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Cardiovascular effects of anti-diabetes drugs

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Abstract

Introduction—Cardiovascular disease remains the major contributor to morbidity and mortality in diabetes. From the need to reduce cardiovascular risk in diabetes and to ensure that such risk is not exacerbated by drug treatments, governmental regulators and drug manufacturers have focused on clinical trials evaluating cardiovascular outcomes.

Areas covered—Findings from mechanistic and clinical trials of biguanides, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose transporter 2 (SGLT-2) inhibitors will be reviewed. These drug classes will be compared within the context of available cardiovascular outcomes data. Clinical implications of new study regulations will be examined.

Expert opinion—Recent cardiovascular studies provide a more comprehensive evaluation of specific anti-diabetes therapy in individuals with high cardiovascular risk. Long-term effects of anti-hyperglycemic agents in patients with lower cardiovascular risk are still speculative. Historical data supports continued use of metformin as a first-line agent. DPP-4 inhibitors and GLP-1 receptor agonists appear to have neutral effects on cardiovascular outcomes. The significantly decreased cardiovascular risk associated with empagliflozin SGLT-2 inhibitor therapy is impressive and may change how practitioners prescribe add-on therapy to metformin.

Keywords

cardiovascular risk; biguanides; dipeptidyl peptidase-4 inhibitors; glucagon-like peptide-1 agonists; sodium-glucose transporter 2 inhibitors; sulfonylureas; thiazolidinediones

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1. Introduction

The association between diabetes and the increased risk for cardiovascular disease (CVD) and events is well established. The risk of vascular diseases is doubled with the diagnosis of diabetes [1], and the relative risk of myocardial infarction (MI) and stroke is increased by 80% and 50%, respectively, in those with versus those without diabetes [2]. Although rates of CVD and CVD mortality have universally decreased, the risk of CVD mortality among the diabetes population remains 2–4-fold higher than that of the non-diabetic population [3,4].

Early on in the series of clinical trials designed to examine intensified glycemic control (Table 1), evidence from the United Kingdom Prospective Diabetes Study (UKPDS) suggested that improving glycemic control could mitigate cardiovascular risk in type 2 diabetes mellitus (T2DM). In newly diagnosed T2DM, 10 years of intensive treatment with insulin or sulfonylurea (SU) was associated with a borderline significant reduction in the aggregate endpoint of non-fatal MI, fatal MI, and sudden cardiac death [5]. In a 10-year post-study follow-up, a significant 15% reduction in risk of MI ($p<0.01$) was detected in the intensive treatment group, despite no difference in HbA1c between the intensive and conventional treatment groups 1 year after the start of the follow-up period [6].

Evidence was less compelling in three later glycemic control trials (Table 1). In the ACCORD study [7], no difference in the primary composite outcome of non-fatal MI, non-fatal stroke, and death from cardiovascular causes was observed between intensive and conventional treatment groups over 3.5 years of follow-up. Further, there was an increased risk of all-cause mortality in the intensively treated group, which led to early cessation of the trial. Using the same composite end point, the ADVANCE study [8] also did not find an improvement in cardiovascular outcomes in intensive- versus standard-treated T2DM after 5 years. Similarly, after 5.6 years of follow-up, the VADT [9] found no difference in major cardiovascular events or death between intensive and standard treatment groups. Contrarily, after 9.8 years of follow-up to the VADT interventional period, intensive glycemic control was significantly associated with an increase in time to the first major cardiovascular event (17% relative reduction in risk), using the composite endpoint of non-fatal MI, non-fatal stroke, new or worsening congestive heart failure, amputations for ischemic gangrene, or death from cardiovascular causes [10]. However, cardiovascular and all-cause mortality were not different between groups.

Synchronously, it also became clear that specific anti-diabetes medications can impact cardiovascular parameters independent of glucose-lowering effects. In the aforementioned UKPDS trial, metformin was associated with greater improvements in any diabetes-related end point, all-cause mortality, and stroke compared to SU or insulin [11]. The UKPDS trial [11] also raised concerns that addition of metformin to SU treatment could lead to an increased risk for diabetes-related mortality. Nearly a decade later, the cardiovascular safety of rosiglitazone came into question when a meta-analysis found the treatment to be significantly associated with an increased risk for MI and borderline significantly associated with an increase in risk of death from cardiovascular causes [12].

In the context of findings from glycemic control trials and relationships between anti-diabetes medications and cardiovascular risk, researchers, clinicians, and regulating bodies face specific challenges in the development, assessment, and prescription of anti-diabetes therapies. First, there is a need to identify therapies that can ameliorate cardiovascular risk whilst improving glycemic control. The lack of consistent association between improved glycemic control and improved cardiovascular outcomes is perhaps not surprising, given that diabetes mellitus is associated with several cardiovascular risk factors that are not universally improved with treatment of hyperglycemia, including obesity, high blood pressure, high cholesterol, systemic inflammation, and endothelial dysfunction. In fact, several studies have now shown that a multifactorial approach to diabetes treatment is beneficial to improving outcomes [13,14]. Given this, therapies that improve one or more cardiovascular parameters concurrently with improvements in glycemic control are highly enticing. However, such single-bullet agents have not caused the expected improvement in cardiovascular outcomes, with discrepancies arising between promising early phase clinical trial findings and neutral cardiovascular outcomes of late phase large clinical trials. In other instances, cardiovascular outcomes are improved with no clear mechanism of action.

Second, there is a need to ensure that current and future therapies do not exacerbate the already excessive cardiovascular risk in patients with type 2 diabetes. As a result of concerns over the potential for adverse cardiovascular outcomes with anti-diabetes therapies, the Food and Drug Administration (FDA) established new guidelines for evaluating cardiovascular effects of anti-diabetes medications [15]. These guidelines have stimulated a number of large pre- and post-approval cardiovascular outcomes studies for the newer anti-diabetes drug classes (Table 2), and data from those trials are becoming available.

The purpose of this review is to describe the cardiovascular effects, as currently understood, of the longer-prescribed drug classes of SUs, biguanides, and thiazolidinediones (TZDs), as well as the newer dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors (Table 3 and 4). The benefits, challenges, and limitations of these cardiovascular studies will be examined, and the clinical implications of published and forthcoming results will be discussed.

To provide a broader view of the evidence available and to cover results from numerous small clinical trials, findings from retrospective analyses, population studies, and meta-analyses have been included. Results from such studies can be controversial. While these studies can pool data from multiple small studies and increase the accuracy in approximating the effects of a therapy, it is acknowledged that, although powerful in number of patients and data pooled, these studies may also in fact provide biased or inaccurate results due to trial inclusion, availability of information, and method of analysis. Where available, large, randomized controlled trials are included, understanding that these study designs represent the gold-standard of clinical evidence.

The literature examining and describing the cardiovascular effects of the insulin drug class is vast and will not be covered in this review. Please see Younk et al [16] for a discussion of this topic. Due to the limited efficacy of and capacity to prescribe certain classes of anti-

diabetes drugs, such as alpha glucosidase inhibitors [17–21], dopamine agonists [22,23], and bile acid sequestrants [24], limited information is available regarding the cardiovascular effects of such medications. For inclusivity, cardiovascular information for these treatments is contained in Table 3.

2. Cardiovascular Effects of Anti-Diabetes Medications by Drug Class

2.1 Sulfonylureas and Meglitinides

As early as the University Group Diabetes Program (UGDP) study, evidence suggested that SU therapy was associated with adverse cardiovascular outcomes [25], with initial data suggesting that tolbutamide therapy was associated with increased cardiovascular mortality. The data and study design were subsequently reviewed and there was no difference in MI or diabetes related deaths between those that were randomized to SU or insulin therapy. However, the relationship of insulin secretagogue therapy and cardiovascular effects was highlighted.

Coincident with the publication of this clinical data, the adenosine triphosphate-sensitive potassium (K_{ATP}) channel, SU receptor, and Kir6.x (therapeutic targets of SUs and glinides in pancreatic beta cells) were identified in cardiac myocytes. Further research elucidated different binding affinities of specific SUs and glinides at the pancreatic and cardiac K_{ATP} channels [26,27]. Thus, a direct connection between insulin secretagogue therapy and the potential for adverse effects on the cardiac system became clearer.

Not long after UGDP, the concept of “ischemic preconditioning” was coined. Pre-clinical studies in dogs demonstrated that a brief ischemic episode in anaesthetized dogs slows the rate of adenosine triphosphate depletion during succeeding ischemic episodes [28]. Later, it was demonstrated that brief episodes of ischemia had a protective cardiac effect on cardiac necrosis or angina [29,30]. Subsequently, studies showed that SUs appeared to abolish any protective preconditioning response [31–33]. However, in a study comparing individuals treated with glyburide (also known as glibenclamide) or glimepiride with repeat balloon dilation, healthy and diabetic glimepiride-treated patients had improvements in ischemic burden which indicated continued protection by ischemic preconditioning. Glyburide therapy abolished the cardio-protective effect of preconditioning and demonstrated no improvements in any ischemic cardiac measures [34]. The preservation of ischemic preconditioning has been replicated in individuals receiving glimepiride [35,36], gliclazide [37] and glipizide [38]. In two studies of patients undergoing consecutive exercise treadmill stress tests, repaglinide appeared to abolish ischemic preconditioning [39,40]. Clinical studies suggest that the differing effects of various SU on ischemic preconditioning may be a result of agent-specific binding affinity for K_{ATP} channels on cardiac myocytes, which could explain why glimepiride and gliclazide generally demonstrate improved morbidity and mortality compared to glyburide [41,42].

Individuals with diabetes and heart disease have been studied in various scenarios of cardiac stress. In conditions of acute MI undergoing angioplasty, higher in-hospital and early mortality were associated with SU therapy [43]. Contractility of atrial tissue with recurrent ischemia and reperfusion is impaired in those taking SU therapy compared to insulin [44].

Glyburide therapy has been associated with worsened myocardial function assessed by echocardiogram stress testing compared to insulin [45] and worsened chest pain after subsequent balloon angioplasty inflations [46].

Large clinical trials have ultimately not demonstrated a consistent effect on long term comprehensive cardiovascular endpoints (Table 4). The UKPDS suggested that glyburide or chlorpropamide improved glycemic control and reduced complications from diabetes and did not increase mortality [5]. The ADVANCE trial found that gliclazide therapy in the intensive treatment group was associated with reduced incidence of the combined outcome of major macro- and microvascular events but did not reduce major cardiovascular events or death at 5 year follow-up [8]. After a median follow-up of 2 years, the DIGAMI 2 trial found that those discharged on a SU after acute MI had no increased risk for mortality, stroke, or recurrent MI, compared to those discharged on insulin [47]. Two retrospective studies and a meta-analysis of observational studies suggested that cardiovascular risk was increased in those on SU therapy compared to metformin [42,48] and in those individuals with combination therapy of metformin and SU therapy compared to diet or monotherapy with metformin or SU [48,49]. However, it must be stressed that the observational design of these studies does not control for confounding variables and therefore findings should be considered with caution.

The cardiovascular effects of glinide therapy have not been extensively studied. Repaglinide therapy has been associated with improvement of surrogate cardiovascular markers [50] and reduced inflammatory markers [50–52]. In a retrospective population-based study, at a median of 3 years, repaglinide improved mortality compared to glyburide, glimepiride, glipizide, and tolbutamide but cardiovascular and overall mortality between repaglinide, gliclazide, and metformin were similar [53]. Additionally, in a randomized, placebo-controlled trial, nateglinide did not reduce incident cardiovascular risk in individuals with impaired glucose tolerance and established CVD or risk factors [54].

2.2 Biguanides: Metformin

Numerous studies have examined the effects of the biguanide, metformin, on cardiovascular parameters to identify possible underlying mechanisms that could result in favorable cardioprotection (Table 3). Metformin has been shown to inhibit release of inflammatory markers in vitro [55] and reduce reactive oxygen species and advanced glycosylation end products [56–58]. In the Diabetes Prevention Program, C-reactive protein was reduced in non-diabetic subjects receiving metformin, but the benefits were lost in those that progressed to T2DM [59]. Metformin has been demonstrated to have neutral to beneficial effects on coagulation markers [60–62].

In an investigation of metformin treatment in previously diet-treated T2DM subjects, carotid artery diameter and blood flow during systole were increased after 4 months [60], but endothelium dependent and independent vasodilation of the brachial artery were unchanged. In two other studies, metformin treatment improved endothelium-independent blood flow in T2DM and endothelium-dependent blood flow in metabolic syndrome [63,64]. Therefore, it appears that metformin may be able to enhance either nitric oxide dependent or independent vasodilation depending on disease state.

The UKPDS trial still dominates morbidity and mortality data for metformin (Table 1 and 4), with respect to the size and duration of the study and the follow-up period. In the UKPDS trial, metformin treatment in obese, newly diagnosed T2DM significantly reduced the risk for any diabetes-related end point, diabetes-related mortality, and all-cause mortality compared to conventional therapy. At the 10-year follow-up, this association was continued, along with a significant decrease in MI [6]. Metformin therapy in obese patients was also found to significantly reduce the diabetes-related end point, all-cause mortality, and stroke compared to insulin and SU-treated non-obese patients [11]. The results of the UKPDS trial have been criticized [65], in part because add-on therapy was allowed for all groups when glycemic goals were not met so that there was considerable treatment overlap among groups (metformin, SU, and insulin groups). Since then, several smaller clinical trials and subsequent meta-analyses have been conducted in attempts to substantiate whether or not a beneficial association exists between metformin and cardiovascular events. A 2005 Cochrane review concluded that additional trials did not alter the findings of the UKPDS trial [66]. In a meta-analysis conducted by Lamanna et al [67], metformin significantly reduced the risk of cardiovascular events compared to placebo or no therapy, but no differences in cardiovascular events were found when compared to other anti-diabetes drugs. In a subsequent meta-analysis, Boussageon et al [68] found no effect of metformin on all-cause or cardiovascular death compared to diet, placebo, or no treatment, in metformin add-on therapy compared to other add-on therapies, and in metformin withdrawal.

Cardiovascular outcomes in those with pre-existing CVD treated with metformin have been studied. The Reduction of Atherothrombosis for Continued Health Registry, a prospective, observational study, demonstrated a reduction in all-cause mortality rates among those with diabetes and established atherothrombosis treated with metformin compared to those who did not receive metformin [69]. In an epidemiological analysis of the data from the DIGAMI 2 study (a prospective, randomized, open-treatment trial), metformin was associated with a lower risk for non-fatal MI and stroke [47]. In a post-hoc analysis of follow-up data from that study, recent exposure to metformin had a lower total mortality rate but risk of cardiovascular death was not affected [70]. Compared to non-metformin anti-diabetes treatment, metformin treatment (plus other anti-diabetes medications) had a reduced adjusted odds ratio for any clinical event (death, MI, ischemia-driven target vessel revascularization), primarily attributable to reductions in death and MI [71].

The FDA places strong warnings against the use of metformin in patients with T2DM and heart failure because of concerns of an increased risk of lactic acidosis. However, there have been calls for a re-evaluation of this labeling, owing to minimal data supporting a significant increase in risk of lactic acidosis and indications of a protective effect of metformin against cardiovascular events in this population [72]. In a meta-analysis of such studies, the adjusted relative risk for all-cause mortality and all-cause hospitalizations was significantly reduced with metformin mono- or combination therapy compared to other treatments [73].

2.3 Thiazolidinediones

Targeting a nuclear receptor, TZDs (peroxisome proliferator-activated receptor gamma agonists) have pleiotropic effects (Table 3). Both pioglitazone and rosiglitazone are

associated with reduced C-reactive protein and plasminogen activator inhibitor-1 [74–76]. TZDs also inhibit inducible nitric oxide synthase, interleukin-1β, interleukin-6, and tumor necrosis factor α [77]. There is considerable concern over the fluid retention effects of TZDs, with increased incidence of edema and congestive heart failure with treatment [78,79]. The edema observed in 5–20% of the treatment population, depending on concomitant therapies, is believed to be the result of renal sodium retention, along with a potential increase in vascular permeability.

The first large cardiovascular outcomes study for the TZD class (Table 4), the PROACTIVE study, examined the effects of pioglitazone treatment on the primary endpoint composite of all-cause mortality, MI, stroke, acute coronary syndrome (ACS), leg vascular surgery, and amputation in patients with T2DM and evidence of macrovascular disease [80]. No difference was observed between pioglitazone and placebo treatment groups. However, the secondary composite endpoint of all-cause mortality, MI, and stroke was significantly reduced with pioglitazone. In a post-hoc analysis of a subset of patients with previous MI, there was a significant reduction in fatal and non-fatal MI and ACS as well as the composite of MI, ACS, and cardiac death [81]. In a separate post-hoc analysis of patients with previous stroke, pioglitazone significantly reduced the risk of recurring fatal or non-fatal stroke, as well as the composite of cardiovascular death, non-fatal MI, and non-fatal stroke [82]. A higher incidence of heart failure or hospitalizations related to heart failure has been detected albeit with no difference in fatal heart failure between groups [80,81]. Subsequent meta-analyses have tended to find no difference or a reduction of cardiovascular events with pioglitazone treatment [83–85]. A meta-analysis of 19 studies, including PROACTIVE, found a reduction in the composite endpoint of death, MI, and stroke, along with an increase in serious heart failure [85]. In a randomized controlled trial published this year, investigators evaluated pioglitazone in patients with insulin resistance (but not T2DM) and recent ischemic stroke or transient ischemic attack [86]. Compared to placebo, pioglitazone significantly reduced the risk of the composite primary outcome of non-fatal stroke, fatal stroke, or MI. All-cause mortality was similar between groups, and risk of weight gain and edema were still present with pioglitazone treatment in this insulin resistance population.

While the RECORD cardiovascular outcomes study was being conducted for rosiglitazone treatment [87], a 2007 meta-analysis by Nissen et al was published, indicating a significantly increased risk for MI and a trend toward an increased risk of cardiovascular death with rosiglitazone [12]. Another meta-analysis published that year found an increased risk of MI, as well as heart failure, but no difference in risk of cardiovascular mortality [88]. A retrospective analysis conducted by Glaxo-Smith-Kline, the maker of rosiglitazone, also identified an increase in MI in the rosiglitazone groups [89]. Analysis of the RECORD trial, published in 2009, found that addition of rosiglitazone to either metformin or SU, compared to metformin plus SU, did not increase the composite endpoint of cardiovascular death, MI, and stroke. MI was non-significantly increased and heart failure was doubled in the rosiglitazone group [87]. This study was criticized for its open-label design and much lower event rates than expected [90]. At the request of the FDA, a re-evaluation and analysis was conducted. Again, no differences were found in cardiovascular outcomes, including MI and all-cause mortality [91,92].

Analyses comparing pioglitazone with rosiglitazone have found a greater risk of stroke, heart failure, and all-cause mortality with rosiglitazone [93,94]. A forthcoming randomized, controlled study, TOSCA. IT, is examining the cardiovascular effects of pioglitazone versus SU on patients experiencing glycemic failure on metformin [95]. Due to continued concerns regarding the previously detected increase in MI, prescription of rosiglitazone is highly restricted. The mechanism of increased heart failure remains elusive but caution is warranted in prescribing TZDs in high risk populations.

2.4 Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors have been predicted to have cardio-protective effects through GLP-1 dependent mechanisms. Additionally, because of the enzymatic action of DPP-4, DPP-4 inhibitors can impact many substrates including growth factors, chemokines, neuropeptides, and vasoactive peptides [96–98]. Therefore, this drug class may also exert GLP-1 independent effects, although whether or not these effects could be beneficial or harmful to the cardiovasculature is not yet known.

A number of studies have explored the potential for cardio/vasculo-protective effects of DPP-4 inhibitors (Table 3). Four weeks of treatment with sitagliptin doubled endothelial progenitor cells, increased stromal cell-derived factor-1α, and decreased monocyte chemotactic protein-1 (MCP-1) [99]. An increase in endothelial progenitor cell release from bone marrow is associated with vascular repair [97], and the reduction in MCP-1 could have anti-inflammatory implications. The effect of gliptins on endothelial function is unclear. Vildagliptin was found to improve endothelium-dependent vasodilation in response to an acetylcholine infusion [100], but more recently Ayaori et al demonstrated a reduction in flow mediated dilation with sitagliptin and alogliptin treatment [101]. There is an ongoing study to determine the effects of 12 weeks of vildagliptin or glyburide as add-on to metformin therapy on endothelial function in patients with T2DM and hypertension [102].

An acute dose of sitagliptin was found to improve left ventricular ejection fraction (LVEF) and mitral annular velocity during a dobutamine stress test following 75 g of oral glucose in patients with known coronary artery disease and normal LV function [103]. A clinical trial designed to evaluate the effects of vildagliptin in patients with heart failure and LVEF ≤40% (VIVIDD) found no difference between treatment groups in the primary outcome of LVEF, but there was a statistically significant increase in left ventricular end diastolic volume and a trend toward an increase in left ventricular end systolic volume [104].

Due to their more recent development, DPP-4 inhibitors must fully undergo the new FDA-required cardiovascular outcomes trials, and results of those studies have been published in the last two years (Table 2 and 4). The SAVOR-TIMI 53 study examined the cardiovascular outcomes of saxagliptin versus placebo in T2DM with a history of or risk for cardiovascular events [105]. No difference in risk was found in the primary composite endpoint of cardiovascular death, MI, and stroke, although surprisingly, there was a higher rate of heart failure hospitalizations. To examine the heart failure findings further, a post-hoc analysis was conducted, finding that the risk of hospitalization for heart failure was evident only in the first 12 months and was greatest in those with previous heart failure, an estimated

glomerular filtration rate of <60 ml/min, or an increased N-terminal pro B-type natriuretic peptide [106].

In the EXAMINE trial, patients with T2DM and either recent MI or unstable angina requiring hospitalization were randomized to alogliptin or placebo. No difference between groups was found for the composite primary endpoint of cardiovascular death, MI, and stroke [107]. In a post-hoc analysis from this study there were numerically more HF events in the alogliptin group, but alogliptin was found to be non-inferior for the composite endpoint of cardiovascular death and heart failure hospitalizations [108]. There is some concern that the risk of hospitalization for heart failure was significantly increased in the subgroup of alogliptin-treated patients with no prior heart failure. No increased risk was associated with alogliptin in patients with a history heart failure.

Two forthcoming randomized controlled studies, the CAROLINA and CARMELINA trials, will compare cardiovascular outcomes of linagliptin versus glimepiride and placebo, respectively, in T2DM with established or an increased risk for CVD [109]. Two pre-specified meta-analyses of phase III studies of linagliptin versus placebo or active comparator have been published. The first found a significantly lower hazard ratio for linagliptin for the primary composite endpoint of cardiovascular death, MI, stroke, and hospitalization for unstable angina [110]. The second however found no difference between groups for this endpoint or risk of heart failure [111].

In the randomized controlled trial, TECOS, sitagliptin was compared to placebo in T2DM with CVD. No difference was reported for the primary composite endpoint of cardiovascular death, MI, stroke, or hospitalization for unstable angina [112]. Additionally, results from a pre-specified secondary analysis showed no increase in heart failure-related outcomes, including hospitalizations, in the sitagliptin group relative to placebo, regardless of baseline heart failure status [113].

In the VIVIDD trial described above, there were numerically more cardiovascular and all-cause deaths with vildagliptin treatment [104]. In a post-hoc analysis from this study, vildagliptin was non-inferior to placebo for risk of worsening HF and hospitalizations for worsening HF [114]. This trial was small (n=254) and lasted only one year. No large, longer-term randomized controlled trials appear to be underway. Beyond this, the cardiovascular outcomes for vildagliptin have been examined by meta-analysis, from which there was a trend for a lower relative risk for the composite endpoint of ACS, transient ischemic attack, stroke, and cardio- or cerebrovascular death [115].

A number of meta-analyses of pooled DPP-4 inhibitor trials have also been conducted. Several have now shown a significantly increased risk of heart failure in this drug class in total compared to placebo or active comparators [116–119]. A mechanism for this association is still speculative.

2.5 GLP-1 Receptor Agonists

GLP-1 receptors are found in the heart, blood vessels, gastrointestinal tract, kidney, lung, breast, and central nervous system, creating potential for altered signaling throughout the

body (Table 3). In vitro, liraglutide increases nitric oxide and suppresses nuclear factor-KB activation, leading to reductions in MCP-1 and vascular adhesion molecules [120]. Endothelin-1, tumor necrosis factor α, interleukin-1β, and interleukin-6 have also been shown to decrease, while adiponectin increases with liraglutide treatment [121,122]. Twice-daily exenatide was associated with reductions in 8-iso-prostaglandin F2α (a marker of oxidative stress), MCP-1, high sensitiviy-C-reactive protein, and resistin [123,124].

Native GLP-1 has a very short half-life, and thus its cardiovascular effects have been explored via continuous intravenous infusion. LVEF, mitral annular systolic velocity, and global and regional wall motion score indices have improved at rest and during pharmacologic stress testing with GLP-1 infusion in those with overt CVD [125,126]. Another study found no difference in LVEF or cardiac index, but controls undergoing coronary artery bypass surgery required more inotropic, vasopressor, and vasodilator infusions to attain the same hemodynamic result [127]. In those with New York Heart Association class III/IV heart failure, GLP-1 infusion for 5 weeks significantly improved LVEF, VO2max, the 6 minute walk test distance, and quality of life scores [128]. Acute infusion of exenatide has also been shown to reduce pulmonary capillary wedge pressure in patients with T2DM and heart failure [129]. In patients with an acute MI undergoing primary percutaneous coronary intervention, short-acting exenatide was associated with a significant reduction in the area under the curve for the myocardial band of creatinine kinase, troponin I, infarct size, and absolute mass of the infarct area. High sensitivity-C-reactive protein and LVEF were improved at follow-up [130]. Due to promising preliminary data, a clinical trial was developed to investigate liraglutide in 300 patients with heart failure and reduced LVEF (≤40%). Following 6 months of follow-up, however, there was no difference between liraglutide and placebo groups in rate of hospitalizations or death [131]. A number of the above studies recruited patients with and without T2DM. Questions remain as to whether or not the beneficial cardiovascular effects of GLP-1 receptor agonists are universal or if they are diminished or lost in obesity and T2DM [132].

Of this class of drugs, cardiovascular outcomes data is thus far only available for lixisenatide, a once-daily GLP-1 receptor agonist [133] (Table 4). In T2DM patients experiencing ACS within the previous 6 months, lixisenatide was non-inferior to placebo with regards to the primary end-point of cardiovascular death, non-fatal stroke, non-fatal MI, and unstable angina. Sub-group analyses indicated no difference between treatment groups for components of the primary endpoint and no increase in hospitalizations for heart failure was detected.

Randomized controlled trials to assess cardiovascular safety are still forthcoming for the remainder of the GLP-1 receptor agonists. Trials for exenatide (EXSCEL), dulaglutide (REWIND), liraglutide (LEADER), and semaglutide (SUSTAIN 6) will provide further understanding of cardiovascular outcomes of chronic GLP-1 receptor agonist therapy [134] (Table 2).

2.6 Sodium-Glucose Co-Transporter-2 Inhibitors

In relation to other classes of anti-diabetes medications, less information is available on the effects of SGLT-2 inhibitors on inflammation, coagulation, endothelial function, etc. (Table

3). Reductions in inflammation and oxidative stress have been found in rodent models treated with SGLT-2 inhibitors [135]. After 4 weeks of empagliflozin treatment, urinary 8-iso-prostaglandin F2α was significantly reduced [136]. In young patients with type 1 diabetes mellitus (T1DM), arterial stiffness was reduced during clamped euglycemia and hyperglycemia following treatment with empagliflozin for 8 weeks [137]. In T2DM, surrogate markers for arterial stiffness were significantly reduced with empagliflozin according to a meta-analysis of phase III and IV clinical trials [138].

A recently published large randomized controlled trial (Table 4) of cardiovascular outcomes in patients at high risk for cardiovascular events treated with empagliflozin (EMPA-REG OUTCOME) demonstrated remarkable beneficial cardiovascular effects. The hazard ratio for the composite endpoint of cardiovascular death, non-fatal MI, and non-fatal stroke was reduced with empagliflozin compared to placebo (0.86; 95.02% confidence interval, 0.74 to 0.99) [139], with empagliflozin statistically non-inferior and superior to placebo. For the composite secondary outcome (the composite primary outcome plus hospitalization for unstable angina), empagliflozin achieved non-inferiority with a reduced hazard ratio of 0.89 (95% CI, 0.78 to 1.01). Significant reductions were achieved for rates of cardiovascular death (−38%), all-cause mortality (−32%), and hospitalizations for heart failure (−35%). No between group difference was detected for MI, and the risk of stroke was non-significantly increased in the empagliflozin treatment group, thus, the improvement in the primary endpoint was driven by the reduction in cardiovascular death. The protective benefits, seen with both 10 mg and 25 mg doses of empagliflozin, occurred early in treatment and were sustained throughout the trial period. In a subsequent analysis, the investigators more closely examined heart failure and cardiovascular events [140]. In the overall analyses of all patients, empagliflozin reduced hazard ratios for heart failure hospitalization or cardiovascular death and hospitalization for heart failure, compared to placebo.

Like the DPP-4 inhibitors and GLP-1 receptor agonists, randomized controlled trials are ongoing to examine the cardiovascular outcomes of SGLT-2 treatment. Forthcoming studies are being conducted for canagliflozin (CANVAS, CANVAS-R, CREDENCE), dapagliflozin (DECLARE-TIMI 58), and ertugliflozin [134] (Table 2). In meta-analyses of cardiovascular events for canagliflozin and/or dapagliflozin treatment, there was no increase in risk for the composite endpoint of cardiovascular death, MI, and stroke [141–143]. In two of these analyses, a disproportionate increase in cardiovascular events, including stroke, was observed in the first month of treatment, after which there was no difference in event rate between groups [142,143]. The cause of this is as of yet unknown; some experts have speculated that the increase in events could be related to acute imbalances due to osmotic diuresis, but further investigation is required to determine if these findings were merely aberrations and to establish the underlying cause if risk does indeed exist [143].

3. Summary

The volume of data and publications on cardiovascular safety of individual agents or therapy interventions is vast and complex. Lessons from rosiglitazone have influenced regulation on the cardiovascular safety of new anti-diabetic therapies. Metformin is safe in high-risk populations and may even be protective, but usage in those with heart failure is still a matter

of debate and continued research. No large clinical trial has specifically investigated the cardiovascular benefits of this drug. Data from the TZD class illustrates the potential for drugs within the same class to have differential effects on cardiovascular outcomes, with rosiglitazone associated with increased risk. While pioglitazone treatment has been shown to provide cardiovascular benefit and is still widely available, edema and increased risk of heart failure remain major monitoring concerns if such treatment is selected. Pre-clinical data on SU therapy also suggest that there may be agent-specific differences in cardiovascular safety favoring one over another (i.e., glimepiride over glyburide/glibenclamide). Studies on cardiovascular outcomes with DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors have exclusively included patients with existing or high risk for CVD, and thus extrapolation from findings of these trials to lower-risk individuals is restricted. However, data suggest that, overall, the class of DPP-4 inhibitors is generally safe, although the signal for increased hospitalizations for heart failure that has arisen in some analyses should be further investigated. Comprehensive assessment of GLP-1 receptor agonist and SGLT-2 inhibitor therapy is ongoing. Results for lixisenatide indicate neutral effects of this treatment on cardiovascular risk. Data on empagliflozin in high risk patients are exciting and encouraging, showing a dramatic reduction of cardiovascular events and death.

4. Expert Opinion

4.1 Cardiovascular risk of individual classes of anti-hyperglycemic agents

Decades of trials and investigative efforts have focused on assessing how to obviate the microvascular and macrovascular complications associated with hyperglycemia. From studies mainly concentrating on improving glycemic control (Table 1), reductions in microvascular complications have occurred [5,7,9,144], but there have been inconclusive findings regarding intensive diabetes therapy and improvement in macrovascular complications. Recent diabetes trials [8,9,144,145] with intensive glucose control did not prevent macrovascular complications in older patients with long-standing diabetes with either CVD or risk for CVD. Additionally, intensive therapy was associated with increased mortality in the ACCORD trial [7].

Using the large clinical trials of the 1990s and early 2000s, treatment guidelines have attempted to create an algorithm that takes into account many of the aspects of individual therapies (i.e., glycemic efficacy, hypoglycemia risk, weight effects, side effects and cost), but have been unable to distinctly prioritize individual therapies based on macrovascular or cardiovascular risk (with the exception of rosiglitazone). Thus, to address how a treatment plan could be individualized from a cardiovascular context, historic data from more established therapies where cardiovascular risk assessment was studied in the setting of glycemic control (i.e., metformin or SU) will need to be balanced by the results of trials with new treatments where cardiovascular risk was the primary outcome of study (i.e., SGLT-2 inhibitors).

Due to its high clinical efficacy and minimal side-effects, including low risk of hypoglycemia, metformin remains first-line therapy for T2DM after lifestyle changes [146,147]. The placement of metformin at the forefront of the treatment algorithm has been historically supported by evidence from the subset of obese patients in the UKPDS that

demonstrated reduced cardiovascular risk [147]. However, metformin has never been studied in a randomized controlled trial powered to explore potential cardiovascular risk benefit. Beyond UKPDS, the cardiovascular benefit of metformin in trials is mixed, but metformin was found to have a lower risk of cardiovascular events when directly compared to SU in high risk patients with T2DM and established CVD [148].

Add- on therapy to metformin offers many potential choices, but when choosing a favorable cardiovascular profile, there is limited head-to-head cardiovascular data. Of the TZD class, only pioglitazone is widely available for use, but the cardiovascular risk status of the patient should be considered, given the increased risk for edema and/or heart failure despite favorable effects on other cardiovascular endpoints. If taking into account pre-clinical data, one could consider bypassing certain SU therapy (i.e., glyburide/glibenclamide) and opt for gliclazide or glimepiride therapy. On the other hand, when taking into account potential for weight gain or hypoglycemia risk, DPP-4 inhibitors may be chosen over SU which may outweigh issues like less significant glucose lowering effects and cost. Additionally, using limited observational data, DPP-4 inhibitors, as a class, may offer a neutral or improved to cardiovascular and mortality risk compared to SU treatment [149–151], although the increase in the secondary endpoint of hospitalization for heart failure seen with some DPP-4 trials should be taken into consideration when selecting treatment for a patient with underlying risk. Ultimately, the consideration of DPP-4 inhibitor or SU therapy will be better informed by the results of the ongoing CAROLINA trial in which the cardiovascular effects of glimepiride versus linagliptin will be reported [109]. GLP-1 receptor agonist treatment provides a good option for a weight sparing regimen with good glycemic efficacy but comes at the expense of injection therapy. Limited cardiovascular data is available, but there is no unfavorable cardiovascular signal to suggest harm (at least with lixisenatide). Although not specifically discussed in this manuscript, the ORIGIN study has clearly demonstrated that insulin does not increase cardiovascular adverse events in individuals with pre-diabetes and T2DM.

Significantly, no studies of anti-diabetes agents prior to empagliflozin [139] have shown as robust of a cardiac and overall mortality risk reduction in individuals with high-risk T2DM. This class of medications has several benefits, including the non-insulin-mediated mechanism of action of glucose lowering, a low risk for hypoglycemia, and the high level of tolerance among a wide range of populations (age, ethnicity, mild renal dysfunction). SGLT-2 inhibitors complement many other therapies including metformin, SU, DPP-4 inhibitors and insulin. They may in fact provide better glycemic control and metabolic improvements when compared to SU and DPP-4 inhibitors as add-on therapy to metformin [152–154].

It is not obvious what mediates the observed cardiovascular risk reduction with empagliflozin. The modest blood pressure lowering effect and weight reduction are significant, but these changes would take time to impact the atherosclerotic process, and MI and stroke outcomes were unaffected. Therefore it is unlikely that reductions in blood pressure or weight explain such an early and robust reduction in cardiovascular risk. From what is known at this point, renal hemodynamic changes, such as osmotic diuresis (with volume depletion and sodium loss), are most likely responsible for the reductions in

cardiovascular events and overall mortality. This theory would align with the reduction in hospitalizations for heart failure that was observed. As a class, SGLT-2 inhibitors induce osmotic diuresis, and therefore, it would be expected that canagliflozin and dapagliflozin would also demonstrate reductions in cardiovascular outcomes. However, the results of studies with these two medications were more neutral. A small increase in cardiovascular events was observed within the first month of the canagliflozin and dapagliflozin trials, but this finding is unlikely to be significant. Further comparison of the different SGLT-2 inhibitors is warranted. The placement of SGLT-2 inhibitors in the treatment algorithm provides a new and exciting addition, although interest in prescribing these medications in light of the new cardiovascular outcomes data may be counter-balanced by caution towards new FDA warnings regarding ketoacidosis and serious urinary tract infections [155]. The continued study of this class on cardiovascular effects is highly anticipated.

4.2 Cardiovascular risk assessment trials

Many of the historic clinical trials focused on the specific interventions such as glycemic control, BP control, and lipid control. These studies have been valuable in demonstrating the benefits of approaching cardiovascular risk reduction in a high risk population via a multi-factorial approach. However, such trials were not primarily designed to test the cardiovascular safety and outcomes of particular anti-diabetes medications. Randomized, placebo-controlled clinical trials are the gold-standard for evaluation of cardiovascular risk of individual therapies. It is unlikely that older medications, such as metformin or SU will be re-studied individually with any rigor, and we continue to rely on historical data to inform treatment decisions with these drugs. However, newer classes of medications are now being subjected to more methodical scrutiny. This is occurring in response to new FDA recommendations for additional cardiovascular safety assessment for therapeutic anti-hyperglycemic medications emerging onto the market, following findings from analyses of rosiglitazone treatment. Many of the new recommendations are tailored to provide more comprehensive, longer duration studies in high risk individuals with event specific end-points. Benefits and drawbacks to the new study designs are outlined in Figure 1.

Enrolling patients with preexisting CVD or risk factors is an important component to new study parameters. Previous studies have demonstrated that young individuals with T1DM and T2DM with shorter-duration of diabetes and less pre-existing vascular disease appear to have a significant benefit from intensive glycemic control. Conversely, intensive glycemic control has not been shown to reduce cardiovascular events in patients with longer-duration T2DM and with high cardiovascular risk or established CVD. The vascular biology of macrovascular disease is complex and multifactorial. Thus intervening to alter one putative mechanism such as blood glucose may be ineffective if other risk factors such as dyslipidemia, smoking, hypertension and obesity are also present. For example, in ACCORD, VADT and BARI2D [7,9,145] weight increased throughout the duration of the trials. Controlling for obesity or BMI, independent risk factors for CVD, may have provided additional information in these studies. Thus alternative approaches to treatment beyond tight glycemic control are required to reduce the progression of CVD in this population. Due to multimodal mechanisms of action, some anti-diabetes medications hold potential to reduce cardiovascular risk independent of glucose control. By including individuals with

advanced age or disease and comorbidities like established renal disease in evaluation of therapies, a more comprehensive understanding is obtained. However, this comes at the expense of not learning if or how risk is modified in lower-risk individuals excluded from these studies.

Study duration is an important factor in capturing changes in cardiovascular outcomes. Early study duration spanned 5+ years (ACCORD was ended early at 3.5 years), with the UKPDS lasting 9–11.5 years [5,7–9]. Long-term follow-up studies of original participants in studies like UKPDS [6] continue to provide meaningful data on outcomes. It is arguable that neutral cardiovascular outcomes in ACCORD, ADVANCE, and VADT could be partially attributable to study length and that intensified glycemic control could still potentially improve cardiovascular risk in studies of longer duration like the UKPDS. New recommendations require an even shorter study duration - a minimum of two years – to assess cardiovascular safety data. Inclusion of high-risk individuals ensures a greater number of outcome events in a shorter period of time, allowing for shorter-duration studies than would be required for lower risk individuals. However, aspects of disease control like “metabolic memory” may not be apparent without ongoing or follow-up studies long after the initial data is collected [156,157]. Additionally, the relatively short duration of the new studies prevents observance of cardiovascular effects of long-term treatment and cardiovascular outcomes in lower risk patients. Pre-clinical mechanistic data on improvements in cardiovascular risk factors such as inflammation and endothelial function have not generally translated to improved cardiovascular outcomes in large clinical trials, but it is likely that such changes would require much longer than 2 years study duration to impact progression of CVD.

Long duration and large population trials provide some specific challenges [158,159]. These include recruitment, participant withdrawal, accrual of missing data, expense and local and regional challenges of differing therapy guidelines and practices. Fewer end-points (and thus potentially fewer recruited patients) are necessary to provide non-inferiority data than to demonstrate superiority. However, a non-inferiority study will not detect a difference between treatments and thus may be difficult to apply to an individual patient in practice. Although cardiovascular death, MI, and stroke are the endpoints selected in many of the current and ongoing studies, these endpoints may need to be expanded if there is a high patient withdrawal. As endpoints increase, trial duration gets longer and cost increases. This may prevent companies from providing additional information beyond pre-specified endpoints due to budgetary constraints.

Secondary endpoints could play an important role in understanding macrovascular outcomes. For example, the observed excess cardiovascular death in the ACCORD was not seen in other trials and multiple potential parameters have been questioned. These include the rapid decline in HbA1c with intensive management, the increased frequency of severe hypoglycemia in the intensively treated group, and/or the complexities of polypharmacy. For example, in ACCORD, mortality was increased in the intensive groups despite an increased use of statins (88 % of patients) and aspirin (76% of patients) as compared to ADVANCE (46 % of patients on statins and 57 % of patients on aspirin) and ORIGIN (54 % of patients on statins) [7,8,144]. Additionally, endpoints such as heart failure admission and acute

hypoglycemia remain important to study and evaluate. Multiple studies have demonstrated an increased risk for heart failure exacerbation or hospitalization (i.e., treatment with TZDs and DPP-4 inhibitors) without fully understanding the mechanisms behind this recurrent secondary endpoint. It is unclear whether heart failure is a consequence of the primary diabetic state or is a consequence of negative cardiac remodeling that could be agent specific. Acute and/or severe hypoglycemia in individuals with T1DM and T2DM has been demonstrated to increase proatherogenic, prothrombotic and proinflammatory responses as well as increases in endothelial dysfunction [160,161]. There have been small studies and case reports suggesting a relationship between acute hypoglycemia and cardiovascular events such as angina and electrocardiogram changes [161–163]. Multiple large studies have demonstrated a relationship between hypoglycemia and mortality risk [8,9,144]. However, in a follow-up of ACCORD, the increased mortality in the intensive group was not able to be explained by the difference in symptomatic severe hypoglycemia [164,165]. The aforementioned studies included treatments (i.e., insulin and SU) which are more likely to have an association with hypoglycemia than newer agents, such as DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors. Thus, additional information about the relationship of these agents, alone or in combination with other therapies, and cardiovascular risk and hypoglycemia is important.

4.3 Conclusion

Intensified glycemic control does not appear to confer cardioprotection for those with established or increased risk of CVD, although studies of longer duration may be necessary to observe an association between glycemic control and CVD risk, such as occurred in the UKPDS extension study. Preliminary findings from mechanistic studies of specific anti-diabetes agents often show promise for ameliorating CVD risk in such individuals, with improvements in cardiovascular risk factors such as inflammation, endothelial function, coagulation, and cardiac function. However, the large clinical trials that have explored the cardiovascular impact of individual anti-diabetes therapies have generally not shown improvements in cardiovascular outcomes in individuals at high risk for cardiovascular events. While it is possible that it is simply the case that the current treatments do not augment cardiovascular risk, it is also highly possible that the neutral findings thus far are a result of limited study duration and non-inferiority design. Empagliflozin data are an exception to recent findings, with early, dramatic reductions in cardiovascular outcomes with this treatment that are unlikely to be related to glycemic improvements. Findings of the recent cardiovascular outcomes studies are restricted to high risk individuals and do not provide an understanding of cardiovascular effects of longer-term usage or cardiovascular impact in low-risk individuals who may benefit more from the small improvements in multiple cardiovascular risk factors observed in small mechanistic studies. The challenges of implementing new cardiovascular study guidelines into clinical trials cannot outweigh the potential benefits of developing and assessing new therapeutic agents to provide optimal diabetes care [166–169].

As we currently have a focus on vascular protection, we cannot abandon adequate glycemic control, which serves to prevent microvascular complications and reduce CVD in patients with shorter T2DM duration. Previous data has demonstrated that it is optimal to control all

risk factors for cardiovascular complications in order to get the most benefit for the patient with diabetes. Therapy should be individualized, taking into account age, additional cardiovascular risk factors (previous CVD, family history of CVD, hypertension, hyperlipidemia, smoking), renal function, and history of previous hypoglycemic events. [170–186]

Abbreviations

ACCORD	Action to control cardiovascular risk in diabetes study
ACS	acute coronary syndrome
ADVANCE	Action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation
BARI2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial
CANVAS	CANagliflozin cardioVascular Assessment Study
CANVAS-R	A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus
CAROLINA	Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes
CREDENCE	Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy
CVD	cardiovascular disease
DECLARE-TIMI 58	Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events
DIGAMI 2	Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction-2
DPP-4	dipeptidyl peptidase-4
ELIXA	Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide)
EMPA-REG OUTCOME	BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
EXSCEL	Exenatide Study of Cardiovascular Event Lowering Trial

EXAMINE	Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome
FDA	Food and Drug Administration
GLP-1	glucagon-like polypeptide-1
HbA1c	hemoglobin A1c
K_{ATP}	ATP-sensitive potassium channel
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation
LVEF	left ventricular ejection fraction
MCP-1	monocyte chemotactic protein-1
MI	myocardial infarction
ORIGIN	basal insulin and cardiovascular and other outcomes in dysglycemia
PROACTIVE	Prospective pioglitazone clinical trial in macrovascular events
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes
REWIND	Researching Cardiovascular Events With a Weekly Incretin in Diabetes
SAVOR-TIMI 53	Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes MedicationsSGLT-2: sodium-glucose transporter 2
SU	sulfonylurea
SUSTAIN 6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TECOS	Sitagliptin Cardiovascular Outcomes Study (MK-0431-082)
TOSCA. IT	Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents. Intervention Trial
TZD	thiazolidinedione

UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

References

Papers of special note have been highlighted as:

*of interest

**of considerable interest

1. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010; 375:2215–2222. [PubMed: 20609967]
2. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, et al. Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med. 2014; 370:1514–1523. [PubMed: 24738668]
3. Preis SR, Hwang SJ, Coady S, Pencina MJ, D'Agostino RBS, Savage PJ, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation. 2009; 119:1728–1735. [PubMed: 19307472]
4. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352:837–853. [PubMed: 9742976]
6. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359:1577–1589. [PubMed: 18784090]
7. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358:2545–2559. [PubMed: 18539917]
8. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008; 358:2560–2572. [PubMed: 18539916]
9. 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; 360:129–139. [PubMed: 19092145]
10. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015; 372:2197–2206. [PubMed: 26039600]
11*. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998; 352:854–865. One of the main clinical trials supporting metformin as first-line therapy for type 2 diabetes mellitus. [PubMed: 9742977]
12*. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007; 356:2457–2471. This meta-analysis raised concern over the potential adverse cardiovascular effects of rosiglitazone. [PubMed: 17517853]
13. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008; 358:580–591. [PubMed: 18256393]

14. Wing RR. Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med. 2010; 170:1566–1575. [PubMed: 20876408]
15. Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER). Guidance for industry: diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 2008.
16. Younk LM, Lamos EM, Davis SN. The cardiovascular effects of insulin. Expert Opin Drug Saf. 2014; 13:955–966. [PubMed: 24899093]
17. Hanefeld M, Chiasson JL, Koehler C, Henkel E, Schaper F, Temelkova-Kurktschiev T. Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. Stroke. 2004; 35:1073–1078. [PubMed: 15073402]
18. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003; 290:486–494. [PubMed: 12876091]
19. Rudovich NN, Weickert MO, Pivovarova O, Bernigau W, Pfeiffer AF. Effects of acarbose treatment on markers of insulin sensitivity and systemic inflammation. Diabetes Technol Ther. 2011; 13:615–623. [PubMed: 21488802]
20. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006; 295:1681–1687. [PubMed: 16609090]
21. Miyamura M, Schnell O, Yamashita C, Yoshioka T, Matsumoto C, Mori T, et al. Effects of acarbose on the acceleration of postprandial hyperglycemia-induced pathological changes induced by intermittent hypoxia in lean mice. J Pharmacol Sci. 2010; 114:32–40. [PubMed: 20703014]
22. Scranton RE, Gaziano JM, Rutty D, Ezrokhi M, Cincotta A. A randomized, double-blind, placebo-controlled trial to assess safety and tolerability during treatment of type 2 diabetes with usual diabetes therapy and either Cycloset or placebo. BMC Endocr Disord. 2007; 7:3. [PubMed: 17592632]
23. Gaziano JM, Cincotta AH, Vinik A, Blonde L, Bohannon N, Scranton R. Effect of bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) on major adverse cardiovascular events in type 2 diabetes subjects. J Am Heart Assoc. 2012; 1:e002279. [PubMed: 23316290]
24. Goldfine AB, Fonseca VA, Jones MR, Wang AC, Ford DM, Truitt KE. Long-term safety and tolerability of colesevelam HCl in subjects with type 2 diabetes. Horm Metab Res. 2010; 42:23–30. [PubMed: 19862667]
25. University Group Diabetes Program. Study of the effect of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes. 1970; 19(Suppl 2):789–830. [PubMed: 4926376]
26. Dabrowski M, Wahl P, Holmes WE, Ashcroft FM. Effect of repaglinide on cloned beta cell, cardiac and smooth muscle types of ATP-sensitive potassium channels. Diabetologia. 2001; 44:747–756. [PubMed: 11440368]
27. Hu S, Wang S, Dunning BE. Tissue selectivity of antidiabetic agent nateglinide: study on cardiovascular and beta-cell K(ATP) channels. J Pharmacol Exp Ther. 1999; 291:1372–1379. [PubMed: 10565863]
28. Reimer KA, Murry CE, Yamasawa I, Hill ML, Jennings RB. Four brief periods of myocardial ischemia cause no cumulative ATP loss or necrosis. Am J Physiol. 1986; 251:H1306–15. [PubMed: 3789183]
29. Schott RJ, Rohmann S, Braun ER, Schaper W. Ischemic preconditioning reduces infarct size in swine myocardium. Circ Res. 1990; 66:1133–1142. [PubMed: 2317890]
30. Okazaki Y, Kodama K, Sato H, Kitakaze M, Hirayama A, Mishima M, et al. Attenuation of increased regional myocardial oxygen consumption during exercise as a major cause of warm-up phenomenon. J Am Coll Cardiol. 1993; 21:1597–1604. [PubMed: 8496525]
31. Inagaki N, Gonoi T, Clement JP, Wang CZ, Aguilar-Bryan L, Bryan J, et al. A family of sulfonylurea receptors determines the pharmacological properties of ATP-sensitive K+ channels. Neuron. 1996; 16:1011–1017. [PubMed: 8630239]

32. Chutkow WA, Simon MC, Le Beau MM, Burant CF. Cloning, tissue expression, and chromosomal localization of SUR2, the putative drug-binding subunit of cardiac, skeletal muscle, and vascular KATP channels. Diabetes. 1996; 45:1439–1445. [PubMed: 8826984]
33. Grover GJ, Sleph PG, Dzwonczyk S. Role of myocardial ATP-sensitive potassium channels in mediating preconditioning in the dog heart and their possible interaction with adenosine A1-receptors. Circulation. 1992; 86:1310–1316. [PubMed: 1394937]
34. Lee TM, Chou TF. Impairment of myocardial protection in type 2 diabetic patients. J Clin Endocrinol Metab. 2003; 88:531–537. [PubMed: 12574175]
35. Klepzig H, Kober G, Matter C, Luus H, Schneider H, Boedeker KH, et al. Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. Eur Heart J. 1999; 20:439–446. [PubMed: 10213347]
36. Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM. Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. Circulation. 2001; 103:3111–3116. [PubMed: 11425777]
37. Maddock HL, Siedlecka SM, Yellon DM. Myocardial protection from either ischaemic preconditioning or nicorandil is not blocked by gliclazide. Cardiovasc Drugs Ther. 2004; 18:113–119. [PubMed: 15162072]
38. Flynn DM, Smith AH, Treadway JL, Levy CB, Soeller WC, Boettner WA, et al. The sulfonylurea glipizide does not inhibit ischemic preconditioning in anesthetized rabbits. Cardiovasc Drugs Ther. 2005; 19:337–346. [PubMed: 16382296]
39. Rahmi RM, Uchida AH, Rezende PC, Lima EG, Garzillo CL, Favarato D, et al. Effect of hypoglycemic agents on ischemic preconditioning in patients with type 2 diabetes and symptomatic coronary artery disease. Diabetes Care. 2013; 36:1654–1659. [PubMed: 23250803]
40. Hueb W, Uchida AH, Gersh BJ, Betti RT, Lopes N, Moffa PJ, et al. Effect of a hypoglycemic agent on ischemic preconditioning in patients with type 2 diabetes and stable angina pectoris. Coron Artery Dis. 2007; 18:55–59. [PubMed: 17172931]
41. Zeller M, Danchin N, Simon D, Vahanian A, Lorgis L, Cottin Y, et al. Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. J Clin Endocrinol Metab. 2010; 95:4993–5002. [PubMed: 20702526]
42. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab. 2012; 14:803–809. [PubMed: 22486923]
43. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol. 1999; 33:119–124. [PubMed: 9935017]
44. Cleveland JC Jr, Meldrum DR, Cain BS, Banerjee A, Harken AH. Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium. Two paradoxes revisited. Circulation. 1997; 96:29–32. [PubMed: 9236412]
45. Scognamiglio R, Avogaro A, Vigili de Kreutzenberg S, Negut C, Palisi M, Bagolin E, et al. Effects of treatment with sulfonylurea drugs or insulin on ischemia-induced myocardial dysfunction in type 2 diabetes. Diabetes. 2002; 51:808–812. [PubMed: 11872684]
46. Tomai F, Crea F, Gaspardone A, Versaci F, De Paulis R, Penta de Peppo A, et al. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K+ channel blocker. Circulation. 1994; 90:700–705. [PubMed: 8044938]
47. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L. DIGAMI 2 Investigators. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. Eur Heart J. 2008; 29:166–176. [PubMed: 18156614]
48. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia. 2006; 49:930–936. [PubMed: 16525843]

49. Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. Diabetes Care. 2008; 31:1672–1678. [PubMed: 18458139]
50. Esposito K, Giugliano D, Nappo F, Marfella R. Campanian Postprandial Hyperglycemia Study Group. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation. 2004; 110:214–219. [PubMed: 15197140]
51. Derosa G, Mugellini A, Ciccarelli L, Crescenzi G, Fogari R. Comparison of glycaemic control and cardiovascular risk profile in patients with type 2 diabetes during treatment with either repaglinide or metformin. Diabetes Res Clin Pract. 2003; 60:161–169. [PubMed: 12757988]
52. Rizzo MR, Barbieri M, Grella R, Passariello N, Paolisso G. Repaglinide has more beneficial effect on cardiovascular risk factors than glimepiride: data from meal-test study. Diabetes Metab. 2005; 31:255–260. [PubMed: 16142016]
53. Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011; 32:1900–1908. [PubMed: 21471135]
54. Holman RR, Haffner SM, McMurray JJ, Bethel MA, Holzhauer B, et al. NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010; 362:1463–1476. [PubMed: 20228402]
55. Isoda K, Young JL, Zirlik A, MacFarlane LA, Tsuboi N, Gerdes N, et al. Metformin inhibits proinflammatory responses and nuclear factor-kappaB in human vascular wall cells. Arterioscler Thromb Vasc Biol. 2006; 26:611–617. [PubMed: 16385087]
56. Beisswenger P, Ruggiero-Lopez D. Metformin inhibition of glycation processes. Diabetes Metab. 2003; 29:6S95–103. [PubMed: 14502106]
57. Bellin C, de Wiza DH, Wiernsperger NF, Rosen P. Generation of reactive oxygen species by endothelial and smooth muscle cells: influence of hyperglycemia and metformin. Horm Metab Res. 2006; 38:732–739. [PubMed: 17111300]
58. Faure P, Rossini E, Wiernsperger N, Richard MJ, Favier A, Halimi S. An insulin sensitizer improves the free radical defense system potential and insulin sensitivity in high fructose-fed rats. Diabetes. 1999; 48:353–357. [PubMed: 10334313]
59. Goldberg RB, Temprosa MG, Mather KJ, Orchard TJ, Kitabchi AE, Watson KE, et al. Lifestyle and metformin interventions have a durable effect to lower CRP and tPA levels in the diabetes prevention program except in those who develop diabetes. Diabetes Care. 2014; 37:2253–2260. [PubMed: 24824548]
60. Machado HA, Vieira M, Cunha MR, Correia MR, Fukui RT, Santos RF, et al. Metformin, but not glimepiride, improves carotid artery diameter and blood flow in patients with type 2 diabetes mellitus. Clinics (Sao Paulo). 2012; 67:711–717. [PubMed: 22892913]
61. Standeven KF, Ariens RA, Whitaker P, Ashcroft AE, Weisel JW, Grant PJ. The effect of dimethylbiguanide on thrombin activity, FXIII activation, fibrin polymerization, and fibrin clot formation. Diabetes. 2002; 51:189–197. [PubMed: 11756340]
62. Gin H, Roudaut MF, Vergnot V, Baillet L, Rigalleau V. Effect of metformin on fibrinolytic parameters in insulin-treated, type 2 diabetic patients. Diabetes Metab. 2003; 29:505–508. [PubMed: 14631327]
63. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol. 2001; 37:1344–1350. [PubMed: 11300445]
64. Vitale C, Mercuro G, Cornoldi A, Fini M, Volterrani M, Rosano GM. Metformin improves endothelial function in patients with metabolic syndrome. J Intern Med. 2005; 258:250–256. [PubMed: 16115299]
65. Nathan DM. Some answers, more controversy, from UKPDS. United Kingdom Prospective Diabetes Study. Lancet. 1998; 352:832–833. [PubMed: 9742972]
66. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005; (3):CD002966. [PubMed: 16034881]

67. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2011; 13:221–228. [PubMed: 21205121]

68. Boussageon R, Supper I, Bejan-Angoulvant T, Kellou N, Cucherat M, Boissel JP, et al. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS Med. 2012; 9:e1001204. [PubMed: 22509138]

69. Roussel R, Travert F, Pasquet B, Wilson PW, Smith SC Jr, Goto S, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med. 2010; 170:1892–1899. [PubMed: 21098347]

70. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L. DIGAMI 2 Investigators. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the diabetes mellitus insulin-glucose infusion in acute myocardial infarction (DIGAMI) 2 study. Diabetologia. 2011; 54:1308–1317. [PubMed: 21359582]

71. Kao J, Tobis J, McClelland RL, Heaton MR, Davis BR, Holmes DR Jr, et al. Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. Am J Cardiol. 2004; 93:1347–50. A5. [PubMed: 15165912]

72. Scheen AJ, Paquot N. Metformin revisited: a critical review of the benefit-risk balance in at-risk patients with type 2 diabetes. Diabetes Metab. 2013; 39:179–190. [PubMed: 23528671]

73. Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circ Heart Fail. 2013; 6:395–402. [PubMed: 23508758]

74. Qayyum R, Adomaityte J. Meta-analysis of the effect of thiazolidinediones on serum C-reactive protein levels. Am J Cardiol. 2006; 97:655–658. [PubMed: 16490432]

75. Zhao Y, He X, Huang C, Fu X, Shi X, Wu Y, et al. The impacts of thiazolidinediones on circulating C-reactive protein levels in different diseases: a meta-analysis. Diabetes Res Clin Pract. 2010; 90:279–287. [PubMed: 20926154]

76. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005; 28:1547–1554. [PubMed: 15983299]

77. Vamecq J, Latruffe N. Medical significance of peroxisome proliferator-activated receptors. Lancet. 1999; 354:141–148. [PubMed: 10408502]

78. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007; 370:1129–1136. [PubMed: 17905165]

79. Roughead EE, Chan EW, Choi NK, Kimura M, Kimura T, Kubota K, et al. Variation in association between thiazolidinediones and heart failure across ethnic groups: retrospective analysis of large healthcare claims databases in six countries. Drug Saf. 2015; 38:823–831. [PubMed: 26216600]

80*. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005; 366:1279–1289. The main clinical trial exploring the cardiovascular outcomes of pioglitazone treatment, finding that the secondary composite endpoint of all-cause mortality, MI, and stroke was significantly reduced in the pioglitazone group, although heart failure was increased. [PubMed: 16214598]

81. Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM, et al. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. J Am Coll Cardiol. 2007; 49:1772–1780. [PubMed: 17466227]

82. Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from proactive (prospective pioglitazone clinical trial In macrovascular events 04). Stroke. 2007; 38:865–873. [PubMed: 17290029]

83. Nagajothi N, Adigopula S, Balamuthusamy S, Velazquez-Cecena JL, Raghunathan K, Khraisat A, et al. Pioglitazone and the risk of myocardial infarction and other major adverse cardiac events: a meta-analysis of randomized, controlled trials. Am J Ther. 2008; 15:506–511. [PubMed: 19127132]
84. Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2008; 10:1221–1238. [PubMed: 18505403]
85. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007; 298:1180–1188. [PubMed: 17848652]
86. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med. 2016; 374:1321–1331. [PubMed: 26886418]
87. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009; 373:2125–2135. [PubMed: 19501900]
88. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA. 2007; 298:1189–1195. [PubMed: 17848653]
89. Cobitz A, Zambanini A, Sowell M, Heise M, Louridas B, McMorn S, et al. A retrospective evaluation of congestive heart failure and myocardial ischemia events in 14,237 patients with type 2 diabetes mellitus enrolled in 42 short-term, double-blind, randomized clinical studies with rosiglitazone. Pharmacoepidemiol Drug Saf. 2008; 17:769–781. [PubMed: 18613278]
90. Retnakaran R, Zinman B. Thiazolidinediones and clinical outcomes in type 2 diabetes. Lancet. 2009; 373:2088–2090. [PubMed: 19501899]
91. Lopes RD, Dickerson S, Hafley G, Burns S, Tourt-Uhlig S, White J, et al. Methodology of a reevaluation of cardiovascular outcomes in the RECORD trial: study design and conduct. Am Heart J. 2013; 166:208–216. e28. [PubMed: 23895802]
92. Mahaffey KW, Hafley G, Dickerson S, Burns S, Tourt-Uhlig S, White J, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013; 166:240–249. e1. [PubMed: 23895806]
93. Varas-Lorenzo C, Margulis AV, Pladevall M, Riera-Guardia N, Calingaert B, Hazell L, et al. The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies. BMC Cardiovasc Disord. 2014; 14:129-2261-14-129. [PubMed: 25260374]
94. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010; 304:411–418. [PubMed: 20584880]
95. Vaccaro O, Masulli M, Bonora E, Del Prato S, Giorda CB, Maggioni AP, et al. Addition of either pioglitazone or a sulfonylurea in type 2 diabetic patients inadequately controlled with metformin alone: impact on cardiovascular events. A randomized controlled trial. Nutr Metab Cardiovasc Dis. 2012; 22:997–1006. [PubMed: 23063367]
96. Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. Circ Res. 2014; 114:1788–1803. [PubMed: 24855202]
97. Jose T, Inzucchi SE. Cardiovascular effects of the DPP-4 inhibitors. Diab Vasc Dis Res. 2012; 9:109–116. [PubMed: 22337893]
98. Scheen AJ. Cardiovascular effects of gliptins. Nat Rev Cardiol. 2013; 10:73–84. [PubMed: 23296071]
99. Fadini GP, Boscaro E, Albiero M, Menegazzo L, Frison V, de Kreutzenberg S, et al. The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in patients with type 2 diabetes: possible role of stromal-derived factor-1alpha. Diabetes Care. 2010; 33:1607–1609. [PubMed: 20357375]
100. van Poppel PC, Netea MG, Smits P, Tack CJ. Vildagliptin improves endothelium-dependent vasodilatation in type 2 diabetes. Diabetes Care. 2011; 34:2072–2077. [PubMed: 21788633]

101. Ayaori M, Iwakami N, Uto-Kondo H, Sato H, Sasaki M, Komatsu T, et al. Dipeptidyl peptidase-4 inhibitors attenuate endothelial function as evaluated by flow-mediated vasodilatation in type 2 diabetic patients. J Am Heart Assoc. 2013; 2:e003277. [PubMed: 23525426]

102. Cosenso-Martin LN, Giollo-Junior LT, Martineli DD, Cesarino CB, Nakazone MA, Cipullo JP, et al. Twelve-week randomized study to compare the effect of vildagliptin vs. glibenclamide both added-on to metformin on endothelium function in patients with type 2 diabetes and hypertension. Diabetol Metab Syndr. 2015; 7 70-015-0062-z. eCollection 2015.

103. Read PA, Khan FZ, Heck PM, Hoole SP, Dutka DP. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with coronary artery disease. Circ Cardiovasc Imaging. 2010; 3:195–201. [PubMed: 20075143]

104. McMurray, JJ., editor. The vildagliptin in ventricular dysfunction diabetes trial (VIVIDD). Heart Failure 2013 Congress; 2013; : Heart Failure Association of the European Society of Cardiology; 2013;

105*. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013; 369:1317–1326. Clinical trial evaluating cardiovascular outcomes of saxagliptin treatment, finding no difference in the primary composite endpoint but an increase in hospitalizations for heart failure for saxagliptin versus placebo. [PubMed: 23992601]

106. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014; 130:1579–1588. [PubMed: 25189213]

107*. 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; 369:1327–1335. Clinical trial evaluating cardiovascular outcomes with alogliptin treatment, showing no difference between placebo and alogliptin for the primary composite endpoint. [PubMed: 23992602]

108. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015; 385:2067–2076. [PubMed: 25765696]

109. Marx N, Rosenstock J, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, et al. Design and baseline characteristics of the cardiovascular outcome trial of linagliptin versus glimepiride in type 2 diabetes (CAROLINA(R)). Diab Vasc Dis Res. 2015; 12:164–174. [PubMed: 25780262]

110. Johansen OE, Neubacher D, von Eynatten M, Patel S, Woerle HJ. Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme. Cardiovasc Diabetol. 2012; 11:3-2840-11-3. [PubMed: 22234149]

111. Rosenstock J, Marx N, Neubacher D, Seck T, Patel S, Woerle HJ, et al. Cardiovascular safety of linagliptin in type 2 diabetes: a comprehensive patient-level pooled analysis of prospectively adjudicated cardiovascular events. Cardiovasc Diabetol. 2015; 14:57-015-0215-2. [PubMed: 25990013]

112*. 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; 373:232–242. Clinical trial exploring cardiovascular outcomes with sitagliptin treatment, showing no difference between placebo and sitagliptin for the primary composite endpoint. [PubMed: 26052984]

113. Van de Werf F. Impact of sitagliptin on heart failure and related outcomes [Abstract]. European Society of Cardiology. 2015:FP 3147.

114. Kothny W. No significant difference in risk of heart failure hospitalization with vildagliptin in diabetic patients with systolic chronic heart failure: VIVIDD study [Abstract]. Diabetes. 2014:1028-P.

115. Schweizer A, Dejager S, Foley JE, Couturier A, Ligueros-Saylan M, Kothny W. Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large Phase III type 2 diabetes population. Diabetes Obes Metab. 2010; 12:485–494. [PubMed: 20518804]

116. Savarese G, Perrone-Filardi P, D'Amore C, Vitale C, Trimarco B, Pani L, et al. Cardiovascular effects of dipeptidyl peptidase-4 inhibitors in diabetic patients: A meta-analysis. Int J Cardiol. 2015; 181:239–244. [PubMed: 25528528]

117. Wu S, Hopper I, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. Cardiovasc Ther. 2014; 32:147–158. [PubMed: 24750644]

118. Clifton P. Do dipeptidyl peptidase IV (DPP-IV) inhibitors cause heart failure? Clin Ther. 2014; 36:2072–2079. [PubMed: 25453730]

119. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2014; 24:689–697. [PubMed: 24793580]

120. Hattori Y, Jojima T, Tomizawa A, Satoh H, Hattori S, Kasai K, et al. A glucagon-like peptide-1 (GLP-1) analogue, liraglutide, upregulates nitric oxide production and exerts anti-inflammatory action in endothelial cells. Diabetologia. 2010; 53:2256–2263. [PubMed: 20593161]

121. Chiquette E, Toth PP, Ramirez G, Cobble M, Chilton R. Treatment with exenatide once weekly or twice daily for 30 weeks is associated with changes in several cardiovascular risk markers. Vasc Health Risk Manag. 2012; 8:621–629. [PubMed: 23166441]

122. Hogan AE, Gaoatswe G, Lynch L, Corrigan MA, Woods C, O'Connell J, et al. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. Diabetologia. 2014; 57:781–784. [PubMed: 24362727]

123. Wu JD, Xu XH, Zhu J, Ding B, Du TX, Gao G, et al. Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus. Diabetes Technol Ther. 2011; 13:143–148. [PubMed: 21284481]

124. Derosa G, Franzetti IG, Querci F, Carbone A, Ciccarelli L, Piccinni MN, et al. Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial. Pharmacotherapy. 2013; 33:817–826. [PubMed: 23744726]

125. Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation. 2004; 109:962–965. [PubMed: 14981009]

126. Read PA, Khan FZ, Dutka DP. Cardioprotection against ischaemia induced by dobutamine stress using glucagon-like peptide-1 in patients with coronary artery disease. Heart. 2012; 98:408–413. [PubMed: 21561896]

127. Sokos GG, Bolukoglu H, German J, Hentosz T, Magovern GJ Jr, Maher TD, et al. Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. Am J Cardiol. 2007; 100:824–829. [PubMed: 17719327]

128. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. J Card Fail. 2006; 12:694–699. [PubMed: 17174230]

129. Nathanson D, Ullman B, Lofstrom U, Hedman A, Frick M, Sjoholm A, et al. Effects of intravenous exenatide in type 2 diabetic patients with congestive heart failure: a double-blind, randomised controlled clinical trial of efficacy and safety. Diabetologia. 2012; 55:926–935. [PubMed: 22246377]

130. Woo JS, Kim W, Ha SJ, Kim JB, Kim SJ, Kim WS, et al. Cardioprotective effects of exenatide in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of exenatide myocardial protection in revascularization study. Arterioscler Thromb Vasc Biol. 2013; 33:2252–2260. [PubMed: 23868944]

131. Margulies, KB., editor. American Heart Association Scientific Sessions. 2015. A randomized trial of liraglutide for high-risk heart failure patients with reduced ejection fraction (FIGHT).

132. Moberly SP, Mather KJ, Berwick ZC, Owen MK, Goodwill AG, Casalini ED, et al. Impaired cardiometabolic responses to glucagon-like peptide 1 in obesity and type 2 diabetes mellitus. Basic Res Cardiol. 2013; 108 365-013-0365-x. Epub 2013 Jun 14.

133*. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015; 373:2247–2257. The only clinical trial published thus far evaluating cardiovascular outcomes with GLP-1 receptor agonist treatment. Lixisenatide was non-inferior to placebo for the primary composite endpoint. [PubMed: 26630143]

134. Desouza CV, Gupta N, Patel A. Cardiometabolic effects of a new class of antidiabetic agents. Clin Ther. 2015; 37:1178–1194. [PubMed: 25754876]

135. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res. 2015; 12:90–100. [PubMed: 25589482]

136. Nishimura R, Tanaka Y, Koiwai K, Inoue K, Hach T, Salsali A, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. Cardiovasc Diabetol. 2015; 14:11-014-0169-9. [PubMed: 25633683]

137. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol. 2014; 13:28-2840-13-28. [PubMed: 24475922]

138. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab. 2015; 17:1180–1193. [PubMed: 26343814]

139**. 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 A remarkable clinical trial evaluating cardiovascular outcomes with empagliflozin treatment, finding empagliflozin to be superior to placebo in reducing the primary composite endpoint.

140. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J. 2016

141. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013; 159:262–274. [PubMed: 24026259]

142. FDA. [Accessed November 1, 2015] Medical review NDA 202293 approved 8 January 2014 (Farxiga). 2014. Available at: http://www.accessdata.fda.gov.proxy-hs.researchport.umd.edu/drugsatfda_docs/nda/2014/202293Orig1s000MedR.pdf

143. FDA. [Accessed November 1, 2015] Medical review NDA 204042, approved 29 March 2013 (Invokana). 2013. Available at: http://www.accessdata.fda.gov.proxy-hs.researchport.umd.edu/drugsatfda_docs/nda/2013/204042Orig1s000MedR.pdf

144. Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, et al. ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012; 367:319–328. [PubMed: 22686416]

145. Bittner V, Bertolet M, Barraza Felix R, Farkouh ME, Goldberg S, Ramanathan KB, et al. Comprehensive cardiovascular risk factor control improves survival: the BARI 2D trial. J Am Coll Cardiol. 2015; 66:765–773. [PubMed: 26271057]

146. American Diabetes Association. (7) Approaches to glycemic treatment. Diabetes Care. 2015; 38(Suppl):S41–8. [PubMed: 25537707]

147. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015; 38:140–149. [PubMed: 25538310]

148. Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013; 36:1304–1311. [PubMed: 23230096]

149. Seong JM, Choi NK, Shin JY, Chang Y, Kim YJ, Lee J, et al. Differential cardiovascular outcomes after dipeptidyl peptidase-4 inhibitor, sulfonylurea, and pioglitazone therapy, all in

combination with metformin, for type 2 diabetes: a population-based cohort study. PLoS One. 2015; 10:e0124287. [PubMed: 25992614]

150. Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality. Diabetes Obes Metab. 2014; 16:977–983. [PubMed: 24762119]
151. Yu OH, Yin H, Azoulay L. The combination of DPP-4 inhibitors versus sulfonylureas with metformin after failure of first-line treatment in the risk for major cardiovascular events and death. Can J Diabetes. 2015; 39:383–389. [PubMed: 25840943]
152. Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013; 382:941–950. [PubMed: 23850055]
153. Ridderstrale M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol. 2014; 2:691–700. [PubMed: 24948511]
154. Lavalle-Gonzalez FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia. 2013; 56:2582–2592. [PubMed: 24026211]
155. Food and Drug Administration. [Accessed December/8, 2015] FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm
156. Ceriello A. Hypothesis: the “metabolic memory”, the new challenge of diabetes. Diabetes Res Clin Pract. 2009; 86(Suppl 1):S2–6. [PubMed: 20115927]
157. Jermendy G. Vascular memory: can we broaden the concept of the metabolic memory? Cardiovasc Diabetol. 2012; 11:44-2840-11-44. [PubMed: 22545680]
158. Hirshberg B, Katz A. Cardiovascular outcome studies with novel antidiabetes agents: scientific and operational considerations. Diabetes Care. 2013; 36(Suppl 2):S253–8. [PubMed: 23882054]
159. Hirshberg B, Katz A. Insights from cardiovascular outcome trials with novel antidiabetes agents: what have we learned? An industry perspective. Curr Diab Rep. 2015; 15:87-015-0663-9. [PubMed: 26370698]
160. Gogitidze Joy N, Hedrington MS, Briscoe VJ, Tate DB, Ertl AC, Davis SN. Effects of acute hypoglycemia on inflammatory and pro-atherothrombotic biomarkers in individuals with type 1 diabetes and healthy individuals. Diabetes Care. 2010; 33:1529–1535. [PubMed: 20587723]
161. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? Diabetes Metab Res Rev. 2008; 24:353–363. [PubMed: 18461635]
162. Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care. 2003; 26:1485–1489. [PubMed: 12716809]
163. Lindstrom T, Jorfeldt L, Tegler L, Arnqvist HJ. Hypoglycaemia and cardiac arrhythmias in patients with type 2 diabetes mellitus. Diabet Med. 1992; 9:536–541. [PubMed: 1643801]
164. Riddle MC, Ambrosius WT, Brillon DJ, Buse JB, Byington RP, Cohen RM, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3. 4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care. 2010; 33:983–990. [PubMed: 20427682]
165. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010; 340:b4909. [PubMed: 20061358]
166. Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet. 2014; 383:2008–2017. [PubMed: 24910232]

167. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. Eur Heart J. 2015; 36:2288–2296. [PubMed: 26063450]
168. Scheen AJ, Charbonnel B. Effects of glucose-lowering agents on vascular outcomes in type 2 diabetes: a critical reappraisal. Diabetes Metab. 2014; 40:176–185. [PubMed: 24792220]
169. Scheen AJ, Esser N, Paquot N. Antidiabetic agents: Potential anti-inflammatory activity beyond glucose control. Diabetes Metab. 2015; 41:183–194. [PubMed: 25794703]
170. Stein SA, Lamos EM, Davis SN. A review of the efficacy and safety of oral antidiabetic drugs. Expert Opin Drug Saf. 2013; 12:153–175. [PubMed: 23241069]
171. Chen YH, Du L, Geng XY, Peng YL, Shen JN, Zhang YG, et al. Effects of sulfonylureas on lipids in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. J Evid Based Med. 2015; 8:134–148. [PubMed: 26066789]
172. Roumie CL, Liu X, Choma NN, Greevy RA, Hung AM, Grijalva CG, et al. Initiation of sulfonylureas versus metformin is associated with higher blood pressure at one year. Pharmacoepidemiol Drug Saf. 2012; 21:515–523. [PubMed: 22431419]
173. Keidan B, Hsia J, Katz R. Plasma lipids and antidiabetic agents: a brief overview. Br J Diabetes Vasc Dis. 2002; 2:40–43.
174. Waugh J, Keating GM, Plosker GL, Easthope S, Robinson DM. Pioglitazone: a review of its use in type 2 diabetes mellitus. Drugs. 2006; 66:85–109. [PubMed: 16398569]
175. Malinowski JM, Bolesta S. Rosiglitazone in the treatment of type 2 diabetes mellitus: a critical review. Clin Ther. 2000; 22:1151–68. discussion 1149–50. [PubMed: 11110228]
176. Qayyum R, Adomaityte J. A meta-analysis of the effect of thiazolidinediones on blood pressure. J Clin Hypertens (Greenwich). 2006; 8:19–28. [PubMed: 16407685]
177. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 2006; 29:2632–2637. [PubMed: 17130196]
178. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R, et al. Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. Curr Med Res Opin. 2009; 25:2401–2411. [PubMed: 19650754]
179. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013; 381:117–124. [PubMed: 23141817]
180. Fakhoury WK, Lereun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology. 2010; 86:44–57. [PubMed: 20616619]
181. Sun F, Wu S, Wang J, Guo S, Chai S, Yang Z, et al. Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. Clin Ther. 2015; 37:225–241.e8. [PubMed: 25554560]
182. Sun F, Wu S, Guo S, Yu K, Yang Z, Li L, et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes Res Clin Pract. 2015; 110:26–37. [PubMed: 26358202]
183. Lovshin JA, Zinman B. Blood pressure-lowering effects of incretin-based diabetes therapies. Can J Diabetes. 2014; 38:364–371. [PubMed: 25284699]
184. Sun F, Wu S, Guo S, Yu K, Yang Z, Li L, et al. Effect of GLP-1 receptor agonists on waist circumference among type 2 diabetes patients: a systematic review and network meta-analysis. Endocrine. 2015; 48:794–803. [PubMed: 25115635]
185. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ. 2012; 344:d7771. [PubMed: 22236411]
186. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens. 2014; 8:262–75.e9. [PubMed: 24602971]

Article Highlights

- Cardiovascular risk reduction in individuals with diabetes is complex and multi-factorial
- New FDA guidelines require comprehensive cardiovascular evaluation for new anti-diabetes medications in high risk populations
- Metformin remains safe in high risk populations.
- DPP-4 inhibitors also appear safe in high risk populations
- Data on GLP-1 receptor agonist and SLGT2 inhibitor therapy is ongoing but early data in SLGT2 inhibitors is encouraging.
- Implementation of the FDA CV assessment guidelines is complex and may not provide the long-term data to fully answer agent-specific cardiovascular risk

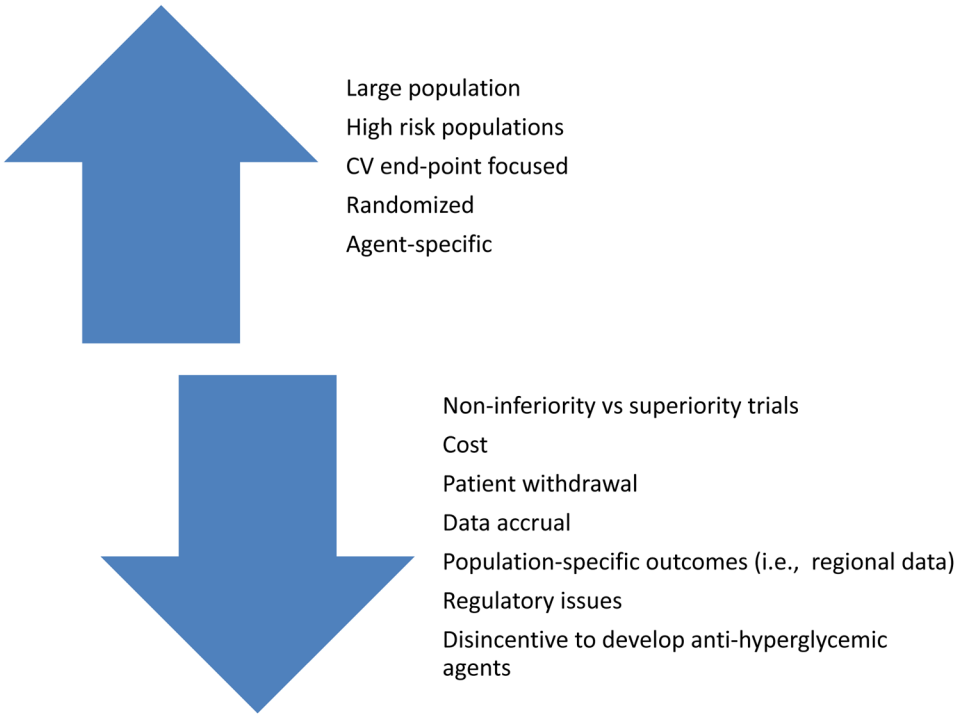

Figure 1.
Benefits and challenges of large cardiovascular outcomes trials.

Table 1

Summary of large diabetes trials.

Trial	Year of publication (+/− study follow-up)	Median follow up (yr)	Number of patients	Mean baseline duration of DM (yr)	Mean baseline HbA1c (%)	CVD at baseline	Treatment	Cardiovascular/Macrovascular Results
UKPDS [5,6,11]	1999 (2008)	10.7	3,867	< 1 (Newly diagnosed DM)	7.1±1.5	none	SU, insulin, and metformin (obese only) vs standard of care	NS in MI NS in any death 15% ↓ in MI † 13% ↓ in any death † 39% ↓ in MI (metformin subgroup only) 36% ↓ in any death (metformin subgroup only) 33% ↓ in MI (metformin subgroup only) † 27% ↓ in any death (metformin subgroup only) †
ACCORD [7]	2008 (2016)	DC after 3.5	10,251	~ 10	8.3±1.1	35%	unrestricted	NS in nonfatal events or CVD death 22% ↑ in death from any cause (CVD, CHF, fatal procedures
ADVANCE [8]	2008 (2014)	5.0	11,140	~ 8	7.5±1.6	32%	SU vs non-SU-based therapy	10%↓ of micro-and macrovascular outcomes NS in mortality
VADT [9, 10]	2009 (2015)	5.6	1,791	~ 12	9.4±2.0	40%	metformin or glimepiride ± rosiglitazone → + insulin ± unrestricted	NS in CVD events, death or hospitalization NS in mortality ↓17% relative rate of CVD risk reduction †
BARI 2D [145]	2009	5.3	2368	~ 10	7.7±1.6	100%	Insulin sensitizing meds and insulin-provision meds	NS in rates of death NS in major CVD events
ORIGIN [144]	2012	6.2	12,537	~ 6	6.47±0.7	60%	Insulin glargine + prior treatment vs standard of care	NS effect on CVD outcomes

† At 10 year follow-up

BMI: body mass index; DM: diabetes mellitus; CVD: cardiovascular disease; DC: discontinued; HbA1c: glycosylate hemoglobin A1c; vs = versus; no = number; NS: not significant yr = years

Table 2

Completed and ongoing randomized controlled trials of cardiovascular outcomes with anti-diabetes medications.

Agent	Study Acronym	Official Title/ ClinicalTrials.gov Identifier	Intervention	Expected Completion Date	Follow-up Duration	Cardiovascular-related Endpoints
Thiazolidinediones						
Pioglitazone	TOSCA. IT	Effects on Incidence of Cardiovascular Events of the Addition of Pioglitazone as Compared With a Sulphonylurea in Type 2 Diabetic Patients Inadequately Controlled With Metformin NCT00700856	once daily pioglitazone vs. sulfonylureas (glyburide, gliclazide, or glimepiride)	December 2018	48 months	**Primary:** Composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, or unplanned coronary revascularization **Secondary:** Composite of sudden death, fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, major amputations, endovascular or surgical intervention on coronary, leg, or carotid arteries; Heart failure
GLP-1 Receptor Agonists						
Exenatide	EXSCEL	Exenatide Study of Cardiovascular Event Lowering Trial: A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly in Patients With Type 2 Diabetes Mellitus NCT01144338	once weekly exenatide vs. placebo	April 2018	36 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** All-cause mortality; CV death; Nonfatal MI; Nonfatal stroke; Hospitalization for acute coronary syndrome; Hospitalization for heart failure
Dulaglutide	REWIND	The Effect of Dulaglutide on Major Cardiovascular Events in Patients With Type 2 Diabetes: Researching Cardiovascular Events With a Weekly Incretin in Diabetes NCT01394952	once weekly dulaglutide vs. placebo	April 2019	≤ 78 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** Hospitalization for unstable angina; CV death; Nonfatal MI; Nonfatal stroke; All-cause mortality; Hospitalization for heart failure
Liraglutide	LEADER	A Long-term, Multi-centre, International, Randomized Double-blind, Placebo-controlled Trial to Determine Liraglutide Effects on Cardiovascular Events NCT01179048	once daily liraglutide vs. placebo	December 2015	≤ 60 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** Composite of CV death, nonfatal MI, non-fatal stroke, revascularization, unstable angina or hospitalization for chronic heart failure; All-cause mortality; CV death; Nonfatal MI; Non-fatal stroke; Revascularization; unstable angina; Hospitalization for chronic heart failure
Semaglutide	SUSTAIN6	A Long-term, Randomized, Double-blind, Placebo-controlled, Multinational,	once weekly semaglutide vs. placebo	March 2016	≤ 37 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke

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Agent	Study Acronym	Official Title/ ClinicalTrials.gov Identifier	Intervention	Expected Completion Date	Follow-up Duration	Cardiovascular-related Endpoints
		Multi-centre Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes NCT01720446				**Secondary:** Composite of expanded CV endpoints; individual components of expanded composite endpoint; All-cause death; Nonfatal MI; Nonfatal stroke
Lixisenatide	ELIXA	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate Cardiovascular Outcomes During Treatment With Lixisenatide in Type 2 Diabetic Patients After an Acute Coronary Syndrome NCT01147250	once daily lixisenatide vs. placebo	February 2015	47 months	**Primary:** Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina **Secondary:** Composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or hospitalization for heart failure; Composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization
DPP-4 Inhibitors						
Linagliptin	CAROLINA	A Multicentre, International, Randomized, Parallel Group, Double Blind Study to Evaluate Cardiovascular Safety of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk NCT01243424	once daily linagliptin vs. glimepiride vs. placebo	September 2018	92 months	**Primary:** Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina **Secondary:** CV death; nonfatal MI; Nonfatal stroke; Hospitalization for unstable angina
Linagliptin	CARMELINA	A Multicenter, International, Randomized, Parallel Group, Double-blind, Placebo-controlled, Cardiovascular Safety and Renal Microvascular Outcome Study With Linagliptin, 5 mg Once Daily in Patients With Type 2 Diabetes Mellitus at High Vascular Risk NCT01897532	once daily linagliptin vs. placebo	January 2018	48 months	**Primary:** Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina **Secondary:** CV death; nonfatal MI; Nonfatal stroke
Saxagliptin	SAVOR-TIMI 53	A Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate the Effect of Saxagliptin on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes NCT01107886	once daily saxagliptin vs. placebo	May 2013	25 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** Composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization; All-cause mortality

Agent	Study Acronym	Official Title/ ClinicalTrials.gov Identifier	Intervention	Expected Completion Date	Follow-up Duration	Cardiovascular-related Endpoints
Sitagliptin	TECOS	A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes After Treatment With Sitagliptin in Patients With Type 2 Diabetes Mellitus and Inadequate Glycemic Control NCT00790205	once daily sitagliptin vs. placebo	March 2015	≤ 60 months	**Primary:** Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina **Secondary:** Composite of CV death, nonfatal MI, or nonfatal stroke; all-cause mortality; congestive heart failure
Alogliptin	EXAMINE	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Cardiovascular Outcomes Following Treatment With Alogliptin in Addition to Standard of Care in Subjects With Type 2 Diabetes and Acute Coronary Syndrome NCT00968708	once daily alogliptin vs. placebo	June 2013	≤ 41 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** Composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or urgent coronary revascularization
SGLT-2 Inhibitors						
Empagliflozin	EMPA-REG OUTCOME	A Phase III, Multicentre, International, Randomized, Parallel Group, Double Blind Cardiovascular Safety Study of BI 10773 (10 mg and 25 mg Administered Orally Once Daily) Compared to Usual Care in Type 2 Diabetes Mellitus Patients With Increased Cardiovascular Risk NCT01131676	once daily empagliflozin vs. placebo	April 2015	≤ 60 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina; Silent MI; Hospitalization for heart failure
Canagliflozin	CANVAS	A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus NCT01032629	once daily canagliflozin vs. placebo	June 2017	≤ 84 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** None
Canagliflozin	CANVAS-R	A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2	once daily canagliflozin vs. placebo	January 2017	≤ 52 months	**Primary:** None **Secondary:** Composite of CV death, nonfatal MI, or nonfatal stroke (listed as Other Outcome Measures)

Agent	Study Acronym	Official Title/ ClinicalTrials.gov Identifier	Intervention	Expected Completion Date	Follow-up Duration	Cardiovascular-related Endpoints
		Diabetes Mellitus NCT01989754				
Canagliflozin	CREDENCE	A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy NCT02065791	once daily canagliflozin vs. placebo	June 2019	≤ 66 months	**Primary:** Composite of end-stage kidney disease, doubling of serum creatinine, renal or CV death **Secondary:** Composite of CV death or hospitalization for heart failure; Composite of CV death, nonfatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina or hospitalization for chronic heart failure; CV death; All-cause mortality
Dapagliflozin	DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes NCT01730534	once daily dapagliflozin vs. placebo	April 2019	≤ 72 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** Composite of CV death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for any revascularization; Hospitalization for heart failure; All-cause mortality
Ertugliflozin	n/a	Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess Cardiovascular Outcomes Following Treatment With Ertugliflozin (MK-8835/ PF-04971729) in Subjects With Type 2 Diabetes Mellitus and Established Vascular Disease NCT01986881	once daily ertugliflozin vs. placebo	June 2020	≤ 76 months	**Primary:** Composite of CV death, nonfatal MI, or nonfatal stroke **Secondary:** Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina

TABLE 3

Mechanism of action, clinical effects, and currently understood cardiovascular effects of anti-diabetes drugs.

DRUG CLASS	MECHANISM OF ACTION	CLINICAL/METABOLIC EFFECTS	CARDIOVASCAULAR EFFECTS
SULFONYLUREAS	Bind sulfonylurea receptor and block KATP channels	Reduced HbA1c 1–1.5% [170] Neutral to reduced HDL, LDL [171] Slight increase in blood pressure [172] Slight increase in body weight [172]	Reduction in aggregate MI endpoints[5] Reduced macrovascular events [8] No increased CV risk after MI versus insulin [47] Blunted ischemic pre-conditioning that appears agent specific [34–37]
MEGLITINIDES	Bind sulfonylurea receptor and block KATP channels Differing selectivity for pancreatic vs cardiac KATP channels	Reduced HbA1c 1–1.5% [170] No significant effect on lipids [173] Neutral effect on weight [170]	Conflicting data on blunted ischemic preconditioning [26,39,40] Regression of carotid intima media thickness [50] Beneficial effects on IL-6, CRP, plasminogen activator inhibitor [50–52]
BIGUANIDES	Activate AMPK secondary to inhibition of mitochondrial respiratory-chain complex 1	Reduced HbA1c 1–2% [66] Neutral effects on body weight, blood pressure, and lipids [66]	Reduction in aggregate CV endpoint [11,47,70] Beneficial effects on reactive oxygen species, IL-6, IL-8, IL-1β [55–58] No change or improvement of flow-mediated dilation [60,63,64] Reduced risk of heart failure [93]
THIAZOLIDINEDIONES	Bind peroxisome-proliferator activated receptor gamma	Reduced HbA1c .1–1.4% [174,175] Slight reductions in blood pressure [176] Increase in LDL-C [76] Pioglitazone – decreased triglycerides and increased HDL-C [76] Rosiglitazone – increased triglycercides and neutral/slightly increased HDL-C [76]	Reduction of aggregate CV endpoint with pioglitazone [80] Increase in MI with rosiglitazone [12,88,89] Reductions in CRP, PAI-1, IL-1β, IL-6, TNFα [74–77] Increased edema [78,79] Increased heart failure [80,81]
DIPEPTIDYL PEPTIDASE-4 INHIBITORS	Block DPP-4 enzyme to prevent degradation of GIP and GLP-1	Reduced HbA1c .5–1% [170] Neutral effects on blood pressure, body weight and lipids [170,177,178]	No increased risk of CV events or death [107] Decreased MCP-1 [99] Increased endothelial progenitor cells [99] Evidence of increased heart failure [116–119]
GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS	Induce pharmacologic agonism of GLP-1 receptor, while avoiding enzymatic degradation by DPP-4	Reduced HbA1c .75–1.5% [179,180] Improvements in lipids [181] Reduced blood pressure [182,183] Reduced body weight and waist circumference [184,185]	Reduced NfKB, MCP-1, ET-1, CRP, and vascular adhesion molecules [120,121] Improved left ventricular ejection fraction [125,126,128,130] Reduced infarct size [130] Increased heart rate [182,183]
SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS	Lower threshold for glucose reabsorption by SGLT2 within the proximal tubule	Reduced HbA1c .5–1% [134] Reduced blood pressure [134] Reduced body weight and fat mass [134] Increased LDL-C and HDL-C [134]	Reduced or no change in CV events and death [139,142,143] Reduced inflammation and reactive oxygen species [135] Reduced arterial stiffness in T1DM [137] Neutral effects on heart rate [186]
ALPHA GLUCOSIDASE INHIBITORS	Inhibit alpha-glucosidase enzymes at the intestinal brush border GLP-1 action may be enhanced	Reduced HbA1c 0.4–0.9% [170] Decreased triglycerides [17] Neutral vs decreased weight compared to SU [170]	Reduction in HTN [17,18] MI and any CV event reduction [17,18] Reduction in progression of intima media thickness [17]

DRUG CLASS	MECHANISM OF ACTION	CLINICAL/METABOLIC EFFECTS	CARDIOVASCAULAR EFFECTS
			Mixed effects on inflammation and prothrombotic markers [19–21]
DOPAMINE AGONIST	Altering the hypothalamic circadian rhythm Altered dopamine action leading to a more insulin sensitive state with improve glucose tolerance	Reduced HbA1c 0.5% [170] Modest decrease in triglycerides, blood pressure and heart rate [24] Small increase in weight [170]	As adjunct therapy, reduction in primary cardiovascular endpoints [22,23]
BILE ACID SEQUESTRANTS	Not clearly elucidated Endogenous glucose production reduced via effects on the farsenoid X receptors and liver X receptors Augmentation of incretin hormone secretion	Reduction in HbA1c 0.5% [170] Reduction in LDL-C [24] Increased triglyceride levels [24] Weight neutral [170]	

TABLE 4

Risk of cardiovascular events with anti-diabetes treatment.

DRUG CLASS	DRUG EVALUATED	OUTCOME	RISK
SULFONYLUREAS	Glyburide/Chlorpropamide Gliclazide	Any diabetes-related endpoint CV death, MI, stroke	RR: 0.88 (95% CI 0.79–0.99) [5] HR: 0.94 (95% CI 0.84–1.06) [8]
BIGUANIDES	Metformin	Any diabetes-related endpoint	RR 0.68 (95% CI 0.53–0.87) [11]
THIAZOLIDINEDIONES	Pioglitazone Rosiglitazone	All-cause mortality, MI, stroke CV death, MI, stroke	HR: 0.84 (95% CI 0.72–0.98) [80] HR: 0.95 (95% CI 0.78–1.17) [92]
DIPEPTIDYL PEPTIDASE-4 INHIBITORS	Saxagliptin Alogliptin Sitagliptin	CV death, MI, stroke CV death, MI, stroke CV death, MI, stroke, hospitalization for unstable angina	HR: 1.00 (95% CI 0.89–1.12) [105] HR: 0.96 (upper 95% CI 1.16) [107] HR: 0.98 (95% CI 0.88 to 1.09) [112]
GLUCAGON-LIKE PEPTIDE AGONISTS	Lixisenatide	CV death, MI, stroke, hospitalization for unstable angina	HR: 1.02 (95% CI 0.89 to 1.17) [133]
SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS	Empagliflozin Canagliflozin Dapagliflozin	CV death, MI, stroke CV death, MI, stroke, and hospitalization for unstable angina CV death, MI, stroke, and hospitalization for unstable angina	HR: 0.86 (95% CI 0.74–0.99)[139] HR: 0.91 (95% CI 0.68–1.22)[143] HR: 0.82 (95% CI 0.59–1.14) [142]