CAN in patients with T2DM have been less conclusive, some trials, including the Steno-2 study found that improving glucose control and other CV risk factors reduced the prevalence of CAN in T2DM patients[104]. Lifestyle interventions that focus on improving exercise endurance and promote weight loss have also improved autonomic dysfunction. Pharmacological therapy in-cluding ACE inhibitors, angiotensin receptor blockers and aldose reductase inhibitors also appear to help slow the progression of CAN[54]. In addition, IGF-1, ACE inhibitors and beta-blockers appear to be beneficial in the treatment of diabetic cardiomyopathy by slowing ventricular hypertrophy and normalizing the calcium homeostasis in diabetic cardiomyocytes[105-109]. Further studies are necessary, however, to validate what the best pharmacological treatment is for diabetic patients with CAN.

FUTURE DIRECTIONS IN THE TREATMENT OF DM

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 one another area where additional research is needed. There is some evidence that improved glycemic control does in fact improve CV outcomes patients with DM[72,73]. 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[110]. While this observational trial suggests an independent association may exist between glycemic

levels and CVD, large randomized control trials such as ADVANCE and ACCORD have shown that the effect of tight glycemic control on subsequent CVD is modest and largely attributable to coexistent traditional risk factors[73-75,110].

One possible explanation for the conflicting results surrounding the relationship between glycemic control and CVD is due to poor measurement tools. For example, fasting plasma glucose (FPG) is often used as a measure of glycemia, but studies have found a day-to-day within-person variance of 12%-15% in FPG levels of diabetic patients[111]. While the day-to-day within-person variance for HbA1c is far better (< 2%), there is evidence that HbA1c does not accurately reflect glycemic control due to biological variations and differences in RBC survival among patients[111-113]. If glycemic control does matter, properly measuring glycemia and correlating it to CV risk is essential in order to set clinically meaningful goals for patients with DM.

The duration and onset of improved glycemic control may also contribute to the progression and severity of CVD. The UKPDS demonstrated that tight glycemic control was associated with reductions in CV outcomes in middle-aged adults (median 54 years) who were recently diagnosed with DM[72]. Conversely, the ADVANCE and ACCORD trials reported that tight glycemic control may not provide any reduction in subsequent CVD and may actually be harmful in patients that were slightly older and with a longer duration of diabetes[74,75]. 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. More studies are needed to better understand the relationship between glycemic control and the development of CVD and determine if the onset and duration of treatment matters in the reduction of CV events in patients with DM.

Further research is also necessary to determine what the best treatment is to decrease the risk and severity of cardiomyopathy and CAN in patients with DM. Many studies have demonstrated that autonomic dysfunction and diabetic cardiomyopathy are disease processes that are not only common in patients with DM, but also place them at increased risk of subsequent CV complications[102]. Lifestyle modification, tighter glycemic control and pharmacological agents appear to provide some benefit in slowing the progression of CAN and diabetic cardiomyopathy[54,102-109]. However, few studies have investigated what specific therapy is most effective in treating these conditions, as well as what might be done to prevent the development of these disease processes altogether.

Additional research is also needed to better understand how traditional CV risk factors including dyslipidemia, obesity and blood pressure should be monitored and managed in diabetic patients. For example, combination therapy may be the best way to treat dyslipidemia, contrary to the current recommendation that focuses primarily on statin mono-therapy. More studies like IMPROVE-IT could help determine what therapy is most effective to manage dyslipidemia in diabetic patients[100]. In addition, the role of HDL on CV health is complicated, and further investigation 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. Five percent weight loss may not be sufficient for diabetic patients with other CV risk factors and comorbidities. Further studies are needed to determine what amount of weight loss is needed attain CV benefit, and what the best treatment method is to reach that weight loss goal. Finally, follow-up regarding the new blood pressure guidelines, particularly in adults over 60 years who now fall under the higher systolic BP threshold, will need to be closely monitored moving forward.

CONCLUSION

As the prevalence of DM continues to rise, associated CVD - through both traditional CV risk factors and the direct effects of DM on CVD - can also be expected to rise. Accordingly, proper control and treatment of DM, along with aggressive treatment of associated CV risk factors is central to curbing the growing prevalence and progression of DM and CVD. Additional research is needed to better understand the disease process and its effects on CV health in order to improve medical management and CV outcomes in diabetic patients.

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