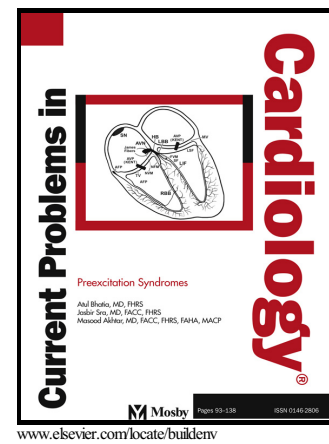


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Diabetes and heart disease; pathophysiology and prevention

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Pathophysiology and Prevention of Heart Disease in Diabetes Mellitus

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ABBREVIATIONS AND ACRONYMS:

ACC = American College of Cardiology

ACE = Angiotensin converting enzyme

ADA = American Diabetes Association

AGEs = Advanced glycation end products
AHA = American Heart Association
APOE = Apolipoprotein-E
ARB = Angiotensin receptor blocker
ASCVD = Atherosclerotic cardiovascular disease
BP = Blood pressure
CAD = Coronary artery disease
CAN = Cardiac autonomic neuropathy
CMP = Cardiomyopathy
CV = Cardiovascular
CVD = Cardiovascular disease
DCCT = Diabetes Control and Complications Trial
DKD = Diabetic kidney disease
DM = Diabetes mellitus
DPP-4 = Dipeptidyl peptidase-4
FFA = Free fatty acid
FHS = Framingham Heart Study
FPG = Fasting plasma glucose
GLP-1 = Glucagon-like peptide-1
HbA1c = Hemoglobin A1c
HDL-C = High-density lipoprotein cholesterol
HF = Heart failure
HFpEF = Heart failure with preserved ejection fraction
HFReEF = Heart failure with reduced ejection fraction
HTN = Hypertension
IR = Insulin resistance
LDL = Low-density lipoprotein
LDL-C = Low-density lipoprotein cholesterol
LV = Left ventricular/ventricle
MetS = Metabolic syndrome
MI = Myocardial infarction
NO = Nitric oxide

PAT = Pericardial adipose tissue
PCSK9 = Proprotein convertase subtilisin/kexin type 9
RAAS = Renin-angiotensin-aldosterone system
RCT = Randomized controlled trial
SBP = Systolic blood pressure
SGLT-2 = Sodium-glucose cotransporter-2
T1DM = Type 1 diabetes mellitus
T2DM = Type 2 diabetes mellitus
US = United States
UKPDS = United Kingdom Prospective Diabetes Study
VLDL-C = Very-low-density lipoprotein cholesterol

ABSTRACT

Diabetes mellitus (DM) has become a public health problem worldwide, and it has large implications for cardiovascular disease (CVD). In this article, we discuss the etiology and pathophysiology of CVD in DM including the effects of abnormal glucose homeostasis, genetic factors, epigenetics, apoptosis, common pathophysiological mechanisms shared by both DM and CVD, and contributions of other comorbidities. We then cover the pathogenesis of both atherosclerotic disease and cardiomyopathy in relation to DM. Finally, we discuss the prevention of heart disease in DM with a focus on hypertension and dyslipidemia management, weight loss, lifestyle changes, antiplatelet therapy, and glycemic control.

SCOPE OF THE PROBLEM

The aging population and global epidemic of obesity due to dietary patterns and sedentary lifestyle have led to the rising burden of diabetes mellitus (DM) worldwide. Since the 1980s, the global prevalence of DM has more than doubled in men and increased by 60% in women.¹ In the United States

(US) the prevalence of DM among adults ranges from 12% to 14% (**Figure 1**). In addition, one-third of US adults are estimated to have pre-diabetes.² The prevalence of DM worldwide was estimated as 6.4% in 2010. The number of people with DM is expected to rise to almost 600 million in the next two decades across the world.³

The prevalence of DM increases with advancing age in both genders. In the US, the prevalence of DM is 5% in individuals aged <45 years and increases to 33% in those ≥65 years of age.² Men usually have a slightly higher prevalence of DM compared to women.⁴ DM has a significant association with ethnicity. It is more commonly seen in non-Hispanic blacks (15.4%) and Mexican-Americans (11.6%) compared to whites (8.6%).⁵ It is estimated that more than one-third of US adults with DM are unaware of their diagnosis (**Figure 1**).²

DM has long been recognized as a major risk factor for cardiovascular disease (CVD). Also, DM is associated with clustering of other major CVD risk factors such as hyperlipidemia, hypertension (HTN) and obesity. Thanks to improvements in diagnostic and therapeutic modalities and health care delivery, cardiovascular (CV) morbidity and mortality has declined in the general population over the past decades. Similar trends were observed in diabetic individuals as well.^{6,7} However, despite these improvements, DM continues to be a cause of CV morbidity and mortality in all age groups and both sexes.⁸ A report from the “early period” (1950-1975) of Framingham Heart Study (FHS) demonstrated 4-fold increased risk of CVD in diabetic individuals compared to non-diabetics. However, this excess risk decreased to 3-fold in the “later period” of the study (1975-2005).⁹ A large population-based study conducted between 1997 and 2002 demonstrated that patients with DM requiring glucose-lowering agents exhibited a CV risk equivalent to non-diabetics with prior myocardial infarction (MI).¹⁰ More specifically, DM increases the risk of each component of CVD such as coronary artery disease (CAD),¹¹ heart failure (HF), atrial fibrillation,¹² and stroke.¹³ Therefore, CVD remains the leading cause of death in individuals with DM. Over 68% of diabetic individuals >65 years of age die from a form of heart disease.⁶

On average, a 50-year-old person with DM dies six years earlier compared to a counterpart without DM.¹⁴

The strong relation between DM and CVD has been a major topic of interest among clinicians and researchers. The ever growing importance of this relationship is represented by the fact that within the past decade many major society guidelines and scientific statements have been dedicated to prevention or management of CVD in individuals with DM.^{15–19}

In this review, we will explore the current state of knowledge linking DM and heart disease with a focus on pathophysiology and prevention.

CLASSIFICATION OF DIABETES MELLITUS

DM is defined as the complex dysregulation of glucose metabolism secondary to deficiencies in insulin secretion, desensitization of the insulin receptors, or a combination of both, which results in chronic hyperglycemia and subsequently leads to acute and chronic complications.²⁰ According to the American Diabetes Association (ADA), DM can be diagnosed by either fasting plasma glucose (FPG), 2-hour plasma glucose after oral glucose tolerance test and hemoglobin A1C (HbA1c).²¹ Based on the etiology, DM is categorized into four main groups: type 1 DM (T1DM), type 2 DM (T2DM), 'other specific types' of DM, and gestational DM.²²

T1DM is characterized by progressive insulin deficiency due to autoimmune destruction of pancreatic β -cells. Although T1DM may occur at any age, it typically affects young and slim individuals and present with an abrupt onset. T2DM, which comprises over 90% of DM among adults, is characterized by a combination of insulin resistance (IR) and pancreatic β -cell dysfunction in association with obesity and metabolic syndrome (MetS). T2DM is a progressive disease, and it is almost always preceded by impairment of glucose metabolism referred as pre-diabetes. Impaired glucose tolerance and impaired fasting glucose are the main manifestations of pre-diabetes.¹⁶

The clear majority of data on the relationship between DM and CVD derives from population studies and clinical trials on cohorts of either patients with T2DM exclusively or all DM patients without distinction of DM type (presumably, the majority is T2DM because of its abundance). Therefore, data on the relationship of CVD and DM types other than T2DM remains limited.

ETIOLOGY AND PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE IN DIABETES MELLITUS

Studies in the past decades have shed light into the pathophysiologic link between DM and CVD. A complex interplay between numerous pathophysiologic mechanisms underlies the increased risk of CVD in patients with DM. These mechanisms can be grouped as follows. 1) CV effects of derangements in glucose homeostasis, 2) shared common mechanisms underlying the pathogenesis of both DM and CVD, 3) contribution of other CV risk factors (such as HTN and hyperlipidemia) that commonly coexist with DM, 4) genetic and 5) epigenetic factors and 6) apoptosis.

Cardiovascular Effects of Abnormal Glucose Homeostasis

IR is the central defect in the natural history of MetS and T2DM. Classically, it refers to the inability of insulin to carry on its metabolic actions at the cellular level.²³ IR and consequent compensatory hyperinsulinemia may precede the diagnosis of T2DM by 10-20 years.²⁴ Epidemiologic data have demonstrated that IR is associated with the presence and progression of CAD even in the absence of overt DM.^{25,26} HF is a well-known insulin resistant state, and IR significantly affects prognosis in HF.²⁷ Moreover, HF contributes to IR. For instance, in patients with advanced HF, hemodynamic recovery after ventricular assist device placement have been shown to result in improvements in systemic and cardiac insulin sensitivity, glucose homeostasis and reduction of toxic lipid products.²⁸

Impaired fasting glucose has been shown to predict future CAD in some prospective epidemiological studies, such as the Heinz Nixdorf Recall Study.²⁹ However, in some other studies (such as FHS), this association became non-significant after adjustment for confounders such as obesity.³⁰ Emerging data suggests that not only the baseline status but also the dynamic nature of glucose

homeostasis abnormalities contribute to the risk of CAD. For example, a recent epidemiologic study from Korea showed that progression from insulin resistant state to T2DM is an independent predictor of the development of CAD (**Figure 2**).³¹ These results indicate the importance of preventing progression to overt DM from MetS.

IR affects tissues and pathways in a selective manner, and this contributes to the development of T2DM and related complications. In simple terms, certain tissues or pathways may retain their insulin sensitivity even in insulin resistant states. For instance, in individuals with T2DM, insulin fails to suppress glucose production but continues to promote synthesis of lipids in the liver.³² Another example for selective IR is the pathogenesis of atherosclerosis. Insulin is known to activate both anti-atherosclerotic and atherosclerotic mechanisms under normal physiologic conditions. It has been suggested that selective IR of anti-atherosclerotic pathways in the vasculature play a role in atherosclerosis and microvascular complications in patients with T2DM.^{32,33}

Shared Common Mechanisms

Renin-angiotensin-aldosterone system (RAAS) is an enzymatic cascade which is involved in a wide variety of physiologic mechanisms in the human body. Over-activation of RAAS has been associated with obesity, HTN, IR, T2DM, left ventricular (LV) remodeling and HF.^{34,35} There is a growing body of evidence that over-activation of RAAS constitutes a pathophysiologic link between obesity, DM, and CVD. RAAS blockade is an essential component of HTN and HF management. Moreover, RAAS blockade has been associated with increased pancreatic insulin secretion and decreased glucose intolerance,³⁶ improved insulin sensitivity³⁷, and prevention of development of DM.³⁸

Inflammation triggered by obesity is a central component of the association between obesity, T2DM, CAD and HF.^{39,40} The expanding adipose tissue in obese individuals recruits immune cells such as macrophages, B-cells, and T-cells. The overproduction of proinflammatory cytokines by these immune cells result in obesity-associated inflammation.^{41,42} This chronic low-grade inflammation promotes the

development of IR and T2DM.^{42,43} Similarly, chronic inflammation (local or systemic) plays a critical role in the pathogenesis of endothelial dysfunction, atherosclerosis, CAD and HF.^{40,44,45}

Recent studies have revealed the significant influence of vasopressin in the pathogenesis of DM and CVD. Vasopressin is a small peptide with a short plasma half-life. Vasopressin activity is more reliably measured using a clinic surrogate marker, copeptin, which is the C-terminal portion of the vasopressin precursor and considered to be a more stable molecule.^{46,47} Elevated plasma copeptin levels have been linked to DM,⁴⁸ abdominal obesity, renal disease⁴⁹ and CVD.⁵⁰ Furthermore, elevated copeptin was found to be an independent predictor of CV morbidity and mortality in patients with DM.^{46,51} These findings suggest that vasopressin activity, measured with copeptin, is a promising marker for identifying individuals who are at risk for DM and its CV complications. Moreover, vasopressin system may be a novel therapeutic target for prevention of heart disease in patients with DM.⁴⁶

Contribution of Other Comorbidities

Adiposity, its regional distribution, and fat quality play a significant role in the development of DM and CVD.⁵² Both subcutaneous and visceral adipose tissue are independent predictors of cardiometabolic risk, though the latter is considered to have a more significant relation with DM and heart disease.⁵³ In the recent decades, adiposity surrounding the heart, referred as pericardial adipose tissue (PAT), has emerged as a strong, independent risk factor for LV hypertrophy, CAD, HF, atrial fibrillation, and CV mortality.⁵⁴⁻⁵⁸ Several distinct mechanisms, which usually derive from the anatomical contiguity of PAT with the myocardium and major coronary arteries, are involved in the link between increased PAT and pathogenesis of CVD. These mechanisms are endothelial dysfunction, increased fibrosis, fatty infiltration of the myocardium, oxidative stress, paracrine and proinflammatory effects of adipokines secreted from pericardial fat.^{59,60} Epidemiologic studies have demonstrated that individuals with pre-diabetes and DM have a significantly higher volume of PAT compared to those with normoglycemia.⁶¹ Moreover, the thickness of PAT significantly correlates with FPG, IR, HbA1c, systolic

blood pressure (SBP), triglyceride levels and risk of CAD in patients with DM.⁶² These findings supports the potential role of PAT in the pathophysiologic link between DM and CVD.⁶³

HTN effects the majority of patients with DM, and its prevalence varies depending on age, gender, ethnicity and type of DM.²¹ The common occurrence of HTN and DM in the same individual is explained by common risk factors and shared pathophysiologic mechanisms such as IR, endothelial dysfunction, oxidative stress, systemic inflammation and over-activation of RAAS and sympathetic nervous system.^{64,65} Coexistent HTN and DM, especially if blood pressure (BP) is uncontrolled, dramatically increases the risk of CV morbidity and mortality.⁶⁶ Limited data exists on the pathophysiological basis of excessive CVD risk in coexistent HTN and DM. One potential explanation comes from a recent study on mice models which demonstrated an increase in susceptibility to HTN-induced hypertrophic remodeling as a consequence of DM.⁶⁷

Dyslipidemia is a major contributor to CVD risk in patients with DM. The lipid patterns in patients with well-controlled T1DM usually does not show a significant difference from the general population. However, patients with T2DM and uncontrolled T1DM tend to have elevated triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), smaller low-density lipoprotein (LDL) particles with normal or increased LDL cholesterol (LDL-C) levels.^{68,69} Hypertriglyceridemia is the hallmark finding of diabetic dyslipidemia mainly due to increased lipolysis. IR increases production of very LDL-C (VLDL-C) by the liver and chylomicrons by the intestines. IR also leads to decreased metabolism of VLDL-C and chylomicrons due to impairment of the function of lipoprotein lipase enzyme.^{68,70} VLDL-C and chylomicrons are rich in triglycerides, and they transfer triglycerides to LDL-C and HDL-C, respectively. Triglyceride-rich HDL-C particles tend to have a shorter half-life which leads to lower HDL-C levels. Also, DM cause alterations in the protein moiety of HDL-C which leads to impairment of vasoprotective role of HDL-C.⁷¹ Additionally, triglyceride-rich LDL-C particles tend to be small and dense, which is the more atherogenic form compared to larger LDL-C particles.^{68,72}

Autonomic nervous system dysfunction is common in patients with DM. Cardiac autonomic neuropathy (CAN) has been shown to cause CVD in patients with DM. In fact, numerous studies have confirmed the relationship of CAN with LV remodeling,⁷³ LV systolic and diastolic dysfunction,^{74, 75} myocardial ischemia,⁷⁶ ischemic stroke,⁷⁷ CV events⁷⁸ and mortality (**Figure 3**).⁷⁹ The primary determinants of CAN are the duration of DM and severity of hyperglycemia.⁸⁰ It has been suggested that sympathetic overactivation occurs in the earlier stages of diabetic CAN because of predominant parasympathetic denervation.⁸¹ At the later stages, CAN results in sympathetic dysregulation as well. CAN may present with resting tachycardia, impaired heart rate variability, blunted heart rate response to exercise, abnormal BP regulation and orthostatic hypotension.⁸²

Genetic Factors

Several genetic polymorphisms have been identified to influence the progression and prognosis of CVD in DM. Only some of these genetic associations will be discussed here.

Variations in haptoglobin genotypes are well-established genetic risk factors for CVD in patients with DM. Haptoglobin is an acute phase protein which binds to free hemoglobin and prevents hemoglobin-induced oxidative tissue damage.¹⁷ In humans, three different haptoglobin genotypes (haptoglobin 1-1, haptoglobin 1-2, haptoglobin 2-2) exist, and the product of each genotype has a different antioxidant capacity. In patients with T1DM, haptoglobin 2-2 genotype was associated with 2-fold increased risk of CAD compared to haptoglobin 1-1 genotype.^{83,84} Another study of two large independent cohorts revealed that individuals with HbA1c level $\geq 6.5\%$ and haptoglobin 2-2 genotype are at >10-fold increased the risk of CAD compared to those with HbA1c level $< 6.5\%$ and haptoglobin 1-1 genotype (**Figure 4**).⁸⁵

APOE (Apolipoprotein E) gene has been studied extensively in case-control studies including individuals with DM and CAD. APOE acts as a ligand and stabilizes and solubilizes circulating lipoproteins.

Some variants of APOE gene have been shown to strongly influence the risk of development of DM and CAD (~2-fold increased risk for CAD and DM).⁸⁶

Genome-wide association studies in the recent decade have provided further evidence for the genetic basis of the relationship between DM and CVD. For instance, genetic variations that reduce the expression of *IRS1* gene were found to be associated with increased risk of IR, DM, and CAD.⁸⁷⁻⁸⁹ The product of this gene, insulin receptor substrate-1, plays a role in intracellular insulin signaling. Interestingly, the same genetic variants were linked to lower body-fat percentage in men.⁸⁷ Another recent study identified ten different genetic loci that modify the risk of both DM and CAD.⁹⁰ It should be noted that the clinical significance of genome-wide association study identified genetic variants remains unclear because of the subtle contribution from each genetic variant in the overall disease risk.

A recent study examined the cardiometabolic effects of a cluster of 11 genetic variants which are known to be linked to indices of IR from prior studies. The analysis demonstrated that the group of these 11 common genetic variants was associated “lipodystrophy-like” phenotype including higher visceral to subcutaneous adipose tissue, lower BMI, and predisposition to MetS, T2DM, and CAD.⁹¹

Epigenetics

Epigenetics is defined as heritable modifications in the genome without any changes in the coding sequence.⁹² Epigenetic mechanisms influence activity of the genes in the genome through several mechanisms such as DNA methylation, histone modifications, non-coding RNA and post-translational changes.⁹³ Epigenetic mechanisms constitute a significant link between environmental exposure and alterations in gene activity. Several epigenetic factors have been shown to play a role in pancreatic β -cell dysfunction and development of DM.⁹⁴⁻⁹⁶ There is also growing evidence that epigenetic changes in CV cells induced by chronic hyperglycemia, inflammation and oxidative stress significantly contribute to the increased risk of vascular dysfunction and CVD in patients with DM.^{97,98}

The pertinent epigenetic modifications are believed to underlie diabetes-related ‘metabolic memory’

which refers to the fact that prolonged hyperglycemia in patients with DM results in diabetic complications even after establishment of normoglycemia with lifestyle modifications and pharmaceutical agents.⁹⁹ Recent studies on animal models suggested that epigenetic modification enzymes such as histone acetylases, deacetylases, or DNA demethylases might emerge as novel targets for reversal of epigenetic changes induced by DM and thus prevention of diabetic complications.^{93,100}

Apoptosis

Apoptosis, the process of programmed cell death, has been implicated in development of diabetic cardiomyopathy (CMP),¹⁰¹ as well as other CVDs such as atherosclerosis, ischemic heart disease and HF.^{102,103} Individuals with DM, compared with non-diabetics, were found to have 85-fold, 61-fold, and 26-fold increase in apoptosis of cardiomyocytes, endothelial cells and fibroblasts, respectively.¹⁰⁴ Autophagy, the lysosomal process that degrades and recycles cellular proteins and organelles, is an essential part of cellular homeostasis. Suppression or prolonged activation have been linked to increased apoptosis.¹⁰³ Recent studies have identified dysregulation of autophagy as a key component of DM-induced apoptosis of the cardiomyocytes.^{105, 106} The cardiomyocyte autophagy patterns demonstrate marked differences between patients with T1DM and T2DM. A recent study in animal models showed that T1DM is associated with over-activation of autophagy while T2DM is related with suppression.¹⁰⁷

PATHOGENESIS OF VASCULOPATHY

Endothelial Dysfunction

Endothelial dysfunction is a hallmark finding implicated in the development of heart disease due to DM. Abnormalities in the metabolism of nitric oxide (NO), an important endothelial cell mediator, appear to play a significant role in the development of endothelial dysfunction, atherosclerosis, and HTN in individuals with IR and DM. Under normal physiologic circumstances, NO induces vasorelaxation and activates anti-atherosclerotic and anti-inflammatory pathways.²³ However, IR and DM impair release of

NO from the endothelial cells, which reduces NO-dependent vasodilation and increases leukocyte adhesion to the endothelium.^{108, 109} Furthermore, decreased NO release can result in activation of platelet adhesion and abnormalities in endothelial layer integrity.¹¹⁰ Interestingly, a recent study on diabetic mice models revealed that activation of NO synthesis using a special peptide called cavNOxin decreased the risk of atherosclerosis due to DM.¹¹¹ Evidence suggest that hyperglycemia can induce oxidative stress in the endothelium due to over-production of reactive oxygen species.¹¹² And the oxidative stress triggers several cascades which play a role in local inflammation and endothelial dysfunction.

Microangiopathy

Persistent endothelial dysfunction and several other pathophysiological mechanisms lead to structural changes in the coronary vascular system such as microangiopathy and atherosclerosis. Microangiopathy -usually defined as the vasculopathy of small arteries, arterioles, capillaries, and venules- is a common finding in the myocardium of patients with DM. The cardiac microangiopathy due to DM is characterized by thickening of the capillary membranes, perivascular fibrosis, and microaneurysms, spasm, and spiral deformation of microvessels.¹¹³ Moreover, DM leads to a reduction of capillary density, apoptosis of endothelial cells and interstitial fibrosis secondary to the down-regulated expression of vascular endothelial growth factor.¹¹⁴ Coronary microvascular dysfunction, even in the absence of obstructive CAD, has been shown to predict CV events in patients with DM.¹¹⁵

Atherosclerosis

Atherosclerosis is the most common cause of CAD in diabetic and non-diabetic individuals. Macrophages constitute an essential component of the link between IR, DM, and atherosclerosis. For instance, the insulin-resistant macrophages increase expression of scavenger receptors which internalize oxidized LDL-C, and this process promotes the formation of foam cells and subsequent development of

fatty streaks.¹⁶ These fatty streaks transform into atherosclerotic plaques over many years.

Atherosclerotic plaques in patients with DM tend to have a higher content of lipids and infiltration of macrophages, compared to those in non-diabetic individuals.¹¹⁶ In the presence of local and systemic inflammation, atherosclerotic plaque becomes unstable which increases the risk for rupture and thrombus formation.

Pro-thrombotic State

DM contributes to the risk of CV events by inducing a pro-thrombotic state. In fact, IR and hyperglycemia result in reduced tissue plasminogen activator, and increased levels of fibrinogen, factor VII and XII and plasminogen-activator-inhibitor-1.¹¹⁷ DM can cause platelet hyperreactivity due to alterations in platelet activation, adhesion, and aggregation. Moreover, hyperglycemia contributes to the pro-thrombotic state by expression of glycoproteins (IIb and IIb/IIIa) and P-selectin and activation of the P2Y₁₂ pathways.¹⁶ Among patients presenting with unstable angina, those with DM were shown to have higher frequency of plaque ulceration and intracoronary thrombus formation compared to those without DM.¹¹⁸

PATHOGENESIS OF HEART FAILURE

HF has a heterogeneous etiology in individuals with DM. The most common causes of HF in diabetic individuals are; myocardial ischemia, HTN, diabetic CMP and renal dysfunction.¹¹⁹

CAD affects patients with DM at earlier ages, and these patients tend to have multivessel CAD with the involvement of distal coronary segments. Moreover, compared to those without DM, patients with DM develop fewer collateral vessels in response to ischemia¹²⁰ and have larger infarct size and higher risk of developing HF following an MI.^{121,122} Studies in animal models have demonstrated that the tendency for larger infarct size in patients with DM derives from impairment of cytoprotective mechanisms and increased susceptibility to ischemia/reperfusion injury.^{113,122,123} It appears that duration

of a diabetic state and plasma level of insulin are some of the major determinants of myocardial tolerance against infarction in patients with DM.¹¹³

Coexistence of HTN and DM significantly increases the risk of development of HF. In fact, a meta-analysis of subjects included in clinical trials demonstrated that presence versus absence of DM in hypertensive individuals increased the risk of HF by more than 4-folds.¹²⁴

Diabetic Cardiomyopathy

DM and IR can also promote the development of CMP and HF independent of traditional risk factors such as CAD and HTN. This unique form of CMP is termed as diabetic CMP (**Figure 5**). Female patients with DM appear to be more susceptible to this type of CMP.¹²⁵ DM usually coexist with other HF risk factors such as HTN, CAD, and renal disease. Therefore, the burden of “pure” diabetic CMP is not as high as the CMP of heterogeneous etiology. However, diabetic CMP has been a hot topic of research since its first description more than four decades ago.¹²⁶ Even though HF in diabetic individuals is usually caused by multiple risk factors, the concept of diabetic CMP carries clinical significance since it emphasizes the influence of DM and IR on the cardiac structure and function.

Per the traditional concept, diabetic CMP is a progressive syndrome initiated with subclinical structural and functional abnormalities, which are followed by diastolic HF, an intermediate form between subclinical abnormalities and the “true” manifestation of the disease; LV systolic dysfunction. Consistently, LV systolic dysfunction has been considered as one of the major diagnostic criteria for diabetic CMP. However, the new line of evidence has challenged some parts of these assumptions. Most importantly, HF with preserved ejection fraction (HFpEF) is now more widely accepted as a distinct phenotype of diabetic CMP, rather than being an intermediate form between risk factors and HF with reduced ejection fraction (HFrEF).¹²⁷ These two different phenotypes (HFpEF vs. HFrEF) of diabetic CMP are mostly underlain by various pathophysiologic mechanisms and the transition from HFpEF to HFrEF

does not occur as commonly as we once thought. The current concepts on the distinct phenotypes of diabetic CMP were recently reviewed in detail by others.¹²⁷

In diabetic CMP with HFpEF phenotype, the LV is usually hypertrophied and stiff with normal LV volume. At the cellular level, cardiomyocytes appear hypertrophied with normal structure of the sarcomere accompanied by increased collagen deposition in the interstitial space. Diabetic CMP with HFrEF phenotype is usually associated with increased LV volume due to dilatation. At the cellular level, cardiomyocytes appear to be damaged with loss of sarcomeres and replacement of some cardiomyocytes with fibrosis.¹²⁷

The impact of DM and IR on the cardiac morphology and function has been studied extensively. In the FHS, higher levels of IR and worsening levels of glucose intolerance were correlated with increased LV mass and wall thickness.¹²⁸ A recent longitudinal study with a long follow-up period (25 years) revealed that DM and poor glycemic control have a cumulative effect on adverse LV remodeling and subclinical LV dysfunction.¹²⁹ Studies on population-based cohorts have indicated that DM (mostly T2DM) and IR are linked to concentric LV remodeling and hypertrophy.^{130,131} DM shows significant association with diastolic dysfunction. In fact, diastolic dysfunction is the most common echocardiographic abnormality observed in patients with T1DM and T2DM.¹¹³ The frequency of diastolic dysfunction in patients with DM ranges between 20% to 75% depending on the criteria used and the population studied.^{128,132} Furthermore, diastolic dysfunction is observed in individuals with DM even in the absence of LV hypertrophy, which suggests that hypertrophy is not an absolute necessity for DM-induced ventricular dysfunction. Systolic LV dysfunction is also commonly seen in patients with DM, although its frequency appears to be lower compared to diastolic dysfunction.¹¹³ Numerous studies have confirmed the high rate of subclinical LV systolic dysfunction (evaluated by strain imaging) in asymptomatic patients with DM.^{133,134} It should be noted that adverse LV remodeling and subclinical

myocardial dysfunction are important predictors of future CV morbidity and mortality, including HF.^{135,136}

At the tissue and cellular level, a complex interaction between numerous pathophysiologic mechanisms plays a role in the development of diabetic CMP. These mechanisms include impaired myocardial insulin signaling and calcium homeostasis, abnormal coronary microcirculation, endoplasmic reticulum stress, autonomic dysfunction, activation of RAAS, oxidative stress and maladaptive immune responses.¹²⁵

Myocardial cells in diabetic individuals demonstrate enhanced free fatty acid (FFA) uptake due to the higher availability of FFAs and IR-mediated impairment in myocardial glucose metabolism.²⁴ This enhanced uptake subsequently leads to the accumulation of triglycerides in myocytes and promotes lipotoxicity, oxidative stress, mitochondrial dysfunction and apoptosis.^{137,138} In diabetic hearts, the energy metabolism shifts from the utilization of glucose to FFA. This alteration results in reduced myocardial efficiency due to the significantly higher oxygen consumption required for FFA oxidation.¹³⁹

DM impairs the contractile force of individual cardiomyocytes secondary to changes in the structure and function of myofibrils.²⁴ Moreover, DM induces perturbation in the function of the cardiomyocyte endoplasmic reticulum which is the primary organelle for handling intracellular calcium. The alterations in calcium homeostasis subsequently lead to contractile dysfunction.¹⁴⁰

Hyperglycemia induces the formation of advanced glycation end products (AGEs) due to the nonenzymatic glycation and oxidation of proteins and lipids. The accumulation of AGEs in the myocardium and vascular wall reduces collagen turnover due to cross-linking and consequently leads to myocardial fibrosis and vascular stiffness, respectively.^{141,142} AGEs also bind to the receptors on cellular membrane and activate several mechanisms in inflammation and fibrosis.¹⁴³ A soluble receptor found in the serum binds to the AGEs and inhibit their pro-inflammatory and pro-fibrotic activity. Unsurprisingly, lower levels of circulating soluble receptors for AGEs predict incident HF in patients with DM.¹⁴⁴ DM also

induces several other pathways that are involved in the production of oxygen-derived oxidants. DM-induced oxidative stress exerts several harmful effects by causing protein and DNA damage, interfering NO production and modulation of intracellular signaling pathways.²⁴

PREVENTION OF HEART DISEASE IN DIABETES MELLITUS

CVD remains the leading cause of morbidity and mortality in patients with DM. Therefore, prevention of CVD is a primary goal in the management of DM and associated co-morbidities. Major components of CVD prevention in patients with DM will be discussed here.

Management of HTN

HTN, defined as a sustained BP >140/90 mmHg, is a leading modifiable risk factor for CVD.²¹ Coexistent DM and HTN poses a dual threat in regards to CV risk. Data from the FHS suggested that much of the excess risk of CVD events and death in patients with DM can be attributed to HTN.⁶⁶ Thus, BP control is an essential component of the management of DM, to decrease the risk of CVD, diabetic nephropathy and other diabetic complications. It should be noted that BP control in diabetic patients can be challenging and it often requires a multidisciplinary approach for optimal results.⁶⁴

Many randomized control trials (RCTs) have confirmed that BP control is an effective method for prevention of complications in diabetic individuals. In the United Kingdom Prospective Diabetes Study (UKPDS) (n=4801, mean follow-up=8.4 years), each 10% reduction of SBP in diabetic individuals was associated 12% lower risk of acute MI, HF, and all-cause mortality.¹⁴⁵ Similarly, a recent meta-analysis of 40 trials with a combined sample size of >100,000 individuals found that reduction of SBP in patients with T2DM results in significantly lower risk of CV events, CAD, stroke, albuminuria, retinopathy, and mortality.¹⁴⁶

Optimal BP goals in general and diabetic population are still actively debated, and there exists some variation among guidelines in regards to target BP levels in patients with DM (**Table 1**). The Eighth Joint National Committee and the ADA recommend a target SBP of <140 mmHg and diastolic BP of <90

mmHg of in adults with DM, regardless of age.^{21,147} The ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes-Blood Pressure) trial examined the effects of tight BP control in T2DM patients with increased CV risk.¹⁴⁸ The investigators did not find any significant difference between standard BP control (targeting SBP of <140mmHg) and tight BP control (targeting SBP of <120mmHg) strategies in regards to the primary outcome which was defined as a composite of nonfatal or fatal CVD events. Tight BP control predicted a small reduction in the risk of ischemic stroke but an increased risk of adverse events secondary to antihypertensive therapy. The recent Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated a small but statistically significant reduction in the risk of CVD events and mortality with intensive BP control (target SBP of <120 mmHg) compared to standard BP control (target SBP of 140 mmHg) in hypertensive individuals with increased CVD risk. It should be noted that results of the SPRINT may not apply to diabetic individuals since DM was an exclusion criterion in the SPRINT.

DM and HTN share multiple common risk factors, and this provides a unique opportunity for prevention or management of DM and HTN with similar lifestyle modifications.⁶⁴ The ADA recommends the following lifestyle changes in diabetic individuals with a BP >120/80 mmHg: 1) weight loss with calorie restriction, if overweight or obese; 2) increased physical activity; 3) a Dietary Approaches to Stop Hypertension-style diet with restriction of sodium intake (2300mg/day); 4) increasing consumption of fruits, vegetables, nuts, and low-fat dairy products (2–3 servings per day); and 5) avoiding excessive alcohol consumption.²¹

Per the current guidelines angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers and thiazide-type diuretics are the effective first-line antihypertensive agents in patients with DM.^{21,147} RCTs have not consistently favored one of these antihypertensives over another in individuals with DM.¹⁴⁹ Making an appropriate choice of antihypertensive medication regimen in patients with DM require consideration of several other factors such as race, age and co-morbidities such as albuminuria, chronic kidney disease, CAD, HF, etc.⁶⁴

Dyslipidemia and Lipid-lowering Medications

Dyslipidemia is a major contributor to the increased CVD risk in patients with DM.¹⁵⁰ The ADA recommends obtaining a lipid profile at the time of diagnosis and at least every five years after that in diabetic adults. Routine screening is not recommended for diabetics over the age of 75 years since there is limited data regarding the benefits of statin therapy in this age group.²¹

The beneficial effects of statins on primary and secondary prevention of atherosclerotic CVD (ASCVD) were demonstrated by subgroup analyses of diabetic patients in large RCTs^{151–153} or specific trials in diabetic patient populations.^{154,155} A meta-analysis of 14 RCTs with data from over 18,000 diabetic patients demonstrated that each mmol/L (39 mg/dL) reduction in LDL-C with use of a statin was associated with 21% reduction in major vascular events, 13% reduction in vascular mortality and 9% reduction in all-cause mortality.¹⁵⁶

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the treatment of hyperlipidemia defined DM as one of the four major statin benefit groups.¹⁵⁷ According to these guidelines, all diabetic adults (aged 40 to 75 years) with LDL-C of 70-189 mg/dL and no known ASCVD should be treated with at least a moderate intensity statin and those with an estimated 10-year ASCVD risk score $\geq 7.5\%$ should be treated with a high-intensity statin. The recommendations of ADA on the treatment of dyslipidemia have been consistent with the recommendations of 2013 ACC/AHA guidelines (**Table 2**).²¹

Several studies have raised a concern regarding a small but statistically significant increase in the risk of incident DM with the use of statins, particularly in older adults.¹⁵⁸ A meta-analysis of 13 studies with a combined sample size above 91,000 and a mean follow-up period of four years found a 9% increase in the risk of incident DM with the use of statins.¹⁵⁹ Overall, one additional patient developed DM for every 255 patients treated with a statin for four years. In another meta-analysis of five statin trials with over 32,000 participants demonstrated a slightly higher risk of incident DM with high-intensity

statins compared to moderate intensity statins.¹⁶⁰ Nevertheless, CV event reduction benefits of statins far outweigh the risk of new-onset DM even in individuals at the highest risk for DM.²¹

The efficacy of non-statin lipid lowering agents (ezetimibe, niacin, fibrates) and their combination with a statin have not been well-established in patients with DM. Therefore, these agents are not considered as a first-line therapy for dyslipidemia in patients with DM. The results of IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) suggested that combination of ezetimibe with a moderate intensity therapy can be considered for secondary prevention of CV events in patients with DM and a history of acute coronary syndromes if they are intolerant to high-intensity statin therapy.¹⁶¹

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, monoclonal antibodies targeting the PCSK9 protein, have recently emerged as a breakthrough in the management of hyperlipidemia.¹⁶² Alirocumab and evolocumab (PCSK9 inhibitors in the market) can result in up to 60% reduction in LDL-C levels on top of a baseline statin therapy.^{163,164} A meta-analysis of three RCTs demonstrated that, compared to placebo, evolocumab therapy in patients with T2DM reduces LDL-C >60%, similar to the reduction in patients without T2DM.¹⁶⁵ PCSK9 inhibitors may be reasonable as adjunctive therapy in diabetic patients who are at risk for ASCVD and intolerant to statins or in need of further lowering of LDL-C despite maximally tolerated statin therapy.²¹

Obesity and Weight Loss

Overweight and obesity play a vital role in the development of T2DM and other major CV risk factors such as HTN and dyslipidemia. Moreover, overweight and obesity can independently induce alterations in the cardiac structure and function and lead to a variety of CVD, such as HF, CAD, stroke, and atrial fibrillation.^{6,166} Therefore, purposeful weight reduction, achieved via diet, exercise or bariatric surgery, is an important part of prevention efforts in individuals with T2DM or at risk for T2DM.

Studies have consistently demonstrated that weight loss can delay progression from pre-diabetes to T2DM,^{167,168} improve glycemic control and insulin sensitivity, and reduce the need for antidiabetics in patients with T2DM.¹⁶⁹⁻¹⁷¹ Intentional weight loss can provide favorable effects on BP in diabetic and non-diabetic individuals.^{168,172,173} Weight loss also leads to a significant improvement in HDL and triglyceride profiles and a modest decline in LDL-C.^{172,174}

Despite the significant impact of weight loss on CV risk factors, the role of weight loss in prevention CVD in diabetic individuals remains not well-established. The Look AHEAD (Action for Health in Diabetes) trial was the first large-scale randomized trial examining the impact of lifestyle interventions on weight and CV outcomes in overweight or obese adults with T2DM (n=5145).^{172,175} The study, after a median follow-up of 9.6 years, did not reveal any significant reduction in the CV events despite a significant improvement in weight, HbA1c, and other CV risk factors. A recent post hoc analysis of The Look AHEAD trial showed that the magnitude of weight loss in patients with T2DM was a determinant of the risk of future CVD.¹⁷⁶ In fact, the study participants in the intensive lifestyle intervention group who lost at least 10% of their body weight had ~20% lower risk of CV events.

The ADA recommends prescription of diet, physical activity and behavioral therapy with the goal of 5% (ideally $\geq 7\%$) weight loss for overweight or obese individuals with T2DM.²¹ To achieve this goal, patients should be instructed about 500-750 kcal/day energy deficit. Enrollment in weight management programs can help with short-term and sustained weight loss. Whenever possible from a clinical standpoint, physicians should choose antidiabetic agents which are weight neutral or promote weight loss (**Table 3**).

The prevalence of severe obesity (body mass index ≥ 40 kg/m²) has been rising and now affects almost 8% of the US adults.¹⁷⁷ In the recent decades, bariatric surgeries have emerged as effective treatment options for severely obese individuals, particularly if performed as a part of a comprehensive weight loss management strategy.²¹ Observational and non-randomized studies have demonstrated that

weight loss with bariatric surgeries can lead to better glucose control, diabetes remission, and improved LV structure and function and a lower rate of CV events.^{178,179} However, we still lack evidence from randomized trials with large sample sizes. The Swedish Obese Subjects (SOS), which included 2010 obese subjects who underwent a bariatric surgery and 2037 contemporaneously matched obese controls, found the significantly lower rate of CV events in the bariatric surgery group.¹⁸⁰ Similarly, a meta-analysis of 14 observation studies with >29,000 patients who underwent bariatric surgery and >166,000 nonsurgical controls demonstrated a significant reduction in CV events in response to bariatric surgery.¹⁸¹

Lifestyle Changes

Physical activity can delay the progression from pre-diabetes to diabetes, improve glycemic control and decrease the risk of CV complications in patients with DM.^{16,182,183} Studies in the general population have demonstrated reduced risk of all-cause and CV mortality even with leisure time running (5-10 minutes per day).¹⁸⁴ Compared with no exercise, any exercise such as walking (as little as 2 hours/week) and physical activity for occupation and leisure can provide substantial benefits on the CV risk in patients with DM.^{185,186} Studies have suggested that patients with diabetes benefit more from combined aerobic and resistance training programs compared to either modality alone.¹⁸⁷

The ADA recommends 1) limiting sedentary lifestyle, 2) ≥ 150 min/week moderate-intensity aerobic physical activity (50-70% of maximum heart rate), spread over \geq days/week, and 3) resistance training at least twice per week (unless contraindicated) in all adults with DM.²¹ The evidence on the benefits of exercise in individuals with T2DM was reviewed by a joint statement from the ADA and American College of Sports Medicine.¹⁸⁸

As in non-diabetics, cigarette smoking can cause numerous deleterious effects in patients with DM such as impaired glycemic control, abnormal lipid profile and increased risk of CV morbidity and mortality.¹⁸⁹⁻¹⁹¹ Smoking has also been linked to significantly increased risk of DM.¹⁹² Unsurprisingly,

smoking cessation leads to many favorable outcomes in patients with DM such as favorable lipid profile and decreased risk of mortality.^{191,193} ADA strongly recommends smoking cessation in patients with DM.²¹ One concern about smoking cessation in patients with prediabetes or T2DM have been the risk of weight gain and associated worsening of the glycemic profile after quitting. Some studies have demonstrated an increased short-term risk of impaired fasting glucose or T2DM after quitting smoking.^{194,195} But the risk decreases as the time from smoking cessation increases.¹⁹² It is recommended that, in at-risk populations, smoking cessation should be supported by lifestyle interventions to prevent weight gain and development of T2DM.¹⁹⁴ A recent meta-analysis of 14 observational studies with a total of >98,000 participants with T1DM and T2DM demonstrated no significant long-term change in HbA1c levels due to quitting.¹⁹¹

Antiplatelet Therapy for Primary Prevention

Antiplatelet therapy is a fundamental component of secondary prevention of CV events in diabetic and non-diabetic patients with a history ASCVD. However, the clinical utility of antiplatelet therapy for primary prevention of CV events in patients with no known ASCVD is controversial.¹⁹⁶ Aspirin use in patients with T2DM results in improvement in biomarkers of CV risk such as high sensitivity C-reactive protein, adiponectin, tumor necrosis factor- α , interleukin-1 β , myeloperoxidase, and soluble CD40 ligand.¹⁹⁷ Several RCTs assessed the efficacy and safety of aspirin for primary CVD prevention in patients with DM. However, they failed to consistently show a significant reduction in overall ASCVD end points with the use of aspirin. A landmark meta-analysis was published in 2009 and included six primary prevention trials with a combined sample size of 95,000 individuals from the general population.¹⁹⁸ The analysis demonstrated a 12% statistically significant reduction in the composite of serious CV events (vascular death, MI, or stroke) with the use of aspirin. People with diabetes in this meta-analysis (n=4000) had a similar (12%) but the non-significant relative reduction of serious vascular events with aspirin. A recent meta-analysis which specifically included subjects with DM (from 10 different primary

prevention trials) demonstrated that aspirin was associated with 10% reduction of all serious CV events, but no statistically significant difference in MI and stroke rates.¹⁹⁹ Aspirin use, even low dose, for primary prevention in patients with DM have been linked to increased bleeding complications.^{200,201} Therefore, the net benefit of aspirin for primary prevention in patients with DM depends on the baseline risks for CVD and bleeding.¹⁵

A significant variation exists among major society guidelines in regards to the use of aspirin for primary prevention in diabetic populations. The most recent guidelines from European Society of Cardiology on prevention of CVD recommended against routine use of aspirin for primary prevention in patients with DM unless they have overt CVD.²⁰² A scientific statement from the ADA and AHA concluded that low-dose aspirin (75-162 mg/day) is reasonable for primary prevention in adults with DM at high risk (10-year CVD risk >10%) and without an increased risk of bleeding.¹⁵ This includes most patients with type-1 or type-2 DM aged ≥50 years who have at least one additional CV risk factor such as HTN, smoking, dyslipidemia, albuminuria and family history of premature ASCVD.²¹

Glycemic Control for Prevention of Heart Disease

Glycemic Control in Type 2 Diabetes Mellitus

CVD risk correlates with plasma glucose levels even below the definition of overt diabetes.^{203,204} In a large prospective cohort study with nearly 19,000 participants (normoglycemic, prediabetic or diabetic) from 21 different countries, every 1 mmol/L (18 mg/dL) increase in FPG was associated with 17% increase in the risk of future CV morbidity and mortality.²⁰⁵ Similarly, every 1% increment in HbA1c was found to predict 18% higher risk of CV events and 19% higher risk of MI.^{206,207} Hyperglycemia shows much stronger correlation with microvascular complications compared to that with macrovascular complications. For instance, every 1% increase in HbA1c was associated with 37% increase in the risk of diabetic nephropathy and retinopathy.²⁰⁸

Intensive glycemic control has consistently been linked to lower risk and severity of microvascular complications in patients with T2DM.²⁰⁹ However, the effects of intensified glucose lowering on the rate of macrovascular complications remain controversial. Several major RCTs have evaluated the impact of intensive blood glucose control on CV events in patients with T2DM. In the UKPDS study, published two decades ago (n=3867 T2DM patients and ~10 years follow-up), intensive blood glucose control with sulfonylurea or insulin did not lead to a significant change in the MI frequency despite a 0.9% (7.9% vs. 7.0%) lower HbA1c level in the intensive control group.²⁰⁹ A post-trial follow-up report of UKPDS study revealed that patients assigned to the intensive blood glucose control during the study period had a lower rate of microvascular complications, myocardial infarction, and all-cause mortality after ten years of follow-up.²¹⁰ It is interesting that this difference was present despite an early loss of glycemic differences between intensive and standard blood glucose control groups after completion of the original trial.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (n=10251 and ~3.5 years follow-up) compared an intensive glucose strategy (achieved HbA1c 6.4%) with standard therapy (achieved HbA1c goal of 7.5%) in patients with T2DM who had a high risk of CVD. The study found increased mortality in the intensive arm, and this was driven mainly by CV mortality.²¹¹ The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) trial evaluated the prognostic effects of intensive glucose lowering and routine BP control in >11,000 patients with T2DM.^{212,213} Compared to standard blood glucose lowering (<HbA1c of 7.3%), intensive lowering (<HbA1c of 6.5%) was linked to a significant reduction in the microvascular events but no change in the rate of macrovascular events. The VADT (Veterans Affairs Diabetes Trial) which included 1791 patients with T2DM revealed a significant reduction in major CV events in response to intensive blood glucose control.²¹⁴ However, no significant change was observed in overall mortality. The ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial (n=12537, follow-up >6 years) examined the prognostic effect of the early use of insulin glargine for a target FPG level of <95 mg/dl in

patients with increased CV risk in addition to pre-diabetes or early T2DM. Compared to the standard care, early use of insulin glargine and associated lower FPG levels did not lead to any improvement or worsening of CV outcomes.^{215,216}

Recent RCTs have demonstrated significant improvement in CV outcomes with some of the relatively novel antidiabetic agents. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors exert their glucose-lowering effects by decreasing renal reabsorption of glucose. Empagliflozin, dapagliflozin and canagliflozin are the SGLT-2 inhibitors in the market. In addition to their antidiabetic effects, SGLT-2 inhibitors have been shown to increase diuresis and reduce weight, glomerular filtration rate, albuminuria, and systolic and diastolic BP.²¹⁷ The effect of Empagliflozin on CV outcomes was evaluated in the EMPA-REG OUTCOME trial which included >7000 patients with a history of T2DM and CVD.²¹⁸ After a median of 3.1-years follow-up, empagliflozin was associated with >30% relative risk reduction of CV mortality, HF hospitalization, and all-cause mortality when compared with placebo in addition to standard care. Currently, it remains unclear which mechanisms are most responsible for the marked CV risk reduction with use of Empagliflozin.²¹⁷ It is also not known whether Empagliflozin would have the similar protective effect in individuals who do not have ASCVD but at high risk for it.

Glucagon-like peptide-1 (GLP-1) agonists (i.e. liraglutide, semaglutide, exenatide) are a group of parenteral antidiabetic agents which improve glucose homeostasis by enhancing the endogenous secretion of insulin induced by meal ingestion and inhibiting glucagon secretion.²¹⁹ The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial examined the CV prognostic impact of Liraglutide in >9300 T2DM patients with either known CVD (age 50 to 60 years) or age of ≥ 60 years with additional CV risk factor(s).²²⁰ The investigators found a significant reduction in the rate of the first occurrence of non-fatal MI, non-fatal stroke, and death from CVD with the use of Liraglutide compared to placebo in addition to standard care. Similar improved CV outcomes were demonstrated with another GLP-1 agonist, semaglutide, in an RCT with a relatively smaller sample size (n=2735).²²¹ Though, it should be noted that this study was powered as a non-inferiority study rather than superiority.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a group of oral antidiabetic agents which reduce blood glucose by enhancing pancreatic insulin secretion and suppressing glucagon secretion.²²² DPP-4

inhibitors such as Saxagliptin, Alogliptin, and Sitagliptin were evaluated in RCTs in regards to their effect on CV outcomes. Overall, DPP-4 inhibitors did not increase or decrease the rate of CV events in patients with T2DM, except an increase in HF hospitalizations with use of Saxagliptin.^{222–225}

Glycemic Control in Type 1 Diabetes Mellitus

It has been well-established in T1DM patients that intensive blood glucose control leads to a reduction in microvascular complications such as nephropathy, retinopathy, neuropathy, etc.²²⁶ Several observational and few RCTs have revealed that tight blood glucose control can improve CV outcomes in patients with T1DM. The Diabetes Control and Complications Trial (DCCT), conducted between 1993 and 2003 and included 1441 patients with T1DM who were randomized to standard or intensive glucose control strategies for a mean duration of 6.5 years (mean follow-up of 17 years).²²⁷ The study demonstrated 42% relative reduction in CV events and 57% relative reduction in nonfatal MI, stroke or death from CVD with intensive blood glucose control. A more recently published long-term follow-up of analysis of DCCT found that ~6.5 years of intensive glucose control strategy at the beginning of the study period predicted less coronary artery calcification, thinner carotid intima-media thickness and lower risk of CV events and cardiac and all-cause mortality (**Figure 6**).^{228,229}

An observational study with ~7500 patients with T1DM showed that each 1% increment in HbA1c resulted in 31-34% higher risk of CAD and 26-32% higher risk of CVD.²³⁰ A nationwide registry data from Sweden which included nearly 34,000 patients with T1DM and nearly 170,000 non-diabetic controls examined the association between HbA1c levels and risk of mortality.²³¹ The investigators found that, compared to non-diabetic controls, T1DM patients with had significantly higher risk of all-cause and CV mortality, even if the HbA1c levels were tightly controlled. Moreover, the risk of all-cause and CV mortality in T1DM patients rose in parallel to HbA1c levels.

Continuous insulin infusion with pump therapy in T1DM has been linked to fewer episodes of hyperglycemia and hypoglycemia compared to multiple daily injections.²³² An observational study utilizing the data from the Swedish National Diabetes Register found that, compared to multiple daily injections, insulin pump therapy led to 42% reduction in CV mortality and 27% reduction in all-cause mortality.²³³ We still need well-designed RCTs to examine the CV benefits of insulin pump therapy.

Albuminuria, Diabetic Kidney Disease, and Cardiovascular Prevention

Diabetic kidney disease (DKD) is a common complication of T1DM and T2DM. DKD can present with albuminuria, impaired GFR or both. Microalbuminuria, usually the earliest manifestation of DKD, is defined as 24-hour urinary albumin excretion rate of 30 to 299 mg. Macroalbuminuria refers to albumin excretion rate of ≥ 300 mg/24-hours.¹⁷ Epidemiologic studies demonstrated a strong correlation between risk of all-cause mortality and severity of DKD, from microalbuminuria to macroalbuminuria to ESRD.²³⁴ The HOPE (Heart Outcomes Prevention Evaluation) study showed that presence of microalbuminuria significantly increases the future risk of CV events, HF hospitalizations and all-cause mortality in individuals with and without diabetes (**Figure 7**).²³⁵ In the ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) study, which included >1700 patients with T2DM and normoalbuminuria at baseline, development of microalbuminuria over time was associated with 80% increase in the risk of CV events.²³⁶ Data from the LIFE (Losartan Intervention for Endpoint Reduction) study, which included diabetic and non-diabetic subjects, demonstrated that every 10-fold increment in the urinary albumin to creatinine ratio resulted in 45%, 51%, and 98% increase in the risk of MI, stroke, and CV mortality, respectively.²³⁷

In conclusion, albuminuria screening carries significance for CVD prevention in diabetic individuals, since it can help with CV risk stratification and identification of individuals at risk for CVD. ACE inhibitors and ARBs are the cornerstone of management albuminuria in patients with DM. Independent of their BP reducing effect, these drugs can delay, prevent and reduce albuminuria.²³⁶ Data

from RENAAL (Reduction in Endpoints in Non-insulin-dependent DM with the Angiotensin II Antagonist Losartan) trial, an RCT which included T2DM patients with nephropathy, revealed that every 50% reduction of albuminuria in the first-6 months resulted in 18% reduction in CVD risk and 27% in HF risk.²³⁸ Another RCT in patients with T2DM and HTN (n=393) demonstrated that change in the urinary albumin excretion over time was a strong independent predictor of CV mortality, and the reduction in urinary albumin excretion across all albuminuria categories (normo-, micro-, macro-) was an independent predictor of improved long-term survival.²³⁹

CONCLUSIONS

DM has become a public health problem worldwide. The rise in the global prevalence of DM has been attributed to obesity, dietary patterns, and sedentary lifestyle. DM is a major independent risk factor for CVD. Increased CVD risk in DM is caused by a complex interplay between numerous pathophysiologic mechanisms. DM and CVD share several common mechanisms which play a role in the development of both conditions. Abnormalities of glucose homeostasis, even at the pre-diabetes stage, can trigger several alterations in the CV structure and function. Patients with DM commonly have comorbidities (i.e. HTN, hyperlipidemia, and chronic kidney disease) which further augment the risk of CVD. Moreover, the CVD risk in diabetic patients is significantly modified by a variety of genetic and epigenetic factors. Research in the recent decades has broadened our knowledge on the pathogenesis of CVD in patients with DM, and this progress raises hope for more effective modalities for prevention of CVD in patients with DM. Prevention of heart disease in diabetic patients usually requires a multidisciplinary approach and active cooperation by the patients. The key components of prevention efforts include lifestyle modification, weight loss, and management of co-morbidities such as HTN, dyslipidemia, albuminuria, etc. The CV benefits of intensified glycemic control remain controversial in patients with T2DM. Some relatively novel antidiabetic agents, such as Empagliflozin and Liraglutide, have emerged with their CV

protective effects supported by RCTs. Available evidence suggests that tight blood glucose control is effective in the prevention of macrovascular complications in patients with T1DM.

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TABLE / FIGURE LEGENDS**Table 1:**

Title: Guideline / scientific statement recommendations on target blood pressure levels in diabetic individuals

Caption: *Individuals with chronic kidney disease, urine albumin excretion <30 mg/day. **Individuals with chronic kidney disease, urine albumin excretion \geq 30 mg/day. DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 2:

Title: Recommendations from the American Diabetes Association for statin and combination treatment in patients with diabetes

Caption: Adapted from the 'Standards of Medical Care in Diabetes-2017' report.²¹ *In addition to intensive lifestyle therapy. **ASCVD risk factors include hypertension, smoking, chronic kidney disease, albuminuria, family history of premature ASCVD, and LDL cholesterol \geq 100 mg/dL. ***High intensity of individuals age 40-75 years. ASCVD, atherosclerotic cardiovascular disease.

Table 3:

Title: Antidiabetic agents by their weight effects

Figure 1:

Title: Trends in the prevalence of diabetes mellitus among US adults (\geq 20 years of age)

Caption: Age-standardized US trends in total-, diagnosed-, and undiagnosed diabetes based on the data from National Health and Nutrition Examination Survey. Diagnosed diabetes was defined by self-report of a previous diagnosis of diabetes. Undiagnosed diabetes was defined by a hemoglobin A1c \geq 6.5% or

fasting plasma glucose ≥ 126 mg/dL despite having no prior diagnosis of diabetes. Error bars indicate 95% confidence intervals. Reproduced from Menke *et al.* with permission from the publisher.²

Figure 2:

Caption: Proportion of individuals with incidental CAD according to baseline insulin resistance levels and glycemic progression over four years (n=2076 non-diabetic participants at baseline). Reproduced from Rhee *et al.* with permission from the publisher.³¹ CAC, coronary artery calcification; IFG, impaired fasting glucose; HOMA-IR, homeostasis model assessment-insulin resistance.

Figure 3:

Title: Cumulative hazard rate of recurrence of CVD according to the stages CAN in patients with type 2 diabetes mellitus

Caption: Reproduced from Cha *et al.* (open-access).⁷⁸ The investigators examined the relationship between CAN and recurrent CVD in a prospective cohort of 206 patients with type 2 diabetes and history of CVD. Cardiovascular autonomic function test was used to evaluate for CAN. In the multivariable model, compared to patients with no CAN, those with early and definite CAN had 2- and 3-fold higher risk of CAN, respectively. CAN, cardiovascular autonomic dysfunction; CV, cardiovascular disease.

Figure 4:

Title: Relative risk of coronary heart disease according to diabetes status and haptoglobin genotype

Caption: Multivariate analysis of data from two different cohorts evaluating the joint effects of HbA1c level and Hp genotype on the relative risk of coronary heart disease. HbA1c, hemoglobin A1c; Hp, haptoglobin; RR, relative risk. Reproduced from Cahill *et al.* with permission from the publisher.⁸⁵

Figure 5:

Title: Pathogenesis of diabetic cardiomyopathy

Caption: SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system. Reproduced from Jia et al. with permission from the publisher.¹²⁵

Figure 6:

Title: Cumulative incidence of mortality by glycemic control strategy in the Diabetes Control and Complications Trial (DCCT)

Caption: Intent-to-treat analysis for the intensive vs. conventional treatment groups using the data from the DCCT (1983-1993) and the subsequent observational follow-up Epidemiology Diabetes Interventions and Complications study. HR, hazard ratio; y, year. Reproduced from Orchard *et al.* with permission from the publisher.²²⁹

Figure 7:

Title: Relative risk of cardiovascular outcomes according to the quartiles of albuminuria in diabetic individuals

Caption: Relative risk of cardiovascular (CV) outcomes in reference to the first quartile in the diabetic participants of the Heart Outcomes Prevention Evaluation (HOPE) Study. CV events include myocardial infarction, stroke, and CV death. *P* for trend was <0.001 for each CV outcome after adjusting for age, sex, systolic and diastolic blood pressure, hemoglobin A1c, waist-to-hip ration. CHF, congestive heart failure. The figure was drawn based on data from Gerstein *et al.*²³⁵

Bios for Current Problems in Cardiology

Ahmet Afsin Oktay

Dr. Ahmet Afsin Oktay is a cardiology fellow at Ochsner Medical Center in New Orleans, Louisiana. Dr. Oktay received his medical degree from Hacettepe University Faculty of Medicine in Ankara, Turkey. He completed his residency training in internal medicine and served as a chief medical resident at St. Francis Hospital of the University of Illinois at Chicago in Illinois. Dr. Oktay received research training at Weatherall Institute of Molecular Medicine of the University of Oxford in the UK and completed a post-doctoral research fellowship in complex disease genetics under the supervision of Dr. Carole Ober at the University of Chicago in Illinois.

Halis Kaan Akturk

Dr. Akturk finished Istanbul University School of Medicine in Turkey. He received internal medicine residency training at Creighton University in Omaha, Nebraska and endocrinology fellowship at Mayo Clinic in Jacksonville, Florida. He is an assistant professor of medicine at the University of Colorado School of Medicine and works as a diabetologist at Barbara Davis Center for Diabetes in Aurora, Colorado.

Kerim Esenboğa

Dr. Kerim Esenboğa is a cardiology consultant at 29 Mayıs State Hospital in Ankara, Turkey. Dr. Esenboğa graduated from Hacettepe University Faculty of Medicine in Ankara, Turkey. He completed his residency training in cardiology at Ankara University, Faculty of Medicine in Ankara, Turkey. And he received further training in interventional cardiology at Türkiye Yüksek İhtisas Research and Education Hospital in Ankara, Turkey.

Fahad Javed

Fahad Javed, MD, is a clinical fellow specializing in cardiovascular diseases at John Ochsner Heart and Vascular Institute, New Orleans, LA. Dr. Javed completed both his post-doctoral research fellowship in obesity and cardiovascular diseases, and a residency in internal medicine at St. Lukes` Roosevelt Hospital Center/Columbia University of New York. He has been involved in both basic and clinical cardiovascular research and has co-authored multiple publications including scientific abstracts, peer reviewed research manuscripts, clinical case series, systematic research review articles and text book chapters in this medical specialty. Dr. Javed will be further sub-specializing in the field of interventional cardiology at John Ochsner Heart and Vascular Institute, New Orleans, LA.

Nichole Polin

Dr. Polin received her Doctor of Medicine from MCP-Hahnemann School of Medicine in Philadelphia in 1999. She completed an Internal Medicine Residency at the Hospital of the University of Pennsylvania in Philadelphia. Upon completion of her residency she completed a Cardiology Fellowship at Drexel University College of Medicine and an Interventional Cardiology Fellowship at the New York-Presbyterian Hospital/Weill Cornell Medical Center. Dr. Polin is board certified by the American Board of Internal Medicine, ABIM — Cardiovascular Disease, ABIM — Interventional Cardiology and Certification Board of Nuclear Cardiology.

Eiman Jahangir

Eiman Jahangir is a Cardiologist with Kaiser Permanente in Northern California (Santa Rosa, CA). He has a special interest in cardiac positron emission tomography (cPET) imaging and Cardio-oncology. He is a Fellow of the American Heart Association (FAHA) and a Fellow of the

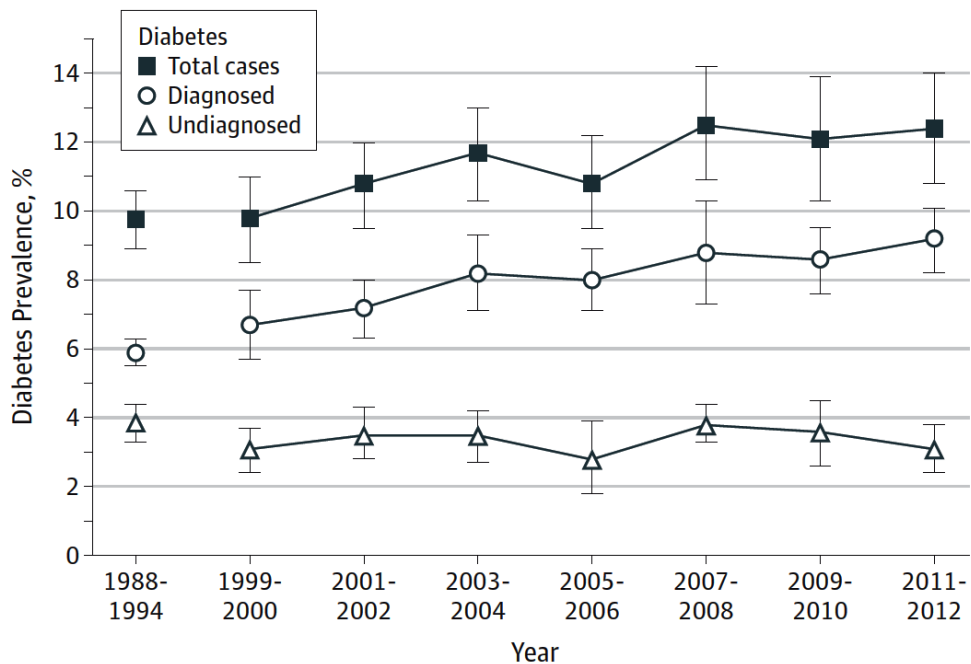
American College of Cardiology (FACC). Dr. Jahangir completed a residency in Internal Medicine at Boston Medical Center (Boston, MA) and fellowship in Cardiovascular Diseases at Vanderbilt University Medical Center (Nashville, TN).

| Guideline | Target SBP (mm Hg) | Target DBP (mm Hg) | Publication Year |
|--|--------------------|--------------------|------------------|
| 8 th Joint National Committee | 140 | 90 | 2014 |
| American Diabetes Association | 140 | 90 | 2017 |
| American Society of Hypertension / International Society of Hypertension | 140 | 90 | 2014 |
| European Society of Hypertension | 140 | 85 | 2013 |
| Canadian Hypertension Education Program | 130 | 80 | 2016 |
| British Hypertension Society / National Institute for Health and Care Excellence | 140 | 90 | 2013 |
| National Kidney Foundation Kidney Disease Outcomes Quality Initiative* | 140 | 90 | 2012 |
| National Kidney Foundation Kidney Disease Outcomes Quality Initiative** | 130 | 80 | 2012 |

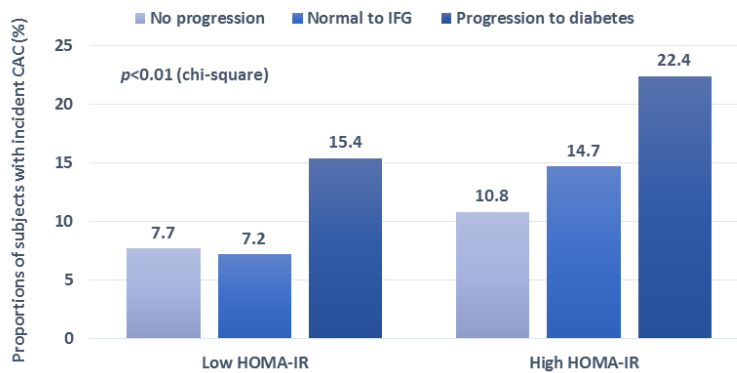
| Age Group | Risk Factors | Intensity of Statin Therapy* |
|---------------------|------------------------|------------------------------|
| <40 years | None | None |
| | ASCVD risk factor(s)** | Moderate or high |

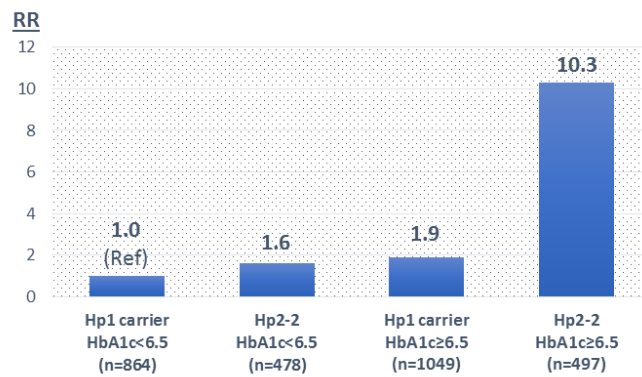
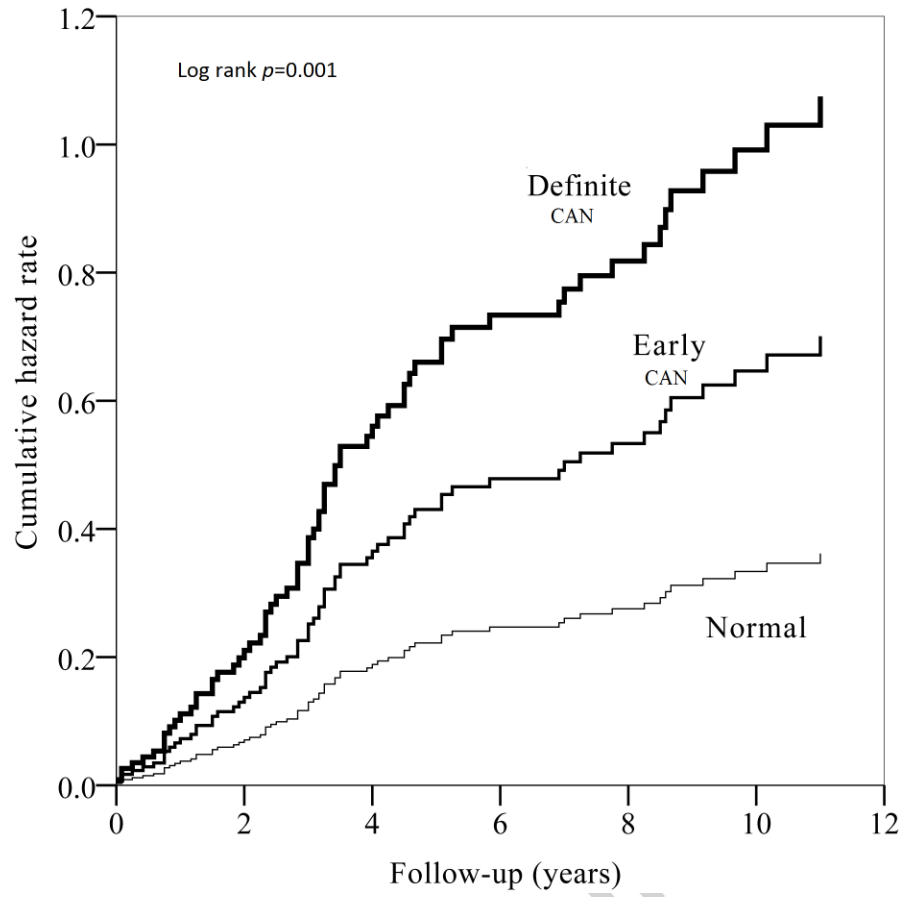
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|------------------|---|-------------------------|
| | ASCVD | High |
| ≥40 years | None | Moderate |
| | ASCVD risk factor(s) | Moderate or high*** |
| | ASCVD | High |
| | ACS and LDL cholesterol ≥50 mg/dL or history of ASCVD with intolerance to high-dose statins | Moderate plus ezetimibe |

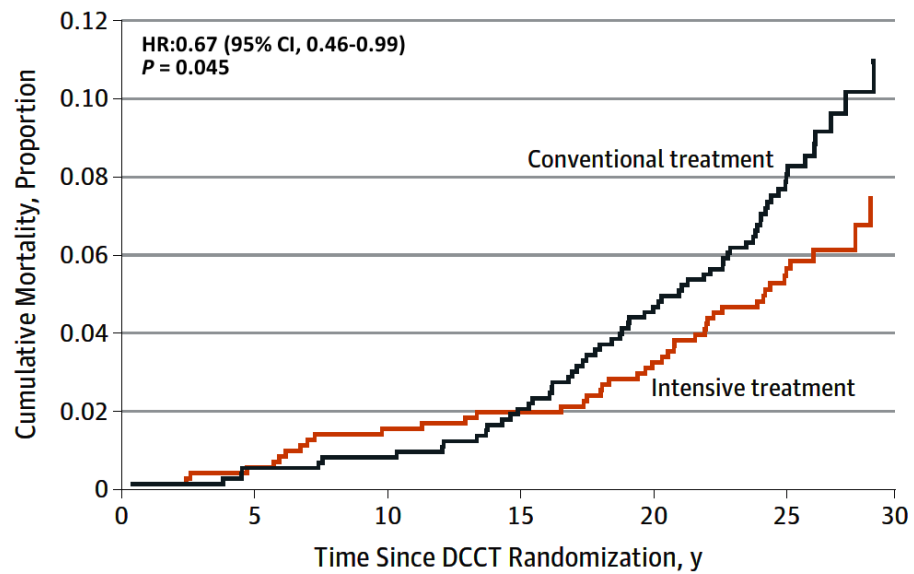
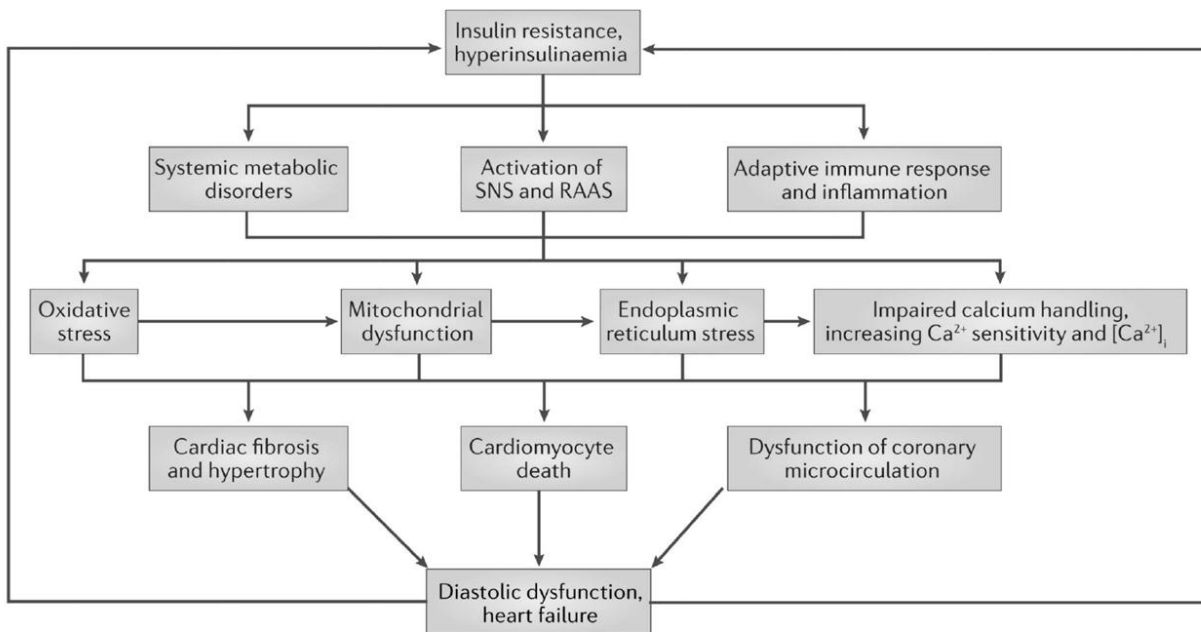
| | |
|-----------------------|---|
| Weight Loss | <ul style="list-style-type: none"> ➤ Metformin ➤ α-glucosidase inhibitors ➤ Glucagon-like peptide 1 agonists ➤ Amylin mimetics ➤ Sodium-glucose cotransporter 2 inhibitors |
| Weight Gain | <ul style="list-style-type: none"> ➤ Insulin secretagogues ➤ Thiazolidinediones ➤ Insulin |
| Weight Neutral | <ul style="list-style-type: none"> ➤ Dipeptidyl peptidase 4 inhibitors |



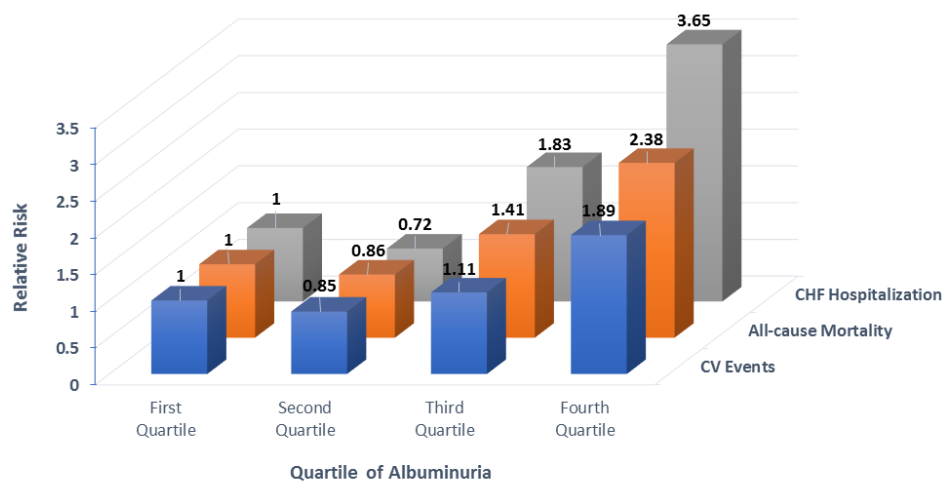
No. of participants 8478 2168 2479 2299 2191 2901 3118 2781







| No. at risk | | | | | | |
|--------------|-----|-----|-----|-----|-----|-----|
| Conventional | 730 | 726 | 721 | 712 | 693 | 476 |
| Intensive | 711 | 706 | 697 | 694 | 685 | 501 |



Accepted manu