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Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes – Mechanisms, Management, and Clinical Considerations

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Abstract

Cardiovascular disease remains the principal cause of death and disability among patients with diabetes mellitus. Diabetes exacerbates mechanisms underlying atherosclerosis and heart failure. Unfortunately, these mechanisms are not adequately modulated by therapeutic strategies focusing solely on optimal glycemic control with currently available drugs or approaches. In the setting of multi-factorial risk reduction with statins and other lipid lowering agents, anti-hypertensive therapies, and anti-hyperglycemic treatment strategies, cardiovascular complication rates are falling, yet remain higher for patients with diabetes than for those without. This review considers the mechanisms, history, controversies, new pharmacologic agents, and recent evidence for current guidelines for cardiovascular management in the patient with diabetes mellitus to support evidence-based care in the patient with diabetes and heart disease outside of the acute care setting.

Introduction

Reducing atherosclerotic cardiovascular disease (ASCVD) burden in diabetes is a major clinical imperative that should be prioritized to reduce premature death, improve quality of life, and lessen individual and economic burdens of associated morbidities, decreased work productivity, and high cost of medical care. Atherosclerotic cardiovascular disease remains the principal cause of death and disability among patients with diabetes mellitus, especially in those with type 2 diabetes in whom it typically occurs 14.6 years earlier,[1] with greater severity, and with more diffuse distribution than in individuals without diabetes.[2,3] Furthermore, about two-thirds of deaths in people with diabetes are due to cardiovascular disease: of these, approximately 40% are from ischemic heart disease, 15% from other forms of heart disease, principally congestive heart failure, and about 10% from stroke. Among

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those with diabetes, excess risks of death from any cause and of ASCVD mortality are particularly prominent in those with younger age, higher burden of glycemia, and greater renal complications, compared to those without.[4] Although the incidences of diabetes-related complications including cardiovascular disease have decreased over the past two decades, patients with diabetes continue to have significantly increased risk for vascular complications as compared with individuals without diabetes (Figure 1).[5] An estimated 382 million people worldwide have diabetes, and this number is expected to reach 592 million by the year 2035,[6] underscoring the global impact of ASCVD in diabetes.

Key manifestations of ASCVD in diabetes include advanced atherosclerosis manifest as coronary heart disease, ischemic stroke, peripheral artery disease, and heart failure. Understanding the mechanisms, strategies for and challenges with managing ASCVD and heart failure risk in diabetes, as well as the potential cardiovascular risks and benefits of glucose-lowering drugs, is important for managing cardiovascular disease in diabetes. In this clinical update, we review the current understanding of the mechanisms of ASCVD and heart failure in diabetes, management of these cardiovascular conditions in the diabetes population, and special considerations for treatment of diabetes in patients with ASCVD and/or heart failure. We discuss evidence-based management and areas of uncertainty for ischemic heart disease and heart failure therapies in type 2 diabetes, as well as the impact of diabetes medications on cardiovascular risks. A structured review of the published literature, involving searches of English-language manuscripts for clinical trials and meta-analyses of those trials that may inform treatment decisions for each section was performed by the authors. Case series and non-randomized trials were not considered for inclusion.

Epidemiology of ASCVD in diabetes

The high prevalence of coronary and peripheral artery disease in individuals with diabetes has been recognized for over a century,[7–9] yet the ability to improve cardiovascular event rates by glucose lowering *per se* has remained elusive. In the landmark Framingham Heart Study published in 1979, Kannel and McGee first prospectively demonstrated a higher incidence of cardiovascular disease across all age groups for individuals with diabetes (defined at the time by random blood glucose of ≥150 mg/dL [8.3 mmol/L]) compared to those without, with an even greater impact of diabetes on cardiovascular morbidity and mortality for women than for men.[10] The increased risk for ASCVD in diabetes could not be fully accounted for by associated traditional cardiovascular risk factors, and the presence of diabetes in conjunction with other risk factors appeared to cause a synergistic rather than additive additional risk. Importantly, the observed effect of diabetes on ASCVD risk was potentially underestimated in the Framingham Heart study, which also included persons with abnormal glucose tolerance (defined then as a random blood glucose >120 mg/dL).

Subsequent studies confirmed the importance of diabetes as an ASCVD risk factor in diverse populations and suggested diabetes as a risk equivalent for established coronary heart disease, although this remains somewhat controversial.[11,12] Persons with diabetes but without a prior myocardial infarction were demonstrated to have high risk of myocardial infarction (20.2% incidence over 7 years), similar to that of individuals with a prior myocardial infarction but no diabetes as shown in the East-West study conducted within the

Finnish population.[13] Likewise, comparable hazard ratios for cardiovascular death were found in persons age 30 years or older with diabetes requiring glucose-lowering medications but without prior myocardial infarction as compared with persons with a prior myocardial infarction, among 3.3 million individuals from Denmark including 71,801 with diabetes and 79,575 with prior myocardial infarction but without diabetes.[14] Furthermore, 21% of all deaths among Alaska Natives with diabetes are from ischemic heart disease.[15] Taken together across multiple populations, these studies support the designation of diabetes as a risk equivalent for coronary heart disease[16] and highlight the need to better understand ASCVD and to optimize treatment among patients with diabetes.

Mechanisms of increased ASCVD risk and mortality in type 2 diabetes

Multiple cellular and molecular pathophysiologic factors participate in ASCVD,[17–20] creating the “perfect storm” for atherosclerosis. Patients with type 2 diabetes have greater atherosclerotic plaque burden, higher atheroma volume, and smaller coronary artery lumen diameter than persons without diabetes.[21] A general overview of atherogenesis, atherosclerosis progression, and atherothrombosis in diabetes is presented in graphic form in Figure 2. Although numerous processes may contribute to ASCVD in diabetes,[22–25] only the following will be described to provide therapeutic context: hyperglycemia, insulin resistance and/or hyperinsulinemia, dyslipidemia, inflammation, reactive oxygen species, endothelial dysfunction, hypercoagulability, and vascular calcification. This discussion is intended to provide a framework for the review of clinical trial evidence and thus is not comprehensive.

Role of hyperglycemia

Diabetes is diagnosed based on fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), 2-hour glucose after 75-gram oral glucose load ≥200 mg/dL (11.1 mmol/L), hemoglobin A_{1c} ≥6.5% (48 mmol/mol), or random plasma glucose ≥200 mg/dL confirmed by repeat testing in the absence of signs and/or symptoms of hyperglycemia or hyperglycemic crisis.[26] Diabetes is a heterogeneous disorder with hyperglycemia required for its diagnosis, and despite markedly different genetic and mechanistic etiologies, both type 1 and type 2 diabetes are associated with higher prevalence of ASCVD. Therefore, it is natural to consider hyperglycemia among the causes for accelerated ASCVD observed in patients with diabetes.

Abundant epidemiologic data supports the association between hyperglycemia and increased cardiovascular risk.[27–32] There is strong evidence demonstrating greater risk for ASCVD with increasing dysglycemia,[33–40] with an estimated 11–16% increase in cardiovascular events for every 1% increase in HbA_{1c}.[30,41] The Swedish National Diabetes Register provided compelling evidence for HbA_{1c} as a predictor of fatal and nonfatal coronary heart disease, fatal and nonfatal stroke, fatal and nonfatal cardiovascular disease, fatal cardiovascular disease, and total mortality in a study of 18,334 persons with type 2 diabetes followed over a mean of 5.6 years.[32] The relationship between HbA_{1c} and macrovascular disease appears linear and not J-shaped and is observed in subgroups of patients with shorter (≤7 years) and longer duration of diabetes, previous history of cardiovascular disease, and different types of glycemic therapy (oral hypoglycemia agent or insulin). Likewise, a 12% increase in ASCVD risk for every 18 mg/dL (1 mmol/L) increase in fasting glucose above

105 mg/dL[33,34] and a similar 13% increased hazard ratio for vascular death for every 18 mg/dL increase in fasting serum glucose above 100 mg/dL (5.6 mmol/L) was demonstrated by the Emerging Risk Factors Collaboration group,[34] with comparable findings in numerous studies.[35–40]

In vitro studies and *in vivo* models in which hyperglycemia is induced in the absence of elevated lipids are consistent with a direct effect of hyperglycemia on endothelial dysfunction,[42,43] atherosclerotic lesion severity and complexity,[44] and plaque burden.[23] A commonly used pre-clinical diabetes model involves streptozotocin-treatment,[45,46] which is toxic to pancreatic β-cells, in an atherosclerosis-prone animal such as an LDL-receptor or apo-E deficient mouse.[47] Hyperglycemia results in atherosclerotic lesion formation which can be prevented by intensive insulin therapy,[48] while accelerated atherosclerosis develops in the setting of hypercholesterolemia. Similarly, pigs develop atherosclerotic lesions closely mimicking those observed in humans when fed a high-fat high-cholesterol diet after streptozotocin-induced diabetes, developing accelerated atherosclerosis in the aorta and coronary arteries with complex lesions, hemorrhage, and calcification.[44,49,50]

Acute hyperglycemia can attenuate endothelial function and reduce nitric oxide (NO) bioavailability[51] while increasing endothelial cell leukocyte adhesion,[43,52] mediated in part by increased oxidative stress and inflammation. Increased flux through the aldose reductase pathway,[53] synthesis of diacylglycerol with protein kinase C activation,[54] and production of advanced glycation end (AGE) products contribute to activation of endothelial cell receptor for AGEs.[55,56] Vascular smooth muscle cells (VSMC) undergo phenotypic switching from a quiescent, contractile state to an activated, proliferative, migratory, dedifferentiated state in the setting of hyperglycemia.[57] High glucose concentrations lead to macrophage inflammation and enhancement of response to inflammation,[58] and even transient hyperglycemia leads to epigenetic changes with activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway that persists even after return to normoglycemia.[59] Under experimental conditions to simulate glycemic variability in individuals with diabetes, 6 hours of hyperglycemia alternating with normoglycemia within a 24 hour period promotes worsening of endothelial function and increased oxidative stress as compared with continuous hyperglycemia even at serum glucose concentrations as high as 282 mg/dL (15.6 mmol/L).[60] Together these represent distinct and overlapping mechanisms by which hyperglycemia can promote atherogenesis and accelerate the progression of atherosclerosis (Figure 2).

Role of insulin resistance/hyperinsulinemia

Epidemiologic evidence strongly associates insulin resistance with cardiovascular risk in humans.[40,61–68] People with insulin resistance have higher rates of hypertension, dyslipidemia, and impaired glucose tolerance,[65,67,69,70] which contribute to development, progression, and complexity of atherosclerosis. Impairment of insulin signaling at multiple points in the insulin signaling pathway in endothelial cells,[71–77] VSMC[44,78–80] and macrophages[22,23,58] promotes development and progression of atherosclerosis, as does the proinflammatory state induced in insulin resistance (Figure 2).[22,23,81]

Both systemic and tissue-specific vascular insulin resistance contribute to atherosclerosis development and plaque vulnerability.[79] In type 2 diabetes, there is selective impairment of insulin signaling through phosphoinositide 3-kinase/protein kinase B, which mediates the metabolic effects of insulin to maintain normal glucose metabolism,[82–84] whereas signaling via the extracellular signal-regulated (ERK)-1/2 mitogen-activated protein (MAP) kinase pathway generally remains intact.[85–87] Compensatory hyperinsulinemia overstimulates the ERK 1/2-MAP kinase pathway, promoting development or progression of atherosclerosis.[79,81] In the apoE-deficient mouse model of atherosclerosis, knocking out the insulin receptor selectively in vascular endothelial cells leads to severe atherosclerosis.[77] Furthermore, insulin signaling impairment disrupts activation of endothelial nitric oxide synthase (eNOS) in endothelial cells[74] and production of NO with resulting endothelial dysfunction.[88–91] VSMC undergo phenotypic modulation[22,44,78,92–95] with selective insulin signaling impairment,[22,44,78,93] which may participate in atherosclerosis progression. Impaired insulin signaling has complex effects in macrophages, depending on the macrophage sub-type.[23,96–98] Multiple additional inflammatory signaling pathways may be activated with insulin resistance and may also stimulate atherosclerotic processes.[79,99–101] (Figure 2)

Approaches to target diabetes with insulin sensitization initially held great promise to simultaneously treat hyperglycemia and reduce residual cardiac risk. While metformin continues to be the first choice agent for diabetes management, thiazolidinediones have been neutral to beneficial with regard to ASCVD event rates in for secondary prevention in type 2 diabetes,[102] and insulin-sparing therapies have not been shown to be preferential to insulin-provisional therapies in patients with type 2 diabetes and stable ischemic heart disease.[103–105] It remains incompletely understood whether the hypothesis of a central pathophysiologic role for insulin resistance promoting both diabetes and ASCVD is incorrect, or whether there are off-target effects of some of these drugs that attenuate potential ASCVD benefits in patients with type 2 diabetes despite effective glucose lowering. Supporting the insulin resistance hypothesis, targeting insulin resistance using the thiazolidinedione pioglitazone reduces fatal or nonfatal stroke or myocardial infarction by 24% and incident diabetes by 52% in patients with insulin resistance and recent ischemic stroke or transient ischemic attack but without type 2 diabetes, albeit with no difference in all-cause mortality between groups.[106]

Role of diabetes dyslipidemia

Diabetes and dyslipidemia commonly occur together, with lipid abnormalities affecting 60–70% of type 2 diabetes,[107] and hyperglycemia accelerates atheroma formation in the setting of diabetic dyslipidemia.[48] LDL-cholesterol particles are more atherogenic in diabetes even in the absence of overt increased LDL concentration,[108] with small, dense particles that are particularly prone to modification.[109] Diabetic dyslipidemia is also characterized by elevated triglycerides, low HDL-cholesterol, and higher concentrations of apolipoprotein B-containing particles.[107,110–112] Mechanisms underlying diabetic dyslipidemia remain incompletely understood. Lipid changes are observed in insulin-resistant persons with normal glucose tolerance and in those with metabolic syndrome years before clinical diagnosis of type 2 diabetes,[113] suggesting either co-associations of independent disorders or

a pathophysiologic role for insulin resistance, rather than hyperglycemia, in the development of diabetic dyslipidemia.[113,114]

Metabolism of very low-density lipoprotein (VLDL), the main transporter for fasting triglycerides, is insulin-regulated at multiple levels.[111,112] Insulin suppresses lipolysis and regulates circulating free fatty acids, which are substrates for VLDL-cholesterol assembly and secretion. In the liver, insulin mediates transfer of triglycerides to apoB and regulates lipoprotein lipase activity to delipidate VLDL-cholesterol. Lipoprotein lipase activity can be disrupted by increased circulating free fatty acids and inhibited by apolipoprotein CIII, while apolipoprotein CIII hinders hepatic uptake of triglyceride-rich lipoproteins, and is itself inhibited by insulin. Thus, in the insulin resistant state, hypertriglyceridemia may be a consequence of elevated free fatty acid level and decreased degradation of apolipoprotein-B leading to overproduction of VLDL-cholesterol, impaired lipoprotein lipase activity, and decreased hepatic uptake of VLDL with reduced VLDL-cholesterol clearance.

Other lipid abnormalities observed in diabetes can be attributed in part to elevated triglycerides. The transfer of triglycerides from triglyceride-rich lipoproteins to HDL- and LDL-cholesterol is facilitated by cholesteryl ester transfer protein (CETP).[111,112] Hypertriglyceridemia stimulates CETP activity, resulting in HDL- and LDL-cholesterol with high triglyceride content. Enrichment with triglycerides makes HDL particles subject to increased catabolism, lowering plasma HDL-cholesterol concentration, while triglyceride-enriched LDL particles undergo hydrolysis, decreasing particle size. Elevated free fatty acids impair insulin signaling and cause subclinical inflammation with subsequent pancreatic beta-cell dysfunction.[107,115,116] Free fatty acid elevation may also be involved in terminal arrhythmias[117] and induction of a prothrombotic state.[118] The CETP inhibitor torcetrapib raises HDL-cholesterol concentration but also improves hyperglycemia.[119] Furthermore, recombinant HDL-cholesterol infusions improve glucose dysregulation in patients with type 2 diabetes.[120] These data suggest a role for HDL-cholesterol in glucose metabolism. Proposed mechanisms include anti-inflammatory properties of HDL-cholesterol and the central role of HDL-cholesterol in mediating reverse cholesterol transport, or cholesterol efflux, which may subsequently improve insulin sensitivity and/or secretion.[107,121,122] Recent investigations suggest a role for impaired HDL function, with decreased cholesterol efflux capacity in diabetes.[123] However, to date pharmacologic means to raise HDL cholesterol levels have not been associated with both glucose lowering and improved cardiovascular outcomes, as discussed below in the section on non-statin lipid lowering trials.

Role of inflammation

Parallel epidemics of obesity, diabetes and ASCVD suggest common molecular mechanisms for these diseases and novel therapeutic targets. Increased inflammatory markers and mediators are found in obesity,[124] with increasing numbers of components of the metabolic syndrome,[125] and predict incident hypertension,[126] type 2 diabetes,[127,128] and cardiovascular event rates.[129,130] High-sensitivity C-reactive protein, a marker of inflammation, adds cardiovascular prognostic information beyond traditional risk factors in all major cohorts evaluated.[131,132]

Hyperlipidemia within the atherosclerotic plaque results in recruitment and migration of monocytes and other immune and inflammatory cells into the vascular subendothelial layer. Recruited monocytes differentiate into macrophages or dendritic cells. Activated macrophages express scavenger receptors to facilitate engulfment of both native and oxidized low density lipoprotein, forming foam cells which, along with other inflammatory cells increase production of chemokines and cytokines. These mechanisms operate in a feed forward cycle, promoting atherosclerotic lesion progression within the inflammatory milieu.[22,23,58] Atherosclerotic lesions contain T-cells in addition to macrophages, but T-cells from individuals with diabetes have been found to have a predominance of the pro-inflammatory Th-1 phenotype.[23] In addition to deleterious effects of low density lipoprotein on macrophage and foam cells, cholesterol crystals themselves within the atherosclerotic lesion can activate the NACHT, LRR and PYD domains-containing protein 3 inflammasome complex.[133] This results in increased transcription of both NF-κB regulated gene products and interleukin-1β, provides an additional feed forward mechanism to amplify the deleterious effects of cholesterol particles that have accumulated in lipid rich plaque,[133,134] which may participate in the accelerated atherosclerosis of diabetic dyslipidemia.

In addition to the interleukin-1β signaling pathway, diverse other cellular stress pathways (including tumor necrosis factor-α, oxidized LDL, the receptor for advanced glycation end-products (RAGE),[56] reactive oxygen species (ROS), members of the protein kinase C enzyme family, and endoplasmic reticulum stress), many of which are increased in diabetes, can all activate the NF-κB transcription factor pathway.[100] NF-κB in turn regulates expression of pro-atherogenic molecules including surface proteins, cytokines, and chemokines. Inhibiting this pathway attenuates the development of atherosclerosis in murine models.[135,136] However, *in vivo* studies yield conflicting results with some pro-atherogenic and some anti-atherogenic effects,[137,138] indicating the pathway has complex roles in atherosclerosis.

Whether targeting inflammation *per se* will reduce cardiovascular event rates is under investigation in multiple large scale clinical trials with diverse agents,[139,140] including targeting of interleukin-1β with the monoclonal antibody canakinumab,[141] tumor necrosis factor-α using etanercept, interleukin-6 using tocilizumab, interleukin-1 receptor with anakinra, and multiple inflammatory targets including the nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 inflammasome with colchicine[142] or multiple targets with low dose methotrexate.[143,144] Low dose methotrexate has been reported to reduce cardiovascular event rates by 20% or more in patients with rheumatoid arthritis or psoriatic arthritis.[145] Additional ongoing investigations target alternative inflammatory pathways including oxidized LDL-cholesterol, lipoprotein-associated phospholipase A2, secretory PLA2, P-selectin, and leukotrienes, among others.[146] Given the complexity of the interactions between the inflammatory, metabolic and vascular pathways, future studies will need to address the clinical benefits of modulating these individual pathways as well as their inter-relationships.

Role of reactive oxygen species

ROS and reactive nitrogen species (RNS) are primarily produced through activity of the electron transport chain in mitochondria, and by other pathways including xanthine oxidase, lipoxygenase, myeloperoxidase and nitric oxide (NO) synthase. Alterations in electron transport chain activity result in increased electrochemical gradients and free radical leakage. Inactivation and degradation of ROS/RNS are regulated by complex networks of proteins and signaling pathways including superoxide dismutase, catalase, glutathione peroxidase, peroxiredoxins and thioredoxins. ROS/RNS participate in compartmentalized signaling pathways that are essential for normal cardiovascular physiology.[147] However, excess ROS/RNS from mitochondrial injury, abnormal vascular hemodynamics, and/or hyperglycemia leads to oxidative stress, with increased cell proliferation, migration, endoplasmic reticulum stress, autophagy, senescence, and necrosis.[148] This is manifest as hypertension from vascular endothelial dysfunction, reperfusion injury in patients with underlying occlusive atherosclerosis, and accelerated atherosclerosis. Hyperglycemia causes increased production of ROS via formation of Amadori products, which are oxidized to form AGEs that in turn activate RAGE to stimulate NADPH Oxidase-1 with intracellular ROS production.[149]

Role of endothelial dysfunction

Endothelial function is attenuated in both type 1 and type 2 diabetes.[150,151] Even short exposure to high glucose concentrations is sufficient to reduce nitric oxide bioavailability and endothelial dependent vasodilation.[42,51,152] Endothelial dysfunction may be an independent risk marker for cardiovascular events.[75,76,153,154] Dysfunctional endothelium promotes leukocyte and platelet adhesion, thrombosis, and inflammation.[76] Insulin stimulates endothelial nitric oxide synthase (eNOS)-induced production of nitric oxide by endothelial cells via the PI3-kinase/Akt pathway, and defects along the insulin signaling pathway seen in insulin resistance and diabetes result in decreased eNOS activity and decreased nitric oxide production, promoting endothelial dysfunction.[74,155] Production of the vasoconstrictors endothelin-1 and angiotensin II are increased in the presence of compensatory hyperinsulinemia and contribute further to endothelial dysfunction and hypertension.[75,156,157] Patients with type 2 diabetes also have abnormal VSMC function[158] and ROS/RNS, which exacerbate diabetes-associated endothelial dysfunction.[159]

Role of hypercoagulability

Patients with diabetes are at increased risk for recurrent atherothrombosis.[160] Experimentally-induced hyperinsulinemia and hyperglycemia results in elevated circulating tissue factor procoagulant activity and other prothrombotic proteins.[161] Patients with diabetes are more thrombogenic[162] and have elevated concentrations of plasminogen activator inhibitor-1 (PAI-1) antigen, von Willebrand factor-antigen, and fibrinogen, which are exacerbated by poor glycemic control.[163] Higher concentrations of coagulation factors (II, V, VII, VIII, X) and lower anticoagulant (protein C) are also related to blood glucose concentration.[164] These prothombotic processes may contribute to atherothrombosis in diabetes, and a recent trial using the thrombin receptor antagonist vorapaxar for secondary prevention of ASCVD in diabetes demonstrated lower major vascular events rates.[165]

Role of vascular calcification

Individuals with diabetes are more likely to have calcified atherosclerotic lesions[166] which occur in more advanced, complex atherosclerotic lesions.[167] Coronary calcium score as measured by electron-beam computed tomography is an independent risk factor for cardiovascular events and all-cause mortality in persons with or without diabetes.[166,168,169] Individuals with diabetes have higher coronary artery calcification scores than those without diabetes[170] and calcified plaque burden similar to that of older individuals without diabetes.[170] In addition, persons with diabetes are at particular risk of developing peripheral artery disease with a predilection for the distal tibial artery circulation. Tibial artery calcification is associated with increased risk of limb amputation and all-cause mortality.[171] Underlying mechanisms for this may be related to the role of hyperglycemia with development of AGEs which accelerate vascular calcification.[172] Hyperglycemia also leads to increased post-translational protein modification, including modification by O-linked N-acetylglucosamine (O-GlcNAc). O-Glc-N-acylation starts a cascade of pro-atherogenic pathways which potentiates vascular calcification.[173] In addition, altered regulation of osteoprotegerin and osteocalcin may promote arterial calcification in diabetes.[174] Lastly, as noted above, diabetes is associated with arterial inflammation with increased levels of tumor necrosis factor-alpha, which is a mediator of arterial calcification.[175]

Atherosclerotic Cardiovascular Risk Reduction in Diabetes

Targeting individual cardiovascular risk factors reduces ASCVD risk in diabetes, but addressing multiple risk factors simultaneously may synergistically reduce cardiovascular event risk even further. This hypothesis is supported by the Steno-2 study, in which 160 participant with type 2 diabetes and albuminuria were randomized to intensive versus conventional control of glycemia, blood pressure, and lipids, and followed for a mean of 7.8 years.[176] The trial showed a statistically and clinically significant 53% reduction [hazard ratio (HR) 0.47; 95% confidence interval (CI), 0.24 to 0.73] for the primary composite cardiovascular event endpoint. Cardiovascular risk differences between intensive and conventional therapy separated after 1 year. The number needed-to-treat was 5 over 7.8 years to achieve this magnitude of ASCVD risk reduction. The Steno-2 trial was not designed to identify which interventions were most effective, but use of statin and antihypertensive drugs may have accounted for much of the cardiovascular benefit. A secondary analysis of the BARI-2D trial evaluating multiple interventions also supports concurrent risk factor control lowers total mortality and the composite of death, myocardial infarction, and stroke in patients with type 2 diabetes and established coronary heart disease.[177] These findings must be interpreted with caution, as the trial was not conducted with randomization to multifactorial control, yet BARI-2D demonstrates not only improved cardiovascular outcomes among those who achieved control of multiple risk factors using a comprehensive approach, but also the feasibility of protocol-guided multi-risk factor targeted intensive medical therapy. While achievement of multiple treatment goals in diabetes care has improved over time, currently only 14.3% of U.S. adults with type 2 diabetes are at recommended goals for HbA_{1c}, blood pressure, and LDL-cholesterol.[178]

Evidence for ASCVD risk reduction in diabetes by addressing risk factors individually from clinical trials of lipid lowering, blood pressure-lowering, aspirin therapy, lifestyle, and glucose-lowering therapies is presented below, beginning with risk factors having the strongest evidence to date for ASCVD risk reduction in diabetes.

Lipid-lowering therapy

There is strong high level evidence from randomized clinical trials that lipid-lowering therapy with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-Co-A) reductase inhibitors (statins) reduces ASCVD event rates in diabetes, with some benefits potentially attributable to non-lipid-lowering, anti-inflammatory effects of statins.[134,179–182] The most recent American College of Cardiology/American Heart Association guidelines recognize patients with diabetes between the ages of 40 and 75 years as one of the four principal groups to benefit from statins and recommend treatment with a moderate intensity statin or a high intensity statin for individuals with a ≥7.5% 10-year risk of cardiovascular disease.[132] In those less than 40 or above 75 years of age, guidelines recommend individualizing statin therapy based on the benefits of ASCVD risk reduction versus the potential for adverse effects, interactions with other drugs, and patient preference.[132]

These recommendations are based on multiple lines of evidence. Statin lowering of LDL-cholesterol levels by 39 mg/dL (1 mmol/L) in high risk individuals reduces coronary mortality risk 19%, as demonstrated in a meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration. Magnitude of mortality benefits were similar for those with or without diabetes as seen in subgroup analyses.[183] A 21% reduction in major vascular events occurred per 1 mmol/L reduction in LDL-cholesterol, irrespective of prior history of vascular disease, gender, age, body mass index (BMI), or baseline systolic or diastolic blood pressure, smoking status, estimated glomerular filtration rate, cholesterol, or predicted annual risk of major vascular events; this finding was confirmed in a separate meta-analysis of 14 randomized trials from the same group.[184] One study, the Collaborative Atorvastatin Diabetes Study (CARDS) trial, specifically assessed patients with type 2 diabetes, including 2838 patients in the United Kingdom and Ireland with a mean baseline LDL-cholesterol of 117 mg/dL (3.0 mmol/L) randomized to atorvastatin 10 mg daily or placebo. A 37% reduction in the primary cardiovascular composite outcome (time to first occurrence of acute coronary heart disease event, coronary revascularization, or stroke) was observed for atorvastatin compared to placebo assigned groups. The Treating to New Targets (TNT) study examined whether lowering LDL-cholesterol below the threshold recommended at the time (100 mg/dL, 2.59 mmol/L) would result in greater cardiovascular risk reduction.[185] The study included 1501 patients with diabetes and coronary heart disease who were randomized to atorvastatin 10 mg versus 80 mg daily, lowering LDL-cholesterol levels to a mean of 98.6 mg/dL (2.55 mmol/L) versus 77 mg/dL (1.99 mmol/L), respectively. There was a 25% reduction in major cardiovascular events (composite of coronary heart disease death, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest and fatal or nonfatal stroke) after a median of 4.9 years of treatment. This study provides further evidence for more aggressive LDL-lowering to reduce ASCVD in diabetes.

Statins and Diabetes—While there are clear benefits of statins to reduce cardiovascular events and mortality in patients with or at risk for ASCVD, [183,184] statins also modestly accelerate the development of diabetes in individuals with pre-existing risk factors.[186–189] In the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), which involved participants without diabetes but with LDL cholesterol levels below 3.4 mmol/L (130 mg/dl) and high-sensitivity C-reactive protein concentrations of 2.0 mg/L or higher, the hazard ratio for newly diagnosed diabetes was increased 25% in the rosuvastatin group compared to the placebo group.[186] Despite the increase in the risk of new-onset diabetes, the participants previously considered to be at low cardiovascular risk had clinically important cardiovascular event reductions over a median follow-up period of only 1.9 years, with a hazard rate 44% lower with rosuvastatin compared to placebo for the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Almost two-thirds of participants had at least 1 major risk factor for developing diabetes: metabolic syndrome as defined by the 2005 American Heart Association/National Heart, Lung, and Blood Institute consensus criteria, impaired fasting glucose (as defined by fasting serum glucose of equal to or greater than 100 and less than 126 mg/dL [5.55 to 7.00 mmol/L]), BMI 30 kg/m^2 or higher, or HbA_{1c} greater than 6%.[190] As expected, incident diabetes was 28% higher those with than without any major diabetes risk factor, and statins accelerated the average time to diagnosis of diabetes by 5·4 weeks. However, statin allocation reduced the risk for the primary endpoint both in participants with and without a major risk factor for diabetes, such that in patients with one or more risk factor for diabetes, in total 54 new cases of diabetes were diagnosed, while 93 first major cardiovascular events or deaths, or 134 total cardiovascular events or deaths were avoided.

Several meta-analyses have now been performed examining the risk of developing diabetes in statin-treated individuals, and relative risks are somewhat lower overall than that found in the index JUPITER trial.[187–189] Diabetes relative risk was 13% higher with no heterogeneity across 5 trials [including HPS (Heart Protection Study),[191] LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease),[192] ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial),[193] JUPITER,[186] and CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure)[194]] with a total of 57,593 patients, mean follow-up of 3.9 years, and 2,082 incident cases of diabetes.[187] Addition of WOSCOPS (West of Scotland Coronary Prevention Study)[195] to the analysis introduced significant heterogeneity and attenuated risk, which no longer retained statistical significance as WOSCOPS reported a protective effect of pravastatin versus placebo on the incidence of diabetes. In a second meta-analysis, a 9% increase in risk for incident diabetes was found (odds ratio (OR) 1.09, 95% CI 1.02–1.17), including 13 trials with 91,140 participants and development of diabetes in 4,278 patients over a mean of 4 years.[188] Investigators were contacted to obtain unpublished data regarding incident diabetes resulting in 7 additional trials (and both JUPITER and WOSCOPS) included as compared with the other meta-analysis. In this analysis little heterogeneity was found across trials despite the inclusion of WOSCOPS, potentially attributable to different criteria used to diagnose diabetes. Statin associated diabetes risk may be slightly higher in women.[196] A meta-regression analysis showed the highest diabetes risk was associated with older age, but not baseline BMI or LDL-cholesterol level.[188] One extra case of diabetes

resulted from treating 225 (95% CI 150–852) patients with statins for 4 years, while 5.4 vascular events were prevented. In the larger context, given that statins are used by approximately 24 million Americans, the population-attributable risk of statin-associated diabetes is not small. However, considering the many treatments for diabetes and the importance of cardiovascular event reduction, providers should not avoid using statins when indicated solely due to concern for risk of diabetes.

Potential effects, if any, of statin-induced diabetes on the development of long-term microvascular complications remain unknown, and current epidemiologic data are reassuring. With recent lower lipid target goals and increasing use of statins, as well as improved screening, early detection, and multifactorial interventions, the age-adjusted percentage of adults with diabetes reporting visual impairment[197] and the incidence of end-stage renal disease in adults with diabetes[198] have decreased over the past few decades. Furthermore, the 10-year risk of myocardial infarction or stroke (approximately 25%) is markedly higher than that of blindness or renal failure (approximately 1 to 2%) for patients with recent-onset diabetes impacting risk-to-benefit considerations.[199]

The risk of developing diabetes appears to be related to statin potency[200] and dose.[189] Cellular mechanisms underlying the increased incidence of diabetes remain incompletely understood. Genome-wide studies do not reveal associations between genes that regulate HMG-CoA reductase or LDL-cholesterol metabolism and type 2 diabetes. Statins may interfere with beta-cell insulin secretion either by decreasing Ca^{2+}-dependent insulin secretion or by interfering with isoprenylation of guanosine triphosphate –binding proteins.[201] Statin inhibition of isoprenoid biosynthesis may lead to lower expression of insulin signaling proteins in adipocytes and to reduced glucose transporter expression or translocation.[202] Fasting insulin levels may increase modestly, suggesting that insulin resistance may be increased, but euglycemic hyperinsulinemic clamp studies do not show consistent changes in insulin sensitivity.[203] Other off-target effects may also be involved.

Overall, the risk of incident diabetes with statin therapy is present but vastly outweighed by the actual cardiovascular benefits.[204] Patients should be educated regarding the risk of incident diabetes with statins as with other risk-benefit of all therapies.[132] Lifestyle modification should be encouraged to lower cardiovascular risk and that for developing diabetes.[205] Patients on statins at higher risk for but without pre-existing type 2 diabetes should undergo periodic screening for diabetes with fasting glucose and HbA_{1c}, and if type 2 diabetes develops, standard of care and national guidelines should be used to manage diabetes.[206,207]

Non-statin lipid lowering—Although statins are effective in reducing ASCVD risk in diabetes, residual cardiovascular risk remains,[185,191,208] and further lowering of lipids may be of value. While most studies do not demonstrate other pharmacologic class agents provide additional benefit, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) supports use of a non-statin LDL-lowering strategy to further lower cardiovascular risk.[209] Vytorin is a combination of simvastatin and ezetimbe, which reduces intestinal cholesterol absorption. The primary composite cardiovascular endpoint of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring

rehospitalization, coronary revascularization, or nonfatal stroke was 6% lower with ezetimibe compared to placebo administered with simvastatin. Ezetimibe lowered LDL-cholesterol 24% despite the relatively low baseline concentrations, which was an unexpectedly potent effect on LDL-cholesterol lowering. Twenty-seven percent of the study population had diabetes, and there was heterogeneity in response with a greater 14% cardiovascular benefit among those with diabetes. This trial supports the hypothesis that lower LDL-cholesterol targets may be important to reduce residual ASCVD risk in patients with diabetes.

The question remains whether targeting the diabetic lipid abnormalities of high triglycerides, low HDL-cholesterol, and small LDL-cholesterol particle size will result in further benefit. Most trials examining effects of fibrates on cardiovascular risk were completed before statin therapy became widely instituted and included individuals with diabetes only as a subgroup. More recent trials include the lipid arms of Action to Control Cardiovascular Risk in Diabetes (ACCORD)[210] which examined fenofibrate versus placebo on a background of simvastatin therapy, and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial[192] involving fenofibrate monotherapy versus placebo. In ACCORD, all patients were randomized to intensive glycemic control (targeting an HbA_{1c} of 6.0%) or standard therapy (targeting HbA_{1c} of 7–7.9%);[211] a subset of patients were enrolled in the ACCORD Lipid trial and were randomized in a 2 × 2 factorial design to receive simvastatin plus fenofibrate or placebo. Inclusion in the ACCORD-Lipid substudy did not require high triglycerides and low HDL-cholesterol levels, a group which might benefit most from fibrate therapy.[210] Although there was no difference in the annual rate of the primary composite outcome of major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) for the fenofibrate compared to placebo group, pre-specified subgroup analysis revealed 29% fewer events in those with baseline triglyceride at or above 204 mg/dL (2.31 mmol/L) and HDL-cholesterol at or below 34 mg/dL (0.88 mmol/L). These results are consistent with the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study of 9,975 individuals with type 2 diabetes not on statin therapy, randomized to micronized fenofibrate versus placebo for 5 years.[192] No effect of fenofibrate was seen on the primary outcome of coronary events (coronary heart disease death or non-fatal myocardial infarction) in the entire cohort, although a 14% cardiovascular event reduction was observed in the subgroup with baseline low HDL-cholesterol (p=0.02), and a similar trend was observed in those with baseline high triglyceride (p=0.07). Interpretation of the FIELD study is complicated due to higher rates of add-on statin use in the placebo-assigned treatment group, which might be expected to attenuate differences between groups. In total, four studies consistently demonstrate favorable effects of fibrates in the subgroup of patients with the specific lipid phenotype of high triglyceride and low HDL-cholesterol,[191,192,210,212] but one must be cautious in interpretation of subgroup analysis, especially when the primary outcome of the trial was not positive, and benefit of adding a fibrate to statin therapy for reducing risk of cardiovascular events in patients with type 2 diabetes remains unproven.[213] Further studies are needed to determine if persons with diabetes who have elevated triglyceride and low HDL cholesterol concentrations may realize a cardiovascular benefit with the addition of a fibrate.

In Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH),[214] a study that evaluated addition of niacin to intensive statin therapy [with simvastatin plus ezetimibe if needed to maintain LDL of 40 to 80 mg/dL (1.04 to 2.07 mmol/L)] in patients with established cardiovascular disease and low HDL-cholesterol [median baseline HDL-cholesterol of 35 mg/dL (0.91 mmol/L), IQR 31–39 mg/dl], approximately one-third of participants had diabetes. No difference in the primary composite endpoint was observed despite increased mean HDL-cholesterol from 35 to 42 mg/dL (0.91 to 1.09 mmol/L), lowering triglycerides from 164 to 122 mg/dL (1.85 to 1.38 mmol/L), and lowering LDL-cholesterol from 74 to 62 mg/dL (1.92 to 1.61 mmol/L). The trial was stopped 18 months early, after a mean follow-up period of 3 years, for lack of efficacy and an unexpected higher rate of ischemic stroke in the niacin group, although the overall rate was low, so it remains uncertain whether this was a true effect versus a chance occurrence. The trial must be interpreted with caution as the rate of the primary composite cardiovascular endpoint was lower than projected, consistent with recent trends, so the protocol was amended to change the primary endpoint of high-risk acute coronary syndrome to include hospitalization for acute coronary syndrome and symptom-driven coronary or cerebral revascularization. Furthermore, there have been no other studies prior to or since showing a causal link between niacin and stroke. Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) included more than 8,000 patients with diabetes (32.3% of the study population) and compared extended-release niacin versus placebo on a background of statin therapy in high risk patients with prior vascular disease, but was likewise stopped early because of futility.[215]

Raising HDL cholesterol levels with the use of CETP inhibitors[216,217] has not been demonstrated to reduce ASCVD risk, and torcetrapib unexpectedly increased ASCVD events, cardiovascular and non-cardiovascular death.[217] Although pharmacologically increasing HDL-cholesterol concentrations has not been demonstrated to reduce ASCVD, it is possible that HDL-cholesterol function, or cholesterol efflux capacity, is a more important determinant of cardiovascular risk.[218]

Given the data presented above, the opinions of the authors are that ezetimibe may represent a reasonable choice for additional cardiovascular risk reduction, especially in those with diabetes and acute coronary syndrome. Consideration can also be given to adding fibrate therapy for an individual with diabetes and residual hypertriglyceridemia with low HDL-cholesterol levels once the patient is on goal statin therapy. The data do not support the specific use of niacin in diabetes, although it may be an alternative for those with true intolerance to statin therapy. These opinions are consistent with the most recent Standards of Medical Care for Diabetes by the American Diabetes Association (ADA),[219] which cite the Level A evidence above to state that the addition of ezetimibe to moderate-intensity statin therapy may be considered for patients with a recent acute coronary syndrome with LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or for those patients who cannot tolerate high intensity statin therapy. It was noted that combination therapy with a statin and fibrate has not been shown to improve ASCVD outcomes in the broad diabetes population and is generally not recommended, but therapy with statin and fenofibrate may be considered for men with both triglyceride level ≥204 mg/dL (2.3 mmol/L) and HDL cholesterol level ≤34 mg/dL (0.9

mmol/L). Lastly, combination therapy with statin and niacin was not generally recommended. Of note, the Scientific Statement on Prevention of Cardiovascular Disease in type 2 diabetes by the American Heart Association and American Diabetes Association (AHA/ADA) does not recommend addition of a fibrate to statin therapy.[220]

Non-statin LDL-lowering with PCSK9 inhibition—The newest class of LDL-lowering medications consists of monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is present in hepatocytes, and binds to and targets the LDL receptor for degradation.[221,222] PCSK9 inhibitors prevent the degradation of LDL receptors, allowing for increased removal of LDL-cholesterol from the circulation. Individuals with loss-of-function PCSK9 mutations have lower LDL-cholesterol levels and lower coronary heart disease incidence,[223,224] while most cases of familial hypercholesterolemia result from gain-of-function mutations, elevated LDL-cholesterol concentrations and resulting early ASCVD.[225,226] Statins upregulate PCSK9, which may be the reason that LDL-cholesterol lowering with statins reaches a plateau.[227] Alirocumab and evolucamab are two PCSK9 inhibitors recently approved by the Food and Drug Administration (FDA) based on their efficacy at lowering LDL-cholesterol concentrations and initial safety based on relatively small trials, with additional clinical trials ongoing.

Alirocumab was approved by the FDA in July 2015 for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia or patients with clinical ASCVD who require additional lowering of LDL-cholesterol. Doses of 75–150 mg subcutaneous administered every two weeks lowered LDL-cholesterol concentrations by 36–59% compared with placebo in patients with hypercholesterolemia and/or at high cardiovascular risk as add-on therapy to background statins, on maximally-tolerated statins, or as monotherapy.[228–234] Three longer-term studies ranged only from 24–78 weeks[229–231] but showed effects to lower LDL-cholesterol are durable over this timespan. A post-hoc analysis of the effect of alirocumab on cardiovascular outcomes was performed in the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial[231] and showed a 48% reduction in major adverse cardiovascular events (MACE HR 0.52, 95% CI 0.31–0.90, nominal P=0.02), but this was based on adverse event reporting and these early trials were not designed as formal cardiovascular outcome trials (CVOT). Thus definitive evidence of cardiovascular benefit awaits completion of a large ongoing trial in persons with a recent acute coronary syndrome event (NCT01663402), with planned enrollment of an estimated 18,600 patients and expected completion in late 2017.[235]

The initial studies of alirocumab did not show an increased risk of diabetes but did suggest a smaller LDL-cholesterol lowering effect in diabetes.[230] Larger populations will need to be studied to substantiate these effects. The most common side effects include itching, swelling, pain, or bruising at the injection site, nasopharyngitis, and flu. Allergic reactions such as hypersensitivity vasculitis have also been reported. A number of additional clinical trials are underway examining the safety and efficacy of alirocumab in statin-intolerant patients,[236] patients at high cardiovascular risk on maximally-tolerated statins,[237] as an add-on to statin therapy,[238] and in patients with familial hypercholesterolemia (FH).[239]

Evolocumab is the second PCSK9 drug currently approved by the FDA to lower LDL-cholesterol levels. Evolocumab was approved by the FDA in August 2015 for use in patients with heterozygous or homozygous familial hypercholesterolemia, or clinical ASCVD (e.g. history of myocardial infarction or stroke), on diet therapy and maximally-tolerated statin therapy who require additional LDL-cholesterol lowering. Evolocumab appears to have similar magnitude LDL-cholesterol lowering effects as alirocumab, but these agents have not been compared in head-to-head investigations. In the evolocumab development program, cardiovascular outcomes were also examined as an exploratory endpoint in trials primarily designed to evaluate the LDL-cholesterol lowering effect of the drug. In a 48-week open-label study of evolocumab, patients were enrolled from either the phase-2 Open-Label Study of Long-Term Evaluation against LDL Cholesterol -1 (OSLER-1) or phase-3 (OSLER-2) trials.[240] A dose of evolocumab 420 mg subcutaneous given monthly (in OSLER-1 and OSLER-2) or 140 mg every 2 weeks (OSLER-2) lowered LDL-cholesterol by 61% at 12 weeks, an effect that was sustained at 58% at 48 weeks, with an absolute LDL-cholesterol reduction of 70.5 mg/dL (1.83 mmol/L) to a mean LDL-cholesterol level of 48 mg/dL (1.24 mmol/L). Likewise, durability of evolocumab lowering of LDL-cholesterol was sustained for 52 weeks in the study of patients with familial hypercholesterolemia or mixed hyperlipidemia either alone or added on to low versus high intensity statin therapy.[241] Additional beneficial effects on serum lipoproteins included decreased apolipoprotein B, lipoprotein (a), triglycerides and non-HDL-cholesterol. Evolocumab has been shown to lower LDL-cholesterol levels in patients with statin intolerance for 12 weeks as compared with statin plus ezetimibe,[242] as an add-on to moderate or high intensity statin therapy for 12 weeks,[243] and as monotherapy for 12 weeks.[244] The pre-specified exploratory outcome of adjudicated cardiovascular events (including death, coronary events of myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization, and cerebrovascular events of stroke or transient ischemic attack, and heart failure requiring hospitalization) was reduced by 53% at 1 year (hazard ratio 0.47, 95% CI 0.28–0.78, P=0.003). The safety profile appeared to be acceptable at this early stage,[240] although the duration of follow-up is short for chronic disease, and the sample size is small to detect less common potential safety signals. Briefly, injection-site reactions were reported in 4.3% of patients on evolocumab and led to discontinuation of the drug in 0.2%. New evolocumab-binding (neutralizing) antibodies were detected in 0.3% in the evolocumab group but in a surprising number of patients (also 0.3%) in the standard-therapy group. Antibody titers were transient in patients who underwent repeat testing, and no neutralizing antibodies against evolocumab were detected. The Further Cardiovascular Outcomes Research with PCSK9 inhibition in Subjects with Elevated Risk (FOURIER) (NCT01764633) plans enrollment of 27,500 high-risk patients with cardiovascular disease on background statin therapy, with a primary MACE endpoint and is also expected to complete in late 2017. Additionally, two CVOT are underway with bococizumab, a PCSK9 inhibitor that has not yet been approved by the FDA: SPIRE-1 (NCT01975376) and SPIRE-2 (NCT01975389).

Although PCSK9 inhibition has a potent and apparent durable effect to lower LDL-cholesterol, the available clinical trial evidence regarding cardiovascular benefit is currently exploratory and preliminary, and definitive evidence is needed for reduction of cardiovascular outcomes. Furthermore, clinical trial data examining the effect of PCSK9

inhibitors on LDL-lowering and cardiovascular endpoints in patients with diabetes are needed, as the effects in this population remain uncertain.

Blood pressure control and angiotensin converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB) therapy

The age-adjusted prevalence of hypertension is 57.3% in U.S. adults with diabetes as compared with 28.6% in those without diabetes, with higher rates seen in older persons.[245] Elevated blood pressure has unequivocally been shown to increase the risk of both micro- and macrovascular disease in diabetes,[246,247] and blood pressure control reduces the risk of death and both micro- and macrovascular complications in type 2 diabetes.[248,249] Initial trials investigated intensive versus moderate blood pressure control with secondary aims to also test particular drug classes. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was a prospective, randomized, controlled trial of intensive (diastolic blood pressure below 75 mmHg) versus moderate (diastolic blood pressure between 80 to 89 mmHg) antihypertensive therapy in 950 individuals with type 2 diabetes followed for 5 years.[250] There was a further randomization to nisoldipine or enalapril. The trial was halted early due to marked lowering of cardiovascular complications (nonfatal myocardial infarction, all myocardial infarction, and myocardial infarction plus cardiovascular death) in patients randomized to enalapril. However at the point of early termination of the randomization between the two drugs, the study had insufficient number of events to test any benefit of intensive blood pressure lowering on cardiovascular outcomes.

The benefits of angiotensin converting enzyme (ACE) inhibition observed in the ABCD trial were extended in the Heart Outcomes Prevention Evaluation (HOPE) study, which randomized 3,577 subjects with diabetes and a prior cardiovascular event (coronary artery disease, stroke, or peripheral artery disease) or at least one other cardiovascular risk factor (elevated total cholesterol, low HDL-cholesterol, hypertension, known microalbuminuria, or current smoking) to either ramipril 10 mg daily or placebo, as well as vitamin E 400 IU versus placebo in a 2 × 2 factorial design.[251] The trial was stopped 6 months early because of a 25% relative risk reduction in the combined primary outcome of myocardial infarction, stroke, or cardiovascular death in the group randomized to ramipril (95% CI 12–36, P=0.0004), and similar reductions in separate components of the primary outcome. The absolute risk reduction by ramipril was 4.5%, and this benefit remained significant even after adjustment for changes in systolic and diastolic blood pressure, suggesting that renin-angiotensin-aldosterone system (RAAS) inhibition may have greater benefits over and above blood pressure control in diabetes.

The impact of the RAAS inhibition approach was studied in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), which involved 1,195 individuals with diabetes, hypertension, and signs of left ventricular hypertrophy to receive the angiotensin receptor blocker (ARB) losartan- or atenolol-based treatment.[252] Both drug groups achieved similar blood pressure control, but the losartan-treated group had a 24% reduction in relative risk of the cardiovascular events (fatal and non-fatal myocardial infarction or stroke), after a mean follow-up of 4.7 years.

In contrast, in the Irbesartan Diabetic Nephropathy Trial (IDNT), a global multicenter trial of 1,715 adults with type 2 diabetes, diabetic nephropathy and hypertension, the use of irbesartan versus amlodipine or placebo in addition to conventional antihypertensive therapy did not confer a reduction in the composite cardiovascular endpoint.[253] Other trials examining the use of ACE inhibition concomitant with angiotensin receptor blockers (ARB) have instead found increased risk for adverse events.[254] Thus, there is not a uniform finding of unique cardiovascular benefit over and above blood pressure control of various strategies for RAAS inhibition in diabetes. However, consistent with the current AHA/ADA guidelines,[220] RAAS blockade with an ACE inhibitor or ARB should be used first- in the treatment of hypertension in diabetes. Because there is evidence that this combination can lead to more adverse events, the opinion of the authors agrees with current guidelines by the ADA that recommend avoiding combined therapy with ACE inhibition and ARBs simultaneously.[219]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was a global, multicenter study conducted in 11,140 patients with type 2 diabetes randomized to fixed combination of the ACE inhibitor, perindopril, and the indoline diuretic, indapamide, or matching placebo in addition to current therapy.[255] Patients were also randomized in a factorial design to standard versus intensive glucose-lowering therapy with a goal HbA_{1c} of less than 6.5%. Approximately one-third of subjects had macrovascular disease at baseline. The initial trial had a mean follow-up of 4.3 years, and the mean achieved blood pressure was 139.3 mmHg systolic and 78.7 mmHg diastolic. The relative risk for the primary endpoint (a composite of major macrovascular and microvascular events), was reduced by 9% (HR 0.91, 95% CI 0.83–1.00, P=0.04), which reflected a 1.3% absolute risk reduction. The nearly 6 year long-term follow up of ADVANCE confirmed a sustained but attenuated benefit in reduction of all-cause and cardiovascular mortality.[256]

Blood Pressure Goals—The intensity of systolic blood pressure lowering was examined in the ACCORD-BP study, which included 4,733 participants with type 2 diabetes at high risk for cardiovascular events randomized to intensive blood pressure lowering therapy targeting a systolic blood pressure below 120 mmHg, or standard therapy targeting a systolic blood pressure below 140 mmHg.[257] The mean achieved systolic blood pressure was 119.3 mmHg in the intensive group and 133.5 mmHg in the standard group. There was no statistical difference between groups in the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes but there was a trend towards benefit after a mean follow-up of 4.7 years. However, there were more serious adverse events in the intensive compared with the standard therapy group (3.3% versus 1.3% of events attributed to blood pressure medications, P<0.001) including hypotension, bradycardia or arrhythmia, and hyperkalemia. Importantly, the mean estimated glomerular filtration rate was lower, and the serum creatinine was higher in the intensive group despite a lower prevalence of macroalbuminuria in the intensive group.

In contrast, results of the Systolic Blood Pressure Intervention Trial (SPRINT) support the benefits of intensive blood pressure control in the broad hypertensive population. Unfortunately this trial excluded patients with diabetes and thus the findings cannot be

directly extrapolated to persons with diabetes.[258] The trial does provide evidence supporting a much lower blood pressure goal than is represented in current guidelines and highlights an area of potential controversy. The study involved 9,361 participants with systolic blood pressure between 130–180 mmHg and an increased risk of cardiovascular events. Patients were randomized (but not fully blinded) to a systolic blood pressure target below 140 mmHg (standard treatment) or below 120 mmHg (intensive treatment). The antihypertensive regimen titration algorithm was similar to that used in the ACCORD-BP trial. The primary composite cardiovascular outcome (myocardial infarction, other acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) was significantly reduced with a hazard ratio of 0.75 with intensive treatment (95% CI 0.64–0.89, $P<0.001$) with participants followed over a mean of 3.26 years. In general, the SPRINT cohort was older than ACCORD (28% of subjects were age 75 or older, mean age 68 years compared with 62 years in ACCORD-BP), and included individuals with chronic kidney disease. There was more syncope and hypotension but not more falls in the intensive treatment group, and there was a higher rate of acute kidney injury and acute renal failure in the intensive treatment group. At this time, it is unclear why there is greater benefit in the primary outcome in SPRINT versus only a trend for benefit in the ACCORD-BP but in fact the point estimates for the primary outcome and components of the primary showed similar trends in both trials. Outcomes data for SPRINT versus ACCORD are compared in Figure 3.[259]

Several meta-analyses provide insight into the collective clinical experience of lowering blood pressure in diabetes. One such meta-analysis identified 40 trials with 100,354 participants performed either exclusively in type 2 diabetes or included trial population subgroups with diabetes.[260] In diabetes every 10 mmHg of systolic blood pressure lowering has an associated 13% reduction in all-cause mortality, 11% reduction in cardiovascular events and 27% reduction in stroke events. This meta-analysis also reveals substantial benefit in lowering blood pressure on reducing microvascular events. Importantly, antihypertensive drug class does not affect the overall results; rather it is the blood pressure lowering *per se* that confers clinical benefit. However, there are differences between particular drugs and individual cardiovascular endpoints. For example, diuretics are associated with a 17% lower relative risk for heart failure (mainly driven by ALLHAT), and ARBs are associated with a lower relative risk of heart failure and mortality (mainly driven by LIFE in which ARBs were compared to beta-blockers). In contrast, calcium channel blockers are associated with a higher relative risk of heart failure but a lower risk of stroke, while beta-blockers appeared to be associated with a higher relative risk of stroke. What is important in putting individual antihypertensive drugs in perspective is that blood pressure lowering by any drug class is associated with cardiovascular benefit in diabetes, but in individual patients, tailoring drug selection to address a particular cardiovascular concern (such as risk of heart failure versus risk of stroke) may be necessary.

In all, only three randomized controlled trials have examined the effect of standard versus more intensive blood pressure lowering in individuals with diabetes.[249,257,261–263] While the ACCORD-BP trial[257] focused on systolic blood pressure, the others targeted control of diastolic blood pressure. A recent meta-analysis including these three trials of a total of 7312 adult participants with type 2 diabetes and hypertension followed for 2–5 years.[264] Intensive reduction of systolic blood pressure to 130 mmHg or lower or diastolic blood pressure to 80

mmHg or lower was associated with a 35% decrease in risk for stroke (RR 0.65, 95% CI 0.48–0.86) and a trend for reduced mortality (RR 0.76, 95% CI 0.55–1.05) as compared with a standard systolic blood pressure target of 140–160 mmHg and diastolic blood pressure target of 85–100 mmHg. However, these results are somewhat inconclusive due to the very different trial designs and blood pressure targets. The total sample size and number of events may not have been sufficient to detect significant benefit for all cardiovascular endpoints. On a cautionary note, ACCORD-BP demonstrated a significant increase in serious adverse events with intensive blood pressure lowering, as described above.

The 2016 Standards of Medical Care by the ADA,[219] the 2015 AHA/ADA Scientific Statement Update,[220] and the most recent American Heart Association guidelines for cardiovascular risk reduction[132] recommend a blood pressure goal of below 140 mmHg for systolic blood pressure and below 90 mmHg for diastolic blood pressure. Initial antihypertensive therapy should include an angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) if the ACEI is not tolerated, for renal protection. If the blood pressure is not at target, the next choice could include a thiazide diuretic or calcium channel blocker. In the context of the recently-published SPRINT results in patients without diabetes, it is the opinion of the authors that it would be reasonable to also consider targeting blood pressure below 120/80 in individuals with diabetes, especially in the presence of renal disease (elevated urine albumin excretion or chronic kidney disease) or increased risk for stroke, while exercising caution in patients with symptoms of hypotension or requiring multiple agents to achieve this target (Table 1).

Antithrombotic medications

Platelet activation and atherothrombosis play key roles in acute coronary syndromes, cerebrovascular events, and the formation and progression of atherosclerotic plaques.[266] The benefits of aspirin in patients with acute or previous vascular disease were first assessed in clinical trials published over 20 years ago involving approximately 100,000 patients in placebo-controlled trials.[267] Meta-analyses of these trials clearly established benefit of aspirin for secondary prevention in patients at high risk due to established cardiovascular disease,[268] defined as patients with an acute or prior history of myocardial infarction, a past history of stroke or transient ischemic attack and patients with stable or unstable angina, vascular surgery, angioplasty, and peripheral artery disease (but not just multiple risk factors). In these patients aspirin was associated with a 27% odds reduction in MACE events. However, in low risk patients (primary prevention) aspirin had a non-significant 10% reduction in MACE events.

In early meta-analyses from 1994, diabetes was included as a high risk group that demonstrated cardiovascular risk reduction with antiplatelet therapy with regimens consisting predominantly of ticlopidine, dipyridamole and sulphinpyrazone.[267] In these early trials in diabetes, only 2 of 10 studies evaluated aspirin (with or without dipyridamole). In those 2 studies of aspirin in diabetes, there were 399 cardiovascular events on the aspirin regimen and 414 on control. In 2002, an update from the antiplatelet trialists' also included diabetes as a high risk subgroup.[269] This update included 4961 patients with diabetes from 9 trials and demonstrated that antiplatelet therapy was associated with only a 7% proportional

reduction in serious vascular events in those with diabetes, as compared with a 25% reduction overall, but wider confidence limits do not exclude benefit for this group. Thus antiplatelet therapy in diabetes, particularly with the use of aspirin, may be less effective at cardiovascular risk prevention than in patients without diabetes. It should also be noted that these trials were performed at a time when intensive management of LDL-cholesterol and blood pressure were not well established.

Therefore, while the benefit of aspirin in secondary prevention is established, benefit of aspirin in primary prevention of ASCVD in individuals with diabetes is less clear.[219, 270] There are three recent published clinical trials of aspirin therapy for primary prevention of cardiovascular disease in diabetes: the Early Treatment Diabetic Retinopathy Study (ETDRS),[271] Prevention of Progression of Arterial Disease and Diabetes (POPADAD),[272] and Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD).[273] ETDRS compared aspirin 650 mg daily versus placebo in 3,711 patients with diabetes (type 1 or type 2 diabetes) and retinopathy, and showed patients receiving aspirin had a numeric decrease in the risk of nonfatal or fatal myocardial infarction; however, the confidence interval crossed 1 (RR 0.85, 95% CI 0.73–1.00). POPADAD was a multicenter study of 1,276 adults with type 1 or type 2 diabetes with subclinical cardiovascular disease defined as a reduced ankle-brachial index in the lower extremity (Figure 4). This study employed a 2 × 2 factorial design with aspirin 100 mg daily and/or an antioxidant capsule. No effect of aspirin (or antioxidant capsule) on the composite primary cardiovascular endpoints (hazard ratio 0.98) was found after a median follow-up period of 6.7 years. JPAD included 2539 patients with type 2 diabetes without known ASCVD in a multicenter study in Japan, randomized to receive 81–100 mg aspirin daily or no aspirin (placebos were not allowed in physician-directed studies at that time) and followed for 4.37 years (Figure 4). The lower rate of the primary endpoint on aspirin treatment did not reach statistical significance (5.4% of subjects in the aspirin group reached the primary endpoint while 6.7% of subjects did so in the non-aspirin group, P=0.16). Importantly, the primary outcome event rate was quite low, and the investigators did not feel that their study was powered to detect a difference between treatment groups. Subsequently, two subgroup analyses of JPAD have been published which need to be interpreted with caution give the overall negative trial. These subgroups had even fewer events but suggested possible benefit of aspirin therapy to reduce cerebrovascular events in patients with type 2 diabetes and poorly controlled blood pressure[274] or high C-reactive protein.[275] An important study limitation is that the initial trial that did not reach statistical significance; hence as subgroup analyses of a negative trial, these present intriguing hypothesis-generating conclusions which must be considered with caution in clinical practice. Several meta-analyses examining the effect of aspirin for primary prevention of ASCVD in diabetes have also been published[276–278] as well as a meta-analysis performed in the general population.[267] Intriguingly, early data suggest that twice daily dosing may increase the beneficial effect,[279,280] and support further study. However, the mechanism for potential greater benefit with twice daily aspirin dosing remains unclear as aspirin covalently modifies cyclooxygenase-1, leading to inhibition of platelet aggregation. As platelets are anucleated cells they cannot synthesize new cyclooxygenase-1, so antiplatelet effects extend over the duration of the platelet lifespan. Taken together, the recent evidence for aspirin in diabetes without baseline clinical

cardiovascular disease has largely been neutral (Figure 4), and recommendations for aspirin use must be tempered by increased risk for bleeding.

The 2016 ADA Standards of Medical Care for Diabetes recommendations regarding aspirin therapy are consistent with the American Heart Association and American College of Cardiology Foundation statement on aspirin for primary prevention of cardiovascular events in people with diabetes, suggesting that low-dose aspirin should be considered in patients with increased CV risk (10-year risk >10%) and for those at intermediate risk, but not for those at low risk for ASCVD (10-year risk <5%).[219, 278] Unfortunately, there is no direct clinical trial evidence to support these risk-based treatment recommendations creating an area of controversy in primary prevention for patients with diabetes. This is in contrast to the clear benefit as outlined in the guidelines for secondary prevention in diabetes which recommend aspirin therapy (75–162 mg daily) in individuals with diabetes and a history of ASCVD. Additionally, dual antiplatelet therapy is reasonable up to 1 year after an acute coronary syndrome. Based on the Dual Antiplatelet Therapy study, in which almost one-third of patients had diabetes, extending dual antiplatelet therapy beyond 1 year after implantation of a drug-eluting stent in patients who have tolerated dual antiplatelet therapy without recurrent ischemic events or bleeding may be considered to reduce major adverse cardiac and cerebrovascular events and stent thrombosis.[281]

Lifestyle

An intensive program including counseling about medical nutrition therapy, physical activity, and behavior change, with ongoing support and frequent follow-up are needed for lifestyle management of weight, cardiovascular risk factors, and glycemia itself in diabetes.[219,282] Weight loss, a healthy eating pattern, and increasing physical activity are also effective for reducing cardiovascular risk factors in individuals without diabetes,[219, 283,284] and are effective for prevention of diabetes.[205] Lifestyle interventions should be recommended in all patients with diabetes, patients at risk for ASCVD, and patients with known ASCVD.

The Look AHEAD trial is the seminal study of lifestyle intervention in type 2 diabetes treatment, conducted as a multi-center, U.S.-only trial of 5145 obese or overweight patients with type 2 diabetes randomized to receive intensive lifestyle intervention consisting of frequent visits, calorie restriction, and physical activity versus a control group who received only standard diabetes education and support.[265] The primary endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina, with a maximum follow-up planned for 13.5 years. Despite greater weight loss, reduction in HbA_{1c}, and improvements in fitness and cardiovascular risk factors in the intervention group, there was no difference in the primary outcome between treatment arms (HR 0.95; 95% CI 0.83 to 1.09; p=0.51), resulting in early trial termination for futility at a median follow-up of 9.6 years.[265] The narrow 95% CI for the primary outcome was consistent with the conclusion that the absence of between-group differences was not due to lack of a sufficient number of primary endpoint events.[285]

More than half of adults in the U.S. with diabetes are obese,[286] while more than 75% are overweight.[178] One of the cornerstones for lifestyle management of ASCVD consists of

weight loss for individuals who are obese or overweight.[283] Weight loss results in increased HDL cholesterol levels,[287,288], decreased triglycerides,[287–289] and decreased blood pressure.[287,290] A modest degree of weight loss (5–7% of body weight) is recommended with similar clinical recommendations for individuals with or without diabetes.[291] Another parallel goal is to prevent weight gain, and certain glucose-lowering medications are more likely to result in weight gain (insulin, sulfonylureas and thiazolidinediones), while others are either weight neutral (dipeptidyl peptidase 4 [DPP4] inhibitors, or gliptins), and some result in weight loss (metformin, glucagon-like peptide [GLP]-1 receptor agonists and sodium-glucose cotransporter [SGLT]2 inhibitors, or gliflozins).[292] Interestingly, the use of insulin does not preclude weight loss,[285] and short- and long-term weight loss can occur with adherence to treatments. The most effective strategies for weight loss in diabetes include a Mediterranean diet[287] and an intensive program combining diet and physical activity.[265] Participants in the intensive lifestyle arm of the Look AHEAD trial maintained a weight loss of 6% of body weight at 10 years as compared with 3.5% in the standard lifestyle group.[265] Strategies that were associated with decreased body mass index (BMI) in the Look AHEAD study included self-weighing on a weekly basis, eating breakfast regularly, and reducing the intake of fast foods, increasing physical activity, decreasing portion sizes, and meal replacements.[293]

Recommendations for healthy eating should be individually tailored according to caloric requirements, personal and cultural food preferences, type of diabetes, prescribed medications, and comorbid medical conditions. General recommendations include reducing the intake of saturated fat (to 5–6% of total calories), eliminating *trans*-fat, lowering sodium intake (to below 2300 mg/day or even lower, to less than 1500 mg/day), and increasing intake of dietary fiber.[282] A Mediterranean-style diet high in monounsaturated fatty acids (MUFAs) is a recommended alternative to consuming a higher carbohydrate low fat diet in order to control glycemia and cardiovascular risk factors.[282] Although there have been many clinical trials examining low versus high carbohydrate diets in patients with insulin resistance and/or diabetes,[288,290,294–298] the long-term cardiovascular effects of diets low in carbohydrates have not been examined adequately,[282] and an optimal combination of macronutrients cannot be recommended for type 2 diabetes to prevent ASCVD. In order to help control lipids and blood pressure, a dietary pattern that focuses on the intake of vegetables, moderate amounts of fruit and whole grains, poultry, fish, low-fat dairy, legumes, non-tropical vegetable oils and nuts, and limits the intake of sweets, sugar-sweetened beverages and red meats is recommended.[283] The Dietary Approaches to Stop Hypertension (DASH) diet,[299,300] the ADA recommendations for medical nutrition therapy,[282] and the American Heart Association/American College of Cardiology lifestyle management guidelines[283] can all be used to guide dietary recommendations. Alcohol intake in patients with diabetes can increase the risk for delayed hypoglycemia and blunt symptom recognition, so patient education regarding management strategies is needed.

Physical inactivity is associated with increased risk of mortality.[301] A number of epidemiologic studies show regular physical activity reduces cardiovascular and total mortality in patients with diabetes or prediabetes.[302–304] Moderate or high levels of physical activity were associated with a reduced risk of total and cardiovascular mortality, independent of BMI, blood pressure, total cholesterol and smoking, in a cohort of 3708

individuals with type 2 diabetes in Finland followed prospectively for a mean of 18.7 years.[305] Even being physically active only occasionally (less than once a week) reduces the risk of all-cause mortality by 28%, while exercising once a week confers a 40% lower risk of mortality compared with being completely sedentary.[306] However, individuals with type 2 diabetes may have more barriers to exercise than people without diabetes that limit successful implementation of a physical activity prescription, including presence of comorbidities, risk of hypoglycemia related to glucose-lowering medications, presence of microvascular complications such as visual impairment, peripheral and autonomic neuropathy and even decreased functional exercise capacity which can increase the discomfort associated with initiating a bout of physical activity.[307] It should also be noted that no clinical trials have demonstrated that physical activity *per se* reduces cardiovascular events in diabetes.

Despite the fact that the Look AHEAD study did not demonstrate a reduction in cardiovascular outcomes for intensive lifestyle intervention as compared with standard advice, there were a number of other benefits including increased physical fitness[308], reduction in diabetic renal disease,[309] and remission of diabetes[310] which have positive impacts on cardiovascular risk, and reduction of glucose-lowering medications[310] and depression,[311–313] which both have direct impact on quality of life. Every attempt must be made to promote and reinforce lifestyle management recommendations and to refer individuals with diabetes to specialists if hypoglycemia or fear of hypoglycemia present a barrier to implementing lifestyle interventions.

Glycemic control

Although patients with type 2 diabetes may be able to achieve glycemic targets without use of glucose-lowering medications, this is often possible only soon after diagnosis when the degree of hyperglycemia is mild to moderate and/or significant modifiable aspects of lifestyle are contributing to the patient's disordered glucose metabolism (e.g. excess weight, a dietary pattern high in excess calories and refined carbohydrates and low in viscous fiber, little to no physical activity). Diabetes is a progressive, chronic condition, and while there are multiple pathophysiologic mechanisms contributing to hyperglycemia in diabetes,[314] progressive beta-cell failure is a key aspect of the natural history of type 2 diabetes,[315–317] with gradually worsening hyperglycemia and rising HbA_{1c}.[199,318] Eighty-five percent of individuals with established diabetes take glucose-lowering medications, making up 17.7 million people in the U.S.[319] Since ASCVD in the form of myocardial infarction and stroke accounts for up to 80% of mortality in type 2 diabetes,[320] medications taken to manage hyperglycemia must not adversely impact cardiovascular risk factors or increase ASCVD, and ideally would ameliorate or reverse atherogenesis and lower cardiovascular risk. However, many of the medications available to treat hyperglycemia in diabetes have no effect on cardiovascular risk or may have a theoretical concern for exacerbating cardiovascular risk factors and/or cardiovascular disease itself.[321–328] While lowering glucose concentrations will ameliorate immediate symptoms of hyperglycemia (polyuria, polydipsia, and weight loss) and longer term microvascular disease, there is less evidence for targeting HbA_{1c} to lower cardiovascular risk.

Intensive glycemic control reduces relative risk of nonfatal myocardial infarction and coronary heart disease events by about 15%, although there is no effect of intensive glycemic control on all-cause mortality in meta-analysis of the multiple randomized clinical trials targeting different intensity of glycemic control.[329] Most studies are of relatively short duration, and long-term follow-up of both the Diabetes Control and Complications Trial (DCCT)[330] and United Kingdom Prospective Diabetes Study (UKPDS)[41] show reduced risk for cardiovascular events emerge over time in those with recently diagnosed type 1 or type 2 diabetes respectively who were previously randomized to intensive glycemic control. However, these effects take years to manifest and few studies extend observations over the extended timeframe which may be necessary to realize benefit of glucose lowering *per se*. Therefore reasonable glycemic control, targeting hemoglobin A_{1c} (HbA_{1c}) below 7% may be appropriate for those with ASCVD or multiple risk factors but long life expectancy, while higher targets, above 7% but below levels associated with signs and symptoms of hyperglycemia, are appropriate for those with more limited life expectancy or in whom lower targets cannot be achieved safely.

The UKPDS follow-up study provides the strongest evidence to date for glucose control and reduction in cardiovascular events and mortality in type 2 diabetes.[41] UKPDS enrolled patients with newly-diagnosed type 2 diabetes who were randomized to intensive versus standard glycemic control and followed for 10 years, with prolonged follow-up study over an additional 10 years of observation without further intervention, during which time participants returned to their primary care physicians for clinical care. The initial separation of HbA_{1c} of 0.9% (mean HbA_{1c} 7.0% in the intensive group and 7.9% in the conventional treatment group) was lost early in the follow-up observation study, during which the average HbA_{1c} in the two groups converged. Although not seen initially over the first 10 years when glycemic differences were achieved,[199] a 15% relative risk reductions for myocardial infarction and 13% risk reductions for death from any cause emerged over time, despite loss of between group differences in HbA_{1c} over the first year of prolonged observation. As similar latent benefits have been seen in type 1 diabetes in the context of the DCCT[330] a “legacy effect” or “metabolic memory” has been postulated, with persistence of benefits of initial good glycemic control (and conversely, persistent adverse effects of poor glycemic control).[331,332] It has been proposed that the long period of time required to see an effect of glycemic control on cardiovascular risk may be partially explained by improved adherence of all study participants to other aspects of cardiovascular risk factor reduction, such as use of statins and ACEI diluting effects of glycemic control *per se* on cardiovascular endpoints.[41] Reductions in cardiovascular risk has not been observed in subsequent large, randomized controlled trials of intensive glucose-lowering in type 2 diabetes over shorter duration in patients with more advanced cardiovascular disease. It remains uncertain whether absence of benefit is due to inclusion of patients with advanced disease beyond a period of reversibility, short trial duration for effect to manifest, safety of glucose lowering with current available interventions, or absence of effect of glucose lowering *per se*. Studies have not revealed improvement in primary cardiovascular endpoints with lowering of HbA_{1c} below 6.5–7%[333–335] and even raise concern about increasing cardiovascular risk, as seen in ACCORD.[333] Meta-analyses of trials that include ACCORD, ADVANCE and the Veterans Affairs Diabetes Trial (VADT) support glucose-lowering as beneficial for reducing

composite cardiovascular endpoints and nonfatal myocardial infarction, but there was no effect on total mortality which warrants further investigation.[329,336–338] Evaluating these potential benefits of intensive glycemic control in low-risk diabetes is challenging due to low event rates needed to achieve adequate statistical power. It should be noted that ACCORD was designed to define the most effective combinatorial treatment of risk factors in type 2 diabetes (glycemia, blood pressure, lipids) to maximally reduce cardiovascular risk.[339] The trial was stopped prematurely due to the unexpected finding of increased all-cause mortality (primarily cardiovascular) (HR 1.21; 95%CI, 1.02 to 1.44), although without difference in the rate of the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (P=0.13) and fewer nonfatal myocardial infarctions. The increase in cardiovascular death was driven in part by congestive heart failure, in the setting of fewer nonfatal myocardial infarctions in the intensive treatment group. Neither ADVANCE nor VADT demonstrated an increased mortality or composite cardiovascular risk with intensive glycemic control as defined by HbA_{1c} below 7%.[334,335]

Several explanations may account for discrepant findings in UKPDS and ACCORD, ADVANCE, and VADT.[24,247] Patients in UKPDS had newly-diagnosed diabetes, whereas patients with type 2 diabetes enrolled in the other three trials had diagnosed diabetes for a mean duration of 7.9–11.5 years. A high proportion of latter trial participants had established coronary artery or macrovascular disease at baseline (32–40%), which was an intentional aspect of trial design in ACCORD, ADVANCE and VADT. Average achieved HbA_{1c} ranged from 6.4–6.9% in the intensive treatment groups in ACCORD, ADVANCE, and VADT, but was higher in UKPDS. As anticipated, there were fewer cardiovascular events in ACCORD subjects without prior cardiovascular disease or with baseline HbA_{1c} below 8%. However, only the subset of participants with baseline HbA_{1c} above 8.5% in the intensive treatment group was found to be at higher risk for mortality. Besides higher baseline HbA_{1c}, increased mortality was associated with history of neuropathy and higher HbA_{1c} on treatment, with higher mortality occurring in the subset of patients randomized to intensive control but unable to achieve target glycemia.[340–343] A higher average on-treatment HbA_{1c} was also a strong predictor of mortality regardless of treatment group.[343] There was a linear increase in risk for mortality with increasing HbA_{1c} across the range of 6% to 9% in the intensive-treatment group, while there was a U-shaped relationship in the standard-treatment group, with lowest hazard rates of all-cause mortality in the intensive control group achieving lowest glycemic targets but at HbA_{1c} of 7–8% for standard-of-care,[343] suggesting factors associated with inability to achieve glycemic targets influence mortality, including diverse factors such as more severe underlying disease, inability to adhere to lifestyle and/or pharmacologic regimens, or drug interactions with use of polypharmacy in attempt to achieve goals. Although individuals with severe hypoglycemia in ADVANCE had a higher risk for death, the higher incidence of severe hypoglycemia in the intensive treatment group was not associated with higher risk for cardiovascular endpoints.[334] Furthermore, although there were more instances of severe hypoglycemia in the intensive treatment group in ACCORD, lower rather than higher mortality was observed for those with severe hypoglycemia in this group.[344]

The VADT follow-up study[345] demonstrated that an expanded MACE endpoint was reduced significantly in the intensive treatment group; however, cardiovascular death was not,

tempering enthusiasm for the results and consistent with prior meta-analyses showing that intensive glycemic control reduces relative risk of nonfatal MI and coronary heart disease events but without an effect on mortality. Subgroup analysis suggests that persons without macrovascular disease at baseline may benefit the most, but these are not necessarily the patients who were enrolled in many of the CV outcome trials.

Insulin-sparing versus insulin-provisional strategies—Epidemiologic studies demonstrate a higher prevalence of cardiovascular disease in patients treated with insulin.[326,346] While this has raised concern about the safety of insulin, this concern has not been born out in multiple studies[104,347] and may be the result of indication bias, since insulin tends to be used more in patients with more severe diabetes of longer duration, which coincides with factors that increase cardiovascular risk. BARI-2D examined insulin provisional versus insulin sparing (sensitization) therapies in 2368 patients with type 2 diabetes and heart disease undergoing prompt revascularization with intensive medical therapy as compared with intensive medical therapy alone.[104] There was no difference in survival or freedom from major adverse cardiovascular events in groups randomized to receive insulin or a sulfonylurea versus metformin or a thiazolidinedione. Likewise, insulin glargine had a neutral effect on cardiovascular outcomes when used to target normal fasting plasma glucose levels for more than 6 years, in patients with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes.[347] Furthermore, randomized controlled trials utilizing insulin therapy as part of the glycemic lowering strategy have not shown an increase in cardiovascular risk with insulin.[199,348] However, it is plausible there could be differences in potential cardiovascular risks for different forms of insulin; the most recent example was a delay in approval of insulin degludec by the Food and Drug Administration because of initial concerns about a signal for increased risk of major adverse cardiovascular events, although the upper limit of risk if present must be small as the FDA has approved degludec based on interim data while the definitive cardiovascular outcome trial is ongoing (NCT01959529).

Hemoglobin A_{1c} as a surrogate endpoint—When the Diabetes Control and Complications Trial (DCCT)[348] showed substantial decreases in microvascular complications with intensive glycemic control in type 1 diabetes, and similar reductions in risk for development and/or progression of microvascular complications with intensive glycemic control were observed in type 2 diabetes,[199,349] HbA_{1c}, as a measure of average glycemia over time became recognized as a surrogate endpoint intended to substitute for the clinical endpoint of microvascular disease. Importantly, an appropriate surrogate endpoint should be highly associated with the disease and disease severity such that a treatment effect on a surrogate biomarker should be directly correlated with clinical benefit, while lack of treatment on a surrogate endpoint should be associated with no clinical benefit. In DCCT, although differences in HbA_{1c} between intensive and standard treatment groups explain virtually all of the differences in risk of retinopathy between groups, total glycemic exposure (HbA_{1C} and duration of diabetes) accounts for only 11% of the variation in retinopathy risk in the complete cohort. Other factors, such as genetics, environment, and non-glycemic risk factors, including dyslipidemia and blood pressure, presumably account for the remaining 89% variability in risk of retinopathy complications in patients with diabetes independent of

HbA_{1c}.[350] Therefore, HbA_{1c} is only one indicator of risk for microvascular complications of diabetes, and whether HbA_{1c} is a valid surrogate endpoint for macrovascular disease risk remains uncertain. Investigation into new risk markers that account for factors not captured by HbA_{1c} that may impact risk of complications[59,351,352] and risk prediction models including these new putative factors is needed.[353]

Bariatric surgery

Bariatric surgery induces substantial and sustained weight loss[354] and remission or improvement in type 2 diabetes in 40–85% of patients, hypertension in 28–75% of patients, and dyslipidemia in 70–90% of patients.[355,356] Rates of improvement in obesity comorbidities vary based on both the specific procedure performed and underlying patient characteristics. Together, these metabolic improvements may lead to reduced ASCVD risk and event rates. Indeed these observational cohort studies suggest bariatric surgery versus usual care may be associated with reduced number of cardiovascular deaths and lower incidence of cardiovascular events in obese adults,[357,358] as well as reduced incidence of myocardial infarction in obese individuals with type 2 diabetes.[359] Total mortality rates appear 30–40% lower in patients who have had bariatric surgery for obesity management[354,357] and may be more prominent in those with diabetes at the time of surgery,[360] although survival benefit effects may take years to manifest. While key observational cohort controlled studies demonstrate mortality benefit, these data originate from non-randomized trials and thus must be interpreted with extreme caution. Randomized controlled clinical trials comparing effectiveness of bariatric surgery to non-surgical medical management of type 2 diabetes are shorter in duration and have small numbers of participants but replicate observational studies for improvement in obesity and diabetes related comorbidities.[361–365] Remission of type 2 diabetes may not be sustained and relapse requiring additional pharmacologic therapy may become necessary. It remains uncertain whether long periods of metabolic improvement following bariatric surgery will improve cardiovascular and/or mortality outcomes, as suggested by longer term follow-up for the UKPDS,[41] Steno-2,[366] and the Swedish Obesity Subjects (SOS) study.[358] However, it is reasonable for surgically-appropriate obese patients with type 2 diabetes to consider bariatric intervention, as associated surgical risks have decreased in the setting of more stringent standards and the formation of Bariatric Centers of Excellence, and with the reduction of short-term surgical risk due to laparoscopic versus open procedures.[367,368] Thus, for patients with diabetes and BMI above 35 kg/m^2 who have undergone appropriate medical and psychologic evaluation, who understand the risks, lifestyle changes, and monitoring involved with bariatric surgery, and have medical, social and psychologic support, bariatric surgery can be recommended when performed by an experienced bariatric surgeon at a bariatric center of excellence. Interestingly, higher baseline fasting insulin, a proxy for insulin resistance, rather than higher BMI best predicts groups most likely to realize lower incident rates for type 2 diabetes and cardiovascular risk among patients without diabetes undergoing bariatric surgery.[358]

Cardiovascular risk of diabetes drugs

The UKPDS showed a cardiovascular benefit for metformin, albeit in a relatively small number of individuals.[103] Although concerns have been raised regarding increased cardiovascular risk with sulfonylureas in epidemiologic studies, this has not been consistent, and intensive glycemic control using sulfonylureas in UKPDS did not demonstrate increased risk.[199] Interestingly, over longer term observation, cardiovascular benefits were realized in the intensive group originally receiving sulfonylureas.

In 2008 the FDA issued a Guidance for Industry requiring that the approval of all new antidiabetic drugs rule out an unacceptable level of excess cardiovascular risk. From 1995 to this time, HbA_{1c} was the sole efficacy endpoint for approval of anti-diabetes therapies. Randomized trials of new glycemic lowering agents were typically 6 months in duration or less, with open label extension; the majority of patients enrolled in the trials were diabetes drug naïve, or had short duration of disease; cardiovascular disease and renal disease were often exclusionary; the safety databases had between 3000 to 5000 patients exposed (the majority less than one year), with longer-term experience uncontrolled; there were sparse cardiovascular events and no central, blinded adjudication process for adverse experiences to facilitate meta-analysis across enabling trials. Thus, experience in the pre-approval trials for new diabetes drugs differed substantially from the way drugs might be used in the broader population, especially relevant for patients with diabetes and cardiovascular disease, which co-occur with high prevalence. FDA concerns regarding diabetes drug development were furthered in part by a meta-analysis of several small trials suggesting excess risk with the drug rosiglitazone.[369] Notably the Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes (RECORD) trial [370] did not substantiate these concerns, even following re-adjudication of the cardiovascular events within the RECORD trial.[371] Furthermore, the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) did not show increased ASCVD risk with pioglitazone.[102]

For these reasons, in 2008 the FDA established a new guidance for industry for approval of diabetes therapeutic agents which remains in effect for all new diabetes drugs, including recently approved agents in multiple novel classes of glucagon-like peptide (GLP)-1 receptor agonists, dipeptidyl peptidase (DPP)-4 inhibitors, and sodium glucose cotransporter-2 (SGLT2) inhibitors, which have become available since implementation of the guidance process. The cardiovascular effects of glucose-lowering drugs have been reviewed recently by Ferrannini and DeFronzo.[372] Recent cardiovascular outcome trials have shown a cardiovascular benefit with empagliflozin, an SGLT2 inhibitor[373] and have been reported for liraglutide,[374] a GLP-1 receptor agonist, although publication of trial data for the latter is still pending. No glucose lowering agent studied under the guidance document has shown increased risk of major adverse cardiac events. Interesting and unexpected findings have come from these cardiovascular outcome trials. The DPP-4 inhibitor saxagliptin appears to modestly increase risk for hospitalization for heart failure without effect on major adverse cardiovascular events (see below section: Management of diabetes in heart failure).[375]

SGLT1 and SGLT2 are the two sodium glucose cotransporters responsible for glucose reabsorption in the proximal tubule of the kidney.[376] Inhibition of SGLT2 results in increased glucose transport to the distal nephron with reduction in renal hyperfiltration[377] and lowering of the serum glucose threshold for renal reabsorption of glucose leading to excretion of 80–100 grams of glucose per day.[376] Three drugs in this class have been approved by the FDA for the treatment of diabetes: dapagliflozin, canagliflozin, and empagliflozin. Several other drugs in this class are in development. These drugs lower HbA_{1c} by 0.5–1.2% and do not cause hypoglycemia except when used with insulin provisional therapies (insulin or sulfonylureas).[378] The SGLT2 inhibitors lower blood pressure without increasing heart rate, increase HDL- and LDL-cholesterol levels, and induce modest weight loss. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) study enrolled 7020 patients with type 2 diabetes at high risk for cardiovascular events, and randomized participants to receive empagliflozin 10 mg versus 25 mg versus placebo.[373] The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the key secondary outcome was hospitalization for heart failure. The study was stopped early, with a mean observation time of 3.1 years. Empagliflozin resulted in a lower risk of the primary outcome (HR 0.86, 95% CI 0.74–0.99, P=0.04 for superiority), lower risk of cardiovascular death and all-cause mortality. Potential mechanisms for the reduction in cardiovascular risk found with empagliflozin include combined reductions in blood pressure, body weight (including visceral adiposity), albuminuria, glucose, arterial stiffness, sympathetic nervous system activation, oxidative stress, uric acid, diuresis and improvement in cardiac function.[379] Other potential mechanisms remain speculative including potential secondary effects on SGLT1[380] and effects on mineralocorticoid metabolism.[377] Whether this beneficial effect on cardiovascular outcomes is a class effect or a drug effect is unknown, and results of other cardiovascular outcome trials with SGLT2 inhibitors will not be available until 2017 for canagliflozin [CANagliflozin cardioVascular Assessment Study (CANVAS), NCT01032629] and 2018 for dapagliflozin [Dapagliflozin Effect on CardiovascuLAR Events (DECLARE)-TIMI58, NCT01730534]. Until then, current evidence supports use of empagliflozin may reduce cardiovascular risk. Because of the beneficial effects on factors that play a role in cardiovascular risk such as weight, visceral fat, blood pressure, arterial stiffness, and albuminuria, the SGLT2 inhibitors may be preferred over other drug classes, although until the additional cardiovascular outcome trials are completed, this approach warrants continued caution. Furthermore, as with any other medical therapy, each individual patient’s comorbidities and complications must be considered prior to initiating SGLT2 inhibitor therapy. Potential adverse effects of SGLT2 inhibitor therapy include genitourinary infections, hypovolemia, “euglycemic” diabetic ketoacidosis, and skeletal fractures.

Importantly, these cardiovascular outcome trials conducted under the 2008 FDA Guidance are designed to evaluate safety of use of diabetes agents in patients with diabetes. Study populations enrolled are at especially high risk for or with underlying ASCVD, as this population is necessary to accrue sufficient events in a short period of time for study conduct. These studies do evaluate cardiotoxicity over short to medium term administration, but they do not address impact of early diabetes intervention, impact of long duration

glycemic control, nor the merit of lowering glucose *per se*, as other anti-diabetes medications outside of the class under investigation are adjusted according to individual glucose goals, permitting assessment of possible drug-specific effects by minimizing potential confounding from differential glucose control.

Management of diabetes in the setting of ASCVD

Since type 2 diabetes confers an increased risk of ASCVD, the vast majority of diabetes patients without ASCVD fall into the moderate or high ASCVD risk category. Though some patients may fall into a lower risk category, all patients should undergo lifestyle intervention. Diabetes therapies should otherwise be selected on an individual basis, with special caution used when treating older patients. In the setting of known ASCVD, we recommend a treatment strategy that primarily focuses on cardiovascular risk reduction (Table 1). Regarding glycemic control, a goal HbA_{1c} 7.0% or less is recommended by the authors if multiple diabetes drugs are tolerated, and polypharmacy does not diminish intensity of cardiovascular risk management; however if this is not the case, a less intensive goal of HbA_{1c} 7.5% or below is recommended. For patients at high risk of ASCVD, an HbA_{1c} 7.0% or below would be reasonable, if this can be achieved with minimal hypoglycemia. For patients without known ASCVD who are at moderate risk, an aggressive goal of HbA_{1c} 6.5% or below will substantially reduce the risk for microvascular complications and may contribute to eventual reduction in ASCVD.[41]

Multiple factors must be considered in the selection of diabetes medications for patients with ASCVD. The strong data supporting the effect of glucose-lowering to reduce microvascular disease which has a direct impact on cardiovascular risk (especially albuminuria) and eventual long-term reduction in ASCVD over 20 years (from the UKPDS follow-up study) must be balanced against potential acute effects of hypoglycemic episodes, increased risk of heart failure (thiazolidinediones and potentially select DPP-4 inhibitors) and weight gain (sulfonylureas, insulin), other side effects, and cost. Upon a background of lifestyle interventions, the first-line pharmacologic therapy for glucose-lowering should be metformin, if renal function is adequate (Table 2),[381–386] and noting recently revised 2016 FDA guidance for renal safety of metformin.[387] eGFR should be assessed before initiation of metformin and at least annually for patients using metformin and more frequently for patients at increased risk for renal impairment; starting metformin is generally not recommended for those with eGFR between 30–45 ml/min/1.73m^2 but may be continued in this range for those already on the drug when the risk-benefit supports ongoing use; for those with or developing eGFR below 30 ml/min/1.73m^2 metformin should be discontinued. In addition to those with heart failure, liver disease, alcoholism, treatment with metformin should be discontinued at the time of iodinated contrast imaging and resumed if renal function is stable when reassessed after 48 hours.

In light of the EMPA-REG trial results with empagliflozin[373] and early reports on the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (LEADER) trial with liraglutide reducing major adverse cardiovascular event rates,[374] the next drug to be considered in a patient with persistent hyperglycemia despite adherence to lifestyle and metformin might include either these

specific drugs or SGLT2 inhibitors or GLP-1 receptor agonists class agents. Although only top-line results are available for LEADER, details supporting these findings are anticipated shortly. Interestingly a neutral cardiovascular profile was seen in the Evaluation of LIXisenatide in Acute Coronary Syndrome (ELIXA) trial with lixisenatide,[382] currently approved by the European Medicines Agency, and additional review of the data is needed to help determine if key aspects of study design underlie potential differences in findings between trials or if differences between class agents may be important. DPP-4 inhibitors are an option except possibly in individuals with heart failure, as discussed in the next section on heart failure.[386] Prioritization for sulfonylureas is lower in the setting of ASCVD because of the risk for hypoglycemia, although with careful monitoring and in selected patients, these agents are a reasonable choice, especially in those with higher baseline HbA_{1c} in whom hypoglycemia is less likely to occur. Insulin is often needed to achieve glycemic targets and has not been shown to increase ASCVD risk,[347] although it carries a high risk of hypoglycemia and increases renal sodium retention.[388–390] The BARI-2D trial showed that an insulin sparing strategy did not confer a cardiovascular benefit, but because of the aforementioned concerns, a basic paradigm of insulin sparing (reduction in insulin dose or discontinuation of insulin preferentially before reducing or stopping other diabetes medications) is generally recommended, recognizing that insulin provision therapy is frequently necessary with longer duration of disease and may be preferred when multiple agents are required to maintain glycemic targets.

For patients requiring multiple agents to achieve their individualized HbA_{1c} goal, a strategy for prioritizing management of diabetes in the setting of CV risk reduction is needed. A suggested approach by the authors is outlined in Table 1. An overview of diabetes treatment including available classes of glucose-lowering agents, magnitude of HbA1c lowering, mechanisms of action, side effects, and key clinical considerations is included in Table 2. Published randomized controlled trials of cardiovascular outcomes for glucose-lowering agents are outlined in Figure 5.[391–396]

Epidemiology of diabetes and heart failure

Heart failure has been called “the frequent, forgotten, and often fatal complication of diabetes.”[397] Risk for heart failure increases 2.4-fold in men and 5-fold in women with compared to those without diabetes, as seen in the Framingham Heart Study.[398] Conversely, diabetes is an important predictor of heart failure, independent of concomitant hypertension or coronary artery disease.[398] Subsequent studies confirm higher prevalence of heart failure, incident diagnosis of new heart failure in patients without baseline heart failure, and risk of heart failure hospitalization or death among patients with compared to those without diabetes.[399–403] Heart failure is the second most common manifestation of cardiovascular disease after peripheral arterial disease, as demonstrated in the largest cohort study of almost 1.9 million patients with type 2 diabetes followed for a median of 5.5 years.[404] Multiple factors, including age, ischemic heart disease, and peripheral artery disease, as well as diabetes-specific risk factors, such as poor glycemic control (higher HbA_{1c}) and insulin resistance, have been associated with heart failure in patients with diabetes.[36, 401–403, 405–407] Accelerated atherosclerosis of diabetes may be diffuse and severe. Consequently, ischemic cardiomyopathy is a major cause of heart failure in the

diabetes population. Even in the absence of epicardial coronary artery disease, microvascular disease, characterized by arterial thickening and fibrosis, as well as endothelial and vasomotor dysfunction, can increase risk of heart failure in diabetes. Hypertension is another common comorbid condition in diabetes causing left ventricular hypertrophy and contributing to the development of heart failure. [408]

The relationship between diabetes and heart failure appears bi-directional. There is increased risk of heart failure in diabetes, and heart failure is a risk factor for diabetes.[409,410] Increased rates of diabetes occur among patients with heart failure: 42% of 48,612 patients hospitalized with heart failure in the Organized Program To Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry and 40% of hospitalized patients with low ejection fraction in the Evalve® Cardiovascular Valve Repair (MitraClip®) System Endovascular Valve Edge-to-Edge REpair STudy (EVEREST) had diabetes.[411,412] The presence of diabetes in hospitalized heart failure patients is associated with worse outcomes, including longer hospital stay, heart failure-related rehospitalization, and greater risk of cardiovascular mortality.[411,413–415] Among stable outpatients with heart failure, diabetes remains an independent predictor of heart failure hospitalization and cardiovascular mortality after adjusting for left ventricular ejection fraction.[416] Even in the absence of overt diabetes, up to two-thirds of heart failure patients exhibit insulin resistance,[417] which not only increases the risk of subsequent diabetes but also independently predicts poor prognosis in patients with heart failure. [418]

In 1954, Lundbaek made the initial observation that myocardial dysfunction was common in elderly patients with diabetes, and he termed this phenomenon “diabetic cardiopathy”.[419,420] Almost two decades later, Rubler reported postmortem findings from four patients with diabetes and heart failure in the absence of significant epicardial coronary atherosclerosis, valvular, congenital, or hypertensive heart disease, or alcoholism.[421] He described myocardial hypertrophy, fibrosis, and microvascular wall thickening and proposed a diabetes-related cardiomyopathy caused by abnormal myocardial metabolism or myocardial microangiopathy. These observations stimulated basic and clinical studies examining phenotypes and pathophysiologic mechanisms of diabetes-related cardiomyopathy. Despite efforts to understand diabetic cardiomyopathy, there is ongoing controversy surrounding its unique pathophysiology, and it remains a vaguely-defined condition only briefly acknowledged in contemporary clinical practice guidelines.[246, 422] Furthermore, although diabetes is now accepted as an independent cause of cardiomyopathy, severity of diabetes-related myocardial abnormalities may be amplified by comorbid conditions which increase the risk of ventricular hypertrophy and/or susceptibility to myocardial ischemia, ultimately increasing the risk for heart failure.

Diabetic cardiomyopathy- clinical phenotype

The natural history of diabetic cardiomyopathy remains incompletely understood. Experimental animal models of diabetes and cardiac imaging-based human studies demonstrate both diastolic and systolic dysfunction.[423–432] Traditionally, diabetic cardiomyopathy has been characterized as a progressive disease beginning with subtle, early features of impaired diastolic dysfunction followed by overt diastolic dysfunction, with or

without ventricular hypertrophy. Thus, diastolic dysfunction is the hallmark characteristic of diabetic cardiomyopathy, with systolic dysfunction representing the final stage of progressive disease.[430–432] Depressed pressure development and decay rates and prolonged cardiac relaxation times occur as early as 2–3 weeks after streptozotocin-induced diabetes in rats, prior to left ventricular remodeling, supporting this diastolic-dysfunction hypothesis.[428,429] Human studies similarly demonstrate early abnormalities in diastolic function, including reduced peak myocardial systolic and early diastolic velocities, seen in 27–70% of asymptomatic patients with diabetes without overt diastolic dysfunction or LV hypertrophy,[423–427] as well as greater LV mass, wall thickness, and arterial stiffness (independent of blood pressure and body mass index) in diabetes patients.[433–435] Clinically, patients with diabetic cardiomyopathy and diastolic dysfunction initially present with a restrictive phenotype as heart failure with *preserved* ejection fraction (HFpEF). [436–438]

However, diabetic cardiomyopathy can also present with systolic dysfunction and a dilated phenotype as heart failure with *reduced* ejection fraction (HFrEF). In animal models, diabetes has been associated with systolic dysfunction,[439,440] with longer duration of diabetes necessary for development of reduced ejection fraction.[441] These findings are paralleled by human studies in which diabetes has been associated with a significant increase in the odds of idiopathic dilated cardiomyopathy (odds ratio 1.75; 95% confidence interval 1.71, 1.79).[442] Additionally, left ventricular systolic dysfunction can be induced with exercise in asymptomatic patients with diabetes and normal resting ejection fraction,[443,444] perhaps representing reduced cardiac reserve and an early, preclinical phase of systolic dysfunction. It is also hypothesized that subtle impairments in longitudinal systolic function may be missed due to the traditional focus on radial myocardial contraction and more sensitive techniques, such as strain and myocardial tissue Doppler velocity, may better detect early systolic abnormalities in patients with diabetes.[445,446] Taken together, these data suggest a spectrum of diabetic cardiomyopathy. [432]

Recently, Seferovic and Paulus proposed a new paradigm in which restrictive and dilated manifestations of diabetic cardiomyopathy are two distinct clinical phenotypes rather than successive stages.[447] This conceptual shift is based on multiple lines of evidence. Normal age-related cardiac remodeling is characterized by decreasing left ventricular dimensions and increasing fractional shortening, a pattern attenuated but not reversed by diabetes.[448] Furthermore, development of symptoms in hypertensive patients with HFpEF is associated with a reduction, not dilatation, of the left ventricle.[449] In the general HFpEF population, progression to a dilated phenotype is uncommon; when it occurs, it is often related to myocardial infarction or older age but not diabetes.[450] Finally, differential mechanisms of left ventricular remodeling specific to HFpEF versus HFrEF have been proposed.[451] Thus, diastolic dysfunction may not be a precursor to systolic dysfunction; rather, specific mechanisms with selective involvement of endothelial cells versus myocytes in diabetes-related metabolic and cellular disturbances, may account for the independent evolution of two distinct forms of diabetic cardiomyopathy.[447]

Pathophysiologic mechanisms of heart failure in diabetes

The pathogenesis of diabetic cardiomyopathy is complex and multifactorial. Although hyperglycemia and insulin resistance are the main physiologic disturbances in diabetes, multiple mechanisms, such as derangements in cellular metabolism, function, and structure, autonomic neuropathy, and neurohormonal dysregulation are believed to play a role in the associated cardiomyopathy (Figure 6). Diabetic cardiomyopathy can be primarily traced to multiple processes: oxidative stress,[452] hyperglycemia,[432,453,454] hyperinsulinemia,[453,454] or hyperlipidemia,[453,454] but no consensus exists regarding a unifying pathophysiologic hypothesis. A general overview of major contributing mechanisms is discussed herein, although the reader is referred to comprehensive reviews focused solely on diabetes-related heart failure for additional information.[431,447,453–458]

Metabolic perturbations

Major energy sources for cardiac metabolism include glucose and free fatty acids. Free fatty acids are preferentially utilized in the fasting state, whereas glucose is the substrate of choice in the post-prandial state or under conditions of stress or ischemia. Healthy cardiomyocytes are able to switch between these sources to accommodate different physiologic conditions. In patients with diabetes, insulin resistance and hyperglycemia cause down regulation of myocardial glucose transporters (primarily GLUT4 in adults), reduced glucose oxidation, and an increase in fatty acid oxidation and levels of free fatty acids.[431,458] A higher oxygen requirement of fatty acid oxidation compared with glucose metabolism leads to relative cardiac ischemia, resulting in an accumulation of lactate and impaired calcium homeostasis and myocyte contraction. Additionally, elevated levels of free fatty acids cause lipid accumulation in cardiomyocytes and lipotoxicity, which manifests as contractile dysfunction and eventual cardiomyocyte apoptosis. [431]

Functional alterations

Impaired calcium handling in cardiomyocytes is a key feature of diabetic cardiomyopathy. In the normal state, excitation-contraction coupling of cardiomyocytes is mediated by several intracellular calcium transporters, including the ryanodine receptor, and relaxation occurs via the ejection of calcium from the cell through the sarcoplasmic reticulum calcium pump 2a (SERCA2a), the sodium-calcium exchanger, and the plasma membrane calcium ATPase.[459] Animal models of diabetes have altered expression, activity, and function of all of these transporters.[458] Reduced SERCA2a activity and consequent calcium overload in the cytosol can cause impaired relaxation as well as altered calcium sensitivity of proteins involved in regulation of the cardiac actomysin system and shifting of cardiac myosin heavy chain isoforms from V1 to V3, which can lead to reduced contractile force.[456,459]

Mitochondrial dysfunction and increased oxidative stress contribute to the pathogenesis of diabetic cardiomyopathy. Proposed mechanisms for diabetes-related mitochondrial dysfunction include fatty acid-induced mitochondrial uncoupling leading to increased myocardial oxygen consumption and reduced cardiac efficiency, impaired mitochondrial calcium handing, and mitochondrial proteomic remodeling via post-translational modifications of mitochondrial proteins.[459–461] Hyperglycemia can cause mitochondrial

production of superoxide in endothelial cells.[447] Although increased production of reactive oxygen species occurs mainly in mitochondria, cytosolic systems, such as NAPDH oxidase, can also generate reactive oxygen species and increase oxidative stress, potentially contributing to diabetic cardiomyopathy via accelerated apoptosis, cardiac hypertrophy, fibrosis, subcellular remodeling, and impaired calcium handling. [455,462,463]

Structural changes

Cardiomyocyte hypertrophy is common in diabetic cardiomyopathy and may result from insulin resistance and cell growth in response to hyperinsulinemia, as occurs in type 2 diabetes.[104,347, 431] This observation has led to concern about the use of insulin but has not been born out in clinical trials. In contrast, patients with type 1 diabetes more frequently exhibit hyperglycemia-related myocardial fibrosis rather than hypertrophy.[431,454] Fibrosis may be related to the formation of AGEs,[459] comprised of cross-linked collagen which may deposit in arterial walls, myocardium, and endothelial cells.[458] Higher serum levels of AGEs are associated with greater ventricular isovolumetric relaxation times, a marker of diastolic dysfunction, and greater arterial stiffness.[431] Deposition of AGEs in arterioles may also result in microvascular remodeling and angiopathy characterized by capillary basement membrane thickening and formation of microaneurysms, leading to subsequent impairment of nitric oxide production.[456,461] Subsequent endothelial dysfunction from decreased nitric oxide bioavailability and endothelial damage from high glucose exposure may explain the reduced coronary blood flow reserve and myocardial hypertrophy observed in diabetic cardiomyopathy. [462]

Cardiac autonomic neuropathy

Under normal conditions, sympathetic stimulation causes vasodilation of coronary resistance vessels and improves left ventricular contraction and left ventricular relaxation rates.[458] Cardiac autonomic neuropathy in diabetes is characterized by sympathetic denervation, depletion of myocardial catecholamine stores, and functional impairment in cardiac sympathetic nerve fibers.[454,458] Each of these processes may contribute to left ventricular systolic and diastolic dysfunction and reduced 8-year survival among patients with cardiac autonomic neuropathy compared with those with normal autonomic function (77% versus 97%, respectively). [464]

Neurohormonal activation

Neurohormonal abnormalities are present in both diabetes and heart failure. There is early activation of RAAS in diabetes,[454] leading to overproduction of angiotensin II and supporting the blood pressure trials discussed above. Excess angiotensin II and aldosterone production induce cardiac hypertrophy and fibrosis via collagen deposition and fibroblast proliferation, as well as oxidative damage and cellular apoptosis.[459] In addition, angiotensin II may cause myocardial ischemia through calcium overloading in cardiomyocytes.[461] These effects of angiotensin II and aldosterone, which clinically manifest as diastolic dysfunction, are intensified by hyperglycemia and compounded by renin stimulation related to sympathetic nervous system over-activity observed in heart failure. [456]

Management of heart failure in diabetes

Multiple pharmacologic and device therapies have proven benefits and are recommended for the treatment of chronic heart failure.[422,465] In chronic heart failure trials, up to 30% of participants generally have comorbid diabetes,[466] and subgroup analyses have not demonstrated significant differences in treatment effects among diabetes patients.[456] Despite previous concern regarding beta-blocker use in diabetes due to potential masking of hypoglycemia and adverse effects on insulin resistance, current literature supports use of beta-blockers in the treatment of heart failure among diabetes patients.[422,456,465,467] Similarly, beneficial effects of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockade, mineralocorticoid-receptor antagonism, and cardiac resynchronization therapy are demonstrated among heart failure patients with diabetes.[401,468–471] Although use of diuretic medications has been associated with impaired glucose tolerance potentially related to hypokalemia and/or visceral fat deposition,[472,473] these drugs are often necessary to treat stable and acutely decompensated heart failure patients; no studies have examined differential effects of these medications according to diabetes status. Based on available data, management of heart failure patients with diabetes should follow standard treatment guidelines for the general heart failure population.[465,474]

Management of diabetes in heart failure

While heart failure management is not different in patients with diabetes, special consideration should be taken in glycemic management as effects on heart failure differ among agents. Studies to date suggest that SGLT2 medications appear to be safe from a cardiovascular perspective,[475,476] and empagliflozin reduces the relative risk for heart failure hospitalization by 35% (HR 0.65, 95% CI 0.50, 0.85) compared with placebo in high-risk cardiovascular patients with type 2 diabetes.[373] Possible mechanisms for this observation include osmotic diuresis and reduced arterial stiffness caused by SLGT-2 inhibition leading to lower plasma volume and blood pressure, as well as altering tubular-glomerular feedback mechanisms,[377] or indirect effect on SGLT1,[380] the transporter primarily responsible for intestinal glucose absorption.[477] As with cardiovascular mortality effects, whether this heart failure benefit is a class effect is not yet known and will be evaluated in the ongoing studies Canagliflozin Cardiovascular Assessment Study (NCT01032629) and Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (NCT01730534).

Potential cardiovascular effects of incretin-based diabetes treatments in patients with heart failure are not well-understood. Incretin mimetics improve glycemia by increasing glucose-dependent insulin secretion, lowering glucagon, inhibiting gluconeogenesis, and increase insulin sensitivity, while promoting weight loss. In endothelial cells and myocytes, the incretin hormone GLP-1 may have cardioprotective effects, including vasodilatory and anti-inflammatory properties, independent of its anti-hyperglycemic action.[478] GLP-1 also has been shown to reduce blood pressure via an atrial natriuretic pathway.[479] Prior data suggested that GLP-1 is involved in maintaining normal cardiac structure and function, as evidenced by the increased thickness, impaired contractility, and elevated end diastolic pressure of the left ventricle, as well as diastolic dysfunction and reduced cardiac reserve

observed in knockout mice deficient in the GLP-1 receptor.[480] However, this hypothesis has been challenged recently by studies in which experimental murine models of myocardial infarction and heart failure have not been affected by lack of GLP-1 receptor expression.[481] The cardiovascular outcome trial with the GLP-1 receptor agonist, lixisenatide which is not yet available in the US, showed no significant between-group differences in the rate of hospitalization for heart failure when compared to placebo and standard of care in persons with type 2 diabetes who had previous myocardial infarction or who had been recently hospitalized for unstable angina. Small studies in humans, some of which were non-randomized and not placebo-controlled, have examined the effects of exenatide or GLP-1 on cardiac function in heart failure patients with mixed results: only two showed an association between GLP-1 infusion with improvement in left ventricular function.[482,483] These findings suggest GLP-1 receptor agonists can be used safely in patients with heart failure, although additional studies using are ongoing. Recently, the Effect of Exenatide Compared with Insulin Glargine on Cardiac Function and Metabolism of Type 2 Diabetic Patients with Congestive Heart Failure: A Randomized Comparator-controlled Trial (NCT00766857) comparing the effect of exenatide versus insulin glargine on left ventricular ejection fraction was completed, but results have not yet been published. Further insight will come from the LEADER trial with liraglutide, and the Exenatide Study of Cardiovascular Event Lowering Trial (NCT01144338), a placebo-controlled, randomized study of ~14,000 patients that will examine the effects of exenatide on cardiovascular outcomes, including heart failure hospitalizations. To date, available data suggest safe use of GLP-1 receptor agonists in patients with heart failure.

Three large randomized cardiovascular outcome trials of DPP-4 inhibitors compared to placebo have now been reported, and effects on heart failure are inconsistent. In the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS)[386] in 14,671 persons with type 2 diabetes and established preexisting vascular disease, hospitalization for heart failure rates were similar in sitaglipitin compared with placebo groups, 3.1% sitagliptin versus 3.1% placebo: hazard ratio 1.00 (95%CI: 0.83–1.20). The hazard ratio for hospitalization for heart failure was similar in the sitagliptin-treated group in those with baseline history of heart failure, although absolute rates were higher. In contrast, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53 trial,[395] which randomized 16,492 participants with established cardiovascular disease or increased cardiovascular risk, demonstrated an unanticipated increased risk of heart failure in the saxagliptin-treated group: event rate 3.5% in saxigliptin versus 2.8% in placebo; hazard ratio 1.27 (95% CI: 1.07–1.51), in the setting of non-inferiority for the primary cardiovascular outcome (cardiovascular death, myocardial infarction, stroke). In this trial, heart failure was a prespecified individual clinical endpoint within the major secondary composite cardiovascular outcome. Increased hospitalization for heart failure was primarily observed in those with highest baseline N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) concentration.[484] The smaller, shorter trial EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE (EXAMINE)[383] with randomization of 5,380 higher risk acute coronary syndrome patients demonstrated a non-statistically significant trend with similar point estimate seen in the SAVOR-TIMI 53 trial of saxagliptin towards increased heart failure in the alogliptin-treated

group: event rate 3.9% alogliptin versus 3.3% placebo; hazard rate 1.19 (95% CI: 0.89–1.58), also in the setting of non-inferiority for the primary cardiovascular outcome (cardiovascular death, myocardial infarction, stroke). Hospitalization for heart failure was not increased in the alogliptin-treated group in those with history of heart failure or higher baseline B-type natriuretic peptide (BNP) concentration.[485]

Increased risk of hospitalization for heart failure was not consistent across SAVOR-TIMI 53, EXAMINE, and TECOS. These were not head-to-head comparisons of the three DPP-4 inhibitors, and caution should be applied when comparing agents. There were differences in patient illness severities, comorbidities, and concomitant therapies, sample size and duration of follow-up, and the potential for altered attentiveness and therapeutic practices due to baseline differences, or variation in definition or acquisition of heart failure events across trials. It is possible there are intrinsic pharmacologic differences between the DPP-4 inhibitors in specificities on and/or off target. However, it is also possible heart failure is a class effect, as a test for heterogeneity for hospitalization for congestive heart failure across trials was not significant. There are plausible mechanisms for increased heart failure with DPP-4 inhibition. DPP-4 cleaves additional protein substrates beyond the incretins GLP-1 and glucose-dependent insulinotropic peptide, and multiple DPP-4 substrates have been identified which may influence the cardiovascular system, including natiuretic peptide which is inactivated by DPP4 and provides a plausible mechanism for altered fluid balance.[486] Alternatively, in preclinical models, diabetic mice treated with the potent DPP-4 inhibitor MK-0626 exhibit modest cardiac hypertrophy, impairment of cardiac function, and dysregulated expression of genes and proteins controlling inflammation and cardiac fibrosis.[487] A recent multinational multicenter observational study of use of incretin based drugs and heart failure involving approximately 1.5 million persons finds no association of incretin based therapies with heart failure as compared with combinations of oral antidiabetes drugs, although both DPP-4 inhibitors and GLP-1 receptor agonists were combined in this analysis and comparative risk of specific agents was not possible.[488] As heart failure is common in patients with type 2 diabetes, providers must select therapeutic agents for the totality of their risk benefit, and in the setting of non-inferiority for major adverse cardiovascular events, watch for signs and symptoms of heart failure in their patients.

Several diabetes medications should be used with caution in patients with concomitant heart failure. Thiazolidinediones increase insulin sensitivity by activating the peroxisome proliferator-activated receptor (PPAR) gamma. In meta-analyses of randomized clinical trials, patients treated with thiazolidinediones versus placebo had an increased risk of heart failure (OR up to 2.1, 95% CI 1.08–4.08).[489–491] Observational data suggest the risk for heart failure appears higher with rosiglitazone than pioglitazone.[492] Although not approved for clinical use, aleglitazar, a dual PPAR alpha and gamma agonist, also increased the risk of heart failure by 22% in the Aleglitazar Acute Coronary Syndrome and Type 2 Diabetes Mellitus (AleCardio) trial.[493] Thiazolidinediones have not been shown to have adverse effects on ventricular remodeling or ventricular contractility and function.[494] Instead, thiazolidinedione-related heart failure may be due to fluid retention from PPAR-gamma stimulation of sodium reabsorption in renal epithelial sodium channels.[495–497] In contrast with the setting of HFrEF, volume retention from thiazolidinediones is typically early, not

progressive, and responsive to withdrawal of therapy.[495,496] Thiazolidinediones have an FDA-issued black box warning and are contraindicated in patients with New York Heart Association class III–IV heart failure.[498] They should be used cautiously in patients with class I–II heart failure with close monitoring for fluid retention. [465,474]

Insulin therapy can also stimulate sodium retention and has been associated with edema.[499] *In vitro* and animal studies have shown that insulin increases the activity of renal sodium transporters, though clinical studies suggest the main effect is in the distal tubule via the same epithelial sodium channel stimulate by thiazolidinediones.[500] Consequently, the risk of edema is greater when insulin and thiazolidinediones are given together (5% with single therapy versus 13–16% in combination).[500] Insulin use in heart failure patients has been associated with worse prognosis, including increased all-cause mortality, cardiovascular mortality, and heart failure hospitalizations.[489,501,502] This relationship may be confounded by the use of insulin later in the course of type 2 diabetes, and increased heart failure was not seen in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, where insulin glargine was used earlier in disease, and a trend toward decreased risk of heart failure hospitalization was observed.[347]

Other diabetes drug classes with potentially deleterious effects in heart failure include biguanides and sulfonylureas. Metformin is a first-line treatment for diabetes. However, the FDA issued a black box warning against the use of metformin in heart failure patients requiring pharmacologic management due to a risk of lactic acidosis.[503] The risk of lactic acidosis is small and related to decreased drug clearance in the setting of hypoperfusion or renal dysfunction, both of which may be worsened in acute heart failure exacerbations. Although metformin-related lactic acidosis has been reported,[504] observational data suggest that metformin use in patients with stable chronic heart failure is associated with a mortality benefit without excess risk of lactic acidosis.[505] Metformin may thus be used with caution in heart failure patients with stable renal perfusion and an adequate glomerular filtration rate. The data for sulfonylureas are also mixed and report variable associations between increased risk of heart failure and first- and second-generation sulfonylureas, but may be used when need for glycemic lowering outweighs these uncertain risk.[478,500,505]

Role of glycemic control

Hyperglycemia in diabetes is associated with increased risk of heart failure. A secondary analysis from the UKPDS showed an adjusted rate of heart failure of 2.3 events/100 person-years among patients with HbA_{1c} levels of <6% compared to 11.9 among those with HbA_{1c} levels >10%.[30] Among 48,858 patients with predominantly type 2 diabetes, each 1% increase in HbA_{1c} is associated with an 8% increased relative risk of heart failure;[9] a similar relationship has been observed among 20,985 patients with type 1 diabetes (30% increased relative risk of heart failure per 1% increase in HbA_{1c}).[506]

Despite a consistent association between hyperglycemia and heart failure, no causal relationship has been proven. Studies have failed to consistently demonstrate a relationship between blood glucose or insulin levels and left ventricular function.[507,508] While the ORIGIN trial targeting normal fasting plasma glucose levels for more than 6 years showed a

trend toward decreased risk of heart failure hospitalization in the insulin glargine group,[347] most trials have failed to show a relationship between strict glycemic control and reductions in heart failure in diabetes.[211,334,336] The optimal glycemic level in diabetes patients with heart failure thus remains unclear and warrants further investigation.

Considerations for the management of concurrent heart failure and diabetes

The prevalence of patients with concomitant heart failure and diabetes is high, and providers should be aware of both restrictive and dilated forms of diabetic cardiomyopathy. While standard heart failure guidelines for the general population should be followed when treating heart failure in patients with diabetes, the converse is not true: careful selection of medications is necessary in the management of diabetes in heart failure patients In particular, inhibition of SGLT2 with empagliflozin appears associated with a reduction in heart failure hospitalizations, making this a preferred therapy if otherwise tolerated, while thiazolidinediones should be avoided in patients with severe heart failure symptoms and used with caution in mildly symptomatic patients. Metformin may be used cautiously in heart failure patients with stable renal function and adequate renal perfusion. To date, there has not been any clear signal for heart failure benefit with incretin-based treatment, and there may even be an excess risk for heart failure hospitalization related to some DPP-4 inhibitors. Thus, heart failure risk differs across diabetes therapeutic classes, and additional prospective study is required to fully understand potential drug effects in this unique population.

What is on the horizon?

A number of new approaches for glucose lowering are under development and may provide agents with dual benefit for diabetes and the diabetic heart. Additionally, drugs that are developed for cardiovascular risk reduction may also lower glycemia. In the meantime, cardiovascular outcome trials will provide useful information on cardiovascular safety of use of diabetes drugs in patients with established heart disease or at high risk for events and additional exposure information that may reveal previously unrecognized positive or negative effects. These trials may help to better address the question of the impact of specific glucose-lowering drugs and pharmacologic class agents on the diabetic heart.

Conclusions

The long-term treatment of diabetes is challenging due to diverse goals: to address metabolic derangements and to reduce risks for both micro- and macrovascular adverse outcomes. Management of hyperglycemia has resulted in substantial reductions in risks for retinopathy with associated preservation of vision, and nephropathy with prevention of end-stage renal disease when combined with aggressive blood pressure control. Progress in prevention and amelioration of these microvascular complications has conversely resulted in a shift in the major causes of long-term morbidity and mortality in diabetes, which now consists of cardiovascular risk with associated ischemic heart disease, ischemic stroke, peripheral artery disease, and congestive heart failure. Diabetes clearly exacerbates mechanisms of atherosclerosis and heart failure. Unfortunately, these mechanisms are not adequately fully

modulated or addressed by focusing solely on optimal glycemic control. Fortunately, aggressive management of cardiovascular risk factors, particularly lowering of LDL-cholesterol concentration and blood pressure along with glycemic management, provide substantial improvements in cardiovascular outcomes. Therefore, we prioritize recommendations for management of cardiovascular and heart failure risk to focus on the most effective therapies, as summarized in Table 1.

Multiple areas of further investigation remain. Potential cardiovascular benefits versus risks of new glucose-lowering agents and timing of (early and/or prolonged) glucose-targeting interventions are incompletely understood. Evidence for a more effective antiplatelet regimen than aspirin in moderate to high risk patients with diabetes without ischemic heart disease is necessary. Recommended blood pressure goals are also not fully evidence-based, and the role of new potent lipid lowering therapies (PCSK9 inhibitors) and lipid lowering drugs that target triglycerides and HDL cholesterol needs further study. Another unaddressed issue is the ultimate risk-benefit ratio for polypharmacy that occurs when physicians add multiple drugs to achieve an optimal level of glycemic control and cardiovascular risk management. These are pragmatic concerns wherein the use of multiple medications can result in less overall medication compliance and increased risk of drug-drug interactions. Although the overall management of diabetes has improved substantially over the past 2 decades, there is a large unmet need for cardiovascular prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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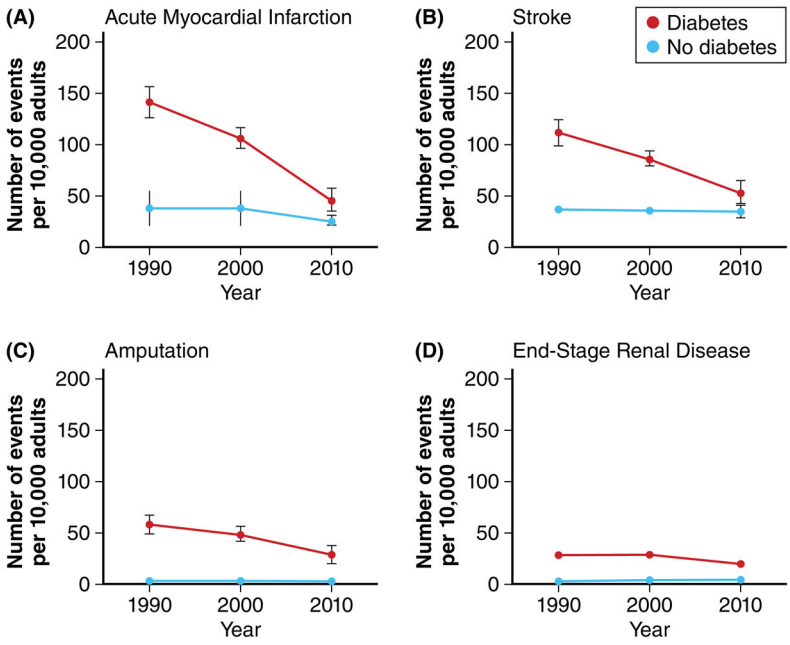

Figure 1. Rates of vascular diseases are decreasing in persons with diabetes but are still higher than in persons without diabetes: Twenty years of surveillance

Age-standardized rates of selected vascular diseases in individuals with or without diabetes in the years 1990, 2000, and 2010. A: Acute myocardial infarction; B: Stroke; C: Amputation; D: End-stage renal disease. Red: Individuals with diabetes. Blue: Individuals without diabetes. Error bars indicate 95% confidence intervals. Data from Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, Williams DE, Geiss L. *New Engl J Med.* 2014;370;1514–1523.

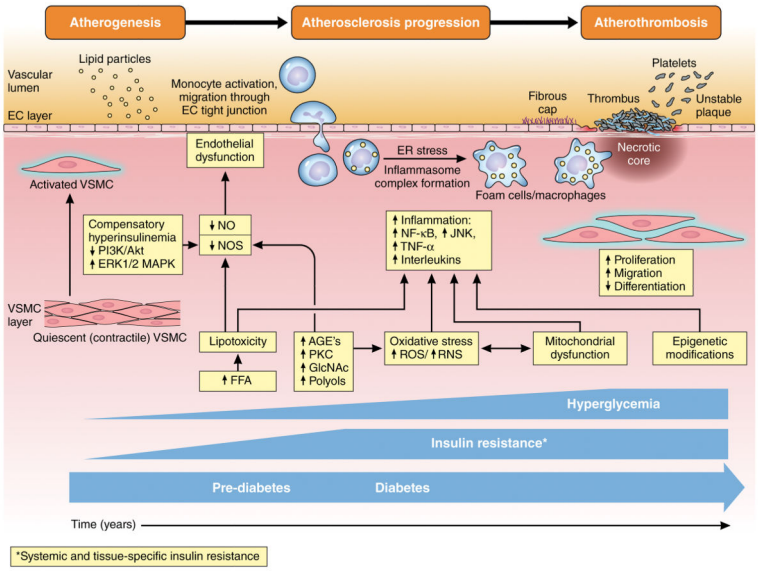

Figure 2. Development and progression of atherosclerosis in diabetes

Insulin resistance is present before the onset of pre-diabetes or diabetes, and increases progressively over time, while hyperglycemia develops in pre-diabetes and worsens with development of diabetes. Insulin resistance with impairment of insulin signaling, hyperinsulinemia and hyperglycemia contribute to multiple processes including elevated free fatty acids (FFA), advanced glycation end product (AGE) production, protein kinase C (PKC) activation, oxidative stress, mitochondrial dysfunction, and epigenetic modifications, which together contribute to endothelial dysfunction and inflammation resulting in activation of vascular smooth muscle cells (VSMC), endothelial cells (EC), and monocytes. Concentrations of modified (oxidized) LDL are higher in diabetes, and are retained in the subendothelial layer of vulnerable sections of the vasculature. Circulating leukocytes attach and migrate through the endothelial wall into the VSMC layer of the intimal media. These monocytes engulf retained lipoproteins and transform into lipid-laden foam cells/ macrophages producing proteinases and inflammatory mediators including tumor necrosis factor alpha (TNF-α) and interleukins. Stress responses including inflammasome complex formation and endoplasmic reticulum (ER) stress result in macrophage proliferation and inflammatory activation with resultant macrophage and VSMC phenotypic switch (proliferation, migration, and dedifferentiation). In response to vascular injury, VSMC secrete collagen to form a fibrous cap, which promotes atherosclerotic plaque stability. However, when stable lesions remodel inward, progressive stenosis of arteries occurs. Plaques can become vulnerable with thinning of the fibrous cap and apoptosis of macrophages in advanced atherosclerotic lesions, where impaired efferocytosis (phagocytic clearance) of lipid laden macrophages results in formation of a necrotic core accelerating vascular inflammation, necrosis, thrombosis. The resulting unstable atherosclerotic lesion complex is prone to sudden expansion from acute thrombus formation forming a nidus for platelet thrombosis, hemorrhage of atherosclerotic plaque microvessels, and rupture of the fibrous cap.

AGE: advanced glycation end-product. Akt: protein kinase B. EC: endothelial cell. NOS: nitric oxide synthase. ER: endoplasmic reticulum. ER: endoplasmi reticulum. ERK:

extracellular signal-regulated kinase. FFA: free fatty acids. GlcNAc: N-Acetylglucosamine. IL: interleukin. JNK: c-Jun N-terminal kinase. LDL: low-density lipoprotein. MAPK: mitogen-activated protein kinase. NF-κβ: nuclear factor-kappa beta. NO: nitric oxide. PKC: protein kinase C. PI3K: phosphoinositide 3-kinase. ROS: reactive oxygen species. RNS: reactive nitrogen species. TNF-α: tumor necrosis factor-alpha. VSMC: vascular smooth muscle cell.

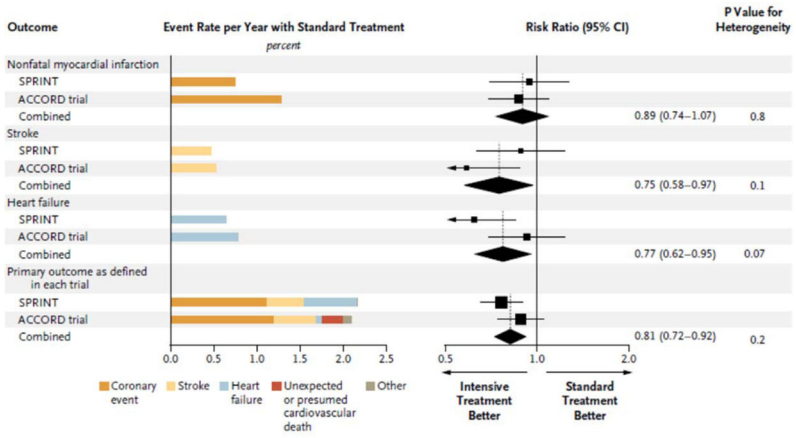

Figure 3. Cardiovascular outcomes in two recent blood pressure lowering trials in patients with and without baseline diabetes

Outcomes data for blood pressure-lowering trials in a high-risk population without diabetes: SPRINT (Systolic Blood Pressure Intervention Trial, n=9,361) and in a high risk population with diabetes: ACCORD (Action to Control Cardiovascular Risk in Diabetes, n=4,733). SPRINT was conducted in patients without Diabetes and ACCORD in patients with diabetes. Although reduction in individual outcomes did not reach statistical significance in ACCORD except for stroke, tendencies for benefits are similar and combining ACCORD with SPRINT demonstrated reduction in primary outcome and individual components with intensive treatment. Reprinted with permission from Perkovic V, Rodgers A. *N Engl J Med.* 2015;373(22):2175–8.

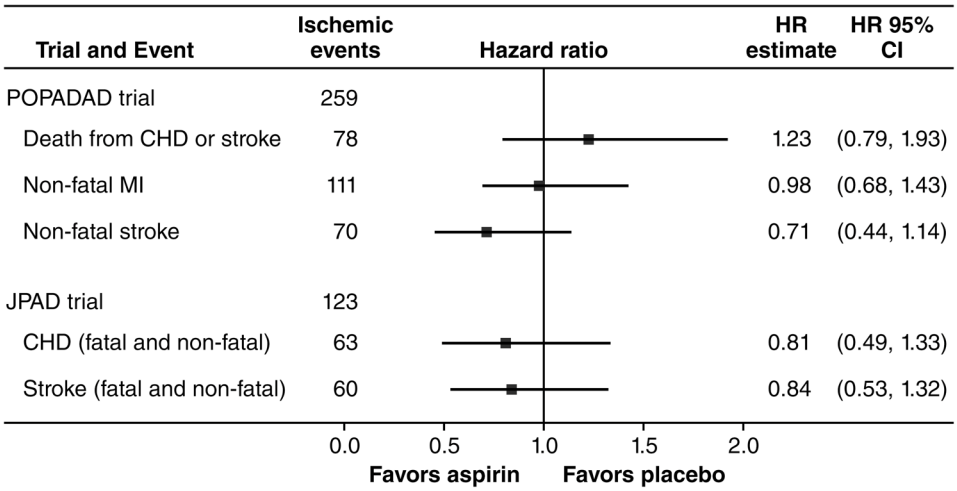

Figure 4. Comparison of data from contemporary trials for aspirin in primary prevention of ASCVD in diabetes

JPAD (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes, n=2,539) and POPADAD (Prevention of Progression of Arterial Disease and Diabetes, n=1,276). Although there was a trend toward reduction in ischemic outcomes with aspirin therapy for primary prevention in diabetes in both trials (except for CHD or stroke death in POPADAD), there were very few events, highlighting an area of potential controversy in ASCVD risk reduction.

Figure 5. Randomized, controlled, cardiovascular outcome trials of glucose-lowering drugs or strategies in people with type 2 diabetes

ACS=acute coronary syndrome; ASCVD=atherosclerotic cardiovascular disease including myocardial infarction or ischemic stroke; CV risk=increase risk for cardiovascular disease based on risk factors, but not ischemic ASCVD; HR=hazard ratio; MACE=major adverse cardiovascular event: cardiovascular mortality, myocardial infarction, stroke; RRR=relative risk reduction; SFU=sulfonylurea. T_2DM=type 2 diabetes mellitus; MACE=cardiovascular mortality, myocardial infarction, stroke.

Studies: ACCORD, Action to Control Cardiovascular Risk in Diabetes;[333] ACCORDION, ACCORD Follow-on study;[391] ADDITION, Intensive Treatment in People With Screen Detected Diabetes in Primary Care;[392] ADVANCE, Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation;[334] BARI 2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes;[104] $DIGAMI_2$, Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction;[393] ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide;[382] EMPA-REG OUTCOME, (Empagliflozin) Cardiovascular

Outcome Event Trial in Type 2 Diabetes Mellitus Patients; [373] EXAMINE trial, EXamination of cArdiovascular outcoMes with alogliptIN versus standard of care;[383] HEART2D, Hyperglycemia and its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in patients with Type 2 Diabetes;[394] Look AHEAD, Action for Health in Diabetes;[284] ORIGIN, Outcome Reduction With Initial Glargine Intervention;[347] PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events;[102] RECORD, Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes;[370] SAVOR-TIMI53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53;[395] Steno-2, Multifactorial Intervention in Type 2 Diabetes at the Steno Diabetes Center;[176,366] TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin; [386] UKPDS, United Kingdom Prospective Diabetes Study;[41,103,199] VADT, Veterans Affairs Diabetes Trial.[335,345]

Reference: Data taken from Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. *Lancet*. 2014;383:2008–2011.[396]

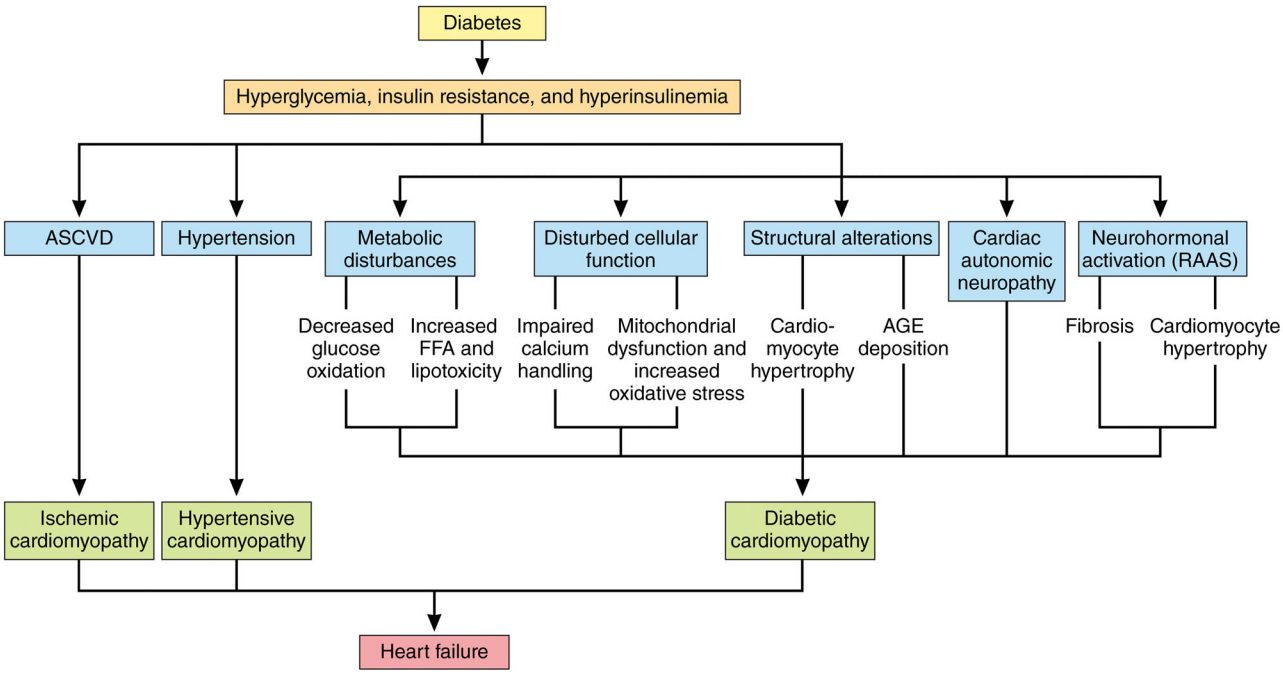

Figure 6. Pathophysiologic mechanisms of heart failure in diabetes

Hyperglycemia, insulin resistance, and hyperinsulinemia, the main physiologic disturbances in diabetes, contribute to atherosclerotic cardiovascular disease (ASCVD), hypertension, and multiple derangements of cellular metabolism, function, and structure, as well as activation of the renin-angiotensin-aldosterone system (RAAS). The different cardiomyopathies that result from these processes clinically present as heart failure in diabetes. AGE, advanced glycation end-product; FFA, free fatty acids.

Table 1
Suggested treatment prioritization to reduce ASCVD risk in type 2 diabetes

Author-recommended approach to cardiovascular risk reduction in type 2 diabetes. Recommendations for aggressive blood pressure control and limitation of aspirin to patients with established coronary artery disease do not necessarily agree with guideline recommendations but do reflect the authors' assessment of the current literature.

	Primary prevention		**Secondary prevention (Coronary/carotid disease[b])**
	Moderate ASCVD risk[a]	**High ASCVD risk**	
	Provide or reinforce lifestyle interventions:[c] diet, exercise, weight loss, and smoking cessation		***Continue emphasis on lifestyle interventions[c]***
Vascular territory			
Macrovascular and microvascular	• Moderate intensity statin • Guidelines recommend BP <140/90 mmHg but consider targeting <120/80 mmHg if tolerated, especially in renal disease or increased stroke risk.[e] Use caution with multiple agents to avoid hypotension • Low dose aspirin or no aspirin[f] • Early glycemic control may reduce later ASCVD risk[g]	• High intensity statin • Consider additional lipid lowering therapies[d] • Guidelines recommend BP <140/90 mmHg but consider targeting <120/80 mmHg if tolerated, especially in renal disease or increased stroke risk.[e] Use caution with multiple agents to avoid hypotension • Low dose aspirin or no aspirin[f]	• High intensity statin • Consider additional lipid lowering therapies[d] • Guidelines recommend BP <140/90 mmHg but consider targeting <120/80 mmHg if tolerated, especially in renal disease or increased stroke risk.[e] Use caution with multiple agents to avoid hypotension • Low dose aspirin
Microvascular	• $HbA_{1c} \leq 6.5\%$ if able to achieve with minimal hypoglycemia	• $HbA_{1c} \leq 7.0\%$ if able to achieve with minimal hypoglycemia	• $HbA_{1c} \leq 7.0\%$ if multiple diabetes drugs are tolerated and polypharmacy does not diminish intensity of CV risk management; $HbA_{1c} \leq 7.5\%$ if not

[a] Diabetes *per se* confers an increased risk of ASCVD, so the vast majority of diabetes patients without ASCVD fall into the moderate or high ASCVD risk category; treatment should be individualized and a few patients may fall into a lower risk category, but all patients should undergo lifestyle intervention. Special caution should be used in the elderly.

[b] Coronary or carotid disease refers to a clinical history of an acute ischemic event (acute coronary syndrome or ischemic stroke) or coronary revascularization.

[c] Randomized trials of lifestyle interventions of diet, exercise and weight loss in diabetes have not shown a reduction in CV events.[265] However lifestyle modification and weight loss help improve CV risk factors and result in other positive health outcomes.

[d] Additional lipid-lowering therapies could include fibrates in persons with diabetes and elevated triglyceride and low HDL cholesterol levels.

[e] The AHA/ADA Guidelines[132,219] recommend BP <140/90 mmHg but consider targeting <120/80 mmHg if tolerated,[258] especially in renal disease or increased stroke risk. Cardiorenal disease includes elevated urine albumin excretion or chronic kidney disease.

[f] The AHA/ADA Guidelines[132,219] recommend low-dose aspirin for those with 10-year CVD risk of ≥10% without increased risk of bleeding as well as those at intermediate risk (10-year CVD risk 5–10%) but the evidence is Level B and C, and data to support this are controversial.

[g] A period of good glycemic control (HbA_{1c} of 7% vs 7.9%) in patients with newly-diagnosed type 2 diabetes led to a reduction in MI and all-cause mortality after 20 years[41]

ASCVD = atherosclerotic cardiovascular disease, BP = blood pressure, CV = cardiovascular, CVD = cardiovascular disease, HbA1c = hemoglobin A_{1c}

Table 2

Glucose-lowering therapy: Key clinical considerations

Lifestyle: **Medical Nutritional Therapy consisting of healthy food choices and portion control** **Exercise as tolerated at least 30 minutes five times weekly**										
		Non-insulin add-on therapies to metformin*, or Monotherapy when metformin is contraindicated **Optimal selection of diabetes medications should be made on an individual basis after consideration of multiple factors such as HbA1c lowering, risk for hypoglycemia, effect on weight and comorbidities, side effects, complexity of regimen, cost, and/or preference such as willingness to use injectable therapies.**								
Class	Biguanide *Metformin is first choice unless contraindicated	Glucagon-like peptide (GLP)-1 Receptor Agonist	Sodium-glucose cotransporter (SGLT) 2 Inhibitor	Dipeptidyl Peptidase (DPP) 4 Inhibitor	Insulin Secretagogue (sulfonylurea, meglitinide, or D-phenylalanine derivative)	Thiazolidinedione (TZD)	α-Glucosidase Inhibitor	Bile Acid Sequestrant	Centrally Acting Agent	Amylin Analog *Only for use with Insulin*
Estimated HbA_{1c} reduction	1%	0.8–1.5%	0.5–0.6%	0.75%	0.75–1.25%	1.0–1.25%	0.5–1.0%	0.3–0.9%	0.4–0.8%	0.5–0.6%
Agents	metformin	exenatide liraglutide albiglutide dulaglutide	canagliflozin dapagliflozin empaglifozin	alogliptin linagliptin saxagliptin sitagliptin	glipizide glyburide glimepiride repaglinide nateglinide	pioglitazone rosiglitazone	acarbose miglitol	colesevelam	Bromocriptine mesylate	Pramlintide
Route	oral	Injectable	oral	oral	oral	oral	oral	oral	oral	injectable
Actions	Decreases hepatic glucose production and intestinal absorption of glucose; improves insulin sensitivity by increasing peripheral glucose uptake and utilization	Increases glucose-dependent insulin secretion, lowers glucagon secretion, slows gastric emptying, and promotes satiety	Lowers the renal threshold for glucose reabsorption to increase urinary glucose excretion	Blocks inactivation of incretin hormones to increase insulin release and decrease glucagon in a glucose-dependent manner	Stimulates insulin release from pancreatic β cells.	Activates PPARγ, increases peripheral glucose utilization, and decreases hepatic glucose production	Reduces absorption of dietary carbohydrate	Uncertain mechanism of glucose lowering; binds bile acids in intestine, impeding their reabsorption and increasing LDL-C clearance	Uncertain mechanism of glucose lowering with increased insulin sensitivity and glucose disposal	Slows gastric emptying, reduces glucagon secretion, and increases satiety
Side Effects	Diarrhea, nausea/ vomiting, flatulence, vitamin B12 deficiency, lactic acidosis	Nausea, diarrhea, possible pancreatitis	Polyuria, urinary frequency, hypovolemia, genital and urinary tract infections, hyperkalemia. Reported diabetic ketoacidosis with serum glucose as low as 200 mg/dl	Occasional gastrointestinal discomfort, upper respiratory tract complaints	Hypoglycemia	Weight gain, edema, congestive heart failure in patients with underlying disease	Gastrointestinal discomfort, flatulence, diarrhea, elevated transaminases	Gastrointestinal discomfort, Reduces gastric absorption of some drugs	Gastrointestinal discomfort, headache	Gastrointestinal discomfort, headache

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Lifestyle: **Medical Nutritional Therapy consisting of healthy food choices and portion control** **Exercise as tolerated at least 30 minutes five times weekly**										
		Non-insulin add-on therapies to metformin*, or Monotherapy when metformin is contraindicated **Optimal selection of diabetes medications should be made on an individual basis after consideration of multiple factors such as HbA1c lowering, risk for hypoglycemia, effect on weight and comorbidities, side effects, complexity of regimen, cost, and/or preference such as willingness to use injectable therapies.**								
Contraindications	Chronic kidney disease with eGFR<30 mL/min; Acidosis; Alcohol excess; severe congestive heart failure; hypovolemia. If IV contrast to be used, hold on day of study and restart 48 hours after IV contrast if eGFR>45 mL/min	History of pancreatitis. personal or family history of medullary thyroid cancer or MEN2. Do not use with DPP4 inhibitors.	Severe renal disease with eGFR<30 mL/min, use with caution in patients with bladder cancer	History of pancreatitis. Do not use with GLP-1 receptor agonists.	Severe liver or renal disease	Severe heart disease at risk for CHF, NYHA Class III or IV heart failure, liver disease. Caution in patients with macular edema	Chronic intestinal disorders, moderate to severe renal impairment (creatinine >2 mg/dl), caution in cirrhosis	Serum triglyceride >500 mg/dl; History of hypertriglyceridemia-related pancreatitis, Bowel obstruction	Lactating women, syncopal migraines or use of ergot class of medications	Gastroparesis. Do not use with α-glucosidase inhibitors, may delay absorption of concomitant medications
Comments	Modest weight loss. Reduced cardiovascular event rates (UKPDS).	Weight loss. Decrease in MACE seen with liraglutide (LEADER). No increase in cardiovascular risk or hospitalizations for heart failure in high risk patients with lixisenatide (ELIXA). Others under evaluation.	Reduced blood pressure, weight loss. Improved cardiovascular and total mortality, and decreased hospitalization for heart failure in high risk patients seen with empagliflozin (EMPA-REG). Others under evaluation.	Weight neutral. No increase in cardiovascular risk compared to other diabetes agents in high risk patients (SAVOR-TIMI53, EXAMINE, TECOS). May increase hospitalization for heart failure, but not seen with sitagliptin (TECOS).	Long duration follow-up of glycemic lowering using SFU is associated with reductions in cardiovascular risk (UKPDS).	Increased risk for bone fractures. Increased fluid retention. Rosiglitazone is not inferior for cardiovascular outcomes (RECORD). Pioglitazone is neutral to beneficial for composite cardiovascular outcomes (PROACTIVE)	May reduce cardiovascular risk in patients with impaired glucose tolerance (STOP-NIDDM).	Lowers LDL-C.	Reduced cardiovascular events in FDA enabling trials Cycloset™ Safety Trials.	

eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; IV, intravenous; LDL-C, low density lipoprotein cholesterol; MEN2, Multiple endocrine neoplasia type 2; NYHA, New York Heart Association; PPARγ, Peroxisome proliferator-activated receptor gamma; SFU, sulfonylurea.

Studies: Cycloset Safety trials;[381] ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide;[382] EMPA-REG, (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients;[373] EXAMINE trial, EXamination of cArdiovascular outcoMes with alogliptIN versus standard of care;[383] LEADER trial, Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results.[384] PROACTIVE, PROspective pioglitAzone Clinical Trial In macroVascular Events;[380] RECORD, Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes;[370] SAVOR-TIMI53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53;[375] STOP-NIDDM, Stop Non-Insulin Dependent Diabetes Mellitus;[385] TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin;[386] UKPDS, United Kingdom Prospective Diabetes Study.[41,103]