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Antidiabetic agents and cardiovascular outcomes in patients with heart diseases

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\textbf{ABSTRACT}

\textbf{Introduction:} This article reviews evidence of the benefits and risk of antidiabetic agents in cardiovascular (CV) outcomes, with a focus on medications approved by the FDA since 2008.

\textbf{Study selection:} Peer-reviewed articles were identified from MEDLINE and Current Content databases (both 1966 to 1 October 2016) using the search terms insulin, metformin, rosiglitazone, pioglitazone, glyburide, glipizide, glimepiride, acarbose, miglitol, albiglutide, exenatide, lixisenatide, dulaglutide, pramlintide, meglitinide, alogliptin, linagliptin, saxagliptin, sitagliptin, canagliflozin, dapagliflozin, empagliflozin, colesevelam, bexomizopride, mortality, myocardial infarction (MI), heart failure (HF), and stroke. Trials were included if they were randomized clinical trials evaluating adult patients (≥18 years) with type 2 diabetes; had a period of intervention and follow-up of ≥12 months; and assessed CV outcomes (CV death, fatal/non-fatal MI or HF) as endpoints. Twenty-three randomized trials were included.

\textbf{Antidiabetic agents:} Of agents approved prior to 2008, metformin has not been associated with measurable harm in patients with diabetes in terms of mortality and CV events (and has a trend of benefit). Controversial results existed with the use of sulfonylureas and thiazolidinediones (TZDs) for CV outcomes. Among agents approved after 2008, lixisenatide and empagliflozin have been shown to be superior to placebo in improving CV outcomes.

\textbf{Conclusions:} The FDA regulatory mandate to demonstrate CV safety in order to approve new diabetes drugs led to an increase in the number of CV outcome trials. However, these trials have placebo-controlled, non-inferiority designs aiming to show absence of CV toxicity. More studies are needed to address other questions, including comparative effectiveness, and longer-term risk versus benefits.

\textbf{Introduction}

Diabetes is a challenging worldwide pandemic. In 2014, it was estimated that 21 million Americans were diagnosed with diabetes (a four-fold increase over 30 years)\textsuperscript{1}. Patients with diabetes are at increased risk of developing cardiovascular (CV) diseases. The death rate from heart disease in patients with diabetes is approximately 1.7 times higher than in those without\textsuperscript{3}. While improving glycemic control with medications has been demonstrated to reduce the risk of microvascular complications\textsuperscript{2–7}, the benefits of reduction in macrovascular complications have been demonstrated by some but not others, and most investigated only short-term effects\textsuperscript{5,8–11}. Not only may there be no real macrovascular benefits from improving glycemic control, two meta-analyses have suggested that rosiglitazone may actually be associated with increased risk of acute myocardial infarction (MI) and death, despite improvement in glycemic control\textsuperscript{12,13}. Furthermore, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial in patients with type 2 diabetes at high risk of developing heart disease was stopped prematurely, due to an increased rate of all-cause mortality in the intensive management arm (hemoglobin A1C <6%) compared to those in the standard arm (A1C 7% to7.9%)\textsuperscript{14}. A similar study, the Action in Diabetes and Vascular Disease: Preterax and DiaMicon MR Controlled Evaluation (ADVANCE) showed that while intensive glycemic control with a sulfonylurea and other drugs reduced microvascular complications, there was no benefit with respect to macrovascular complications\textsuperscript{15}. This information has led the US Food and Drug Administration (FDA), and subsequently the European Medicines Agency, to mandate CV safety outcome trials before licensing new glucose-lowering drugs after 2008\textsuperscript{16,17}. This regulatory requirement has led to a substantial increase in the number of randomized, double blinded, type 2 diabetes CV outcome trials. This article reviews current evidence of the benefits and risk of different antidiabetic agents with CV outcomes, with a focus on newer agents approved since 2008.

\textbf{Study selection and data extraction}

Peer-reviewed articles/abstracts were identified from MEDLINE and Current Content database (both 1966 to 1 October 2016) using the search terms insulin, metformin,
rosiglitazone, pioglitazone, glyburide, glipizide, glibenpiride, acarbose, miglitol, albiglutide, exenatide, liraglutide, lixisenatide, dulaglutide, pramlintide, meglitinide, alogliptin, linagliptin, saxagliptin, sitagliptin, canagliflozin, dapagliflozin, empagliflozin, colesevelam, bromocriptine, mortality, MI, heart failure, and stroke. Citations from available articles were also reviewed for additional references. The FDA and clinical trials.gov websites were also explored for recent announcements, warnings and ongoing studies regarding the use of antidiabetic agents and CV outcomes. We included the trial if it was a randomized clinical trial evaluating adult patients (≥18 years) with type 2 diabetes; had a period of intervention and follow-up to 12 months or more; and it evaluated cardiovascular outcomes (cardiovascular death, fatal or nonfatal MI or HF) as primary endpoints. Twenty-three randomized clinical trials are included and discussed. Table 1 summarizes studies on agents approved after 2008.

Insulin, biguanide, sulfonylurea, and thiazolidinediones

Prior to 2008, few clinical trials were structured to specifically evaluate cardiovascular outcomes as a primary endpoint of a single class of antidiabetic agent in a prospective manner. The University Group Diabetes Program (UGDP) randomized patients with type 2 diabetes to a standard insulin regimen (once daily dosing of insulin lente [adjusted to a fasting blood glucose of 170–186 mg/dL]), a variable insulin regimen (insulin lente plus regular insulin adjusted to a fasting plasma glucose level of <130 mg/dL), sulfonylurea (tolbutamide), biguanide (phenformin) or diet alone (approximately 200 patients per group) in terms of their impact on macrovascular and microvascular outcomes. The trial was stopped because of concerns that therapies seemed to increase cardiovascular risk. Although this study was underpowered to evaluate cardiovascular outcomes, controversies from this trial led to the delay in the introduction of metformin on the market in US, and the warning label on sulfonylureas increasing cardiovascular risk.

The 1998 United Kingdom Prospective Diabetes Study (UKPDS) Group randomized 4209 newly diagnosed type 2 diabetes patients to evaluate the efficacy and safety of two different glucose-lowering strategies. The 1138 patients randomly assigned to the conventional treatment group were allocated to diet alone, with secondary randomization to active glucose lowering treatments if their fasting plasma glucose subsequently became greater than 270 mg/dL. The 3867 patients randomly assigned to the intensive treatment group were allocated to monotherapy with insulin, sulfonylurea, or metformin (if actual body weight >120% ideal body weight). After a mean follow-up of 10 years, intensive therapy or sulfonylurea did not improve macrovascular diseases (MI, stroke, and heart failure [HF]). In patients who were randomly assigned to metformin, a 39% relative risk reduction occurred in fatal and nonfatal MI (metformin: 11%; conventional therapies: 18%, \( p = .010 \)), and a 36% relative risk reduction in all-cause mortality (metformin: 13.6%; conventional therapies: 20.6%, \( p = .011 \)). Despite the small cohort (n = 342), this finding has led to most diabetes management guidelines adopting metformin as a foundation treatment for type 2 diabetes. There are no further cardiovascular outcomes trials of metformin performed.

More recently, in 2012, the results of the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial became available. The ORIGIN trial randomized patients >50 years of age with new-onset or established type 2 diabetes receiving none or one oral antidiabetic agent, to once daily insulin glargine to achieve a fasting glucose of 95 mg/dL or standard care. A total of 12,537 patients were included with a median follow-up of 6.2 years. The co-primary outcomes were cardiovascular events (nonfatal MI, nonfatal stroke, or death from cardiovascular causes) and revascularization or hospitalization for heart failure. Rates of primary outcomes were similar in the insulin-glargine and standard-care groups: 2.94 and 2.85 per 100 person-years, respectively (hazard ratio, 1.02; 95% confidence interval [CI], 0.94 to 1.11; \( p = .63 \)). Rates of severe hypoglycemia were 1.00 versus 0.31 per 100 person-years. Median weight increased by 1.6 kg in the insulin-glargine group and fell by 0.5 kg in the standard-care group. This is the first large scale prospective randomized clinical trial evaluating insulin therapy in type 2 diabetes patients and CV outcome. It demonstrated a neutral CV outcome and an increased rate of side effects including hypoglycemia and weight gain.

Over the past decade, thiazolidinediones (TZDs) have been heavily scrutinized for their potential to increase CV events, which may be different between the two currently approved agents. Rosiglitazone was briefly restricted by the US FDA due to concerns of increased risk for MI due to two meta-analyses, but the restrictions were later lifted based on the final results of the RECORD trial. RECORD was a randomized, prospective, multicenter, open label trial that enrolled 4447 patients with type 2 diabetes who were treated with either metformin or a sulfonylurea monotherapy and who had suboptimal glucose control defined as an HBA1c of >7–9.0%. Patients were randomized to receive rosiglitazone titrated to a maximum dose of 8 mg daily or the combination of metformin plus sulfonylurea, and they were followed for a duration of 5–7 years. The primary endpoint of the RECORD trial was a composite endpoint of time to first occurrence of CV death or CV hospitalization, defined as any acute or unplanned hospital admission for HF, transient ischemic attack (TIA), MI, stroke, other thrombotic events, CV revascularizations, and amputations of extremities, with an objective to show that rosiglitazone was non-inferior to combination therapy with regards to cardiovascular risk. After a mean follow-up of 5.5 years, there were no differences in the primary endpoint between the two groups, with the primary outcome occurring in 321 patients (14.5%) of rosiglitazone versus 323 (14.5%) in patients assigned to combination therapy, which met criteria for non-inferiority because the 95% confidence interval for the hazard ratio was below the prespecified level of 1.20 (HR 0.99, [0.86–1.16], \( p = .93 \)).

The CV effects of pioglitazone were evaluated in the PROActive study, which enrolled 5238 patients with type 2 diabetes and a history of previous macrovascular complications. They were randomized to pioglitazone or placebo, with
<table>
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<td>Placebo (3034)</td>
<td>1. CV mortality, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina 2. Hospitalization for HF 3. All-cause mortality</td>
<td>1. Adjusted Hazard Ratio (95% CI) 1.02 (0.89–1.17)  ( p &lt; .001 ) for non-inferiority;  ( p = .81 ) for superiority 2. Adjusted Hazard Ratio (95% CI) 0.96 (0.75–1.23)  ( p = .75 ) 3. Adjusted Hazard Ratio (95% CI) 0.94 (0.78–1.13)  ( p = .50 )</td>
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<td>Randomized trial, short follow-up period, high CVD at baseline</td>
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<td>LEADER trial²⁻⁸</td>
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<td>Liraglutide 4668</td>
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<td>CV mortality, nonfatal MI, or nonfatal stroke                                         Hazard ratio (95% CI) 0.87 (0.78–0.97)  ( p &lt; .001 ) (non-inferiority);  ( p = .01 ) (superiority)</td>
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<td>1. Hazard ratio (95% CI) 0.86 (0.74–0.99)  ( p &lt; .001 ) (non-inferiority);  ( p &lt; .04 ) (superiority) 2. Hazard ratio (95% CI) 0.89 (0.78–1.01)  ( p &lt; .001 ) (non-inferiority);  ( p &lt; .08 ) (superiority)</td>
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<td>Randomized trial, long follow-up period</td>
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<td>SAVOR-TIMI 53²²</td>
<td>Type 2 DM with CVD or high risk for CVD</td>
<td>Saxagliptin</td>
<td>Placebo</td>
<td>Primary composite endpoint: CV death, nonfatal MI or nonfatal stroke                  Saxagliptin 3.7% vs. 3.7% placebo  ( p = .99 ) (superiority)</td>
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<td>Hospitalization for HF: saxagliptin 3.5% vs. 2.8% placebo HR: 1.27 (1.07–1.51)  ( p = .007 )</td>
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<td>EXAMINE²¹</td>
<td>Type 2 DM and recent ACS</td>
<td>Alogliptin</td>
<td>Placebo</td>
<td>Primary composite endpoint: CV death, nonfatal MI or nonfatal stroke                  Alogliptin 11.3% vs. 11.8% placebo  ( p &lt; .001 ) (non-inferiority);  ( p = .32 ) (superiority)</td>
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<td>Hospitalization for HF: 3.9% alogliptin vs. 3.3% placebo HR: 1.19 (0.90–1.58)  ( p = .22 )</td>
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<td>Type 2 DM</td>
<td>Sitagliptin</td>
<td>Placebo</td>
<td>Primary composite endpoint: CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina</td>
<td>Sitagliptin 11.4% vs. 11.6% placebo  ( p &lt; .001 ) (non-inferiority);  ( p = .84 ) (superiority)</td>
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<td>Hospitalization for HF: 3.1% sitagliptin vs. 3.1% placebo HR: 1.00 (0.83–1.20)  ( p = .98 )</td>
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background therapy including sulfonylureas, metformin, or insulin in any combination. The primary composite endpoint consisted of all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or extremity arteries as well as amputations above the ankles. After a mean follow-up of 34.5 months, there were no differences observed between the two groups. The primary composite occurred in 514 patients treated with pioglitazone versus 572 patients treated with placebo (HR: 0.90, 95% CI 0.80–1.02, \( p = .095 \)). There were differences observed in the main secondary composite endpoint of death, MI and stroke, which occurred less frequently in pioglitazone treated patients (301 patients vs. 358 patients, HR: 0.84, 95% CI 0.72–0.98, \( p = .027 \)).

More recently, the Insulin Resistance Intervention after Stroke (IRIS) trial investigators evaluated the role of pioglitazone in 3876 patients with recent ischemic stroke or TIA in a randomized double-blind multicenter trial. Patients were enrolled if they had insulin resistance based on a homeostasis model assessment of insulin resistance (HOMA-IR) scores of >3.0, but did not have to have a diagnosis of type 2 DM. After 4.8 years of follow-up, patients in the pioglitazone groups experienced a significantly lower rate of the primary composite endpoint of fatal or nonfatal stroke or MI (9.0% vs. 11.8%, HR: 0.76, 95% CI 0.62–0.93, \( p = .007 \)).

Less controversial is the increased risk for HF which has been well documented for both rosiglitazone and pioglitazone. TZDs are thought to increase renal sodium and water retention through PPAR-\( \gamma \) mediated activation of the epithelium’s sodium channel (ENaC) in the collecting duct and stimulate sodium transporters in the proximal tubule. HF exacerbation was increased in rosiglitazone treated patients in RECORD, and in pioglitazone treated patients in PROactive. In the IRIS study, there was a non-significant increase in HF in pioglitazone treated patients, although edema was significantly higher, as was weight gain >4.5 kg and >13.6 kg. Not surprisingly, consensus guidelines continue to recommend avoidance of TZDs in patients with Class III and IV HF.

**Dipeptidyl peptidase-4 inhibitors**

This is one of the newer class of medications that are subject to the FDA’s requirement for CV safety trials prior to approval. From 2009 to 2013, four agents were approved by the FDA: sitagliptin, saxagliptin, linagliptin and alogliptin.

To date, three agents have published clinical trials evaluating the overall CV risks and benefits, the SAVOR-TIMI 53 study with saxagliptin, the EXAMINE study with alogliptin and the TECOS trial with sitagliptin. SAVOR, EXAMINE and TECOS were all randomized, double-blinded, non-inferiority placebo controlled trials designed to assess long-term CV safety in type 2 DM patients who were at high risk for, or had a history of, CV events. Each agent met the pre-specified non-inferiority margin for CV safety compared with placebo.

SAVOR enrolled 16,492 patients. Patients had to be at least 40 years old and had to have a documented history of a clinical atherosclerotic event involving the coronary, peripheral vascular or cerebrovascular systems, or be at least 55–60 years old (depending upon gender) with at least one of the following additional CV risk factors: hypertension, dyslipidemia, or active smoking. Standard of care comprised patients receiving glucose-lowering agents (metformin: 69.5%; sulfonylurea: 45.3%; insulin: 41.5%) and other CV drugs (ACEI/ARB: 54%; beta-blocker: 61.6%; statin: 78.3%; aspirin: 75%). The mean age of patients was 65.1 years, 67% were male, and they had a mean BMI of 31.1 kg/m\(^2\). The mean follow-up was 2.1 years, and the primary composite endpoint of CV death, MI or ischemic stroke occurred in 7.3% of saxagliptin patients versus 7.2% of placebo treated patients (HR: 1.00, 95% CI 0.89–1.12, \( p = .99 \) for superiority, \( p < .001 \) for non-inferiority). Surprisingly, hospitalization for HF was increased in saxagliptin treated patients (3.5% vs. 2.8%, HR: 1.27, 95% CI 1.07–1.51, \( p = .007 \)).

EXAMINE enrolled 5380 patients who had recently experienced an MI or hospitalization for unstable angina within 15–90 days prior to enrollment. Standard of care comprised patients receiving glucose-lowering agents (metformin: 67.4%; sulfonylurea: 46.2%; insulin: 30.3%) and other CV drugs (ACEI/ARB: 82.5%; beta-blocker: 82.2%; statin: 90.3%; aspirin: 90.8%) for acute coronary syndrome. The median age of patients was 61 years, 68% were male, and they had a median BMI of 28.7 kg/m\(^2\). Patients were followed for a maximum of 40 months, with a median follow-up duration of 18 months. The primary composite endpoint of CV death, MI and ischemic stroke occurred in 11.3% of alogliptin treated patients versus 11.8% of patients assigned to placebo (HR: 0.96, upper bound 95% CI <1.16, \( p = .32 \) for superiority, \( p < .001 \) for non-inferiority). Hospitalization for HF was non-significantly increased in alogliptin patients (3.9% vs. 3.3%, HR: 1.19, 95% CI 0.90–1.58, \( p = .22 \)).

The TECOS trial enrolled 14,671 patients who were at least 50 years old and had a documented history of established CV disease, defined as a history of major coronary artery disease (CAD), ischemic cerebrovascular disease, or atherosclerotic peripheral vascular disease. Standard of care comprised patients receiving glucose-lowering agents (metformin: 81.6%; sulfonylurea: 45.3%; insulin: 23.2%) and other CV drugs (ACEI/ARB: 78.8%; beta-blocker: 63.5%; statin: 79.9%; aspirin: 78.5%). The mean age of patients was 65.5 years, 70% were male, and mean BMI of 30.2 kg/m\(^2\). Patients were followed for a median duration of 3 years, and the primary composite endpoint was defined as the first confirmed occurrence of CV death, MI, stroke or hospitalization of unstable angina. There were no observed differences in sitagliptin treated patients compared with placebo, as the primary endpoint occurred in 11.4% versus 11.6% (HR: 0.98, 95% CI 0.88–1.09, \( p < .001 \) for non-inferiority). Rates of hospitalization for heart failure also did not differ between the two groups (HR: 1.00, 95% CI 0.83–1.20, \( p = .98 \)).

**Glucagon-like peptide-1 agonists**

Glucagon-like peptide-1 (GLP-1) receptor agonists are another new generation of anti-hyperglycemic agents. Numerous prospective clinical trials on CV outcomes exist due to the post-2008 FDA approval requirement.
The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was designed to assess the CV outcomes of lixisenatide. It was a double-blind randomized placebo controlled trial (in addition to standard therapy) performed in 6068 patients with type 2 diabetes who had an MI or who had been hospitalized for unstable angina within the previous 6 months. Standard of care comprised patients receiving glucose-lowering agents (metformin: 66%; sulfonylurea: 32%; insulin: 39%) and other CV drugs (ACEI/ARB: 85%; beta-blocker: 84%; statin: 93%; aspirin: 98%) for acute coronary syndrome. The mean age of patients was 60 years, 70% were male, and they had a mean BMI of 30 kg/m². The primary composite endpoints were CV death, MI, stroke, and hospitalization for unstable angina. After a median of 25 months of follow-up, the primary outcome occurred in 406 patients (13.4%) in the lixisenatide group and in 399 (13.2%) in the placebo group (HR: 0.89, 95% CI 0.89–1.17) which showed non-inferiority of lixisenatide compared to placebo (p < .001) but failed to show superiority (p = .81).

In contrast to the ELIXA trial, the Liraglutide Effect and Action in Diabetes (LEADER) trial showed a CV benefit of liraglutide in patients with type 2 diabetes. LEADER is a double blind, randomized, placebo controlled trial randomizing 9340 patients with type 2 diabetes and high CV risk to receive liraglutide 1.8 mg daily or placebo in addition to standard therapy. The primary composite endpoints were the first occurrence of CV mortality, nonfatal MI, or nonfatal stroke. Standard of care comprised patients receiving glucose-lowering agents (metformin: 76%; sulfonylurea: 51%; insulin: 44%) and other CV drugs (ACEI/ARB: 51%; beta-blocker: 55%; statin: 72%; aspirin: 63%) as a majority of the patients had pre-existing CV disease (81%). Thirty percent of patients had CAD, and 16% had a previous stroke. The mean age of patients was 64 years, 64% were male, and they had a mean BMI of 32.5 kg/m². After a median of 3.8 years of follow-up, the primary outcome occurred in 608 (13.0%) in the lixisenatide group and in 592 (12.8%) in the placebo group (HR: 0.85, 95% CI 0.77–0.95) which showed the non-inferiority of liraglutide compared to placebo (p < .001) and superiority of liraglutide compared to placebo (p = .01). CV mortality and all-cause mortality were significantly lower in the lixisenatide group compared to the placebo group.

The Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) trial was another study designed to evaluate the CV benefit of a GLP-1 agonist in patients with type 2 diabetes. Semaglutide is not currently approved by the FDA. SUSTAIN-6 was a double blind, randomized, placebo controlled trial. A total of 3297 patients with type 2 diabetes and established CV diseases and/or chronic kidney disease were randomized to receive semaglutide (0.5 mg or 1.0 mg) or placebo in addition to standard therapy. The primary composite endpoints were the first occurrence of CV mortality, nonfatal MI, or nonfatal stroke. Standard of care comprised patients receiving glucose-lowering agents (metformin: 73%; sulfonylurea: 43%; insulin: 58%) and other CV drugs (ACEI: 50%; beta-blocker: 57%; statin: 73%; aspirin: 64%) as a majority of the patients had pre-existing CV disease (93%). The mean age of patients was 64 years, 61% were male, and the average BMI was 32.8 kg/m². After a median of 2.1 years of follow-up, the primary outcome occurred in 108 (6.6%) in the semaglutide group and in 146 (8.9%) in the placebo group (HR: 0.74, 95% CI 0.58–0.95) which showed the non-inferiority of semaglutide compared to placebo (p < .001) and superiority of semaglutide compared to placebo (p = .02). Cardiovascular mortality was also significantly lower in the semaglutide group compared to the placebo group.

**Sodium–glucose co-transporter 2 inhibitors**

The sodium–glucose co-transporter 2 (SGLT2) inhibitors are the newest class of antihyperglycemics to be approved for use in the US market. Currently, there are three agents approved by the FDA: dapagliflozin, canagliflozin, and empagliflozin. The CV outcome study has only been published for empagliflozin.

Empagliflozin is the first SGLT2 inhibitor to show a reduction in the risk of CV events. The EMPA-REG OUTCOME (Empagliﬂozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial was a multicenter, randomized, double-blind, placebo-controlled trial. The objective of this trial was to evaluate CV morbidity and mortality in patients with type 2 diabetes and established CV disease. A total of 7028 patients were recruited from 590 sites in 42 countries. Seventy-five percent of the patients had CAD, 23% had a previous stroke, 20% had peripheral arterial disease, and 25% had a coronary artery bypass graft. The mean age of patients was 63 years, 71% were male, and 5% were African-American with a mean BMI of 30.6 kg/m². Patients included in this trial had either received no glucose-lowering agents for 12 weeks and had an A1c of 7.0–9.0%, or had received glucose-lowering therapy for 12 weeks and had an A1c of 7.0–10.0%. Patients were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard care. Standard of care comprised patients receiving glucose-lowering agents (metformin: 75%; insulin: 53%; sulfonylurea: 43%) and other CV drugs (ACEI/ARB: 81%; beta-blocker: 65%; statin: 77%; aspirin: 83%) as a majority of the patients had pre-existing CV disease.

The primary outcome was a composite of CV death, nonfatal MI, or nonfatal stroke. Patients were followed for a median of 3.1 years and results for the two empagliflozin doses were pooled. Empagliflozin reduced the risk of CV death, nonfatal MI or nonfatal stroke by 14% versus placebo (HR: 0.86, 95% CI 0.74–0.99, p < .001 for non-inferiority and p = .004 for superiority). CV death was reduced by 38% (HR: 0.62, 95% CI 0.49–0.77, p < .001) but with no significant differences in the risk of non-fatal MI or non-fatal stroke. Additionally, empagliflozin reduced all-cause mortality by 32% (HR: 0.68, 95% CI 0.57–0.82, p < .001) and hospitalization for HF by 35% (HR: 0.65, 95% CI 0.50–0.85, p = .002). There were more episodes of genital infections in both men and women in the empagliflozin groups. In contrast, the incidence of confirmed hypoglycemia, acute renal failure,
thromboembolic events, diabetic ketoacidosis and bone fractures was similar between the two study groups.

**Future perspective and discussion**

The new FDA regulatory requirement for demonstration of the CV safety of antidiabetic agents prior to approval has led to numerous risk avoidance, non-inferiority studies becoming available. Although these studies have shed some light on the effect on CV outcomes of many of the newer classes of antidiabetics, the real vascular effects of glucose-lowering treatments may take up to 5 years or more to become obvious. Aside from the ORIGIN study evaluating insulin glargine (~6 years’ follow-up), most other studies have a median duration of follow-up of 2–4 years. For that reason, studies with longer-term follow-up are needed to fully elucidate the CV effect.

Also important to consider is that the newly completed trials evaluating CV outcomes are testing new classes of antidiabetic agents for non-inferiority against placebo, when administered in addition to usual diabetes care. This may limit clinical interpretation and application, as they provide no direct comparison with existing treatments.

Many recently completed or ongoing CV outcome trials are being carried out in populations at high CV risk (such as those with established CV events or acute coronary syndrome) who have had type 2 diabetes for many years in order to see beneficial effect (if any) sooner. Although impact on secondary CV event prevention is important to evaluate, this may have limited the trials’ ability to assess treatments that might be more effective for primary CV disease prevention, and identifying potentially greater benefits of intervention earlier in the progression of diabetes.

The increased risk of hospitalization for HF in DPP-4 inhibitors is, however, noteworthy. Recently, the FDA released a safety communication adding a warning to the prescribing information for saxagliptin and alogliptin about the potential increase in HF risk, particularly in patients with existing heart or renal disease. Such an increase in HF hospitalization was not observed with GLP-1 agonists. Furthermore, in the EMPA-REG OUTCOME study, empagliflozin was associated with a reduction in HF admission. Although the exact mechanism by which these agents may increase the risk of HF is unknown, there are many potential explanations. The DPP-4 enzyme also degrades a variety of other vasoactive peptides such as brain natriuretic peptide, peptide substance P or neuropeptide Y, which could result in sympathetic tone mediated vasoconstriction. In the SAVOR-TIMI 53 and EXAMINE studies, there was a slight increase in hypoglycemia in DPP-4 inhibitor treated patients versus placebo, and hypoglycemia is known to stimulate both the sympathetic and the renin–angiotensin–aldosterone systems, which when chronically elevated could result in progression to HF in susceptible patients. While it may appear that the risk of HF is highest with saxagliptin and was not increased with sitagliptin based on their respective HF data in SAVOR and TECOS, a recent case control study using worldwide spontaneous reports contained in the FDA Adverse Event Reporting System (FAERS) demonstrated significantly elevated reporting odds ratio for HF with sitagliptin, saxagliptin and vildagliptin. Given the inconsistencies of HF occurrence within the SAVOR, EXAMINE and TECOS trials, along with the fact that, in SAVOR, there were no differences in body weight, fluid retention, and patient reported edema between groups, it is possible the increased risk of HF may have been a chance finding. Therefore, further data is needed to clarify whether there is an increased risk of HF and, if so, if the HF risk is a class effect or unique to certain agents within the DPP-4 inhibitor class, and by what mechanisms HF risk is increased. Equally important would be better understanding of the mechanism on CV effect of other newer classes of antidiabetic agents to help refine what patient population may benefit (if any). Table 2 summarizes the postulated mechanisms of CV effect of different classes of antidiabetic agents.

**Conclusion**

Examining current literature revealed that among agents for diabetes management available prior to 2008, metformin is the only agent, demonstrated in a small cohort, which has demonstrated improvement in cardiovascular outcomes. Clinical studies have demonstrated controversial results in the use of sulfonylureas, and TZDs for diabetes management and CV outcomes. The degree of control of other CV risk factors, such as hypertension or hyperlipidemia was not evaluated. Therefore, it is difficult to conclude whether it is a true effect of the agents themselves, or it is simply confounded by indication.

Among newer antidiabetic agents (DDP-4 inhibitors, GLP-1 agonist and SGLT inhibitors), lixivatide, semaglutide (not FDA approved to date) and empagliflozin have been shown to be superior to placebo, when added to standard therapy in improving CV outcomes. It is however important to note that these trials have placebo-controlled, non-inferiority designs aiming to show an absence of CV toxicity. Many essential questions are unanswered, including comparative effectiveness and real long-term risk versus benefits.

The American Diabetes Association in their latest 2017 consensus statement continues to recommend metformin as a first-line oral agent in addition to lifestyle changes for patients with type 2 diabetes. For add on therapy, if patients are symptomatic and/or have HgA1C ≥10%, insulin therapy should be considered. If HgA1C is <10%, choices include TZDs, sulfonylureas, DDP-4 inhibitor, SGLT inhibitor, and GLP-1 receptor agonist. Specific choices should be based on a variety of patient and disease factors. The new consensus statement also recommended that in patients with long-standing suboptimally controlled type 2 diabetes who have established atherosclerotic cardiovascular disease, empagliflozin or lixivatide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Similarly, the FDA has approved the use of empagliflozin for reduction of risk of cardiovascular death in adult patients with type 2 diabetes and established cardiovascular disease.
This review has shown the positive and negative CV risks associated with antidiabetic agents, with a great deal of data being either inconclusive or lacking, and more long-term data is needed.

### Transparency

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**Declaration of financial/other relationships**

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### References


### Table 2. Cardiovascular outcomes of hyperglycemic agents and proposed mechanisms

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>CV Outcomes</th>
<th>Proposed Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Neutral CV outcomes</td>
<td>- Improved glycemic control may be offset by hypoglycemia - Mixed anti- and pro-atherosclerotic effects</td>
</tr>
<tr>
<td>Metformin</td>
<td>Decreased mortality, MI and HF</td>
<td>- Improved glycemic control - Decrease weight - Decrease VLDL and TGs - Hypoglycemia and weight gain - Interferes with ischemic preconditioning</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Possible increase in CV death</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Increase HF</td>
<td>- Increase renal sodium and water retention through PPAR-γ mediated activation of the epithelium’s sodium channel (ENaC) in the collecting duct - Stimulate sodium transporters in the proximal tubule - Decreased degradation of BNP, substance P, neuropeptide Y - Increased SNS and RAAS from hypoglycemia</td>
</tr>
<tr>
<td>Dipeptidyl peptidase 4 (DPP-4) inhibitors</td>
<td>Increase HF</td>
<td></td>
</tr>
<tr>
<td>Glucagon like peptide-1 agonist</td>
<td>Decrease death from any cause</td>
<td>- Decrease body weight, visceral adiposity - Decrease BP - Decrease TC, LDL, TGs - Increase HDL - Increase HR, improved LVEF and cardiac output - Decrease BP by reduced arterial stiffness, vascular resistance and osmotic diuresis - Decrease body weight, visceral adiposity - Decrease uric acid and oxidative stress - Shift in myocardial fuel energetics</td>
</tr>
<tr>
<td>Sodium–glucose co-transporter 2 (SGLT2) inhibitors</td>
<td>Decrease CV death</td>
<td>- Shift in myocardial fuel energetics</td>
</tr>
<tr>
<td></td>
<td>Decrease HF hospitalization</td>
<td></td>
</tr>
</tbody>
</table>

CV: cardiovascular; HF: heart failure; MI: myocardial infarction; VLDL: very low-density lipoprotein; TGs: triglycerides; BNP: brain natriuretic peptide; SNS: sympathetic nervous system; RAAS: renin–angiotensin–aldosterone system; BP: blood pressure; LVEF: left ventricular ejection fraction; HR: heart rate; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein.


