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# Newer Diabetes Drugs and Cardiovascular Disease Outcomes: Update

## Systematic Review

February 2020

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# Executive Summary

## Background

Traditional therapies for glycemic control in patients with type 2 diabetes (e.g., metformin) are effective in managing blood glucose levels in some patients.[1,2] However, since the development of metformin, several classes of newer diabetes drugs have been approved by the U.S. Food and Drug Administration (FDA) as monotherapy and combination therapies, including[3]:

- Glucagon-like peptide-1 (GLP-1) agonists
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Sodium-glucose cotransporter 2 (SGLT-2) inhibitors

Historically, antidiabetic therapies had been approved by the FDA based on surrogate laboratory measures (e.g., reductions in body weight, blood glucose, cholesterol) without evidence of additional health outcomes or long-term effects. In 2005, analysis of phase 2 and 3 clinical trial data of the investigational diabetic drug muraglitazar found it was associated with an increased incidence of death, major adverse cardiovascular events (MACE), and chronic heart failure.[4] In 2007, a meta-analysis of cardiovascular (CV) morbidity and mortality outcomes associated with the type 2 diabetes drug rosiglitazone, reported a significant association between treatment and increased risk of myocardial infarction (MI) and CV death.[5] These results raised concern as an estimated 32.2% of individuals with type 2 diabetes around the world are affected by cardiovascular disease (CVD), the main cause of death for individuals with type 2 diabetes.[6] This prompted the FDA to release a 2008 guidance requiring that new antidiabetic therapies for type 2 diabetes not be associated with an unacceptable increase (i.e., more than 30%) in CV event risk.[7] State Medicaid administrators are interested in a targeted update of the 2017 Drug Effectiveness Review Project (DERP) systematic review on newer diabetes drugs[8] focused specifically on the drugs' ability to prevent mortality and CVD outcomes associated with these interventions.

## PICOS and Key Questions

### *Population*

- Adults with type 2 diabetes

### *Interventions*

Table 1. Eligible Interventions for this Report

| Class | Generic Names | Brand Names | FDA Approval Date |
|---|---|---|---|
| **Oral Drugs** | | | |
| SGLT-2 inhibitors | Ertugliflozin<br>Empagliflozin<br>Dapagliflozin<br>Canagliflozin | Steglatro<br>Jardiance<br>Farxiga<br>Invokana | 12/19/17<br>8/1/14<br>1/8/14<br>3/29/13 |
| DPP-4 inhibitors | Alogliptin<br>Linagliptin<br>Saxagliptin<br>Sitagliptin | Nesina<br>Tradjenta<br>Onglyza<br>Januvia | 1/25/13<br>5/2/11<br>7/31/09<br>10/16/06 |
| **Fixed-Dose Combination Products of Oral Drugs** | | | |
| SGLT-2 inhibitor with DPP-4 inhibitor | Dapagliflozin-saxagliptin<br>Empagliflozin-linagliptin | Qtern<br>Glyxambi | 2/27/17<br>1/30/15 |
| SGLT-2 inhibitor with metformin | Ertugliflozin-metformin<br>Empagliflozin-metformin ER<br>Canagliflozin-metformin ER<br>Empagliflozin-metformin<br>Dapagliflozin-metformin ER<br>Canagliflozin-metformin | Segluromet<br>Synjardy XR<br>Invokamet XR<br>Synjardy<br>Xigduo XR<br>Invokamet | 12/19/17<br>12/9/16<br>9/20/16<br>8/26/15<br>10/29/14<br>8/8/14 |
| DPP-4 inhibitor with TZD | Alogliptin-pioglitazone | Oseni | 1/25/13 |
| DPP-4 inhibitor with metformin | Linagliptin-metformin ER<br>Alogliptin-metformin<br>Sitagliptin-metformin ER<br>Linagliptin-metformin<br>Saxagliptin-metformin ER<br>Sitagliptin-metformin | Jentadueto XR<br>Kazano<br>Janumet XR<br>Jentadueto<br>Kombiglyze XR<br>Janumet | 5/27/16<br>1/25/13<br>2/2/12<br>1/30/12<br>11/5/10<br>3/30/07 |
| **Subcutaneous Injection Drugs** | | | |
| GLP-1 agonists | Oral semaglutide<br>Semaglutide<br>Lixisenatide<br>Dulaglutide<br>Albiglutide<br>Exenatide ER<br>Liraglutide<br>Exenatide | Rybelsus<br>Ozempic<br>Adlyxin<br>Trulicity<br>Tanzeum<br>Bydureon<br>Victoza<br>Byetta | 9/20/19<br>12/5/17<br>7/27/16<br>9/18/14<br>4/15/14<br>1/27/12<br>1/25/10<br>4/28/05 |
| GLP-1 agonist with long-acting insulin | Liraglutide-insulin degludec U100/3.6 mg<br>Lixisenatide-insulin glargine U100/33 mg | Xultophy<br>Soliqua | 11/21/16<br>11/21/16 |

*Abbreviations. DPP-4: dipeptidyl peptidase 4; ER: extended release; FDA: U.S. Food and Drug Administration; GLP-1: glucagon-like peptide 1; SGLT-2: sodium-glucose cotransporter-2; TZD: thiazolidinediones; XR: extended release.*

### *Comparators*

- Another listed intervention (head-to-head comparisons)
- Combination therapies versus monotherapy of included intervention types
- Placebo

### *Outcomes*

- Mortality (all-cause and cardiovascular-related)
- CVD outcomes (fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalization for heart failure [hHF])
- Serious adverse events (e.g., serious adverse events [SAEs], withdrawals due to adverse events [AEs], condition-specific AEs)

### *Study Design*

- Randomized controlled trials (RCTs)
- Large prospective and retrospective cohort studies
  - Sample size of ≥ 10,000 participants

## Key Questions

1. What is the effectiveness of newer diabetes medications for cardiovascular events, including mortality, in adults with type 2 diabetes?
   a. Does the effect differ when used as monotherapy versus combination therapy?
   b. Does the effect differ in patients with and without prior CVD?
   c. Is there evidence of a class effect?
   d. What are the harms associated with treatment?
2. What are the characteristics of ongoing studies for newer diabetes medications and CVD outcomes?

## Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, and several other websites to identify new eligible studies of newer diabetes drugs for CVD outcomes, from January 1, 2017 to October 2, 2019. Additional eligibility criteria included publication in English and a human study population. We rated the methodological quality of eligible RCTs and large cohort studies using standard instruments adapted from national and international quality standards.[9-11] We rated the quality of the body of evidence for 5 outcomes (i.e., all-cause mortality, fatal or nonfatal stroke, fatal or nonfatal MI, hHF, and SAEs) when possible, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[12,13] Imprecision was not assessed formally (i.e., by meta-analysis) in this report. We extracted data for outcomes of interest from eligible studies. If relevant statistical tests were not reported, we used OpenEpi (version 3.01) to calculate risk ratios, incidence rate ratios, and accompanying 95% confidence intervals (CI) based on data provided in the studies. We used OpenEpi (version 3.01) to test outcomes using a two-tailed Mantel-Haenzel chi-square test with mid-exact *P*-values based on data provided in the studies. We indicate calculated values with *italics*.

## Key Findings

We identified 16 eligible RCTs (in 50 publications) assessing CV outcomes in adults with type 2 diabetes. We identified 10 new RCTs in this updated review with 6 publications from the original systematic review:

- **GLP-1 agonists:** 7 placebo-controlled trials[14-20] (in 17 publications)
- **DPP4-inhibitors**: 4 placebo-controlled trials[21-24] (in 13 publications) and 1 head-to-head RCT[25] (in 1 publication) comparing linagliptin to glimepiride
- **SGLT-2 inhibitors**: 4 placebo-controlled trials[26-30] (in 19 publications)

### *Effectiveness and Harms*

In each trial, all groups were allowed standard of care (SOC) therapy for glycemic and CV risk management adherent to local guidelines, and all comparison groups included a placebo. For succinctness, we have interpreted findings as the newer diabetes drug vs. placebo, and only significant findings for individual drugs within each class are provided.

#### *GLP-1 Agonists*

We downgraded the quality of the evidence one level to moderate for all-cause mortality and hHF due to indirectness (i.e., applicability of findings) and risk of bias between studies. We downgraded the quality of the evidence from moderate to low for stroke and SAEs due to additional inconsistent effects between studies. We downgraded the quality of the evidence for MI two levels to very low due to high inconsistency in effects between studies.

##### All-cause Mortality

- We found evidence for small risk reductions for all-cause mortality within the GLP-1 agonist class when compared to placebo (moderate quality of evidence).
    - No evidence of an effect on all-cause mortality risk was observed with albiglutide (Tanzeum), dulaglutide (Trulicity), lixisenatide (Adlyxin), or semaglutide (Ozempic).
    - Exenatide ER (extended release, Bydureon) significantly reduced risk by 14% over placebo; however, the absolute difference in individuals reporting events was small between groups (6.9% vs. 7.9%; hazard ratio [HR], 0.86; 95% CI, 0.77 to 0.97; *P* = .02).
    - Compared to placebo, liraglutide (Victoza) significantly reduced risk of all-cause mortality by 15% (8.2% vs. 9.6%; HR, 0.85; 95% CI, 0.74 to 0.97; *P* = .02), a significant effect given the number of events reported.
    - Oral semaglutide (Rybelsus) significantly reduced risk by 51% (1.4% vs. 2.8%; HR, 0.49; 95% CI, 0.27 to 0.92) over placebo, a strong effect given the infrequency of events reported in the trial.

##### Stroke

- GLP-1 agonists had no evidence of an effect on risk of stroke compared to placebo (low quality of evidence).
    - This outcome was not assessed in semaglutide. No evidence of an effect on stroke risk was observed with albiglutide, exenatide ER, liraglutide, lixisenatide, or oral semaglutide.
    - Dulaglutide significantly reduced stroke risk by 24% over placebo (3.2% vs. 4.1%; HR, 0.76; 95% CI 0.62 to 0.94; *P* = .01); however, the absolute difference in stroke incidence between treatment groups was less than 1 percentage point.

##### Myocardial Infarction

- We cannot make clear conclusions for risk of MI within the GLP-1 agonist class (very low quality of evidence).
    - This outcome was not assessed in semaglutide. No evidence of an effect on MI risk was observed with dulaglutide, exenatide ER, lixisenatide, or oral semaglutide.
    - Albiglutide significantly reduced MI risk by 25% over SOC but the absolute risk reduction was small at 1 percentage point (4.0% vs. 5.0%; HR, 0.75; 95% CI, 0.61 to 0.90; *P* = .003).

- Liraglutide reduced MI risk by 14% over placebo, but the finding was marginally significant (6.3% vs. 7.3%; HR, 0.86; 95% CI, 0.73 to 1.00; *P* = .05). Overall, this is a modest effect given the number of events reported and small absolute difference in events between groups.

#### Hospitalization for Heart Failure

- Compared to placebo, GLP-1 agonists did not reduce risk of hHF (moderate quality of evidence).
  - This outcome was not assessed in albiglutide and no evidence of an effect on hHF risk was observed with dulaglutide, exenatide ER, liraglutide, lixisenatide, semaglutide, or oral semaglutide.

#### Serious Adverse Events

- We found evidence of reduced risk for SAEs within the GLP-1 agonist drug class when compared to placebo (low quality of evidence).
  - No evidence of an effect on risk for SAEs was observed with exenatide ER, liraglutide, or lixisenatide.
  - Reductions in risk for SAEs were reported with albiglutide (27.3% vs. 35.5%; *risk ratio [RR], 0.77; 95% CI, 0.72 to 0.81; P < .0001*), dulaglutide (69.4% vs. 72.5%; *RR, 0.96; 95% CI, 0.93 to 0.98; P = .0006*), semaglutide (34.3% vs. 38.0%; *RR, 0.90; 95% CI, 0.82 to 0.99; P = .03*), and oral semaglutide (18.9% vs. 22.5%; *RR, 0.84; 95% CI, 0.73 to 0.96; P = .02*) compared to a placebo.

### *DPP-4 Inhibitors*

We downgraded the quality of the evidence one level to moderate for all-cause mortality, stroke, and SAEs due to indirectness (i.e., applicability of findings) and risk of bias between studies. We downgraded the quality of the evidence from moderate to low for MI and hHF due to additional inconsistent effects between studies.

#### All-Cause Mortality

- We found no evidence of an effect on all-cause mortality risk with DPP-4 inhibitor treatment compared to placebo (moderate quality of evidence).
  - No evidence of an effect on all-cause mortality risk was observed with alogliptin (Nesina), saxagliptin (Onglyza), or sitagliptin (Januvia).
  - Linagliptin (Tradjenta) had no evidence of an effect when compared to placebo or glimepiride.

#### Stroke

- We found no evidence of an effect on risk of stroke with DPP-4 inhibitor treatment compared to placebo (moderate quality of evidence).
  - This outcome was not assessed in alogliptin and no evidence of an effect on stroke risk was observed with saxagliptin or sitagliptin.
  - Linagliptin had no evidence of an effect when compared to placebo or glimepiride.

#### Myocardial Infarction

- We found no evidence of an effect on risk of MI with DPP-4 inhibitor treatment compared to placebo (low quality of evidence).
  - This outcome was not assessed in alogliptin and no evidence of an effect on MI risk was observed with saxagliptin or sitagliptin.

- Linagliptin had no evidence of an effect when compared to placebo or glimepiride.

### Hospitalization for Heart Failure

- We found no evidence of an effect on risk of hHF with DPP-4 inhibitor treatment compared to placebo (low quality of evidence).
  - This outcome was not assessed in alogliptin and no evidence of an effect on hHF risk was observed with sitagliptin.
  - Linagliptin had no evidence of an effect on risk of hHF when compared to placebo or glimepiride.
  - Saxagliptin significantly increased hHF risk 27% over placebo (3.5% vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; *P* = .007); however, the absolute difference in risk was small at less than one percentage point.

### Serious Adverse Events

- Within the DPP-4 inhibitor class, we found no evidence of an effect on risk for SAEs compared to placebo (moderate quality of evidence).
  - No evidence of an effect on risk for SAEs was observed with alogliptin or sitagliptin.
  - Linagliptin had no evidence of an effect when compared to placebo or glimepiride.
  - A significant 5% increase in risk for SAEs was found with saxagliptin over placebo (41.4% vs. 39.6%; *RR, 1.05; 95% CI, 1.01 to 1.09; P = .02*), a moderate effect given the number of events reported and absolute difference in events between groups.

## *SGLT-2 Inhibitors*

We downgraded the quality of the evidence one level to moderate for all-cause mortality, MI, hHF, and SAEs due to indirectness (i.e., applicability of findings) and risk of bias between studies. We downgraded the quality of the evidence from moderate to low for stroke due to additional inconsistent effects between studies.

### All-cause Mortality

- No evidence of an effect on risk of all-cause mortality was found within the SGLT-2 inhibitor class (moderate quality of evidence).
  - No evidence of an effect on all-cause mortality risk was observed with canagliflozin (Invokana) or dapagliflozin (Farxiga).
  - Empagliflozin (Jardiance) significantly reduced risk of all-cause mortality by 32% (5.7% vs. 8.3%; HR, 0.68; 95% CI, 0.57 to 0.82; *P* < .001) over placebo, a strong effect with an absolute difference in risk of over 2.5 percentage points.

### Stroke

- SGLT-2 inhibitors had no evidence of an effect on stroke risk when compared to placebo (low quality of evidence).
  - No evidence of an effect on stroke risk was observed with canagliflozin, dapagliflozin, or empagliflozin.

### Myocardial Infarction

- We found no evidence of an effect on MI risk within the SGLT-2 inhibitor class compared to placebo (moderate quality of evidence).
  - No evidence of an effect on stroke risk was observed with canagliflozin, dapagliflozin, or empagliflozin.

### Hospitalization for Heart Failure

- We found evidence of significant reductions in risk of hHF across the SGLT-2 inhibitor class when compared to placebo (moderate quality of evidence).
    - Canagliflozin reduced risk by 33% over placebo in the CANVAS program trial (5.5 vs. 8.7 events per 1000 patient-years; HR, 0.67; 95% CI, 0.52 to 0.87) and reduced risk by 39% over placebo in the CREDENCE trial (4.0% vs. 6.4%; HR, 0.61; 95% CI, 0.47 to 0.80; *P* < .001). Both were strong effects with larger absolute differences in events experienced between groups.
    - Dapagliflozin significantly reduced risk by 27% (2.5% vs. 3.3%; HR, 0.73; 95% CI, 0.61 to 0.88) over placebo, but had a small absolute reduction in events reported between groups.
    - Empagliflozin significantly reduced risk by 35% over placebo (2.7% vs. 4.1%; HR, 0.65; 95% CI 0.50 to 0.85; *P* = .002).

### Serious Adverse Events

- We found evidence of significant reductions in risk of SAEs across the SGLT-2 inhibitor class when compared to placebo (moderate quality of evidence).
    - Canagliflozin did not reduce risk of SAEs over placebo in the CANVAS program trial (104.3 vs. 120 events per 1,000 patient-years; *incidence rate ratio [IRR], 0.87; 95% CI, 0.67 to 1.13; P = .29*). A significant 9% reduction in risk of SAEs with canagliflozin over placebo was reported in the CREDENCE trial (*33.5% vs. 36.7%; RR, 0.91; 95% CI, 0.84 to 0.99; P = .03*).
    - Dapagliflozin significantly reduced risk for SAEs by 6% over placebo (34.1% vs. 36.2%; *RR, 0.94; 95% CI, 0.91 to 0.98; P = .005*).
    - Empagliflozin significantly reduced risk for SAEs by 10% over placebo (38.2% vs. 42.3%; *RR, 0.90; 95% CI, 0.85 to 0.96; P = .0007*).

### *Monotherapy vs. Combination Therapy*

- We did not find any eligible RCTs assessing efficacy or safety in monotherapy vs. combination therapy for included interventions across drug classes.

### *With and Without Prior CVD*

We were unable to formally assess the 5 outcomes of interest between individuals with and without prior CVD due to a lack of studies assessing these individuals and heterogeneity in disease phenotype. We are unable to draw meaningful conclusions for individuals with prior CVD due to inconsistent findings reported across studies in each drug class.

### *GLP-1 Agonists*

#### Established CVD at Baseline

- No significant difference in MACE risk was found between individuals with and without prior CVD (*P* = .97) randomized to dulaglutide in the REWIND[19] trial.
- Liraglutide reduced MACE risk by 18% among individuals with baseline single vascular disease (HR, 0.82; 95% CI, 0.71 to 0.95) but had no evidence of an effect in those with baseline polyvascular disease (HR, 0.82; 95% CI, 0.66 to 1.02) in the LEADER[17] trial.
    - In contrast, liraglutide reduced risk of CV death 33% in individuals with single vascular disease (HR, 0.67; 95% CI, 0.53 to 0.85) but had no evidence of an effect on individuals with polyvascular disease (HR, 0.92; 95% CI, 0.63 to 1.32) in LEADER.[17]
- No significant difference in MACE risk was reported between individuals with and without baseline heart failure (HF) history randomized to lixisenatide in the ELIXA[16] trial.

- In the EXSCEL[15] trial, exenatide ER had a significantly different effect on all-cause mortality risk between individuals without baseline HF, who experienced a 21% reduction in risk (HR, 0.79; 95% CI, 0.69 to 0.92), and individuals with baseline HF, who did not show evidence of an effect (HR, 1.05; 95% CI, 0.85 to 1.29).
    - Exenatide ER had a significantly different effect on risk for the composite outcome of all-cause mortality or hHF between individuals without baseline HF, who experienced a 19% reduction in risk (HR, 0.81; 95% CI, 0.71 to 0.93), and individuals with baseline HF, who did not have evidence of an effect (HR, 1.07; 95% CI, 0.89 to 1.29) in EXSCEL.[15]
- In the LEADER[17] trial, liraglutide had a significantly different effect on hHF risk between baseline CVD status subgroups. A smaller number of hHF events occurred with liraglutide among individuals with MI or stroke history (5.9% vs. 7.3%) and individuals with CVD without prior MI or stroke (3.4% vs. 4.7%) compared to placebo, but those with only CV risk factors had similar event rates to placebo (0.7% vs. 0.6%).

#### Baseline Renal Function

- In the LEADER[17] trial, liraglutide had a significantly different effect on MACE risk between individuals with a baseline estimated glomerular filtration rate (eGFR) < 60 mL and ≥ 60 mL (*P* = .01). Only individuals with a baseline eGFR < 60 mL experienced reductions in MACE risk (HR, 0.69; 95% CI, 0.57 to 0.85).[17]

### *DPP-4 Inhibitors*

#### Established CVD at Baseline

- No significant difference in MACE risk was reported between individuals with baseline CVD and individuals with CV risk factors randomized to saxagliptin in the SAVOR-TIMI 53[22] trial.
- No significant difference in risk of hHF or risk of CV death was reported between individuals with and without baseline HF randomized to linagliptin in the CARMELINA[25] trial.

### *SGLT 2 Inhibitors*

#### Established CVD at Baseline

- In the CANVAS[28,31] program and CREDENCE[26] trials, canagliflozin had no evidence of a differential effect on CV outcomes between individuals ≤ 30 years of age with baseline atherosclerotic CVD or individuals ≥ 50 years of age with CV risk factors.
- No significant difference in risk for CV outcomes was reported between individuals with and without baseline HF randomized to canagliflozin in the CANVAS[28,31] program trial.
- Dapagliflozin reduced the risk of non-CV death by 50% among individuals with prior HF, but no treatment benefit for non-CV death risk was observed for individuals without prior HF.[30]
- In the DECLARE-TIMI 58[30] trial, dapagliflozin reduced the risk of CV death by 45%, hHF risk by 36%, and all-cause mortality risk by 41% in individuals with baseline HF with reduced ejection fraction (HFrEF), but had no evidence of an effect on individuals with baseline HF with preserved ejection fraction (HFpEF).
- No significant difference in CV event risk was reported between individuals with and without prior MI or stroke, or between individuals with and without baseline peripheral artery disease (PAD) randomized to empagliflozin in the EMPA-REG OUTCOME[27] trial.
- Individuals with prior MI history randomized to dapagliflozin had significant reductions in MACE risk (HR, 0.84; 95% CI 0.72 to 0.99; *P* = .04) and recurrent MI risk (HR, 0.78; 95% CI, 0.63 to 0.95), but no evidence of an effect was reported for individuals without prior MI history in the DECLARE-TIMI 58[30] trial.

- Individuals with prior MI randomized to dapagliflozin in the DECLARE-TIMI 58 trial had nearly 7 times the risk of diabetic ketoacidosis than individuals with prior MI randomized to placebo, although not statistically significant (HR, 6.98; 95% CI, 0.86 to 56.76). This finding is limited by the small sample of individuals with prior MIs.[30]
- Canagliflozin significantly reduced hemorrhagic stroke risk by 57% (HR, 0.43; 95% CI, 0.20 to 0.89; *P* = .02) over placebo in individuals with baseline cerebrovascular disease in the CANVAS program trial.[28,31]
- In the EMPA-REG OUTCOME[27] trial, greater reductions in risk for CV death, all-cause mortality, hHF, and the composite of hHF or CV death were reported in individuals with prior coronary artery bypass grafting (CABG) than those without prior CABG randomized to empagliflozin.

### Baseline Renal Function

- In the CANVAS[28,31] program trial, canagliflozin had a significantly different effect on stroke risk between individuals with varying levels of baseline renal function (e.g., eGFR < 45 mL, eGFR 60 to < 90 mL, and eGFR ≥ 90 mL) and stroke risk was only reduced among individuals with a baseline eGFR < 45 mL (HR, 0.32; 95% CI, 0.11 to 0.96).
- No significant differences in risk of CV events were reported with dapagliflozin between the baseline eGFR, HbA1c (glycated hemoglobin test of blood glucose), or urinary albumin-to-creatinine-ratio (UACR) subgroups in the DECLARE-TIMI 58[30] trial.

## Ongoing Studies

- We identified 6 ongoing studies assessing CVD outcomes for included interventions:
  - 4 ongoing RCTs: dapagliflozin and pioglitazone combination therapy vs. SOC, ertugliflozin vs. SOC, empagliflozin vs. metformin; semaglutide vs. SOC
  - 1 prospective cohort study: comparing empagliflozin and/or SGLT-2 inhibitors vs. DPP-4 inhibitors
  - 1 retrospective cohort study: comparing empagliflozin vs. DPP-4 inhibitors
- We identified 1 completed RCT assessing CV outcomes comparing an exenatide implant to a placebo implant.

## Conclusion

Overall, the newer diabetes drugs included in this report do not appear to be associated with a significant increase in morality and CV events, and may have positive benefits in risk reduction for individuals with type 2 diabetes and established CVD or with CV risk factors. Evidence for small reductions in risk of all-cause mortality and SAEs were found in GLP-1 agonists, but inconsistent findings between studies lessens our confidence of reported findings. We found GLP-1 agonists had no evidence of an effect on risk of stroke, MI, hHF, or SAEs. DPP-4 inhibitors had no evidence of an effect on risk for any of the 5 outcomes. As a class, SGLT-2 inhibitors had evidence for significant reductions in risk of hHF and SAEs, but had no effect on risk of all-cause mortality, stroke, or MI. Significant differences in CV event risk between individuals with and without established CVD at baseline were reported in the GLP-1 agonist and SGLT-2 inhibitor classes, but not found for DPP-4 inhibitors. GLP-1 agonists and SLGT-2 inhibitors were associated with significant reductions in MACE risk, but there was no evidence that DPP-4 inhibitors had an effect on MACE risk. Evidence of significant differences in treatment effect on MACE risk were reported among individuals with impaired renal function at baseline across all three drug classes. Consistent reductions in hHF risk with SGLT-2 inhibitors and consistent reductions in all-cause mortality risk with GLP-1 agonists were reported in identified cohort studies.

In contrast to the significant increase in hHF risk found with the DPP-4 inhibitor saxagliptin (3.5% vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; P = .007),[22] 1 retrospective cohort of U.S. individuals with type 2 diabetes reported starting saxagliptin reduced hHF risk 26% over starting a GLP-1 agonist (2.7% vs. 4.2%; HR, 0.74; 95% CI, 0.69 to 0.84).[32] However, evidence from cohort studies should be interpreted with caution. We did not identify any eligible studies assessing the CV effectiveness and safety of included interventions when used as monotherapy compared to combination therapy. With no eligible head-to-head trials identified, we are unable to make direct comparisons between drug classes for included interventions.

Usage of placebo run-in periods prior to randomization may have artificially reduced treatment discontinuation rates and the number of AEs associated with treatment in the trial (e.g., injection-site reactions, gastrointestinal events). It is possible that exposure time to included interventions in some trials was inadequate to accurately capture CV risk. Additionally, generalizability of findings to a U.S. Medicaid population are limited by variation in local care guidelines, potential usage of non-FDA approved therapies, and variation in access to quality health care due to the multisite, international design of the included RCTs. There may be potential differences in SOC therapies participants received at the time of randomization throughout the trial that potentially influenced outcomes.

Coverage for specific therapies could be structured around eligibility criteria of the included studies such as stable doses of other glucose-lowering drugs, renal function, no history of dialysis or renal transplant, and stable HbA1c levels. Prescribers and payers might consider assessing individual patient risk factors and comorbidities to determine whether the purpose of added therapy is to prevent or to decrease risk for specific CV events (e.g., reducing risk of end-stage renal disease vs. reducing HF) when considering therapy with GLP-1 agonists, DPP-4 inhibitors, or SGLT-2 inhibitors.

## Table 1. List of Brand Names and Generics

Table 1. Eligible Interventions for this Report

| Class | Generic Names | Brand Names | FDA Approval Date |
|---|---|---|---|
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| **Fixed-Dose Combination Products of Oral Drugs** | | | |
| SGLT-2 inhibitor with DPP-4 inhibitor | Dapagliflozin-saxagliptin<br>Empagliflozin-linagliptin | Qtern<br>Glyxambi | 2/27/17<br>1/30/15 |
| SGLT-2 inhibitor with metformin | Ertugliflozin-metformin<br>Empagliflozin-metformin ER<br>Canagliflozin-metformin ER<br>Empagliflozin-metformin<br>Dapagliflozin-metformin ER<br>Canagliflozin-metformin | Segluromet<br>Synjardy XR<br>Invokamet XR<br>Synjardy<br>Xigduo XR<br>Invokamet | 12/19/17<br>12/9/16<br>9/20/16<br>8/26/15<br>10/29/14<br>8/8/14 |
| DPP-4 inhibitor with TZD | Alogliptin-pioglitazone | Oseni | 1/25/13 |
| DPP-4 inhibitor with metformin | Linagliptin-metformin ER<br>Alogliptin-metformin<br>Sitagliptin-metformin ER<br>Linagliptin-metformin<br>Saxagliptin-metformin ER<br>Sitagliptin-metformin | Jentadueto XR<br>Kazano<br>Janumet XR<br>Jentadueto<br>Kombiglyze XR<br>Janumet | 5/27/16<br>1/25/13<br>2/2/12<br>1/30/12<br>11/5/10<br>3/30/07 |
| **Subcutaneous Injection Drugs** | | | |
| GLP-1 agonists | Oral semaglutide<br>Semaglutide<br>Lixisenatide<br>Dulaglutide<br>Albiglutide<br>Exenatide ER<br>Liraglutide<br>Exenatide | Rybelsus<br>Ozempic<br>Adlyxin<br>Trulicity<br>Tanzeum<br>Bydureon<br>Victoza<br>Byetta | 9/20/19<br>12/5/17<br>7/27/16<br>9/18/14<br>4/15/14<br>1/27/12<br>1/25/10<br>4/28/05 |
| GLP-1 agonist with long-acting insulin | Liraglutide-insulin degludec U100/3.6 mg<br>Lixisenatide-insulin glargine U100/33 mg | Xultophy<br>Soliqua | 11/21/16<br>11/21/16 |

*Abbreviations. DPP-4: dipeptidyl peptidase 4; ER: extended release; FDA: U.S. Food and Drug Administration; GLP-1: glucagon-like peptide 1; SGLT-2: sodium-glucose cotransporter-2; TZD: thiazolidinediones; XR: extended release.*

## Background

Type 2 diabetes is a chronic disease that affects an individual's production of and response to insulin, a hormone controlling glucose (blood sugar) metabolism. Type 2 diabetes is associated with increased risk of heart disease and stroke, nerve damage, kidney damage, foot problems, eye disease, gum disease, and sexual and bladder problems.[33] An influx of newly approved treatments lacking cardiovascular (CV) safety and efficacy data led the U.S. Food and Drug Administration (FDA) to publish 2008 guidelines[34] requiring marked improvement in cardiovascular disease (CVD) outcomes (e.g., myocardial infarction [MI], stroke, hospitalization for heart failure [hHF]) for new treatments of type 2 diabetes. Three new drug classes have been approved for treatment of type 2 diabetes as monotherapy and combination therapies: glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. GLP-1 agonists vary in individual chemical structure and duration of action.[35] Since these drugs have gone to market, the FDA has issued drug safety communications warning about the potential increased risk for adverse events (AEs) related to treatment within the SGLT-2 inhibitor and DPP-4 inhibitor classes.[36-39] State Medicaid administrators are interested in a targeted update of the 2017 Drug Effectiveness Review Project (DERP) systematic review[8] focused specifically on newer diabetes drugs to prevent mortality and CVD outcomes associated with these interventions.

## PICOS

### *Population*

- Adults with type 2 diabetes

### *Interventions*

See Table 1.

### *Comparators*

- Another listed intervention (head-to-head comparisons)
- Combination therapies versus monotherapy of included intervention types
- Placebo

### *Outcomes*

- Mortality (all-cause and cardiovascular-related)
- CVD outcomes (fatal or nonfatal MI, fatal or nonfatal stroke, hHF)
- Serious adverse events (e.g., serious adverse events [SAEs], withdrawals due to AEs, condition-specific AEs)

### *Study Design*

- Randomized controlled trials (RCTs)
- Large prospective and retrospective cohort studies
    - Sample size of ≥ 10,000 participants

## Key Questions

1. What is the effectiveness of newer diabetes medications for cardiovascular events, including mortality, in adults with type 2 diabetes?
   a. Does the effect differ when used as monotherapy versus combination therapy?
   b. Does the effect differ in patients with and without prior CVD?
   c. Is there evidence of a class effect?
   d. What are the harms associated with treatment?
2. What are the characteristics of ongoing studies for newer diabetes medications and CVD outcomes?

## Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, and several other websites to identify new eligible studies of newer diabetes drugs for CVD outcomes, from January 1, 2017 to October 2, 2019. Additional eligibility criteria included publication in English and a human study population. We rated the methodological quality of eligible RCTs or large cohort studies using standard instruments adapted from national and international quality standards.[9-11] We rated the quality of the body of evidence for 5 included outcomes (i.e., all-cause mortality, fatal or nonfatal stroke, fatal or nonfatal MI, hHF, SAEs) when possible, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[12,13] Imprecision was not assessed formally (i.e., by meta-analysis) in this report. We extracted data for outcomes of interest from eligible studies. If relevant measures were not reported, we used OpenEpi (version 3.01) to calculate risk ratios, incidence rate ratios, and accompanying 95% Confidence Intervals based on data provided in the studies. We used OpenEpi (version 3.01) to test outcomes using a two-tailed Mantel-Haenzel chi-square test with mid-exact *P*-values based on data provided in the studies. We indicate calculated values with *italics*.

## Findings

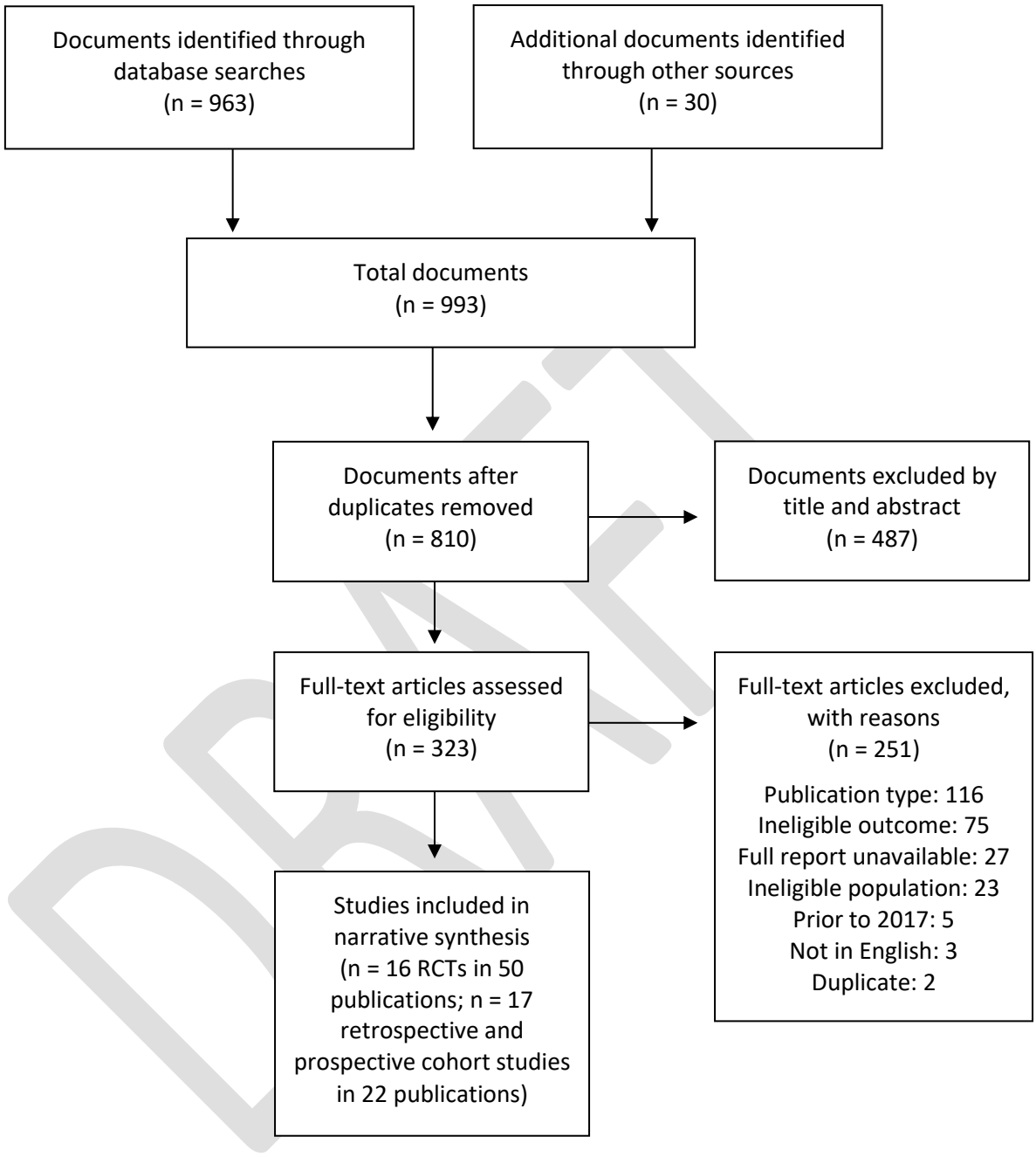
We included 15 parallel-arm, placebo-controlled, multisite, international RCTs[14-24,26-30] and 1 head-to-head multisite, international RCT[25] identified in 50 publications (Figure 1). The evaluated drugs in eligible RCTs covered 3 diabetic drug classes: GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors. Sample sizes of eligible trials ranged from 3,183 to 17,160.

We identified no head-to-head studies assessing CV outcomes between drug classes or CV outcomes with monotherapy vs. combination therapies. We identified 17 large prospective and retrospective cohort studies (in 22 publications[32,40-60]) to provide insight into drug class comparisons, monotherapy, and combination therapy when possible.

The remaining sections of this report are organized by drug class (i.e., GLP-1 agonists, SGLT-2 inhibitors, and DPP-4 inhibitors) and if available, evidence on differential effect between individuals with and without prior CVD.

Detailed evidence tables are in Appendix B, Table B1 (study characteristics) and Appendix B, Table B2 (efficacy and safety outcomes). Appendix C lists the bibliography of included studies and Appendix D lists the bibliography of excluded studies.

Figure 1. PRISMA Flow Diagram



## GLP-1 Agonists

We identified 7 RCTs[14-20] (in 16 publications) of poor- to fair-methodological quality and 1 post-hoc analysis[61] examining CVD outcomes with GLP-1 agonist drugs. Table 2 summarizes the findings (GRADE) of the primary research evidence for GLP-1 agonists. We downgraded the quality of evidence to moderate for all outcomes due to risk of bias and indirectness (i.e., applicability to a U.S. Medicaid population). We downgraded the quality of evidence for stroke and SAEs to low due to inconsistency (i.e., differing treatment effects within the class). We downgraded the quality of evidence to very low for MI due to additional inconsistency.

### *All-cause Mortality (moderate quality of evidence)*

- No evidence of an increased all-cause mortality risk was observed with albiglutide (Tanzeum), dulaglutide (Trulicity), lixisenatide (Adlyxin), or semaglutide (Ozempic).
- Exenatide ER (extended release, Bydureon) significantly reduced risk by 14% over placebo; however, the absolute difference in individuals reporting events was small between groups (6.9% vs. 7.9%; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.77 to 0.97; *P* = .02).
- Compared to placebo, liraglutide (Victoza) significantly reduced risk of all-cause mortality by 15% (8.2% vs. 9.6%; HR, 0.85; 95% CI, 0.74 to 0.97; *P* = .02), a significant effect given the number of events reported.
- Oral semaglutide (Rybelsus) significantly reduced risk by 51% (1.4% vs. 2.8%; HR, 0.49; 95% CI, 0.27 to 0.92) over placebo, a strong effect given the infrequency of events reported in the trial.

### *Stroke (low quality of evidence)*

- This outcome was not assessed in semaglutide. No evidence of an effect on stroke risk was observed with albiglutide, exenatide ER, liraglutide, lixisenatide, or oral semaglutide.
- Dulaglutide significantly reduced stroke risk by 24% over placebo (3.2% vs. 4.1%; HR, 0.76; 95% CI 0.62 to 0.94; *P* = .01); however, the absolute difference in stroke incidence between treatment groups was less than 1 percentage point.

### *Myocardial Infarction (very low quality of evidence)*

- This outcome was not assessed in semaglutide. No evidence of an effect on MI risk was observed with dulaglutide, exenatide ER, lixisenatide, or oral semaglutide.
- Albiglutide significantly reduced MI risk by 25% over SOC but the absolute risk reduction was small at 1 percentage point (4.0% vs. 5.0%; HR, 0.75; 95% CI, 0.61 to 0.90; *P* = .003).
- Liraglutide reduced MI risk by 14% over placebo, but the finding was marginally significant (6.3% vs. 7.3%; HR, 0.86; 95% CI, 0.73 to 1.00; *P* = .05). Overall, this is a modest effect given the number of events reported and a small absolute difference in events between groups.

### *Hospitalization for Heart Failure (moderate quality of evidence)*

- This outcome was not assessed in albiglutide and no evidence of an effect on hHF risk was observed with dulaglutide, exenatide ER, liraglutide, lixisenatide, semaglutide, or oral semaglutide.

### *Serious Adverse Events (low quality of evidence)*

- No evidence of an effect on risk for SAEs was observed with exenatide ER, liraglutide, or lixisenatide.
- Reductions in risk for SAEs were reported with albiglutide (27.3% vs. 35.5%; *risk ratio [RR], 0.77; 95% CI, 0.72 to 0.81; P < .0001*), dulaglutide (69.4% vs. 72.5%; *RR, 0.96; 95% CI, 0.93 to 0.98; P = .0006*), semaglutide (34.3% vs. 38.0%; *RR, 0.90; 95% CI, 0.82 to 0.99; P = .03*), and

oral semaglutide (18.9% vs. 22.5%; *RR, 0.84; 95% CI, 0.73 to 0.96; P = .02*) compared to a placebo.

Table 2. GRADE Summary of Findings for GLP-1 Agonists

| Outcome<br>Number of Studies | Quality of the Evidence | Relationship | Rationale |
|---|---|---|---|
| All-cause mortality<br>N = 7 studies<br>(in 16 publications) | Moderate<br>●●●○ | Small but meaningful reductions in risk within the class. | We downgraded one level for indirectness and risk of bias. |
| Stroke<br>N = 6 studies<br>(in 15 publications) | Low<br>●●○○ | No evidence of an effect within the class. | We downgraded one level for indirectness and risk of bias, and one level for inconsistency. |
| Myocardial infarction<br>N = 6 studies<br>(in 15 publications) | Very low<br>●○○○ | Uncertainty in the effect as a class, but some evidence of small reductions in risk. | We downgraded one level for indirectness and risk of bias, and two levels for high inconsistency. |
| Hospitalization for heart failure<br>N = 6 studies<br>(in 15 publications) | Moderate<br>●●●○ | No evidence of an effect within the class. | We downgraded one level for indirectness and risk of bias. |
| Serious adverse events<br>N = 7 studies<br>(in 16 publications) | Low<br>●●○○ | Small but meaningful reductions in risk within the class. | We downgraded one level for indirectness and risk of bias, and one level for inconsistency. |

*Note. For methods and interpretation of GRADE ratings, see Appendix A.*

Table 3 summarizes the primary study characteristics of eligible RCTs comparing GLP-1 agonists to placebo. All eligible RCTs were multisite studies conducted internationally, allowing background therapies for glycemic control and CV risk management in accordance to local guidelines.

We rated 3 RCTs as fair-methodological quality due to risk of bias such as failure to account for baseline differences between groups, short follow-up durations, placebo run-in periods, author conflicts of interest, or involvement of manufacturers in trial funding, data collection, data analysis, and interpretation. We rated 4 RCTs as poor-methodological quality due to use of fixed-dose escalation procedures, short follow-up durations, or variation in active treatment doses in addition to the previously mentioned potential biases. These factors may cause imprecision in findings (e.g., risk of random errors) or potentially create differential bias that favors active treatment.

A full study characteristics table is in Appendix B, Table B1 and a full evidence table of GLP-1 agonist outcomes is in Appendix B, Table B2.

Table 3. Eligible GLP-1 Agonist RCT Characteristics

| Trial Name; Trial Type; Author (Year); Generic Drug (Alternate Name); N<br>Study Quality | Trial Regimen | Study Population | Characteristics |
|---|---|---|---|
| HARMONY OUTCOMES<br>Multisite international<br>Hernandez et al. (2018)[14]<br>Albiglutide (Tanzeum)<br>Total N = 9,463<br>• 30 to 50 mg, n = 4,731<br>• Placebo, n = 4,732<br>Fair | • Weekly SC injections with SOC excluding GLP-1 agonists<br>• Potential to increase dose to 50 mg after 5 weeks if tolerated<br>• Follow-up visits occurred every 4 months | Individuals with type 2 diabetes and CVD<br>• Prior CAD, n = 6,678 (71%)<br>• Prior PAD, n = 2,354 (25%)<br>• Prior CBD, n = 2,342 (25%)<br>• Prior HF, n = 1,922 (20%) | • 31.0% Female<br>• Mean age: 64.1 years (SD, 8.7)<br>• Mean HbA1c: 8.7% (SD, 1.5)<br>• Mean diabetic duration: 14.15 years (SD, 8.75)<br>• Median follow-up: 1.6 years (IQR, 1.3 to 2.0) |
| REWIND<br>Multisite international<br>Gerstein et al. (2019)[19]<br>Dulaglutide (Trulicity)<br>Total N = 9,901<br>• 1.5 mg, n = 4,949<br>• Placebo, n = 4,952<br>Fair | • Weekly SC injections with SOC (if currently taking) and up to 2 oral AHAs excluding GLP-1 agonists or pramlintide<br>• Eligibility required 100% compliance to 3-week single-blind placebo run-in<br>• Follow-up visits at 2 weeks, 3 months, 6 months, every 3 months for drug dispensing and every 6 months for assessment | Individuals with type 2 diabetes, BMI ≥ 23, and established CVD or CV risk factors<br>• Prior CVD n = 3,114 (31.5%)<br>• Prior MI or ischemic stroke, n = 2,035 (20.6%)<br>• Prior HF, n = 853 (8.6%) | • 46.3% Female<br>• Mean age: 66.2 years (SD, 6.5)<br>• Median HbA1c: 7.2% (IQR, 6.6 to 8.1)<br>• Median diabetic duration: 9.5 years (IQR, 5.5 to 14.5)<br>• Median follow-up: 5.4 years (IQR, 5.1 to 5.9) |
| EXSCEL<br>Multisite international<br>Holman et al. (2019)[15]<br>Exenatide ER (Bydureon)<br>Total N = 14,752<br>• 2 mg, n = 7,356<br>• Placebo, n = 7,396<br>Poor | • Weekly SC injections with SOC up to 3 oral AHAs, insulin, or insulin with up to 2 oral AHAs excluding GLP-1 agonists<br>• Follow-up visits at 1 week, 2 months, 6 months, and every 6 months after | Individuals with type 2 diabetes with or without prior CVD<br>• Prior CVD, n = 10,782 (73.1%)<br>• No CVD, n = 3,970 (26.9%)<br>• Prior CAD, n = 7,794 (52.8%)<br>• Prior CBD, n = 2,509 (17.0%)<br>• Prior PAD, n = 2,800 (19.0%)<br>• Prior CHF, n = 2,389 (16.2%) | • 38.0% Female<br>• Median Age: 62 years (IQR, 56 to 68)<br>• Median HbA1c: 8.0% (IQR, 7.3 to 8.9)<br>• Median diabetic duration: 12 years (IQR, 7.0 to 17.5)<br>• Median follow-up: 3.2 years (IQR, 2.2 to 4.4) |

| Trial Name; Trial Type; Author (Year); Generic Drug (Alternate Name); N<br>Study Quality | Trial Regimen | Study Population | Characteristics |
|---|---|---|---|
| LEADER<br>Multisite international<br>Marso et al. (2016)[17]<br>Liraglutide (Victoza)<br>Total N = 9,340<br>• 1.8 mg, n = 4,668<br>• Placebo, n = 4,672<br>Fair | • Daily SC injections with SOC excluding pramlintide, GLP-1 agonists, or DPP-4 inhibitors<br>• Eligibility required ≥ 50% compliance to 2- to 3-week open-label placebo run-in<br>• Follow-up visits at 1 month, 3 months, 6 months, then every 6 months until trial end | Individuals with type 2 diabetes ≥ 18 years with established CVD or CV risk factors<br>• Prior CVD, n = 6,764 (72.4%)<br>• Prior CKD, n = 2,307 (24.7%)<br>• Prior CVD & CKD, n = 1,473 (15.8%)<br>• Prior HF, n = 1,667 (17.8%) | • 35.7% Female<br>• Mean age: 64.3 years (SD, 7.2)<br>• Mean HbA1c: 8.7% (SD, 1.6)<br>• Mean diabetic duration: 12.8 years (SD, 8.1)<br>• Median follow-up: 3.8 years* |
| ELIXA<br>Multisite international<br>Pfeffer et al. (2015)[16]<br>Lixisenatide (Adlyxin)<br>Total N = 6,068<br>• 10 to 20 µg, n = 3,034<br>• Placebo, n = 3,034<br>Poor | • Daily SC injections with SOC excluding GLP-1 agonists or DPP-4 inhibitors<br>• Fixed-dose escalation of 10 µg for 2 weeks & increased to 20 µg at investigator discretion<br>• Eligibility required 1-week unblinded placebo run-in<br>• Follow-up schedule was not reported | Individuals with type 2 diabetes with an ACS event within 180 days of screening<br>• Prior HF, n = 1,358 (22.4%)<br>• Prior CABG, n = 507 (8.4%)<br>• Prior stroke, n = 331 (5.5%)<br>• Prior PAD, n = 466 (7.7%)<br>• Prior AF, n = 366 (6.0%) | • 30.7% Female<br>• Mean age: 60.3 years (SD, 9.6)<br>• Mean diabetic duration: 9.3 years (SD, 8.3)<br>• Mean HbA1c: 7.65% (SD, 1.3)<br>• Median follow-up: 25 months* |
| SUSTAIN-6<br>Multisite international<br>Marso et al. (2016)[18]<br>Semaglutide (Ozempic)<br>Total N = 3,297<br>• 0.5 mg, n = 826<br>• 1.0 mg, n = 822<br>• 0.5 mg Placebo, n = 824<br>• 1.0 mg Placebo, n = 825<br>Poor | • Weekly SC injections with SOC excluding DPP-4 inhibitors or GLP-1 agonists<br>• Fixed-dose escalation of 0.25 mg for 4 weeks, 0.5 mg for an additional 4 weeks, until reaching maintenance dose of 0.5 or 1.0 mg<br>• Follow-up visits quarterly for a minimum of 104 weeks | Individuals with type 2 diabetes and established CVD or at CV risk<br>• Prior CKD, n = 353 (10.7%)<br>• Prior HF, n = 777 (23.6%)<br>• Prior MI, n = 1,072 (32.5%)<br>• Prior CVD, n = 1,940 (58.8%)<br>• Prior CKD & CVD, n = 442 (17%)<br>• CV risk, n = 560 (17%) | • 39.3% Female<br>• Mean age: 64.6 years (SD, 7.4)<br>• Mean diabetic duration: 13.9 years (SD, 8.11)<br>• Mean HbA1c: 8.7% (SD, 1.46)<br>• Median follow-up: 2.1 years* |

| Trial Name; Trial Type; Author (Year); Generic Drug (Alternate Name); N<br>Study Quality | Trial Regimen | Study Population | Characteristics |
|---|---|---|---|
| PIONEER-6<br>Multisite international<br>Husain et al. (2019)[20]<br>Oral semaglutide (Rybelsus)<br>Total N = 3,183<br>• 3 mg, n = 1,591<br>• Placebo, n = 1,592<br>Poor | • Daily oral administration with SOC excluding GLP-1 agonists or DPP-4 inhibitors<br>• Fixed-dose escalation until target maximum of 14 mg reached<br>• Follow-up visits occurred every 6 to 7 weeks in-person or via telephone | Individuals with type 2 diabetes and established CVD or CVD risk factors<br>• Prior CVD, n = 2,695 (84.7%)<br>• CV risk, n = 488 (15.3%)<br>• Prior MI, n = 1,150 (36.1%)<br>• Prior HF, n = 388 (12.2%)<br>• Prior CHD, n = 731 (23.0%) | • 31.6% Female<br>• Mean age: 66 years (SD, 7)<br>• Mean diabetic duration 14.9 years (SD, 8.5)<br>• Mean HbA1c: 8.2% (SD, 1.6)<br>• Median time in trial: 15.9 months (range 0.4 to 20.0) |

*Note. * Denotes interquartile range, standard deviation, or range was not reported. Abbreviations. ACS: acute coronary syndrome; AF: atrial fibrillation; AHA: antihyperglycemic agents; BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CBD: cerebrovascular disease; CHD: coronary heart disease; CHF: congestive heart failure; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin test of blood glucose (sugar); HF: heart failure; IQR: interquartile range; MI: myocardial infarction; PAD: peripheral artery disease; RCT: randomized controlled trial; SC: subcutaneous; SD: standard deviation; SOC: standard of care.*

### *Albiglutide*

We identified 1 fair-methodological quality RCT (HARMONY OUTCOMES[14]) investigating the effectiveness and safety of albiglutide (Tanzeum) among individuals with type 2 diabetes and established CVD (defined in Table B1). A pooled safety analysis of the HARMONY phase 3 trials (HARMONY 1-8) was also identified.[62] The study was rated as fair quality because of failure to account for variation in active treatment dosage and short follow-up duration (median follow-up 1.6 years). At baseline, individuals randomized to albiglutide reported less usage of angiotensin-converting-enzyme (ACE) inhibitors (48% vs. 50%), but more usage of angiotensin receptor blockers (ARB; 34% vs. 32%) and insulin (60% vs. 58%) than the placebo group.[62] Additionally, the manufacturer sponsored the study and was involved in the data collection, analysis, and interpretation.

#### *Findings*

In the HARMONY OUTCOMES[14] trial, albiglutide significantly reduced the risk of major adverse cardiovascular events (MACE) by 22% (7.1% vs. 9.0%; HR, 0.78; 95% CI, 0.68 to 0.90; *P* = .0006) compared to a placebo. By individual MACE outcomes, albiglutide significantly reduced MI risk by 25% (4.0% vs. 5.0%; HR, 0.75; 95% CI, 0.61 to 0.90; *P* = .003), but the absolute reduction was 1 percentage point. Albiglutide did not reduce the risk for CV death, stroke, all-cause mortality, or the composite of CV death or hHF (all *P* > .05, Table B2). Treatment discontinuation due to AEs (9.0% vs. 6.0%) and injection-site reactions (2.0% vs. 1.0%) were higher with albiglutide but not significantly different between treatment groups.[14] A significant 23% reduction in SAEs was observed with albiglutide over placebo (27.3% vs. 35.5%; *RR, 0.77, 95% CI, 0.72 to 0.81; P < .0001*). Among SAEs, albiglutide increased the risk of a bilirubin level two or more times the upper limit of normal by 71%, pancreatitis by 43%, pancreatic cancer by 20%, hepatobiliary disorders by 24%, and hematological neoplasia by 80%, when compared with placebo treatment (Table B2). A pooled safety analysis by Ahren et al.[62] reported similar findings for AEs leading to discontinuation and injection-site reactions. However, more occurrences were observed for atrial fibrillation, appendicitis, and pneumonia among those receiving albiglutide (Table B2). Ahren et al.[62] report hypoglycemia occurred more frequently when albiglutide was used with sulfonylurea or insulin relative to combination therapy without sulfonylurea or insulin (Table B2).

### *Dulaglutide*

We identified 1 fair-methodological quality RCT (REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes [19]) assessing the effect of dulaglutide (Dulicity) among individuals with type 2 diabetes with or at risk of CVD (defined in Table B1). We rated this RCT as fair for manufacturer funding and requiring 100% adherence to a 3-week single-blind placebo run-in to be eligible for randomization,[19] which may have artificially reduced the number of AEs related to treatment. The dulaglutide group had fewer individuals using other non-specified blood pressure drugs at baseline (55.9% vs. 57.2%).[19] Additionally, the manufacturer funded the trial.

#### *Findings*

In the REWIND[19] trial, dulaglutide significantly reduced MACE risk by 22% (12.0% vs. 13.4%; HR, 0.88; 95% CI, 0.79 to 0.99; *P* = .03) compared to placebo. Among individual MACE components, dulaglutide had no evidence of an effect on risk of CV death or nonfatal MI (all *P* > .05, Table B2).[19] Dulaglutide significantly reduced risk for nonfatal stroke 24% compared to placebo but the absolute risk reduction was less than 1 percentage point (2.7% vs. 3.5%; HR, 0.76; 95% CI, 0.61 to 0.95; *P* = .02, Table B2). No evidence of an effect on risk of MI, CV death, all-cause mortality, hHF, or hospitalization for unstable angina (hUA) was observed with dulaglutide (all *P* > .05,

Table B2).[19] Stroke risk was significantly reduced by 24% with dulaglutide over placebo (3.2% vs. 4.1%; HR, 0.76; 95% CI, 0.62 to 0.94; *P* = .01). No evidence of an effect on risk of MACE was found for prior CVD, body mass index (BMI), sex, age, diabetic duration, or between baseline glycated hemoglobin test of blood glucose (HbA1c) < 7.2% vs. ≥ 7.2% (all *P* > .05, Table B2).[19] Subgroup analyses found a significant difference in MACE risk by geographic location (*P* = .008, Table B2), which may suggest variation in local guidelines for background therapy influenced MACE outcomes.[19] Dulaglutide significantly reduced risk of SAEs when compared to placebo (*69.4% vs. 72.5%; RR, 0.96 95% CI, 0.93 to 0.98; P = .0006*). Individuals randomized to dulaglutide were significantly more likely to report endocrine disorder-related SAEs (0.5% vs. 0.2%; *P* = .05) and gastrointestinal issues (47.4% vs. 34.1%; *P* < .001) than those randomized to placebo.[19]

### *Exenatide ER*

We identified 1 poor-methodological quality RCT (EXSCEL, the EXenatide Study of Cardiovascular Event Lowering),[15] in 2 publications, assessing exenatide ER (Bydureon) among individuals with type 2 diabetes with or without previous CVD (defined in Table B1). We rated this study as poor-methodological quality due to study funding being provided by the manufacturer and significant differences between groups in baseline medications. Exenatide recipients reported significantly higher usage of concomitant lipid-lowering medications (77.9% vs. 76.2%, *P* = .01), statins (74.3% vs. 72.7%, *P* = .03), and SGLT-2 inhibitors (1.2% vs. 0.7%, *P* = .01), specifically dapagliflozin (0.9% vs. 0.4%, *P* = .008) than placebo recipients.[15] Usage of niacin was significantly higher (1.5% vs. 2.0%, *P* = .02) in the placebo group.[15]

#### *Findings*

In the EXSCEL[15] trial, exenatide ER had a marginally significant effect on MACE risk (11.4% vs. 12.2%; HR, 0.91; 95% CI, 0.83 to 1.00; *P* = .06) or individual MACE components when compared to placebo (Table B2). All-cause mortality risk was reduced 14% with exenatide ER over placebo; however, the absolute risk reduction was 1 percentage point (6.9% vs. 7.9%; HR, 0.86; 95% CI, 0.77 to 0.97; *P* = .02). No evidence of an effect on risk of MI, stroke, hHF, or hospitalization for acute coronary syndrome was observed with exenatide ER (all *P* > .05, Table B2).[15] Premature treatment discontinuation was similar among treatment groups (43% exenatide, 45.2% placebo) with the leading cause reported as 'patient-decision' in both groups.[15] No significant difference in risk of SAEs was found between those treated with exenatide ER and placebo (16.8% vs. 16.6%; *RR, 1.01; 95% CI, 0.94 to 1.09; P = .71*).

A significant difference (*P* = .005) in the effect of exenatide ER on MACE risk was found between participant age groups, with a 20% reduced risk for MACE among participants aged ≥ 65 years and no evidence of an effect on those < 65 years (Table B2).[15] Secondary analysis of CV outcomes stratified by baseline heart failure (HF) status by Fudim et al.[63] found no evidence of an effect with exenatide ER on the risk of MACE, stroke, MI, CV death, or all-cause mortality for individuals with baseline HF (Table B2). Risk of all-cause mortality was reduced 21% with exenatide ER among individuals without prior HF (HR, 0.79; 95% CI, 0.68 to 0.92) but had no evidence of an effect on individuals with prior HF (HR, 1.05; 95% CI, 0.85 to 1.29; *P* = .03).[63] Similarly, risk of all-cause mortality or hHF risk was reduced 19% for those without prior HF (HR, 0.81; 95% CI 0.71 to 0.93), but had no evidence of an effect on those with prior HF (HR, 1.07; 95% CI, 0.89 to 1.29; *P* = .02).[63] No significant difference in incidence of CV outcomes was reported between left-ventricle ejection fraction (LVEF) subgroups (LVEF < 40 vs. ≥ 40) treated with exenatide ER compared to placebo.[63]

### *Liraglutide*

We identified 1 fair-methodological quality RCT (LEADER, Liraglutide Effect and Action in Diabetes),[17] in 8 publications, assessing the effect of liraglutide (Victoza) among individuals with type 2 diabetes and established CVD or CV risk factors (defined in Table B1). During LEADER, "the median daily dose of liraglutide was 1.78 mg (interquartile range [IQR] 1.54 to 1.79), including periods during which the patients did not receive liraglutide."[17] We rated this RCT as fair for failure to account for liraglutide dosage differences in statistical analyses and requiring a 2- to 3-week maximum open-label placebo run-in prior to randomization, which may have artificially reduced the number of AEs related to treatment. Significantly more liraglutide recipients than placebo recipients were using beta blockers at baseline (56.8% vs. 54.1%; *P* = .009).[17] Additionally, the drug manufacturer funded the trial, selected derived data rather than raw data for analysis, and selected and paid the data analysis team.

#### *Findings*

In the LEADER[17] trial, liraglutide significantly reduced risk of MACE by 13% over placebo (13.0% vs. 14.9%; HR, 0.87; 95% CI, 0.78 to 0.97; *P* = .01). Among individual MACE components, liraglutide significantly reduced risk of CV death by 22% (4.7% vs. 6.0%; HR, 0.78; 95% CI, 0.66 to 0.93; *P* = .01), but the absolute risk reduction was less than 2 percentage points. Liraglutide demonstrated no evidence of an effect on risk of nonfatal stroke, nonfatal MI, hHF, or hUA (all *P* > .05, Table B2). All-cause mortality risk was significantly reduced by 15% with liraglutide over placebo; however, the absolute risk reduction was less than 1.5 percentage points (8.2% vs. 9.6%; HR, 0.85; 95% CI, 0.74 to 0.97; *P* = .02). Liraglutide demonstrated no evidence of an effect on risk of SAEs (49.7% vs. 50.4%; *RR, 0.99; 95% CI, 0.95 to 1.03; P = .51*). During the trial period, liraglutide significantly increased the likelihood of experiencing injection-site reactions (*P* = .002) and AEs leading to discontinuation (*P* < .001, Table B2) relative to placebo.[17] AEs leading to discontinuation were most frequently attributed to nausea, vomiting, diarrhea, abdominal pain, abdominal discomfort, and decreased appetite, which were all significantly higher among liraglutide recipients (all *P* < .05, Table B2).[17]

Relative to placebo, no statistically significant increase in risk of neoplasm events was found with liraglutide despite a higher number of events reported (Table B2).[64] Liraglutide significantly increased the risk of acute gallstone disease (3.1% vs. 1.9%; RR, 1.61; *P* < .001) relative to placebo.[65] Similar significant increases in risk for gallbladder and biliary-tract related events and complicated gallbladder stones occurred with liraglutide when compared to placebo (all *P* < .05, Table B2).[65] Nauck et al.[65] reported that weight loss of 1 kg during the trial was associated with an approximately 4% increased risk of a gallbladder- or biliary tract-related event. Steinberg et al.[66] did not find evidence to support an increased risk of acute pancreatitis with liraglutide or interaction between treatment and baseline characteristics for this risk. Liraglutide did not reduce time to first diabetes-related foot ulcer (DFU) events (all *P* > .05, Table B2).[67] No significant differences were found between treatments for all DFU events including recurrent events or between those with and without baseline DFU history (all *P* > .05, Table B2).[67] DFU-related amputation risk was significantly reduced 35% with liraglutide (HR, 0.65; 95% CI, 0.45 to 0.95; *P* = .03) and was sustained 1-year post-randomization.[67] Risk reduction was more pronounced for major amputations (*P* = .06) than minor amputations (*P* = .17).[67]

Post-hoc analysis[68] found significant differences in the effect of liraglutide between individuals with a baseline estimated glomerular filtration rate (eGFR) < 60 mL who experienced a 31% reduction in risk of MACE (HR, 0.69; 95% CI, 0.57 to 0.85), a 49% reduction in nonfatal stroke risk (HR, 0.51; 95% CI, 0.33 to 0.80), and a 47% reduction in risk of any stroke (HR, 0.53; 95% CI,

0.36 to 0.79), but had no evidence of an effect for individuals with a baseline eGFR ≥ 60 mL. Liraglutide reduced MACE risk by 18% (HR, 0.82; 95% CI 0.71 to 0.95) and CV death risk by 33% (HR, 0.67; 95% CI 0.53 to 0.85) among individuals with a baseline history of single vascular disease, but had no evidence of an effect on individuals with baseline history of polyvascular disease (TableB2).[69] In contrast, liraglutide reduced nonfatal MI risk for those with baseline polyvascular disease by 35% (HR, 0.65; 95% CI 0.57 to 0.89) but had no evidence of an effect on risk among individuals with baseline single vascular disease (Table B2).[69] The effect of liraglutide on hHF risk was significantly different between baseline CVD status subgroups (*P* = .03).[70] A smaller number of hHF events occurred with liraglutide among individuals with MI or stroke history (5.9% vs. 7.3%) and individuals with CVD without prior MI or stroke (3.4% vs. 4.7%) compared to placebo, but those with only CV risk factors had similar event rates to placebo (0.7% vs. 0.6%).[70]

### *Lixisenatide*

We identified 1 poor-methodological quality RCT (ELIXA, the Evaluation of Lixisenatide in Acute Coronary Syndrome[16]) assessing the effects of lixisenatide (Adlyxin) in individuals with type 2 diabetes and a recent acute coronary syndrome (ACS) event (defined in Table B1). During ELIXA, participants received study drugs on a fixed-dose escalation procedure starting at 10 µg for 2 weeks and could be increased to 20 µg at the investigator' discretion.[16] We rated this trial as poor for failure to account for lixisenatide dosage differences in statistical analysis, short follow-up duration (median follow-up of 25 months), potential group imbalances, and requiring a 1-week unblinded placebo run-in period which may have artificially reduced the number of AEs related to treatment. Additionally, the drug manufacturer funded the trial. At baseline, the lixisenatide group reported fewer individuals identifying as White (74.4% vs. 76.4%), identifying as of Hispanic ethnicity (28.5% vs. 29.8%), with prior stroke (4.7% vs. 6.2%), with prior atrial fibrillation (5.8% vs. 6.3%), and with hypertension at randomization (75.6% vs. 77.1%) than the placebo group.[16] Concomitant baseline usage of beta blockers (83.6% vs. 85.3%) and sulfonylureas (32.6% vs. 33.5%) was lower in the lixisenatide group. However, this group reported more usage of statins (93.3% vs. 92.2%), metformin (67.2% vs. 65.4%), and other non-specified diabetes medications (5.8% vs. 4.7%) than the placebo group.[16]

#### *Findings*

In the ELIXA[16] trial, lixisenatide had no evidence of an effect on risk of MACE (13.4% vs. 13.2%; HR, 1.02; 95% CI, 0.89 to 1.17; *P* = .81) or individual MACE components in individuals with a recent ACS event over placebo (Table B2). Similarly, lixisenatide demonstrated no evidence of an effect on risk of all-cause mortality, hHF, MI, stroke, or hUA (all *P* > .05, Table B2). Pfeffer et al.[16] report no significant interactions between pre-specified or post-hoc subgroups and treatment, including individuals with baseline history of HF who did not benefit from lixisenatide (HR, 0.93; 95% CI, 0.66 to 1.30). AEs leading to permanent treatment discontinuation occurred significantly more often in the lixisenatide group (11.4% vs. 7.2%; *RR, 1.54; 95% CI, 1.31 to 1.81; P* < .001). Lixisenatide did not affect risk for SAEs compared to placebo (20.6% vs. 22.1%; *RR, 1.07; 95% CI, 0.97 to 1.18; P = .17*). Gastrointestinal AEs (4.9% vs. 1.2%; *P* < .001) and nausea or vomiting were significantly higher in the lixisenatide group (4.1% vs. 0.5%; *P* < .001).[16]

### *Semaglutide*

We identified 1 poor-methodological quality RCT (SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes[18]) evaluating semaglutide (Ozempic) in individuals with type 2 diabetes and with kidney disease, CVD, both, or CV risk factors (defined in Table B1). The average treatment duration differed between

treatments: 86.5% of the total study time in the semaglutide group (0.5 mg 87.7%; 1.0 mg 85.3%), compared to 89.5% in the placebo group (0.5 mg 89.4%; 1.0 mg 89.6%).[18] We rated this trial as poor for differences in average treatment exposure duration, short follow-up (median 2.1 years), potential group imbalances, using a fixed-dose escalation procedure, and a relatively small sample size. Additionally, the manufacturer funded the trial and was involved in the trial design, site-monitoring, data collection, and analysis. At baseline, the semaglutide group had fewer individuals with severe renal impairment (e.g., eGFR, 15 to < 30 mL; 0.5 mg, 2.4% vs. 3.0%; 1.0 mg, 2.6% vs. 3.5%), prior ischemic stroke (0.5 mg, 10.8% vs. 11.7%; 1.0 mg, 10.8% vs. 13.2%), and prior MI (0.5 mg, 32.2% vs. 32.4%; 1.0 mg, 32.1% vs. 33.3%).[18] Baseline concomitant medications varied between groups including biguanide usage (0.5 mg, 74.7% vs. 71.1%; 1.0 mg, 72.3% vs. 74.8%), sulfonylurea usage (0.5 mg, 42.3% vs. 44.1%; 1.0 mg, 42.5% vs. 42.3%), basal insulin (0.5 mg, 31.0% vs. 31.4%; 1.0 mg, 31.5% vs. 33.0%), and basal plus bolus insulin (0.5 mg, 27.0% vs. 26.6%; 1.0 mg, 26.5% vs. 25.1%).[18] The 0.5 mg-semaglutide group contained fewer individuals with prior ischemic heart disease (59.7% vs. 61.9%) at baseline than the volume-matched placebo group.[18] Individuals randomized to 1.0 mg semaglutide reported a longer average duration of diabetes (14.1 years [SD, 8.17] vs. 13.2 years [SD, 7.44]) and never smoking more often (44.3% vs. 42.2%), but fewer prior hemorrhagic stroke (2.9% vs. 3.5%) and prior HF (21.9% vs. 25.0%), than the volume-matched placebo group at baseline.[18]

#### *Findings*

In the SUSTAIN-6[18] trial, semaglutide significantly reduced MACE risk by 26% over placebo, but the magnitude of the absolute risk reduction was very small (6.6% vs. 6.9%; HR, 0.74; 95% CI, 0.58 to 0.95; *P* = .02). No significant differences in risk of MACE or individual MACE components were found between 0.5 mg and 1.0 mg semaglutide doses (Table B2).[18] Semaglutide demonstrated no evidence of an effect on risk of all-cause mortality, hHF, or hUA compared to placebo (all *P* > .05, Table B2).[18] Premature treatment discontinuation occurred in 20% of all participants and was higher among semaglutide recipients (13.0% vs. 6.7%).[18] Semaglutide significantly reduced the risk of SAEs over placebo (34.3% vs. 38.0%; *RR, 0.90; 95% CI, 0.82 to 0.99; P = .03*). Semaglutide recipients were more likely to experience gastrointestinal disorders, occurring most often during the first 30 weeks of treatment (4.5% vs. 3.0%; *RR, 1.30; 95% CI 1.19 to 1.42; P* value not reported).[18] Individuals treated with semaglutide were at a significant, nearly doubled risk of retinopathy complications (3.0% vs. 1.8%; HR, 1.76; 95% CI, 1.11 to 2.78; *P* = .02) and retinal photocoagulation (2.3% vs. 1.2%; HR, 1.91; 95% CI, 1.11 to 3.28; *P* = .02) relative to those treated with placebo.[18] Semaglutide significantly reduced the risk of new or worsening nephropathy by 36% over placebo (3.8% vs. 6.1%; HR, 0.64; 95% CI 0.46 to 0.88; *P* = .005). Relative to placebo, benign neoplasms were 56% more likely with 1.0 mg of semaglutide (6.6% vs. 4.1%; *RR, 1.56; 95% CI 1.03 to 2.37; P = .04*) but not found at 0.5 mg or when doses were pooled (Table B2).[18]

### *Oral Semaglutide*

We identified 1 poor-methodological quality RCT (PIONEER-6, Peptide Innovation for Early Diabetes Treatment[20]) evaluating oral semaglutide (Rybelsus) in individuals with type 2 diabetes with established CVD and/or chronic kidney disease or at CV risk (defined in Table B1). Only 75% of the trial participants received the study drug for longer than 1 year.[20] We rated this trial as poor for short follow-up duration (median follow-up 15.9 months), inadequate treatment exposure duration, potential group imbalances, using a fixed-dose escalation procedure, and using a relatively small sample size. Additionally, the manufacturer funded the trial and was involved in the trial design, site-monitoring, data collection, and analysis. At baseline, individuals randomized to oral semaglutide were more often than those randomized to placebo to be aged

50 to 64 years (44.0% vs. 39.8%), have a BMI < 30 (40.9% vs. 39.5%), have an HbA1c ≤ 8.5% (67.7% vs. 66.4%), and be current smokers (11.6% vs. 10.4%).[20] However the placebo group had more individuals ≥ 65 years (56.0% vs. 60.2%), with a BMI ≥ 30 (59.1% vs. 60.5%), and HbA1c > 8.5% (32.3% vs. 33.6%) than the oral semaglutide group.[20]

#### *Findings*

During the PIONEER-6[20] trial, oral semaglutide demonstrated no evidence of an effect on MACE risk when compared to placebo (3.8% vs. 4.8%; HR, 0.79; 95% CI, 0.57 to 1.11; *P* = .17). Oral semaglutide reduced the risk of CV death by 49%; a meaningful reduction considering the infrequent number of overall events (0.9% vs. 1.9%; HR, 0.51; 95% CI, 0.31 to 0.84; *P* value not reported). No evidence of an effect on risk of stroke, MI, hUA, or hHF was observed with oral semaglutide (Table B2). All-cause mortality risk was reduced by 51% with oral semaglutide when compared to placebo (1.4% vs. 2.8%; HR, 0.49; 95% CI, 0.27 to 0.92; *P* value not reported) with an absolute risk reduction of 1.4 percentage points, which is significant considering the infrequency of the event. Subgroup analyses did not find statistically significant differences in treatment effect for participant baseline characteristics, including history of stroke prior to randomization (*P* = .16), or between individuals with established CVD vs. CV risk factors (*P* = .44).[20] The oral semaglutide group was more likely to permanently discontinue treatment (11.6% vs. 6.5%; *RR, 1.69; 95% CI, 1.34 to 2.13; P < .001*), primarily driven by significantly higher risk of gastrointestinal AE (6.8% vs. 1.6%; *RR, 3.99; 95% CI, 2.59 to 6.04; P < .0001*).[20] The risk for severe hypoglycemia AEs was higher in the oral semaglutide group but not significantly different from the placebo group (1.4% vs. 0.8%, Table B2), and individuals in both groups reporting an event were taking concomitant insulin or sulfonylurea at the time of the event.[20] Oral semaglutide led to a significant increase in risk for metabolism and nutrition disorder –related AEs, nearly 3 times higher than placebo treatment (1.2% vs. 0.4%; *RR, 2.70 (1.14 to 6.39); P = .02*). Oral semaglutide significantly reduced risk of SAEs by 16% when compared to placebo (18.9% vs. 22.5%; *RR, 0.84; 95% CI, 0.73 to 0.96; P = .02*).

### *Within-Class Effects*

#### *Liraglutide vs. Semaglutide*

We identified 1 additional post-hoc analysis of the LEADER and SUSTAIN-6 trial data by Verma et al.[61] analyzed CV outcomes stratified by participants' baseline duration with type 2 diabetes: < 5 years, 5 to < 15, 15 to < 25, and ≥ 25 years. When compared to individuals with a disease duration less than 5 years, the occurrence of MACE events and CV death increased as disease duration increased in the LEADER trial (Table B2). No significant interaction was found between diabetic duration and treatment for MACE (*P* = .53) or CV death (*P* = .54) in LEADER (Table B2). The risk of the primary MACE outcome was lower in SUSTAIN-6 than LEADER for each diabetic duration subgroup but the risk of CV death appeared to increase with diabetic duration in SUSTAIN-6 (Table B2). No significant interaction was found between diabetic duration and treatment for MACE (*P* = .75) or CV death (*P* = .24) in SUSTAIN-6 (Table B2).

## DPP-4 Inhibitors

We identified 4 RCTs[21-24] (in 13 publications) of poor- to fair-methodological quality and 1 head-to-head RCT[25] of poor-methodological quality (in 1 publication) assessing CVD outcomes with linagliptin. Table 4 summarizes the findings (GRADE ratings) of the primary research evidence for DPP-4 inhibitors. We downgraded the quality of evidence to moderate for all outcomes due to risk of bias and indirectness (i.e., applicability to a U.S. Medicaid population). We downgraded the quality of evidence for MI and hHF to low due to additional inconsistency (e.g., differing treatment effects within the DPP-4 inhibitor class).

*All-Cause Mortality (moderate quality of evidence)*

- No evidence of an effect on all-cause mortality risk was observed with alogliptin (Nesina), saxagliptin (Onglyza), or sitagliptin (Januvia). Linagliptin (Tradjenta) had no evidence of an effect when compared to placebo or glimepiride.

*Stroke (moderate quality of evidence)*

- This outcome was not assessed in alogliptin and no evidence of an effect on stroke risk was observed with saxagliptin or sitagliptin. Linagliptin had no evidence of an effect when compared to placebo or glimepiride.

*Myocardial Infarction (low quality of evidence)*

- This outcome was not assessed in alogliptin and no evidence of an effect on MI risk was observed with saxagliptin or sitagliptin. Linagliptin had no evidence of an effect when compared to placebo or glimepiride.

*Hospitalization for Heart Failure (low quality of evidence)*

- This outcome was not assessed in alogliptin and no evidence of an effect on hHF risk was observed with sitagliptin. Linagliptin had no evidence of an effect on risk of hHF when compared to placebo or glimepiride.
- Saxagliptin significantly increased hHF risk 27% over placebo (3.5% vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; *P* = .007); however, the absolute difference in risk was small at less than one percentage point.

*Serious Adverse Events (moderate quality of evidence)*

- No evidence of an effect on risk for SAEs was observed with alogliptin or sitagliptin. Linagliptin had no evidence of an effect when compared to placebo or glimepiride.
- A significant 5% increase in risk for SAEs was found with saxagliptin over placebo (41.4% vs. 39.6%; *RR, 1.05; 95% CI, 1.01 to 1.09; P = .02*), a moderate effect given the number of events reported and absolute difference in events between treatment groups.

Table 4. GRADE Summary of Findings for DPP-4 Inhibitors

| Outcome<br>Number of Studies | Quality of the Evidence | Relationship | Rationale |
|---|---|---|---|
| All-cause mortality<br>N = 5 studies<br>(in 14 publications) | Moderate<br>●●●○ | No evidence of an effect within the class. | We downgraded one level for indirectness and risk of bias |
| Stroke<br>N = 4 studies<br>(in 10 publications) | Moderate<br>●●●○ | No evidence of an effect within the class. | We downgraded one level for indirectness and risk of bias. |
| Myocardial infarction<br>N = 4 studies<br>(in 10 publications) | Low<br>●●○○ | No evidence of an effect within the class. | We downgraded one level for indirectness and risk of bias, and one level for inconsistency. |
| Hospitalization for heart failure<br>N = 4 studies<br>(in 10 publications) | Low<br>●●○○ | No evidence of an effect within the class, some evidence of increased risk. | We downgraded one level for indirectness and risk of bias, and one level for inconsistency. |
| Serious adverse events<br>N = 5 studies<br>(in 14 publications) | Moderate<br>●●●○ | No evidence of effect within the class, some evidence of a small, but increased risk. | We downgraded one level for indirectness and risk of bias. |

*Note. For methods and interpretation of GRADE ratings, see Appendix A.*

Table 5 summarizes the primary study characteristics of eligible RCTs comparing DPP-4 inhibitors to placebo and linagliptin to glimepiride. All eligible RCTs were multisite studies conducted internationally, allowing background therapies for glycemic control and CV risk management in accordance to local guidelines. This may limit applicability of findings to a U.S. Medicaid population due to potential inclusion of non-U.S. approved therapies and variation in access to quality health care.

We rated 1 RCT as fair-methodological quality for risk of bias due to short follow-up durations, variation in active treatment dosages, potential imbalances between groups, or manufacturer funding. However the risk of bias was mediated by statistical analysis conducted independently of the manufacturer. We rated 4 RCTs as of poor-methodological quality for additional lack of intention-to-treat (ITT) analysis, short follow-up duration, small sample size, or involvement of the manufacturers in trial design, data collection, and analysis.

A full characteristics table is in Appendix B, Table B1 and a full evidence table of DPP-4 inhibitor outcomes is in Appendix B, Table B2.

Table 5. Eligible DPP-4 Inhibitor RCT Characteristics

| Trial Name; Trial Type; Author (Year); Generic Drug (Alternate Name); N<br>Study Quality | Trial Regimen | Study Population | Characteristics |
|---|---|---|---|
| EXAMINE<br>Multisite international<br>White et al. (2013)[23]<br>Alogliptin (Nesina)<br>Total N = 5,380<br>• 25 mg, n = 1,929<br>• 12.5 mg, n = 694<br>• 6.25 mg, n = 78<br>• Placebo, n = 2,679<br>Poor | • Daily oral administration with SOC excluding additional DPP-4 inhibitors or GLP-1 agonists<br>• Dose stratified by eGFR (mL): 25 mg if eGFR ≥ 60, 12.5 mg if eGFR 30 to < 60, 6.25 mg if eGFR < 30<br>• Follow-up visits at 1, 3, 6, 9, 12 months and at 4-month intervals for the remaining trial duration | Individuals with type 2 diabetes ≥ 18 years and recent ACS 15 to 90 days prior to randomization<br>• Prior MI, n = 4,152 (77.2%)<br>• Prior hUA, n = 1,214 (22.6%)<br>• Prior CHF, n = 1,501 (27.9%)<br>• Prior PAD, n = 514 (9.5%) | • 32.0% Female<br>• Median age: 61 years*<br>• Median HbA1c: 8.0% (SD, 1.1)<br>• Median diabetic duration: 7.2 years (IQR, 2.7 to 13.7)<br>• Median follow-up: 18 months* (max 40) |
| CARMELINA<br>Multisite international<br>Rosenstock et al. (2019)[25]<br>Linagliptin (Tradjenta)<br>Total N = 6,979<br>• 5 mg, n = 3,494<br>• Placebo, n = 3,485<br>Poor | • Daily oral administration with SOC excluding GLP-1 agonists, DPP-4 inhibitors, or SGLT-2 inhibitors<br>• Required stable AHA dose ≥ 8 weeks prior to randomization<br>• Follow-up visits after 12 weeks and every 24 weeks until study end with final visit 30 days after stopping treatment | Individuals with type 2 diabetes ≥ 18 years with BMI ≤ 45 at CV and renal risk<br>• Prior HF, n = 1,873 (26.8%)<br>• Prior IHD, n = 4,081 (58.5%)<br>• Prior AF, n = 673 (9.6%)<br>• Prior CVD, n = 3,978 (57%)<br>• Prior KD, n = 5,165 (74%)<br>• CVD and KD, n = 2,303 (33%) | • 37.1% Female<br>• Mean age: 65.9 years (SD, 9.1)<br>• Mean HbA1c: 7.95% (SD, 1.0)<br>• Mean diabetic duration: 14.8 years (SD, 9.45)<br>• Median follow-up: 2.2 years (IQR, 1.6 to 3.0) |
| CAROLINA<br>Multisite international<br>Rosenstock et al. (2019)[25]<br>Linagliptin (Tradjenta)<br>Total N = 6,042<br>• 5 mg, n = 3,023<br>• 1 to 4 mg glimepiride, n = 3,010<br>Poor | • Daily oral administration with SOC<br>• Glimepiride started at 1 mg/day and up titrated to a max of 4 mg/day every 4 weeks for first 16 weeks of the trial<br>• Eligibility required 80% to 100% compliance with a 2-week placebo run-in period<br>• Follow-up visits at 16 weeks and every 16 weeks after until trial end | Individuals with early type 2 diabetes, HbA1c 6.5% to 8.5% with CV risk factors and/or established ASCVD<br>• Prior HF, n = 271 (4.5%)<br>• Prior CAD, n = 1,905 (31.6%)<br>• Prior PAD, n = 407 (6.7%)<br>• Prior CBD, n = 727 (12.0%)<br>• Prior ASCVD, n = 2,534 (42%) | • 40.0% Female<br>• Mean age: 64.0 years (SD, 9.5)<br>• Mean HbA1c: 7.2% (SD, 0.6)<br>• Median diabetic duration: 6.2 years (IQR, 2.95 to 11.05)<br>• Median follow-up: 6.3 years (IQR, 5.9 to 6.6) |

| Trial Name; Trial Type; Author (Year); Generic Drug (Alternate Name); N<br>Study Quality | Trial Regimen | Study Population | Characteristics |
|---|---|---|---|
| SAVOR-TIMI 53<br>Multisite international<br>Scirica et al. (2013)[22]<br>Saxagliptin (Onglyza)<br>Total N = 16,492<br>• 2.5 mg, n = 1,294<br>• 5.0 mg, n = 6,986<br>• Placebo, n = 8,212<br>Poor | • Daily oral administration with SOC excluding GLP-1 agonists or DPP-4 inhibitors<br>• Baseline eGFR ≤ 50 mL received 2.5 mg saxagliptin (n = 1,294) and remaining received 5 mg (n = 6,986)<br>• Follow-up visits every 6 months until trial end | Individuals with type 2 diabetes and CVD or CV risk factors<br>• Prior atherosclerotic disease n = 12,959 (78.6%)<br>• Prior MI, n = 6,237 (37.8%)<br>• Prior HF, n = 2,105 (12.8%) | • 33.1% Female<br>• Mean Age: 65 years (SD, 8.55)<br>• Mean HbA1c: 8.0% (SD, 1.4)<br>• Median diabetic duration: 10.3 years (IQR, 5.2 to 16.7)<br>• Median follow-up: 2.1 years (IQR, 1.8 to 2.3) |
| TECOS<br>Multisite international<br>Green et al. (2015)[24]<br>Sitagliptin (Januvia)<br>Total N = 14,671<br>• 100 mg, n = 6,646<br>• 50 mg, n = 686<br>• Placebo, n = 7,339<br>Fair | • Daily oral administration with SOC excluding GLP-1 agonists or DPP-4 inhibitors<br>• Baseline eGFR 30 and < 50 mL received 50 mg sitagliptin and eGFR ≥ 50 mL received 100 mg sitagliptin<br>• Required HbA1c 6.5% to 8.0% if treated with stable doses of 1 or 2 oral AHAs or insulin<br>• Follow-up visits at month 4, 8, 12 and then every 6 months until trial end; telephone follow-ups at month 15 and every 6 months until trial end | Individuals with type 2 diabetes ≥ 50 years with CVD<br>• Prior CVD, n = 10,863 (74.0%)<br>• Prior MI, n = 6,255 (42.6%)<br>• Prior CBD, n =3,588 (24.5%)<br>• Prior PAD, n = 2,433 (16.6%)<br>• Prior CHF, n = 2,643 (18.0%) | • 29.3% Female<br>• Mean Age: 65.5 years (SD, 8.0)<br>• Mean HbA1c: 7.2% (SD, 0.5)<br>• Mean diabetic duration: 11.6 years (SD, 8.1)<br>• Median follow-up: 3.0 years (IQR, 2.3 to 3.8) |

*Note. * Denotes interquartile range, standard deviation, or range was not reported. Abbreviations. ACS: acute coronary syndrome; AF: atrial fibrillation; AHA: antihyperglycemic agents; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CBD: cerebrovascular disease; CHF: congestive heart failure; CV: cardiovascular; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin test of blood glucose (sugar); HF: heart failure; hUA: hospitalization for unstable angina; IHD: ischemic heart disease; IQR: interquartile range; KD: kidney disease; MI: myocardial infarction; PAD: peripheral artery disease; RCT: randomized controlled trial; SD: standard deviation; SGLT-2: sodium-glucose cotransporter-2; SOC: standard of care.*

### *Alogliptin*

One poor-methodological quality RCT (EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard Care[23]), in 4 publications, assessed alogliptin in individuals with type 2 diabetes and recent ACS 15 to 90 days prior to randomization (defined in Table B1). We rated the study as poor quality for using a relatively small sample size, variation in active treatment dosage, potential group imbalances, and short follow-up time (median 18 months). Additionally, the manufacturer funded the trial and had voting representatives on the trial steering committee. At baseline the alogliptin group contained fewer current smokers (13.0% vs. 14.3%), and fewer individuals with hypertension (82.5% vs. 83.6%) or with an eGFR < 60 mL (28.6% vs. 29.6%), but more individuals with prior MI (88.4% vs. 87.5%) and an eGFR ≥ 60 mL (71.4% vs. 70.4%).[23] Baseline usage of thienopyridine (79.8% vs. 80.8%), insulin (29.4% vs. 30.3%), metformin (65.0% vs. 67.4%), calcium-channel blockers (21.7% vs. 22.8%), and renin-angiotensin system-blocking agents (81.5% vs. 82.5%) was lower in the alogliptin group.[23]

#### *Findings*

In the EXAMINE[23] trial, approximately 67% of all participants were exposed to the study drug for more than 1 year (68% alogliptin, 66.7% placebo).[23] Alogliptin had no evidence of an effect on risk of MACE, individual MACE components, all-cause mortality, or the composite of MACE or revascularization for unstable angina when compared to placebo (all $P > .05$, Table B2).[23] EXAMINE did not assess hHF outcomes. No evidence of an effect on risk of SAEs was reported with alogliptin comparted to placebo (33.6% vs. 35.5%; *RR, 0.95; 95% CI, 0.88 to 1.02; P = .13*). The effect of alogliptin on MACE risk was significantly different between baseline smoking status ($P = .03$), diabetic duration ($P = .01$), insulin use ($P = .02$), biguanide use ($P = .03$), renal impairment ($P = .05$), and geographic region ($P = .03$)[23], which may suggest variation in the study population influenced MACE outcomes. Individuals who were former smokers, had diabetes for 10 years or longer, used insulin at baseline, did not use baseline biguanide, had moderate or severe renal impairment, and were treated in the U.S., Canada, Western Europe, Australia, New Zealand, or the Middle East reported higher incidences of MACE with alogliptin (Table B2).[23]

Cavender et al.[71] reported that history of MI or revascularization prior to an EXAMINE qualifying ACS event significantly predicted occurrence of CV events (revascularization, unstable angina [UA], stroke, MI, or CV death). Alogliptin increased the number of initial CV events (20.2% vs. 12.2%) and recurrent CV events (20.5% vs. 12.6%), but was not significantly different when compared to placebo ($P = .52$).[71] Sharma et al.[72] found 45.6% of all MACE events occurred during early DPP-4 initiation (randomization to 6 months) and 62.6% of all MACE events occurred during late initiation (6 months to trial end), which suggests the trial follow-up duration was inadequate. Risk of hHF increased by 23% during early initiation and 10% during late initiation (Table B2).[72] No significant difference in risk for any CV outcome was found between early or late DPP-4 initiation with alogliptin.[72]

#### *Combination Therapy*

We identified 1 secondary publication[73] of individuals in the EXAMINE trial taking baseline dual therapy of metformin and sulfonylurea compared CV outcomes between those randomized to alogliptin and placebo. White et al.[73] report participants taking dual therapy randomized to alogliptin did not differ from those randomized to placebo in risk of MACE, MI, stroke, hHF, hUA, or the composite of CV death or hHF. Alogliptin added to dual therapy significantly reduced CV death risk by 51% (3.9% vs. 10.5%; HR, 0.49; 95% CI, 0.28 to 0.84; $P = .01$) and significantly reduced all-cause mortality risk by 39% (5.7% vs. 10.5%; HR, 0.61; 95% CI, 0.38 to 0.96; $P = .03$) when compared to dual therapy with placebo. Individuals taking dual therapy at baseline had

higher rates of serious hypoglycemia (1.4% vs. 0.5%; *P* = .07) with alogliptin but were not significantly different than rates with placebo.[73]

### *Linagliptin*

We identified 1 poor-methodological quality RCT (CARMELINA, the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin[74]), in 2 publications, evaluating linagliptin (Tradjenta) in individuals with type 2 diabetes at CV or renal risk (defined in Table B1). CARMELINA included a large proportion of individuals at later stages of renal disease progression: 74% of the trial population had a baseline eGFR < 60 mL and/or urinary albumin-to-creatinine-ratio (UACR) > 300 mg/g and 15.2% had a baseline eGFR < 30 mL.[74] We rated the study as poor quality for requiring stable doses of anti-hyperglycemic agents (AHAs) for at least 8 weeks prior to randomization, short follow-up (median 2.2 years), and conducting analysis in the modified ITT population (assessed in those who received ≥ 1 treatment dose) that could create differential bias in favor of linagliptin. Additionally, the manufacturer funded the trial and was responsible for the study design, collection, analysis, and manuscript preparation. There may be potential bias due to baseline imbalances between treatment groups for sex (male, 61.5% vs. 64.3%; female, 38.5% vs. 35.7%), smoking status (never, 54.3% vs. 53.3%; former, 35.2% vs. 36.6%), prior atrial fibrillation (9.1% vs. 10.2%), and severe renal impairment (eGFR < 30 mL, 14.8% vs. 15.7%).[74] Baseline concomitant medication varied between treatment groups for metformin (53.8% vs. 55.3%), sulfonylurea (31.5% vs. 32.7%), diuretics (54.1% vs. 55.6%), statins (71.4% vs. 72.4%), and ACE inhibitors or ARBs (81.9% vs. 80.3%).[74]

We also identified 1 head-to-head RCT (CAROLINA, the Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Type 2 Diabetes[25]) evaluating linagliptin compared to glimepiride, a sulfonylurea, among individuals with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD) or CV risk factors (defined in Table B1). We rated this study as poor-methodological quality for enrolling individuals who had 80% to 100% compliance with a 2-week placebo run-in period prior to randomization, variation in comparator dosage, potential group imbalances, and conducting analysis in the modified ITT population (assessed in those who received ≥ 1 treatment dose) that could create differential bias in favor of linagliptin. Additionally, the manufacturer funded the trial and was responsible for the study design, collection, analysis, and manuscript preparation. At baseline, the linagliptin group had fewer women (39.2% vs. 40.8%), individuals aged ≥ 70 (18.7% vs. 19.7%), with any microvascular disease (28.1% vs. 29.4%), using statins (63.5% vs. 66.2%), using diuretics (36.5% vs. 37.9%), and individuals taking ≥ 1 blood pressure-lowering medication (88.3% vs. 89.4%) than the glimepiride group.[25] The linagliptin group reported higher baseline beta blocker usage (39.6% vs. 38.6%).[25]

#### *Findings*

In the CARMELINA[74] trial, linagliptin had no evidence of an effect on risk of MACE, individual MACE components, or any CV event outcomes when compared to placebo with standard or when compared to glimepiride in the CAROLINA[25] trial. No evidence of an effect on risk of SAEs was observed with linagliptin (37.0% vs. 38.5%; *RR, 0.96; 95% CI, 0.90 to 1.02; P = .19*) when compared to placebo or glimepiride (46.4% vs. 48.1%; *RR, 0.96; 95% CI, 0.91 to 1.02; P = .19*). In both CARMELINA and CAROLINA, occurrences of pemphigoid, skin lesions, and pancreatitis were higher among individuals randomized to linagliptin (Table B2).[25,74] Of those reporting acute pancreatitis in the CARMELINA trial, 2 cases in the linagliptin group were fatal while no cases in the placebo group were fatal.[74] Individuals randomized to linagliptin in CAROLINA had a significant increase of 16% in the likelihood of hypersensitivity reaction AEs than individuals randomized to glimepiride (*13.4% vs. 11.5%; RR, 1.16; 95% CI, 1.02 to 1.33; P = .03*).[25] Rates of

hypoglycemia were numerically higher in the linagliptin group but risk was not significantly different from placebo in CARMELINA (all *P* > .05, Table B2).[74] In the CAROLINA trial, those randomized to linagliptin had significantly lower incidences of moderate or severe hypoglycemic events, severe hypoglycemic events, and hospitalizations for hypoglycemia than those randomized to glimepiride (all *P* < .05, Table B2).[25] No evidence of differential treatment effect on risk of hHF or CV death was reported with linagliptin among individuals with baseline history of HF in the CARMELINA trial.[21] Evidence of significant associations between risk of hHF and baseline insulin use (*P* = .04), blood pressure (*P* = .007), and region (*P* = .04) were reported in CARMELINA, which may suggest these factors influenced MACE outcomes and were not adjusted for in analysis.[21]

### *Saxagliptin*

We identified 1 poor-methodological quality RCT (SAVOR-TIMI 53, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53[22]) evaluating saxagliptin (Onglyza) in individuals with type 2 diabetes and CVD or CV risk factors (defined in Table B1). We rated this study as poor quality for a short follow-up duration (median 2.1 years), potential group imbalances, and variation in active treatment dosage, which could create differential bias in favor of saxagliptin. Additionally, trial funding was provided by the manufacturer but analysis was conducted independently of the sponsor by the TIMI Study Group.[22] At baseline, the saxagliptin group had fewer individuals with hypertension (81.2% vs. 82.4%) and HbA1c < 6.5% (7.3% vs. 8.3%), but more individuals with a baseline HbA1c 7.0 to < 8.0% (33.9% vs. 32.9%) than the placebo group.[22] Significantly fewer individuals randomized to placebo were taking no concomitant diabetes medications at baseline (4.1% vs. 4.8%; *P* = .05).[22]

#### *Findings*

In the SAVOR-TIMI 53[22] trial, individuals randomized to saxagliptin with an eGFR ≤ 50 mL received 2.5 mg (n = 1,294) and the remaining saxagliptin recipients received 5 mg (n = 6,986).[22] No evidence of an effect on risk for MACE, individual MACE components, all-cause mortality, hUA, or hospitalization for coronary revascularization was observed with saxagliptin (pooled across doses) compared to placebo (all *P* > .05, Table B2).[22] A significant 27% increased risk of hHF occurred with saxagliptin when compared to placebo (3.5% vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; *P* = .007), but the absolute difference of events was similar between groups. A significant yet small increased risk of SAEs occurred with saxagliptin (41.4% vs. 39.6%; *RR, 1.05; 95% CI, 1.01 to 1.09; P = .02*). The saxagliptin group was at significantly higher risk of experiencing a major or minor hypoglycemic event, with significantly more recipients reporting at least one hypoglycemic event relative to placebo (all *P* ≤ .05, Table B2).[22] Saxagliptin was associated with a small, statistically significant increase in risk for renal abnormality relative to placebo (5.8% vs. 5.1%; RR, 1.15; *P* = .04).[22]

### *Sitagliptin*

We identified 1 fair-methodological quality RCT (TECOS, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin[24]) in 6 publications evaluating sitagliptin (Januiva) in individuals with type 2 diabetes and CVD (defined in Table B1). We rated this study as fair-quality for variation in active treatment dosage, potential baseline medication imbalances, and requiring participants to have an HbA1c between 6.5% and 8.0% prior to randomization if they were receiving stable doses of oral AHAs or insulin. Despite the study being sponsored by the manufacturer, the trial was run and analyzed by the Duke Clinical Research Institute and University of Oxford Diabetes Trial Unit.[24] Concomitant use of metformin (81.0% vs. 82.2%), calcium-channel blockers (33.3%

vs. 34.3%), diuretics (40.6% vs. 41.5%), and ACE inhibitors or ARBs (78.3% vs. 79.2%) was less frequent in those randomized to sitagliptin than placebo at baseline.[24]

### *Findings*

In the TECOS[24] trial, no evidence of an effect on risk of MACE or any CV outcomes was reported with sitagliptin treatment over placebo (all $P > .05$, Table B2). Sitagliptin had a significantly different effect on MACE risk between individuals with a BMI < 30 (HR, 1.08; 95% CI, 0.95 to 1.24) than individuals with a BMI > 30 (HR, 0.88; 95% CI, 0.76 to 1.01; $P = .03$).[24] Sitagliptin had no evidence of an effect on risk for SAEs (*12.7% vs. 12.8%; RR, 0.99; 95% CI, 0.91 to 1.08; P = .78*). Individuals treated with sitagliptin were roughly 25% more likely to develop diabetic eye disease and diabetic retinopathy than individuals treated with placebo (all $P < .05$, Table B2).[24] Buse et al.[75] report a higher frequency of acute pancreatitis events were reported in the sitagliptin group but sitagliptin was not significantly associated with an increased risk of pancreatitis over placebo (0.11% vs. 0.06%; HR, 1.93; 95% CI, 0.96 to 3.88). No evidence of differential risk for SAEs or AEs was found between sitagliptin and placebo among individuals with chronic kidney disease (eGFR <60 mL).[76] Bethel et al.[77] found sitagliptin had no evidence of an effect on CV or safety outcomes among TECOS participants ≥ 75 years compared to placebo. Josse et al.[78] report severe hypoglycemic events were independently associated with an 85% increased risk of fracture (adjusted HR, 1.85; 95% CI, 1.14 to 2.99; $P = .01$) but did not find significant associations between sitagliptin treatment and incident fracture ($P = .74$), major osteoporotic fracture ($P = .67$), or hip fracture ($P = .76$). Alfredsson et al.[79] report risk of acute pancreatitis was significantly associated with sitagliptin compared to placebo treatment in men (HR, 4.03; 95% CI 1.51 to 10.76) but was not found in women (HR, 0.46; 95% CI, 0.12 to 1.79; $P = .01$).

## SGLT-2 Inhibitors

We identified 4 RCTs[26-30] (in 19 publications) of poor- to good-methodological quality assessing CVD outcomes with SGLT-2 inhibitor treatment. Table 6 summarizes the findings (GRADE ratings) of the primary research evidence for SGLT-2 inhibitors. Due to moderate risk of bias and indirectness (i.e., applicability to a U.S. Medicaid population), we downgraded the quality of evidence to moderate for all outcomes. We downgraded the quality of evidence for stroke to low for additional inconsistency.

### *All-cause Mortality (moderate quality of evidence)*

- No evidence of an effect on all-cause mortality risk was observed with canagliflozin (Invokana) or dapagliflozin (Farxiga).
- Empagliflozin (Jardiance) significantly reduced risk of all-cause mortality by 32% (5.7% vs. 8.3%; HR, 0.68; 95% CI, 0.57 to 0.82; $P < .001$) over placebo, a strong effect with an absolute difference in risk of over 2.5 percentage points.

### *Stroke (low quality of evidence)*

- No evidence of an effect on stroke risk was observed with canagliflozin, dapagliflozin, or empagliflozin.

### *Myocardial Infarction (moderate quality of evidence)*

- No evidence of an effect on stroke risk was observed with canagliflozin, dapagliflozin, or empagliflozin.

*Hospitalization for Heart Failure (moderate quality of evidence)*

- Canagliflozin reduced risk by 33% over placebo in the CANVAS program trial (5.5 vs. 8.7 events per 1000 patient-years; HR, 0.67; 95% CI, 0.52 to 0.87) and reduced risk by 39% over placebo in the CREDENCE trial (4.0% vs. 6.4%; HR, 0.61; 95% CI, 0.47 to 0.80; *P* < .001). Both were strong effects with larger absolute differences in events experienced between groups.
- Dapagliflozin significantly reduced risk by 27% (2.5% vs. 3.3%; HR, 0.73; 95% CI, 0.61 to 0.88) over placebo, but had a small absolute reduction in events reported between groups.
- Empagliflozin significantly reduced risk by 35% over placebo (2.7% vs. 4.1%; HR, 0.65; 95% CI 0.50 to 0.85; *P* = .002).

*Serious Adverse Events (moderate quality of evidence)*

- Canagliflozin did not reduce risk of SAEs over placebo in the CANVAS program trial (104.3 vs. 120 events per 1,000 patient-years; *incidence rate ratio [IRR], 0.87; 95% CI, 0.67 to 1.13; P = .29*). A significant 9% reduction in risk of SAEs with canagliflozin over placebo was reported in the CREDENCE trial (*33.5% vs. 36.7%; RR, 0.91; 95% CI, 0.84 to 0.99; P = .03*).
- Dapagliflozin significantly reduced risk of SAEs by 6% over placebo (34.1% vs. 36.2%; *RR, 0.94; 95% CI, 0.91 to 0.98; P = .005*).
- Empagliflozin significantly reduced risk of SAEs by 10% over placebo (38.2% vs. 42.3%; *RR, 0.90; 95% CI, 0.85 to 0.96; P = .0007*).

Table 6. GRADE Summary of Findings for SGLT-2 Inhibitors

| Outcome<br>Number of Studies | Quality of the Evidence | Relationship | Rationale |
|---|---|---|---|
| All-cause mortality<br>N = 4 studies<br>(in 19 publications) | Moderate<br>●●●○ | No evidence of effect within the class. | We downgraded one level for indirectness and risk of bias. |
| Stroke<br>N = 3 studies<br>(in 17 publications) | Low<br>●●○○ | No evidence of an effect within the class. | We downgraded one level for indirectness and risk of bias, and one level for inconsistency. |
| Myocardial infarction<br>N = 3 studies<br>(in 17 publications) | Moderate<br>●●●○ | No evidence of an effect within the class. | We downgraded one level for indirectness and risk of bias. |
| Hospitalization for heart failure<br>N = 4 studies<br>(in 19 publications) | Moderate<br>●●●○ | Meaningful reductions in risk across the class. | We downgraded one level for indirectness and risk of bias. |
| Serious adverse events<br>N = 4 studies<br>(in 19 publications) | Moderate<br>●●●○ | Meaningful reductions in risk across the class. | We downgraded one level for indirectness and risk of bias. |

*Note. For methods and interpretation of GRADE ratings, see Appendix A.*

Table 7 summarizes the primary study endpoint characteristics of eligible RCTs comparing SGLT-2 inhibitors to placebo. All eligible RCTs were multisite studies conducted internationally, allowing background therapies for glycemic control and management of CV or renal risk in accordance to local guidelines. This may limit applicability of findings to a U.S. Medicaid

population due to potential inclusion of non-U.S. approved therapies and variation in access to quality health care.

We rated 2 RCT as of fair-methodological quality for requiring a placebo run-in period, dosage variation in the active treatment arm, potential treatment imbalances, and for manufacturer sponsorship of the trial. We rated 2 RCTs as poor-methodological quality for additional short follow-up duration and treatment exposure differences between treatment groups.

A full characteristics table is in Appendix B, Table B1 and a full evidence table of SGLT-2 inhibitor outcomes is in Appendix B, Table B2.

Table 7. Eligible SGLT-2 Inhibitor RCT Characteristics

| Trial Name; Trial Type; Author (Year); Generic Drug (Alternate Name); N<br>Study Quality | Trial Regimen | Study Population | Characteristics |
|---|---|---|---|
| CANVAS<br>Multisite international<br>Mahaffey et al. (2018)[31]<br>Neal et al. (2017)[28]<br>Canagliflozin (Invokana)<br>Total N = 10,142<br><u>CANVAS</u><br>• 100 mg, n = 1,445<br>• 300 mg, n = 1,443<br>• Placebo, n = 1,441<br><u>CANVAS-R</u><br>• 100 mg, n = 2,904<br>• Placebo, n = 2,903<br>Poor | • Daily oral administration with SOC excluding SGLT-2 inhibitors, corticosteroids, immunosuppressives or rosiglitazone<br>• CANVAS-R started at 100 mg and could increase to 300 mg after 13 weeks of treatment<br>• Required 2-week single-blind, placebo run-in<br>• Required stable AHA regimen ≥ 8 weeks prior to screening and throughout run-in<br>• Follow-up visits quarterly or 1 year and then at 6 month intervals until trial end | Individuals with type 2 diabetes ≥ 30 years with ASCVD or CV events and ≥ 50 years with ≥ 2 CV risk factors<br>• Prior CVD, n = 6,656 (65.6%)<br>• Prior HF, n = 1,461 (14.4%)<br>• Prior coronary vascular disease, n = 5,721 (56.4%)<br>• Prior CBD, n = 1,958 (19.3%)<br>• Prior PVD, n = 2,113 (20.8%) | • 35.8% Female<br>• Mean Age: 63.3 years (SD, 8.3)<br>• Mean HbA1c: 8.2% (SD, 0.9)<br>• Mean diabetic duration: 13.5 years (SD, 7.8)<br>• Mean follow-up:<br>  ○ CANVAS 294.5 weeks (SD, 75.05)<br>  ○ CANVAS-R 107.95 weeks (SD, 19.9) |
| CREDENCE<br>Multisite international<br>Perkovic et al. (2019)[26]<br>Canagliflozin (Invokana)<br>Total N = 4,401<br>• 100 mg, n = 2,202<br>• Placebo, n = 2,199<br>Poor | • Daily oral administration with SOC excluding GLP-1 agonists, DPP-4 inhibitors, or SGLT-2 inhibitors<br>• Required stable AHA dose ≥ 8 weeks prior to randomization<br>• Eligibility required 80% adherence to 2-week single-blind placebo run-in<br>• Dosage stratified by eGFR<br>• Follow-up at weeks 3, 13, 26 and then alternated between phone calls and in-person visits every 13 weeks | Individuals with type 2 diabetes ≥ 30 years of age and CKD<br>• Prior CVD, n = 2,220 (50.4%)<br>• Prior HF, n = 652 (14.8%)<br>• Prior amputation, n = 234 (5.3%) | • 33.9% Female<br>• Mean age: 63.0 years (SD, 9.2)<br>• Mean HbA1c: 8.3% (SD, 1.3)<br>• Mean diabetic duration: 15.8 years (SD, 8.6)<br>• Median follow-up: 2.62 years (range 0.02 to 4.53) |

| Trial Name; Trial Type; Author (Year); Generic Drug (Alternate Name); N<br>Study Quality | Trial Regimen | Study Population | Characteristics |
|---|---|---|---|
| DECLARE-TIMI 58<br>Multisite international<br>Wiviott et al. (2019)[30]<br>Dapagliflozin (Farxiga)<br>Total N = 17,160<br>• 10 mg, n = 8,582<br>• Placebo, n = 8,578<br>Fair | • Daily oral administration with SOC excluding pioglitazone, rosiglitazone, or other SGLT-2 inhibitors<br>• Required 4-to-8 week single-blind placebo run-in<br>• Follow-up visits in-person every 6 months and via telephone every 3 months between in-person visits until study end | Individuals with type 2 diabetes ≥ 40 years and eGFR of ≥ 60 mL with CV risk factors or established ASCVD<br>• Prior ASCVD, n = 6,974 (40.6%)<br>• Prior CAD, n = 5,658 (32.9%)<br>• Prior PAD, n = 1,025 (5.9%)<br>• Prior CBD, n = 1,301 (7.6%)<br>• Prior HF, n = 1,724 (10.0%) | • 37.4% Female<br>• Mean age: 63.9 years (SD, 6.8)<br>• Mean HbA1c: 8.3% (SD, 1.2)<br>• Median diabetic duration: 10.5 years (IQR, 6.0 to 16.0)<br>• Median follow-up: 4.2 years (IQR, 3.9 to 4.4) |
| EMPA-REG OUTCOME<br>Multisite international<br>Zinman et al. (2015)[27]<br>Empagliflozin (Jardiance)<br>Total N = 7,020<br>• 10 mg, n = 2,345<br>• 25 mg, n = 2,342<br>• Placebo, n = 2,333<br>Fair | • Daily oral administration with SOC<br>• Dose stratified by baseline HbA1c, BMI, eGFR, and geographic region<br>• Background AHAs unchanged for first 12 weeks and adjusted after 12 weeks if medically necessary<br>• Required 2-week open-label placebo run-in<br>• Required ≥ 12 week washout from all AHAs if HbA1c ≥ 7.0% and ≤ 9.0% or stable doses of AHAs for ≥ 12 weeks if HbA1c ≥ 7.0% and ≤ 10.0%<br>• Follow-up visits every 4 weeks through week 16, then every 12 weeks through week 52, then every 14 weeks until trial end, for a final trial end + 30-day follow-up visit | Individuals with type 2 diabetes ≥ 18 years with BMI < 45, eGFR > 30 mL, and high CV risk factors<br>• Prior HF, n = 706 (10.1%)<br>• Prior MI, n = 3,273 (46.6%)<br>• Prior PAD, n = 1,461 (20.8%)<br>• Prior stroke, n = 1,637 (23.3%)<br>• Prior CAD, n = 5,308 (75.6%) | • 28.8% Female<br>  ○ 10 mg 29.5% Female<br>  ○ 25 mg 28.1% Female<br>• Mean age: 63.1 years (SD, 8.6)<br>• Mean HbA1c: 8.07% (SD, 0.85)<br>• Time since type 2 diabetes diagnosis:<br>  ○ ≤ 1 year, n = 128 (2.7%)<br>  ○ >1 to 5 years, n = 712 (15.2%)<br>  ○ > 5 to 10 years, n = 1,175 (25.1%)<br>  ○ > 10 years, n = 2,672 (57.0%)<br>• Median follow-up: 3.1 years (IQR, 1.9 to 3.4) |

*Note. * Denotes interquartile range, standard deviation, or range was not reported. Abbreviations. AHA: antihyperglycemic agents; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CBD: cerebrovascular disease; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin test of blood glucose (sugar); HF: heart failure; IQR: interquartile range; MI: myocardial infarction; PAD: peripheral artery disease; PVD: peripheral vascular disease; RCT: randomized controlled trial; SD: standard deviation; SGLT-2: sodium-glucose cotransporter-2; SOC: standard of care.*

### *Canagliflozin*

We identified 2 RCTs (CANVAS, the Canagliflozin Cardiovascular Assessment Study [28,31] and CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation[26]), in 8 publications, assessing canagliflozin in individuals with type 2 diabetes and established CVD, CV risk factors, renal disease, or renal risk factors (defined in Table B1). We rated CANVAS as poor quality for requiring a 2-week single-blind placebo run-in period which may reduce the number of reported AEs, potential imbalances between groups, failure to account for dosage and treatment exposure differences, removal of all study time and mortality events accrued prior to trial end, and manufacturer funding and involvement in data collection and data analysis.[31] At baseline, the canagliflozin group had fewer females (35.1% vs. 36.7%), individuals with prior HF (13.9% vs. 15.1%), prior coronary vascular disease (55.8% vs. 57.2%), prior peripheral vascular disease (20.3% vs. 21.6%), prior CVD (64.8% vs. 66.7%), and macroalbuminuria (7.1% vs. 8.2%) than the placebo group.[28,31]

We rated CREDENCE as poor quality for requiring participants to take stable doses of ACE inhibitors or ARB for ≥ 4 weeks prior to randomization, randomizing participants 80% adherent to 2-week single-blind placebo run-in period which may reduce the number of reported AEs, relatively small sample size, and inadequate follow-up duration (median follow-up 2.62 years) during which the trial ended early.[26] Additionally, the manufacturer funded CREDENCE and performed analysis which was verified by an independent contract research organization.[26] At baseline the canagliflozin group in CREDENCE contained more individuals identifying as White (67.5% vs. 65.7%), current smokers (15.5% vs. 13.6%), female (34.6% vs. 33.3%), from Europe (20.6% vs. 18.6%), individuals using antithrombotics (60.9% vs. 58.3%), and with non-nephrotic range macroalbuminuria (i.e., UACR > 300 and ≤ 3000 mg/g; 77.3% vs. 75.9%).[26] In comparison, the placebo group at baseline had more individuals from North America (26.1% vs. 27.6%), using a sulfonylurea (27.8% vs. 29.8%), and with nephrotic range macroalbuminuria (i.e., UACR > 3000 mg/g).[26]

#### *Findings*

In the CANVAS program, participants began at 100 mg of canagliflozin and could increase dosage to 300 mg of canagliflozin after 13 weeks of treatment.[28,31] Follow-up time varied during the CANVAS program which pooled analysis of CANVAS and CANVAS-R (CANVAS-RENAL) data. In CANVAS, mean follow-up time for canagliflozin was 298.6 weeks (SD 70.2) and placebo 290.4 weeks (SD 79.9).[28] CANVAS-R participants were followed for a much shorter duration, the canagliflozin group mean follow-up was 108.2 weeks (SD 19.7) and placebo group 107.7 weeks (SD 20.1).[28] Canagliflozin significantly reduced MACE risk compared to a placebo (14% in CANVAS [HR, 0.86; 95% CI, 0.75 to 0.97; *P* = .02] and 20% in CREDENCE [9.8% vs. 12.2%; HR, 0.80; 95% CI, 0.67 to 0.95; *P* = .01]). No evidence of an effect on risk of other CV outcomes was observed with canagliflozin in the CANVAS program (all *P* > .05, Table B2).[28,31]

Canagliflozin recipients had numerically lower rates of all-cause mortality than placebo recipients (7.6% vs. 9.1%; HR, 0.83; 95% CI, 0.68 to 1.02; *P* value not reported) in the CREDENCE trial but this difference was not statistically significant. CREDENCE did not assess individual MACE components, MI, or stroke outcomes. Significant reductions in risk of hHF occurred with canagliflozin in the CANVAS program (HR, 0.67; 95% CI, .52 to 0.87; *P* value not reported) and CREDENCE trial (4.0% vs. 6.4%; HR, 0.61; 95% CI, 0.47 to 0.80; *P* < .001). In CREDENCE, canagliflozin significantly lowered risk for the primary composite outcome of end-stage kidney disease, doubling serum creatinine, or renal/CV death by 30% compared to placebo (11.1% vs. 15.5%; HR, 0.70; 95% CI, 0.59 to 0.82; *P* = .00001). Risk for end-stage kidney disease was

significantly reduced 32% with canagliflozin compared to placebo (5.3% vs. 7.5%; HR, 0.68; 95% CI, 0.54 to 0.86; *P* = .002).

Risk for SAEs was significantly reduced with canagliflozin in CREDENCE (33.5% vs. 36.7%; *RR, 0.91 (0.84 to 0.99); P = .03*) but did not occur in CANVAS (104.3 events vs. 120.0 per 1000 patient-years*; IRR, 0.87 (0.67 to 1.13); P = .29*). Canagliflozin significantly increased the risk of genital infection in men and women, amputation, and fracture in the CANVAS program (all *P* < .05, Table B2)[28,31] with similar increases in risk found in CREDENCE.[26] Canagliflozin increased the likelihood of breast cancer 2.5 times more than placebo among women in CREDENCE[26] and risk of breast cancer was higher among the primary cohort receiving canagliflozin than the primary cohort receiving placebo in CANVAS (Table B2).[28,31] Exploratory analysis of fracture events during CANVAS reported by both treatment groups by Zhou et al.[80] found a higher proportion of women (fracture 49.4% vs. no fracture 35.1%) and individuals with prior fracture history (fracture 33.9% vs. no fracture 21.2%) reported fracture events.

No significant difference in risk for CV events was reported between the primary prevention cohort (≥ 50 years with at least 2 CV risk factors) and secondary prevention cohort (≥ 30 years with ASCVD) treated with canagliflozin in CANVAS.[28,31] Secondary publication by Mahaffey et al.[29] reported results consistent with original findings when CREDENCE participants were analyzed by primary and secondary cohorts. Three secondary publications assessing CANVAS program outcomes by presence of baseline kidney disease, baseline cerebrovascular disease, and baseline heart failure were identified. Neuen et al.[81] report no differential treatment effects on risk of MACE, CV death, MI, or hHF among individuals with baseline chronic kidney disease. Evidence of heterogeneity for stroke risk was reported between eGFR subgroups (*P* = .01, Table B2), with reduction in risk occurring for those with eGFR < 45 mL (HR, 0.32; 95% CI, 0.11 to 0.96) and no effect for those with eGFR ≥ 90 mL (HR, 1.42; 95% CI, 0.86 to 2.36).[81] Zhou et al.[82] found no significant differences the effect of canagliflozin on MI risk between individuals with and without baseline cerebrovascular disease (*P* = .19, Table B2). Canagliflozin showed a statistically significant, but small protective effect against risk of hemorrhagic stroke over placebo for individuals with baseline cerebrovascular disease (HR, 0.43; 95% CI, 0.20 to 0.89; *P* = .02).[82] Radholm et al.[83] reported no statistically significant differences in the effect of canagliflozin between individuals with and without baseline HF in risk of MACE, CV death, MI, stroke, all-cause mortality, or serious kidney decline (all *P* > .05). No evidence of absolute risk differences in safety outcomes were found among participants with and without baseline HF (all *P* for interaction > .16) except for osmotic diuresis-related AEs, which were significantly lower among participants with baseline HF taking canagliflozin (*P* = .03).[83]

### *Dapagliflozin*

We identified 1 fair-methodological quality RCT (DECLARE-TIMI 58, the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58[30]), in 4 publications, assessing dapagliflozin (Farxiga) treatment in individuals with type 2 diabetes and established CVD or CV risk factors (defined in Table B1). We rated this trial as fair for potential group imbalances and for requiring completion of a 4- to 8-week single-blind placebo run-in period to be eligible for randomization, which may artificially reduce the number of AEs reported. Additionally, the manufacturer sponsored the trial but analysis was conducted independently by the TIMI study group.[30] At baseline, the dapagliflozin group had fewer women (36.9% vs. 37.9%) and less frequent use of sulfonylureas (42.1% vs. 43.2%) and DPP-4 inhibitors (16.5% vs. 17.1%), but more individuals using insulin (41.6% vs. 40.2%) than the placebo group.[30]

### *Findings*

In the DECLARE-TIMI 58[30] trial, dapagliflozin had no evidence of an effect on risk for MACE, individual MACE components, all-cause mortality, or non-CV death when compared to placebo (all *P* > .05, Table B2). Dapagliflozin showed evidence for a significant reduction in risk of hHF by 27% compared to placebo (2.5% vs. 3.3%; HR, 0.73; 95% CI, 0.61 to 0.88; *P* value not reported).[30] Similarly, a significant 17% reduction in risk of CV death or hHF occurred with dapagliflozin but the absolute risk reduction was less than one percentage point (4.9% vs. 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; *P* = .005).[30] Risk of SAEs was reduced by 6% with dapagliflozin treatment (34.1% vs. 36.2%; *RR, 0.94; 95% CI, 0.91 to 0.98; P = .005*) but AEs leading to discontinuation were significantly higher in the dapagliflozin group (8.1% vs. 6.9%; HR, 1.15; 95% CI, 1.03 to 1.28; *P* = .01). The risk of diabetic ketoacidosis was significantly increased roughly 2-fold and risk for genital infection significantly increased nearly 8.5-fold with dapagliflozin compared to placebo (all *P* < .05, Table B2).[30]

Dapagliflozin significantly reduced MACE risk by 16% among individuals with baseline history of MI (HR, 0.84; 95% CI, 0.72 to 0.99; *P* = .04) but had no evidence of an effect on MACE risk in individuals without baseline MI, baseline ASCVD, or with multiple CV risk factors (all *P* > .05, Table B2) [30,84] Similarly, dapagliflozin reduced the risk for recurrent MI risk by 22% in individuals with baseline MI (HR, 0.78; 95% CI, 0.63 to 0.95) but no evidence of an effect occurred for those without an MI , ASCVD, or multiple CV risk factors at baseline (all *P* > .05, Table B2).[84] Diabetic ketoacidosis risk was nearly 7 times higher among individuals with a history of MI treated with dapagliflozin than placebo, however wide confidence intervals lessen the certainty of this increased risk (HR, 6.98; 95% CI, 0.86 to 56.76, Table B2).[84] Furtado et al.[84] report participants closer in time to their previous MI received greater MACE risk reduction with dapagliflozin. Mosenzon et al.[85] report no evidence of heterogeneity on CV outcomes between baseline eGFR, HbA1c, or UACR subgroups. Dapagliflozin had a significantly different effect on risk of non-CV death between individuals with prior HF who benefited from treatment with a 50% reduction in risk (HR, 0.50; 95% CI, 0.29 to 0.86; Table B2), and individuals without prior HF who did not benefit from treatment (Table B2).[30] Dapagliflozin reduced risk of CV death by 45%, hHF by 36%, and all-cause mortality by 41% among individuals with HF with reduced ejection fraction (HFrEF) compared to placebo (Table B2).[86] Risk of CV death was increased 41% in participants with HF with preserved ejection fraction (HFpEF) randomized to dapagliflozin (Table B2). Risk of amputation, fracture, volume depletion, and urinary tract infection occurred more frequently among individuals with HFrEF treated with dapagliflozin than individuals without HFrEF (Table B2).[86]

## *Empagliflozin*

We identified 1 fair-methodological quality RCT (EMPA-REG OUTCOME, BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients[27]), in 7 publications, evaluating empagliflozin (Jardiance) among individuals with type 2 diabetes at high CV risk (defined in Table B1). We rated this study as fair-quality for requiring a 2-week open label placebo run-in period which may reduce the number of AEs reported. Additionally, the manufacturer provided funding and analyzed the data.[27]

### *Findings*

In the EMPA-REG OUTCOME[27] trial, a significant 14% reduction in MACE risk occurred with empagliflozin compared to placebo (10.5% vs. 12.1%; HR, 0.86; 95% CI, 0.74 to 0.99; *P* = .04). No significant differences in risk of MACE were observed between 10 mg and 25 mg doses of empagliflozin (Table B2).[27] Among individual MACE components, empagliflozin significantly

reduced risk for CV death by 38% over placebo (3.7% vs. 5.9%; HR, 0.62; 95% CI, 0.49 to 0.77; *P* < .001), and risk was consistently reduced at both 10 mg and 25 mg empagliflozin doses (Table B2).[27] Similarly, no evidence of an effect on risk of hUA, coronary revascularization, transient ischemic attack, stroke, or MI were reported with empagliflozin (all *P* > .05, Table B2).[27] Strong significant reductions in risk for hHF (2.7% vs. 4.1%; HR, 0.65; 95% CI, 0.50 to 0.85; *P* = .002) and all-cause mortality (5.7% vs. 8.3%; HR, 0.68; 95% CI, 0.57 to 0.82; *P* < .001) occurred with empagliflozin, which remained at 10 mg and 25 mg doses of empagliflozin (Table B2). Empagliflozin significantly reduced risk of the composite of hHF or CV death excluding stroke by 24% (5.7% vs. 8.5%; HR, 0.66; 95% CI, 0.55 to 0.79; *P* < .001), again consistent reductions in risk occurred at both 10 mg and 25 mg empagliflozin doses (Table B2).

SAEs were significantly reduced with empagliflozin which reduced risk by 10% in comparison to placebo (38.2% vs. 42.3%; *RR, 0.90; 95% CI, 0.85 to 0.96; P = .0007*). Individuals randomized to empagliflozin were almost 4 times more likely to develop genital infections (6.4% vs. 1.8%; *RR, 3.57; 95% CI, 2.59 to 4.91; P < .0001*), with women experiencing more genital infections at the 10 mg than 25 mg dose (9.2% vs. 10.8%, respectively) and more events than men at both doses (5.4% vs. 4.6%, respectively) (Table B2). Empagliflozin had a significantly different effect on MACE risk between individuals < 65 years and ≥ 65 years, and between individuals with a baseline HbA1c < 8.5% and ≥ 8.5% (all *P* < .05, Table B2).[27] Individuals ≥ 65 years of age experienced a 29% reduction in MACE risk with empagliflozin (HR, 0.71; 95% CI, 0.59 to 0.87), while individuals < 65 years of age had no evidence of an effect on MACE. Similarly, empagliflozin reduced MACE risk by 24% in individuals with a baseline HbA1c < 8.5% (HR, 0.76; 95% CI, 0.60 to 0.91), but had no evidence of an effect for those with a baseline HbA1c ≥ 8.5% (Table B2).[27]

We identified 6 secondary publications analyzing data from the EMPA-REG OUTCOME trial by baseline presence of coronary artery bypass grafting, baseline MI or stroke, baseline peripheral arterial disease (PAD), baseline kidney disease, sex, and among individuals identifying as Asian. Verma et al.[87] report individuals with a baseline history of coronary artery bypass grafting (CABG) randomized to empagliflozin had fewer incidences of CV death, all-cause mortality, hHF, and hHF or CV death than those without CABG history. Verma et al.[87] reported stroke risk was increased among individuals with CABG history (HR, 1.26; 95% CI, 0.69 to 2.28), but was not significantly different from those without prior CABG. Individuals with prior CABG reported more AEs consistent with urinary tract infection with empagliflozin than placebo (15.0% vs. 13.9%), but individuals without CABG did not experience higher rates with empagliflozin (18.7% vs. 19.5%).[87] Both individuals with prior CABG (7.7% vs. 2.1%) and without prior CABG (6.0% vs. 1.7%) reported more AEs consistent with genital infection than their placebo counterparts.[87]

Individuals with baseline history of MI or stroke treated with empagliflozin experienced numerically larger reductions in risk of CV death, all-cause mortality, and MACE but the effects were not significantly different from those without baseline MI history (Table B2).[88] Analysis stratified by baseline presence of PAD found those with and without PAD benefited from reduced risk of hHF, CV death, hHF or CV death, and all-cause mortality with empagliflozin (Table B2).[89] Risk for lower limb amputation was increased among empagliflozin recipients without baseline PAD (Table B2).[89] Consistent reductions in risk of CV death (39%), hHF (34%), all-cause mortality (24%), and all-cause hospitalization (19%) were reported in individuals with baseline kidney disease (eGFR < 60 mL or UACR > 300 mg/g) treated with empagliflozin.[90]

Wanner et al.[90] report homogenous benefit across doses and stratified eGFR and UACR subgroups with empagliflozin. Individuals with eGFR < 45 and 45 to < 60 mL were more likely to

develop genital infections at 10 mg (IRR, 1.47 and IRR, 1.62, respectively; CI not reported; *P* not reported) and more than twice as likely at 25 mg (IRR, 2.36; IRR, 3.12; CI not reported; *P* not reported) doses of empagliflozin than placebo.[90] For individuals with an eGFR ≥ 60 mL, genital infections were more likely at 10 mg (IRR, 3.03; CI not reported; *P* not reported) than 25 mg (IRR, 2.45; CI not reported; *P* not reported).[90] Secondary analysis of participants identifying as Asian by Kaku et al.,[91] report empagliflozin reduced risk for MACE (32%), CV death (56%), and hHF or CV death (43%) but had no evidence of an effect on other outcomes (all *P* > .05, Table B2) or increased risk for AE among individuals identifying as Asian. No significant differences in treatment effect with empagliflozin were found between sex; however, reduction in risk of CV death was greater for males (females HR, 0.76; 95% CI, 0.48 to 1.20; males HR, 0.58; 95% CI, 0.45 to 0.75; *P* = .32), while females experienced greater reductions in risk of hHF (females HR, 0.50; 95% CI, 0.31 to 0.81; males HR, 0.73; 95% CI, 0.53 to 1.01; *P* = .20).[92] Women taking empagliflozin were more likely to experience genital infections than those taking placebo (10.0% vs. 2.6%), while genital infections occurred less frequently in men taking empagliflozin (1.5% vs. 2.6%).[92]

## Combination Therapy

### *GLP-1 Agonists*

#### *GLP-1 exposed vs. GLP-1 unexposed*

We identified 1 additional good-methodological quality retrospective cohort study[58] of the U.K. The Health Improvement Network (THIN) database assessing CV outcomes between those exposed to a GLP-1 agonist (n = 8,345) and those unexposed to a GLP-1 agonist (n = 16,541). Mean follow-up time for the GLP-1 exposed cohort was 32.7 months (SD 19.9) and 30.7 months (SD 19.8) in the unexposed cohort. Overall, 20.9% of study participants had prior CVD events (ischemic heart disease, stroke, and/or HF).[58] Within the GLP-1 exposed cohort, 55% were taking liraglutide (n = 4,566), 42% exenatide (n = 3,525), and 3% lixisenatide (n = 254).[58] Individuals exposed to a GLP-1 agonist were significantly less likely to experience all-cause mortality than those unexposed to a GLP-1 (IRR, 0.69; 95% CI 0.61 to 0.79; *P* < .0001).[58] After adjusting for covariates, all-cause mortality was significantly reduced with liraglutide (adjusted IRR, 0.56; 95% CI, 0.46 to 0.67; *P* < .0001) and exenatide (adjusted IRR, 0.72; 95% CI, 0.61 to 0.85; *P* < .0001) but was not assessed in lixisenatide due to the lack of events reported (Table B2).[58] Individuals without prior CVD events exposed to a GLP-1 were significantly less likely to experience all-cause mortality (*P* < .0001) but not incident CVD events (*P* = .26) compared to those unexposed to a GLP-1 (Table B2).[58]

### *DPP-4 Inhibitors*

#### *Metformin + DPP-4 inhibitors vs. Metformin + Sulfonylureas vs. Metformin + Thiazolidinediones*

A fair-methodological quality retrospective cohort study by Gordon et al.[45] assessed CV outcomes in individuals ≥ 65 years with type 2 diabetes taking metformin adding second-line therapies (n = 10,484) of sulfonylureas, thiazolidinediones (TZDs), or DPP-4 inhibitors, using data from the UK's Clinical Practice Research Datalink. We rated this study as fair because the follow-up was relatively short, the manufacturer sponsored the study, and the authors report several conflicts of interest. Over an average follow-up of 2.44 years (7 max, range not reported), no significant difference in time to first MI, stroke, or the composite of MI/stroke was found between any second-line therapy combination when compared to combination therapy of metformin and sulfonlyureas.[45] Individuals taking metformin + DPP-4 inhibitor had the lowest overall event rate (101.88 per 1,000 person-years), lowest mortality event rate (16.15 per 1,000 person-years), and the lowest event rate for the composite of MI/stroke among all the second-

line treatment regimens (7.93 per 1,000 person-years) when compared to other combination and monotherapies.[45] DPP-4 inhibitors alone had lower event rates of amputation, blindness, congestive HF, and ulcers than combination therapy of metformin + DPP-4 (Table B2).[45] Combination therapy of metformin + DPP-4 lowered event rates of ischemic heart disease, MI, nephropathy, neuropathy, renal failure, retinopathy, stroke, mortality, and the composite of MI/stroke when compared to DPP-4 inhibitors used as monotherapy (Table B2).[45]

#### *Metformin + DPP-4 Inhibitors vs. Metformin + Liraglutide*

Risk of MACE between individuals taking metformin either initiating liraglutide or initiating DPP-4 inhibitors (n = 23,402 pairs) was assessed in a fair-methodological quality retrospective cohort study by Svanstrom et al.[57] using national health registry data from Denmark and Sweden. We rated this study as fair quality for author conflict of interest and funding provided by industry. Over a mean follow-up of 3.4 years, those initiating metformin and liraglutide had a 10% reduction in MACE risk when compared to those initiating metformin and a DPP-4 inhibitor (4.8% vs. 4.9%; HR, 0.90; 95% CI, 0.83 to 0.98; *P* value not reported) [57] Initiating liraglutide with metformin was also associated with a 22% reduction in risk of CV death (1.4% vs. 1.6%; HR, 0.78; 95% CI, 0.68 to 0.91; *P* value not reported) and a 17% reduction in all-cause mortality risk (4.7% vs. 5.1%; HR, 0.83; 95% CI 0.77 to 0.90; *P* value not reported), but the absolute difference in the proportions of individuals experiencing each outcome was small. Individuals taking metformin starting liraglutide or DPP-4 inhibitor treatment did not differ in risk of MI, stroke, or heart failure (Table B2) [57]

#### *Metformin + DPP-4 Inhibitors vs. Metformin+ Other Glucose-Lowering Drugs*

Analysis of hospitalization for CV outcomes by O'Brien et al.[52] was assessed in U.S. adults with type 2 diabetes enrolled in commercial or Medicare Advantage health insurance plans taking metformin initiating a second glucose-lowering drug: GLP-1 agonists (n = 11,351), SGLT-2 inhibitors (n = 5,677), DPP-4 inhibitors (n = 28,898), basal insulin (n = 16,249), TZD (n = 7,368), or sulfonylureas (n = 63,194). We rated this retrospective cohort study as fair-methodological quality because of conflicts of interest reported by the authors. The primary outcome was the composite of hospitalization for 4 CV events: congestive HF, stroke, ischemic heart disease, or peripheral artery disease.[52] DPP-4 inhibitor initiators had a 22% reduction in risk for the primary outcome when compared to GLP-1 agonist initiators (0.9% vs. 1.9%; HR, 0.78; 95% CI, 0.63 to 0.96; *P* value not reported) but did not differ in risk from those initiating SGLT-2, TZD, basal insulin, or sulfonylureas (Table B2) [52] No difference in risk for the primary outcome was reported between individuals with or without prior CV events using metformin adding any of the drug classes studied.[52] Risk for the primary outcome as well as the individual components was nearly doubled with both basal insulin initiation and sulfonylurea initiation when compared to DPP-4 initiation (Table B2) [52] Starting a DPP-4 inhibitor was significantly reduced the risk of hospitalization for stroke by 35% compared to GLP-1 agonists (HR, 0.65; 95% CI 0.44 to 0.97; *P* value not reported) but did not differ in risk of other outcomes or from those starting an SGLT-2 or TZD (Table B2).[52]

## Drug Class Comparisons

### *DPP-4 Inhibitors vs. Other Glucose-Lowering Drugs*

#### *DPP-4 Inhibitors vs. GLP-1 Agonists*

A fair-methodological quality retrospective cohort study by Dawwas et al.[32] of U.S. commercial and Medicare claims data assessed differences in hHF rates between patients naïve to DPP-4 inhibitors and GLP-1 agonists (n = 160,803 pairs). We rated this study as fair quality for not

reporting on participants that were lost-to-follow up and the short follow-up durations between cohorts (DPP-4: mean follow-up 170 days [SD 290] for DPP-4 inhibitors vs. GLP-1: mean follow-up 159 days [SD 285]), which could create differential bias in favor of DPP-4 inhibitors.[32] Use of DPP-4 inhibitors decreased hHF risk by 14% compared to use of GLP-1 agonists (3.6% vs. 3.8%; adjusted HR, 0.86; 95% CI, 0.83 to 0.90; *P* value not reported). DPP-4 inhibitors reduced hHF risk by 18% in those with baseline CVD, by 16% in those without CVD, and by 15% in those without baseline HF (Table B2) when compared to GLP-1 agonists.[32] Individuals with baseline HF using DPP-4 inhibitors did not differ in risk of hHF from those using GLP-1 agonists (Table B2).[32] Individuals initiating saxagliptin had fewer hHF events (2.7% vs. 4.2%) and a 26% reduced risk for hHF (HR, 0.74; 95% CI, 0.69 to 0.84) when compared to individuals initiating GLP-1 agonist treatment (Table B2). Sitagliptin initiation was associated with an 8% reduced risk of hHF (3.8% vs. 3.9%; HR, 0.92; 95% CI, 0.89 to 0.95) but the absolute risk reduction was very small (Table B2).

### *DPP-4 Inhibitors vs. Sulfonylureas*

A fair-methodological quality retrospective cohort study by Kim et al.[47] examined hHF and CV outcomes in individuals with type 2 diabetes initiating DPP-4 inhibitors or sulfonylurea with data from the Korean Health Insurance Review and Assessment Service database. We rated this study as fair because Korea has socialized health care, a more homogenous population than the U.S., and DPP-4 inhibitors used included vildagliptin which is not approved in the U.S. These issues limit the generalizability of results to the U.S. Medicaid population. Participants who received a DPP-4 inhibitor or sulfonylurea (n = 255,691 pairs) were propensity-score matched and assessed for time to first hHF, hospitalization for MI, hUA, percutaneous coronary intervention, or CABG stratified by CVD history.[47] As a class, DPP-4 inhibitors were significantly associated with reductions in risk of hHF (HR, 0.78; 95% CI 0.69 to 0.87; P < .001) and risk of stroke (HR, 0.63; 95% CI, 0.60 to 0.67; *P* < .001) but did not reduce risk of unstable angina, percutaneous coronary intervention, or CABG when compared to sulfonylureas (all *P* > .05, Table B2). Consistent and significant reductions in risk of hHF and risk of stroke were observed between both individuals with and without CVD (Table B2).[47] Risk of unstable angina, percutaneous coronary intervention, or CABG was not different between individuals with and without CVD (Table B2).[47] Among those initiating DPP-4 inhibitors, MI risk was significantly lowered by 34% in those with CVD (HR, 0.74; 95% CI, 0.62 to 0.88; *P* = .001) but risk was not reduced among individuals without CVD (Table B2).[47] In comparison to sulfonylurea, hHF risk was reduced by 24% with sitagliptin (HR, 0.76; 95% CI 0.67 to 0.86; *P* < .001) and by 26% with linagliptin (HR, 0.74; 95% CI, 0.59 to 0.92; *P*= .007), but hHF risk was not significantly different from those treated with saxagliptin (Table B2). Stroke risk was significantly reduced by 35% with sitagliptin (HR, 0.65; 95% CI, 0.59 to 0.71; *P* < .001), by 29% with linagliptin (HR, 0.71; 95% CI, 0.62 to 0.82; *P* < .001), and by 34% with saxagliptin (HR, 0.66; 95% CI, 0.49 to 0.88; *P* = .005) when compared to sulfonylurea treatment. MI risk was significantly reduced by 34% with sitagliptin over sulfonylurea (HR, 0.66; 95% CI, 0.55 to 0.79; *P* < .001), but no evidence of risk reduction was observed with linagliptin or saxagliptin (Table B2). In contrast, saxagliptin significantly reduced the risk of unstable angina by 23% (HR, 0.77; 95% CI, 0.59 to 0.99; *P* = .04) over sulfonylurea but no reduction in risk occurred with sitagliptin or linagliptin (Table B2).

### *DPP-4 Inhibitors vs. Sulfonylureas and DPP-4 Inhibitors vs. Thiazolidinediones*

Two good-methodological quality retrospective cohort studies[44,46] used a random sampling of U.S. Medicaid beneficiaries with type 2 diabetes to compare CV outcomes and acute pancreatitis risk among those initiating DPP-4 inhibitors, sulfonylureas, or TZDs. We rated these studies as good because of insufficient definitions for inclusion criteria. No increased risk of acute

pancreatitis was found between those initiating DPP-4 inhibitors or sulfonylurea or between those initiating DPP-4 inhibitors or TZDs (Table B2).[46] Similarly, Hong et al.[46] reported individuals with CVD initiating DPP-4 inhibitors did not differ in acute pancreatitis risk from individuals initiating sulfonylurea or TZD (Table B2). Gokhale et al.[78] found DPP-4 initiators reduced all-cause mortality risk by 24% (adjusted HR, 0.76; 95%CI, 0.72 to 0.79; *P* value not reported) reduced risk of all-cause mortality when comparted to those initiating sulfonylureas. DPP-4 inhibitors reduced risk for the composite of nonfatal MI, stroke, or all-cause mortality by 22% (adjusted HR, 0.78; 95% CI 0.75 to 0.81; *P* value not reported), and reduced risk was observed for both those with and without CVD history when compared to sulfonylureas (Table B2).[78] All-cause mortality risk did not differ between DPP-4 inhibitor and TZD initiators or among individuals with and without CVD history (Table B2).[78] DPP-4 initiation reduced risk for the composite of nonfatal MI, stroke, or all-cause mortality by 11% (adjusted HR, 0.89; 95% CI, 0.84 to 0.95; *P* value not reported) when compared to TZD initiators.[78]

### *SGLT-2 Inhibitors vs. Other Glucose-Lowering Drugs*

#### *SGLT-2 Inhibitors vs. DPP-4 Inhibitors*

Pasternak et al.[53] used nationwide data registries in Sweden, Norway, and Denmark to compare MACE, hHF or HF death, and all-cause mortality outcomes between patients naïve to SGLT-2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) and DPP-4 inhibitors (n = 20,983 pairs) over a median follow-up of 1.4 years (IQR 0.7 to 2.3). We rated this retrospective cohort study as fair-methodological quality for inclusion of non-U.S. approved DPP-4 inhibitors which limits generalizability to the U.S. Medicaid population, author conflict of interest and funding provided by industry. Risk of MACE and individual components of MI, stroke, and CV death were not significantly different between individuals initiating a SGLT-2 or DPP-4 inhibitor (Table B2).[53] All-cause mortality risk was reduced by 20% with SGLT-2 initiation (1.3% vs. 2.4%; HR, 0.80; 95% CI, 0.69 to 0.92; *P* value not reported) when compared to DPP-4 initiation, which is a strong reduction considering the infrequency of the event overall. Risk for the composite of hHF or HF death was reduced by 34% with SGLT-2 initiation (0.6% vs. 1.3%; HR, 0.66; 95% CI, 0.53 to 0.81; *P* value not reported) over DPP-4 initiation, another large reduction given the infrequency of the event during follow-up. No significant difference in risk of lower limb amputation was observed between SGLT-2 or DPP-4 inhibitor initiation (Table B2).[53] SGLT-2 initiators had nearly twice the risk of diabetic ketoacidosis (0.1% vs. 0.07%; HR, 2.14; 95% CI, 1.17 to 4.09; *P* value not reported than DPP-4 initiators, but overall diabetic ketoacidosis was a rare event.[53]

#### *Canagliflozin vs. DPP-4 Inhibitors, GLP-1 Agonists, and Sulfonylureas*

A fair–methodological quality retrospective cohort study by Patorno et al.[54] of U.S. commercial insurance claims data compared hHF and the composite of hospitalization for acute MI, ischemic stroke, or hemorrhagic stroke between individuals initiating canagliflozin vs. DPP-4 inhibitors (n = 17,667 pairs), canagliflozin vs. GLP-1 agonists (n = 20,539 pairs), and canagliflozin vs. sulfonylurea (n = 17,354 pairs). We rated this study as fair for short follow-up duration (mean 0.6 years per cohort [SD 0.5]) and conflicts of interest among the authors.[54] Canagliflozin significantly reduced hHF by 30% compared to DPP-4 inhibitors (8.9% vs. 12.8%; HR, 0.70; 95% CI, 0.54 to 0.92), by 39% compared to GLP-1 agonists (7.5% vs. 12.4%; HR, 0.61; 95% CI 0.47 to 0.78), and by 49% compared to sulfonylureas (7.3% vs. 14.4%; HR, 0.51; 95% CI, 0. 38 to 0.67) (*P* values not reported). No evidence of reduced risk for the composite outcome was observed with canagliflozin compared to DPP-4 inhibitors, GLP-1 agonists, or sulfonylurea (Table B2).[54]

Post-hoc analysis by Clegg et al.[42] of the EXCEL trial placebo arm adjusted for covariates of interest did not find evidence for reduced 3-component MACE risk between individuals treated

with open-label SGLT-2 inhibitors (adjusted HR, 0.79; 95% CI, 0.49 to 1.28; *P* = .34) or dapagliflozin (adjusted HR, 0.55; 95% CI, 0.26 to 1.15; *P* = .11) when compared to individuals unexposed to SGLT-2 inhibitors or dapagliflozin. No significant difference in risk of CV death, nonfatal MI, nonfatal stroke, hHF, PAD or peripheral vascular disease, diabetic eye complications, or amputation was reported between individuals taking SGLT-2 inhibitors or dapagliflozin relative to those not receiving treatment.[42] SGLT-2 inhibitor use was associated with a modest reduction in all-cause mortality risk compared to non-use (adjusted HR, 0.51; 95% CI, 0.27 to 0.95; *P* = .03) but was not observed with dapagliflozin use (adjusted HR, 0.66; 95% CI, 0.25 to 1.72; *P* = .39). No benefit was observed with SGLT-2 inhibitors or dapagliflozin treatment in individuals with prior CVD history.[42] Individuals treated with dapagliflozin experienced higher incidence of amputation (4 vs. 1), nonfatal stroke (3 vs. 1), and peripheral arterial disease (PAD) or peripheral vascular disease (9 vs. 5) than individuals not treated with dapagliflozin or an SGLT-2 inhibitor.[42]

The EASEL[60] (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World) trial used U.S. Department of Defense Military Health System data to assess CV outcomes and amputation risk in adults ≥ 18 with type 2 diabetes and established CVD (i.e., coronary artery disease [CAD], HF, cerebrovascular disease, or PAD) between individuals starting an SGLT-2 inhibitor (n = 12,629) vs. other glucose-lowering drugs (n = 12,629; i.e., GLP-1 agonists, DPP-4 inhibitors, TZD, sulfonylurea, insulin, repaglinide, acarbose, miglitol, nateglinide, acarbose). We rated this retrospective cohort as fair–methodological quality for short follow-up duration (median 1.6 years [IQR 0.79 to 2.9]), conflicts of interest among the authors, and no reporting of lost-to-follow-up.[60] Additionally, Janssen Research & Development, LLC., a SGLT-2 inhibitor manufacturer, funded the study and was involved in the study design, conduct, data collection, analysis, interpretation, and article writing.[60] Among SGLT-2 initiators, most individuals were taking canagliflozin (n = 7,333 [58.1%]), followed by empagliflozin (n = 3,341 [26.4%]), and dapagliflozin (n = 1,955 [15.5%]).[60] Overall, the average duration of participant CVD was 4.4 years (SD 2.2) and type 2 diabetes was 5.6 years (SD 2.0).[60] In comparison to non-SGLT-2 initiation, starting a SGLT-2 inhibitor was associated with a significant 43% reduction in the risk of all-cause mortality (HR, 0.57; 95% CI, 0.49 to 0.66; *P* < .0001), hHF (HR, 0.57; 95% CI 0.45 to 0.73; *P* < .0001), and the composite of all-cause mortality or hHF (HR, 0.57; 95% CI 0.50 to 0.65; *P* < .0001). Similarly SGLT-2 initiation reduced risk for the composite of all-cause mortality, nonfatal MI, or nonfatal stroke by 33% (HR, 0.67; 95% CI, 0.60 to 0.75; *P* < .0001) and the composite of all-cause mortality, nonfatal stroke, nonfatal MI, or hHF by 34% (HR, 0.66; 95% CI, 0.60 to 0.74; *P* < .0001) over non-SGLT-2 initiation. Incidence rate ratios per 100 person-years for all-cause mortality from lowest to highest occurred with dapagliflozin, empagliflozin, and canagliflozin (IRR, 0.86; 1.09; 1.42 respectively) but for hHF occurred with empagliflozin, canagliflozin, and dapagliflozin (IRR, 0.43; 0.51; 0.58 respectively).[60] A nearly doubled risk of below knee amputation (BKA), excluding individuals with a prior BKA event, was significantly associated with SGLT-2 initiation (HR, 1.99; 95% CI, 1.12 to 3.51; *P* = .02) when compared to non-SGLT-2 inhibitor initiation. Higher incidences of BKA occurred with canagliflozin (IRR, 0.19 per 100 person-years) and empagliflozin (IRR, 0.12) but was lower with dapagliflozin (IRR, 0.09).[60]

The CVD-REAL[49] (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter 2 Inhibitors) study assessed hHF and death outcomes between initiation of SGLT-2 inhibitors (n = 154,528) vs. other glucose-lowering drugs (n = 154,528) across Germany, Norway, Denmark, Sweden, the U.K. and the U.S. We rated this prospective cohort study (in 3 publications) as fair-methodological quality due to short follow-up durations,

varying index dates between countries, author conflicts of interest, and funding provided by AstraZeneca, a SGLT-2 inhibitor manufacturer. During CVD-REAL the proportion of total exposure time was distributed as 53% to canagliflozin, 42% to dapagliflozin, and 5% to empagliflozin.[49] During a mean follow-up of 225 days, SGLT-2 inhibitors significantly reduced risk for hHF by 39% when compared to other glucose-lowering drugs across all countries (pooled HR, 0.61; 95% CI, 0.51 to 0.73; $P < .001$). SGLT-2 inhibitors were significantly associated a 51% reduced risk of all-cause mortality across countries (pooled HR, 0.49; 95% CI, 0.41 to 0.57; $P \leq .001$) over an average follow-up of 261 days. In comparison to other glucose-lowering drugs, modest reductions in stroke risk (HR, 0.83; 95% CI, 0.71 to 0.97; $P = .02$) were observed with SGLT-2 inhibitors, but no reduction in MI risk was observed (pooled HR, 0.85; 95% CI, 0.72 to 1.00; $P = .05$).[48] Secondary analysis of CVD-REAL stratified by baseline CVD (i.e., acute MI, UA, stroke HF, transient ischemic attack, coronary revascularization, or occlusive PAD) reported consistent reductions in risk of death, HF, and the composite of death or HF with no significant differences in risk between those with and without prior CVD taking SGLT-2 inhibitors.[41]

Kosiborod et al.[50] report during CVD-REAL 2, conducted in South Korea, Japan, Singapore, Australia, Israel, and Canada, that SGLT-2 initiation significantly reduced risk across countries for all-cause mortality by 49% (HR, 0.51; 95% CI, 0.37 to 0.70; $P < .001$), hHF by 36% (HR, 0.64; 95% CI, 0.50 to 0.82; $P = .001$), MI by 19% (HR, 0.81; 95% CI, 0.74 to 0.88; $P < .001$), stroke by 32% (HR, 0.68; 95% CI 0.55 to 0.84; $P < .001$), and the composite of all-cause mortality or hHF by 40% (HR, 0.60; 95% CI, 0.47 to 0.76; $P < .001$) when compared to other glucose-lowering drugs. During CVD-REAL 2, "dapagliflozin, empagliflozin, ipragliflozin, canagliflozin, tofogliflozin, and luseogliflozin accounted for 75%, 9%, 8%, 4%, 3%, and 1% of exposure time in the SGLT-2 group, respectively,"[50] which may limit generalizability to a U.S. Medicaid population due to inclusion of non-U.S. approved drugs. CVD-REAL NORDIC conducted in Denmark, Norway, and Sweden, for an average follow-up of 0.9 years (SD 4.1), found no evidence of reductions in risk of nonfatal MI, nonfatal stroke, or atrial fibrillation with SGLT-2 inhibitors when compared to other glucose-lowering drugs.[40] Dapagliflozin, empagliflozin, and canagliflozin accounted for 94%, 5%, and 1% of total exposure time respectively in CVD-REAL NORDIC.[40] Consistent with other CVD-REAL studies, SGLT-2 inhibitors significantly reduced CV death risk by 47% (HR, 0.53; 95% CI, 0.40 to 0.71; $P < .0001$), hHF risk by 30% (HR, 0.70; 95%CI, 0.61 to 0.81; $P < .0001$), MACE risk by 32% (HR, 0.78; 95% CI, 0.69 to 0.87; $P < .0001$), and all-cause mortality risk by 49% (HR, 0.51; 95% CI, 0.45 to 0.58; $P < .0001$) over other glucose–lowering drugs.[40] SGLT-2 inhibitors did not reduce the risk of atrial fibrillation (HR, 0.95; 95% CI 0.84 to 1.08; $P = .46$) but were significantly associated with a 24% reduction in severe hypoglycemia risk in CVD-REAL NORDIC compared to other glucose-lowering drugs (HR, 0.76; 95% CI, 0.65 to 0.90; $P = .001$).[40] All CVD-REAL and associated findings are limited in generalizability by a lack of knowledge of the type of other glucose-lowering drug used, dosage, and treatment duration in the comparator cohort.

### *Dapagliflozin vs. Other Glucose-Lowering Drugs*

One fair-methodological quality prospective cohort study by Norhammar et al.[51] used Sweden's nationwide public health care system to compare CV safety and event rates in propensity-score matched patients naïve to dapagliflozin (n = 7,102) and other glucose-lowering drugs besides SGLT-2 inhibitors (n = 21,306). We rated this study as fair-quality for not disclosing the baseline characteristics for propensity score matching, short follow-up (1.6 years), and being funded by the drug manufacturer. Dapagliflozin significantly reduced the risk of hHF or CV death by 21% (HR, 0.79; 95% CI 0.69 to 0.91; $P = .002$), hHF by 21% (HR, 0.79; 95% CI, 0.67 to 0.93; $P = .005$), CV death by 25% (HR, 0.75; 95% CI 0.58 to 0.97; $P = .003$), and all-cause mortality by 37% (HR,

0.63; 95% CI, 0.54 to 0.74; *P* < .001) compared to those initiating other glucose-lowering drugs. No significant difference in the risk of MI, stroke, atrial fibrillation, or severe hypoglycemia was reported between dapagliflozin and other glucose-lowering drug initiators (Table B2).[51]

Dawwas et al.[43] conducted a good–methodological quality retrospective cohort study and examined CV outcomes between individuals starting SGLT-2 inhibitors (n = 66,633) vs. DPP-4 inhibitors (n = 66,633) and vs. sulfonylureas (n = 62,767) using U.S. Medicare claims and Truven Health MarketScan data. We rated this study as good quality for not reporting loss to follow-up or directly stating follow-up duration. During an average follow-up of approximately one year, the proportion of individuals experiencing nonfatal stroke or nonfatal MI was lower in those starting SGLT-2 inhibitors (0.91%) than both DPP-4 inhibitors (2.28%) and sulfonylureas (2.02%).[43] SGLT-2 inhibitors significantly reduced the risk of nonfatal stroke or MI by 50% compared to sulfonylureas (HR, 0.50; 95% CI 0.45 to 0.55; *P* value not reported) and by 43% compared to DPP-4 inhibitors (HR, 0.57; 95% CI 0.52 to 0.62; *P* value not reported [43] SGLT-2 inhibitors significantly reduced the risk of hHF by 46% compared to DPP-4 inhibitors (0.54% vs. 0.97%; HR, 0.54; 95% CI 0.48 to 0.60; *P* value not reported) and by 52% compared to sulfonylureas (0.59% to 1.22%; HR, 0.48; 95% CI 0.40 to 0.57; *P* value not reported). The proportion of lower extremity amputations was lower with initiating a SGLT-2 inhibitor over a DPP-4 inhibitor (0.18% vs. 0.26%), but risk was not significantly different between the two cohorts (HR, 0.88; 95% CI 0.65 to 1.15; *P* value not reported). In contrast, SGLT-2 inhibitors significantly reduced lower extremity amputation risk when compared to sulfonylureas (0.15% vs. 0.25%; HR, 0.74; 95% CI, 0.57 to 0.96; *P* value not reported). However lower extremity amputations were rare events overall and the absolute difference in the proportions of events was small between cohorts.

A poor-methodological quality retrospective cohort study by Toulis et al.[59] using the U.K. THIN database report dapagliflozin initiators (n = 4,444) had significantly fewer all-cause mortality events (adjusted IRR, 0.50; 95% CI, 0.33 to 0.75; *P* = .001) when compared to SGLT-2 unexposed individuals (n = 17,680). Similarly, a significant reduction in the number of all-cause mortality events among individuals without prior CVD events was associated with dapagliflozin (adjusted IRR, 0.44; 95% CI, 0.25 to 0.78; *P* = .005), but no reduction in incident CV events was observed with dapagliflozin (adjusted IRR, 0.89; 95% CI, 0.61 to 1.30; *P* = .55) when compared to those unexposed to SGLT-2 inhibitors. We rated this study as poor quality for not accounting for differences in previous CV events between cohorts, differences in short follow-up duration (dapagliflozin 9.3 months [SD 6.5] vs. unexposed 8.9 months [SD 6.3]), not disclosing a funding source, and conflicts of interest reported by the authors.[59]

### *Dapagliflozin vs. DPP-4 inhibitors*

One fair-methodological quality retrospective cohort study by Persson et al.[56] assessed MACE risk in patients naïve to dapagliflozin (n = 10,227) vs. naïve to DPP-4 inhibitors (n = 30,681) using public health care data from Sweden, Norway, and Denmark. We rated this study as fair-quality for being funded by the manufacturer and short follow-up duration (mean follow-up < 1-year). Dapagliflozin significantly reduced MACE risk by 21% compared to DPP-4 inhibitors but no reductions in risk were observed for individual MACE components of nonfatal MI, nonfatal stroke, or CV death (Table B2).[56] In comparison to DPP-4 inhibitors, dapagliflozin significantly reduced the risk of hHF by 38% (HR, 0.62; 95% CI 0.50 to 0.77; *P* value not reported) and risk of all-cause mortality by 41% (HR, 0.59; 95% CI 0.49 to 0.72; *P* value not reported). Similarly dapagliflozin reduced risk for the composite of MACE plus unstable angina by 19% and MACE plus unstable angina or hHF by 25% when compared to DPP-4 inhibitors (Table B2).[56] Risk of

atrial fibrillation and severe hypoglycemia did not differ between those initiating dapagliflozin or DPP-4 inhibitors (Table B2).[56]

### *Empagliflozin vs. Sitagliptin*

The EMPRISE[55] (Empagliflozin Comparative Effectiveness and Safety) study used U.S. commercial insurance and Medicare claims data to compare hHF outcomes among adults with type 2 diabetes initiating empagliflozin (n = 18,880) vs. sitagliptin (n = 201,839) for a mean follow-up of 5.3 months (median 112 days). We rated this retrospective cohort study as fair-methodological quality for short follow-up duration, no mention of loss to follow-up, funding through a grant from empagliflozin's manufacturer, and author employment at empagliflozin's manufacturer.[55] In comparison to sitagliptin, empagliflozin reduced risk for hHF by 46% (HR, 0.52; 95% CI, 0.29 to 0.98]) and risk for hHF-broad (i.e., any hospital discharge related to HF) by 46% (HR, 0.52; 95% CI, 0.41 to 0.71; *P* value not reported). Incidence rates per 1000 person-years were lower with empagliflozin than sitagliptin for hHF (2.1 vs. 6.7) and hHF-broad (10.5 vs. 22.2).[55] Risk reductions with empagliflozin were consistent across participant subgroups for prior CV history, HF history, and sex.[55]

## Cohort Studies: Evidence Summary

The retrospective cohort studies identified primarily focused on comparisons between DPP-4 inhibitors and SGLT-2 inhibitors. Consistent reductions in risk of hHF with SGLT-2 inhibitors and consistent reductions in risk for all-cause mortality with GLP-1 agonists were reported in identified retrospective cohort studies. In contrast to the significant increase in hHF risk found with the DPP-4 inhibitor saxagliptin, 1 retrospective cohort of U.S. individuals with type 2 diabetes reported starting saxagliptin reduced hHF risk 26% over starting a GLP-1 agonist (2.7% vs. 4.2%; HR, 0.74; 95% CI, 0.69 to 0.84).[32]

There is a lack of clear evidence for drug classes and for additional CV outcomes in the identified cohort studies. Evidence from cohort studies should be interpreted with caution because of their likelihood of bias (e.g., study in homogenous populations) and indirectness. Additionally, cohort studies stratified by treatment are prone to potential bias due to confounding by indication - patient phenotype which determines diabetic therapy may be the true cause of an outcome, rather than exposure to the diabetic therapy.

## Ongoing Studies

We identified 5 placebo-controlled trials[93-97] planning to evaluate CVD outcomes and 2 large cohort studies.[98,99] Table 8 displays the registry number (NCT) for each study, treatment groups, eligible outcomes, estimated enrollment, and estimated completion date of these ongoing studies. Estimated sample sizes in interventional studies range from 648 to 9,642. One prospective cohort[98] has an estimated enrollment of 200,000 participants and 1 retrospective cohort[99] has an estimated enrollment of 80,000 participants. One multisite international RCT with 8,000 participants assessing CV outcomes with ertugliflozin, a SGLT-2 inhibitor, is projected to be completed in early 2020.[95] One ongoing U.S. observational cohort study with 80,000 participants assessing the effects of empagliflozin, a SGLT-2 inhibitor, compared to DPP-4 inhibitors is projected to be completed at the end of 2021.[99] We identified 1 completed RCT[94] assessing CV outcomes comparing an exenatide implant (a GLP-1 agonist), to a placebo implant with SOC. In May 2016 a press release announced the trial met primary endpoints but no publications have been identified.[100]

Table 8. Included Ongoing Studies of Newer Diabetes Drugs for CVD Outcomes

| NCT Number<br>Trial Name | Treatment Groups | Eligible Outcomes | Estimated Enrollment | Estimated Completion Date |
|---|---|---|---|---|
| NCT01001962[93]<br>PREHYPD | • Empagliflozin 25 mg<br>• Metformin 2,000 mg | • CV-related mortality and morbidity | 1,054 | January 2020 |
| NCT01455896[94] | • Exenatide implant 60 µg<br>• Placebo implant | • CV-related death<br>• Nonfatal MI<br>• Nonfatal stroke | 4,156 | March 2016;<br>in May 2016, a press release announced the trial met primary endpoints.[100] No publications have been identified. |
| NCT01986881[95]<br>VERTIS CV Study | • Ertugliflozin 5 mg<br>• Ertugliflozin 15 mg<br>• Placebo matched to ertugliflozin dose | • All-cause mortality<br>• CV-related death<br>• Nonfatal MI<br>• Nonfatal stroke<br>• hHF | 8,000 | January 2020 |
| NCT03363464[99]<br>EMPRISE | Retrospective cohort study<br>• Empagliflozin<br>• Any DPP-4 Inhibitor | • Hospitalization for MI, stroke, or CV death<br>• hHF<br>• All-cause mortality | 80,000 | November 2021<br>Published preliminary results are addressed in this report update. |
| NCT03794518[96] | • Dapagliflozin 10 mg and pioglitazone 15 mg<br>• Placebo and SOC | • First hHF<br>• All-cause mortality | 648 | December 2021 |
| NCT03817463[98] | Prospective cohort study<br>• Empagliflozin or any SGLT-2 inhibitor<br>• Any DPP-4 inhibitor | • All-cause mortality<br>• hHF<br>• MACE<br>• CV-related death<br>• End-stage renal disease | 200,000 | January 2021 |
| NCT03914326[97]<br>SOUL | • Semaglutide 3 mg, 7 mg, or 14 mg<br>• Placebo | • MACE<br>• All-cause mortality<br>• CV-related death<br>• Nonfatal MI<br>• Nonfatal stroke<br>• hHF<br>• Renal mortality | 9,642 | July 2024 |

*Abbreviations. CV: cardiovascular; DPP-4: dipeptidyl peptidase-4; hHF: hospitalization for heart failure; MACE: major adverse cardiovascular event; MI: myocardial infarction; NCT: U.S. National Clinical Trials number; SGLT-2: sodium-glucose cotransporter-2; SOC: standard of care.*

## Discussion

This report includes a narrow update of a larger DERP systematic review completed in 2017. This update focuses on the effectiveness and safety of newer diabetes drugs on CVD outcomes. Overall the newer diabetes drugs included in this report do not appear to be associated with a significant increase in mortality and CV events, and may have positive benefits in risk reduction.

As a class, we found:

- GLP-1 agonists demonstrated small absolute reductions in the risk of all-cause mortality when compared to placebo (moderate-quality evidence), in contrast to no effect observed with DPP-4 inhibitors (moderate-quality evidence) or SGLT-2 inhibitors (moderate-quality evidence).
- No included drug classes (GLP-1 agonists [low-quality evidence], DPP-4 inhibitors [moderate-quality evidence], or SGLT-2 inhibitors [low-quality evidence]), had evidence of an effect on risk of stroke.
- No evidence of an effect on risk of MI was observed with SGLT-2 inhibitors (very low-quality evidence) or DPP-4 inhibitors (low-quality evidence), which contrasts with uncertainty surrounding the effects of GLP-1 agonists (very low-quality evidence).
- Significant and meaningful reductions in risk of hHF were found in SGLT-2 inhibitors (moderate-quality evidence), which contrasts with no evidence of an effect found in GLP-1 agonists (moderate-quality evidence) or DPP-4 inhibitors (low-quality evidence).
- Significant and meaningful reductions in risk for SAEs were found with GLP-1 agonists (low-quality evidence) and SGLT-2 inhibitors (moderate-quality evidence), which contrasts with no evidence of an effect found in DPP-4 inhibitors (moderate-quality evidence).
- Significant differences in CV event risk between individuals with and without prior CVD (i.e., prior CV event, CV risk factors, CVD, renal disease, or renal impairment) were reported in the GLP-1 agonist and SGLT-2 inhibitor classes.

No eligible RCTs were identified assessing newer diabetes medications used as monotherapy compared to combination therapy and we are unable to answer this question using published RCTs. With no eligible head-to-head trials identified, we are unable to make direct comparisons between drug classes for included interventions. As a class, consistent reductions in hHF risk with SGLT-2 inhibitors were reported in 5 retrospective cohort studies with sample sizes of at least 10,000. In contrast to the significant increase in hHF risk found with the DPP-4 inhibitor saxagliptin (3.5% vs. 2.8%; HR, 1.27; 95% CI, 1.07 to 1.51; P = .007)[22], 1 retrospective cohort of U.S. individuals with type 2 diabetes reported starting saxagliptin reduced hHF risk 26% over starting a GLP-1 agonist.[81]

### *Limitations of the evidence*

It is important to note that all included RCTs were designed as non-inferiority trials and received premarketing FDA approval if an excess of 80% risk for the primary outcome with treatment was ruled out (i.e., upper limit of the 95% CI for the hazard ratio is ≤ 1.80). All trials were designed to detect differences in the time to first composite CV event, which can over- or underestimate results depending on the performance of the individual component outcomes. Given the small number of events reported in each trial, it is possible that the statistical power for detecting additional outcomes was reduced (e.g., potentially inadequate sample size to detect non-MACE outcomes).

Marked differences in trial characteristics such as duration of follow-up, dosage tested, treatment discontinuation, and participant population (i.e., diabetic duration, baseline HbA1c,

established CVD or CVD risk, renal disease, geographic location) may account for the variation in effects observed within each drug class. Increased use of background therapies for CV risk and glycemic control were adherent to local guidelines at investigator discretion and lack of standardization may account for variation in findings reported. Usage of non-U.S. approved therapies and variation in access to health care at randomization may also limit generalizability to a U.S. population.

Required run-in periods may have artificially selected participants with higher rates of treatment adherence, decreasing the overall number of discontinuations and events reported. Additionally, it is possible that active and placebo treatment exposure durations were not adequate to capture CV risk. Dosage stratification by baseline renal function in RCTs may introduce additional indirectness and imprecision, creating potential bias in favor of active treatment. These limitations reduce the generalizability of trial findings and the ability to detect true differences in outcomes.

Included RCTs recruited participants with established CVD or at high CVD risk and relatively stable HbA1c levels (i.e., 6.5% to 8.5%; most were close to 8%) with predominately long-standing disease (i.e., average diabetic duration ≥ 10 years), which may or may not be applicable to the general population that has type 2 diabetes. However, safety in high-risk populations commonly transfers to safety in low-risk populations. The evidence reviewed for this report does not provide knowledge of CV effectiveness and safety in individuals with type 2 diabetes without high risk, and findings should be replicated in additional trials for this population. Inferences regarding differential treatment effect between individuals with and without prior CVD are limited due to heterogeneity within drug classes and cannot be directly compared due to variation in the type of CVD assessed. Direct comparison studies are required to assess the true difference in CV safety and efficacy between and within the 3 diabetic drug classes covered in this report.

Coverage for specific therapies could be structured around eligibility criteria of the included studies such as stable doses of other glucose-lowering drugs, no history of dialysis or renal transplant, and stable HbA1c levels. Prescribers and payers might consider assessing individual patient risk factors and comorbidities to determine whether the purpose of added therapy is to prevent or to decrease risk for specific CV events (e.g., reducing risk of end-stage renal disease vs. reducing heart failure) when considering therapy with GLP-1 agonists, DPP-4 inhibitors, or SGLT-2 inhibitors.

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# Appendix A. Methods

## Search Strategy

We searched Drug Effectiveness Review Project (DERP) clinical evidence sources to identify randomized controlled trials (RCTs) and retrospective cohort studies using the terms *type 2 diabetes*, *sodium glucose cotransporter 2 inhibitors*, *dipeptidyl peptidase-4 inhibitors*, *glucagon-like peptide-1 agonists*, *cardiovascular*, and *diabetes mellitus, type 2*. We limited searches of evidence sources to citations published after January 1, 2017.

We searched the following DERP evidence sources:

- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-based Practice Centers (EPC) Reports
  - Effective Health Care (EHC) Program
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE), Evidence
- Ovid MEDLINE
- Veterans Administration Evidence-based Synthesis Program (ESP)

We used Google and Google Scholar to conduct targeted gray literature searches using the following search terms *type 2 diabetes*, *sodium glucose cotransporter 2 inhibitors*, *dipeptidyl peptidase-4 inhibitors*, *glucagon-like peptide-1 agonists*, *cardiovascular*, and *diabetes mellitus, type 2*.

### *Ovid MEDLINE Search Strategy*

**Date:** 10/2/2019
**Database:** Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, 1946 to October 01, 2019

| | |
|---|---|
| 1 | *Diabetes Mellitus, type 2/ or Diabetes Mellitus, Type 2, Experimental/ or Diabetes Mellitus, Type 2/co, dt, th [Complications, Drug Therapy, Therapy] |
| 2 | (T2DM or type 2 diabetes).ti,ab,kw. or ((T2DM or type 2 diabetes) adj6 complications).ti,kw,ab. or ((T2DM or type 2 diabetes) adj6 drug therapy).ti,kw,ab. or ((T2DM or type 2 diabetes) adj6 therapy).ti,ab,kw. |
| 3 | or/1-2 |
| 4 | Cardiovascular Diseases/ci, co, dt, th [Chemically Induced, Complications, Drug Therapy, Therapy] |
| 5 | cardiovascular disease.ti,kw,ab. or CVD.ti,ab,kw. or cardio*.ti,ab,kw. or ASCVD.ti,ab,kw. or (cardio* adj6 chemically induced).ti,kw,ab. or (cardio* adj6 complications).ti,kw,ab. or (cardio* adj6 drug therapy).ti,kw,ab. |
| 6 | or/4-5 |
| 7 | 3 and 6 |
| 8 | *Dipeptidyl Peptidase 4/ or *Dipeptidyl-Peptidase IV Inhibitors/ |
| 9 | (Dipeptidyl-Peptidase IV Inhibitors or Dipeptidyl-Peptidase 4*).ti,kw,ab. or DPP 4.ti,ab,kw. or DPP IV.ti,kw,ab. or (Dipeptidyl-Peptidase IV adj5 metformin).ti,ab,kw. or |

(DPP IV adj4 metformin).ti,ab,kw. or (DPP 4 adj4 metformin).ti,kw,ab. or (Dipeptidyl-Peptidase 4 adj4 metformin).ti,ab,kw.

10 (alogliptin* or linagliptin* or saxagliptin* or sitagliptin* or nesina or tradjenta or onglyza or januvia or oseni or jentadueto* or kazano* or janumet* or kombiglyze*).ti,kw,ab.

11 *Glucagon-Like Peptide 1/ or Glucagon-Like Peptide 1/ad, ae, ag, de, tu [Administration & Dosage, Adverse Effects, Agonists, Drug Effects, Therapeutic Use]

12 glucagon-like peptide?1.ti,ab,kw. or GLP-1.ti,kw,ab. or (GLP-1 adj4 insulin).ti,ab,kw. or (Glucagon-like Peptide? 1 adj4 insulin).ti,kw,ab.

13 (oral semaglutide or rybelsus or semaglutide* or ozempic or lixisenatide* or adlyxin or dulaglutide* or trulicity or albiglutide* or tanzeum or exenatide* or bydureon or byetta or liraglutide* or victoza or xultophy or soliqua).ti,kw,ab.

14 (liraglutide* adj5 insulin).ti,ab,kw.

15 *Sodium-Glucose Transporter 2/ or Sodium-Glucose Transporter 2 Inhibitors/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]

16 sodium-glucose transporter 2*.ti,kw,ab. or SGLT?2.ti,ab,kw. or (sodium-glucose transporter 2 inhibitor adj6 DPP?4).ti,kw,ab. or (SGLT?2 adj6 DPP?4).ti,kw,ab. or (SGLT?2 adj6 DPP?IV).ti,kw,ab. or (sodium-glucose transporter 2 inhibitor adj6 DPP?IV).ti,kw,ab.

17 (ertugliflozin* or empagliflozin* or dapagliflozin* or canagliflozin* or steglatro or jardiance or farxiga or invokana or qtern or glyxambi or segluromet or synjardy* or invokamet* or xigduo).ti,ab,kw.

18 or/8-17

19 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/

20 (cohort or prospective or retrospective).ti,ab.

21 double-blind method/ or equivalence trial as topic/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/

22 ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*)) or ("4 arm" or "four arm")).ti,ab,kw. or ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt.

23 or/19-22

24 7 and 18 and 23

25 limit 24 to (english language and yr="2017 -Current")

*Cochrane Library Search Strategy*

**Date Run:** 07/10/2019 21:46:34
**Year:** Custom year range (entered 2017 to 2019)

| ID | Search |
|---|---|
| #1 | "Diabetes Mellitus, Type 2" OR "T2DM" or "Type 2 Diabetes" NOT "Type 1 Diabetes" NOT "T1DM" |
| #2 | MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees |
| #3 | #1 or #2 |
| #4 | "Cardiovascular Disease" OR "Cardiovascular Outcome" |
| #5 | MeSH descriptor: [Cardiovascular Diseases] this term only and with qualifier(s): [chemically induced - CI, drug therapy - DT, mortality - MO, therapy - TH] |
| #6 | #4 or #5 |
| #7 | "GLP-1" OR "Glucagon-Like Peptide-1 Receptor" |
| #8 | MeSH descriptor: [Glucagon-Like Peptide-1 Receptor] explode all trees and with qualifier(s): [administration & dosage - AD, analysis - AN, drug effects - DE, therapeutic use - TU, agonists - AG] |
| #9 | MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees |
| #10 | "oral semaglutide" or rybelsus or semaglutide or ozempic or lixisenatide or adlyxin or dulaglutide or trulicity or albiglutide or tanzeum or exenatide or bydureon or byetta or liraglutide or victoza or xultophy or soliqua OR "liraglutide insulin" |
| #11 | "Dipeptidyl-peptidase 4 inhibitors" OR "DPP-4" |
| #12 | MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] explode all trees and with qualifier(s): [administration & dosage - AD, adverse effects - AE, analysis - AN, therapeutic use - TU] |
| #13 | MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] 1 tree(s) exploded |
| #14 | alogliptin or linagliptin or saxagliptin or sitagliptin or nesina or tradjenta or onglyza or januvia or oseni or jentadueto or kazano or janumet or kombiglyze |
| #15 | "Sodium-Glucose Transporter 2 Inhibitors" OR "SGLT-2" |
| #16 | MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees and with qualifier(s): [administration & dosage - AD, adverse effects - AE, analysis - AN, therapeutic use - TU] |
| #17 | MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] 1 tree(s) exploded |
| #18 | ertugliflozin or empagliflozin or dapagliflozin or canagliflozin or steglatro or jardiance or farxiga or invokana or qtern or glyxambi or segluromet or synjardy or invokamet or xigduo |
| #19 | #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 |
| #20 | #3 AND #6 AND #19 |

### *Ongoing Studies*

We searched the following DERP sources for ongoing studies using the search terms *type 2 diabetes*, *sodium glucose cotransporter 2 inhibitors*, *dipeptidyl peptidase-4 inhibitors*, *glucagon-like peptide-1 agonists*, *cardiovascular*, and *diabetes mellitus, type 2*.

- ClinicalTrials.gov
- ISRCTN Registry
- U.S. Food and Drug Administration
- GlaxoSmithKline website
- Eli Lilly website
- AstraZeneca website
- Novo Nordisk website
- Sanofi's website
- Takeda Pharmaceuticals website
- Boehringer Ingelheim website
- Merck Sharp & Dohme website

### *Inclusion Criteria*

Included studies studied adults with type 2 diabetes, and assessed the included interventions in Table 1 for mortality outcomes (all-cause and cardiovascular-related), cardiovascular disease outcomes (fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, or hospitalization for heart failure), or adverse events (serious adverse events, withdrawals due to adverse events, condition-specific adverse events). Eligible study designs were randomized controlled trials, head-to-head trials, and large prospective and retrospective cohort studies with sample sizes of at least 10,000 participants. Publication date was limited to January 1, 2017.

### *Exclusion Criteria*

We excluded studies if they were not published in English, the study population was non-human, the study was conducted in a country with a UN developmental index score < 0.75, or did not assess outcomes of interest.

## Screening

One experienced researcher independently screened all titles and abstracts of identified documents.

## Quality Assessment

### *Methodological Quality of Included Studies*

We assessed the methodological quality of the included randomized controlled trials and cohort studies using standard instruments developed and adapted by DERP, which are modifications of instruments used by national and international standards for quality.[9-11] One experienced researcher independently rated the methodological quality of included studies.

#### *Randomized Controlled Trials*

Good-quality randomized controlled trials include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. These trials also have low potential for bias from conflicts of interest and funding source(s). Fair-quality randomized controlled trials

have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. Poor-quality randomized controlled trials have clear flaws that could introduce significant bias.

### *Cohort Studies*

Good-quality cohort studies include a sample that is representative of the source population, have low loss to follow-up, and measure and consider relevant confounding factors. These studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Fair-quality cohort studies might not have measured all relevant confounding factors or adjusted for them in statistical analyses, have loss to follow-up that could bias findings, consist of a sample that is not representative of the source population, or have potential conflicts of interest that are not addressed. Poor-quality cohort studies have a clear, high risk of bias that would affect findings.

## Quality of Evidence Assessment

### *Overall Quality of Evidence*

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group.[12,13] Two independent experienced researchers assigned ratings. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are randomized controlled trials with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

## Appendix B. Full Evidence Tables

Table B1. Demographics Table for Included Clinical Trials

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| **GLP-1 Receptor Agonists** | | |
| Hernandez et al. (2018)[14]<br>NCT02465515<br>GlaxoSmithKline<br>Albiglutide (Tanzeum)<br>HARMONY OUTCOMES<br>Total N = 9,463<br>• 30 to 50 mg, n = 4,731<br>• Placebo, n = 4,732 | • Weekly SC injections with concomitant cardiovascular, anti-hyperglycemic, and insulin secretagogue medications managed by usual care providers excluding additional GLP-1 agonists<br>○ At ≥ 5 weeks dose could be increased to 50 mg at investigator discretion or decreased back to 30 mg if not tolerated<br>• Individuals with type 2 diabetes ≥ 40 years & CVD:<br>○ CAD, n = 6,678 (71%)<br>○ PAD, n = 2,354 (25%)<br>○ CBD, n = 2,342 (25%)<br>○ Prior HF, n = 1,922 (20%) | • Mean age: 64.1 years (SD 8.)<br>• Mean HbA1c: 8.7% (SD 1.5)<br>• Mean diabetic duration: 14.15 years (SD 8.75)<br>• Median follow-up: 1.6 years (IQR 1.3-2.0, max 2.6)<br>• 31.0% female<br>Excluded for eGFR < 30 mL; severe gastroparesis; prior pancreatitis or risk factors; history of pancreatic neuroendocrine tumors; or personal/family history of MCT or MEN type 2. |
| Gerstein et al. (2019)[19]<br>NCT01394952<br>Eli Lilly<br>Dulaglutide (Trulicity)<br>REWIND<br>Total N = 9,901<br>• 1.5 mg, n = 4,949<br>• Placebo, n = 4,952 | • Weekly SC injections with SOC of up to 2 (i.e., 1 to 2) oral AHAs with or without basal insulin adherent to local guidelines, excluding additional GLP-1 agonists or pramlintide<br>• Individuals with type 2 diabetes with a BMI ≥ 23 and:<br>○ ≥ 50 years with vascular disease (MI, ischemic stroke, revascularization, hUA)<br>○ ≥ 55 years with myocardial ischemia; coronary, carotid, or lower extremity artery stenosis; LV hypertrophy; eGFR < 60 mL or albuminuria<br>○ ≥ 60 years with ≥ 2 risk factors of tobacco use, dyslipidemia, hypertension, or abdominal obesity<br>• Prior CVD, n = 3,114 (31.5%)<br>• Prior MI or ischemic stroke, n = 2,035 (20.6%)<br>• Prior HF, n = 853 (8.6%) | • Mean age: 66.2 years (SD 6.5)<br>• Median HbA1c: 7.2% (IQR 6.6 to 8.1)<br>• Median diabetic duration: 9.5 years (IQR 5.5 to 14.5)<br>• Median follow-up: 5.4 years (IQR 5.1 to 5.9)<br>• 46.3% female<br>Excluded for eGFR < 15 mL; cancer in previous 5 years; severe hypoglycemia within last year; coronary or cerebrovascular event within 2 months; or plans for revascularization. |

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| Holman et al. (2019)[15]<br>NCT01144338<br>AstraZeneca<br>Exenatide ER (Bydureon)<br>EXSCEL<br>Total N = 14,752<br>• 2 mg, n = 7,356<br>• Placebo, n = 7,396 | • Weekly abdominal injections with SOC of up to 3 (i.e., 0 to 3) oral AHAs, insulin alone, or insulin with up to 2 (i.e., 0 to 2) oral AHAs excluding additional GLP-1 agonists<br>• Individuals with type 2 diabetes ≥ 18 years with or without previous CVD: CAD, ischemic CBD, or atherosclerotic peripheral disease<br>○ With previous CVD, n = 10,782 (73.1%)<br>○ Without previous CVD, n = 3,970 (26.9%)<br>○ Prior CAD, n = 7,794 (52.8%)<br>○ Prior CBD, n = 2,509 (17.0%)<br>○ Prior PAD, n = 2,800 (19.0%)<br>○ Prior CHF, n = 2,389 (16.2%) | • Median age: 62 years (IQR 56 to 68)<br>• Median HbA1c: 8.0% (IQR 7.3 to 8.9)<br>• Median diabetic duration: 12 years (IQR 7.0 to 17.5)<br>• Median follow-up: 3.2 years (IQR 2.2 to 4.4, max 6.8)<br>• 38.0% female<br>Excluded for ≥ 2 hypoglycemic episodes within prior 12 months; ESKD; eGFR < 30 mL; baseline calcitonin > 40 ng/L; or history of MCT or MEN type 2. |
| Marso et al. (2016)[17]<br>NCT01179048<br>Novo Nordisk<br>Liraglutide (Victoza)<br>LEADER<br>Total N = 9,340<br>• 1.8 mg, n = 4,668<br>• Placebo, n = 4,672 | • Daily SC injection with SOC excluding GLP-1 agonists, pramlintide or DPP-4 inhibitors<br>○ Injections started at 0.6 mg for 1 week, to 1.2 mg for 1 week, to 1.8 mg after an additional week. If not tolerated participants may decrease to 0.6 or 1.2 mg<br>• Eligible participants demonstrated ≥ 50% adherence to 2- to 3-week maximum open-label placebo run-in period with no dose escalation<br>• Individuals with type 2 diabetes:<br>○ ≥ 50 years with ≥ 1 CV condition: coronary heart disease, CBD, PAD, CKD (≥ stage 3), or CHF (NYHA class II or III).<br>○ ≥ 60 years with ≥ 1 CV risk factor: hypertension microalbuminuria or proteinuria; LV dysfunction; or ABI < 0.9<br>• History of CVD, n = 6,764 (72.4%)<br>• History of CKD, n = 2,307 (24.7%)<br>• History of CVD and CKD, n = 1,473 (15.8%)<br>• History of HF, n = 1,667 (17.8%) | • Mean age: 64.3 years (SD 7.2)<br>• Mean HbA1c: 8.7% (SD 1.55)<br>• Mean diabetic duration: 12.8 years (SD 8.05)<br>• Median follow-up: 3.8 years*<br>• 35.7% female<br>Excluded for use of rapid-acting insulin; familial/personal history of MEN type 2 or MCT; or an acute coronary or cerebrovascular event 14 days prior to screening or randomization. |

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| Pfeffer et al. (2015)[18]<br>NCT01147250<br>Sanofi<br>Lixisenatide (Adlyxin)<br>ELIXA<br>Total N = 6,068<br>• 10 to 20 µg, n = 3,034<br>• Placebo, n = 3,034 | • Daily SC injections with SOC aside from additional GLP-1 agonists or DPP-4 inhibitors<br>○ Fixed-dose escalation starting at 10 µg for 2 weeks and increased to the daily maximum 20 µg dose at the investigator's discretion<br>• Participants completed a 1-week unblinded placebo run-in period prior to randomization<br>• Individuals with type 2 diabetes experiencing an acute coronary event within 180 days of screening:<br>○ History of HF, n = 1,358 (22.4%)<br>○ History of CABG, n = 507 (8.4%)<br>○ History of stroke, n = 331 (5.5%)<br>○ History of PAD, n = 466 (7.7%)<br>○ History of atrial fibrillation, n = 366 (6.0%) | • Mean age: 60.25 years (SD 9.63)<br>• Mean HbA1c: 7.65% (SD 1.3)<br>• Mean diabetic duration: 9.3 years (SD 8.25)<br>• Median follow-up: 25 months*<br>• 30.7% female<br>Excluded for age < 30 years; percutaneous coronary intervention within previous 15 days; CABG surgery for the qualifying event; planned coronary revascularization 90 days after screening; eGFR < 30 mL; or HbA1c < 5.5% or > 11.0%. |
| Marso et al. (2016)[18]<br>NCT01720446<br>Novo Nordisk<br>Semaglutide (Ozempic)<br>SUSTAIN-6<br>Total N = 3,297<br>• 0.5 mg, n = 826<br>• 0.5 mg placebo, n = 824<br>• 1.0 mg, n = 822<br>• 1.0 mg placebo, n = 825 | • Weekly SC injections with SOC aside from additional incretin therapies<br>○ Injections started at 0.25 mg for 4 weeks, 0.5 mg for an additional 4 weeks until reaching a maintenance dose of either 0.5 or 1.0 mg<br>• Individuals with type 2 diabetes:<br>○ ≥ 50 years with CKD (≥ stage 3) or CVD: CVD, CBD, PVD, or CHF (NYHA class II or III)<br>○ ≥ 60 years with CV risk factors: hypertension; microalbuminuria or proteinuria; LV dysfunction; or ABI < 0.9<br>• History of CKD, n = 353 (10.7%)<br>• History of CVD, n = 1,940 (58.8%)<br>• History of CKD and CVD, n = 442 (17.0%)<br>• CV risk factors, n = 560 (17%) | • Mean age: 64.6 years (SD 7.4)<br>• Mean HbA1c: 8.7% (SD 1.46)<br>• Mean diabetic duration: 13.9 years (SD 8.11)<br>• Median follow-up: 2.1 years*<br>• 39.3% female<br>Excluded for DPP-4 inhibitor use 30 days prior to screening; GLP-1 agonist or non-basal/premixed insulin use 90 days prior to screening; history of acute coronary or cerebrovascular events 90 days prior to randomization; planned revascularization; or dialysis. |

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| Husain et al. (2019)[20]<br>NCT02692716<br>Novo Nordisk<br>Oral semaglutide (Rybelsus)<br>PIONEER-6<br>Total N = 3,183<br>• 3 mg, n = 1,591<br>• Placebo, n = 1,592 | • Daily oral administration with SOC excluding GLP-1 agonists or DPP-4 inhibitors.<br>○ A fixed dose escalation procedure was used to reach the target daily maximum of 14 mg<br>• Individuals with type 2 diabetes:<br>○ ≥ 50 years with CVD or CKD (n = 2,695, 84.7%): prior MI, stroke, TIA, or revascularization; arterial stenosis > 50%; coronary heart disease; cardiac ischemia; CHF (NYHA class II to III); eGFR 30 to 59 mL<br>○ ≥ 60 years with CV risk factors (n = 488, 15.3%): microalbuminuria or proteinuria; hypertension & LV hypertrophy; LV dysfunction; or ABI < 0.9<br>• Prior CVD, n = 2,695 (84.7%)<br>• CV risk, n = 488 (15.3%)<br>• Prior MI, n = 1,150 (36.1%)<br>• Prior HF, n = 388 (12.2%)<br>• Prior CHD, n = 731 (23.0%) | • Mean age: 66 years (SD 7)<br>• Mean HbA1c: 8.2% (SD 1.6)<br>• Mean diabetic duration 14.9 years (SD 8.5)<br>• Median time in trial: 15.9 months (range 0.4 to 20.0)<br>• 31.6% female<br>Excluded for usage of any GLP-1 agonist, DPP-4 inhibitor, or pramlintide 90 days prior to screening; NYHA class IV HF; planned coronary, carotid, or peripheral artery revascularization; MI, stroke, hUA, or hospitalization for TIA 60 days prior to screening; dialysis; eGFR < 30 mL; or proliferative retinopathy or maculopathy. |
| DPP-4 Inhibitors | | |
| White et al. (2013)[23]<br>NCT0096878<br>Takeda Pharmaceutical<br>Alogliptin (Nesina)<br>EXAMINE<br>Total N = 5,380<br>• 25 mg, n = 1,929<br>• 12.5 mg, n = 694<br>• 6.25 mg, n = 78<br>• Placebo, n = 2,679 | • Daily oral administration with SOC excluding additional DPP-4 inhibitors or GLP-1 agonists<br>○ Dose stratified by baseline eGFR: ≥ 60 mL 25 mg alogliptin, 30 to < 60 mL 12.5 mg alogliptin, < 30 mL 6.25 mg alogliptin<br>• Individuals with type 2 diabetes ≥ 18 years and recent ACS 15 to 90 days prior to randomization:<br>○ History of MI, n = 4,152 (77.2%)<br>○ History of hUA, n = 1,214 (22.6%)<br>○ History of CHF, n = 1,501 (27.9%)<br>○ History of PAD, n = 514 (9.5%) | • Median age: 61 years*<br>• Median HbA1c: 8.0% (SD 1.1)<br>• Median diabetic duration: 7.2 years (IQR 2.7 to 13.7)<br>• Median follow-up: 18 months* (max 40)<br>• 32.0% female<br>Excluded for unstable cardiac disorders; dialysis 14 days prior to screening; GLP-1 agonist use at screening; DPP-4 inhibitor use > 14 days or within 3 months of screening. |

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| Rosenstock et al. (2019)[74]<br>NCT01897532<br>Boehringer Ingelheim<br>Linagliptin (Tradjenta)<br>CARMELINA<br>Total N = 6,979<br>• 5 mg, n = 3,494<br>• Placebo, n = 3,485 | • Daily oral administration with SOC excluding GLP-1 agonists, SGLT-2 inhibitors, or DPP-4 inhibitors<br>○ Required stable AHA dose ≥ 8 weeks prior to randomization<br>• Individuals with type 2 diabetes ≥ 18 years with BMI ≤ 45 at high CV and renal risk: prevalent ASCVD with micro- or macroalbuminuria; or impaired kidney function:<br>○ History of HF, n = 1,873 (26.8%)<br>○ IHD, n = 4,081 (58.5%)<br>○ History of hypertension, n = 6,349 (91.0%)<br>○ Baseline atrial fibrillation, n = 673 (9.6%)<br>○ Baseline CVD, n = 3,978 (57%)<br>○ Baseline kidney disease, n = 5,165 (74%)<br>○ Baseline CVD and kidney disease, n = 2,303 (33%) | • Mean age: 65.9 years (SD 9.1)<br>• Mean HbA1c: 7.95% (SD 1.0)<br>• Mean diabetic duration: 14.8 years (SD 9.45)<br>• Median follow-up: 2.2 years (IQR 1.6 to 3.0)<br>• 37.1% female<br>Excluded for ESRD (eGFR < 15 mL or maintenance dialysis); GLP-1 agonist, DPP-4 inhibitor, or SGLT-2 inhibitor treatment ≥ 7 consecutive days. |
| Rosenstock et al. (2019)[25]<br>NCT01243424<br>Boehringer Ingelheim<br>Linagliptin (Tradjenta)<br>CAROLINA<br>Total N = 6,042<br>• 5 mg, n = 3,023<br>• 1 to 4 mg glimepiride, n = 3,010 | • Daily oral administration with SOC<br>○ Glimepiride started at 1 mg/day and up titrated to a max of 4 mg/day every 4 weeks for first 16 weeks of the trial<br>• Individuals with type 2 diabetes with HbA1c 6.5 to 8.5% at high CV risk: established ASCVD or diabetic duration > 10 years, SBP > 140 mmHG, current smoker, LDL ≥ 135 mg/dL, age ≥ 70 years, or evidence of microvascular complications:<br>○ History of HF, n = 271 (4.5%)<br>○ History of CAD, n = 1,905 (31.6%<br>○ History of PAD, n = 407 (6.7%)<br>○ History of CBD, n = 727 (12.0%)<br>○ Established ASCVD, n = 2,534 (42%) | • Mean age: 64.05 years (SD 9.5)<br>• Mean HbA1c: 7.2% (SD 0.6)<br>• Median diabetic duration: 6.25 years (IQR 2.95 to 11.05)<br>• Median follow-up: 6.3 years (IQR 5.9 to 6.6)<br>• 40.0% female<br>Excluded for insulin therapy; previous use of DPP-4 inhibitors, GLP-1 agonists, or TZDs; or NYHA HF class III to IV. |

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| Scirica et al. (2013)[22]<br>NCT01107886<br>AstraZeneca & Bristol Myers Squibb<br>Saxagliptin (Onglyza)<br>SAVOR-TIMI 53<br>Total N = 16,492<br>• 2.5 mg, n = 1,294<br>• 5.0 mg, n = 6,986<br>• Placebo, n = 8,212 | • Daily oral administration with SOC excluding additional GLP-1 agonists or DPP-4 inhibitors<br>○ Dose stratified by baseline eGFR: ≤ 50 mL 2.5 mg saxagliptin, > 50 mL 5.0 mg saxagliptin<br>• Individuals with type 2 diabetes and CVD or CV risk factors:<br>○ CVD: ≥ 40 years with a prior clinical atherosclerotic event involving the coronary, cerebrovascular, or peripheral vascular system<br>○ CV risk factors: men ≥ 55 years & women ≥ 60 years with either dyslipidemia, hypertension, or current tobacco use<br>• Prior atherosclerotic disease, n = 12,959 (78.6%)<br>• History of MI, n = 6,237 (37.8%)<br>• History of HF, n = 2,105 (12.8%) | • Mean age: 65 years (SD 8.55)<br>• Mean HbA1c: 8.0% (SD 1.4)<br>• Median diabetic duration: 10.3 years (IQR 5.25 to 16.65)<br>• Median follow-up: 2.1 years (IQR 1.8 to 2.3)<br>• 33.1% female<br>Excluded for current incretin treatment or within 6 months, end-stage renal disease with long-term dialysis, kidney transplantation, or serum creatinine > 6.0 mg/dL. |
| Green et al. (2015)[24]<br>NCT00790205<br>Merck Sharp & Dohme<br>Sitagliptin (Januvia)<br>TECOS<br>Total N = 14,671<br>• 100 mg, n = 6,646<br>• 50 mg, n = 686<br>• Placebo, n = 7,339 | • Daily oral administration with SOC excluding GLP-1 agonists or DPP-4 inhibitors<br>○ Individuals required to obtain HbA1c of 6.5 to 8% if treated with stable doses of 1 or 2 oral AHAs or insulin<br>○ Dose stratified by baseline eGFR: > 50 mL 100 mg sitagliptin, ≥ 30 mL and < 50 mL 50 mg sitagliptin<br>• Individuals with type 2 diabetes ≥ 50 years and CVD (history of CAD, ischemic CBD, or atherosclerotic PAD):<br>○ Prior CVD, n = 10,863 (74.0%)<br>○ Prior MI, n = 6,255 (42.6%)<br>○ Prior CBD, n =3,588 (24.5%)<br>○ Prior PAD, n = 2,433 (16.6%)<br>○ Prior CHF, n = 2,643 (18.0%) | • Mean age: 65.5 years (SD 8.0)<br>• Mean HbA1c: 7.2% (SD 0.5)<br>• Mean diabetic duration: 11.6 years (SD 8.1)<br>• Median follow-up: 3.0 years (IQR 2.3 to 3.8, max 5.7)<br>• 29.3% female<br>Excluded for use of DPP-4 inhibitors, GLP-1 agonists, or TZDs (except pioglitazone) within preceding 3 months; history of ≥ 2 severe hypoglycemic episodes during preceding year; or eGFR < 30 at baseline. |

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| **SGLT-2 Inhibitors** | | |
| Mahaffey et al. (2018)[31]<br>Neal et al. (2017)[28]<br>NCT01032629<br>NCT01989754<br>Janssen Pharmaceuticals<br>Canagliflozin (Invokana)<br>Program Total N = 10,142<br>CANVAS, N = 4,330<br>• 100 mg, n = 1,445<br>• 300 mg, n = 1,443<br>• Placebo, n = 1,441<br>CANVAS-R, N = 5,812<br>• 100 mg, n = 2,904<br>• Placebo, n = 2,903 | • Daily oral administration with SOC excluding SGTL-2 inhibitors, corticosteroids, immunosuppressives, or rosiglitazone<br>○ CANVAS-R started at 100 mg and could increase to 300 mg after 13 weeks of treatment<br>○ Required 2-week single-blind, placebo run-in<br>○ Required stable AHA regimen ≥ 8 weeks prior to screening and throughout run-in<br>• Individuals with type 2 diabetes:<br>○ Secondary Cohort: ≥ 30 years with history of ASCVD or CV events<br>○ Primary Cohort: ≥ 50 years with ≥ 2 CV risk factors: diabetic duration ≥ 10 years, SBP > 140 mmHG, current smoker, micro- or macroalbuminuria, or HDL < 38.7 mg/dL<br>• History of CVD, n = 6,656 (65.6%)<br>• History of HF, n = 1,461 (14.4%)<br>• History of coronary vascular disease, n = 5,721 (56.4%)<br>• History of CBD, n = 1,958 (19.3%)<br>• History of PVD, n = 2,113 (20.8%) | • Mean age: 63.3 years (SD 8.3)<br>• Mean HbA1c: 8.2% (SD 0.9)<br>• Mean diabetic duration: 13.5 years (SD 7.8)<br>• Mean follow-up:<br>○ CANVAS, 294.5 weeks (SD 75.05)<br>○ CANVAS-R, 107.95 weeks (SD 19.9)<br>• 35.8% female<br>Excluded for eGFR < 30 mL; history of dialysis; renal transplant; inadequately controlled thyroid disorder; ≥ 1 hypoglycemia episode within 6 months of screening, renal glycosuria, or hereditary glucose-galactose malabsorption. |

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| Perkovic et al. (2019)[26]<br>NCT02065791<br>Janssen Pharmaceuticals<br>Canagliflozin (Invokana)<br>CREDENCE<br>Total N = 4,401<br>• 100 mg, n = 2,202<br>• Placebo, n = 2,199 | • Daily oral administration with SOC excluding dual use of ACE inhibitors & ARBs, direct renin inhibitors, mineralocorticoid receptor agonists, or SGLT-2 inhibitors<br>○ Required to have stable doses of an ACE inhibitor or ARB for ≥ 4 weeks prior to randomization<br>○ Required 2 week, single-blind placebo run-in and randomization eligible if received ≥ 80% of the run-in<br>• Individuals with type 2 diabetes ≥ 30 years of age and CKD defined as eGFR 30 to < 90 mL and UACR >300 to 5000<br>○ History of CVD, n = 2,220 (50.4%)<br>○ History of HF, n = 652 (14.8%)<br>○ History of amputation, n = 234 (5.3%) | • Mean age: 63.0 years (SD 9.2)<br>• Mean HbA1c: 8.3% (SD 1.3)<br>• Mean diabetic duration: 15.8 years (SD 8.6)<br>• Median follow-up: 2.62 years (range 0.02 to 4.53)<br>• 33.9% female<br>Excluded for non-diabetic kidney disease; immunosuppressant treatment for kidney disease; history of dialysis, kidney transplantation, diabetic ketoacidosis, renal glycosuria, hereditary glucose-galactose malabsorption, uncontrolled hypertension. |
| Wiviott et al. (2019)[30]<br>NCT01730534<br>AstraZeneca<br>Dapagloflozin (Farxiga)<br>DECLARE-TIMI 58<br>Total N = 17,160<br>• 10 mg, n = 8,582<br>• Placebo, n = 8,578 | • Daily oral administration with SOC excluding pioglitazone, rosiglitazone, or other SGLT-2 inhibitors<br>○ Required 4-to-8 week single-blind placebo run-in<br>• Individuals with type 2 diabetes ≥ 40 years and eGFR of ≥ 60 mL with:<br>○ CV risk factors: men ≥ 55 or women ≥ 60 with hypertension, dyslipidemia, or current tobacco use.<br>○ Established ASCVD: IHD, ischemic CBD, or PAD<br>• Established ASCVD, n = 6,974 (40.6%)<br>• History of CAD, n = 5,658 (32.9%)<br>• History of PAD, n = 1,025 (5.9%)<br>• History of CBD, n = 1,301 (7.6%)<br>• History of HF, n = 1,724 (10.0%) | • Mean age: 63.9 years (SD 6.8)<br>• Mean HbA1c: 8.3% (SD 1.2)<br>• Mean diabetic duration: 10.5 years (IQR 6.0 to 16.0)<br>• Median follow-up: 4.2 years (IQR 3.9 to 4.4)<br>• 37.4% female<br>Excluded for creatinine clearance < 60 mL/min at enrollment; acute CV or cerebrovascular event within 8 weeks of randomization; history of bladder cancer or radiation to lower abdomen/pelvis. |

| Study Authors; Registration Number; Manufacturer; Generic Drug (Brand Name); Trial Name; N | Frequency; Study Population | Study Demographics; Exclusion Criteria |
|---|---|---|
| Zinman et al. (2015)[27]<br>NCT01131676<br>Boehringer Ingelheim<br>Empagliflozin (Jardiance)<br>EMPA-REG OUTCOME<br>Total N = 7,020<br>• 10 mg, n = 2,345<br>• 25 mg, n = 2,342<br>• Placebo, n = 2,333 | • Daily oral administration with SOC<br>○ AHAs unchanged for first 12 weeks and adjusted after 12 weeks if medically necessary<br>○ Required 2-week open-label placebo run-in<br>○ Required ≥ 12 week washout from all AHAs if HbA1c ≥ 7.0% and ≤ 9.0% or stable doses of AHAs for ≥ 12 weeks if HbA1c ≥ 7.0% and ≤ 10.0%<br>• Individuals with type 2 diabetes ≥ 18 years with BMI < 45, eGFR > 30 mL, and high CV risk: history of MI, UA, or stroke > 2 months prior; CAD in ≥ 2 major coronary arteries; single-vessel CAD; or occlusive PAD:<br>○ History of HF, n = 706 (10.1%)<br>○ History of MI, n = 3,273 (46.6%)<br>○ History of PAD, n = 1,461 (20.8%)<br>○ History of stroke, n = 1,637 (23.3%)<br>○ History of CAD, n = 5,308 (75.6%) | • Mean age: 63.1 years (SD 8.6)<br>• Mean HbA1c: 8.07% (SD 0.85)<br>• Time since type 2 diabetes diagnosis:<br>○ ≤ 1 year n = 128 (2.7%)<br>○ >1 to 5 years n = 712 (15.2%)<br>○ > 5 to 10 years n = 1,175 (25.1%)<br>○ > 10 years n = 2,672 (57.0%)<br>• Median follow-up: 3.1 years (IQR 1.9 to 3.4)<br>• 28.8% female: 10 mg 29.5%, 25 mg 28.1%<br>Excluded for uncontrolled hyperglycemia; eGFR < 30 mL; liver disease; planned cardiac or angioplasty within 3 months; bariatric surgery within 2 years; chronic malabsorption surgery; anti-obesity drugs within 3 months; systemic steroid treatment at informed consent; history of cancer. |

*Note. * Denotes interquartile range, standard deviation, or range was not reported. Abbreviations. ABI: ankle-brachial index; ACE: angiotensin-converting-enzyme; ACS: acute coronary syndrome; AHA: anti-hyperglycemic agent; ARB: angiotensin-receptor blocker; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CBD: cerebrovascular disease; CHD: coronary heart disease; CHF: congestive heart failure; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; ESRD: end-stage renal disease; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin test of blood glucose (sugar); HDL: high-density lipoprotein (cholesterol); HF: heart failure; hUA: hospitalization for unstable angina; IHD: ischemic heart disease; IQR: interquartile range; LV: left ventricular; MCT: medullary thyroid cancer; LDL: low-density lipoprotein (cholesterol); MEN: multiple endocrine neoplasia; MI: myocardial infarction; NCT: U.S. National Clinical Trials number; NYHA: New York Heart Association; PAD: peripheral artery disease; PVD: peripheral vascular disease; SBP: systolic blood pressure; SC: subcutaneous; SD: standard deviation; SGLT-2: sodium-glucose cotransporter-2; SOC: standard of care; TIA: transient ischemic attack; TZD: thiazolidinediones; UA: unstable angina; UACR: urinary albumin-creatinine ratio.*

Table B2. Full Evidence Tables for Included Clinical Trials

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| **GLP-1 Receptor Agonists** | | | |
| Hernandez et al. (2018)[14]<br>NCT02465515<br>GlaxoSmithKline<br>Albiglutide (Tanzeum)<br>HARMONY OUTCOMES<br>Multisite international<br>Total N = 9,463<br>• 30 to 50 mg, n = 4,731<br>• Placebo, n = 4,732 | • All-cause mortality: 4.0% vs. 4.0%<br>○ HR 0.95 (0.79 to 1.16); *P* = .64<br>• MACE: 7.0% vs. 9.0%<br>○ HR 0.78 (0.68 to 0.90); *P* = .0006<br>○ CV death: 3.0% vs. 3.0%; HR 0.93 (0.73 to 1.19); *P* = .58<br>○ Fatal or nonfatal MI: 4.0% vs. 5.0%; HR 0.75 (0.61 to 0.90); *P* = .003<br>○ Fatal or nonfatal stroke: 2.0% vs. 2.0%; HR 0.86 (0.66 to 1.14); *P* = .30<br>• †*SAE: 27.3% vs. 35.5%*<br>○ RR 0.77 (0.72 to 0.81); *P* < .00000001<br>• Expanded composite: 8.0% vs. 10.0%<br>○ HR 0.78 (0.69 to 0.90); *P* = .0005<br>• CV death or hHF: 4.0% vs. 5.0%<br>○ HR 0.85 (0.70 to 1.04); *P* = .11 | • *Pancreatitis: 0.2% vs. 0.1%<br>○ RR 1.43 (0.54 to 3.75)<br>• *Injection site reactions: 2.0% vs. 1.0%<br>○ RR 2.96 (1.95 to 4.51)<br>• *Hematological neoplasia: 0.2% vs. 0.1%<br>○ RR 1.80 (0.60 to 5.36)<br>• *Pancreatic cancer: 0.1% vs. 0.1%<br>○ RR 1.20 (0.3 to 3.93)<br>• *Hepatobiliary disorders: 1.1% vs. 0.9%<br>○ RR 1.24 (0.83 to 1.87)<br>• *Bilirubin ≥ 2x ULN: 0.2% vs. 0.1%<br>○ RR 1.71 (0.68 to 4.35) | <u>HARMONY 1-8 pooled analysis</u>[62]<br>• Injection-site AE 16% vs. 7%<br>• Reactions 1.6% vs. 0%<br>• Nausea AE 0.6% vs. 0.5%<br>• Vomiting AE 0.4% vs. 0.2%<br>• Diarrhea AE 0.3% vs. 0.4%<br>• Hypoglycemia (% of events)<br>○ Albiglutide + SU (10-19%)<br>○ Albiglutide + insulin (19%)<br>○ Albiglutide + other (1-3%)<br>• SAE leading to discontinuation<br>○ AF 0.5% vs. 0.1%<br>○ Appendicitis 0.3% vs. 0%<br>○ Pancreatitis 0.3% vs. 0.1% |
| Gerstein et al. (2019)[19]<br>NCT01394952<br>Eli Lilly<br>Dulaglutide (Trulicity)<br>REWIND<br>Multisite international<br>Total N = 9,901<br>• 1.5 mg, n = 4,949<br>• Placebo, n = 4,952 | • All-cause mortality: 10.8% vs. 12.0%<br>○ HR 0.90 (0.80 to 1.01); *P* = .07<br>• MACE: 12.0% vs. 13.4%<br>○ HR 0.88 (0.79 to 0.99); *P* = .03<br>○ CV death: 6.4% vs. 7.0%; HR 0.91 (0.78 to 1.06); *P* = .21<br>○ Nonfatal MI: 4.1% vs. 4.3%; HR 0.96 (0.79 to 1.16) , *P* = .65<br>○ Nonfatal stroke: 2.7% vs. 3.5%; HR 0.76 (0.61 to 0.95) , *P* = .02<br>• Fatal or nonfatal MI: 4.5% vs. 4.7%<br>○ HR 0.96 (0.79 to 1.15); *P* = .63<br>• Fatal or nonfatal stroke: 3.2% vs. 4.1% | • Endocrine disorder SAE: 0.5% vs. 0.2%<br>○ RR 2.00; *P* = .05<br>• Reproductive system & breast disorder SAE: 1.1% vs. 0.8%<br>○ RR 1.33; *P* = .18<br>• Reproductive system & breast disorder AE: 8.2% vs. 8.1%<br>○ RR 1.02; *P* = .76<br>• GI SAE: 4.8% vs. 4.6%<br>○ RR 1.04; *P* = .70<br>• GI AE: 47.4% vs. 34.1%<br>○ RR 1.39; *P* < .0001 | <u>Subgroup analyses</u><br>• With vs. Without CVD *P* = .97<br>• Age *P* = .57<br>• Sex *P* = .60<br>• Diabetic duration *P* = .88<br>• BMI < 32 vs. ≥ 32 *P* = .21<br>• Geographic region *P* = .008<br>• Baseline HbA1c < 7.2% vs. ≥ 7.2% *P* = .75 |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ HR 0.76 (0.62 to 0.94); *P* = .01<br>• hHF: 4.3% vs. 4.6%<br>○ HR 0.93 (0.77 to 1.13); *P* = .46<br>• *SAE: 69.4% vs. 72.5%*<br>○ RR 0.96 (0.93 to 0.98), *P* = .0006<br>• Fatal stroke, *P* = .34<br>○ 0.5% vs. 0.7%; HR 0.78 (0.47 to 1.30)<br>• Fatal MI: 0.5% vs. 0.4%<br>○ HR 1.29 (0.72 to 2.30); *P* = .40<br>• hUA: 1.8% vs. 1.6%<br>○ HR 1.14 (0.84 to 1.54); *P* = .41 | | |
| Holman et al. (2019)[15]<br>NCT01144338<br>AstraZeneca<br>Exenatide ER (Bydureon)<br>EXSCEL<br>Multisite international<br>Total N = 14,752<br>• 2 mg, n = 7,356<br>• Placebo, n = 7,396 | • All-cause mortality: 6.9% vs. 7.9%<br>○ HR 0.86 (0.77 to 0.97); *P* = .02<br>• MACE: 11.4% vs. 12.2%<br>○ HR 0.91 (0.83 to 1.00); *P* = .06<br>○ *CV death: 4.6% vs. 5.2%; HR 0.88 (0.73 to 1.05)<br>○ *Nonfatal stroke: 2.1% vs. 2.4%; HR 0.86 (0.70 to 1.07)<br>○ *Nonfatal MI: 6.2% vs. 6.4%; HR 0.95 (0.84 to 1.09)<br>• hHF: 3.0% vs. 3.1%<br>○ HR 0.94 (0.78 to 1.13); *P* = .48<br>• Nonfatal or fatal MI: 6.6% vs. 6.7%<br>○ HR 1.29 (0.63 to 2.66); *P* = .62<br>• Nonfatal or fatal stroke: 2.5% vs. 2.9%<br>○ ITT: HR 0.85 (0.70 to 1.03); *P* = .10<br>• †*SAE: 16.8% vs. 16.6%*<br>○ RR 1.01 (0.94 to 1.09), P =.71<br>• Fatal stroke: 0.2% vs. 0.3%<br>○ HR 0.71 (0.39 to 1.30)<br>• Fatal MI: 0.2% vs. 0.2% | • †Pancreatitis: 0.4% vs. 0.3%<br>○ RR 1.19 (0.67 to 2.09); P = .55<br>• †Any cancer: 4.8% vs. 4.0%<br>○ RR 0.99 (0.86 to 1.14); P = 87<br>• †Pancreatic cancer: 0.2% vs. 0.2%<br>○ RR 0.94 (0.47 to 1.90); P = .87<br>• †Medullary thyroid carcinoma: 0.02% vs. 0.01%<br>○ RR 2.01 (0.18 to 22.13); P = .62<br>• †Thyroid papillary carcinoma: 0.1% vs. 0.05%<br>○ RR 2.51 (0.79 to 7.99); P = .12<br>• †Severe hypoglycemia: 3.4% vs. 3.0%<br>○ RR 1.13 (0.95 to 1.35); P = .17<br>• *Premature discontinuation: 43.0% vs. 45.2%<br>○ RR 0.95 (0.93 to 1.01) | <u>Subgroup analyses</u><br>• MACE by age<br>○ ≥ 65 years HR 0.80 (0.71 to 0.91)<br>○ < 65 years HR 1.05 (0.92 to 1.21); *P* = .005<br>○ ≥ 75 years HR 0.82 (0.64 to 1.05)<br>○ < 75 years HR 0.94 (0.84 to 1.03); *P* = .34<br>• ACM by baseline HF; *P* = .03<br>○ With HR 1.05 (0.85 to 1.29)<br>○ Without HR 0.79 (0.69 to 0.92)<br>• ACM or HF by baseline HF; *P* = .02<br>○ With HR 1.07 (0.89 to 1.29)<br>○ Without HR 0.81 (0.71 to 0.93)<br>• First + recurrent hHF |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ HR 1.29 (0.63 to 2.66)<br>• Hospitalization for ACS: 8.2% vs. 7.7%<br>○ HR 1.05 (0.94 to 1.18); *P* = .40 | | ○ HR 0.82 (0.68 to 0.99); *P* = .04 |
| Marso et al. (2016)[17]<br>NCT01179048<br>Novo Nordisk<br>Liraglutide (Victoza)<br>LEADER<br>Multisite international<br>Total N = 9,340<br>• 1.8 mg, n = 4,668<br>• Placebo, n = 4,672 | • All-cause mortality: 8.2% vs. 9.6%<br>○ HR 0.85 (0.74 to 0.97); *P* = .02<br>• MACE: 13.0% vs. 14.9%<br>○ HR 0.87 (0.78 to 0.97); *P* = .01<br>○ CV death: 4.7% vs. 6.0%; HR 0.78 (0.66 to 0.93); *P* = .01<br>○ Nonfatal MI: 6.0% vs. 6.8%; HR 0.88 (0.75 to 1.03); *P* = .11<br>○ Nonfatal stroke: 3.4% vs. 3.8%; HR 0.89 (0.72 to 1.11); *P* = .30<br>• hHF: 4.7% vs. 5.3%<br>○ HR 0.87 (0.73 to 1.05); *P* = .14<br>• Fatal or nonfatal MI: 6.3% vs. 7.3%<br>○ HR 0.86 (0.73 to 1.00); *P* = .05<br>• Fatal or nonfatal stroke: 3.7% vs. 4.3%<br>○ HR 0.86 (0.71 to 1.06); *P* = .16<br>• SAE: 49.7% vs. 50.4%<br>○ RR 0.99 (0.95 to 1.03), P = .51<br>• MACE + coronary revascularization, hHF, or hUA: 20.3% vs. 22.7%<br>○ HR 0.88 (0.81 to 0.96); *P* = .005<br>• Coronary revascularization: 8.7% vs. 9.4%<br>○ HR 0.91 (0.80 to 1.04); *P* = .18<br>• hUA: 2.6% vs. 2.7%<br>○ HR 0.98 (0.76 to 1.26); *P* = .87<br>• Non-CV death: 3.5% vs. 3.6%<br>○ HR 0.95 (0.77 to 1.18); *P* = .66<br>• Fatal MI: 0.4% vs. 0.6%<br>○ HR 0.60 (0.33 to 1.10); *P* = .10 | • *Any neoplasm HR 1.12 (0.98 to 1.28)<br>○ *Malignant HR 1.06 (0.90 to 1.25)<br>○ *Benign HR 1.16 (0.93 to 1.44)<br>○ *Skin (non-melanoma) HR 1.25 (0.90 to 1.75)<br>○ *Breast HR 1.06 (0.57 to 1.96)<br>○ *Urinary bladder HR 1.24 (0.58 to 2.66)<br>○ *Kidney/renal pelvis HR 1.88 (0.84 to 4.22)<br>○ *Hepatic/biliary HR 1.62 (0.67 to 3.90)<br>○ *Pancreatic HR 2.59 (0.92 to 7.27)<br>○ *Melanoma HR 2.59 (0.92 to 7.27)<br>○ *Cervical/vaginal HR 3.03 (0.61 to 15.0)<br>○ *Lymphoma HR 1.33 (0.46 to 3.82)<br>○ *Oral cavity/pharynx HR 1.16 (0.39 to 3.46)<br>○ *Thyroid HR 1.66 (0.40 to 6.95)<br>• Hypothyroidism RR 1.33, *P* = .21<br>• Hyperthyroidism RR 1.63, *P* = .27<br>• Allergic reaction RR 1.34, *P* = .14<br>• Injection-site reaction RR 2.67; *P* = .002<br>• AE leading to discontinuation<br>○ RR 1.31; *P* < .001<br>○ Nausea RR 4.28; *P* < .001<br>○ Vomiting RR 15.51; *P* < .001<br>○ Diarrhea RR 5.40; *P* < .001 | <u>Subgroup analyses</u><br>• MACE by baseline eGFR; *P* = .01<br>○ < 60 mL HR 0.69 (0.57 to 0.85)<br>○ ≥ 60 mL HR 0.94 (0.83 to 1.07)<br>• Nonfatal stroke by baseline eGFR; *P* = .004<br>○ < 60 mL HR 0.53 (0.36 to 0.79)<br>○ ≥ 60 mL HR 1.07 ( 0.84 to 1.37)<br>• Any stroke by baseline eGFR; *P* = .01<br>○ < 60 mL HR 0.53 (0.36 to 0.79)<br>○ ≥ 60 mL HR 1.03 (0.81 to 1.31)<br>• *MACE by vascular disease<br>• Polyvascular HR 0.82 (0.66 to 1.02)<br>○ Single HR 0.82 (0.71 to 0.95)<br>• *Nonfatal MI by vascular disease<br>○ Polyvascular HR 0.65 (0.57 to 0.89)<br>○ Single HR 0.96 (0.78 to 1.19)<br>• *CV death by vascular disease |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | • Fatal stroke: 0.3% vs. 0.5%<br>○ HR 0.64 (0.34 to 1.19); *P* = .16<br>• TIA: 1.0% vs. 1.3%<br>○ HR 0.79 (0.54 to 1.16); *P* = .23<br>• Microvascular event: 7.6% vs. 8.9%<br>○ HR 0.84 (0.73 to 0.97); *P* = .02<br>• Retinopathy: 2.3% vs. 2.0%<br>○ HR 1.15 (0.87 to 1.52); *P* = .33<br>• Nephropathy: 5.7% vs. 7.2%<br>○ HR 0.78 (0.67 to 0.92); *P* = .003 | ○ Increased lipase RR 1.36; *P* = .43<br>○ Abdominal pain RR 3.67; *P* = .03<br>○ Decreased appetite RR 5.50; *P* = .01<br>○ Abdominal discomfort *P* = .002<br>• Acute gallstone disease RR 1.61; *P* < .001<br>• Cholelithiasis RR 1.36; *P* = .09<br>○ Acute cholecystitis RR 1.72; *P* = .05<br>• Gallbladder & biliary-tract related events<br>○ HR 1.60 (1.23 to 2.09); *P* < .001<br>• Complicated gallbladder stones<br>○ HR 3.19 (1.17 to 8.70); *P* = .02<br>• *First acute pancreatitis<br>○ HR 0.78 (0.42 to 1.44)<br>• DFU<br>○ HR 0.92 (0.75 to 1.13); *P* = .41<br>○ 1-year post-randomization HR 0.85 (0.67 to 1.07); *P* = .16<br>○ Involving underlying structure HR 0.80 (0.57 to 1.11); *P* = .17<br>○ Requiring revascularization HR 0.87 (0.48 to 1.58); *P* = .64<br>• Baseline DFU<br>○ HR 0.97 (0.69 to 1.35); *P* =.84<br>• No baseline DFU<br>○ HR 0.86 (0.66 to 1.11); *P* = .60<br>• Recurrent DFU<br>○ HR 0.97 (0.82 to 1.16); *P* = .76<br>• DFU-related amputations<br>○ HR 0.65 (0.45 to 0.95); *P* = .03<br>○ 1-year post-randomization HR 0.55 (0.36 to 0.84); *P* = .01 | ○ Polyvascular HR 0.92 (0.63 to 1.32)<br>○ Single HR 0.67 (0.53 to 0.85)<br>• hHF by baseline CV status; *P* = .03<br>○ MI/stroke HR 0.80 (0.62 to 1.03)<br>○ CVD only HR 0.70 (0.49 to 1.00)<br>○ CV risk factors HR 1.37 (0.92 to 2.05) |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | | • DFU-related infections<br>○ HR 0.81 (0.63 to 1.05); *P* = .11 | |
| Pfeffer et al. (2015)[16]<br>NCT01147250<br>Sanofi<br>Lixisenatide (Adlyxin)<br>ELIXA<br>Multisite international<br>Total N = 6,068<br>• 10 µg, n = 3,034<br>• Placebo, n = 3,034 | • All-cause mortality: 7.0% vs. 7.4%<br>○ HR 0.94 (0.78 to 1.13); *P* = .50<br>• MACE: 13.4% vs. 13.2%<br>○ HR 1.02 (0.89 to 1.17); *P* = .81<br>○ CV death 21.7% vs. 23.3%<br>○ Nonfatal MI 62.8% vs. 61.9%<br>○ Nonfatal stroke 13.3% vs. 12.3%<br>○ hUA 2.2% vs. 2.5%<br>• hHF: 4.0% vs. 4.2%<br>○ HR 0.96 (0.75 to 1.23); *P* = .75<br>• Fatal or nonfatal MI: 8.9% vs. 8.6%<br>○ HR 1.03 (0.87 to 1.22); *P* = .71<br>• Fatal or nonfatal stroke: 2.2% vs. 2.0%<br>○ HR 1.12 (0.79 to 1.58); *P* = .54<br>• hUA: 2.2% vs. 2.5%<br>○ HR 1.11 (0.47 to 2.62); *P* = .81<br>• CV Death: 5.1% vs. 5.2%<br>○ HR 0.98 (0.78 to 1.22); *P* = .85<br>• MACE or hHF: 15.0% vs. 15.5%<br>○ HR 0.97 (0.85 to 1.10); *P* = .63<br>• MACE, hHF, or revascularization: 21.8% vs. 21.7%<br>○ HR 1.00 (0.90 to 1.11); *P* = .96<br>• †SAE: 20.6% vs. 22.1%<br>○ RR 1.07 (0.97 to 1.18), P = .17 | • AE leading to discontinuation: 11.4% vs. 7.2%; *P* < .001<br>○ RR 1.54 (1.31 to 1.81); P < .0001<br>• †Psychiatric AE: 0.3% vs. 0.5%<br>○ RR 1.80 (0.60 to 5.37); P = .29<br>• †Pancreatitis AE: 0.2% vs. 0.3%<br>○ RR 1.60 (0.52 to 4.89); P = .41<br>• †Pancreatic cancer AE: 0.1% vs. 0.3%<br>○ RR 0.33 (0.09 to 1.23); P = .08<br>• †GI AE: 4.9% vs. 1.2%; *P* < .001<br>○ RR 4.03 (2.82 to 5.75); P < .0001<br>• †Hepatobiliary SAE: 1.2% vs. 0.9%<br>○ RR 1.29 (0.79 to 2.10); P = .32<br>• †Immune system SAE: 0.1% vs. 0.1%<br>○ RR 2.00 (0.37 to 10.91); P = .41<br>• †Neoplasm SAE: 2.4% vs. 2.0%<br>○ RR 1.18 (0.84 to 1.65); P = .33<br>• †Reproductive system SAE: 0.4% vs. 0.2%<br>○ RR 2.60 (0.93 to 7.29); P = .06<br>• †Systemic allergic reaction SAE: 0.9% vs. 0.8%<br>○ RR 1.08 (0.63 to 1.86); P = .78<br>†GI SAE: 2.2% vs. 2.7%<br>○ RR 0.82 (0.59 to 1.12); P = .21 | <u>Subgroup analyses</u><br>• MACE by baseline HF<br>○ With: 2.4% vs. 2.5%; HR 0.97 (0.67 to 1.40)<br>○ Without: 9.7% vs. 10.2%; HR 0.93 (0.66 to 1.30); *P* = .87 |
| Marso et al. (2016)[18]<br>NCT01720446<br>Novo Nordisk<br>Semaglutide (Ozempic)<br>SUSTAIN-6 | • All-cause mortality: 3.8% vs.3.6%<br>○ HR 1.05 (0.74 to 1.50); *P* = .79<br>• MACE: 6.6% vs. 6.9%<br>○ HR 0.74 (0.58 to 0.95); *P* = .02<br>○ CV death: 2.7% vs. 2.8%; HR 0.98 (0.65 to 1.48); *P* = .92 | • Retinopathy complications: 3.0% vs. 1.8%<br>○ HR 1.76 (1.11 to 2.78); *P* = .02<br>• Retinal photocoagulation: 2.3% vs. 1.2%<br>○ HR 1.91 (1.11 to 3.28); *P* = .02 | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
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| Multisite international<br>Total N = 3,297<br>• 0.5 mg, n = 826<br>• 0.5 mg, placebo n = 824<br>• 1.0 mg, n = 822<br>• 1.0 mg placebo, n = 825 | ○ Nonfatal MI: 2.9% vs. 3.9%; HR 0.74 (0.51 to 1.08); *P* = .12<br>○ Nonfatal stroke: 1.6% vs. 2.7%; HR 0.61 (0.38 to 0.99); *P* = .04<br>• hHF: 3.6% vs. 3.3%<br>○ HR 1.11 (0.77 to 1.61); *P* = .57<br>• SAE: 34.3% vs.38.0%<br>○ RR 0.90 (0.82 to 0.99), P = .03<br>• MACE + revascularization + hUA or hHF<br>○ 12.1% vs. 16.0%<br>○ HR 0.74 (0.62 to 0.89); *P* = .002<br>• ACM, nonfatal MI or nonfatal stroke<br>○ 7.4% vs. 9.6%<br>○ HR 0.77 (0.61 to 0.97); *P* = .03<br>• hUA: 1.3% vs. 1.6%<br>○ HR 0.82 (0.47 to 1.44); *P* = .49<br>• MACE 0.5 mg<br>○ HR 0.77 (0.55 to 1.08); *P* = .13<br>○ CV death: HR 1.02 (0.55 to 1.86); *P* = .96<br>○ Nonfatal MI: HR 0.88 (0.52 to 1.48); *P* = .62<br>○ Nonfatal stroke: HR 0.57 (0.31 to 1.06); *P* = .07<br>• MACE 1.0 mg<br>○ HR 0.71 (0.49 to 1.02); *P* = .06<br>○ CV death: HR 0.95 (0.54 to 1.67); *P* = .85<br>○ Nonfatal MI: HR 0.62 (0.36 to 1.07); *P* = .09<br>○ Nonfatal stroke: HR 0.68 (0.32 to 1.47); *P* = .33 | • Intravitreal agent: 1.0% vs. 0.8%<br>○ HR 1.23 (0.59 to 2.56); *P* = .58<br>• Vitreous hemorrhage: 1.0% vs. 0.4%<br>○ HR 2.29 (0.94 to 5.57); *P* = .07<br>• Diabetic blindness: 0.3% vs. 0.1%<br>○ HR 5.01 (0.59 to 42.88); *P* = .14<br>• New or worsening nephropathy: 3.8% vs. 6.1%<br>○ HR 0.64 (0.46 to 0.88); *P* = .005<br>• GI SAE:4.5% vs. 3.0%<br>○ RR 1.46 (1.34 to 1.58); P < .0001<br>○ 0.5 mg: 4.8% vs. 2.7%; RR 1.42 (1.27 to 1.59); P < .0001<br>○ 1.0 mg: 4.3% vs. 3.4%; RR 1.49 (1.33 to 1.67); P < .0001<br>• Acute pancreatitis SAE: 0.5% vs. 0.7%<br>○ RR 0.75 (0.32 to 1.78); P = .51<br>○ 0.5 mg: 0.7% vs. 0.4%; RR 1.99 (0.50 to 7.95); P = .32<br>○ 1.0 mg: 0.4% vs. 1.1%; RR 0.34 (0.09 to 1.23); P = .08<br>• Acute renal failure SAE: 3.9% vs. 4.2%<br>○ RR 0.94 (0.67 to 1.31); P = .73<br>○ 0.5 mg: 5.1% vs. 4.1%; RR 1.23 (0.79 to 1.92); P = .35<br>○ 1.0 mg: 2.8% vs. 4.2%; RR 0.66 (0.39 to 1.11); P = .11<br>• Neoplasms: 9.4% vs. 8.4%<br>○ *HR 1.12 (0.89 to 1.41)<br>○ RR 1.12 (0.90 to 1.39); P = .33<br>○ 0.5 mg: 8.0% vs. 8.5%; RR 0.94 (0.68 to 1.30); P = .71<br>○ 1.0 mg: 10.8% vs. 8.4%; RR 1.30 (0.96 to 1.75); P = .09 | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | | • Premalignant neoplasm: 0.6% vs. 0.3%<br>○ RR 2.00 (0.69 to 5.84); P = .20<br>○ 0.5 mg: 0.5% vs. 0.4%; RR 1.33 (0.30 to 5.92); P = .71<br>○ 1.0 mg: 0.7% vs. 0.2%; RR 3.01 (0.61 to 14.87); P = .16<br>• Benign neoplasms: 5.7% vs. 8.4%<br>○ RR 1.34 (0.99 to 1.81); P = .05<br>○ 0.5 mg: 4.8% vs. 4.4%; RR 1.11 (0.72 to 1.73); P = .63<br>○ 1.0 mg: 6.6% vs. 4.1%;RR 1.51 (1.00 to 2.28); P = .05<br>• Malignant neoplasms: 4.0% vs. 4.2%<br>○ *HR 0.94 (0.67 to 1.32)<br>○ RR 0.94 (0.68 to 1.32); P = .73<br>○ 0.5 mg: 3.1% vs. 4.2%; RR 0.74 (0.45 to 1.22); P = .24<br>○ 1.0 mg: 4.9% vs. 4.2%; RR 1.15 (0.74 to 1.79); P = .54<br>• *Breast neoplasm: 0.8% vs. 0.2%<br>○ HR 1.73 (0.41 to 7.24)<br>• *Lung/bronchus neoplasm: 0.5% vs. 0.4%<br>○ HR 1.33 (0.46 to 3.82)<br>• Pancreatic neoplasm: 0.1% vs. 0.2%<br>○ *HR 0.25 (0.03 to 2.23)<br>○ RR 0.25 (0.03 to 2.24); P = .18<br>○ *0.5 mg: 0% vs. 0.1%<br>○ 1.0 mg: 0.1% vs. 0.2%; RR 0.50 (0.05 to 5.52); P = .57<br>• *Skin neoplasm: 1.5% vs. 1.0%<br>○ HR 1.41 (0.76 to 2.63)<br>• Severe hypoglycemia: 22.4% vs. 21.2% | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | | ○ RR 1.06 (0.93 to 1.20); P = .42<br>○ 0.5 mg: 23.1% vs. 21.5%; RR 1.08 (0.90 to 1.29); P = .42<br>○ 1.0 mg: 21.7% vs. 21.0%; RR 1.03 (0.86 to 1.24); P = .73 | |
| Husain et al. (2019)[20]<br>NCT02692716<br>Novo Nordisk<br>Oral semaglutide (Rybelsus)<br>PIONEER-6<br>Multisite international<br>Total N = 3,183<br>• 3 mg, n = 1,591<br>• Placebo, n = 1,592 | • All-cause mortality: 1.4% vs. 2.8%<br>○ HR 0.51 (0.31 to 0.84)<br>• MACE: 3.8% vs. 4.8%<br>○ HR 0.79 (0.57 to 1.11); *P* = .17<br>○ *CV death: 0.9% vs. 1.9%; HR 0.51 (0.31 to 0.84)<br>○ *Nonfatal MI: 2.3% vs. 1.2%; HR 1.18 (0.73 to 1.90)<br>○ *Nonfatal stroke: 0.8% vs. 1.0%; HR 0.74 (0.35 to 1.57)<br>• *Fatal or nonfatal MI: 2.3% vs. 2.2%<br>○ HR 1.04 (0.66 to 1.66)<br>• *Fatal or nonfatal stroke: 0.8% vs. 1.1%<br>○ HR 0.76 (0.37 to 1.56)<br>• *hHF: 3.6% vs.3.3%<br>○ HR 0.86 (0.48 to 1.55)<br>• SAE: 18.9% vs. 22.5%<br>○ RR 0.84 (0.73 to 0.96), P = .02<br>• *hUA: 0.7% vs. 0.4%<br>○ HR 1.56 (0.60 to 4.01) | • SAE leading to permanent discontinuation: 2.6% vs. 3.0%<br>○ RR 0.85 (0.57 to 1.29); P = .45<br>• AE leading to permanent discontinuation: 11.6% vs. 6.5%<br>○ RR 1.77 (1.41 to 2.23); P < .0001<br>• GI AE: 6.8% vs. 1.6%<br>○ RR 2.68 (1.13 to 6.37); P = .02<br>• Metabolism and nutrition disorder AE: 1.2% vs. 0.4%<br>○ RR 2.70 (1.14 to 6.39); P = .02<br>• Nervous system disorder AE: 1.1% vs. 0.8%<br>○ RR 1.31 (0.64 to 2.69); P = .46<br>• Severe hypoglycemia AE: 1.4% vs. 0.8%<br>○ RR 1.77 (0.90 to 3.48); P = .09<br>• Retinopathy or related complication AE: 7.1% vs. 6.3%<br>○ RR 1.19 (0.92 to 1.54); P = .19<br>• Acute pancreatitis AE: 0.1% vs. 0.2%<br>○ RR 0.33 (0.03 to 3.20); P = .32<br>• Acute kidney injury AE: 2.0% vs. 2.3%<br>○ RR 0.86 (0.54 to 1.38); P = .54<br>• Malignant neoplasm AE: 2.6% vs. 3.0%<br>○ RR 0.85 (0.57 to 1.29); P = .45 | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
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| Verma et al. (2019)[61]<br><br>Post-hoc analysis of LEADER and SUSTAIN-6 stratified by years of diabetic duration<br><br>In LEADER:<br>• < 5 years 15%, n = 1,377<br>• 15 to < 25 years 50%, n = 4,692<br>• 15 to < 25 years, 27% n = 2,504<br>• ≥ 25 years 8%, n = 748<br><br>In SUSTAIN-6:<br>• < 5 years 13%, n = 422<br>• 5 to < 15 years, 48% n = 1,582<br>• 15 to < 25 years, 30% n = 977<br>• ≥ 25 years 10%, n = 316 | • *MACE, < 5 years<br>○ LEADER HR 0.77 (0.57 to 1.05)<br>○ SUSTAIN-6 HR 0.61 (0.30 to 1.22)<br>• *MACE, 5 to < 15 years<br>○ LEADER HR 0.90 (0.77 to 1.05)<br>○ SUSTAIN-6 HR 0.68 (0.46 to 0.99)<br>• *MACE, 15 to < 25 years<br>○ LEADER HR 0.91 (0.75 to 1.12)<br>○ SUSTAIN-6 HR 0.90(0.57 to 1.40)<br>• *MACE, ≥ 25 years<br>○ LEADER HR 0.70 (0.49 to 1.02)<br>○ SUSTAIN-6 HR 0.76 (0.38 to 1.51)<br>• *CV death, < 5 years<br>○ LEADER HR 0.66 (0.38 to 1.14)<br>○ SUSTAIN-6 HR 0.24 (0.05 to 1.08)<br>• *CV death, 5 to < 15 years<br>○ LEADER HR 0.77 (0.60 to 1.00)<br>○ SUSTAIN-6 HR 1.13 (0.60 to 2.14)<br>• *CV death, 15 to < 25 years<br>○ LEADER HR 0.92 (0.67 to 1.26)<br>○ SUSTAIN-6 HR 1.07 (0.50 to 2.28<br>• *CV death, ≥ 25 years<br>○ LEADER HR 0.61 (0.34 to 1.08)<br>○ SUSTAIN-6 HR 1.54 (0.50 to 4.71) | | |
| Toulis et al. (2017)[58]<br><br>Retrospective cohort<br><br>U.K. THIN<br><br>Total N = 24,886<br>• GLP-1 exposed, n = 8,345<br>• GLP-1 unexposed, n = 16,541 | • All-cause mortality<br>○ IRR 0.69 (0.61 to 0.79); *P* < .0001<br>○ Liraglutide: aIRR 0.56 (0.46 to 0.67); *P* < .0001<br>○ Exenatide: aIRR 0.72 (0.61 to 0.85);*P* < .0001<br>○ Lixisenatide: 0 events | | <u>Subgroup analyses</u><br>• No baseline CVD events<br>○ All-cause mortality IRR 0.68 (0.57 to 0.81); *P* < .0001<br>○ Incident CVD event IRR 1.09 (0.94 to 1.26); *P* = .26 |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| Dawwas et al. (2018)[32]<br>Retrospective cohort<br>U.S. Truven Health Analytic MarketScan<br>Total N = 321,606<br>• DPP-4 inhibitors vs. GLP-1 agonists, n = 160,803 each<br>• Saxagliptin vs. GLP-1 agonists, n = 49,214, each<br>• Sitagliptin vs. GLP-1 agonists, n = 160,609 each | • *hHF: 3.6% vs. 3.8%<br>○ HR 0.86 (0.83 to 0.90)<br>• *hHF with prior HF: 10.0% vs. 10.9%<br>○ HR 0.90 (0.74 to 1.07)<br>• *hHF without prior HF: 3.5% vs. 3.7%<br>○ HR 0.85 (0.82 to 0.89)<br>• *hHF with prior CVD: 9.2% vs. 9.2%<br>○ HR 0.82 (0.77 to 0.86)<br>• *hHF without prior CVD: 2.4% vs. 2.6%<br>○ HR 0.84 (0.80 to 0.88)<br>• *Saxagliptin: 2.7% vs. 4.2%<br>○ HR 0.74 (0.69 to 0.84)<br>• *Sitagliptin: 3.8% vs. 3.9%<br>○ HR 0.92 (0.89 to 0.95) | | |
| Svanstrom et al. (2019)[57]<br>Retrospective cohort<br>National health registry data: Denmark and Sweden<br>Total N =46,804<br>• Metformin + liraglutide, n = 23,402<br>• Metformin + DPP-4, n = 23,402 | • *MACE: 4.8% vs. 4.9%<br>○ HR 0.90 (0.83 to 0.98)<br>• *MI: 2.5% vs. 2.4%<br>○ HR 0.94 (0.84 to 1.06)<br>• *Stroke: 1.8% vs. 1.9%<br>○ HR 0.88 (0.77 to 1.01)<br>• *CV death: 1.4% vs. 1.6%<br>○ HR 0.78 (0.68 to 0.91)<br>• *HF: 2.1% vs. 2.1%<br>○ HR 0.90 (0.80 to 1.03)<br>• *All-cause mortality: 4.7% vs. 5.1%<br>○ HR 0.83 (0.77 to 0.90) | | <u>Subgroup analyses</u><br>• MACE by CVD status, *P* = .06<br>○ With: 9.9% vs. 10.9%; HR 0.81 (0.71 to 0.92)<br>○ Without: 3.6% vs. 3.4%; HR 0.96 (0.86 to 1.06)<br>• MACE by age, *P* = .06<br>○ < 65 years: 3.8% vs. 3.6%; HR 0.97 (0.86 to 1.09)<br>○ ≥ 65 years: 7.1% vs. 7.6%; HR 0.82 (0.73 to 0.93)<br>• MACE by baseline insulin use<br>○ Yes: 6.0% vs. 6.8%; HR 0.85 (0.75 to 0.96)<br>○ No: 4.3% vs. 3.9%; HR 0.96 (0.86 to 1.07); *P* = .16 |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| DPP-4 Inhibitors | | | |
| White et al. (2013)[23]<br>NCT0096878<br>Takeda Pharmaceutical<br>Alogliptin (Nesina)<br>EXAMINE<br>Multisite international<br>Total N = 5,380<br>• 25 mg, n = 1,928<br>• 12.5 mg, n = 694<br>• 6.25 mg, n = 78<br>• Placebo, n = 2,679 | • All-cause mortality: 5.7% vs. 6.5%<br>○ HR 0.88 (0.71 to 1.09); *P* = .23<br>• MACE: 11.3% vs. 11.8%<br>○ HR 0.96 (One-sided repeated 95% CI UB ≤ 1.16); *P* = .36<br>○ CV death: 3.3% vs. 4.1%; HR 0.79 (0.60 to 1.04); *P* = .10<br>○ Nonfatal MI: 6.9% vs. 6.5%;HR 1.08 (0.88 to 1.33); *P* = .47<br>○ Nonfatal stroke: 1.1% vs. 1.2%; HR 0.91 (0.55 to 1.50); *P* = .71<br>• SAE: 33.6% vs. 35.5%<br>○ RR 0.95 (0.88 to 1.02); P = .13<br>• MACE + revascularization for UA: 12.7% vs. 13.4%<br>○ HR 0.95 (≤ 1.14); *P* = .26<br>• *MACE<br>○ Early initiators: 45.6% vs. 45.6%; HR 0.96; (0.76 to 1.21)<br>○ Late initiators: 64.9% vs. 60.4%; HR 1.03; (0.84 to 1.26)<br>• *CV death<br>○ Early HR 0.82 (0.55 to 1.23)<br>○ Late HR 0.88 (0.63 to 1.21)<br>• *Nonfatal MI<br>○ Early HR 1.02 (0.75 to 1.37)<br>○ Late HR 1.16 (0.90 to 1.50)<br>• *Nonfatal Stroke<br>○ Early HR 1.08 (0.48 to 2.45)<br>○ Late HR 0. 76 (0.43 to 1.36)<br>• *hHF<br>○ Early HR 1.23 (0.84 to 1.82) | • *Any discontinuation: 20.9% vs. 22.6%<br>○ Due to AE 10.0% vs. 10.3%<br>• Any AE<br>○ 80.0% vs. 78.8%; RR 1.01, *P* = .30<br>• Hypoglycemia SAE<br>○ 0.7% vs. 0.6%; RR 1.12, *P* = .86<br>○ Baseline metformin + SU<br>• Hypoglycemia AE<br>○ 6.7% vs. 6.5%; RR 1.04, *P* = .74<br>• Malignancy AE<br>○ 2.0% vs. 1.9%; RR 1.07, *P* = .77<br>• Renal dialysis AE<br>○ 0.9% vs. 0.8%; RR 1.08, *P* = .88<br>• Acute pancreatitis AE<br>○ 0.4% vs. 0.3%; RR 1.49, *P* = .50<br>• Chronic pancreatitis AE<br>○ 0.2% vs. 0.1%; RR 1.24, *P* = 1.00<br>• Angioedema AE<br>○ 0.6% vs. 0.5%; RR 1.30, *P* = .58<br>• ALT > 3x ULN AE<br>○ 2.4% vs. 1.7%; RR 1.38, *P* = .10<br>• AST > 3x ULN AE<br>○ 1.8% vs. 1.6%; RR 1.11, *P* = .67 | <u>Subgroup analyses of MACE</u><br>• Smoking Status, *P* = .03<br>○ Never HR 0.87 (0.69 to 1.10)<br>○ Current HR 0.65 (0.41 to 1.03)<br>○ Former HR 1.21 (0.95 to 1.55)<br>• Diabetic duration (years), *P* = .01<br>○ < 5 HR 0.74 (0.54 to 1.01)<br>○ ≥ 5 and < 10 HR 0.81 (0.58 to 1.13)<br>○ ≥ 10 HR 1.22 (0.98 to 1.53)<br>• Baseline insulin use *P* = .02<br>○ Yes HR 1.23 (0.95 to 1.29)<br>○ No HR 0.83 (0.68 to 1.02)<br>• Baseline biguanide use *P* = .03<br>○ Yes HR 0.81 (0.66 to 1.00)<br>○ No HR 1.17 (0.92 to 1.50)<br>• Renal impairment, *P* = .05<br>○ Normal to mild HR 0.84 (0.68 to 1.04)<br>○ Moderate or severe HR 1.15 (0.91 to 1.46)<br>• Geographic region *P* = .03<br>○ US, Canada HR 1.30 (0.91 to 1.88)<br>○ Mexico, Central/South America HR 0.92 (0.67 to 1.27) |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ Late HR 1.10 (0.76 to 1.59)<br>• *All-cause mortality<br>○ Early HR 0.79 (0.55 to 1.13)<br>○ Late HR 0.94 (0.71 to 1.23)<br>• *CV death/hHF<br>○ Early HR 1.01 (0.76 to 1.34)<br>○ Late HR 1.01 (0.79 to 1.30)<br>• *MACE + revascularization for UA + hHF<br>○ Early HR 0.96 (0.79 to 1.16)<br>○ Late HR 1.64 (0.88 to 1.23) | | ○ Western Europe, Australia, New Zealand, Middle East HR 1.40 (0.92 to 2.12)<br>○ Eastern Europe, Africa HR 0.69 (0.51 to 0.94)<br>○ Asia/Pacific HR 0.87 (0.59 to 1.30) |
| Rosenstock et al. (2019)[74]<br>NCT01897532<br>Boehringer Ingelheim<br>Linagliptin (Tradjenta)<br>†CARMELINA<br>Multisite international<br>Total N = 6,979<br>• 5 mg, n = 3,494<br>• Placebo, n = 3,485 | • †All-cause mortality: 10.5% vs. 10.7%<br>○ HR 0.98 (0.84 to 1.13); *P* = .74<br>• †MACE: 12.4% vs. 12.1%<br>○ HR 1.02 (0.89 to 1.17); *P* = .74<br>○ CV death: 6.3% vs. 6.5%<br>○ Nonfatal MI: 4.4% vs. 3.8%<br>○ Nonfatal stroke: 1.7% vs. 1.8%<br>• †hHF: 6.0% vs. 6.5%<br>○ HR 0.90 (0.74 to 1.08); *P* = .26<br>• †Fatal or nonfatal MI: 4.7% vs. 4.2%<br>○ HR 1.12 (0.90 to 1.40); *P* = .30<br>• †Fatal or nonfatal stroke: 2.3% vs. 2.5%<br>○ HR 0.91 (0.67 to 1.23); *P* = .53<br>• †SAE: 37.0% vs. 38.5%<br>○ RR 0.96 (0.90 to 1.02); P = .19<br>• †CV death, *P* = .63<br>○ 7.3% vs. 7.6%; HR 0.96 (0.81 to 1.14)<br>• †Fatal MI: 0.3% vs. 0.4%<br>○ HR 0.78 (0.36 to 1.72); *P* = .54<br>• †Nonfatal MI: 4.5% vs. 3.9% | • †Any AE: 77.2% vs. 78.1%<br>○ RR 0.99 (0.96 to 1.01); P = .34<br>• †Acute pancreatitis AE: 0.2% vs. 0.1%<br>○ RR 1.80 (0.60 to 5.35); P = .29<br>• †Pancreatic cancer AE: 0.3% vs. 0.1%<br>○ RR 2.74 (0.87 to 8.61); P = .07<br>• †Skin lesion AE: 0.1% vs. 0.02%<br>○ RR 4.99 (0.58 to 42.66); P = .10<br>• *†Pemphigoid AE: 0.2% vs. 0.0%<br>• †Hypoglycemia AE: 29.7% vs. 29.4%<br>○ RR 1.01 (0.94 to 1.09); P = .81 | <u>Secondary analysis</u><br>• hHF or CV death, *P* = .39<br>○ HR 0.90 (0.82 to 1.08)<br>• hHF or ACM, *P* = .40<br>○ HR 0.95 (0.84 to 1.07)<br>• hHF or HF AE, P = .31<br>○ HR 0.92 (0.79 to 1.08)<br>• First + recurrent hHF, *P*= .63<br>○ HR 0.94 (0.75 to 1.20)<br>• Initiation of loop diuretics, *P* = .47<br>○ HR 0.94 (0.81 to 1.10)<br>• Initiation of loop diuretics or hHF, *P* = .53<br>○ HR 0.95 (0.82 to 1.11)<br><u>Subgroup analyses</u><br>• hHF by baseline HF status<br>○ With HR 0.88 (0.68 to 1.14); *P* = .33<br>○ Without HR 0.92 (0.70 to 1.22); *P* = .56<br>• CV death by baseline HF status |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ HR 1.15 (0.91 to 1.45); *P* = .23<br>• †Fatal stroke: 0.5% vs. 0.5%<br>○ HR 1.05 (0.53 to 2.09); *P* = .88<br>• †Nonfatal stroke: 1.9% vs. 2.1%<br>○ HR 0.88 (0.63 to 1.23); *P* = .45<br>• †hUA: 1.2% vs. 1.4%<br>○ HR 0.87 (0.57 to 1.31); *P* = .50<br>• †CR: 4.6% vs. 4.3%<br>○ HR 1.07 (0.85 to 1.33); *P* = .57 | | ○ With HR 0.96 (0.73 to 1.26); *P* = .77<br>○ Without HR 0.95 (0.76 to 1.19); *P* = .67 |
| Rosenstock et al. (2019)[25]<br>NCT01243424<br>Boehringer Ingelheim<br>Linagliptin (Tradjenta)<br>†CAROLINA<br>Multisite international<br>Total N = 6,042<br>• 5 mg, n = 3,023<br>• 1 to 4 mg glimepiride, n = 3,010 | • †All-cause mortality: 10.2% vs. 11.2%<br>○ HR 0.91 (0.78 to 1.06); *P* = 23<br>• †MACE: 11.8% vs. 12.0%<br>○ HR 0.98 (0.84 to 1.14); *P* = .76<br>○ †CV death: 4.3% vs. 4.2%<br>○ †Nonfatal MI: 4.7% vs. 4.6%<br>○ †Nonfatal stroke: 2.8% vs. 3.4%<br>• †Fatal or nonfatal stroke: 3.4% vs. 4.0%<br>○ HR 0.86 (0.66 to 1.12)<br>• †Fatal or nonfatal MI: 5.1% vs. 4.9%<br>○ HR 1.03 (0.82 to 1.29)<br>• †hHF: 3.7% vs. 3.1%<br>○ HR 1.21 (0.92 to 1.59)<br>• †SAE: 46.4% vs. 48.1%<br>○ RR 0.96 (0.91 to 1.02); P = .19<br>• †CV death: 5.6% vs. 5.6%<br>○ HR 1.00 (0.81 to 1.24)<br>• †Nonfatal stroke: 3.0% vs. 3.5%<br>○ HR 0.87 (0.66 to 1.15)<br>• †Nonfatal MI: 4.8% vs. 4.7%<br>○ HR 1.00 (0.80 to 1.28)<br>• †hUA: 2.0% vs. 1.9%<br>○ HR 1.07 (0.74 to 1.54) | • †Any AE: 93.6% vs. 95.2%<br>○ RR 0.98 (0.97 to 1.00); P = .009<br>• †Hypersensitivity reaction AE: 13.4% vs. 11.5%<br>○ RR 1.16 (1.02 to 1.33); P = .03<br>• *†Pemphigoid AE: 0.2% vs. 0.0%<br>• †Skin lesion AE: 0.3% vs. 0.1%<br>○ RR 2.24 (0.69 to 7.27); P = .17<br>• *†Chronic pancreatitis AE: 0.1% vs. 0.0%<br>• †Moderate or severe hypoglycemia<br>○ HR 0.18 (0.15 to 0.21); *P* < .001<br>• †Severe hypoglycemia<br>○ HR 0.15 (0.08 to 0.29); *P* < .001<br>• †Hospitalization for hypoglycemia<br>○ HR 0.07 (0.02 to 0.31); *P* < .001 | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | • †TIA: 0.8% vs. 1.1%<br>○ HR 0.75 (0.45 to 1.26) | | |
| Scirica et al. (2013)[22]<br>NCT01107886<br>AstraZeneca & Bristol Myers Squibb<br>Saxagliptin (Onglyza)<br>SAVOR-TIMI 53<br>Multisite international<br>Total N = 16,492<br>• 2.5 mg, n = 1,294<br>• 5.0 mg, n = 6,986<br>• Placebo, n = 8,212 | • All-cause mortality: 4.9% vs. 4.2%<br>○ HR 1.11 (0.96 to 1.27); *P* = .15<br>• MACE: 7.3% vs. 7.2%<br>○ HR 1.00 (0.89 to 1.12); *P* = .99<br>○ Fatal or nonfatal MI: 3.2% vs. 3.4%; HR 0.95 (0.80 to 1.12); *P* = .52<br>○ Fatal or nonfatal ischemic stroke: 1.9% vs. 1.7%; HR 1.11 (0.88 to 1.39); *P* = .38<br>○ CV death: 3.2% vs. 2.9%; HR 1.03 (0.87 to 1.22); *P* = .72<br>• hHF: 3.5% vs. 2.8%<br>○ HR 1.27 (1.07 to 1.51); *P* = .007<br>• SAE: 41.4% vs. 39.6%<br>○ RR 1.05 (1.01 to 1.09); P = .02<br>• MACE + hUA, hHF, or CR: 12.8% vs. 12.4%<br>○ HR 1.02 (0.94 to 1.11); *P* = .66<br>• hUA: 1.2% vs. 1.0%<br>○ HR 1.19 (0.89 to 1.60); *P* = .24<br>• Hospitalization for CR: 5.2% vs. 5.6%<br>○ HR 0.91 (0.80 to 1.04); *P* = .18 | • Hospitalization for hypoglycemia: 0.6% vs. 0.5%<br>○ HR 1.22 (0.82 to 1.83); *P* = .33<br>• Hypoglycemic events: 15.3% vs. 13.4%<br>○ Major RR 1.25; *P* = .05<br>○ Minor RR 1.13; P = .002<br>○ ≥ 1 event RR 1.14; P < .001<br>• Lymphocytopenia<br>○ 0.6% vs. 0.5%; RR 1.21, *P* = .40<br>• Renal abnormality<br>○ 5.8% vs. 5.1%; RR 1.15, *P* = .04<br>• Any pancreatitis<br>○ 0.3% vs. 0.3%; RR 1.13, *P* = .77<br>• Acute Pancreatitis<br>○ 0.5% vs. 0.4%; RR 1.87, *P* = .17 | <u>Subgroup analyses</u><br>• MACE by baseline CVD status; *P* = .07<br>○ CVD 8.4% vs. 8.5%; HR 0.96 (0.86 to 1.09)<br>○ CV risk factors 3.6% vs. 2.6%; HR 1.34 (0.95 to 1.90) |
| Green et al. (2015)[24]<br>NCT00790205<br>Merck Sharp & Dohme<br>Sitagliptin (Januvia)<br>TECOS<br>Multisite international<br>Total N = 14,671 | • All-cause mortality: 7.5% vs. 7.3%<br>○ HR 1.01 (0.90 to 1.14); *P* = .88<br>• Primary MACE: 11.4% vs. 11.6%<br>○ HR 0.98 (0.89 to 1.08); *P* = .65<br>○ CV death 4.2% vs. 4.0%<br>○ Nonfatal MI 3.8% vs. 3.9%<br>○ Nonfatal stroke 2.0% vs. 2.1%<br>○ hUA 1.5% vs. 1.6%<br>• Secondary MACE: 10.2% vs. 10.2% | • Acute pancreatitis: 0.3% vs. 0.2%<br>○ HR 1.93 (0.90 to 1.15); *P* = .07<br>○ Participants ≥ 75 years HR 2.01 (0.36 to 11.04); *P* = .42<br>• Acute pancreatitis by sex, *P* = .01<br>○ Men HR 4.03 (1.51 to 0.76)<br>○ Women HR 0.46 (0.12 to 1.79)<br>○ Josse et al. [78] aHR 1.25 (0.81 to 1.92); *P* = .32 | <u>Subgroup analyses</u><br>• Primary MACE by BMI, *P* = .03<br>○ < 30 HR 1.08 (0.95 to 1.24)<br>○ > 30 HR 0.88 (0.76 to 1.01)<br>• Primary MACE by sex, *P* = .64<br>○ Men HR 1.00 (0.90 to 1.12)<br>○ Women HR 0.95 (0.78 to 1.15)<br>• CV death by sex, *P* = .57 |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
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| • 100 mg, n = 6,646<br>• 50 mg, n = 686<br>• Placebo, n = 7,339 | ○ HR 0.99 (0.89 to 1.08); *P* = .84<br>○ CV death 4.3% vs. 4.0%<br>○ Nonfatal MI 4.3% vs. 4.0%<br>○ Nonfatal stroke 2.0% vs. 2.2%<br>• Fatal or nonfatal MI: 4.1% vs. 4.3%<br>○ HR 0.95 (0.81 to 1.11); *P* = .49<br>• Fatal or nonfatal stroke: 2.4% vs. 2.5%<br>○ HR 0.97 (0.79 to 1.19); *P* = .76<br>• hHF: 7.5% vs. 7.3%<br>○ HR 1.00 (0.83 to 1.20); *P* = .98<br>• SAE: 12.7% vs. 12.8%<br>○ RR 0.99 (0.91 to 1.08); P = .78<br>• hHF or CV death: 7.3% vs. 7.2%<br>○ HR 1.02 (0.90 to 1.15); *P* = .74<br>• CV death: 5.2% vs. 5.0%<br>○ HR 1.03 (0.89 to 1.19); *P* = .71<br>• hUA: 1.6% vs. 1.8%<br>○ HR 0.90 (0.70 to 1.16); *P* = .42 | • Charter-defined cancer: 3.7% vs. 4.0%<br>○ HR 0.91 (0.77 to 1.08); *P* = .27<br>○ Participants ≥ 75 years HR 0.95 (95% CI 0.67–1.36); *P* = 0.78<br>• Cancer by sex, *P* = .23<br>○ Men HR 0.98 (0.81 to 1.18)<br>○ Women HR 0.76 (0.42 to 1.36)<br>• Pancreatic cancer: 0.1% vs. 0.2%<br>○ HR 0.66 (0.28 to 1.51); *P* = .32<br>○ Participants ≥ 75 years HR 0.28 (0.03 to 2.50); *P* = .25<br>• Severe hypoglycemia: 2.2% vs. 1.9%<br>○ HR 1.12 (0.89 to 1.40); *P* = .33<br>○ Participants ≥ 75 years HR 1.03 (95% CI 0.62–1.71); P = 0.92<br>• Severe hypoglycemia by sex, *P* = .92<br>○ Men HR 1.11 (0.84 to 1.47)<br>○ Women HR 1.14 (0.78 to 1.66)<br>• Renal failure by sex, *P* = .48<br>○ Men HR 0.96 (0.71 to 1.30)<br>○ Women HR 0.76 (0.42 to 1.36)<br>• Diabetic eye disease: 3.1% vs. 2.5%<br>○ RR 1.26 (1.04 to 1.52); P = .02<br>• Diabetic retinopathy: 2.8% vs. 2.2%<br>○ RR 1.30 (1.06 to 1.59); P = .01<br>• Diabetic blindness: 0.3% vs. 0.3%<br>○ RR 0.96 (0.55 to 1.68); P = .89<br>• Diabetic neuropathy: 4.1% vs. 3.8%<br>○ RR 1.08 (0.92 to 1.27); P = .35<br>• Bone fractures in those ≥ 75 years<br>○ Bethel et al.[77] HR 1.21 (0.78 to 1.85); *P* = .40<br>○ Josse et al. [78] aHR 1.25 (0.81 to 1.92); *P* = .32 | ○ Men HR 1.02 (0.86 to 1.21)<br>○ Women HR 1.12 (0.85 to 1.49)<br>• MI by sex, *P* = .25<br>○ Men HR 1.00 (0.83 to 1.19)<br>○ Women HR 0.80 (0.57 to 1.12)<br>• Stroke by sex, *P* = .99<br>○ Men HR 0.96 (0.75to 1.22)<br>○ Women HR 0.96 (0.64 to 1.43)<br>• hUA by sex, *P* = .33<br>○ Men HR 0.85 (0.64 to 1.13)<br>○ Women HR 1.14 (0.68 to 1.91)<br>• ACM by sex, *P* = .80<br>○ Men HR 1.04 (0.90 to 1.19)<br>○ Women HR 1.00 (0.79 to 1.27)<br>• hHF by sex, *P* = .98<br>○ Men HR 1.01 (0.82 to 1.25)<br>○ Women HR 1.10 (0.70 to 1.46)<br>• Among participants ≥ 75 years<br>○ Primary MACE HR 1.10 (0.89 to 1.36); *P* = .39<br>○ Secondary MACE HR 1.01 (0.81 to 1.26); *P* = .94<br>○ hHF HR 0.99 (0.65 to 1.49); P = .94<br>○ hHF/death HR 1.00 (0.77 to 1.29); *P* = .99<br>○ ACM HR 1.05 (0.83 to 1.32); P = .71 |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
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| Hong et al. (2018)[46]<br>Retrospective cohort<br>US Medicaid beneficiaries with fee-for-service Part A, B, and D coverage ≥ 1 month<br>• DPP-4, n = 49,374 vs. SU, n = 132,223<br>• DPP-4, n = 57,301 vs. TZD, n = 32,612 | | *Acute Pancreatitis<br>• DPP-4 vs. SU<br>○ HR 1.00 (0.83 to 1.20)<br>○ Weighted HR 1.10 (0.83 to 1.24)<br>• DPP-4 vs. TZD<br>○ HR 1.11 (0.85 to 1.43)<br>○ Weighted HR 1.11 (0.76 to 1.62) | |
| Gokhale et al. (2017)[52]<br>Retrospective cohort<br>US Medicare beneficiaries ≥ 65 years with fee-for-service Part A, B, and D coverage ≥ 1 month<br>DPP-4 vs. SU, N = 98,512<br>• DPP-4, n = 30,130<br>• SU, n = 68,382<br>DPP-4 vs. TZD, N = 34,122<br>• DPP-4, n = 20,596<br>• TZD, n = 13,526 | DPP-4 vs. SU<br>• *All-cause mortality<br>○ HR 0.66 (0.63 to 0.70)<br>○ aHR 0.76 (0.72 to 0.79)<br>• *Nonfatal MI, stroke, or ACM<br>○ HR 0.70 (0.67 to 0.72)<br>○ aHR 0.78 (0.75 to 0.81)<br>• *Prior CVD<br>○ HR 0.67 (0.64 to 0.70)<br>○ aHR 0.76 (0.72 to 0.79)<br>• *No CVD<br>○ HR 0.67 (0.64 to 0.70)<br>○ aHR 0.76 (0.72 to 0.79)<br>*DPP-4 vs. TZD<br>• All-cause mortality<br>○ HR 0.96 (0.88 to 1.06)<br>○ aHR 0.96 (0.87 to 1.05)<br>• Nonfatal MI, stroke, or ACM<br>○ HR 0.91 (0.85 to 0.97)<br>○ aHR 0.89 (0.84 to 0.95)<br>• Prior CVD<br>○ HR 0.94 (0.86 to 1.02)<br>○ aHR 0.95 (0.87 to 1.04) | | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | • No CVD<br>○ HR 0.94 (0.86 to 1.02)<br>○ aHR 0.95 (0.87 to 1.04) | | |
| Kim et al. (2017)[47]<br>Retrospective cohort<br>Korean Health Insurance Review & Assessment Service<br>Total N = 511,652<br>• Sulfonylurea, n = 255,691<br>• DPP-4, n = 255,691<br>○ Saxagliptin, n = 13,632<br>○ Sitagliptin, n = 109,176<br>○ Linagliptin, n = 66,986<br>○ Vildagliptin, n = 36,616 | • hHF: HR 0.78 (0.69 to 0.87); *P* < .001<br>○ Sitagliptin<br>HR 0.76 (0.67 to 0.86); *P* < .001<br>○ Linagliptin<br>HR 0.74 (0.59 to 0.92); *P*= .007<br>○ Saxagliptin<br>HR 0.93 (0.57 to 1.54); *P* = .79<br>• Stroke: HR 0.63 (0.60 to 0.67); *P* < .001<br>○ Sitagliptin<br>HR 0.65 (0.59 to 0.71); *P* < .001<br>○ Linagliptin<br>HR 0.71 (0.62 to 0.82); *P* < .001<br>○ Saxagliptin<br>HR 0.66 (0.49 to 0.88); *P* = .005<br>• MI: HR 0.76 (0.67 to 0.87); *P* < .001<br>○ Sitagliptin<br>HR 0.66 (0.55 to 0.79); *P* < .001<br>○ Linagliptin<br>HR 0.77 (0.59 to 1.02); *P* = .07<br>○ Saxagliptin<br>HR 1.07 (0.62 to 1.84); *P* = .81<br>• UA: HR 0.98 (0.92 to 1.01); *P* = .48<br>○ Sitagliptin<br>HR 1.02 (0.93 to 1.11); *P* = .57<br>○ Linagliptin<br>HR 1.02 (0.89 to 1.16); *P* = .78<br>○ Saxagliptin<br>HR 0.77 (0.59 to 0.99); *P* = .04<br>• PCI: HR 1.00 (0.95 to 1.05); *P* = .95 | | <u>Subgroup analyses</u><br>• With baseline CVD<br>○ hHF HR 9.77 (0.68 to 0.79); *P* < .001<br>○ Stroke HR 0.64 (0.59 to 0.69); *P* < .001<br>○ MI HR 0.74 (0.62 to 0.88); *P* = .001<br>○ UA HR 1.02 (0.94 to 1.09); *P* = .70<br>○ PCI HR 1.01 (0.95 to 1.07); *P* = .87<br>○ CABG HR 0.74 (0.52 to 1.06); *P* = .10<br>• Without baseline CVD<br>○ hHF HR 0.71 (0.56 to 0.90); *P* = .004<br>○ Stroke HR 0.57 (0.51 to 0.65); *P* < .001<br>○ MI HR 0.83 (0.68 to 1.00); *P* = .06<br>○ UA HR 0.99 (0.88 to 1.11); *P* = .85<br>○ PCI HR 1.02 (0.94 to 1.10); *P* = .72<br>○ CABG HR 0.79 (0.48 to 1.31); *P* = .36 |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ Sitagliptin<br>HR 1.03 (0.97 to 1.09); *P* = .39<br>○ Linagliptin<br>HR 0.99 (0.90 to 1.09); *P* = .83<br>○ Saxagliptin<br>HR 1.01 (0.84 to 1.22); *P* = .93<br>• CABG: HR 0.95 (0.70 to 1.28); *P* = .73<br>○ Sitagliptin<br>HR 0.90 (0.61 to 1.32); *P* = .58<br>○ Linagliptin<br>HR 1.19 (0.62 to 2.30); *P* = .60<br>○ Saxagliptin<br>HR 0.24 (0.03 to 2.10); *P* = .20 | | |
| Gordon et al. (2017)[45]<br>Retrospective cohort<br>UK Clinical Practice Research Datalink<br>Total N = 10,484<br>• Metformin + DPP-4, n = 1,463<br>• Metformin + SU, n = 4,451<br>• Metformin + TZD, n = 705<br>• DPP-4, n = 676<br>• TZD, n = 268<br>• SU, n = 2,921<br>(Events are per 1000 person-years) | • *Metformin + DPP-4 Inhibitor<br>○ All MI HR 0.60 (0.31 to 1.16)<br>○ Incident MI HR 0.56 (0.25 to 1.24)<br>○ Prevalent MI HR 0.71 (0.21 to 2.43)<br>○ MI rate 3.52/1000 person-years<br>○ All stroke HR 0.82 (0.38 to 1.77)<br>○ Incident stroke HR 0.66 (0.28 to 1.57)<br>○ Stroke rate 4.40/1000 person-years<br>○ All MI/stroke HR 0.74 (0.46 to 1.19)<br>○ Incident MI/stroke HR 0.77 (0.44 to 1.34)<br>• *DPP-4 Inhibitor<br>○ All MI HR 1.01 (0.46 to 2.21)<br>○ Incident MI HR 1.06 (0.42 to 2.67)<br>○ Prevalent MI HR 0.98 (0.22 to 4.31)<br>○ MI rate 8.63/1000 person-years<br>○ All stroke HR 1.60 (0.67 to 3.80)<br>○ Incident stroke HR 1.17 (0.41 to 3.29)<br>○ Stroke rate 6.28/1000 person-years | • *Amputation<br>○ DPP-4 (n = 0) 0/1000<br>○ Met + DPP-4 (n = 6) 1.76/1000<br>• *Blindness<br>○ DPP-4 (n = 0); 0/1000<br>○ Met + DPP-4 (n = 3); 0.88/1000<br>• *Congestive HF<br>○ DPP-4 (n = 9); 7.06/1000<br>○ Met + DPP-4 (n = 54); 15.85/1000<br>• *Ischemic Heart Disease<br>○ DPP-4 (n = 12); 9.42/1000<br>○ Met + DPP-4 (n = 14); 4.11/1000<br>• *Nephropathy<br>○ DPP-4 (n = 1); 0.78/1000<br>○ Met + DPP-4 (n = 1); 0.29/1000<br>• *Neuropathy<br>○ DPP-4 (n = 2); 1.57/1000<br>○ Met + DPP-4 (n = 2); 0.59/1000<br>• *Renal failure<br>○ DPP-4 (n = 8); 6.28/1000<br>○ Met + DPP-4 (n = 8); 2.35/1000 | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ All MI/stroke HR 1.28 (0.73 to 2.24)<br>○ Incident MI/stroke HR 1.39 (0.72 to 2.68) | • *Retinopathy<br>○ DPP-4 (n = 91); 71.43/1000<br>○ Met + DPP-4 (n = 229); 67.24/1000<br>• *Ulcer<br>○ DPP-4 (n = 0); 0/1000<br>○ Met + DPP-4 (n = 3); 0.88/1000<br>• *Mortality<br>○ DPP-4 (n = 28); 21.98/1000<br>○ Met + DPP-4 (n = 55); 16.15/1000 | |
| Pasternak et al. (2019)[53]<br>Retrospective cohort<br>Nationwide health registries:Denmark, Norway, Sweden<br>Total N = 41,966<br>• New SGLT-2 inhibitor initiators vs. new DPP-4 inhibitor initiators, n = 20,983 each | • *MACE: 2.2% vs. 3.2%<br>○ HR 0.94 (0.84 to 1.06)<br>• *MI: 1.2% vs. 1.7%<br>○ HR 0.99 (0.85 to 1.17)<br>• *Stroke: 0.8% vs. 1.1%<br>○ HR 0.94 (0.77 to 1.15)<br>• *CV death: 0.5% vs. 1.0%<br>○ HR 0.84 (0.65 to 1.08)<br>• *hHF or HF death: 0.6% vs. 1.3%<br>○ HR 0.66 (0.53 to 0.81)<br>• *All-cause mortality: 1.3% vs. 2.4%<br>○ HR 0.80 (0.69 to 0.92) | • *Lower limb amputation: 0.3% vs. 0.3%<br>○ HR 1.26 (0.88 to 1.81)<br>• *DKA: 0.1% vs. 0.07%<br>○ HR 2.14 (1.17 to 4.09) | |
| O'Brien et al. (2018)[52]<br>Retrospective cohort<br>U.S. United Healthcare Insurance data: commercial & Medicare Advantage plans<br>Total N = 132,737<br>• DPP-4 inhibitors, n = 28,898<br>• Other glucose-lowering drugs: | • *GLP-1: 0.9% vs. 1.9%<br>○ HR 0.78 (0.63 to 0.96)<br>○ CHF HR 0.65 (0.42 to 1.02)<br>○ Stroke HR 0.65 (0.44 to 0.97)<br>○ IHD HR 0.91 (0.67 to 1.24)<br>○ PAD HR 0.90 (0.42 to 1.95)<br>• *SGLT-2: 0.6% vs. 1.9%<br>○ HR 0.81 (0.57 to 1.53)<br>○ CHF HR 0.54 (0.24 to 1.22)<br>○ Stroke HR 0.56 (0.26 to 1.12)<br>○ IHD HR 1.18 (0.74 to 1.87) | | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| ○ SGLT-2s, n = 5,677<br>○ GLP-1s, n = 11,351<br>○ TZDs, n = 7,368<br>○ Basal insulin, n = 16,249<br>○ SUs, n = 63,194 | ○ PAD HR 1.11 (0.33 to 3.65)<br>• *TZDs: 1.8% vs. 1.9%<br>○ HR 0.92 (0.76 to 1.11)<br>○ CHF HR 0.93 (0.63 to 1.36)<br>○ Stroke HR 0.73 (0.51 to 1.05)<br>○ IHD HR 0.95 (0.71 to 1.28)<br>○ PAD HR 1.67 (0.94 to 2.97)<br>• *Basal insulin vs. DPP-4 4.4% vs. 1.9%<br>○ HR 2.03 (1.81 to 2.27)<br>○ CHF HR 2.33 (1.90 to 2.87)<br>○ Stroke HR 1.77 (1.44 to 2.19)<br>○ IHD HR 1.92 (1.59 to 2.32)<br>○ PAD HR 2.92 (1.96 to 4.35)<br>• *SUs: 3.1% vs. 1.9%<br>○ HR 1.36 (1.23 to 1.49)<br>○ CHF HR 1.47 (1.23 to 1.75)<br>○ Stroke HR 1.28 (1.08 to 1.52)<br>○ IHD HR 1.35 (1.16 to 1.57)<br>○ PAD HR 1.65 (1.16 to 2.36) | | |
| SGLT-2 Inhibitors | | | |
| Mahaffey et al. (2018)[31]<br>Neal et al. (2017)[28]<br>NCT01032629<br>NCT01989754<br>Janssen Pharmaceuticals, Inc.<br>Canagliflozin (Invokana)<br>Multisite international<br>Program Total N = 10,142<br>CANVAS, N = 4,330<br>• 100 mg, n = 1,445 | • *All-cause mortality<br>○ HR 0.87 (0.74 to 1.01)<br>• Primary 3-component MACE<br>○ HR 0.86 (0.75 to 0.97); *P* = .02<br>○ CV death HR 0.87 (0.72 to 1.06)<br>○ Nonfatal MI HR 0.85 (0.69 to 1.05)<br>○ Nonfatal stroke HR 0.90 (0.71 to 1.15)<br>• *hHF<br>○ HR 0.67 (0.52 to 0.87)<br>• *Nonfatal or fatal MI<br>○ HR 0.89 (0.73 to 1.09)<br>• *Nonfatal or fatal stroke | • Male genital infection, *P* < .001<br>○ 34.9 vs. 10.8 events per 1000 patient-years<br>○ *Primary HR 3.98 (2.60 to 6.10)<br>○ *Secondary HR 3.68 (2.72 to 4.98)<br>• Female genital infection, *P* < .001<br>○ 68.8 vs. 17.5 events per 1000 patient-years<br>○ *Primary HR 4.81 (2.51 to 9.24)<br>○ *Secondary HR 3.98 (2.12 to 7.48)<br>• *Urinary tract infection<br>○ Primary HR 1.28 (0.94 to 1.74)<br>○ Secondary HR 0.98 (0.75 to 1.29) | <u>Subgroup analyses</u><br>• Stroke outcomes in those with cerebrovascular disease<br>○ Any HR 0.87 (0.69 to 1.09); *P* = .23<br>○ Fatal HR 0.84 (0.44 to 1.59); *P* = .59<br>○ Nonfatal HR 0.90 (0.71 to 1.15); *P* = .40<br>○ Ischemic HR 0.95 (0.74 to 1.22); *P* = .69<br>○ Hemorrhagic HR 0.43 (0.20 to 0.89); *P* = .02 |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| • 300 mg, n = 1,443<br>• Placebo, n = 1,441<br>CANVAS-R, N = 5,812<br>• 100 mg, n = 2,904<br>• Placebo, n = 2,903 | ○ HR 0.87 (0.69 to 1.09)<br>• ‡SAE: IRR 0.87 (0.67 to 1.13); P = .29<br>• *CV death or hHF<br>○ HR 0.78 (0.67 to 0.91)<br><br><u>*Primary cohort</u><br>• MACE HR 0.98 (0.74 to 1.30)<br>○ CV death HR 0.93 (0.60 to 1.43)<br>○ Nonfatal MI HR 1.21 (0.73 to 2.00)<br>○ Nonfatal stroke HR 0.97 (0.59 to 1.61)<br>• hHF HR 0.64 (0.35 to 1.15)<br>• ACM HR 0.79 (0.58 to 1.07)<br>• CV death or hHF HR 0.83 (0.58 to 1.19)<br><br><u>*Secondary cohort</u><br>• MACE HR 0.82 (0.72 to 0.95)<br>○ CV death HR 0.86 (0.70 to 1.06)<br>○ Nonfatal MI HR 0.79 (0.63 to 0.99)<br>○ Nonfatal stroke HR 0.88 (0.67 to 1.16)<br>• hHF HR 0.68 (0.51 to 0.90)<br>• ACM HR 0.89 (0.75 to 1.07)<br>• CV death or hHF HR 0.77 (0.65 to 0.92) | • Amputation, *P* < .001<br>○ 6.3 vs. 3.4 events per 1000 patient-years<br>• *Amputation of toes, feet, or legs<br>○ HR 1.97 (1.41 to 2.75)<br>• *Minor amputation<br>○ HR 1.94 (1.31 to 2.88)<br>• *Major amputation<br>○ HR 2.03 (1.08 to 3.82)<br>• *Lower extremity amputation<br>○ Primary HR 1.52 (0.70 to 3.29)<br>○ Secondary HR 2.07 (1.43 to 3.00)<br>• Fracture<br>○ HR 1.26 (1.04 to 1.52); *P* = .005<br>○ Low-trauma fracture HR 1.23 (0.99 to 1.52); *P* = .003<br>○ *Primary HR 1.28 (0.94 to 1.75)<br>○ *Secondary HR 1.25 (0.99 to 1.59)<br>• DKA<br>○ HR 2.33 (0.76 to 7.17)<br>○ *Primary HR 1.57 (0.40 to 6.16)<br>○ *Secondary HR 4.61 (0.56 to 38.03)<br>• Acute pancreatitis<br>○ *Primary HR 1.69 (0.17 to 16.71)<br>○ *Secondary HR 1.21 (0.30 to 4.93)<br>• Volume depletion, *P* = .009<br>○ 26.0 vs. 18.5 events per 1000 patient-years<br>○ *Primary HR 1.59 (0.97 to 2.59)<br>○ *Secondary HR 1.38 (0.98 to 1.93)<br>• Hypoglycemia<br>○ *Primary HR 1.04 (0.78 to 1.39)<br>○ *Secondary HR 1.18 (0.94 to 1.50) | ○ Undetermined HR 1.04 (0.48 to 2.22); *P* = .93<br>○ TIA HR 0.86 (0.56 to 1.32)<br>○ Stroke or TIA HR 0.89 (0.73 to 1.10)<br>• MACE by baseline cerebrovascular disease status; *P* = .41<br>○ Without HR 0.82 (0.70 to 0.95)<br>○ With HR 0.96 (0.75 to 1.23)<br>• MI by baseline cerebrovascular disease status; *P* = .19<br>○ Without HR 0.83 (0.67 to 1.03)<br>○ With HR 1.24 (0.77 to 1.99)<br>• hHF by baseline cerebrovascular disease status; *P* = .33<br>○ Without HR 0.71 (0.53 to 0.95)<br>○ With HR 0.57 (0.67 to 1.41)<br>• CV death by baseline cerebrovascular disease status; *P* = .76<br>○ Without HR 0.84 (0.68 to 1.05)<br>○ With HR 0.97 (0.67 to 1.41)<br>• ACM by baseline cerebrovascular disease status; *P* = .83<br>○ Without HR 0.85 (0.71 to 1.01)<br>○ With HR 0.92 (0.67 to 1.26) |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | | • Renal AE<br>○ *Primary HR 0.90 (0.56 to 1.43)<br>○ *Secondary HR 1.36 (0.93 to 1.99)<br>• Thromboembolism<br>○ *Primary HR 1.07 (0.45 to 2.51)<br>○ *Secondary HR 0.76 (0.36 to 1.61)<br>• Renal cell cancer<br>○ *Primary HR 0.74 (0.12 to 4.44)<br>○ *Secondary HR 5.72 (0.73 to 44.50)<br>• Bladder cancer<br>○ *Primary HR 0.39 (0.14 to 1.11)<br>○ *Secondary HR 1.59 (0.65 to 3.92)<br>• Breast cancer<br>○ *Primary HR 2.52 (0.83 to 7.64)<br>○ *Secondary HR 0.57 (0.22 to 1.50) | • Serious kidney decline by baseline cerebrovascular disease status; *P* = .48<br>○ Without HR 0.63 (0.47 to 0.83)<br>○ With HR 0.49 (0.28 to 0.85)<br>• Fatal/nonfatal stroke by baseline eGFR, *P* = .01<br>○ < 45 HR 0.32 (0.11 to 0.96)<br>○ 45 to < 60 HR 0.56 (0.31 to 1.00)<br>○ 60 to < 90 HR 0.89 (0.65 to 1.21)<br>○ ≥ 90 HR 1.42 (0.86 to 2.36) |
| Perkovic et al. (2019)[26]<br>NCT02065791<br>Janssen Pharmaceuticals, Inc.<br>Canagliflozin (Invokana)<br>CREDENCE<br>Multisite international<br>Total N = 4,401<br>• 100 mg, n = 2,202<br>• Placebo, n = 2,199 | • *All-cause mortality: 7.6% vs. 9.1%<br>○ HR 0.83 (0.68 to 1.02)<br>• hHF: 4.0% vs. 6.4%<br>○ HR 0.61 (0.47 to 0.80); *P* < .001<br>• SAE: 33.5% vs. 36.7%<br>○ RR 0.91 (0.84 to 0.99); P = .03<br>• Primary composite renal outcome:<br>○ 11.1% vs. 15.5%; HR 0.70 (0.59 to 0.82); *P* = .00001<br>• Doubling of serum creatinine level: 5.4% vs. 8.5%<br>○ HR 0.60 (0.48 to 0.76); *P* < .001<br>• ESKD: 5.3% vs. 7.5%<br>○ HR 0.68 (0.54 to 0.86); *P* = .002<br>• CV death: 5.0% vs. 6.3%<br>○ HR 0.78 (0.61 to 1.00); *P* = .05<br>• CV death or hHF: 8.1% vs. 11.5%<br>○ HR 0.69 (0.57 to 0.83); *P* < .01 | • *Any AE: 81.0% vs. 84.6%<br>○ HR 0.87 (0.82 to 0.93)<br>• *Amputation: 3.2% vs. 2.9%<br>○ HR 1.11 (0.79 to 1.56)<br>• *DKA: 0.5% vs. 0.05%<br>○ HR 10.80 (1.39 to 83.65)<br>• *Bladder cancer: 0.5% vs. 0.4%<br>○ HR 1.10 (0.45 to 2.72)<br>• *Breast cancer (female only): 1.1% vs. 0.4%<br>○ HR 2.59 (0.69 to 9.76)<br>• *Thromboembolism: 0.9% vs. 0.7%<br>○ HR 1.28 (0.67 to 2.45)<br>• *Genital mycotic infection<br>○ Male 1.9% vs. 0.2%; HR 9.30 (2.83 to 30.60)<br>○ Female 2.9% vs. 1.4%; HR 2.10 (1.00 to 4.45) | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | • CV death, MI, or stroke: 9.8% vs. 12.2%<br>○ HR 0.80 (0.67 to 0.95); *P* = .01<br>• ESKD, doubling serum creatinine level, or renal death: 6.9% vs. 10.2%<br>○ HR 0.66 (0.53 to 0.81); *P* < .001<br>• *CV death, MI, stroke, or hhF or unstable angina: 12.3% vs. 16.4%<br>○ HR 0.74 (0.63 to 0.86)<br>• *ESKD, renal death, or CV death: 9.7% vs. 13.1%<br>○ HR 0.73 (0.61 to 0.87)<br>• *Dialysis, kidney transplantation, or renal death: 3.5% vs. 4.8%<br>○ HR 0.72 (0.54 to 0.97) | • *Osmotic diuresis: 2.3% vs. 1.8%<br>○ HR 1.25 (0.83 to 1.89)<br>• *Volume depletion: 6.5% vs. 5.2%<br>○ HR 1.25 (0.97 to 1.59)<br>• *Acute pancreatitis: 0.2% vs. 0.1% | |
| Wiviott et al. (2019)[30]<br>NCT01730534<br>AstraZeneca<br>Dapagliflozin (Farxiga)<br>DECLARE-TIMI 58<br>Multisite international<br>Total N = 17,160<br>• 10 mg, n = 8,582<br>• Placebo, n = 8,578 | • All-cause mortality: 6.2% vs. 6.6%<br>○ HR 0.93 (0.82 to 1.04)<br>• MACE: 8.8% vs. 9.4%<br>○ HR 0.93 (0.84 to 1.03); *P* = .17<br>○ *CV death: 2.9% vs. 2.9%; HR 0.98 (0.82 to 1.17)<br>○ *Fatal or nonfatal MI: 4.6% vs. 5.1%; HR 0.89 (0.77 to 1.01)<br>○ *Fatal or nonfatal ischemic stroke: 2.7% vs. 2.7%; HR 1.01 (0.84 to 1.21)<br>• *hHF:2.5% vs. 3.3%<br>○ HR 0.73 (0.61 to 0.88)<br>• †SAE: 34.1% vs. 36.2%<br>○ RR 0.94 (0.91 to 0.98); P = .005<br>○ HR 0.91 (0.87 to 0.96); *P* < .001<br>• *Non-CV death: 2.5% vs. 2.7%<br>○ HR 0.88 (0.73 to 1.08)<br>• CV death or hHF: 4.9% vs. 5.8% | • AE leading to discontinuation: 8.1% vs. 6.9%<br>○ HR 1.15 (1.03 to 1.28); P = .01<br>• DKA: 0.3% vs. 0.1%<br>○ HR 2.18 (1.10 to 4.30); *P* = .02<br>○ *MI HR 6.98 (0.86 to 56.76)<br>○ *No MI HR 1.74 (0.83 to 3.63)<br>• Amputation: 1.4% vs. 1.3%<br>○ HR 1.09 (0.84 to 1.40); *P* =. 53<br>○ *MI HR 1.72 (1.03 to 2.88)<br>○ *No MI HR 0.89 (0.69 to 1.25)<br>○ *HFrEF HR 1.59 (0.62 to 4.11)<br>• Genital infection: 0.9% vs. 0.1%<br>○ HR 8.36 (4.19 to 16.68); *P* < .001<br>○ *MI HR 6.07 (1.36 to 27.10)<br>○ *No MI HR 9.01 (4.13 to 19.67)<br>• Fracture: 5.3% vs. 5.1%<br>○ HR 1.04 (0.91 to 1.18); *P* = .59<br>○ *HFrEF HR 1.20 (0.66 to 2.19) | <u>Subgroup analyses</u><br>• MACE by baseline CVD history<br>○ Prior MI HR 0.84 (0.72 to 0.99); *P* = .04<br>○ No MI HR 1.00 (0.88 to 1.13); *P* = .97<br>○ Prior ASCVD HR 0.98 90.81 to 1.19); *P* = .85<br>○ MRF HR 1.01 (0.86 to 1.20); *P* = .87<br>• Non-CV death by baseline HF, *P* = .03<br>○ Prior HF HR 0.50 (0.29 to 0.86)<br>○ No HF HR 0.96 (0.78 to 1.17)<br>• *CV death or hHF by baseline CVD history |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ HR 0.83 (0.73 to 0.95); *P* = .005 | ○ *No HFrEF HR 1.03 (0.90 to 1.18)<br>• Volume depletion<br>○ *HFrEF HR 1.52 (0.79 to 2.93)<br>○ *No HFrEF HR 0.96 (0.79 to 1.18)<br>• Urinary tract infection: 1.5% vs. 1.6%<br>○ HR 0.93 (0.73 to 1.18); *P* = .54<br>○ *HFrEF HR 1.45 (0.24 to 8.68)<br>○ *No HFrEF HR 0.92 (0.72 to 1.17) | ○ Prior MI HR 0.81 (0.65 to 1.00)<br>○ No MI HR 0.85 (0.72 to 1.00)<br>○ Prior ASCVD HR 0.87 (0.68 to 1.12)<br>○ MRF HR 0.84 (0.67 to 1.04)<br>○ HFrEF HR 0.62 (0.45 to 0.86)<br>○ HFpEF HR 0.88 (0.66 to 1.17)<br>• *Recurrent MI by baseline MI<br>○ Prior MI HR 0.78 (0.63 to 0.95)<br>○ No MI HR 0.99 (0.83 to 1.19)<br>• *Type 1 MI by baseline MI<br>○ Prior MI HR 0.80 (0.63 to 1.02)<br>○ No MI HR 1.08 (0.87 to 1.34)<br>• *Type 2 MI by baseline MI<br>○ Prior MI HR 0.64 (0.42 to 0.97)<br>○ No MI HR 1.01 (0.70 to 1.45)<br>• *Coronary heart disease death by baseline MI<br>○ Prior MI HR 0.84 (0.60 to 1.19)<br>○ No MI HR 1.05 (0.81 to 1.35)<br>• *CV death by baseline CVD history<br>○ MI HR 0.92 (0.69 to 1.23)<br>○ No MI HR 1.03 (0.82 to 1.28)<br>○ HFrEF HR 0.55 (0.34 to 0.90)<br>○ HFpEF HR 1.41 (0.93 to 2.13)<br>• *hHF by HF status |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | | | ○ HFrEF HR 0.64 (0.43 to 0.95)<br>○ HFpEF HR 0.72 (0.50 to 1.04)<br>• *All-cause mortality by baseline CVD history<br>○ Prior MI HR 0.83 (0.66 to 1.30)<br>○ No MI HR 0.97 (0.85 to 1.12)<br>○ HFpEF HR 1.02 (0.75 to 1.38)<br>○ HFrEF HR 0.59 (0.40 to 0.88) |
| Zinman et al. (2015)[27]<br>NCT01131676<br>Boehringer Ingelheim<br>Empagliflozin (Jardiance)<br>EMPA-REG OUTCOME<br>Multisite international<br>Total N = 7,028<br>• 10 mg, n = 2,345<br>• 25 mg, n = 2,342<br>• Placebo, n = 2,333 | • All-cause mortality: 5.7% vs. 8.3%<br>○ HR 0.68 (0.57 to 0.82); *P* < .001<br>○ *10 mg HR 0.70 (0.56 to 0.87)<br>○ *25 mg HR 0.67 (0.54 to 0.83)<br>• MACE: 10.5% vs. 12.1%<br>○ HR 0.86 (0.74 to 0.99); *P* = .04<br>○ CV death: 3.7% vs. 5.9%; HR 0.62 (0.49 to 0.77); *P* < .001<br>○ Nonfatal MI: 4.5% vs. 5.2%; HR 0.87 (0.70 to 1.09); *P* = .22<br>○ Nonfatal stroke: 3.2% vs. 2.6%; HR 1.24 (0.92 to 1.67); *P* = .16<br>• Fatal or nonfatal MI: 4.8% vs. 5.2%<br>○ HR 0.87 (0.70 to 1.09); *P* = .23<br>○ *10 mg HR 0.79 (0.61 to 1.03)<br>○ *25 mg HR 0.95 (0.74 to 1.22)<br>• Fatal or nonfatal stroke: 3.5% vs. 3.0%<br>○ HR 1.18 (0.89 to 1.56); *P* = .26<br>○ *10 mg HR 1.22 (0.89 to 1.68)<br>○ *25 mg HR 1.13 (0.82 to 1.56)<br>• hHF: 2.7% vs. 4.1%<br>○ HR 0.65 (0.50 to 0.85); *P* = .002<br>○ *10 mg HR 0.62 (0.45 to 0.86) | • Any AE: 90.2% vs. 91.7%<br>○ RR 0.98 (0.97 to 1.00); *P* = .05<br>○ *10 mg: 90.1%<br>○ *25 mg: 90.4%<br>• Genital Infection AE: 6.4% vs. 1.8%<br>○ *RR 3.57 (2.59 to 4.91); P < .0001*<br>○ *10 mg: 6.5%; male: 5.4%; female: 9.2%<br>○ *25 mg: 6.3%; male: 4.6%; female: 10.8%<br>• DKA AE: 0.1% vs. 0.0004%<br>○ RR 2.13 (0.24 to 19.02); *P* = .49<br>○ *10 mg: 0.1%<br>○ *25 mg: 0.0004%<br>• Lower limb amputation, *P* = .27<br>○ PAD HR 0.84 (0.54 to 1.32)<br>○ No PAD HR 1.30 (0.69 to 2.46)<br>• New or worsening nephropathy, *P* = .33<br>○ PAD HR 0.54 (0.41 to 0.71)<br>○ No PAD HR 0.63 (0.54 to 0.73) | <u>Subgroup analyses</u><br>• MACE by age, *P* = .01<br>○ < 65 years HR 1.04 (0.84 to 1.29)<br>○ ≥ 65 years HR 0.71 (0.59 to 0.87)<br>• MACE by baseline HbA1c, *P* = .01<br>○ < 8.5% HR 0.76 (0.60 to 0.91)<br>○ ≥ 8.5% HR 1.14 (0.86 to 1.50)<br>• MACE by baseline history of MI or stroke; *P* = .79<br>○ With HR 0.84 (0.71 to 1.00)<br>○ Without HR 0.88 (0.66 to 1.18)<br>• CV death by baseline history of MI or stroke; *P* = .62<br>○ With HR 0.60 (0.46 to 0.77)<br>○ Without HR 0.69 (0.43 to 1.10) |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ *25 mg HR 0.68 (0.50 to 0.93)<br>• SAE: 38.2% vs. 42.3%<br>○ *RR 0.90 (0.85 to 0.96); P = .0007*<br>• 10 mg MACE<br>○ HR 0.85 (0.72 to 1.01); *P* = .07<br>○ *CV death HR 0.65 (0.50 to 0.85)<br>○ *Nonfatal MI HR 0.79 (0.60 to 1.03)<br>○ *Nonfatal stroke HR 1.27 (0.91 to 1.79)<br>• 25mg MACE<br>○ HR 0.86 (0.73 to 1.02); *P* = .09<br>○ *CV death HR 0.59 (0.45 to 0.77)<br>○ *Nonfatal MI HR 0.95 (0.74 to 1.23)<br>○ *Nonfatal stroke HR 1.20 (0.85 to 1.69)<br>• MACE plus hUA: 12.8% vs. 14.3%<br>○ HR 0.89 (0.78 to 1.01); *P* = .08<br>○ *10 mg HR 0.89 (0.72 to 1.01)<br>○ *25 mg HR 0.88 (0.76 to 1.03)<br>• Silent MI: 1.6% vs. 1.2%<br>○ HR 1.28 (0.70 to 2.33); *P* = .42<br>○ *10 mg HR 1.32 (0.67 to 2.60)<br>○ *25 mg HR 1.24 (0.63 to 2.45)<br>• hUA: 2.8% vs. 2.8%<br>○ HR 0.99 (0.84 to 1.34); *P* = .97<br>○ *10 mg HR 1.03 (0.74 to 1.45)<br>○ *25 mg HR 0.96 (0.68 to 1.35)<br>• CR: 7.0% vs. 8.0%<br>○ HR 0.86 (0.72 to 1.04); *P* = .11<br>○ *10 mg HR 0.81 (0.65 to 1.00)<br>○ *25 mg HR 0.92 (0.75 to 1.13)<br>• TIA: 0.8% vs. 1.0%<br>○ HR 0.85 (0.51 to 1.42); *P* = .54<br>○ *10 mg HR 0.82 (0.45 to 1.53) | | ○ ACM by baseline history of MI or stroke; *P* = .38<br>○ With HR 0.65 (0.52 to 0.80)<br>○ Without HR 0.78 (0.55 to 1.11)<br>• hHF by baseline history of MI or stroke; *P* = .56<br>○ With HR 0.68 (0.50 to 0.94)<br>○ Without HR 0.57 (0.25 to 0.95)<br>• hHF or CV death by history of baseline MI or stroke; *P* = .77<br>○ With HR 0.64 (0.52 to 0.80)<br>○ Without HR 0.69 (0.48 to 0.99)<br>• MACE by baseline PAD status; *P* = .90<br>○ HR 0.84 (0.62 to 1.14)<br>○ HR 0.86 (0.73 to 1.02)<br>• CV death by baseline PAD status; *P* = .67<br>○ With HR 0.57 (0.37 to 0.88)<br>○ Without HR 0.64 (0.49 to 0.82)<br>• ACM by baseline PAD status; *P* = .56<br>○ With HR 0.62 (0.44 to 0.88)<br>○ Without HR 0.70 (0.57 to 0.87)<br>• hHF by baseline PAD status; *P* = .53<br>○ With HR 0.56 (0.35 to 0.92)<br>○ Without HR 0.68 (0.49 to 0.93) |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | ○ *25 mg HR 0.87 (0.48 to 1.58)<br>• hHF or CV death: 5.7% vs. 8.5%<br>○ HR 0.66 (0.55 to 0.79); *P* < .001<br>○ *10 mg HR 0.66 (0.53 to 0.83)<br>○ *25 mg HR 0.65 (0.52 to 0.81) | | • hHF/CV death by baseline PAD status; *P* = .99<br>○ With HR 0.65 (0.45 to 0.93)<br>○ Without HR 0.65 (0.52 to 0.81)<br>• *Outcomes in individuals identifying as Asian<br>○ MACE HR 0.68 (0.48 to 0.95)<br>○ CV death HR 0.44 (0.25 to 0.78)<br>○ hHF or CV death HR 0.57 (0.36 to 0.89) |
| Norhammar et al. (2019)[51]<br>Observational cohort<br>National health care registry: Sweden<br>Total N = 28,408<br>• Dapagliflozin, n = 7,102<br>• Other glucose lowering drugs, n = 21,306 | • CV death or hHF<br>○ ITT HR 0.79 (0.69 to 0.92); *P* = .002<br>○ hHF<br>○ HR 0.79 (0.67 to 0.93) *P* = .005<br>• CV death<br>○ HR 0.75 (0.57 to 0.97) *P* = .003<br>• All-cause mortality<br>○ HR 0.63 (0.54 to 0.74); *P* < .001<br>• MI<br>○ HR 0.91 (0.74 to 1.11) *P* = .35<br>• Stroke<br>○ HR 1.06 (0.87 to 1.30) *P* = .53<br>• AF<br>○ HR 0.94 (0.80 to 1.10) *P* = .43 | • Severe hypoglycemia<br>○ HR 0.91 (0.78 to 1.06) *P* = .24 | |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| Persson et al. (2018)[56]<br>Retrospective cohort<br>Prescribed Drug Registers, Cause of Death Registers, National Patient Registers; Sweden, Denmark, Norway<br>Total N = 40,908<br>• Dapagliflozin, n = 10,227<br>• DPP-4 Inhibitors, n = 30,681 | • MACE HR 0.79 (0.67 to 0.94)<br>○ *Nonfatal MI HR 0.91 (0.72 to 1.16)<br>○ *Nonfatal stroke HR 0.79 (0.61 to 1.03)<br>○ *CV death HR 0.76 (0.53 to 1.08)<br>• *hHF<br>○ HR 0.62 (0.50 to 0.77)<br>• *All-cause mortality<br>○ HR 0.59 (0.49 to 0.72)<br>• *MACE + UA<br>○ HR 0.81 (0.69 to 0.94)<br>• *MACE + UA + hHF<br>○ HR 0.75 (0.66 to 0.86) | • *AF<br>○ HR 0.92 (0.76 to 1.12)<br>• *Severe hypoglycemia<br>○ HR 0.94 (0.74 to 1.19) | |
| Toulis et al. (2017)[59]<br>Retrospective cohort<br>U.K. THIN<br>Total N = 22,124<br>• Dapagliflozin, n = 4,444<br>• SGLT-2 unexposed, n = 17,680 | • All-cause mortality<br>○ aIRR 0.50 (0.33 to 0.75); *P* = .001<br>• All-cause mortality in those without history of CVD events<br>○ aIRR: 0.44 (0.25 to 0.78); *P* = .005 | | |
| Udell et al. (2018)[60]<br>Retrospective cohort<br>U.S. Department of Defense Military Health System<br>EASEL<br>Total N = 25,258<br>• New SGLT-2 initiators vs. new non-SGLT-2 initiators, both n = 12,629 | • All-cause mortality or hHF<br>○ HR 0.57 (0.50 to 0.65); *P* < .0001<br>○ *IRR 1.73 vs. 3.01 per 100 person-years<br>• All-cause mortality<br>○ HR 0.57 (0.49 to 0.66); *P* < .0001<br>○ *IRR 1.29 vs. 2.26 per 100 person-years<br>• hHF<br>○ HR 0.57 (0.45 to 0.73); *P* < .0001<br>○ *IRR 0.51 vs. 0.90 per 100 person-years | • Below knee amputation<br>○ HR 1.99 (1.12 to 3.51); *P* = .02<br>○ *IRR 0.17 vs. 0.09 per 100 person-years<br>○ *Canagliflozin IRR 0.19 vs. 0.07<br>○ *Dapagliflozin IRR 0.09 vs. 0.12<br>○ *Empagliflozin IRR 0.12 vs. 0.09 | <u>IRR per 100 person-years</u><br>• *All-cause mortality or hHF<br>○ Canagliflozin 1.83<br>○ Dapagliflozin 1.41<br>○ Empagliflozin 1.52<br>• *All-cause mortality<br>○ Canagliflozin 1.42<br>○ Dapagliflozin 0.86<br>○ Empagliflozin 1.09<br>• *hHF<br>○ Canagliflozin 0.51<br>○ Dapagliflozin 0.58 |

| Authors; Registration Number; Manufacturer; Generic Drug; Trial Name; Trial Type; N | Outcomes<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value | Harms*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value | Other findings*<br>No (%) vs. comparator (%)<br>HR (95% CI); *P* value<br>RR (95% CI); *P* value |
|---|---|---|---|
| | • MACE (ACM, nonfatal MI, nonfatal stroke)<br>○ HR 0.67 (0.60 to 0.75); *P* < .0001<br>• Nonfatal MI<br>○ HR 0.85 (0.66 to 1.10); *P* = .22<br>• Nonfatal stroke<br>○ HR 0.81 (0.64 to 1.03); *P* = .09<br>• MACE or hHF<br>○ HR 0.66 (0.60 to 0.74); *P* < .0001 | | ○ Empagliflozin 0.43<br>• *Nonfatal MI<br>○ Canagliflozin 0.57<br>○ Dapagliflozin 0.69<br>○ Empagliflozin 0.47<br>• *Nonfatal stroke<br>○ Canagliflozin 0.53<br>○ Dapagliflozin 0.52<br>○ Empagliflozin 0.52 |
| Patorno et al. (2018)[54]<br>Retrospective cohort<br>U.S. Optum Clinformatics<br>Total N = 55,560<br>• Canagliflozin vs. DPP-4, n = 17,667 each<br>• Canagliflozin vs. GLP-1, n = 20,539 each<br>• Canagliflozin vs. SU, n = 17,354 each | • *hHF vs. DPP-4 initiators 8.9% vs. 12.8%<br>○ HR 0.70 (0.54 to 0.92)<br>• *hHF vs. GLP-1 initiators: 7.5% vs. 12.4%<br>○ HR 0.61 (0.47 to 0.78)<br>• *hHF vs. SU initiators: 7.3% vs. 14.4%<br>○ HR 0.51 (0.38 to 0.67)<br>• Composite endpoint (hospitalization for acute MI, ischemic stroke, hemorrhagic stroke)<br>○ *vs. DPP-4 initiators: 9.9 vs. 11.1% HR 0.89 (0.68 to 1.17)<br>○ *vs. GLP-1 initiators: 8.8% vs. 8.5% HR 1.03 (0.79 to 1.35)<br>○ *vs. SU initiators: 8.8% vs. 10.3% HR 0.86 (0.65 to 1.13) | | |

*Note. * denotes P value not reported; † denotes outcome assessed in the per-protocol population; ‡ denotes outcome assessed in the on-treatment population. Abbreviations. ACM: all-cause mortality; ACS: acute coronary syndrome; AE: adverse event; AF: atrial fibrillation; aHR: adjusted hazard ratio; aIRR: adjusted incidence rate ratio; ALT: alanine transaminase; ASCVD: atherosclerotic cardiovascular disease; AST: aspartate transaminase; BMI: body mass index; CABG: coronary artery bypass graft; CHF: congestive heart failure; CI: confidence interval; CR: coronary revascularization; CV: cardiovascular; CVD: cardiovascular disease; DFU: diabetes-related foot ulcer; DKA: diabetic ketoacidosis; DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; GI: gastrointestinal; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin test of blood glucose (sugar); HF: heart failure; HFrEF: HF with reduced ejection fraction; HFpEF: HF with preserved ejection fraction; hHF: hospitalization for heart failure; HR: hazard ratio; hUA: hospitalization for unstable*

*angina; IHD: ischemic heart disease; IRR: incidence rate ratio; ITT: intention-to-treat; MACE: major adverse cardiovascular events; Met: Metformin; MI: myocardial infarction; MRF: multiple risk factors; NCT: U.S. National Clinical Trials number; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; RR: risk ratio; SAE: serious adverse event; SGLT-2: sodium-glucose cotransporter-2; SU: sulfonylureas; TIA: transient ischemic attack; TZD: thiazolidinediones; UA: unstable angina; U.K. THIN: United Kingdom's The Health Improvement Network; UB: upper bound; ULN: upper limit of normal.*

## Appendix C. Bibliography of Included Studies


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## Appendix D. Bibliography of Excluded Studies

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