Current Diabetes Reports (2019) 19:161
https://doi.org/10.1007/s11892-019-1239-x

OTHER FORMS OF DIABETES AND ITS COMPLICATIONS (JJ NOLAN AND H THABIT, SECTION EDITORS)

Diabetes and Cardiovascular Disease: an Update

Rajaa Almourani[1] · Bhavana Chinnakotla[1] · Richa Patel[1] · L. Romayne Kurukulasuriya[1] · James Sowers[1,2]

Abstract

Purpose of Review Cardiovascular disease (CVD) is the leading cause of mortality in people with diabetes. Our aim was to review the pathophysiology of CVD in diabetes, review related landmark trials, and discuss the cardiovascular benefit of glucose-lowering agents. We have also discussed the role of controversial anti-platelet therapy.

Recent Findings Recent studies have shown the impact of glucose-lowering agents on CVD in people with diabetes. Statins are now recommended for all patients with diabetes over the age of 40 regardless of the LDL level given the cardiovascular benefit of these drugs. Current recommendations suggest a blood pressure < 130/80 for individuals with high cardiovascular risk.

Summary Cardiovascular risk reduction should be an important part of the management of diabetes. Focusing solely on glycemic control may not be the best therapeutic strategy. Multifactorial risk reduction should be taken into account. Lipid-lowering agents and anti-hypertensives should be a corner stone of treatment of diabetes. With currently available data, glucose-lowering agents with cardiovascular benefit should be started early in the disease process.

Keywords Cardiovascular disease · Diabetes · Hypertension · Dyslipidemia · Legacy effect · Memory effect

Introduction

Diabetes mellitus (DM) is a heterogeneous disorder characterized by hyperglycemia, insulin deficiency, and/or insulin resistance. According to 2017 National Diabetes Statistics Report by Centers for Disease Control and Prevention (CDC), 30.3 million adults had diabetes in the USA, accounting for 9.4% of the population [1] (an estimated 5% of people with DM have type 1 diabetes). It is an increasing health and economic burden throughout the world. In fact, the American Diabetes Association (ADA) estimated that direct medical cost related to DM in the USA was around $237 billion in addition to $90 billion in reduced productivity in 2017, representing a 26% increase in the cost of this disease over a five-year period [2].

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality among people with diabetes. Coronary artery disease (CAD), peripheral vascular disease (PVD), ischemic stroke, and heart failure are major manifestations of CVD associated with diabetes. Adverse CVD events such as acute myocardial infarction (MI), stroke or death from any cardiovascular cause occur at an earlier age (average 14.6 years) in men and women with diabetes [3]. Women with diabetes are at an even higher risk of CVD events due to loss of protective effects of estrogen in women with diabetes [4]. Additionally, diabetes is often accompanied by synergistic risk factors such as hypertension, obesity, systemic inflammation, hypercoagulability, and dyslipidemia; which further increase CVD death rates [5]. There are various biochemical mechanisms that independently increase the risk of CVD in people with diabetes, and these will be explored in this review. Further, in this review, we summarize the pathophysiologic abnormalities that promote CVD in diabetes as well as contemporary preventative and therapeutic approaches.

This article is part of the Topical Collection on *Other Forms of Diabetes and Its Complications*

✉ L. Romayne Kurukulasuriya
kurukulasuriyar@health.missouri.edu

✉ James Sowers
Sowersj@health.missouri.edu

Rajaa Almourani
Almouranir@health.missouri.edu

Bhavana Chinnakotla
Chinnakotalab@health.missouri.edu

Richa Patel
Patelr@health.missouri.edu

[1] Department of Medicine, Division of Endocrinology, University of Missouri, Columbia, MO, USA

[2] Harry S Truman VA Hospital, Columbia, MO, USA

Published online: 11 December 2019

Pathophysiology

The underlying pathophysiology of atherosclerotic cardiovascular disease (ASCVD) in diabetes is multifactorial which not only involves macro vascular plaque formation but also chronic insults at various cellular and molecular levels due to hyperglycemia and insulin resistance (Fig. 1).

Obesity especially visceral obesity which often precedes development of type 2 diabetes (T2DM) is associated with other metabolic risk factors such as insulin resistance, atherogenic dyslipidemia, hypertension, and a pro-thrombotic and pro-inflammatory state [6]. Obesity and related dysfunctional adipose tissue is often associated with excess release of non-esterified fatty acids into the skeletal muscle and liver which promotes development of systemic insulin resistance [7]. Increased flux of free fatty acids into the liver also leads to hepatic production of atherogenic lipids. Resultant increases in triglycerides and very low-density lipoproteins (VLDL) and oxidized small dense LDL particles leads to activation of cholesteryl ester transfer protein which enriches HDL and LDL with triglyceride particles. These triglyceride-rich HDL molecules are more prone to catabolism. Triglyceride-rich small dense LDL particles are more prone to oxidation leading to LDL particles that are more amenable to get incorporated into plaques in arterial walls thus making them profoundly atherogenic [8].

Obesity, especially abdominal obesity, also promotes a pro-inflammatory environment, with dysregulated secretion of various inflammatory cytokines, and chemokines (chemotactic cytokines). These chemokines recruit macrophages to adipose tissue and also induce a phenotypic switch from an anti-inflammatory M2 state to a pro-inflammatory M1 state [9]. Conversely, production of insulin-sensitizing adipokines such as adiponectin is reduced in obese states. Abnormalities in coagulation and hemostasis are well known features of obesity. Concentrations of pro-coagulant factors such as fibrinogen, protein C, and von Willebrand factor are elevated in individuals with obesity compared to lean individuals, which along with increased levels of plasminogen activator inhibitor-1 generates a prothrombotic state [10]. Additionally, increased production of angiotensinogen and aldosterone from an expanded adipocyte mass activates the renin-angiotensin-aldosterone system (RAAS) and in turn, induces vascular stiffness and hypertension [11].

Insulin resistance as seen in obesity, pre-diabetes, and diabetes promotes atherosclerosis through development of vascular stiffness, hypertension, diabetic dyslipidemia, and increased systemic and vascular tissue inflammation. Reduction in endothelial nitric oxide (NO) synthase and NO production along with increased production of endothelin and adhesion molecules lead to endothelial cell dysfunction, vascular stiffness, and increased entry of inflammatory cells into the vasculature promoting plaque formation [12].

Hyperglycemia promotes CVD by a number of mechanisms. Elevated glucose levels lead to the activation of protein kinase C, the polyol and hexamine pathways with increased

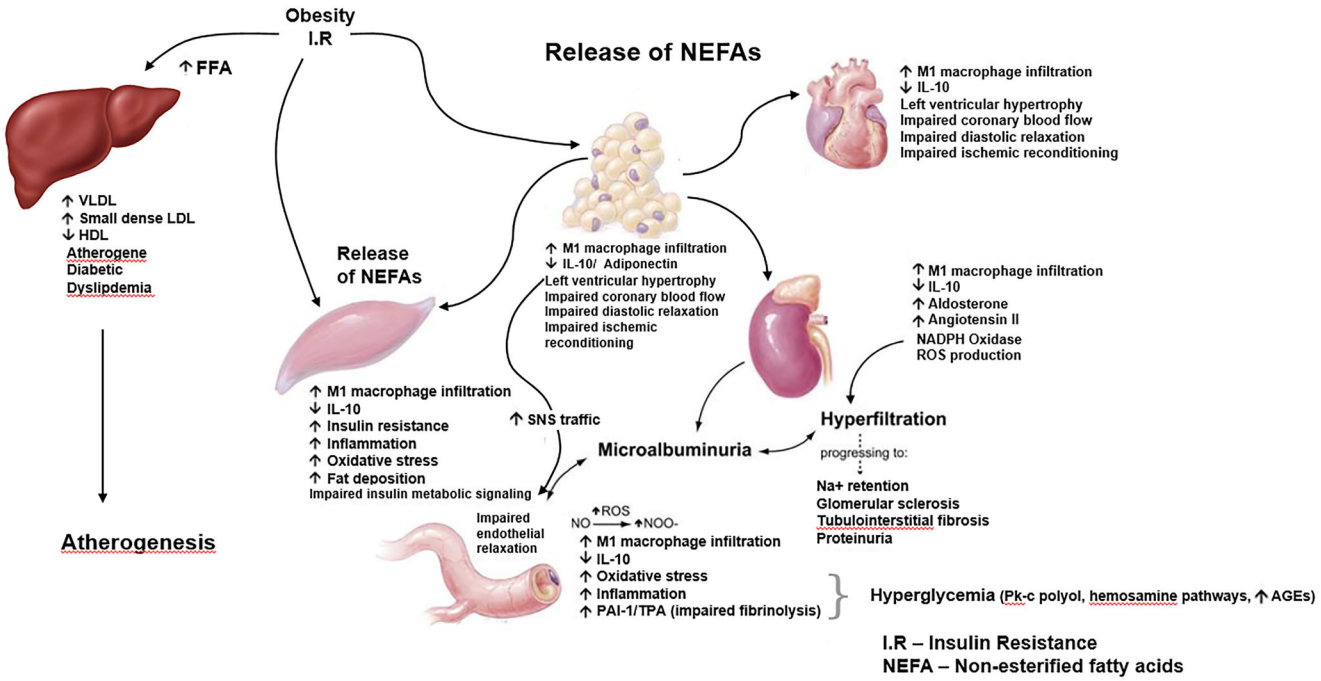

Fig. 1 The pathophysiological factors that contribute to increased CVD in diabetes [13]

formation of advanced glycation end-products which deplete intracellular anti-oxidants and accumulation of radical oxygen species [14]. Excess radical oxygen species causes endothelial dysfunction via mitochondrial injury and reduced endothelial NO production. Additionally, activation of nuclear factor κB leads to increased expression of pro-inflammatory and pro-coagulant genes and increased production of tumor necrosis factor alpha (TNF-α), monocyte chemotactic protein-1 (MCP-1), and interleukins [15]. Increased MCP-1 promotes adhesion of monocytes and macrophages to the endothelium and trans-endothelial migration to vessels. These inflammatory macrophages contribute to early atherogenesis [12]. Furthermore, a hyperglycemic environment in animal models has shown to cause increased glucose uptake in vascular smooth muscle cells leading to impaired contractility and induction of a pro-inflammatory and atherogenic vascular smooth muscle cell phenotype in response to various vascular injuries [16].

Diabetic Cardiomyopathy

Diabetes is a well-known risk factor for development of abnormal myocardial structure and function even without other risk factors such as CAD, hypertension, and significant valvular disease [17]. This phenomenon was first described in a series of four postmortem reports in 1972, with diffuse fibrosis, ventricular hypertrophy, and narrowing of intramural arterioles [18]. Many epidemiological, animal, and clinical studies have supported an association between DM and heart failure since that original observation [17, 19]. Primary features of diabetic cardiomyopathy include cardiac stiffness, myocardial fibrosis, and diastolic dysfunction which eventually lead to impaired systolic function and heart failure [17].

Insulin resistance, abnormal metabolic insulin signaling in cardiac myocytes, and hyperglycemia contribute to the development and progression of diabetic cardiomyopathy. The complex pathophysiology often involves an interplay of oxidative stress, mitochondrial dysfunction, increased advanced glycation end-products, inappropriate activation of the systemic and cardiac RAAS, cardiac autonomic neuropathy, inflammation, maladaptive immune function, and depletion of NO which contributes to coronary microvascular dysfunction and impaired mitochondrial calcium handling [20••].

During the initial stages, diabetic cardiomyopathy is clinically silent, characterized by microstructural changes in myocytes, increased ventricular fibrosis and stiffness leading to diastolic dysfunction [19]. This is followed by accelerated myocyte apoptosis due to oxidative stress, defects in calcium transport, increased TGFβ1, and mild cardiac autonomic neuropathy eventually resulting in further myocardial fibrosis. These abnormalities may reflect changes in left ventricular structure and hypertrophy with detectable changes in diastolic and later systolic function on echocardiography [21].

Interventions to Decrease CVD in Patients with Diabetes

Lifestyle modification is the cornerstone in managing diabetes as emphasized in diabetes management guidelines [22••, 23••].This approach aims for weight loss of 5% or more (in overweight and obese patients) with intensified physical activity, individualized diet, and behavioral therapy.

The Diabetes Prevention Program (DPP) demonstrated that metformin as well as intensive changes in lifestyle (goal of 7% weight loss and 150 min of moderate intensity exercise per week), reduce T2DM incidence in pre-diabetic patients. In that trial 3234 participants with elevated risk of T2DM (high BMI, pre-diabetes) were randomized to standard lifestyle modification and placebo, standard lifestyle modification and metformin, or an intensive lifestyle intervention (ILI) program and participants were followed for 2.8 years. The trial was terminated early due to efficacy of both metformin and ILI. ILI and metformin both reduced the incidence of T2DM by 58% and 31% respectively, and both interventions were well tolerated [24].

The Look AHEAD (Action for health in Diabetes) study was a multicenter, randomized controlled trial (RCT) published in 2013, which at the time was the largest trial designed to evaluate the effect of weight management on CVD risk in overweight participants with T2DM. Five thousand one hundred forty-five participants were randomly assigned to ILI or to usual care (diabetes support and education "DSE"). The primary outcome was death from CVD, non-fatal MI, non-fatal stroke, or hospitalization for angina over 13.5 years of follow-up. The trial had to be terminated early (9.6 years) due to futility, and it showed greater weight loss in the ILI group, greater reduction in glycated hemoglobin (HbA1c), greater improvement in fitness, and all CVD risk factors except VLDL levels, but failed to show clinically significant reduction in CVD event rates in overweight and obese T2DM ($P = 0.51$) [25].

The PREDIMED-Plus trial, whose first-year interim results were published in 2019, was designed to evaluate the long-term effects of intensive lifestyle modification on primary CVD prevention. In the initial report, 626 overweight/obese participants were randomized to an intensive weight loss intervention with a caloric restricted Mediterranean diet, enhanced physical activity and behavioral support, or a control group. After 1 year, those in the intervention group lost more weight ($P < 0.001$) with improvement in multiple CVD risk factors: waist circumference, fasting blood glucose, triglycerides, HDL, insulin resistance, HbA1c, leptin level, interlukin-18, and MCP-1 (all $P < 0.005$) [26]. While this rather intensive

lifestyle modification is effective, it may be difficult to accomplish in a real life.

In primary care-led weight management for remission of people with type 2 diabetes (DiRECT), an open-labeled cluster randomized trial showed remission of type 2 diabetes with weight management. Three hundred six patients from 49 primary care practices in Scotland participated. Patients aged 20–65 with BMI 27–45 kg/m^2 with type 2 diabetes for less than 6 years were selected. Intervention comprised withdrawal of anti-diabetic and anti-hypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance. Co-primary outcomes were weight loss of 15 kg or more, and remission of diabetes, defined as glycated HbA1c of less than 6.5% after at least 2 months off all anti-diabetic medications. At 12 months, 46% of participants achieved remission to non-diabetic state off of anti-diabetic drugs, with 86% remission rate in the group that lost more than 15 kg, and none in the group that gained weight [27]. This shows that weight loss will help with remission of T2DM in patients not on insulin with a relatively recent onset of diabetes.

The Role of Glycemic Control

The Diabetes Control and Complications Trial (DCCT) was a landmark trial for type 1 diabetes (T1DM). This showed the importance of tight control of diabetes. This multicenter controlled study, published in 1993, randomized 1441 participants with T1DM to either intensive insulin therapy with the goal of tight glucose control, or conventional therapy with the goal of attaining asymptomatic hyperglycemia [28]. The results showed lower risk of diabetic retinopathy (76%), diabetic nephropathy (50%), and diabetic neuropathy (60%), but initially it was not able to definitively determine the effect on CVD risk given the small number of patient with CVD [28]. This prompted a follow-up observational study, the Epidemiology of Diabetes Interventions and Complications (EDIC) to evaluate the potential CVD legacy effects of the more rigorous glucose-lowering arm of the DCCT. In EDIC, there was a lower risk of CVD (myocardial infarction and stroke) and CVD-related death in the intensive treatment group, with 57% risk reduction at 11 years, and 32% at 20 years after the end of DCCT. It also showed a persistent beneficial effect of intensive treatment on retinopathy (48% risk reduction at 17 years), nephropathy (50% risk reduction at 18 years) and neuropathy (40% risk reduction at 14 years). Thus, EDIC demonstrated a metabolic memory, as the effect of tight glycemic control showed sustained benefit well after the trial ended [29].

The United Kingdom Prospective Diabetes Study (UKPDS) published in 1999 evaluated the impact of intensive treatment in patients with newly diagnosed T2DM [30]. This trial was followed by a 10-year follow-up to assess longevity (legacy) of the CVD benefit of more intensive treatment. Of 5102 persons with newly diagnosed T2DM, 4209 were randomized to conventional treatment (targeting asymptomatic hyperglycemia) with diet only, or intensive therapy (targeting tight control of blood glucose, median HbA1c of 7%) using one or more of the following (insulin, sulfonylurea, and metformin "in overweight patients") and were followed for a median of 10 years. At 10 years, there was a reduction in microvascular complications (retinopathy, nephropathy, and neuropathy) by 24% ($P = 0.001$), reduction in CVD by 15% ($P = 0.01$) and in all-cause mortality by 13% ($P = 0.007$) with intensive therapy. It also showed that metformin significantly decreased any diabetes related endpoint (21% risk reduction, $P = 0.01$), MI (33% risk reduction, $P = 0.005$), and death from any cause (27% risk reduction, $P = 0.002$). A legacy effect was seen again in UKPDS as it had been seen in EDIC [30–32]. Differences in HbA1c levels between intensively and conventionally treated participants disappeared within 1 year of the trial's end. Outcomes continued to favor the intensively treated group: significant relative reduction in microvascular disease persisted, and significant reductions in MI and all-cause mortality emerged in the intensive-control group.

The intensified multifactorial intervention in patients with T2DM and microalbuminuria (the Steno 2) RCT evaluated the effect of stepwise intensified treatment (behavioral modification, medications targeting blood glucose control [mostly metformin and sulfonylureas], hypertension and hyperlipidemia) vs. standard treatment (following Danish guidelines) on participants with T2DM and microalbuminuria. The trial showed lower risk of progression of microvascular complications in participants randomized to the intervention arm [33]. This multifactorial intervention was followed by a 21-year follow-up to evaluate the impact of tight glycemic control for 7.8 years on CVD risk. The study showed a median of 7.9 years longer life in the intensified intervention group ($P = 0.005$), with an 8.1-year delay in CVD in this group compared to the standard treatment group [34].

In 2008, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial was instituted to evaluate if targeting lower HbA1c (< 6.5%) has benefit in improving the outcome of T2DM treatment. It was a multicenter, multifactorial, RCT, involving 11,140 participants who were followed for 5 years [35]. Participants were randomly assigned to intensive vs. standard glucose control using mostly sulfonylurea-based intensive glycemic therapy. The intensive therapy reduced microvascular events by 23% ($P = 0.01$), but it failed to show a statistically significant reduction in CVD [35].

The Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) study, published in 2008, had to be terminated early secondary to futility. It was a double factorial

RCT aimed to compare intensive (goal of HbA1c < 6%) vs. standard (HbA1c 7–7.9%) glycemic control, with the use of glucose-lowering agents (metformin, sulfonylureas, thiazolidinediones, insulin, and/or an alpha glucoside inhibitor) on macro vascular complications in participants with T2DM and either risk or history of CVD. Ten thousand two hundred fifty-one participants were evaluated and followed for 3.7 years, and the trial showed worse all-cause mortality ($P = 0.04$) and CV mortality ($P = 0.02$) in the intensive control group [36].

The Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes (VADT) trial was published in 2009. A total of 1791 participants with suboptimal glycemic control were randomized to either intensive or standard treatment, with the goal of a reduction in HbA1c of 1.5% absolute points in the intensive treatment group. The treatment was assigned based on the participant's BMI (> 27 kg/m^2: metformin and rosiglitazone; < 27 kg/m^2: glimepiride and rosiglitazone). VADT showed no clinically significant CVD risk reduction, microvascular complications, or all-cause mortality with intensive glycemic control in these veterans with T2DM. However, a significant improvement was observed in diabetic nephropathy. A 15-year follow-up was recently reported showing no mortality benefit or CVD legacy effect [37, 38•].

The results of the ORIGIN trial designed to evaluate the effects of intensifying basal insulin to normalize fasting glucose on CVD risk was published in 2012 [39]. This was a multicenter RCT assigning 12,537 participants with impaired fasting glucose, impaired glucose tolerance or T2DM and CVD risk to either insulin glargine targeting a fasting glucose goal of < 95 mg/dL or standard care. Participants were followed for 6.2 years, and there were similar CVD outcomes in the two groups [39]. These negative study results, however, did reinforce the notion that intensive insulin therapy does not increase CVD in patients with diabetes.

Meta-analysis of ACCORD, ADVANCE, UKPDS, and VADT had 27,049 participants with 2370 major vascular events. There was a 9% reduction in cardiovascular events in the intensive glucose control group compared to less intensive mainly due to a 15% reduction in myocardial infarction. This meta-analysis showed that with intensive glucose control there was a 16% reduction in CVD in those with no history of macro vascular disease and no cardiovascular benefit in those who had a history [40]. There is data to support that genetic predisposition to hyperglycemia increases CAD separate from T2DM and other CAD risk factors such as hypertension, hyperlipidemia, and obesity. These findings provide ancillary evidence that modulating glycemia may provide cardiovascular benefit [41].

Studies of the impact of newer glucose-lowering agents on CVD, designed as a result of the FDA mandate regarding CVD outcomes for newer anti-diabetic drugs, have yielded promising results. These included studies of sodium-glucose cotransporter 2 (SGLT2) inhibitors and their impact on CVD. The results of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial involving 7028 participants with diabetes at high risk for CVD was published in 2015 [42]. These participants were randomized to receive empagliflozin or placebo. While the trial showed no significant difference between the groups in the rates of MI or stroke, it showed significant superiority for the empagliflozin group for total CVD-related mortality, CHF hospitalization, and all-cause death.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program and CANVAS–Renal were published in 2017 [43]. These two trials were pooled and included 9734 participants with T2DM, 65.6% of whom had baseline CVD. The participants were randomized to canagliflozin vs. placebo. The composite results showed superiority of the canagliflozin group in CVD mortality, non-fatal MI, or non-fatal stroke. The canagliflozin group had non-significant less death from any cause or death from CVD, fewer hospitalizations for heart failure, and progression of albuminuria. There was an increased risk of amputation of the toes, feet, or legs (71% of the affected participants had their highest amputation at the level of toes or metatarsal) in the canagliflozin group, and increase in the risk of infection of male genitalia and mycotic genital infection in women [43].

The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction (DECLARE–TIMI) 58 was published in 2019 [44]. It was a multi-national, randomized, double-blind trial, designed to evaluate the CVD safety profile of dapagliflozin. The trial randomized 17,150 participants with T2DM and either CVD or at CVD risk to receive dapagliflozin vs. placebo and followed them for a median of 4.5 years. CVD-related mortality and heart failure hospitalization improved in the dapagliflozin group. However, genital infections were increased in the dapagliflozin group [44]. Collectively, these three trials suggest that the SGLT2 inhibitors have a positive effect on CVD outcomes in patients with T2DM.

Another group of anti-diabetic agents that have been shown to have potential CVD benefits are the glucagon-like peptide-1 receptor agonists (GLP-1 RA). The FDA has approved twice-daily injections of exenatide, once-daily injections of liraglutide and lixisenatide, and once-weekly injections of dulaglutide, semaglutide, and exenatide. First oral form of GLP-RA semaglutide was approved in September 2019. There have been several major clinical trials evaluating their effect on CVD outcomes, with two of them showing superiority and two non-inferiority. The primary outcome for all of them was the composite of first occurrence of death from CVD causes, non-fatal MI, or non-fatal stroke.

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial studied 6068 participants with

T2DM and a recent history of an acute coronary event (within 180 days prior to enrollment) along with hospitalization for unstable angina. Participants were followed for a median of 25 months. The lixisenatide treatment group showed non inferiority for the primary outcome but failed to show superiority [45].

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was published in 2016 [46]. It included 9340 participants. 81.3% had established CVD. They had a median follow-up of 3.8 years. The liraglutide group had less CVD events and lower all-cause mortality and nephropathy. The study showed increased risk for acute cholecystitis but not acute pancreatitis [46].

The trial to Evaluate Cardiovascular and Other Long term outcomes with Semaglutide in Subjects with T2DM (SUSTAIN-6) was published in 2016. This trial enrolled 3297 participants and 83% had CVD. They underwent randomization to semaglutide or placebo. The primary CVD outcome and incidence of non-fatal strokes was lower in the semaglutide group. There was however no significant difference in frequency of nonfatal MI or CV-related death [47].

The Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 was a double-blind, placebo-controlled cardiovascular outcomes trial for oral semaglutide. This evaluated the cardiovascular safety of oral semaglutide vs placebo when added to standard of care in 3183 people with T2DM at high risk of cardiovascular events. After a median follow-up of 16 months, the study showed that the first occurrence of primary outcome (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was significantly lower with the semaglutide group. All-cause mortality was lower and weight reduction was greater with the semalutide group. This trial showed that semiglutide is not inferior to placebo [48].

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) Study Group evaluated exenatide in 14,752 participants, of whom 73.1% had pre-existing CVD. The study, published in 2017, showed no inferiority or superiority to placebo [49].

Three of the dipeptidyl peptidase 4 (DPP-4) inhibitors have been studied for CVD safety; while none showed superiority, they did show non-inferiority. The saxagliptin study showed increased risk of heart failure hospitalization, but the two consecutive studies with alogliptin and sitagliptin did not show this risk. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53, published in 2013, randomized 16,492 participants with T2DM and increased risk for CVD events to receive saxagliptin or placebo in addition to standard care [50]. The primary endpoint was the same as the GLP-1 agonist trials, the secondary endpoints were (1) composite primary endpoint plus hospitalization for heart failure, coronary revascularization, or unstable angina; (2) death from any cause; and (3) CVD-related death. It showed non-inferiority of saxagliptin ($P < 0.001$), but increased heart failure hospitalization by 2.5% [50, 51••].

Another trial, the Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care (EXAMINE), was published in 2013 [51••, 52]. This trial evaluated 5380 participants with T2DM and a history of MI or unstable angina requiring hospitalization within 15–90 days prior to the enrollment. Participants were randomized to alogliptin or placebo and followed for 40 months. The primary end point was composite major cardiovascular adverse events (MACE); the secondary outcomes were all-cause mortality, death from CVD and with post hoc analysis heart failure hospitalizations. Alogliptin showed non-inferiority with no statically significant difference in adverse events or other outcomes [51••, 52].

In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), 14,671 participants with T2DM with a history of major CAD, ischemic stroke, or atherosclerotic peripheral arterial disease were randomized to receive sitagliptin or placebo (on top of the existing treatment) [53]. The primary outcome composite was as for EXAMINE plus hospitalization for unstable angina. Secondary outcomes were the same as above. Sitagliptin was non-inferior to placebo for primary cardiovascular outcome [53]. Thus, these trials indicate that DPP-4 inhibitors are safe but do not lessen CVD events,

Dyslipidemia Management in Diabetes

American Diabetes Association (ADA) guidelines emphasize that lifestyle modification is the first step in managing diabetes and its complications. Dyslipidemia is a well-known risk factor for CVD, especially in patients with diabetes; therefore, screening for it is recommended at the time of diagnosis and every 5 years in patients younger than 40 years of age, or more often with longstanding disease and in patients receiving lipid-lowering medications. In this regard, it is recommended that LDL levels be rechecked 1–3 months after starting medication, either changing the dose or adding another agent after evaluating medication adherence [54]. Statins are recommended for primary prevention of CVD in patients with diabetes who are older than 40 years of age as diabetes is major CVD risk factor in the 10-year atherosclerotic cardiovascular disease risk calculator. For patients younger than 40 years of age with CVD or significant risk factors for CVD, use of high-intensity statin treatment should be considered. In patients older than 40 years without risk factors, moderate-intensity statin should be considered. It is recommended that any patient with diabetes over the age of 40 years with > 20% CVD risk should be treated with high-intensity statin therapy. In case of statin intolerance, the maximally tolerated dose of statin or an alternative lipid lowering agent should be used. If LDL goals are not met with the use of statins, ezetimibe, or Proprotein convertase subtilisin/kexin type 9 (PCSK 9), inhibitors should be added [54].

There have been several trials designed to assess dyslipidemia management in patients with diabetes and CVD risk. Primary prevention of cardiovascular disease with atorvastatin in T2DM in the Collaborative Atorvastatin Diabetes Study (CARDS) was published in 2004. It was a multicenter randomized placebo-controlled trial with a goal to assess the benefits of using 10 mg of atorvastatin daily in primary prevention of MI, stroke, or MACE in participants with T2DM but without what was considered high LDL levels. Accordingly, 2838 participants were followed for a median of 3.9 years, and the study was terminated 2 years earlier than expected as it met the pre-specified early stopping rule for efficacy. Atorvastatin reduced CVD by 37% and death rate by 27% without an excess of adverse effects [55].

A trial to evaluate intensive vs. moderate lipid lowering with statins after acute coronary syndromes, The Pravastatin or Atorvastatin Evaluation and—Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial was published in 2004. This involved 1462 participants with prior hospitalization for acute coronary syndrome within 10 days of enrollment. Participants were assigned to receive 40 mg of pravastatin daily or 80 mg of atorvastatin daily (intensive therapy), and followed for a mean of 24 month. The primary endpoint was a composite of death from any cause, MI, documented unstable angina requiring re-hospitalization, revascularization (performed at least 30 days after randomization), and stroke. Study results showed more reduction in LDL level in the atorvastatin group and also showed superiority of this intensive statin therapy [56].

In 2010, the ACCORD lipid investigators studied the benefits of adding fibrate to statins in reducing CVD endpoint in participants with T2DM who were at risk of CVD. Accordingly, 5518 simvastatin-treated participants were randomized to receive fenofibrate or placebo. The primary outcome was the first occurrence of non-fatal MI, non-fatal stroke, or death from CVD with a mean follow-up of 4.7 years. In this milestone study, there was no statistically significant benefit of adding fenofibrate to statins [57].

The benefit of adding ezetimibe, which works by decreasing intestinal cholesterol absorption, was evaluated in the IMPROVE IT trail (Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes) [58]. It was a double-blind RCT involving 18,144 participants with acute coronary syndrome requiring hospitalization within the preceding 10 days. The subjects had LDL cholesterol levels of 50 to 100 mg/dL on lipid-lowering therapy or 50 to 125 mg/dL if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) was compared with simvastatin (40 mg) and placebo. The primary endpoint was a composite of CVD deaths, non-fatal MI requiring re-hospitalization, coronary revascularization (≥ 30 days after randomization), or non-fatal stroke. Follow-up was 6 years. The simvastatin-ezetimibe group showed superiority for reduction of endpoints in conjunction with more LDL reduction [58].

PCSK9 increases LDL-receptor degradation. PCSK9 Inhibitors reduce degradation of LDL receptors and increase hepatic uptake of LDL causing significant LDL reduction. There are currently two FDA-approved medications in this group, alirocumab and evolocumab. They were approved in 2015 in addition to diet and maximally tolerated statins to treat homozygous and heterozygous familial hypercholesterolemia. They lower the risk of MACE and MI as well as the need for revascularization, and should be used to achieve lipid-lowering goals that cannot be achieved with statins in patients with diabetes [59•].

In 2018, a sub-analysis of current studies to evaluate the impact of PCSK9 inhibitors on managing dyslipidemia in patients with diabetes and high CVD risk was published. This was based on the Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease (FOURIER) trial. This trial followed a total of 27,564 participants, 11,031 with diabetes, 10,344 with pre-diabetes, and the rest without glycemic abnormalities. The trial demonstrated that treatment with evolocumab resulted in a 57% reduction in LDL levels in participants with and without diabetes, with CVD risk prevention being more pronounced in those with diabetes (greater absolute risk reduction) compared to those without diabetes (2.7% vs 1.6% respectively) over 3 years [60–62].

Hypertension

Hypertension in patients with both type 1 and type 2 diabetes poses a significant risk for micro- and macro-vascular complications. Furthermore, over 50% of patients with diabetes have hypertension [63]. Hypertension is associated with arterial dysfunction which can lead to impaired NO-mediated vasodilator capacity. Activation of the RAAS and sympathetic nervous activity increases in oxidative stress and tissue inflammation can lead to progression of arterial stiffening, hypertension, and associated CVD [64].

Lifestyle intervention with weight loss, decreased alcohol consumption, and increase in activity is recommended as the initial approach for individuals with blood pressure > 120/80 mmHg and is included in the treatment algorithm outlined by the ADA [54]. RAAS blockade using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) remains the first-line medical therapy for hypertension in patients with diabetes and/or albuminuria, as activation of the RAAS is considered to be a primary pathological process leading to a vicious cycle of hypertension and renal failure in diabetes. Dihydropyridine calcium channel blockers, and diuretics, especially indapamide and chlorthalidone, can be added to ACE inhibitors or ARBs if more than one drug is needed. Beta blockers and mineralocorticoid receptor antagonists are reserved for patients with cardiomyopathy, ischemic heart disease, or resistant hypertension.

There has seen significant debate over defining targets for blood pressure (BP) in patients with diabetes. The more conservative 8th Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommended a systolic BP of < 140 mm Hg. There have been several clinical trials investigating intensive vs. moderate blood pressure control which have resulted in informative data [65]. For example, the ACCORD-Blood Pressure (ACCORD-BP) trial included 4733 participants to test the cardiovascular benefits of lower systolic BP targets. Participants were randomized into an intensive BP group with a goal systolic BP of < 120 mmHg (average 119.3 mmHg) or a standard BP group with a goal systolic blood pressure of < 140 mmHg (average 133.5 mmHg). After 4.9 years, there was no significant difference in CVD outcomes ($P = 0.20$). The incidence of stroke was lower in the intensive group, but the risk of renal injury and hypokalemia were higher [66]. The ACCORD follow-on study (ACCORDION) then assessed the randomized groups of the ACCORD study for long-term effects of intensive versus standard blood pressure control. Over a follow-up period of 8.8 years among the 3957 participants (87% of living participants at the end of the ACCORD trial), there was no difference in the cardiovascular mortality among both groups, and the stroke benefit was no longer seen as the difference in blood pressure waned [67]. This contrasts to the results of the Systolic Pressure Interventional (SPRINT) trial [68]. Among 9361 participants who were randomized into < 120 mmHg intensive systolic BP treatment group vs. < 140 mmHg standard systolic BP treatment group, a significant decrease in the fatal and non-fatal cardiovascular events were noted in the < 120/80 mmHg arm. The SPRINT trial did not include patients with diabetes, leaving the controversy regarding appropriate systolic blood pressure targets in this population open. A post hoc analysis in ACCORD and a meta-analysis suggest that a systolic blood pressure target of < 130 mmHg may be more appropriate in the diabetic population [69, 70•, 71]. A study of 3159 diabetic non-hypertensive patients from a large Chinese cohort of 101,510 individuals showed that having a BP < 120/80 or a decline in BP to less than 120/80 was associated with increased all-cause mortality, whereas development of hypertension with a BP over 140/90 increased the risk of cardiovascular events [72]. The more recent ADVANCE trial that studied 10,948 participants over 4.5 years using Cox models showed that perindopril-indapamide reduced mortality and major vascular events compared to placebo, regardless of baseline systolic BP (evaluated down to < 120 mm Hg), diastolic BP (evaluated down to <70 mm Hg), or whether the 10-year CVD risk was ≥ 20% or < 20% [73••]. These data indicate that patients with diabetes would gain cardiovascular benefit with a blood pressure somewhere between 120 and 135 mmHg, while a blood pressure of < 120 mmHg may be beneficial in patients at risk of stroke [70•]. As per ADA guidelines for individuals with diabetes and hypertension with ASCVD or a 10-year ASCVD risk > 15%, a blood pressure target of < 130/80 mmHg may be appropriate, if it can be safely attained. For individuals with 10-year atherosclerotic cardiovascular disease (ASCVD), risk < 15% treatment to a blood pressure target of < 140/90 mmHg is recommended [54].

Diabetic Nephropathy

Poor glycemic control leads to diabetic kidney disease which, in turn, can worsen hypertension, heart failure and increase CVD mortality. The ADVANCE ON trial showed that intensive glucose control reduced the risk of progression to end-stage renal disease even after 9.9 years of post-trial follow-up [75]. Inhibition of RAAS, along with good glucose and BP control, is key in slowing down the progression of diabetic kidney disease to end-stage renal disease. Given the effectiveness of ACE inhibitors or ARBs, the combination therapy of these agents was also explored, but unfortunately the adverse events of hyperkalemia and renal dysfunction limit this approach [75].

Newer agents like SGLT2 inhibitors have gained particular interest with their novel mechanism of action and beneficial effects on albuminuria [76•]. Large-scale clinical trials with GLP-1 RA, SGLT-2 inhibitors, and DPP4 inhibitors and their effects on BP and kidney disease are summarized in Table 1.

Antiplatelet Therapy

Antiplatelet agents like aspirin block platelet aggregation and prevent the progression of atherosclerotic plaques. Meta-analysis of data published over 20 years has shown the benefit of aspirin in the secondary prevention of acute coronary disease and stroke [78•]. However, the use of aspirin for primary prevention of major vascular events remained controversial, as the net benefit was outweighed by risk of bleeding events. The ASCEND trial (effects of aspirin for primary prevention in persons with diabetes mellitus) focused on the use of aspirin for primary prevention of CVD in diabetes. This was a large RCT where 15,480 individuals with diabetes were randomized to receive 100 mg aspirin daily and placebo and followed through a mean duration of 7.4 years. There was a 12% lower risk of major CVD events (MI, stroke, and transient ischemic episodes) but a 29% higher risk of major bleeding (intracranial, gastrointestinal, ophthalmic, etc.) in the aspirin group compared to the placebo group [78•].

The use of aspirin for primary prevention in patients without diabetes was studied in two other large RCTs, ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) and ASPREE (Aspirin in Reducing Events in the Elderly) in the elderly [79, 80]. ARRIVE, with 12,546 participants over a period of 60 months follow-up, showed no difference in the incidence of adverse events ($P = 0.6$) but an increase in the

Table 1 Results of large-scale studies on the cardiovascular and renal benefit of newer hypoglycemic agents

Trial	Medication	*N* with HTN	Years followed (median)	CV results HR (95% CI)/*P* value	Mean systolic BP change in mmHg (95% CI)/*P* value	Mean diastolic BP change in mmHg (95% CI)	Renal benefit: HR (95% CI)
CANVAS	Canagliflozin	9125	1.5	Superior 0.86 (0.75–0.97)	− 3.93 (− 4.3 to − 3.56)	− 1.39 (− 1.61 to − 1.17)	Superior 0.6 (0.47–0.77)
EMPA-REG OUTCOME	Empagliflozin	7028	3.1	Superior 0.86 (0.74–0.99)	For both 10 mg and 25 mg dose: about − 4 HR not given	For both 10 mg and 25 mg dose: − 1 to − 2 HR not given	Superior 0.61 (0.53–0.7)
LEADER	Liraglutide	9340	3.8	Superior 0.784 (0.66–0.93)	− 1.2 (− 1.9 to − 0.5)	0	Superior 0.74 (0.6–0.91)
SUSTAIN6	Semaglutide	3297	2.1	Non-inferior 0.74 (0.58–.95)	For 0.5 mg dose − 1.3 ($P = 0.1$) For 1 mg dose − 2.6($P < 0.001$)	0	Superior 0.64 (0.46–0.88)
EXCSEL	Exenatide	14,752	3.2	Non-inferior 0.91 (0.83–1)	− 1.57 (− 1.92 to − 1.21)	+ 0.25 (0.04 to 0.47)	N/A
ELIXA	Lixisenatide	6068	2.1	Non-inferior 1.02 (0.89–1.17)	− 0.8 (− 1.3 to − 0.3)	0	Not significant ($p = 0.07$)
SAVOR-TIMI	Saxagliptin	16,492	2,1	Non-inferior 1.0 (0.89–1.12)	N/A	N/A	N/A
EXAMINE	Alogliptin	5380	1.5	Non-inferior 0.96 ($P < 0.001$)	N/A	N/A	N/A
TECOS	Sitagliptin	14,671	3.0	Non-inferior 0.98 (0.88–1.01)	N/A	N/A	N/A
CREDENCE	Cangliflozin	4401	2.6	Not significant 0.78 (0.61–1)	− 3.3 (− 2.73 to 3.87)	− 0.95 (− 0.61 to − 1.28)	Superior 0.6 (0.48–0.76)

HR hazards ratio, *N/A* not applicable

(Adapted from Khangura D et al. Am J Hypertens. 2018 Apr 13;31(5):515–521. https://doi.org/10.1093/ajh/hpy025, by permission of Oxford University Press) [77]

incidence of bleeding ($P = 0.0007$) in the aspirin group compared to placebo. In the ASPREE trial, with 19,114 persons over a median of 4.7 years of follow-up, the rates of all-cause mortality per 1000 person-years were 12.7 in the aspirin arm vs. 11.1 in the placebo arm (HR 1.14; 95% CI 1.01–1.29). The rate of major hemorrhage per 1000 person-years was 8.6 events vs. 6.2, respectively (HR 1.38; 95% CI 1.18–1.62; $P < 0.001$).

Based on current evidence, aspirin appears to be beneficial for secondary prevention of ASCVD in patients with diabetes, but the risk of major bleeding limits the use of aspirin as primary prevention. The 2019 ADA standards of care in diabetes suggest that for adults with ASCVD risk of > 1% per year, the use of aspirin may be considered, with the caveat that the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health [54].

Future Trends

In this rapidly evolving age of technology, diabetes management has witnessed the development of high-technology solutions including use of continuous glucose monitoring which helps maintain glycemic control and increases the time in target range. The DIAMOND study showed that in adults with T1DM who used multiple daily insulin injections, the use of continuous glucose monitoring compared with usual care resulted in significant less time with Glucose level below 70 mg/dl and a greater decrease in HbA1c [82]. .The VADT trial showed that longitudinal variation in fasting glucose was associated with all-cause mortality independent of other risk factors [83].

In addition, bariatric surgery has shown favorable outcomes in diabetes management and treatment of the obesity epidemic, thereby addressing key risk factors for CVD.

The trend of conducting large RCTs examining the cardiovascular benefit of every new anti-glycemic agent may help address ASCVD risk from the very beginning of diabetes management and assist in tailoring evidence based individualized treatment plans for patients with diabetes.

Conclusion

Diabetes mellitus is a chronic disease with serious life-threatening complications. CVD remains the commonest cause of mortality and morbidity. Uncontrolled diabetes, hypertension, dyslipidemia, and obesity are some of the key predisposing risk factors in the development of CVD. Risk factor modification is a critical part of management. Long-term follow-up of DCCT and UKPDS showed that initial tight glycemic control is associated with lower cardiovascular risk in later life, though the VADT trial was not able to confirm this legacy effect. The mechanism of accelerated atherosclerosis associated with diabetes is poorly understood, though it has been suggested that epigenetics may play a role in this process. Landmark trials have shown the importance of lipid-lowering therapy, anti-hypertensive, and glucose-lowering agents in reducing cardiovascular risk. Recent trials showing cardiovascular benefit of newer anti-diabetic agents have changed diabetes treatment algorithms. The need exists for safer antiplatelet drugs. Aggressive management of modifiable risk factors is associated with improvement in cardiovascular outcomes. Management of CVD in patients with diabetes requires multidisciplinary groups of health care providers including primary care providers, endocrinologists, cardiologists, dieticians, diabetic educators, etc. More research is needed to better understand the relationship between diabetes and CVD.

Acknowledgments The authors would like to thank Brenda Hunter for her assistance in preparing this review by helping with the figure.

Compliance with Ethical Standards

Conflict of Interest Rajaa Almourani, Bhavana Chinnakotla, Richa Patel, L. Romayne Kurukulasuriya, and James Sowers declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Control CfD, Prevention. National diabetes statistics report, 2017. Atlanta: Centers for Disease Control and Prevention; 2017.
2. Association AD. Economic costs of diabetes in the US in 2017. Diabetes Care. 2018;41(5):917–28.
3. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet. 2006;368(9529):29–36.
4. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care. 2000;23(7):962–8.
5. Stamler J, Vaccaro O, Neaton JD, Wentworth D, Group MRFITR. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care. 1993;16(2):434–44.
6. Sowers JR. Obesity as a cardiovascular risk factor. Am J Med. 2003;115(8):37–41.
7. Randle P, Garland P, Hales C, Newsholme E. The glucose fatty-acid cycle its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet. 1963;281(7285):785–9.

8. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Rev Endocrinol. 2009;5(3):150–9.
9. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest. 2007;117(1):175–84.
10. De Pergola G, De Mitrio V, Giorgino F, Sciaraffia M, Minenna A, Di Bari L, et al. Increase in both pro-thrombotic and anti-thrombotic factors in obese premenopausal women: relationship with body fat distribution. Int J Obes. 1997;21(7):527–35.
11. Aroor AR, DeMarco V, Jia G, Sun Z, Nistala R, Meininger GA, et al. The role of tissue renin-angiotensin-aldosterone system in the development of endothelial dysfunction and arterial stiffness. Front Endocrinol. 2013;4:161.
12. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. Cell Metab. 2011;14(5):575–85.
13. Sowers JR. Hypertension and vascular disease. Hypertension. 2013;61(5):943–7.
14. Vanessa Fiorentino T, Prioletta A, Zuo P, Folli F. Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases. Curr Pharm Des. 2013;19(32):5695–703.
15. Li Q, Verma IM. NF-κB regulation in the immune system. Nat Rev Immunol. 2002;2(10):725–34.
16. Adhikari N, Basi DL, Carlson M, Mariash A, Hong Z, Lehman U, et al. Increase in GLUT1 in smooth muscle alters vascular contractility and increases inflammation in response to vascular injury. Arterioscler Thromb Vasc Biol. 2011;31(1):86–94.
17. Regan TJ, Lyons MM, Ahmed SS, Levinson GE, Oldewurtel HA, Ahmad MR, et al. Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest. 1977;60(4):885–99.
18. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol. 1972;30(6):595–602.
19. Mizushige K, Yao L, Noma T, Kiyomoto H, Yu Y, Hosomi N, et al. Alteration in left ventricular diastolic filling and accumulation of myocardial collagen at insulin-resistant prediabetic stage of a type II diabetic rat model. Circulation. 2000;101(8):899–907.
20.•• Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circ Res. 2018;122(4):624–38. **Diabetic cardiomyopathy can occur in patients without coronary artery disease or other conventional risk factors. This review discusses mechanisms for diabetic cardiomyopathy and stratifies for prevention and treatment.**
21. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. Endocr Rev. 2004;25(4):543–67.
22.•• Care D. Standards of medical care in diabetes 2019. Diabetes Care. 2019;42:S81. **Annual update from American Diabetes Association gives current guidelines and changes for the year regarding the care for patients with diabetes.**
23.•• Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm–2019 executive summary. Endoc Pract. 2019;25(1):69–100. **Important management algorithm that guides evidence-based patient care.**
24. Group DPPR. The diabetes prevention program (DPP): description of lifestyle intervention. Diabetes Care. 2002;25(12):2165–71.
25. Group LAR. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity. 2014;22(1):5–13.
26. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, Basora J, Fitó M, Corella D, et al. Effect of a lifestyle intervention program with energy-restricted mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-plus trial. Diabetes Care. 2019;42(5):777–88.
27. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541–51.
28. Control D, Group CTR. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.
29. Cleary PA, Orchard TJ, Genuth S, Wong ND, Detrano R, Backlund J-YC, et al. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the diabetes Control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) study. Diabetes. 2006;55(12):3556–65.
30. King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. Br J Clin Pharmacol. 1999;48(5):643–8.
31. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
32. Genuth S, Eastman R, Kahn R, Klein R, Lachin J, Lebovitz H, et al. Implications of the United Kingdom prospective diabetes study. Diabetes Care. 2003;26:S28.
33. Gæde P, Vedel P, Parving H-H, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet. 1999;353(9153):617–22.
34. Gæde P, Oellgaard J, Carstensen B, Rossing P, Lund-Andersen H, Parving H-H, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia. 2016;59(11):2298–307.
35. Group AC. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–72.
36. Group AtCCRiDS. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–59.
37. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129–39.
38.• Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, McCarren M, et al. Intensive glucose control in patients with type 2 diabetes—15-year follow-up. NEJM. 2019;380:2215–24. https://doi.org/10.1056/NEJMoa1806802. **Important follow-up trial that did not show metabolic memory of legacy effect as oppsed to DCCT and UKPDS long-term trials.**
39. Investigators OT. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). Am Heart J. 2008;155(1):26.e1–e13.
40. Turnbull F, Abraira C, Anderson RJ, Byington R, Chalmers J, Duckworth W, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Berlin: Springer; 2009.
41. Merino J, Leong A, Posner DC, Porneala B, Masana L, Dupuis J, et al. Genetically driven hyperglycemia increases risk of coronary artery disease separately from type 2 diabetes. Diabetes Care. 2017;40(5):687–93.
42. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
43. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.

44. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57.
45. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373(23):2247–57.
46. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–22.
47. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44.
48. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381:841–51.
49. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228–39.
50. Bhatt DL, editor. Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus (SAVOR)–TIMI 53. Presentation delivered at the European Association for the Study of Diabetes 49th annual meeting on; 2013.
51.•• Cutshall BT, Twilla JD, Olinger AS, Oliphant CS. A review on cardiovascular effects of newer hypoglycaemic medications. Ann Med. 2017;49(7):603–12. **Reviews the importance of selecting medications that provide diabetes control while maintaining cardiovascular safety.**
52. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35.
53. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373(3):232–42.
54. Association AD. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2019. Diab Care. 2019;42(Supplement 1):S103–S23.
55. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685–96.
56. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495–504.
57. Group AS. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563–74.
58. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387–97.
59.• Ghadban R, Enezate T, Omran J, Almourani R, Singla A, Balla S. Clinical outcomes of PCSK9Is: a meta-analysis of randomized clinical trials. Cardiovasc Diag Ther. 2017;7(6):598–606. **This meta-analysis shows the importance of PCSK9 inhibitors in improving clinical outcomes in patients at high risk for atherosclerotic cardiovascular disease.**
60. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–22.
61. Handelsman Y, Lepor NE. PCSK9 inhibitors in lipid management of patients with diabetes mellitus and high cardiovascular risk: a review. J Am Heart Assoc. 2018;7(13):e008953.
62. Giugliano RP, Pedersen TR, Park J-G, De Ferrari GM, Gaciong ZA, Ceska R, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet. 2017;390(10106):1962–71.
63. Lastra G, Syed S, Kurukulasuriya LR, Manrique C, Sowers JR. Type 2 diabetes mellitus and hypertension: an update. Endocrinol Metab Clin. 2014;43(1):103–22.
64. Jia G, Aroor AR, Martinez-Lemus LA, Sowers JR. Potential role of antihypertensive medications in preventing excessive arterial stiffening. Curr Hypertens Rep. 2018;20(9):76.
65. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint National Committee (JNC 8). Jama. 2014;311(5):507–20.
66. Group AS. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575–85.
67. Cushman WC, Evans GW, Cutler JA. Long-term cardiovascular effects of 4.9 years of intensive blood pressure control in type 2 diabetes mellitus: the action to control cardiovascular risk in diabetes follow-on blood-pressure study. Am Heart Assoc. 2015.
68. Group SR. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.
69. Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care. 2014;37(6):1721–8.
70.• Whaley-Connell A, Sowers JR. Blood pressure related outcomes in a diabetic population. Hypertension. 2016;68(1):34. **Evidence-based review of BP control in patients with diabetes.**
71. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. Jama. 2015;313(6):603–15.
72. Wu Z, Jin C, Vaidya A, Jin W, Huang Z, Wu S, et al. Longitudinal patterns of blood pressure, incident cardiovascular events, and all-cause mortality in normotensive diabetic people. Hypertension. 2016;68(1):71–7.
73.•• Rahman F, McEvoy JW, Ohkuma T, Marre M, Hamet P, Harrap S, et al. Effects of blood pressure lowering on clinical outcomes according to baseline blood pressure and cardiovascular risk in patients with type 2 diabetes mellitus: the ADVANCE trial. Hypertension. 2019:HYPERTENSIONAHA.118.12414. **This study shows that adults with DM appear to benefit from more intensive BP management than what current guidelines recommend.**
74. Zoungas S, Chalmers J, Bruce N, Billot Laurent , Li Q, et al ADVANCE On Collaborative group- Follow uo of Blood pressure 2 Lowering and glucose control in Type 2 diabetes New Eng J Med 2014;371:1392-1406
75. Investigators O. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547–59.
76.• Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New Engl J Med. 2019. **Effect of an antidiabetic agent on reducing the risks of kidney disease and cardiovascular events.**
77. Khangura D, Kurukulasuriya LR, Whaley-Connell A, Sowers JR. Diabetes and hypertension: clinical update. Am J Hypertens. 2018;31(5):515–21. https://doi.org/10.1093/ajh/hpy025.

78.• Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Elsevier; 2009. **Strong message about aspirin in primary prevention. Aaspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds.**

79. Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018;392(10152):1036–46.

80. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med. 2018;379(16):1519–28.

81. Mcneil J, Wolfe R, Woods, R, Tonkin A, Geoffrey A et al ASPree investigator group. Effect of Aspirin on cardiovascular events and bleeding in the healthy Elderly New End J Med 2018 379:1509-1518

82. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. Jama. 2017;317(4):371–8.

83. Zhou JJ, Koska J, Bahn G, Reaven P. Glycaemic variation is a predictor of all-cause mortality in the veteran affairs diabetes trial. Diabetes and Vascular Disease Research. 2019;16(2):178–85.