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Cardiovascular Benefits and Harms of Step Therapy in the Treatment of Type 2 Diabetes in Adults with and without Atherosclerotic Cardiovascular Disease

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Summary

Question 1. In persons with type 2 diabetes with or without known atherosclerotic cardiovascular disease (ASCVD) who cannot attain adequate glucose control with metformin, what is the benefit of GLP-1 agonists or SGLT-2 inhibitors on cardiovascular morbidity and mortality?

- Evidence of benefit in persons with known ASCVD on cardiovascular disease (CVD) outcomes, CVD mortality and all-cause mortality (ACM)
    - Based on limited evidence in persons without ASCVD, no evidence of benefit on CVD outcomes
- Presumed class effect of benefit for both GLP-1 agonists and SGLT-2 inhibitors
    - For GLP-1 agonists, there is more convincing data of benefit for 'glutides' than 'natides'
    - Each medication evaluated in only one cardiovascular outcome trial; clinical heterogeneity amongst trials prohibits medication-specific conclusions of benefits

Question 2. In persons with type 2 diabetes with or without known ASCVD who cannot attain adequate glucose control with metformin, what are the serious harms of GLP-1 agonists or SGLT-2 inhibitors?

- Evidence of the potential for retinopathy and biliary disease for GLP-1 agonists, but certainty and magnitude for these harms are still uncertain
- Evidence for genital infections for SGLT-2 inhibitors
- Evidence for the potential for lower extremity amputations, urinary tract infections, bone fractures, and ketoacidosis for SGLT-2 inhibitors, but the certainty and magnitude for these harms are still uncertain
- Presumed class effect of harms for both GLP-1 agonists and SGLT-2 inhibitors
    - For SGLT-2 inhibitors, the is more convincing data of harms for canagliflozin than other SGLT-2 inhibitors
    - Each medication evaluated in only one cardiovascular outcome trial; clinical heterogeneity amongst trials and heterogeneity and limitations of observational studies prohibit making medication-specific conclusions of harms
- Evidence harms by ASCVD status not known

Conclusions

- Despite potential harms for GLP-1 agonists and SGLT-2 inhibitors, there is still a likely net benefit for both classes of medications
- Harms signal the need for monitoring or greater vigilance for biliary disease (if significant weight loss) with use of GLP-1 agonists, and for lower extremity vascular disease, genitourinary infections, bone density and ketoacidosis with use of SGLT-2 inhibitors
- Other large cardiovascular outcome trials and observational data on harms may change or refine our understanding of the risk benefit ratio, the class effect on both benefits and harms, as well as safety monitoring considerations

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Context/Background

Standard of care in clinical practice is to use metformin as the first-line medication for glucose-lowering in type 2 diabetes.[1-3] A number of different medications are available as next line therapy in persons whose diabetes is not adequately controlled on metformin, or for whom metformin is contraindicated or not tolerated, including: sulfonylureas (SU), thiazolidinediones (TZD), basal insulin, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, or sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Each class of medications has different benefits, risks, and acceptability to patients (e.g., oral versus injectable, impact on weight, frequency of dosing, tolerability/side effect profile, and cost) (**Table 1**).

While each of these classes of medications are effective for glycemic control, to date, only GLP-1 agonists and SGLT-2 inhibitors have trial evidence to demonstrate their ability to reduce major cardiovascular disease (CVD) outcomes such as myocardial infarction (MI), cerebrovascular accidents (CVA), and CVD mortality. Recent comprehensive and well conducted meta-analyses have estimated the effectiveness and safety of individual classes of medications in comparison to placebo and other classes of medications.[4, 5] Because the FDA began requiring cardiovascular outcome trials in 2008 for diabetes medications, large trials with primary outcomes of CVD events are available for newer medication classes (i.e., DPP-4 inhibitors, GLP-1 agonists, or SGLT-2 inhibitors) but not older medications (i.e., SU, TZD or insulin). Evidence evaluating the CVD benefit of older medications consist of meta-analyses of smaller and shorter-term trials that have glycemic control as the primary outcome; these studies are limited by a small number of CVD events and deaths. Nonetheless, a 2016 meta-analysis by Palmer and colleagues demonstrates that neither SU nor TZD are associated with a reduction in CVD mortality, all-cause mortality, or any individual CVD outcome either as monotherapy or when added to metformin as dual therapy (**Appendix A Table 1**).[4] A more recent meta-analysis from 2018 by Zheng and colleagues estimated the effectiveness and safety of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors on mortality and CVD outcomes (**Appendix A Table 2**).[5] This meta-analysis demonstrated that DPP-4 inhibitors were not associated with a reduction in all-cause or CVD mortality, heart failure, MI, or CVA compared to placebo or the other two medication classes. Only SGLT-2 inhibitors and GLP-1 agonists were associated with any benefit for all-cause or CVD mortality, MI (SGLT-2 only), or heart failure (SGLT-2 only) outcomes.[5] This meta-analysis did not stratify results by studies using medications as monotherapy versus studies evaluating medications when added to metformin. Neither of these two systematic reviews reported results in persons with known atherosclerotic cardiovascular disease (ASCVD) versus those without ASCVD.

Because of these findings of CVD benefit for GLP-1 agonists and SGLT-2 inhibitors, major diabetes management guidelines have emphasized the role of these two classes of medications as secondary therapies. Most recently, in the 2018 American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guideline, GLP-1 agonists and SGLT-2 inhibitors are recommended as second line therapy after metformin failure (i.e., intolerance, contraindication, or suboptimal glycemic control with metformin alone) in the presence of ASCVD or chronic kidney disease (CKD).[3] In the 2017 guideline from the National Institute for Heath and Care Excellence (NICE), GLP-1 agonists are recommended only if goal hemoglobin A1c is not achieved with metformin and 2 other oral medications and are to be continued only if A1c is lowered by 1.0% and weight loss of 3% of initial body weight is achieved in 6 months.[1] SGLT-2 inhibitors are recommended in a dual-therapy regimen together with metformin if a SU is contraindicated or not tolerated, or if the patient is at high risk of hypoglycemia.[6-8] SGLT-2 inhibitors (i.e., canagliflozin and empagliflozin) can also be used in a triple oral-therapy regimen together with metformin and a SU or metformin and a TZD.

In this review we focus on the benefits and harms of GLP-1 agonists and SGLT-2 inhibitors in persons with type 2 diabetes who cannot attain adequate control with metformin.

Methods

Questions

The objective of this report is to inform Kaiser Permanente's diabetes national clinical practice guideline by synthesizing available evidence on the following questions:

- Question 1. In persons with type 2 diabetes with or without known ASCVD who cannot attain adequate glucose control with metformin, what is the benefit of GLP-1 agonists or SGLT-2 inhibitors on cardiovascular morbidity and mortality?
- Question 2. In persons with type 2 diabetes with or without known ASCVD who cannot attain adequate glucose control with metformin, what are the serious harms of GLP-1 agonists or SGLT-2 inhibitors?

Identification of included literature

We developed eligibility criteria to guide study selection **(Appendix B)**. During the initial work to determine the scope of this review, a targeted search for recent systematic reviews and meta-analyses of GLP-1 agonists and SGLT-2 inhibitors yielded recent and comprehensive reviews by Zheng and colleagues[5] and NICE.[1] For Question 1, we evaluated the included trials from these reviews to identify studies that had cardiovascular events specified as primary outcomes, and that were either explicitly conducted in persons with metformin failure or in which the majority of participants were on metformin at baseline and A1c was uncontrolled. In total, 178 articles from the Zheng and NICE reviews were screened and 128 were relevant to metformin failure (**Appendix C**). Of those 128 articles, 6 were trials with CVD outcomes as primary endpoints. The reviews by Zheng and colleagues and NICE included a broader set of studies that had glycemic control or weight loss as the primary outcome and assessed CVD events or deaths as harms; as such these trials were shorter and had very few events or reported that no CVD events or deaths occurred. Through news alerts and targeted searches in ClinicalTrials.gov, we were alerted to several ongoing cardiovascular outcome trials that were released during the period for this work, including data presented at meetings for the European Association for the Study of Diabetes (EASD) and the American Heart Association (AHA). In total, 8 trials were identified (6 from the Zheng review and 2 through active surveillance). Other ongoing trials are noted in **Appendix D**.

For Question 2, in addition to the trials included for Question 1, we searched for existing systematic reviews and observational studies on the harms of GLP-1 agonists and SGLT-2 inhibitors. Medline was searched for systematic reviews and meta-analyses and 441 citations were identified; of those 441 citations, 16 were reviewed at full-text and 3 were included in results. For observational studies, Medline, PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched, yielding 881 citations; of those 881 citations, 52 were reviewed in full-text and 46 were included in the results. Search strategies are available in **Appendix E**. For observational studies, a threshold of 1,000 participants was set based on the adequate size estimated to detect less common adverse events (i.e., based on event rates observed in the cardiovascular outcome trials).

Critical appraisal and data synthesis

One person critically appraised the 8 included cardiovascular outcome trials to assess whether there were any major methodological flaws or important limitations that could invalidate trial results. RCTs were rated as good or fair; there were no poor-quality studies. In general, a good-quality study met all criteria well (**Appendix F**). A fair-quality study did not meet (or it was unclear whether it met) at least one criterion but also had no known important limitation that could invalidate its results. The one trial that was rated as fair was downgraded based on lack of baseline comparability that was not adjusted for and differential treatment discontinuation.[9] Observational studies evaluating harms were not critically appraised although we used an evidence hierarchy (described below) to capture the relative risk of bias across the different study designs.

For Question 1, we conducted quantitative analyses for the primary composite CVD outcome, cardiovascular mortality, all-cause mortality, and individual CVD outcomes for each medication class. When possible, we stratified analyses by populations with known ASCVD versus without ASCVD. Stratified results by ASCVD status were not available or not reported for individual CVD outcomes. We performed random-effects inverse-variance weighted meta-analyses using the "meta" package (version 4.3-2) in R (version 3.1.2). The I^2 statistic was used to measure the statistical heterogeneity between studies.

For Question 2, evidence was synthesized in a narrative format given the heterogeneity of outcomes and study designs. We organized results by medication class and type of harm. We used an evidence hierarchy and stratified results by type of study design: trials, systematic reviews of trials, prospective observational studies, large retrospective database studies, and adverse event reporting systems (e.g., FDA Adverse Event Reporting system). Trials and systematic reviews of trials are located at the top of the hierarchy due to their randomized comparator/control group, however, the included populations of these trials may be restricted and therefore less generalizable to the relevant population. Observational studies have an increased risk of bias, but generally have greater applicability to real world practice. Retrospective studies using primarily administrative or limited electronic records have greater risk of bias than included prospective studies due to limitations in data quality; however, these studies have greater power to detect rare or longer-term adverse events. Last, the FDA Adverse Event Reporting System has numerous limitations, and while it can provide a signal for possible harms, does not provide any denominators and therefore cannot inform estimates of the magnitude of adverse events. In addition to reviewing published literature that analyzed FDA Adverse Event Reporting System data, we also we queried this source by medication using the "Public Dashboard" for potential adverse events to evaluate whether there was a medication effect beyond a class effect for individual agents (**Appendix G**).

For both Questions 1 and 2, we used a modified GRADE approach to evaluate the strength of evidence for each outcome.[10] At least two reviewers participated in the rating of the risk of bias, inconsistency, indirectness, imprecision, and overall quality (or strength of evidence) for each outcome.

Results

FDA approval of GLP-1 agonists and SGLT-2 inhibitors

Based on 2008 guidance from the FDA, all new diabetes medications must show that they do not increase the risk for CVD events.[11] This guidance was instituted based on controversy regarding increased cardiovascular risk with the TZD rosiglitazone (Avandia) which came to light in 2007 with the publication of a meta-analysis showing an increased risk for MI.[12] While new agents may be approved based on meta-analysis of smaller phase II and III trials whose primary outcome is generally glucose control that secondarily evaluate CVD events as safety outcomes, additional large post-marketing safety trials evaluating CVD events (referred to as cardiovascular outcome trials) are generally required to achieve adequate power to demonstrate CVD safety.

Currently, 6 GLP-1 agonists are available in the United States (**Table 2**).[13, 14] GLP-1 agonists are administered by subcutaneous injection. Since exenatide (Byetta) first came on the market in 2005 which had twice a day dosing, several extended-release formulations have become available to increase acceptability to patients.

Table 2. GLP-1 Agonists Available in the United States

Medication	Dosing, SQ	FDA Approval Year	Cardiovascular Outcome Trials
Exenatide (Byetta)	BID	2005	Predates FDA requirement
Exenatide extended-release (Bydureon)*	Weekly	2012	EXSCEL
Liraglutide† (Victoza)	QD	2009	LEADER
Albiglutide (Tanzeum)	Weekly	2014‡	Harmony
Dulaglutide (Trulicity)	Weekly	2014	REWIND (Expected June 2019)
Lixisenatide (Adlyxin)	QD	2016	ELIXA
Semiglutide (Ozempic)	Weekly	2017	SUSTAIN-6

Abbreviations: BID = twice a day; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; FDA = US Food and Drug Administration; GLP-1 = Glucagon-like peptide-1; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; mg = milligrams; QD = once a day; REWIND = Researching Cardiovascular Events With a Weekly INcretin in Diabetes; SQ = subcutaneous administration; SUSTAIN-6 = Trail to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

Notes:
* BYDUREON BCise was approved in 2017; this is a new formulation available in a pre-filled pen with pre-attached hidden needle.

† Saxenda is a formulation approved for weight loss
‡ Albiglutide (Tanzeum), originally approved by the FDA in 2014, was discontinued in 2017, one month after the FDA added risk of anaphylactic reaction to its label; GlaxoSmithKline stated that discontinuation of the medication was due to limited prescribing and not safety concerns.[15]

Currently, four SGLT-2 inhibitors are available in the United States (**Table 3**).[16] All are administered orally, and all are available as combination formulations with metformin, metformin extended-release, or various DPP-4 inhibitors. These combinations are not reviewed here as no trials powered to evaluate CVD outcomes are available on these combination formulations.

Table 3. SGLT-2 Inhibitors Available in the United States

Medication	Dosing, oral	FDA Approval Year	Cardiovascular Outcome Trials
Canagliflozin (Invokana)	100 mg, 300 mg	2013	CANVAS
Dapagliflozin (Farxiga)	5 mg, 10 mg	2014	DECLARE-TIMI-58
Empagliflozin (Jardiance)	10 mg, 25 mg	2014	EMPAREG OUTCOME
Ertugliflozin (Steglatro)	5 mg, 15 mg	2017	VERTIS CV (Expected September 2019)

Abbreviations: CANVAS = Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI-58 = Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPAREG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial; FDA = US Food and Drug Administration; mg = milligrams; VERTIS CV = Ertugliflozin in Subjects With Type 2 Diabetes Mellitus and Established Cardiovascular Disease

Cardiovascular Outcome Trials

CVD trials for both GLP-1 agonists and SGLT-2 inhibitors were generally good quality large trials ranging from 3,297 to 17,160 included participants (**Tables 4-5**). The average duration of included trials ranged from 1.6 to 4.2 years. Trial participants were exclusively adults with suboptimal control of their type 2 diabetes, with mean A1c in trials ranging from 8.0 to 8.7; however, trials generally excluded adults with very poor control (A1c >10.0 or 10.5). Trial participants were all on medications for control of their diabetes, and 73% to 82% of trial participants were taking metformin. The vast majority of participants had known ASCVD, although inclusion criteria varied across trials. All trials included persons with heart failure, with prevalence ranging from 10% to 24% across trials; it was unclear whether heart failure was systolic or diastolic. All studies excluded persons with CKD Stage 4 or greater (eGFR less than 30 ml/min/1.73 m^2). ELIXA, a trial evaluating the GLP-1 agonist lixisenatide, is an outlier amongst cardiovascular outcome trials; this trial restricted inclusion to persons with diabetes with an acute coronary event in the past 180 days; the mean A1c was 7.6 amongst trial participants, and 66% of participants were taking metformin.[9] All trials except ELIXA had the same primary composite CVD outcome, consisting of cardiovascular death, nonfatal MI and nonfatal stroke; the primary composite outcome from ELIXA additionally included unstable angina. As a result of differences in the population and composite outcome studied, ELIXA had a higher event rate for CVD events compared with other included cardiovascular outcome trials.

CVD Benefits of GLP-1 agonists and SGLT-2 inhibitors

Across 5 CVD trials (n=42,920), overall, GLP-1 agonists decrease primary composite CVD outcomes, CVD mortality and all-cause mortality (**Table 6 and Figures 1-3**).[9, 17-20] Pooled results for individual CVD outcomes are not statistically significant. Only composite CVD outcomes are reported stratified in persons with or without known ASCVD. Stratified pooled analyses by ASCVD status at baseline demonstrate a reduction in composite CVD events in persons with known ASCVD but not in persons without known ASCVD (**Figure 1**). Although there is a stronger suggestion of benefit for the glutides, there is substantial clinical and methodologic heterogeneity across trials that precludes definitive conclusions. And as mentioned above, ELIXA (evaluating lixisenatide) is an outlier amongst the included trials and demonstrated a null effect on CVD outcomes. The absolute effect (in events per 1000 person-years) of GLP-1 agonists in persons with known ASCVD was not widely reported; the absolute effects from these trials in all persons (regardless of ASCVD status) ranged from approximately 3 to 13 fewer CVD events per 1000 person-years in persons randomized to taking GLP-1 agonists versus placebo controls, excluding ELIXA which found no difference between groups (**Table 4**).

Across 3 CVD trials (n=34,322), overall, SGLT-2 inhibitors also decrease primary composite CVD outcomes, CVD mortality, and all-cause mortality; although the trend for benefit observed for CVD mortality was not statistically significant (**Table 7 and Figures 4-6**).[21-23] Pooled results for stroke are not statistically significant. Pooled results demonstrate a statistically significant reduction for both MI (HR 0.89 [95% CI, 0.80 to 0.98]) and heart failure outcomes (HR 0.69 [95% CI, 0.61 to 0.79]). Ten to 14% of participants in the three trials had heart failure at baseline; it was unclear whether heart failure was systolic or diastolic. Composite CVD outcomes are reported stratified by persons with and without known ASCVD in all 3 SGLT-2 trials. DECLARE (evaluating dapagliflozin), the largest of the SGLT-2 trials with 17,160 participants, additionally reports individual outcomes by ASCVD status, although interaction testing revealed no statistically significant effect modification by ASCVD status for any outcome. Stratified pooled analyses by ASCVD status demonstrate a reduction in composite CVD events in persons with known ASCVD but not in persons without known ASCVD (**Figure 4**). The absolute effect of SGLT-2 inhibitors in trials including those with and without ASCVD ranged from approximately 2 to 5 fewer CVD events per 1000 person-years. In persons with known ASCVD, the absolute effect ranged from approximately 6 to 7 fewer CVD events per 1000 person-years in persons randomized to SGLT-2 inhibitors versus placebo controls (with 2 of 3 trials reporting) (**Table 5**).

Table 8. Meta-Analysis Results from Randomized Controlled Trials, SGLT-2 Inhibitors or GLP-1 Agonists vs. Placebo in Patients with Type 2 Diabetes Not Controlled by Metformin

Outcome	SGLT-2 Inhibitors				GLP-1 Agonists			
	K	Total N	I^2 (%)	HR (95% CI)	K	Total N	I^2 (%)	HR (95% CI)
Primary (Composite)	3	34,322	0	0.89 (0.83 – 0.96)	5	42,920	58.8	0.88 (0.80 – 0.96)
In Patients with CVD	3	20,650	0	0.86 (0.80 – 0.93)	5	35,278	57.3	0.87 (0.79 – 0.96)
In Patients without CVD	2	13,672	0	1.00 (0.87 – 1.16)	3	7,642	52.3	0.96 (0.73 – 1.26)
All-Cause Mortality	3	34,322	74.5	0.83 (0.70 – 0.98)	5	42,920	0	0.89 (0.83 – 0.95)
CVD Mortality	3	34,322	80.6	0.81 (0.63 – 1.06)	5	42,920	0	0.88 (0.80 – 0.96)
Any Myocardial Infarction	3	34,322	0	0.89 (0.80 – 0.98)	2	24,215	78.6	0.86 (0.67 – 1.11)
Fatal MI	0	NA	NA	NA	1	14,752	NA	1.29 (0.63 – 2.66)
Nonfatal MI	2	17,162	0	0.86 (0.74 – 1.00)	3	18,705	39.2	0.92 (0.79 – 1.07)
Any Stroke	3	34,322	27.8	1.00 (0.86 – 1.16)	2	24,215	0	0.85 (0.73 – 1.00)
Fatal Stroke	0	NA	NA	NA	1	14,752	NA	0.71 (0.39 – 1.30)
Nonfatal Stroke	2	17,162	62.7	1.02 (0.85 – 1.23)	3	24,215	50.9	0.88 (0.67 – 1.16)
Heart Failure	3	34,322	0	0.69 (0.61 – 0.79)	4	33,457	0	0.93 (0.83 – 1.04)

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; GLP-1 = Glucagon-like Peptide-1; HR = hazard ratio; K = number of studies analyzed; MI = myocardial infarction; N = number of participants analyzed; NA = not applicable; SGLT-2 = SLGT-2 = Sodium-glucose Cotransporter-2

Results from our pooled analyses of CVD outcome trials (**Table 8**) are generally consistent with findings from a 2018 systematic review and network meta-analysis by Zheng and colleagues[5] pooling all trials evaluating these two classes of medications with at least 12 weeks follow-up. Trials included in the Zheng review were not limited to participants with metformin failure, nor was it required that trials be designed or powered to assess CVD outcomes. This network meta-analysis examined the same outcomes reported here; however, it did not analyze composite CVD outcomes and therefore does not report outcomes stratified by ASCVD status.

Harms of GLP-1 agonists and SGLT-2 inhibitors

The CVD benefit for GLP-1 agonists and SGLT-2 inhibitors are offset by the potential for serious harms of these medications. Overall, meta-analyses of harms from trials do not show an overall increase in serious harms when compared to other classes of medications; however, GLP-1 agonists and SGLT-2 inhibitors do demonstrate a greater increase in adverse events leading to discontinuation of the medication.[5, 24] The available trials were not designed to detect all serious harms due to limited length of follow-up and the often selective nature of participants enrolled. Below we provide a high-level summary of serious harms from cardiovascular outcome trials, meta-analyses (including meta-analyses of regulatory data), prospective cohorts, retrospective database studies and FDA or other medication reporting systems. While data for serious harms are only available for specific medications, we describe and attribute harms

by class of medication because the clinical heterogeneity and inconsistency across studies, as well as individual study limitations, prohibit making conclusions that harms are limited to specific medications within each class. Meta-analyses and individual studies of harms do not report outcomes stratified by ASCVD status.

Across 5 CVD trials (n=42,920), 1 existing systematic review, 25 observational studies, and examination of the FDA Adverse Events Reporting System, GLP-1 agonists **do** increase the risk of hypoglycemia but not severe hypoglycemia, and **may** increase the risk of diabetic retinopathy and biliary disease, but the studies often have mixed findings or are extremely limited (**Table 9**). One systematic review demonstrated that GLP-1 agonists increase the risk of hypoglycemia,[5] but not serious hypoglycemia. Two trials reported an increase risk of severe hypoglycemia, but statistical significance was not reported (**Table 10**).[18, 19] The risk of increased retinopathy or biliary disease with GLP-1 agonists is uncertain. Two trials report an increase in retinopathy,[19, 20] but results are only statistically significant in SUSTAIN-6 (evaluating semiglutide). Overall, trials and one large retrospective database study do not detect an increase in retinopathy compared to controls or other oral diabetes medications. While no trials report on the outcome of biliary disease (e.g., cholelithiasis, cholecystitis or cholangitis), the FDA Adverse Reporting System has captured a number of reports for these outcomes (**Appendix G Table 1**) and one large retrospective database study estimates an excess incidence of 2.8 cases of biliary disease per 1000 person-years associated with the use of GLP-1 agonists.[25] Based on limited data, there does not appear to be a clinically significant harm on renal function, lower limb amputation, pancreatitis, or cancer (pancreatic, breast or thyroid) from GLP-1 inhibitors.

Across 3 CVD trials (n=34,322), 4 existing systematic reviews, 21 observational studies, and an examination of the FDA Adverse Events Reporting System, SGLT-2 inhibitors **do** increase the risk of genital infections, and **may** increase the risk of lower extremity amputations, urinary tract infections, bone fractures, and ketoacidosis (**Table 11**). The risk for lower extremity amputations is uncertain. CANVAS (evaluating canagliflozin), but not EMPA-REG OUTCOME (evaluating empagliflozin) or DECLARE (evaluating dapagliflozin), reported an increase in lower extremity amputations in participants randomized to SGLT-2 inhibitors versus placebo (**Table 12**). In CANVAS, the highest absolute risk of amputation occurred in persons with a history of amputation or PAD, but the relative risk was similar in persons with PAD versus those who did not have PAD. The trial demonstrated 2.9 excess cases of lower extremity amputation per 1000 person-years in persons taking canagliflozin versus placebo.[22] One large industry-sponsored observational study using 4 databases did not demonstrate an increased incidence of lower extremity amputation for canagliflozin in persons with ASCVD.[26] However, large retrospective claims database studies demonstrate an increased association of lower extremity amputation compared with metformin, SU, and TZD, and a non-statistically significant increased association of amputation compared with DPP-4s and GLP-1 agonists.[27-29] Both trials and observational studies demonstrate that SGLT-2 inhibitors increase the risk of genital, but not urinary, infections. In CANVAS (evaluating canagliflozin), the only trial allowing for estimation of absolute excess cases per 1000 person-years, the excess number of genital infections in men is 24.1 cases per 1000 person-years and in women is 51.3 cases per 1000 person-years in persons randomized to taking SGLT-2 inhibitors versus placebo controls (**Table 12**). Observational studies support these findings. One systematic review found that regulatory data, but not published trials, demonstrated a risk of urinary tract infections in addition to genital infections.[24] CANVAS (evaluating canagliflozin), but not EMPA-REG OUTCOME (evaluating empagliflozin) or DECLARE (evaluating dapagliflozin), reported an increase in fractures in participants randomized to SGLT-2 inhibitors versus placebo (**Table 12**). The trial demonstrated 3.5 excess fractures per 1000 person-years in persons taking canagliflozin versus placebo.[22] We found no observational studies examining the risk of fractures from SGLT-2 inhibitors. One trial, DECLARE (evaluating dapagliflozin) reported an increase in ketoacidosis in participants randomized to SGLT-2 inhibitors versus placebo; neither of the other two SGLT-2 inhibitor cardiovascular outcome trials reported ketoacidosis as a potential harm (**Table 12**). Two systematic reviews of trials and 2 retrospective studies did not find an association of increased ketoacidosis with SGLT-2 inhibitors. The FDA Adverse Reporting System has captured several reports for acute pancreatitis (**Appendix G Table 2**), but only one trial and no observational studies examine the risk of pancreatitis from SGLT-2 inhibitors. Based on limited data, there do not appear to be a clinically significant risks of serious hypoglycemia or renal function from SGLT-2 inhibitors.

Limitations

We completed a focused but up-to-date look at both the CVD benefits and serious harms of GLP-1 agonists and SGLT-2 inhibitors. Our understanding of CVD benefits is primarily limited by the small number cardiovascular outcome trials, such that each medication only has one trial. Given the clinical heterogeneity between trials, we are unable to conclude if CVD benefits or harms are medication-specific or represent a class effect. We did not explicitly examine renal protective benefits, although renal impairment was evaluated as a potential harm. Given time and resource considerations, we did not search the gray literature or regulatory data for a full understanding of harms. Two existing systematic reviews explicitly included a review of regulatory data.[24, 30] One 2016 AHRQ-funded EPC report by Bolen and colleagues[30] reviewed FDA medical reviews and statistical reviews, and found that data from 37 of 40 regulatory submissions had been published for metformin, SU, TZD, DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors. They found that published data were consistent with data in FDA reviews on select outcomes (A1c, hypoglycemia, and ACM) but do not mention the consistency of data for other outcomes including CVD events and harms other than hypoglycemia. A second systematic review on SGLT-2 inhibitors by Wu and colleagues[24] in 2016 found that data for CVD benefit and harms were generally consistent between regulatory data and published studies; however, the regulatory data (but not the published studies) demonstrated an increased risk of urinary tract infections not identified in published trials, and a greater magnitude of risk for genital infections than reported in published trials. Additionally, we did not address dose-specific harms or costs (and cost-effectiveness) of medications.

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Tables

Table 1. Medication-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes (Reproduced from ADA Guidelines[3] Table 8.1)

Medication		Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/ SQ	Renal Effects		Additional Considerations
					ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin		High	No	Loss	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 Inhibitors		Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Canagliflozin: not recommended with eGFR <45 • Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 •Empagliflozin: contraindicated with eGFR <30	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑ LDL cholesterol
GLP-1 RAs		High	No	Neutral	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	• Exenatide: not indicated with eGFR <30 • Lixisenatide: caution with eGFR <30 • Increased risk of side effects in patients with renal impairment	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects common (diarrhea, nausea) • Injection site reactions • ? Acute pancreatitis risk
DPP-4 Inhibitors		Intermediate	No	Gain	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required; can be used in renal impairment	• Potential for acute pancreatitis • Joint pain
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑ LDL cholesterol
Sulfonylureas (2nd Generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	• Lower insulin doses require a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

Abbreviations: CVD = cardiovascular disease, DKA = diabetic ketoacidosis, DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; FDA = US Food and Drug Administration; LDL = low-density lipoprotein; NASH = nonalcoholic steatohepatitis; NPH = neutral protamine Hagedorn; RAs = receptor agonists; SQ = subcutaneous administration; T2DM = type 2 diabetes

Notes:
* Efficacy defined as categories of mean A_{1c} reduction: Low = ≤0.5% (≤5.5 mmol/mol); Intermediate = >0.5–1% (>5.5–11 mmol/mol); High = >1–2% (>11–22 mmol/mol); Highest = Potential of >2% (>22 mmol/mol)
† FDA-approved for CVD benefit

Table 2. GLP-1 Agonists Available in the United States

Medication	Dosing, SQ	FDA Approval Year	Cardiovascular Outcome Trials
Exenatide (Byetta)	BID	2005	Predates FDA requirement
Exenatide extended-release (Bydureon)*	Weekly	2012	EXSCEL
Liraglutide† (Victoza)	QD	2009	LEADER
Albiglutide (Tanzeum)	Weekly	2014‡	Harmony
Dulaglutide (Trulicity)	Weekly	2014	REWIND (Expected June 2019)
Lixisenatide (Adlyxin)	QD	2016	ELIXA
Semiglutide (Ozempic)	Weekly	2017	SUSTAIN-6

Abbreviations: BID = twice a day; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; FDA = US Food and Drug Administration; GLP-1 = Glucagon-like peptide-1; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; mg = milligrams; QD = once a day; REWIND = Researching Cardiovascular Events With a Weekly INcretin in Diabetes; SQ = subcutaneous administration; SUSTAIN-6 = Trail to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

Notes:
* BYDUREON BCise was approved in 2017; this is a new formulation available in a pre-filled pen with pre-attached hidden needle.
† Saxenda is a formulation approved for weight loss
‡ Albiglutide (Tanzeum), originally approved by the FDA in 2014, was discontinued in 2017, one month after the FDA added risk of anaphylactic reaction to its label; GlaxoSmithKline stated that discontinuation of the medication was due to limited prescribing and not safety concerns.[15]

Table 3. SGLT-2 Inhibitors Available in the United States

Medication	Dosing, oral	FDA Approval Year	Cardiovascular Outcome Trials
Canagliflozin (Invokana)	100 mg, 300 mg	2013	CANVAS
Dapagliflozin (Farxiga)	5 mg, 10 mg	2014	DECLARE-TIMI-58
Empagliflozin (Jardiance)	10 mg, 25 mg	2014	EMPA-REG OUTCOME
Ertugliflozin (Steglatro)	5 mg, 15 mg	2017	VERTIS CV (Expected September 2019)

Abbreviations: CANVAS = Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI-58 = Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial; FDA = US Food and Drug Administration; mg = milligrams; VERTIS CV = Ertugliflozin in Subjects With Type 2 Diabetes Mellitus and Established Cardiovascular Disease

Table 4. Evidence Table of Randomized Clinical Trials of GLP-1 Agonists for Prevention of Cardiovascular Events

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean/Median A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable[§]	Individual Endpoints[¶]	Study Limitations
Harmony Outcomes Hernandez, 2018[17] Good 28 countries	9,463 Median 1.6 years	Include: Men and women aged ≥40 years with DM2 and established coronary, cerebrovascular, or peripheral artery disease who had A1c >7.0% Exclude: eGFR <30 mL/min per 1.73 m^2, severe gastroparesis, previous pancreatitis or substantial risk factors for pancreatitis, a personal or family history of medullary carcinoma of the thyroid or multiple endocrine neoplasia type 2, a history of pancreatic neuroendocrine tumors	Mean age, yrs: 64.1 (range NR) % women: 30.6 Mean A1c, %: 8.7 Median duration of DM, yrs: 14.1 Other DM meds, %: Metformin: 73.6[*] SU: 28.8 DPP-4 inhibitor: 15.2 Insulin: 59.1 SGLT-2: 6.1 TZD: 2.0 CVD Risk Factors % HTN: 86.5 % smokers: 15.7 % dyslipidemia: NR, 84.1% on statin Mean BMI kg/m^2: 32.3 % with ASCVD: 100[†]	Albiglutide 30–50 mg once weekly[‡] Comparison: Matching placebo Background Therapy: Other glucose-lowering medications could be adjusted or added (expect for other GLP-1 agonists) to achieve glycemic control based on local guidelines	**Primary composite outcome definition:** First occurrence of death from CV causes, nonfatal MI, or nonfatal stroke **Overall population (100% with ASCVD)[‖]** IG: 45.7 per 1,000 p-y 338/4731 (7%) CG: 58.7 per 1,000 p-y 428/4732 (9%) HR 0.78 (0.68 to 0.90)	**CVD Mortality** IG: 16.1 per 1,000 p-y 122/4731 (3%) CG: 17.2 per 1,000 p-y 130/4732 (3%) HR 0.93 (0.73 to 1.19) **All-Cause Mortality** IG: 24.4 per 1,000 p-y 196/4731 (4%) CG: 25.6 per 1,000 p-y 205/4732 (4%) HR 0.95 (0.79 to 1.16) **Heart Failure[#**]** IG: per 1,000 p-y not reported 66/4731 (1.4%) CG: per 1,000 p-y not reported 88/4732 (1.8%) HR NR **Fatal and Nonfatal MI** IG: 24.3 per 1,000 p-y 181/4731 (4%) CG: 32.6 per 1,000 p-y 240/4732 (5%) HR 0.75 (0.61 to 0.90) **Nonfatal MI** IG: per 1,000 p-y not reported 160/4731 (3.4%) CG: per 1,000 p-y not reported 228/4732 (4.8%) HR NR **Fatal and Nonfatal Stroke** IG: 12.5 per 1,000 p-y 94/4731 (2%) CG: 14.5 per 1,000 p-y 108/4732 (2%)	No major study limitations; other glucose-lowering agents were added more often in the CG than the IG

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean/Median A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable[§]	Individual Endpoints[¶]	Study Limitations
						HR 0.86 (0.66 to 1.14) **Nonfatal Stroke** IG: per 1,000 p-y not reported 76/4731 (1.6%) CG: per 1,000 p-y not reported 91/4732 (1.9%) HR NR **Unstable Angina** NR	
EXSCEL Holman, 2017[18] Good 35 countries	14,752 Median 3.2 years	Include: Adults with DM and A1c 6.5% to 10.0%. Patients were permitted to receive up to 3 oral glucose-lowering agents or to receive insulin, either alone or in combination with up to 2 oral glucose-lowering agents. Exclude: ≥2 episodes of severe hypoglycemia during previous year, eGFR <30 ml/min/1.73 m^2, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, or baseline calcitonin level >40 ng/L	Mean age, yrs: 62.0 (range 21-92) % women: 38.0 Median A1c, %: 8.0 Median duration of DM, yrs: 12.0 Other DM meds, %: Metformin: 76.6[*] SU: 36.6 DPP-4 inhibitor: 14.9 Insulin: 46.3 SGLT-2: 0.5 CVD Risk Factors % HTN: NR, 48.7% on ACE-I, 31.2% on ARB, 43.7% on diuretic, 55.7% on BB, 32.0% on CCB % smokers: 11.7 % dyslipidemia: NR, 77.1% on lipid-lowering meds Mean BMI kg/m^2: 31.7 % with ASCVD: NR in the aggregate; 73.1% with prior CVD event, 52.8% with history of CAD, 17.0% with history of cerebrovascular disease, 19.0% with history	Extended-release exenatide 2 mg once weekly Comparison: Matching placebo Background Therapy: Use of open-label glucose-lowering agents (including DPP-4 inhibitors but not GLP-1 receptor agonists) was encouraged to promote glycemic equipoise between the two trial groups and to help patients reach A1c targets	**Primary composite outcome definition:** First occurrence of death from CV causes, nonfatal MI, or nonfatal stroke **Overall population** IG: 37 per 1,000 p-y 839/7356 (11.4%) CG: 40 per 1,000 p-y 905/7396 (12.2%) HR 0.91 (0.83 to 1.00) **Patients with ASCVD[†††‡‡] (73.1% of sample)** IG: 722/5394 (13.4%) CG: 786/5388 (14.6%) HR 0.90 (0.82 to 1.00) **Patients without ASCVD (26.9% of sample)** IG: 117/1962 (6.0%) CG: 119/2008 (5.9%) HR 0.99 (0.77 to 1.28) p-value for heterogeneity=0.50	**CVD Mortality** IG: 14 per 1,000 p-y 340/7356 (4.6%) CG: 15 per 1,000 p-y 383/7396 (5.2%) HR 0.88 (0.76 to 1.02) **All-Cause Mortality** IG: 20 per 1,000 p-y 507/7356 (6.9%) CG: 23 per 1,000 p-y 584/7396 (7.9%) HR 0.86 (0.77 to 0.97) **Heart Failure[#]** IG: 9 per 1,000 p-y 219/7356 (3.0%) CG: 10 per 1,000 p-y 231/7396 (3.1%) HR 0.94 (0.78 to 1.13) **Fatal and Nonfatal MI** IG: 21 per 1,000 p-y 483/7356 (6.6%) CG: 21 per 1,000 p-y 493/7396 (6.7%) HR 0.97 (0.85 to 1.1) **Fatal MI** IG: per 1,000 p-y not calculated 17/7356 (0.2%) CG: per 1,000 p-y not calculated	No major study limitations or limitations pertaining to subgroup analyses by ASCVD status

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean/Median A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable[§]	Individual Endpoints[¶]	Study Limitations
			of PAD, 16.2% with history of CHF			13/7396 (0.2%) HR 1.29 (0.63 to 2.66) **Fatal and Nonfatal Stroke** IG: 8 per 1,000 p-y 187/7356 (2.5%) CG: 9 per 1,000 p-y 218/7396 (2.9%) HR 0.85 (0.70 to 1.03) **Fatal Stroke** IG: per 1,000 p-y not calculated 18/7356 (0.2%) CG: per 1,000 p-y not calculated 25/7396 (0.3%) HR 0.71 (0.39 to 1.30) **Unstable Angina** NR	
SUSTAIN-6 Marso, 2016[19] Good 20 countries	3,297 Median 2.1 years	Include: Adults with DM and A1c ≥7% with no antihyperglycemic treatment or treated with ≤2 oral antihyperglycemic agents (with or without basal or premixed insulin). Key inclusion criteria were ≥50 years with established ASCVD, chronic HF, or CKD stage 3 or higher **or** age ≥60 years with ≥1 cardiovascular risk factor (microalbuminuria or proteinuria; HTN and LVH; left ventricular systolic or diastolic dysfunction; ABI <0.9) Exclude: Long-term dialysis, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, baseline calcitonin level ≥50 ng/L	Mean age, yrs: 64.6 (range NR) % women: 39.3 Median A1c, %: 8.7 Median duration of DM, yrs: 13.9 Other DM meds, %: Metformin: 73.2[*] SU: 42.8 DPP-4 inhibitor: 0.2[§§] Insulin: 58.0 SGLT-2: 0.2 TZD: 2.3 CVD Risk Factors % HTN: 92.8 % smokers: 54.7 former or current % dyslipidemia: NR, 76.5 on meds	Semaglutide 0.5 mg or 1.0 mg once weekly (doses combined for analysis) Comparison: matching placebo Background Therapy: Investigators were encouraged to treat all patients according to local guidelines to achieve the most effective glycemic control and additional non-investigational antihyperglycemic medication (nonincretin-based therapy) could be added or adjusted	**Primary composite outcome definition:** First occurrence of death from CV causes, nonfatal MI, or nonfatal stroke **Overall population** IG: 32.4 per 1,000 p-y 108/1648 (6.6%) CG: 44.4 per 1,000 p-y 146/1649 (8.9%) HR 0.74 (0.58 to 0.95) **Patients with ASCVD[†††‡] (41.5% of sample)** IG: 66/673 (9.8%) CG: 88/694 (12.7%) HR 0.76 (0.55 to 1.05) **Patients without ASCVD (58.5% of sample)** IG: 42/975 (4.3%) CG: 58/955 (6.1%) HR 0.70 (0.47 to 1.04)	**CVD Mortality** IG: 12.9 per 1,000 p-y 44/1648 (2.7%) CG: 13.5 per 1,000 p-y 46/1649 (2.8%) HR 0.98 (0.65 to 1.48) **All-Cause Mortality** IG: 18.2 per 1,000 p-y 62/1648 (3.8%) CG: 17.6 per 1,000 p-y 60/1649 (3.6%) HR 1.05 (0.74 to 1.50) **Heart Failure[#]** IG: 17.6 per 1,000 p-y 59/1648 (3.6%) CG: 16.1 per 1,000 p-y 54/1649 (3.3%) HR 1.11 (0.77 to 1.61) **Nonfatal MI** IG: 14.0 per 1,000 p-y 47/1648 (2.9%) CG: 19.2 per 1,000 p-y	Throughout the trial a greater proportion of patients in placebo group received additional CV meds, including antiHTN meds, diuretics, and lipids lowering meds No major study limitations or limitations around subgroup analyses by CVD status

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean/Median A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable[§]	Individual Endpoints[¶]	Study Limitations
			Mean BMI kg/m^2: 32.8 % with ASCVD: 41.5 with prior MI or stroke[‖‖]		p-value for heterogeneity= 0.75	64/1649 (3.9%) 0.74 (0.51 to 1.08) **Nonfatal Stroke** IG: 8.0 per 1,000 p-y 27/1648 (1.6%) CG: 13.1 per 1,000 p-y 44/1649 (2.7%) HR 0.61 (0.38 to 0.99) **Unstable Angina**[#] IG: 6.5 per 1,000 p-y 22/1648 (1.3%) CG: 8.0 per 1,000 p-y 27/1649 (1.6%) HR 0.82 (0.47 to 1.44)	
LEADER Marso, 2016[20] Good 32 countries	9,340 3.8 years	Include: Adults with DM and A1c ≥7% with no antihyperglycemic treatment or treated with ≥1 oral antihyperglycemic agents or insulin (human neutral protamine Hagedorn, long-acting analogue, or premixed) or a combination of these agents. Key inclusion criteria were: age ≥50 years with established ASCVD (coronary, cerebrovascular, peripheral), CKD stage 3 or greater, or CHF, or age of ≥60 years with at least one CVD risk factor, as determined by the investigator (microalbuminuria or proteinuria, HTN and LVH, left ventricular systolic or diastolic dysfunction, or ABI <0.9) Exclude: Current continuous renal replacement therapy, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, baseline calcitonin level ≥50 ng/L	Mean age, yrs: 64.3 (range NR) % women: 35.7 Median A1c, %: 8.7 Median duration of DM, yrs: 12.8 Other DM meds, %: Metformin: 76.5 SU: 50.7 DPP-4 inhibitor: 0.06[§§] Insulin: 44.6 SGLT-2: NA[¶¶] CVD Risk Factors % HTN: NR, 92.4% on meds % smokers: NR % dyslipidemia: NR, 75.8% on meds Mean BMI kg/m^2: 32.5 % with ASCVD: 30.7% with prior MI, 16.1% with prior stroke or TIA, 39.0% with prior revascularization, 17.8% with HF[##]	Liraglutide 1.8 mg (or max tolerated dose) once daily Comparison: matching placebo Background Therapy: Goal was A1c ≤7%. If >7%, additional measure taken after 3m. If still >7.0%, treatment intensified. Lifestyle modification and metformin considered foundational therapy in most countries. Add-on therapy could include TZD, SU, alpha glucosidase inhibitors according to local labels (DPP-4 and other incretin-based therapies not allowed) Insulin therapy allowed based on local practice, including basal, basal/bolus, premix, and mealtime bolus.	**Primary composite outcome definition:** First occurrence of death from CV causes, nonfatal MI, or nonfatal stroke **Overall population** IG: 34 per 1,000 p-y 608/4668 (13.0%) CG: 39 per 1,000 p-y 694/4672 (14.9%) HR 0.87 (0.78 to 0.97) **Patients with ASCVD[‡‡]*** (81.3% of sample)** IG: 536/3831 (14.0%) CG: 629/3767 (16.7%) HR 0.83 (0.74 to 0.93) **Patients without ASCVD[†††] (18.7% of sample)** IG: 72/837 (8.6%) CG: 65/905 (7.2%) HR 1.20 (0.86 to 1.67) p-value for heterogeneity= 0.04	**CVD Mortality** IG: 12 per 1,000 p-y 219/4668 (4.7%) CG: 16 per 1,000 p-y 278/4672 (6.0%) HR 0.78 (0.66 to 0.93) **All-Cause Mortality** IG: 21 per 1,000 p-y 381/4668 (8.2%) CG: 25 per 1,000 p-y 447/4692 (9.6%) HR 0.85 (0.74 to 0.97) **Heart Failure**[#] IG: 12 per 1,000 p-y 218/4668 (4.7%) CG: 14 per 1,000 p-y 248/4672 (5.3%) HR 0.87 (0.73 to 1.05) **Nonfatal MI**[‡‡‡] IG: 16 per 1,000 p-y 281/4668 (6.0%) CG: 18 per 1,000 p-y 317/4672 (6.8%) HR 0.88 (0.75 to 1.03) **Nonfatal Stroke**[§§§] IG: 9 per 1,000 p-y 159/4668 (3.4%)	Throughout the trial a greater proportion of patients in placebo group received additional CV meds, including antiHTN meds, diuretics, lipid lowering meds, and platelet aggregation inhibitors No major study limitations or limitations around subgroup analyses by CVD status

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean/Median A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable[§]	Individual Endpoints[¶]	Study Limitations
						CG: 10 per 1,000 p-y 177/4672 (3.8%) HR 0.89 (0.72 to 1.11) **Unstable Angina**[#] IG: 7 per 1,000 p-y 122/4668 (2.6%) CG: 7 per 1,000 p-y 124/4672 (2.7%) HR 0.98 (0.76 to 1.26)	
ELIXA Pfeffer, 2015[9] Fair 49 countries	6,068 Median 2.1 years	Include: Adults with DM and acute coronary event (STEMI, NSTEMI, or unstable angina) within 180 days before screening Exclude: Age <30 years, PCI in the previous 15 days, CABG for the qualifying event, planned coronary revascularization procedure within 90 days, eGFR <30 ml/min/1.73 m^2, A1c <5.5% or >11.0%	Mean age, yrs: 60.2 (range NR) % women: 30.7 Mean A1c, %: 7.6 Mean duration of DM, yrs: 9.3 Other DM meds, %: Metformin: 66.3 SU: 33.0 DPP-4 inhibitor: NR[IIII] Insulin: 39.1 SGLT-2: NR[IIII] TZD: 1.6 CVD Risk Factors % HTN: 76.4 % smokers: 11.7 % dyslipidemia: NR, 92.7% on statin Mean BMI kg/m^2: 30.2 % with ASCVD: 100	Lixisenatide 10 µg (max dose 10 µg) once daily Comparison: matching placebo Background Therapy: Glycemic control managed by investigators in accordance with local clinical practice guidelines. Investigator could adjust background antidiabetic treatment, increase lixisenatide (or placebo) dose up to 10 µg or prescribe additional antidiabetic medications (except for other GLP-1 agonists or DPP-4 inhibitors). This approach was expected to yield similar glycemic control in the two study groups	**Primary composite outcome definition:** First occurrence of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina[¶¶¶] **Overall population (100% with ASCVD)**[###] IG: 64 per 1,000 p-y 406/3034 (13.4%) CG: 63 per 1,000 p-y 399/3034 (13.2%) HR 1.02 (0.89 to 1.17)	**CVD Mortality**[****] IG: 23 per 1,000 p-y 156/3034 (5.1%) CG: 24 per 1,000 p-y 158/3034 (5.2%) HR 0.98 (0.78 to 1.22) **All-Cause Mortality** IG: 31 per 1,000 p-y 211/3034 (7.0%) CG: 33 per 1,000 p-y 223/3034 (7.4%) HR 0.94 (0.78 to 1.13) **Heart Failure**[#] IG: 18 per 1,000 p-y 122/3034 (4.0%) CG: 19 per 1,000 p-y 127/3034 (4.2%) HR 0.96 (0.75 to 1.23) **Nonfatal MI**[****] IG: 42 per 1,000 p-y 270/3034 (8.9%) CG: 41 per 1,000 p-y 261/3034 (8.6%) HR 1.03 (0.87 to 1.22) **Nonfatal Stroke**[****] IG: 10 per 1,000 p-y 67/3034 (2.2%) CG: 9 per 1,000 p-y 60/3034 (2.0%) HR 1.12 (0.79 to 1.58) **Unstable Angina**[****] IG: 2 per 1,000 p-y 11/3034 (0.4%)	Groups non-equivalent at baseline on a number of variables, including A1c, stroke history, and age, and the primary analyses didn't adjust for these characteristics. Treatment discontinuation significantly higher in the GLP1 group (11.4% vs 7.2%, p>0.001).

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean/Median A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable[§]	Individual Endpoints[¶]	Study Limitations
						CG: 1 per 1,000 p-y 10/3034 (0.3%) HR 1.11 (0.47 to 2.62)	

Abbreviations: ABI = ankle brachial index; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CABG = coronary artery bypass grafting; CG = control group; CHF = congestive heart failure; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; DPP-4 = Dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; GLP-1 = Glucagon-like peptide-1; A1c = hemoglobin A1c; HF = heart failure; HR = hazard ratio; HTN = hypertension; IG = intervention group; kg/m2 = kilograms per meter squared; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LVH = left ventricular hypertrophy; m2 = meters squared; mg = milligrams; MI = myocardial infarction; ml/min = millimeters per minute; N = number of participants analyzed; NA = not applicable; ng/L = nanograms per liter; NR = not reported; NSTEMI = non-ST segment elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; p-y = person-years; SLGT-2 = Sodium-glucose Cotransporter-2 inhibitor; STEMI = ST segment elevation myocardial infarction; SU = sulfonylurea; SUSTAIN-6 = Trail to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TIA = transient ischemic attack; TZD = thiazolidinediones; yrs = years; µg = micogram

Notes:
* Reported as biguanides
† 71% with CAD, 25% with cerebrovascular disease, 25% with PAD
‡ No longer on market
§ Insufficient data is reported to calculate events per 1,000 p-y in subgroups
‖ Separate subgroup analyses available by presence of coronary, cerebrovascular, and peripheral artery disease as well as HF.
¶ No individual endpoints were reported by ASCVD status
# Hospitalizations
** Calculated number of events by subtracting death from CV causes from composite of death from CV causes and hospital admissions for heart failure to isolate HF hospitalizations
†† Prior CV Event
‡‡ Subgroup analysis by history of CHF also available, not abstracted
§§ Patients on this class were to be excluded per criteria and these participants were randomized in error
‖‖ As reported in Figure S3; Paper reports that overall, 83.0% had established CVD at baseline (this value includes prior events, HF, and CKD)
¶¶ Not approved at baseline
81.3% overall had established CVD at baseline (this value includes prior events, HF, and CKD)
***Subgroup analysis reported for those with established ASCVD, CKD stage 3 or greater, or CHF
††† Patients without established ASCVD, CKD stage 3 or greater, or CHF; eligible for trial based on ≥60 years and microalbuminuria or proteinuria, HTN and LVH, left ventricular systolic or diastolic dysfunction, or ABI <0.9
‡‡‡ Fatal and total MI also reported, but these analyses were not prespecified
§§§ Fatal and total stroke also reported, but these analyses were not prespecified
‖‖‖ 5.3% on “other” diabetes medications
¶¶¶ Unstable angina is unique to the EXILA composite outcome
Subgroup analysis by history of CHF also available, not abstracted; detailed data available in Supplemental Table S5
**** Patients with each event; in analyses for separate components of the primary composite endpoint, patients were included regardless of whether it was their first event

Table 5. Evidence Table of Randomized Clinical Trials of SGLT-2 Inhibitors for Prevention of Cardiovascular Events

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable	Individual Endpoints[§]	Study Limitations
DECLARE-TIMI 58 Wiviott, 2018[21] Good 33 Countries	17,160 Median 4.2 years	Include: Men and women ≥40 years with DM (A1c ≥6.5% and ≤12.0%). Eligible participants needed to have multiple risk factors for ASCVD or established ASCVD (coronary, cerebrovascular, or peripheral). Participants with multiple risk factors were men ≥55 years or women ≥60 years with one or more traditional risk factors, including hypertension, dyslipidemia (LDL >130 mg/dL or the use of lipid-lowering therapies), or use of tobacco. Exclude: Creatinine clearance <60 ml/min	Mean age, yrs: 63.9 (range NR) % women: 37.4 Mean A1c, %: 8.3 Median duration of DM, yrs: 11.0 Other DM meds, %: Metformin: 82.0 SU: 42.7 GLP-1 agonist: 4.4 DPP-4 inhibitor: 16.8 Insulin: 40.9 CVD Risk Factors % HTN: NR[*] % smokers: NR % dyslipidemia: NR[†] Mean BMI kg/m^2: 32.0 % with ASCVD: 40.6	Dapagliflozin 10 mg daily Comparison: placebo Background Therapy: Use of other glucose-lowering agents was at the discretion of the treating physician other than open-label SGLT2 inhibitors, pioglitazone, or rosiglitazone which were not allowed	**Primary composite outcome definition:** Death from CV causes, MI, or ischemic stroke[‡] **Overall population** IG: 22.6 per 1000 p-y 756/8,582 (8.8%) CG: 24.2 per 1000 p-y 803/8578 (9.4%) HR 0.93 (0.84 to 1.03) **Patients with ASCVD (40.6% of sample)** IG: 483/3,474 (13.9%) CG: 537/3,500 (15.3%) HR 0.90 (0.79 to 1.02) **Patients without ASCVD (59.4% of sample)** IG: 273/5,108 (5.3%) CG: 266/5,078 (5.2%) HR 1.01 (0.86 to 1.20) p-value for heterogeneity=0.25	**CVD Mortality** IG: 7.0 per 1000 p-y 245/8,582 (2.9%) CG: 7.1 per 1000 p-y 249/8,578 (2.9%) HR 0.98 (0.82 to 1.17) **All-Cause Mortality** IG: 15.1 per 1000 p-y 529/8,582 (6.2%) CG: 16.4 per 1000 p-y 570/8,578 (6.6%) HR 0.93 (0.82 to 1.04) **Heart Failure[ǁ]** IG: 6.2 per 1000 p-y 212/8,582 (2.5%) CG: 8.5 per 1000 p-y 286/8,578 (3.3%) HR 0.73 (0.61 to 0.88) **Fatal and Nonfatal MI** IG: 11.7 per 1000 p-y 393/8,582 (4.6%) CG: 13.2 per 1000 p-y 441/8,578 (5.1%) HR 0.89 (0.77 to 1.01) **Fatal and Nonfatal Ischemic Stroke** IG: 6.9 per 1000 p-y 235/8,582 (2.7%) CG: 6.8 per 1000 p-y 231/8,578 (2.7%) HR 1.01 (0.84 to 1.21) **Unstable Angina** NR	Patients participating in run-in period could be excluded from randomization at the investigator's discretion; 8,538/25,698 (33.2%) were excluded in this way.

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable	Individual Endpoints[§]	Study Limitations
CANVAS[¶] Neal, 2017[22] Good 30 countries	10,142 Mean 3.6 years	Include: Men and women with DM (A1c ≥7.0% and ≤10.5%) who were ≥30 years with history of symptomatic ASCVD **or** ≥50 years with ≥2 CVD risk factors, including: DM duration ≥10 years, SBP >140 mm Hg while on ≥1 anti-HTN agent, current smoking, microalbuminuria or macroalbuminuria, or HDL cholesterol <38.7 mg/dL. Participants could either not currently be on antihyperglycemic agents or could be on mono or combo therapy with metformin, SU, PPARγ agonist, alpha-glucosidase inhibitor, GLP-1, DPP-4 inhibitor, or insulin. Exclude: eGFR <30 ml/min/1.73 m^2	Mean age, yrs: 63.3 (range NR) % women: 35.8 Mean A1c, %: 8.2 Duration of DM, yrs: 13.5 Other DM meds, %: Metformin: 77.2 SU: 43.0 GLP-1 agonist: 4.0 DPP-4 inhibitor: 12.4 Insulin: 50.2 CVD Risk Factors % HTN: 90.0 % smokers: 17.8 % dyslipidemia: NR[#] Mean BMI kg/m^2: 32.0 % with ASCVD: 65.6	Canagliflozin 300 mg or 100 mg daily[**] Comparison: placebo Background Therapy: Use of other background therapy for glycemic management and other control of risk factors was guided by local guidelines	**Primary composite outcome definition:** Death from CV causes, nonfatal MI, or nonfatal stroke **Overall population** IG: 26.9 per 1000 p-y CG: 31.5 per 1000 p-y HR 0.86 (0.75 to 0.97) **Patients with ASCVD (65.6% of sample)** IG: 34.1 per 1000 p-y CG: 41.3 per 1000 p-y HR 0.82 (0.72 to 0.95) **Patients without ASCVD (34.4% of sample)** IG: 15.8 per 1000 p-y CG: 15.5 per 1000 p-y HR 0.98 (0.74 to 1.30) p-value for heterogeneity=0.18	**CVD Mortality** IG: 11.6 per 1000 p-y CG: 12.8 per 1000 p-y HR 0.87 (0.72 to 1.06) **All-Cause Mortality** IG: 17.3 per 1000 p-y CG: 19.5 per 1000 p-y HR 0.87 (0.74 to 1.01) **Heart Failure**[‖] IG: 5.5 per 1000 p-y CG: 8.7 per 1000 p-y HR 0.67 (0.52 to 0.87) **Fatal and Nonfatal MI** IG: 11.2 per 1000 p-y CG: 12.6 per 1000 p-y HR 0.89 (0.73 to 1.09) **Nonfatal MI** IG: 9.7 per 1000 p-y CG: 11.6 per 1000 p-y HR 0.85 (0.69 to 1.05) **Fatal and Nonfatal Stroke** IG: 7.9 per 1000 p-y CG: 9.6 per 1000 p-y HR 0.87 (0.69 to 1.09) **Nonfatal Stroke** IG: 7.1 per 1000 p-y CG: 8.4 per 1000 p-y HR 0.90 (0.71 to 1.15) **Unstable Angina** NR	No major study limitations or limitations around subgroup analyses by ASCVD status Harms outcomes by CVD status: highest absolute risk of amputation occurred among those with history of amputation or PAD with similar relative risk between groups; no other harms reported out by CVD status.

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable	Individual Endpoints[§]	Study Limitations
EMPAREG-OUTCOME Zinman, 2015[23] Fitchett, 2016[31] Wanner, 2016[32] Inzucchi, 2018[33] Good 42 countries	7,020 Median 2.6 years for treatment and 3.1 years observation time	Include: Adult men and women with DM, established CVD (coronary, cerebrovascular, or peripheral), and A1c ≥7.0% to <9.0 if no glucose-lowering agents for ≥12 weeks before randomization or A1c ≥7.0% to <10.0% if received stable glucose-lowering therapy for ≥12 weeks before randomization. Exclude: eGFR <30 ml/min/1.73 m^2, BMI >45 kg/m^2	Mean age, yrs: 63.1 (range NR) % women: 28.5 Mean A1c, %: 8.1 Duration of DM, yrs: Mean NR, 57.1% with duration >10 yrs Other DM meds, %: Metformin: 74.0 SU: 42.8 GLP-1 agonist: 11.3 DPP-4 inhibitor: 2.8 Insulin: 48.2 TZD: 4.2 CVD Risk Factors % HTN: 95.0 on meds % smokers: NR % dyslipidemia: 81.0 on meds Mean BMI kg/m^2: 30.6 % with ASCVD: 100[††]	Empagliflozin 10 mg or 25 mg daily[**] Comparison: placebo Background Therapy: Background glucose lowering therapy allowed at investigator discretion to achieve glycemic control according to local guidelines	**Primary composite outcome definition:** Death from CV causes, nonfatal MI, or nonfatal stroke **Overall population (100% with ASCVD)[††]** IG: 37.4 per 1,000 p-y 490/4687 (10.5%) CG: 43.9 per 1,000 p-y 282/2333 (12.1%) HR 0.86 (0.74 to 0.99)	**CVD Mortality** IG: 12.4 per 1,000 p-y 172/4687 (3.7%) CG: 20.2 per 1,000 p-y 137/2333 (5.9%) HR 0.62 (0.49 to 0.77) **All-Cause Mortality** IG: 19.4 per 1,000 p-y 269/4687 (5.7%) CG: 28.6 per 1,000 p-y 194/2333 (8.3%) HR 0.68 (0.57 to 0.82) **Heart Failure[‖]** IG: 9.4 per 1,000 p-y 126/4687 (2.7%) CG: 14.5 per 1,000 p-y 95/2333 (4.1%) HR 0.65 (0.50 to 0.85) **Fatal and Nonfatal MI[‡‡]** IG: 16.8 per 1,000 p-y 223/4687 (4.8%) CG: 19.3 per 1,000 p-y 126/2333 (5.4%) HR 0.87 (0.70 to 1.09) **Nonfatal MI[‡‡]** IG: 16.0 per 1,000 p-y 213/4687 (4.5%) CG: 18.5 per 1,000 p-y 121/2333 (5.2%) HR 0.87 (0.70 to 1.09) **Fatal and Nonfatal Stroke** IG: 12.3 per 1,000 p-y 164/4687 (3.5%) CG: 10.5 per 1,000 p-y 69/2333 (3.0%)	Placebo subjects more likely to receive other CV meds during study (other glucose meds, 31.5% vs 19.5%; anti-HTN meds 47.4% vs 40.6%; lipid meds, 27.6% vs 26.6%, and anticoagulants, 26.7% vs 25.3%). Differential treatment discontinuation in the SGLT2 (23.4%) and placebo groups (29.3%)(statistical significance NR) and no other information on adherence.

Study Name Quality Location	N Duration	Major Inclusion and Exclusion Criteria	Population Characteristics: Mean Age (range) % Women Mean A1c Duration of DM DM Medications CVD Risk Factors Mean BMI % Known CVD	Intervention/ Comparator	Primary Composite Outcome, including results by ASCVD status if applicable	Individual Endpoints[§]	Study Limitations
						HR 1.18 (0.89 to 1.56) **Nonfatal Stroke** IG: 11.2 per 1,000 p-y 150/4687 (3.2%) CG: 9.1 per 1,000 p-y 60/2333 (2.6%) HR 1.24 (0.92 to 1.67) **Unstable Angina**[‖] IG: 10.0 per 1,000 p-y 133/4687 (2.8%) CG: 10.0 per 1,000 p-y 66/2333 (2.8%) HR 0.99 (0.74 to 1.34)	

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CANVAS = Canagliflozin Cardiovascular Assessment Study; CG = control group; CVD = cardiovascular disease; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; DM = diabetes mellitus; DPP-4 = Dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; EMPA-REG OUTCOME = (Empagliflozin) Cardiovascular Outcome Event Trial; GLP-1 = Glucagon-like peptide-1; A1c = hemoglobin A1c; HDL = high-density lipoprotein; HR = hazard ratio; HTN = hypertension; IG = intervention group; kg/m^2 = kilograms per meter squared; LDL = low-density lipoprotein; m^2 = meters squared; mg = milligrams; mg/dL = milligrams per deciliter; MI = myocardial infarction; ml/min = millimeters per minute; mm Hg = millimeter of mercury; N = number of participants analyzed; NR = not reported; PAD = peripheral artery disease; PPARγ = Peroxisome proliferator-activated receptor gamma; p-y = person-years; SBP = systolic blood pressure; SLGT-2 = Sodium-glucose Cotransporter-2 inhibitor; SU = sulfonylurea; yrs = years; TZD = thiazolidinediones

Notes:
* 81.3% on ACE inhibitor or ARB; 40.6% on diuretic
† 75.0% on statin or ezetimibe
‡ DECLARE specified both a primary safety outcome and 2 primary efficacy outcomes. The primary safety and efficacy outcome were the same composite used in other trials in this review (death from CV causes, MI, or ischemic stroke); an additional primary efficacy outcome was also specified as the composite of CV death or hospitalization for heart failure. The additional efficacy endpoint was added after the results of the EMPA-REG OUTCOME trial were published, showing benefit for CVD death and heart failure; the decision to add the outcome was made blinded to DECLARE data.
§ Individual endpoints were reported by ASCVD status only for DECLARE-TIMI 58; testing for interaction was not statistically significant for any outcome.
‖ Hospitalizations
¶ CANVAS is an integrated analysis of 2 related studies; CANVAS was initiated prior to the approval of canagliflozin by the FDA; CANVAS-R was designed to meet post-approval regulatory requirements for cardiovascular safety. The studies are analyzed together to maximize power.
# 74.9% on statin
** Both doses combined in analysis

Table 6. Modified GRADE Evidence Profile – GLP-1 Agonists

Quality Assessment						Total N	Effect		
N Studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**		**HR (95% CI)**	**Absolute excess cases per 1,000 p-y[*] for GLP-1 compared to control**	**Quality**
Primary Composite Outcome (Cardiovascular Death, Nonfatal MI, Nonfatal Stroke)[†‡§]									
Overall									
5[9, 17-20]	5 RCT	Not serious	Inconsistent[‖]	Direct	Precise	42,920	0.88 (0.84 – 0.94)	--	Moderate[¶]
With ASCVD									
5[9, 17-20]	5 RCT	Not serious	Inconsistent[‖]	Direct	Precise	35,278	0.88 (0.83 – 0.93)	--	Moderate[¶]
Without ASCVD									
3[18-20]	3 RCT	Not serious	Inconsistent#	Direct	Imprecise	7,642	0.98 (0.82 – 1.17)	--	Low
CVD Mortality									
5[9, 17-20]	5 RCT	Not serious	Inconsistent	Direct	Precise	42,920	0.88 (0.80 – 0.96)	--	Moderate
All-cause Mortality									
5[9, 17-20]	5 RCT	Not serious	Inconsistent	Direct	Precise	42,920	0.89 (0.83 – 0.95)	--	Moderate
Harms									
Serious AEs									
5[5, 9, 18-20]	4 RCT 1 SR/MA	Serious[**]	Consistent	Direct	Precise	130,488	0.98 (0.94 – 1.03)[††]	-	Moderate
Severe hypoglycemia									
8[5, 9, 17-20, 34, 35]	5 RCT 1 SR/MA 2 cohorts	Not serious	Inconsistent	Direct	Imprecise	123,703	0.95 (0.72-1.34)[†††‡‡]	-	Moderate
Acute Pancreatitis									
19 5, 9, 17-20, 36-48	5 RCT 1 SR/MA 13 Retrospective studies	Not serious	Consistent	Direct	Imprecise	3,237,614[§§]	0.89 (0.63 – 1.28) [†††‡‡]	-	Moderate
Diabetic retinopathy									
6[5, 17-20, 49]	4 RCT 1 SR/MA 1 Retrospective study	Serious	Inconsistent	Direct	Imprecise	113,917[‖‖]	1.15 (0.83-1.59)[†††‡‡]	[¶¶]	Low##
Acute renal failure									
3[17, 19, 50]	2 RCT 1 Retrospective Study	Not serious[***]	Consistent	Direct	[†††]	491,539	No signal for harm[‡‡‡]	-	Moderate[§§§]
Biliary Disease									
1[25]	1 Retrospective Study	Serious	[‖‖‖]	Direct	Precise	71,369	1.79 (1.21-2.67)	2.8	Low
Other Potential Harms									

Quality Assessment						Total N	Effect		
N Studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**		**HR (95% CI)**	**Absolute excess cases per 1,000 p-y* for GLP-1 compared to control**	**Quality**
Amputations[17, 18]	2 RCT	Serious	Consistent	Direct	Precise	24,165	No signal for harm‡‡‡	-	Moderate
Cancer 6[38, 41, 43, 51, 52, 53¶¶¶]	1 Prospective Cohort 5 Retrospective studies	Serious	Consistent###	Direct	****	Variable by cancer††††	No signal for harm‡‡‡	--	Low

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MA = meta-analysis; N = number of studies analyzed; p-y = person-years; RCT = randomized clinical trial; GLP-1 = Glucagon-like peptide-1; SR = systematic review

Notes:

* Absolute effects per 1,000 p-y could not be calculated for trials based on reported data and measures of dispersion not consistently reported
† The composite outcome of ELIXA additionally includes unstable angina, however there were only 10 events in the CG and 9 events in the IG so it was determined that this composite was not materially different
‡ Subgroup analyses by ASCVD status are reported only for the primary composite outcome
§ Individual components of the primary composite outcome are not graded; pooled results for total MI and total stroke each suggest a benefit but the upper confidence interval is 1.00 for each outcome
‖ Statistical heterogeneity is moderate to substantial which may be explained by 2 different chemical compounds in this class (glutides vs natides) where results for natides tend closer to HRs of 1.00; each medication is only studied once
¶ For class effect, with potentially important heterogeneity by chemical compound within the class
# 2 studies of glutides and 1 of natides in this population with no consistent pattern of effect within type or class
** Length of F/U possibly not sufficient to detect AE
†† From Zheng, 2018[5]
‡‡ Using pooled HR of trials from Zheng, 2018 and not estimates from observational data
§§ The SR/MA includes 4 of the 5 RCTs evaluated separately so the N from Zheng is not included in this estimate; no overall N reported for Funch, 2014 so cases were used in the estimate and this represents an underreporting of overall N
‖‖ The SR/MA includes 3 of the 4 RCTs evaluated separately so the N from Zheng is not included in this estimate
¶¶ Diabetic retinopathy was reduced in 2 trials (absolute risk difference -0.3% in both trials [not significant in 1 trial and significance not reported in the other trial] and increased in 2 trials (statistically significant absolute risk difference +1.2% in 1 trial and +1 per 1,000 p-y in the other trial with significance not reported)
Signal for harm from semaglutide and liraglutide
*** Based on assumption that there was sufficient length of F/U in trials
††† Cannot be determined because confidence intervals are not reported for trials and design limitations in the retrospective claims analysis
‡‡‡ HR not reported
§§§ Downweighted because precision cannot be assessed
‖‖‖ Only one study
¶¶¶ 5 for pancreatic cancer, 1 for breast cancer, 1 for thyroid cancer
Only 1 study for breast cancer and only 1 study for thyroid cancer
**** Variable for pancreatic cancer, precise for breast cancer, imprecise for thyroid cancer
†††† Estimated at 325,259 for pancreatic cancer, although this is an underestimate because Funch, 2014 reports only cases and not N; 44,984 for breast cancer; 65,664 for thyroid cancer

Table 7. Modified GRADE Evidence Profile – SGLT-2 Inhibitors

Quality Assessment					Total N		Effect		
N Studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**		**HR (95% CI)**	**Absolute excess cases per 1,000 p-y[*] (95% CI) for SGLT-2 compared to control**	**Quality**
Primary Composite Outcome (Cardiovascular Death, Nonfatal MI, Nonfatal Stroke)[†‡]									
Overall									
3[21-23]	3 RCT	Not serious	Consistent[§]	Direct	Precise	34,322	0.89 (0.83 – 0.96)	-1.6 to -6.5[‖]	High[¶]
With ASCVD									
3[21-23]	3 RCT	Not serious	Consistent[§]	Direct	Precise	20,650	0.86 (0.80 – 0.93)	-6.5 to -7.2[‖]	High[¶]
Without ASCVD									
2[21, 22]	2 RCT	Not serious	Consistent[§]	Direct	Imprecise	13,672	1.00 (0.87 – 1.16)	0.3[**]	Moderate[††]
CVD Mortality									
3[21-23]	3 RCT	Not serious	Inconsistent[‡‡]	Direct	Imprecise	34,322	0.81 (0.63 – 1.06)	-0.1 to -7.8[‖]	Low
All-cause Mortality									
3[21-23]	3 RCT	Not serious	Inconsistent[‡‡]	Direct	Imprecise	34,322	0.83 (0.70 – 0.98)	-1.3 to -9.2[‖]	Low
Harms									
Serious Adverse Events									
6[5, 21-23, 54, 55]	3 RCT 1 SR/MA 2 Prospective Cohorts	Serious[§§]	Consistent	Direct	Precise	132,919	0.90 (0.85 to 0.96)[‖‖]	-	Moderate
Severe Hypoglycemia									
6[21-24, 56, 57]	3 RCT 1 SR/MA 2 Retrospective studies	Not serious	Consistent	Direct	Imprecise	738,610	1.02 (0.75 to 1.41)[‖‖]	-	Moderate
Lower Limb Amputation									
12[5, 21-23, 26-29, 58-60]	3 RCT 2 SR/MA 5 Retrospective studies 2 Med Reporting System Analyses	Serious[§§]	Inconsistent[¶¶]	Direct	Imprecise	2,600,094[###]	1.55 (0.96 to 2.50)[‖‖]	[***]	Low[†††]
Genitourinary Infection									
Genital infections 5, 21-24, 61-64	3 RCT 2 SR/MA 3 Retrospective studies 1 Med Reporting System Analysis	Not serious	Consistent	Direct	Precise	449,485[‡‡‡]	4.19 (3.45 to 5.09)[‖‖]	+24.1 per 1,000 p-y for men (CI NR) and +51.3 per 1,000 p-y for women (CI NR)[§§§]	High
UTI 5, 21, 23, 24, 62-64	2 RCT 2 SR/MA	Serious[‖‖‖]	Inconsistent[‖‖‖]	Direct	Imprecise	152,662[‡‡‡]	Regulatory submissions: 1.15 (1.06 to 1.26)	-	Low

Quality Assessment					Total N		Effect		
N Studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**		**HR (95% CI)**	**Absolute excess cases per 1,000 p-y* (95% CI) for SGLT-2 compared to control**	**Quality**
	2 Retrospective studies 1 Med Reporting System Analysis						Published data: 1.02 (0.95 to 1.10)¶¶¶		
Renal Impairment									
Acute Renal Failure 4[21-24, 65, 66]	3 RCT 1 SR/MA 1 Retrospective Study 1 Med Reporting System Analysis	Not serious###	Consistent Direct	Direct	****	91,280††††	No signal for harm‡‡‡‡	-	Moderate§§§§
Other Potential Harms									
Acute Pancreatitis 1[22]	1 RCT	Not serious	NAǁǁǁǁ	Direct	Preciseǁǁǁǁ	10,142	No signal for harm‡‡‡‡	-	Moderateǁǁǁǁ
Ketoacidosis 5[21, 24, 67-71]	1 RCT 2 SR/MA 2 Retrospective Studies 2 Med Reporting System Analyses	Not serious	Inconsistent¶¶¶¶	Direct	Imprecise	209,778####	1.99 (0.22 to 17.80)*****	-	Low
Bone Fracture[21-24]	3 RCT 1 SR/MA	Serious§§	Inconsistent†††††	Direct	Imprecise	77,208	0.96 (0.78 to 1.18)‡‡‡‡‡	§§§§§	Lowǁǁǁǁǁ

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MA = meta-analysis; Med – medication; N = number of studies analyzed; p-y = person-years; RCT = randomized clinical trial; SGLT-2 = Sodium-glucose Cotransporter-2; SR = systematic review

Notes:
* Absolute effects could not be pooled because measures of dispersion not consistently reported
† Subgroup analyses by ASCVD status are reported only for the primary composite outcome
‡ Individual components of the primary composite outcome are not graded; pooled results for total MI suggest benefit but do not achieve statistical significance and pooled results for stroke suggest no benefit with somewhat wide confidence intervals
§ However, only 2 trials
ǁ Statistically significant in the one trial reporting confidence intervals
¶ Based on 3 studies for a class effect, no replication for any single medication
# Only 1 trial
** Confidence intervals not reported
†† Subgroup analysis results from 2 trials
‡‡ High statistical heterogeneity which could be due to different ASCVD risk in the 2 trials, medication, or length of F/U
§§ Length of F/U possibly not sufficient to detect AE
ǁǁǁ Using pooled HR of trials from Zheng, 2018 and not estimates from observational data
¶¶ Statistically significant increase only in CANVAS
The SR/MA includes 2 of the 3 RCTs evaluated separately so the N from Zheng is not included in this estimate; no overall N reported for Fadini so cases were used in the estimate and this represents and underreporting of overall N
*** The signal of harm is for canagliflozin only; +2.9 per 1,000 p-y absolute increase (confidence intervals not reported)

††† Signal for increased risk for amputation is for canagliflozin only
‡‡‡ The SR/MA includes 2 of the 3 RCTs evaluated separately so the N from Zheng is not included in this estimate; no overall N reported for Raschi so cases were used in the estimate and this represents and underreporting of overall N
§§§ Only one trial, CANVAS, reporting per 1,000 p-y
‖‖‖ Wu, 2016 showed discordant results depending on data source (e.g., regulatory submissions vs published data)
¶¶¶ RR, from Wu, 2016
Based on the assumption that there was sufficient length of F/U in trials
**** Potential clinical heterogeneity of outcome definitions
†††† Underestimate as Perlman reports cases only, not patients
‡‡‡‡ HR NR
§§§§ Down weighted because we cannot assess precision
‖‖‖‖ One study only
¶¶¶¶ Evidence from one trial DECLARE only
Underestimate as Bonora, Blau, and Fadini report N of cases only, not patients
***** Pooled RR of published literature from Wu, 2016 but the RR does not incorporate data from DECLARE; pooled data from regulatory submissions only reports 1 case of ketoacidosis
††††† Statistically significant in CANVAS only
‡‡‡‡‡ Pooled RR of published literature from Wu, 2016
§§§§§ The signal of harm is for canagliflozin only; +3.5 per 1,000 p-y absolute increase (confidence intervals not reported)
‖‖‖‖‖ Signal for increased risk for fracture is for canagliflozin only

Table 8. Meta-Analysis Results from Randomized Controlled Trials, SGLT-2 Inhibitors or GLP-1 Agonists vs. Placebo in Patients with Type 2 Diabetes Not Controlled by Metformin

Outcome	SGLT-2 Inhibitors				GLP-1 Agonists			
	K	Total N	I^2 (%)	HR (95% CI)	K	Total N	I^2 (%)	HR (95% CI)
Primary (Composite)	3	34,322	0	0.89 (0.83 – 0.96)	5	42,920	58.8	0.88 (0.80 – 0.96)
In Patients with CVD	3	20,650	0	0.86 (0.80 – 0.93)	5	35,278	57.3	0.87 (0.79 – 0.96)
In Patients without CVD	2	13,672	0	1.00 (0.87 – 1.16)	3	7,642	52.3	0.96 (0.73 – 1.26)
All-Cause Mortality	3	34,322	74.5	0.83 (0.70 – 0.98)	5	42,920	0	0.89 (0.83 – 0.95)
CVD Mortality	3	34,322	80.6	0.81 (0.63 – 1.06)	5	42,920	0	0.88 (0.80 – 0.96)
Any Myocardial Infarction	3	34,322	0	0.89 (0.80 – 0.98)	2	24,215	78.6	0.86 (0.67 – 1.11)
Fatal MI	0	NA	NA	NA	1	14,752	NA	1.29 (0.63 – 2.66)
Nonfatal MI	2	17,162	0	0.86 (0.74 – 1.00)	3	18,705	39.2	0.92 (0.79 – 1.07)
Any Stroke	3	34,322	27.8	1.00 (0.86 – 1.16)	2	24,215	0	0.85 (0.73 – 1.00)
Fatal Stroke	0	NA	NA	NA	1	14,752	NA	0.71 (0.39 – 1.30)
Nonfatal Stroke	2	17,162	62.7	1.02 (0.85 – 1.23)	3	24,215	50.9	0.88 (0.67 – 1.16)
Heart Failure	3	34,322	0	0.69 (0.61 – 0.79)	4	33,457	0	0.93 (0.83 – 1.04)

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; GLP-1 = Glucagon-like Peptide-1; HR = hazard ratio; K = number of studies analyzed; MI = myocardial infarction; N = number of participants analyzed; NA = not applicable; SGLT-2 = SLGT-2 = Sodium-glucose Cotransporter-2

Table 9. Summary Table – Harms Associated with glucagon-like peptide-1 (GLP-1) agonists

Study Type	Total AE	Hypoglycemia	Lower limb amputation	Acute Pancreatitis	Diabetic Retinopathy	Acute Renal Failure	Cancer	Bile Duct and Gallbladder Disease
RCTs	Serious AE: ↔ (k=4[9, 18-20])†‡ AE leading to discontinuation: ↑ (k=5[9, 17-20])	↓† (k=3[9, 17, 20])‖ ↑† (k=2[18, 19]) severe	↔ (k=2[17, 18])¶	↔ (k=5[9, 17-20])†	↓ (k=2[19, 20])†# ↑ (k=2[17, 18])†	↔ (k=2[17, 19])†	Thyroid: ↔ (k=3[18-20])	NR
SR/MA*	Serious AE: ↔ (k=1[5])§ AE leading to discontinuation: ↑ (k=1[5])	↑(k=1[5]) any hypoglycemia ↔ (k=1[5]) severe	NR	↔ (k=1[5])	↔ (k=1[5])	NR	NR	NR
Prospective cohort	Serious AE: NR AE leading to discontinuation: NA	↓ (k=2[34, 35])† mild and severe	NR	NR	NR	NR	Breast: ↔ (k=1[53])	NR
Retrospective study (e.g., claims database)	Serious AE: NR AE leading to discontinuation: NA	NR	NR	↔ (k=13[36-48])	↔ (k=1[49])	↔ (k=1[50]) ↓ (k=2[72, 73])**	Pancreatic: ↔ (k=5[38, 41, 43, 51, 52]) Thyroid: ↔ (k=1[51])	↑ (k=1[25])
FDA or other Drug Reporting System	Serious AE: NR AE leading to discontinuation: NA	NR	NR	NR	↓ (k=1[74])	NR		NR

Abbreviations: AEs = adverse events; eGFR = estimated glomerular filtration rate; FDA = U.S. Food and Drug Administration; k = number of studies reporting each outcome; MA = meta-analysis; NR = not reported; RCTs = randomized controlled trials; SR = systematic review

Notes:
↔ = No increased risk of harms
↓ = Lower risk of harms compared with other (or no) medications
↑ = Higher risk of harms compared with other (or no) medications
* For acute pancreatitis and diabetic retinopathy, the same studies are represented for RCTs[9, 17-20] and SR/MA.[5]
† Statistical significance not reported in ≥1 cited study
‡ Results for one trial[20] were reported as not statistically significant. Statistical significance was not reported in remaining three trials: In 2 trials,[9, 19] serious AEs were reported as higher in CG, and in one trial,[18] serious AEs were reported as higher in IG by 0.2%.
§ Higher risk of AEs leading to trial withdrawal (HR, 2.00 [95% CI, 1.70 to 2.37])[5]
‖ A lower number of severe hypoglycemic events were reported in the intervention group compared with the control group in 3/5 studies[9, 17, 20] (only 1[20] of which reported a p value, and it is significant). A higher number of severe hypoglycemic events were reported in intervention group compared with the control group in 2/5 studies[18, 19] with no p values; higher by 0.4%[18] in 1 trial and 1.2% in the other.[19]
¶ A lower number of lower limb amputations were reported for the intervention group compared with the control group (1 vs. 2 amputations) in one[17] of the trials. Nontraumatic amputations in the other reporting trial are the same.[18]
# A higher number of diabetic retinopathy events occurred in the intervention group compared with the control group in two trials,[17, 18] but the trend for harm was only statistically significant in one trial[19] (not statistically significant in the other). A lower number of diabetic retinopathy events occurred in the intervention group compared with the control group in two other trials,[19, 20] but neither trial reported on statistical significance.
** eGFR decrease

Table 10. Evidence Table of Adverse Events in Randomized Clinical Trials of GLP-1 Agonists (values are number of patients with events unless otherwise noted)

Study Name Author, Year Medication	Serious AE	AE Leading to Discontinuation	Hypoglycemia	Lower Limb Amputation	Acute Pancreatitis	Diabetic Retinopathy	Acute Kidney Injury
Harmony Outcomes Hernandez, 2018[17] Albiglutide	NR in the aggregate, only by system organ class	IG: 406/4,717 (8.6%) CG: 307/4,715 (6.5%) p NR	Severe hypoglycemia IG: 31/4,717 (0.6%) CG: 55/4,715 (1.2%) p NR	IG: 1/4,717 (0.02%) CG: 2/4,715 (0.04%) p NR	IG: 10/4,717 (0.2%) CG: 7/4,715 (0.1%) RR 1.43 (0.54 to 3.75)	IG: 78/4,717 (1.6%) CG: 89/4,715 (1.9%) RR 0.88 (0.65 to 1.18)	IG: 70/4,717 (1.5%) CG: 80/4,715 (1.7%) p NR
EXSCEL Holman, 2017[18] Exenatide extended-release	IG: 1,234/7,344 (16.8%) CG: 1,222/7,372 (16.6%) p NR	IG: 108/7,344 (1.5%) CG: 104/7,372 (1.4%) p NR	Severe hypoglycemia IG: 247/7,344 (3.4%) CG: 219/7,372 (3.0%) p NR	Traumatic IG: 2*/7,344 (0.03%) CG: 6*/7,389 (0.8%) p NR Nontraumatic IG: 128*/7,344 (1.7%) CG: 127*/7,389 (1.7%) p NR	IG: 26/7,344 (0.4%) CG: 22/7,372 (0.3%) p NR	IG: 214*/7,344 (2.9%) CG: 238*/7,389 (3.2%) p NR	NR
SUSTAIN-6 Marso, 2016[19] Semiglutide	IG: 565/1,648 (34.3%) CG: 627/1,649 (38.0%) p NR	IG: 214/1,648 (13.0%) CG: 110/1,649 (6.7%) p NR	Severe or symptomatic hypoglycemia confirmed by plasma glucose test IG: 369/1,648 (22.4%) CG: 350/1,649 (21.2%) p NR	NR	IG: 9/1,648 (0.5%) CG: 12/1,649 (0.7%) p NR	IG: 50/1,648 (3.0%) CG: 29/1,649 (1.8%) HR 1.76 (1.11 to 2.78)	IG: 65/1,648 (3.9%) CG: 69/1,649 (4.2%) p NR
LEADER Marso, 2016[20] Liraglutide	IG: 2,320/4,668 (49.7%) CG: 2,354/4,672 (50.4%) p = 0.51	IG: 444/4,668 (9.5%) CG: 339/4,672 (7.3%) P < 0.001	Severe hypoglycemia IG: 114/4,668 (2.4%) CG: 153/4,672 (3.3%) p = 0.02 Confirmed hypoglycemia IG: 2,039/4,668 (43.7%) CG: 2,130/4,672 (45.6%) p = 0.06	NR	IG: 18/4,668 (0.4%) CG: 23/4,672 (0.5%) p = 0.44	IG: 6 per 1,000 p-y CG: 5 per 1,000 p-y HR 1.15 (0.87 to 1.52)	NR
ELIXA Pfeffer, 2015[9] Lixisenatide	IG: 625/3,031 (20.6%) CG: 669/3,032 (22.1%) p NR	IG: 347/3,031 (11.4%) CG: 217/3,032 (7.2%) P <0.001	Serious hypoglycemic episodes IG: 14 patients (16 events); (0.5% of patients) CG: 24 patients (37 events); (0.8% of patients) Hypoglycemic episodes IG: 504/3,031 (16.6%) CG: 462/3,032 (15.2%) p = 0.14	NR	IG: 5/3,031 (0.2%) CG: 8/3,032 (0.3%) p NR	NR	NR

Abbreviations: AE = adverse event; CG = control group; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; IG = intervention group; HR = hazard ratio; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; NR = not reported; RR = risk ratio; GLP-1 = glucagon-like peptide-1; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

Notes:

* Number of events, not number of patients with events

Table 11. Summary Table – Harms Associated with Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors

Study Type	Total AE	Hypoglycemia	Lower limb amputation	Genitourinary Infection	Acute Pancreatitis	Acute Renal Failure	Bone Fracture	Ketoacidosis
RCTs	Serious AE: ↓ (k=3[21-23, 31, 32]) AE leading to discontinuation: ↔ (k=2[22, 23]) ↑ (k=1[21])	↔ (k=2[22, 23, 31, 32]) ↓ (k=1[21])	↑ (k=1[22]) ↔ (k=2[21, 23, 31-33])	Genital infection: ↑ (k=3[21-23, 31-33]) UTI: ↔ (k=3[21, 23, 31-33])	↔ (k=1[22])	↔ (k=1[22]) ↓ (k=2[21, 23, 31-33])	↑ (k=1[22]) ↔ (k=2[21, 23, 31-33])	↑ (k=1[21])
SR/MA*	Serious AE: ↓ (k=1[5]) AE leading to discontinuation: ↔ (k=1[5])	↔ (k=1[24])	↑ (k=2[5, 58])	Genital infection: ↑ (k=2[5, 24]) UTI: ↑/↔ (k=2[5, 24])¶	NR	↔ (k=1[24])#	↔ (k=1[24])	↔ (k=2[24, 67])††
Prospective cohort	Serious AE: ↔ (k=2[54, 55]) AE leading to discontinuation: NA	NR	NR	NR	NR	NR	NR	NR
Retrospective study (e.g., claims database)	Serious AE: NR AE leading to discontinuation: NA	↔ (k=1[56]) ↓ (k=1[57])	↑/↔ (k=1[28])† ↓/↔(k=1[29])‡ ↔ (k=2[26, 27]) ↑ (k=1[75])	Genital infection: ↑ (k=3[61-63]) UTI: ↔ (k=2[62, 63])	NR	↓ (k=1[65]) ↔ (k=1[65])**	NR	↔ (k=2[68, 69])
FDA or other Drug Reporting System	Serious AE: NR AE leading to discontinuation: NA	NR	↑ (k=1[59]) ↑/↔ (k=1[60])§	Genital infection + UTI: ↑ (k=1[64])	NR	↑ (k=1[66])	NR	↑ (k=2[70, 71])

Abbreviations: AEs = adverse events; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; FDA = U.S. Food and Drug Administration; MA = meta-analysis; NR = not reported; RCTs = randomized controlled trials; SR = systematic review; UTI = urinary tract infection

Notes:
↔ = No increased risk of harms
↓ = Lower risk of harms compared with other (or no) medications
↑ = Higher risk of harms compared with other (or no) medications
* Same studies represented for RCTs[33] and SR/MA[5] for lower limb amputations and genitourinary infections
† Use of SGLT-2 inhibitors was statistically significantly associated with increased risk of amputation when compared with use of sulfonylureas, metformin, or thiazolidinediones (HR=2.12 [95% CI, 1.19 to 3.77); however, the association was not significant when compared with users of DPP-4s (HR=1.40 [95% CI, 0.85 to 2.67]) and GLP-1 agonists (HR=1.47 [95% CI, 0.64 to 3.36]).[28]
‡ Use of SGLT-2 inhibitors was statistically significantly associated with reduced risk of amputation when compared with use of sulfonylureas (HR=0.74 [95% CI, 0.57 to 0.96]), but not when compared with use of DPP-4 inhibitors (HR=0.88 [95% CI, 0.65 to 1.15]).[29]
§ Compared with non-SGLT-2 medications, PRR was higher for canagliflozin (5.33 [95% CI, 4.04 to 7.04], p<0.0001) and empagliflozin (2.37 [95% CI, 0.99 to 5.70], p=0.054), but lower for dapagliflozin (0.25 [95% CI, 0.03–1.76], p=0.163).[60]
¶ In Wu, 2016, meta-analyzed data from regulatory reports showed a statistically significant increase; data from meta-analyzed published literature was not statistically significant.
# Reported as kidney disease with variable definitions in the primary trials
** Reported as a 30% reduction in eGFR
†† No quantitative comparative analysis was performed, but conclusion was ketoacidosis is a “rare side effect and is unlikely to impact the clinical use of SGLT-2, provided that it is appropriate”.{Bonora, 2018 #1115

Table 12. Evidence Table of Adverse Events in Randomized Clinical Trials of SGLT-2 Inhibitors (values are number of patients with events unless otherwise noted)

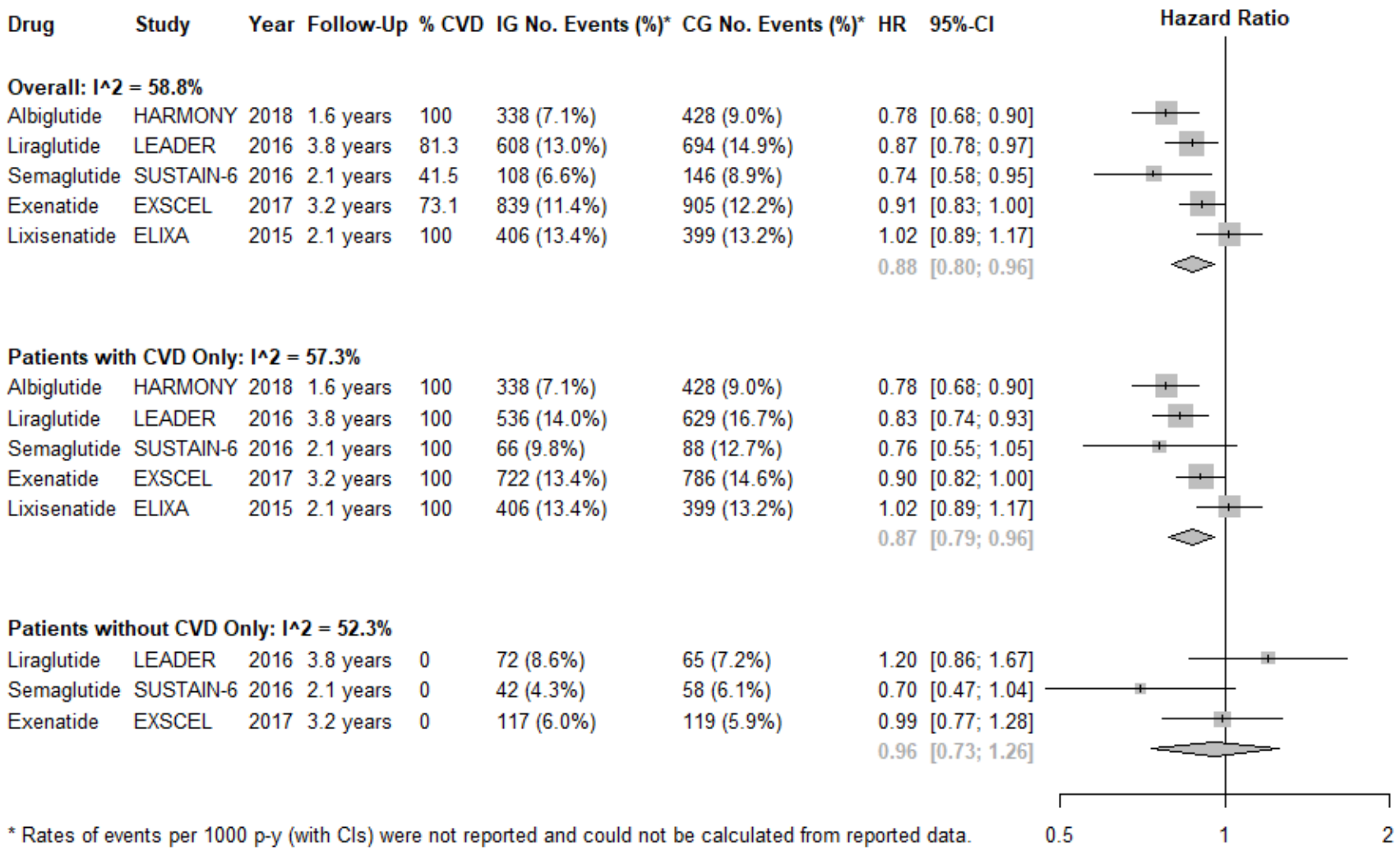
Study Name Author, Year	Serious AE	AE Leading to Discontinuation	Hypoglycemia	Lower Limb Amputation	Genitourinary Infection	Acute Pancreatitis	Acute Kidney Injury	Bone Fracture	Diabetic Ketoacidosis
DECLARE-TIMI 58 Wiviott, 2018[21] Dapagliflozin	IG: 2,925/8,574 (34.1%) CG: 3,100/8,569 (36.2%) HR 0.91 (0.87 to 0.96)	IG: 693/8,574 (8.1%) CG: 592/8,569 (6.9%) HR 1.15 (1.03 to 1.28)	IG: 58/8,574 (0.7%) CG: 83/8,569 (1.0%) HR 0.68 (0.49 to 0.95)	IG:123 /8,574 (1.4%) CG: 113/8,569 (1.3%) HR 1.09 (0.84 to 1.40)	IG: 76/8,574 (0.9%) CG: 9/8,569 (0.1%) HR 8.36 (4.19 to 16.68)* UTI: IG: 127/8,574 (1.5%) CG: 133/8,569 (1.6%) HR 0.93 (0.73 to 1.18)	NR	IG: 125/8,574 (1.5%) CG: 175/8,569 (2.0%) HR 0.69 (0.55 to 0.87)	IG: 457/8,574 (5.3%) CG: 440/8,569 (5.1%) HR 1.04 (0.91 to 1.18)	IG: 27/8,574 (0.3%) CG: 12/8,569 (0.1%) HR 2.18 (1.10 to 4.30)
CANVAS Neal, 2017[22] Canagliflozin	IG: 104.3 per 1000 p-y CG: 120.0 per 1000 p-y p = 0.04	IG: 35.5 per 1,000 p-y CG: 32.8 per 1.000 p-y P = 0.07	IG: 50.0 per 1000 p-y CG: 46.4 per 1000 p-y p=0.20	IG: 6.3 per 1,000 p-y CG: 3.4 per 1,000 p-y P <0.001†	Men: IG: 34.9 per 1000 p-y CG: 10.8 per 1000 p-y p < 0.001 Women: IG: 68.8 per 1000 p-y CG: 17.5 per 1000 p-y p < 0.001	IG: 0.5 per 1000 p-y CG: 0.4 per 1000 p-y p = 0.63	IG: 3.0 per 1000 p-y CG: 4.1 per 1000 p-y p = 0.33	IG: 15.4 per 1000 p-y CG: 11.9 per 1000 p-y p = 0.02	NR
EMPA-REG OUTCOME Zinman, 2015[23] Fitchett, 2016[31] Wanner, 2016[32] Inzucchi, 2018[33] Empagliflozin	IG: 1,789/4,687 (38.2%) CG: 988/2,333 (42.3%) p < 0.001	IG: 813/4,687 (17.3%) CG: 453/2,333 (19.4%) P < 0.001	Hypoglycemic event requiring assistance IG: 63/4,687 (1.3%) CG: 36/2,333 (1.5%) p NS Any confirmed hypoglycemic event IG: 1,303/4,687 (27.8%) CG: 650/2,333 (27.9%) p NS	IG: 88/4,687 (1.9%) CG: 43/2,333 (1.8%) HR 1.00 (0.70 – 1.44)	UTI: Men: IG: 350/4,687 (10.5%) CG: 158/2,33 (9.4%) p NS Women: IG: 492/4,687 (36.4%) CG: 265/2,333 (40.6%) p <0.05 Genital Infection: Men: IG: 166/4,687 (5.0%) CG: 25/2,333 (1.5%) p < 0.001 Women: IG: 135/4,687 (10.0%) CG: 17/2,333 (2.6%) p < 0.001	NR	IG: 45/4,687 (1.0%) CG: 37/2,333 (1.6%) p < 0.05	IG: 179/4,687 (3.8%) CG: 91/2,333 (3.9%) p NS	NR

Abbreviations: AE = adverse event; CANVAS = Canagliflozin Cardiovascular Assessment Study; CG = control group; DECLARE-TIMI-58 = Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; IG = intervention group; HR = hazard ratio; NR = not reported; NS = not statistically significant; p-y = person-years; UTI = urinary tract infection

Notes:
* 6 cases of Fournier's gangrene: 1 in IG and 5 in CG
† Amputation of toes, feet, or legs; for 71% the highest amputation was at the level of the toe or metatarsal

Figures

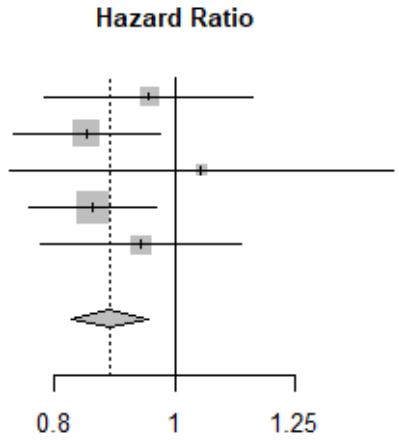
Figure 1. Meta-Analysis of GLP-1 Agonists vs. Placebo for Trial-Defined Primary Composite Outcome (Cardiovascular Death, Nonfatal MI, or Nonfatal Stroke)



* Rates of events per 1000 p-y (with CIs) were not reported and could not be calculated from reported data.

Figure 2. Meta-Analysis of GLP-1 Agonists vs. Placebo for All-Cause Mortality

Drug	Study	Year	Follow-Up	% CVD	IG No. Events (%)*	CG No. Events (%)*	HR	95%-CI
Albiglutide	HARMONY	2018	1.6 years	100	196 (4.1%)	205 (4.3%)	0.95	[0.79; 1.16]
Liraglutide	LEADER	2016	3.8 years	81.3	381 (8.2%)	447 (9.6%)	0.85	[0.74; 0.97]
Semaglutide	SUSTAIN-6	2016	2.1 years	41.5	62 (3.8%)	60 (3.6%)	1.05	[0.74; 1.49]
Exenatide	EXSCEL	2017	3.2 years	73.1	507 (6.9%)	584 (7.9%)	0.86	[0.77; 0.97]
Lixisenatide	ELIXA	2015	2.1 years	100	211 (7.0%)	223 (7.4%)	0.94	[0.78; 1.13]
							0.89	**[0.83; 0.95]**

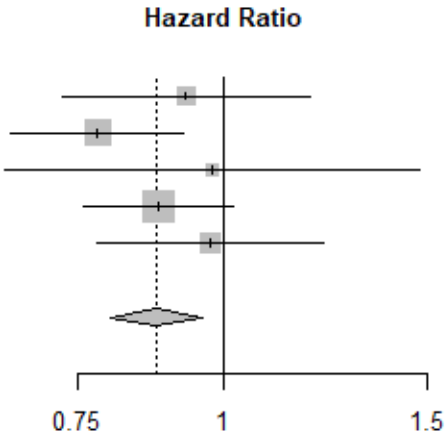


I^2 = 0%

* Rates of events per 1000 p-y (with CIs) were not reported and could not be calculated from reported data.

Figure 3. Meta-Analysis of GLP-1 Agonists vs. Placebo for Mortality from Cardiovascular Causes

Drug	Study	Year	Follow-Up	% CVD	IG No. Events (%)*	CG No. Events (%)*	HR	95%-CI
Albiglutide	HARMONY	2018	1.6 years	100	122 (2.6%)	130 (2.7%)	0.93	[0.73; 1.19]
Liraglutide	LEADER	2016	3.8 years	81.3	219 (4.7%)	278 (6.0%)	0.78	[0.66; 0.93]
Semaglutide	SUSTAIN-6	2016	2.1 years	41.5	44 (2.7%)	46 (2.8%)	0.98	[0.65; 1.48]
Exenatide	EXSCEL	2017	3.2 years	73.1	340 (4.6%)	383 (5.2%)	0.88	[0.76; 1.02]
Lixisenatide	ELIXA	2015	2.1 years	100	156 (5.1%)	158 (5.2%)	0.98	[0.78; 1.22]
							0.88	**[0.80; 0.96]**



I^2 = 0%

* Rates of events per 1000 p-y (with CIs) were not reported and could not be calculated from reported data.

Figure 4. Meta-Analysis of SGLT-2 Inhibitors vs. Placebo for Trial-Defined Primary Composite Outcome (Cardiovascular Death, Nonfatal MI, or Nonfatal Stroke)

Drug	Study	Year	Follow-Up	% CVD	IG Events/1000 P-Y	CG Events/1000 P-Y	ARR (95% CI)	HR	95%-CI
Overall: I^2 = 0%									
Dapagliflozin	DECLARE	2018	4.2 years	40.6	22.6	24.2	-1.6 (NR)	0.93	[0.84; 1.03]
Canagliflozin	CANVAS	2017	2.4 years	65.6	26.9	31.5	-4.6 (NR)	0.86	[0.75; 0.97]
Empagliflozin	EMPAREG	2015	3.1 years	100	37.4	43.9	-6.5 (-12.6 - -0.4)	0.86	[0.74; 0.99]
								0.89	[0.83; 0.96]
Patients with CVD Only: I^2 = 0%									
Dapagliflozin	DECLARE	2018	4.2 years	100	NR	NR	NR	0.90	[0.79; 1.02]
Canagliflozin	CANVAS	2017	2.4 years	100	34.1	41.3	-7.2 (NR)	0.82	[0.72; 0.95]
Empagliflozin	EMPAREG	2015	3.1 years	100	37.4	43.9	-6.5 (-12.6 - -0.4)	0.86	[0.74; 0.99]
								0.86	[0.80; 0.93]
Patients without CVD Only: I^2 = 0%									
Dapagliflozin	DECLARE	2018	4.2 years	0	NR	NR	NR	1.01	[0.86; 1.20]
Canagliflozin	CANVAS	2017	2.4 years	0	15.8	15.5	0.3 (NR)	0.98	[0.74; 1.29]
								1.00	[0.87; 1.16]

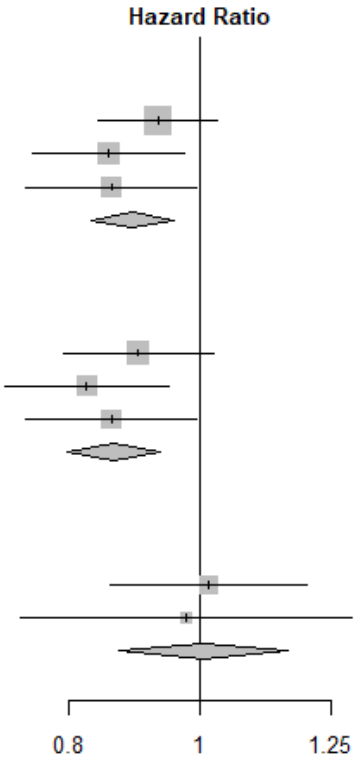


Figure 5. Meta-Analysis of SGLT-2 Inhibitors vs. Placebo for All-Cause Mortality

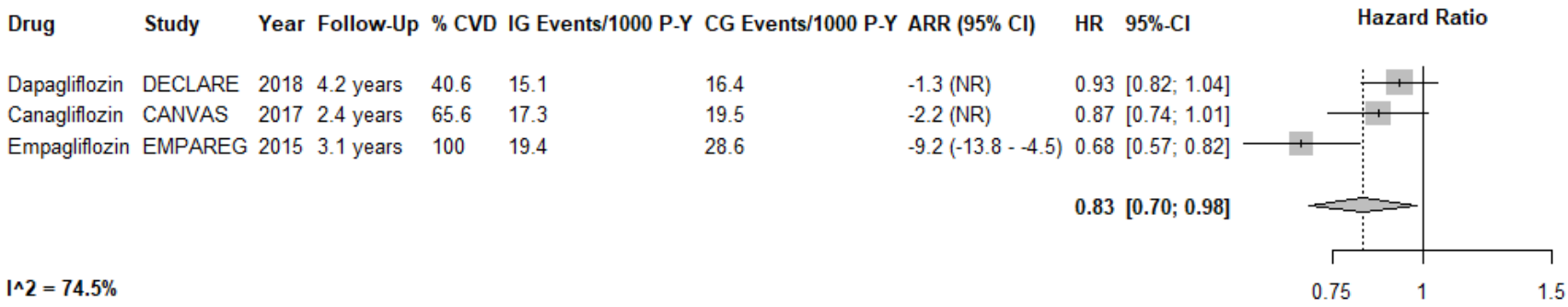
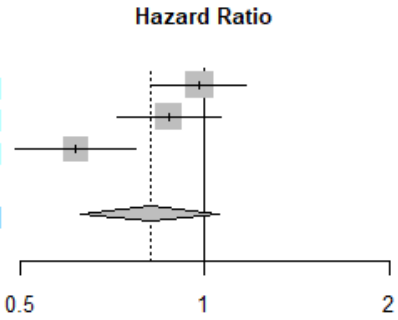


Figure 6. Meta-Analysis of SGLT-2 Inhibitors vs. Placebo for Mortality from Cardiovascular Causes

Drug	Study	Year	Follow-Up	% CVD	IG Events/1000 P-Y	CG Events/1000 P-Y	ARR (95% CI)	HR	95%-CI
Dapagliflozin	DECLARE	2018	4.2 years	40.6	7	7.1	-0.1 (NR)	0.98	[0.82; 1.17]
Canagliflozin	CANVAS	2017	2.4 years	65.6	11.6	12.8	-1.2 (NR)	0.87	[0.72; 1.06]
Empagliflozin	EMPAREG	2015	3.1 years	100	12.4	20.2	-7.8 (-11.6 - -3.9)	0.62	[0.49; 0.77]
								0.81	**[0.63; 1.06]**

I^2 = 80.6%



Appendices

Appendix A. Summarized Estimates of Treatment Effects

Appendix A Table 1. Estimates* of Treatment Effect of Sulfonylureas and Thiazolidinediones from Palmer, 2016[4]

	Comparison	Outcome	OR (95% CI)	No. of Trials (N with event/N [%])
Monotherapy	SU vs Placebo	CVD mortality	3.03 (0.12 to 75.95)	SU: 1 (1/92 [1.1%]) Placebo: 1 (1/92 [1.1%])
	SU vs Placebo	All-cause mortality	5.11 (0.24 to 108.40)	SU: 1 (2/92 [2.2%]) Placebo: 1 (0/92 [0%])
	SU vs Placebo	MI	--	No trials
	SU vs Placebo	CVA	--	No trials
	TZD vs Placebo	CVD mortality	0.24 (0.01 to 5.69)	TZD: 1 (1/1749 [0.1%]) Placebo: 1 (0/137 [0%])
	TZD vs Placebo	All-cause mortality	0.39 (0.02 to 7.92)	TZD: 1 (2/1749 [0.1%]) Placebo: 1 (0/137 [0%])
	TZD vs Placebo	MI	0.37 (0.04 to 3.51)	TZD: 4 (2/2106 [0.1%]) Placebo: 4 (0/231 [0%])
	TZD vs Placebo	CVA	0.55 (0.03 to 10.57)	TZD: 1 (3/1749 [0.2%]) Placebo: 1 (0/137 [0%])
Dual Therapy in Addition to Metformin	SU vs Placebo	CVD mortality	--	No Trials
	SU vs Placebo	All-cause mortality	0.99 (0.10 to 9.57)	SU: 1 (3/307 [1.0%]) Placebo: 1 (1/101 [1.0%])
	SU vs Placebo	MI	0.69 (0.10 to 4.90)	SU: 2 (2/551 [0.4%]) Placebo: 2 (1/223 [0.4%])
	SU vs Placebo	CVA	0.33 (0.02 to 5.18)	SU: 2 (1/551 [0.2%]) Placebo: 2 (1/223 [0.4%])
	SU vs TZD	CVD mortality	0.37 (0.01 to 8.98)	SU: 1 (0/185 [0%]) TZD: 1 (1/204 [0.5%])
	SU vs TZD	All-cause mortality	0.70 (0.05 to 9.16)	SU: 2 (2/498 [0.4%]) TZD: 2 (1/521 0.2%])
	SU vs TZD	MI	0.34 (0.01 to 8.21)	SU: 1 (0/313 [0%]) TZD: 1 (1/317 [0.3%])
	SU vs TZD	CVA	--	No Trials
	SU vs DPP-4	CVD mortality	1.32 (0.55 to 3.15)	SU: 6 (10/4335 [0.2%]) DPP-4: 6 (10/5219 [0.2%])
	SU vs DPP-4	All-cause mortality	1.29 (0.74 to 2.24)	SU: 10 (27/6467 [0.4%]) DPP-4: 10 (24/7374 [0.3%])
	SU vs DPP-4	MI	1.70 (0.89 to 3.24)	SU: 7 (21/3996 [0.5%]) DPP-4: 7 (14/4880 [0.3%])
	SU vs DPP-4	CVA	3.22 (1.55 to 6.70)†	SU: 8 (26/5379 [0.5%]) DPP-4: 8 (8/6269 [0.1%])
	SU vs SGLT-2	CVD mortality	1.00 (0.06 to 15.97)	SU: 1 (1/408 [0.2%]) SGLT-2: 1 (1/406 0.2%])
	SU vs SGLT-2	All-cause mortality	1.42 (0.55 to 3.67)	SU: 3 (10/1670 [0.6%]) SGLT-2: 3 (8/2139 [0.4%])
	SU vs SGLT-2	MI	4.44 (0.96 to 20.53)	SU: 2 (9/1188 [0.8%])

	Comparison	Outcome	OR (95% CI)	No. of Trials (N with event/N [%])
				SGLT-2: 2 (2/1171 0.2%])
	SU vs SGLT-2	CVA	0.23 (0.04 to 1.33)	SU: 2 (1/118 [0.8%]) SGLT: 2 (6/1171 [0.5%])
	SU vs GLP-1	CVD mortality	--	No Trials
	SU vs GLP-1	All-cause mortality	1.00 (0.37 to 2.66)	SU: 2 (8/821 [1.0%]) GLP-1: 2 (8/817 [1.0%])
	SU vs GLP-1	MI	0.81 (0.23 to 2.81)	SU: 3 (4/1059 [0.4%]) GLP-1: 3 (7/1538 [0.4%])
	SU vs GLP-1	CVA	0.53 (0.10 to 2.66)	SU: 3 (1/1059 [0.1%]) GLP-1: 3 (4/1538 [0.3%])
	TZD vs Placebo	CVD mortality	1.70 (0.26 to 11.13)	TZD: 3 (3/624 [0.5%]) Placebo: 1 (0/253 [0%])
	TZD vs Placebo	All-cause mortality	1.70 (0.26 to 11.12)	TZD: 3 (3/627 [0.5%]) Placebo: 1 (0/253 [0%])
	TZD vs Placebo	MI	1.01 (0.04 to 24.59)	TZD: 1 (1/387 [0.2%]) Placebo: 1 (0/129 [0%])
	TZD vs Placebo	CVA	0.11 (0.00 to 2.61)	TZD: 1 (0/387 [0%]) Placebo: 1 (1/129 [0.8%])
	TZD vs DPP-4	CVD mortality	0.82 (0.08 to 7.87)	TZD: 2 (1/552 [0.2%]) DPP-4: 2 (1/423 [0.2%])
	TZD vs DPP-4	All-cause mortality	0.82 (0.08 to 7.87)	TZD: 2 (1/552 [0.2%]) DPP-4: 2 (1/423 [0.2%])
	TZD vs DPP-4	MI	2.28 (0.44 to 11.78)	TZD: 3 (4/833 [0.5%]) DPP-4: 3 (1/718 [0.1%])
	TZD vs DPP-4	CVA	2.59 (0.51 to 13.18)	TZD: 3 (5/833 [0.6%]) DPP-4: 3 (2/718 0.3%])
	TZD vs GLP-1	CVD mortality	0.97 (0.02 to 49.34)	TZD: 1 (1/165 [0.6%]) GLP-1: 1 (1/160 [0.6%])
	TZD vs GLP-1	All-cause mortality	0.97 (0.02 to 49.34)	TZD: 1 (0/165 [0%]) GLP-1: 1 (0/160 [0%])
	TZD vs GLP-1	MI	4.85 (0.23 to 100.14)	TZD: 1 (2/165 [1.2%]) GLP-1: 1 (0/160 [0%])
	TZD vs GLP-1	CVA	2.91 (0.12 to 71.03)	TZD: 1 (1/165 [0.6%]) GLP-1: 1 (0/160 [0%])

Abbreviations: CI = confidence interval; CVA = cerebrovascular accident; CVD = cardiovascular disease; DPP-4 = = Dipeptidyl peptidase-4 inhibitor; GLP-1 = Glucagon-like peptide-1; MI = myocardial infarction; N = number of participants analyzed; No. = number; OR = odds ratio; SLGT-2 = Sodium-glucose Cotransporter-2 inhibitor; SU = sulfonylurea; TZD = thiazolidinediones

Notes:
* Direct estimates are reproduced in this table (network estimates not reproduced)
† Effect is statistically significant

Appendix A Table 2. Estimates of Treatment Effect of DPP-4s, GLP-1s, and SGLT-2s from Zheng, 2018[5]

Comparison	Outcome	HR (95% CI)	No. of Trials (N with event/N [%])
DPP-4 vs Control	All-cause mortality	1.02 (0.94 to 1.11)	Control: 88 (2955/57022 [5.2%]) DPP-4: 49 (1171/30178 [3.9%])
DPP-4 vs Control	CVD mortality	1.00 (0.91 to 1.11)	Control: 50 (1833/50869 [3.6%]) DPP-4: 27 (763/24519 [3.1%])
DPP-4 vs Control	Heart failure events	1.13 (1.00 to 1.28)	Control: 55 (1370/48362 [2.8%]) DPP-4: 24 (544/22327 [2.4%])
DPP-4 vs Control	Nonfatal MI	1.05 (0.86 to 1.28)	Control: 44 (1579/31538 [5.0%]) DPP-4: 25 (208/7956 [2.6%])
DPP-4 vs Control	Nonfatal CVA	1.05 (0.68 to 1.63)	Control: 43 (674/31958 [2.1%]) DPP-4: 20 (43/6815 [0.6%])
GLP-1 vs Control	All-cause mortality	0.88 (0.81 to 0.94)*	Control: 88 (2955/57022 [5.2%]) GLP-1: 32 (1195/27373 [4.4%])
GLP-1 vs Control	CVD mortality	0.85 (0.77 to 0.94)*	Control: 50 (1833/50869 [3.6%]) GLP-1: 19 (704/23554 [3/0%])
GLP-1 vs Control	Heart failure events	0.93 (0.84 to 1.02)	Control: 55 (1370/48362 [2.8%]) GLP-1: 21 (638/23363 [2.7%])
GLP-1 vs Control	Nonfatal MI	0.94 (0.86 to 1.02)	Control: 44 (1579/31538 [5.0%]) GLP-1: 7 (1042/17954 [5.8%])
GLP-1 vs Control	Nonfatal CVA	0.87 (0.76 to 0.99)*	Control: 43 (674/31958 [2.1%]) GLP-1: 12 (398/18463 [2.2%])
SGLT-2 vs Control	All-cause mortality	0.80 (0.71 to 0.89)*	Control: 88 (2955/57022 [5.2%]) SGLT-2: 29 (714/19587 [3.6%])
SGLT-2 vs Control	CVD mortality	0.79 (0.69 to 0.91)*	Control: 50 (1833/50869 [3.6%]) SGLT-2: 19 (468/18407 [2.5%])
SGLT-2 vs Control	Heart failure events	0.62 (0.54 to 0.72)*	Control: 55 (1370/48362 [2.8%]) SGLT-2: 19 (266/15989 [1.7%])
SGLT-2 vs Control	Nonfatal MI	0.84 (0.72 to 0.98)*	Control: 44 (1579/31538 [5.0%]) SGLT-2: 18 (438/14583 [3.0%])
SGLT-2 vs Control	Nonfatal CVA	1.00 (0.83 to 1.21)	Control: 43 (674/31958 [2.1%]) SGLT-2: 13 (320/13621 [2.3%])

Abbreviations: CI = confidence interval; CVA = cerebrovascular accident; CVD = cardiovascular disease; DPP-4 = = Dipeptidyl peptidase-4 inhibitor; GLP-1 = Glucagon-like peptide-1; MI = myocardial infarction; N = number of participants analyzed; No. = number; OR = odds ratio; SLGT-2 = Sodium-glucose Cotransporter-2 inhibitor

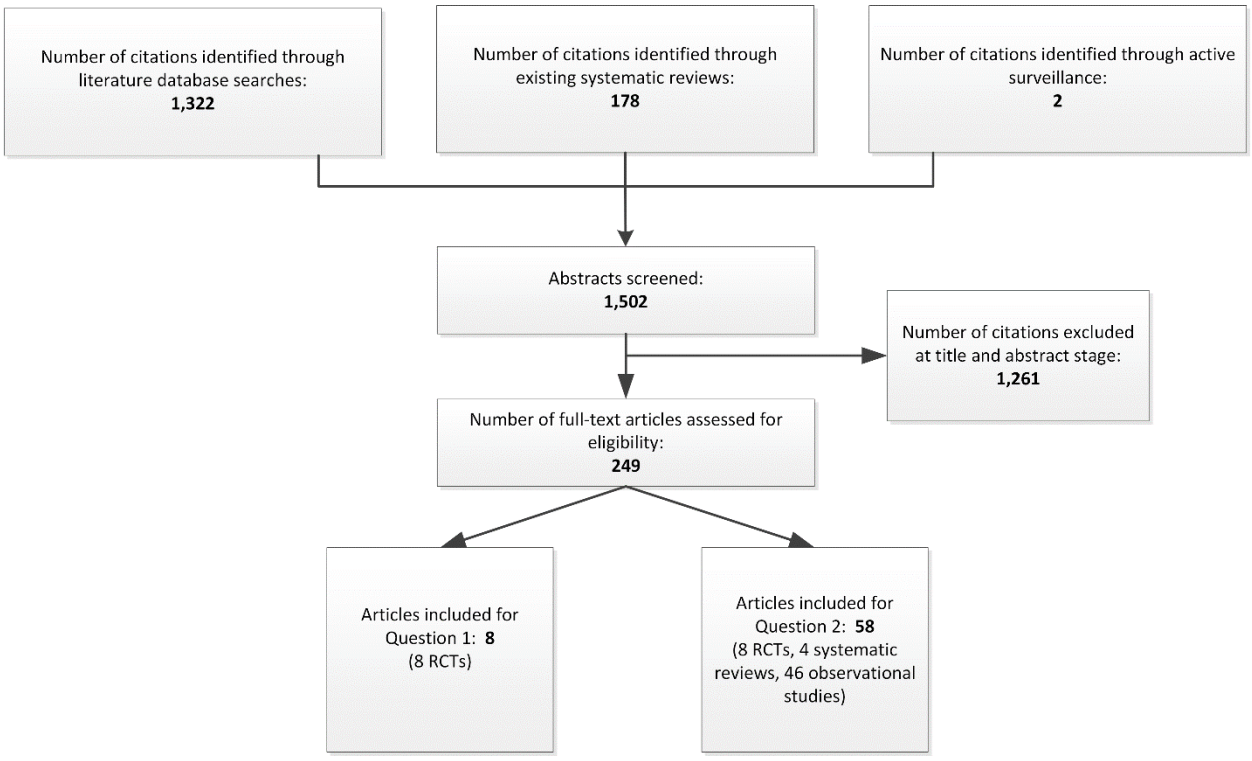
Notes:
* Effect is statistically significant

Appendix B. Eligibility Criteria for Randomized Clinical Trials

	Inclusion	Exclusion
Population	Adults with type 2 diabetes with or without known ASCVD who cannot attain adequate glucose control with metformin, or for whom metformin cannot be used	Type 1 diabetes; Adults not on metformin or without contraindication or intolerance for metformin
Interventions	GLP-1 (receptor) agonists; SGLT-2 inhibitors	DPP-4 inhibitors; Sulfonylureas; Thiazolidinediones; Insulin
Comparator	Placebo control; Active comparator using another medication (within class or different class of medication)	
Outcomes	All-cause mortality; Cardiovascular mortality; Heart failure; Myocardial infarction; Unstable angina; Stroke Composite CVD events, as defined by study; Adverse event (serious events or effects leading to study withdrawal), including hypoglycemia, lower-limb amputation, genitourinary infections, acute pancreatitis, and retinopathy	

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; DPP-4 = Dipeptidyl peptidase-4; GLP-1 = Glucagon-like peptide-1

Appendix C. Literature Flow Diagram



Appendix D. Ongoing Studies

Class	Medication	Trial Name	Population	Primary Outcome	Expected Date	NCT #
SGLT-2	Canagliflozin	CREDENCE	4,401 with DM, eGFR ≥30 to <90 mL/min/1.73 m^2, and albuminuria	Composite of end-stage kidney disease, doubling of serum creatinine, and renal or cardiovascular death	June 2019	NCT02065791
SGLT-2	Ertugliflozin	VERTIS CV	~8,000 with DM and established CVD	Composite of CVD death, MI, stroke	September 2019	NCT01986881
GLP-1	Dulaglutide	REWIND	9,901 with DM and established CVD or CVD risk factors	Composite of CVD death, MI, stroke	June 2019 (ADA Meeting)	NCT01394952
GLP1	Semaglutide	SELECT	~17,500 with BMI ≥27 kg/m^2 and established ASCVD*	Composite of CVD death, MI, stroke	September 2023	NCT03574597

Abbreviations: ADA = American Diabetes Association; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CREDENCE = Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; CVD = cardiovascular disease; DM = Diabetes Mellitus; eGFR = estimated glomerular filtration rate; GLP-1 = Glucagon-like peptide-1; MI = myocardial infarction; REWIND = Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SELECT = Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity; SGLT-2 = SLGT-2 = Sodium-glucose Cotransporter-2; VERTIS-CV = Ertugliflozin in Subjects With Type 2 Diabetes Mellitus and Established Cardiovascular Disease

Notes:
* Conducted in participants without DM2; this trial is designed to elucidate whether the potential beneficial effect of GLP-1 receptor agonists are mediated through glycemic control.

Appendix E. Search Strategies for Observational Studies

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of search: 2 October 2018

1 (sodium-glucose co?transporter 2 inhibit* or sodium glucose cotransporter 2 inhibit* or sodium-glucose cotransporter-2 inhibit*).mp.
2 (SGLT-2 inhibit* or SGLT-2i* or SGLT2i or SGLT2).mp.
3 Gliflozin*.mp.
4 (Canagliflozin* or Invokana or Sulisent or Prominad).mp.
5 (Dapagliflozin* or Forxiga or Farxiga).mp.
6 (Empagliflozin* or Jardiance).mp.
7 (Ertugliflozin* or Steglatro).mp.
8 or/1-7
9 exp Glucagon-Like Peptide 1/
10 (GLP-1 agonist* or GLP?1R or GLP-1RA or GLP-1 RA).mp.
11 (Glucagon-like peptide-1 receptor agonist* or GLP-1 receptor agonist*).mp.
12 incretin mimetic*.mp.
13 (exenatide or Byetta or Bydureon or liraglutide or Victoza or lixisenatide or adlyxin or Lyxumia or dulaglutide or Trulicity or semaglutide or Ozempic).mp.
14 or/9-13
15 "Drug Related Side Effects and Adverse Reactions"/
16 ae.fs.
17 co.fs.
18 (side-effect* or side effect*).mp.
19 (adverse adj2 (outcome* or event* or effect* or reaction*)).mp.
20 (serious adj2 event*).mp.
21 complication*.mp.
22 harm*.mp.
23 (safe or safety).mp.
24 toxicit*.mp.
25 yellow card?.ti,ab.
26 hypoglyc?emia.ti,ab.
27 amputation*.ti,ab.
28 (ketoacidosis or lactic acidosis).ti,ab.
29 infection*.ti,ab.
30 injur*.ti,ab.
31 pancreatitis.ti,ab.
32 retinopathy.ti,ab.
33 (kidney or renal).ti,ab.
34 or/15-33
35 (8 or 14) and 34
36 limit 35 to english language
37 (((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.
38 36 and 37
39 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab. or observational.ti,ab.

40 registries/ or registr*.ti,ab.
41 (FDA Adverse Event Reporting System or FAER?).ti,ab.
42 or/39-41
43 36 and 42
44 43 not 38
45 animals/ not (animals/ and humans/)
46 44 not 45

CENTRAL

Date of search: 2 October 2018

#1 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees
#2 side effect* or side-effect*
#3 (adverse or serious) near/3 (outcome* or event* or effect* or reaction*)
#4 toxicit*
#5 safety or safe
#6 complication*
#7 harm*
#8 Yellow Card*
#9 hypoglycemia or hypoglycaemia
#10 amputation*
#11 ketoacidosis or lactic acidosis
#12 infection*
#13 injur*
#14 pancreatitis
#15 retinopathy
#16 kidney or renal
#17 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE]
#18 MeSH descriptor: [] explode all trees and with qualifier(s): [complications - CO]
#19 {OR #1-#18} 547560
#20 sodium-glucose cotransporter 2 inhibit* or sodium-glucose co-transporter 2 inhibit*
#21 sodium glucose cotransporter 2 inhibit* or sodium glucose co-transporter 2 inhibit* or sodium-glucose cotransporter-2 inhibit*
#22 SGLT-2 inhibit* or SGLT-2i* or SGLT 2 inhibit*
#23 sglt2i* or sglt2
#24 Gliflozin*
#25 Canagliflozin* or Invokana or Sulisent or Prominad
#26 Dapagliflozin* or Forxiga or Farxiga
#27 Empagliflozin* or Jardiance
#28 Ertugliflozin* or Steglatro
#29 {OR #20-#28}
#30 MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees
#31 GLP-1 agonist* or GLP?1R or GLP-1RA or GLP-1 RA
#32 Glucagon-like peptide-1 receptor agonist* or GLP-1 receptor agonist*
#33 incretin mimetic*
#34 exenatide or Byetta or Bydureon or liraglutide or Victoza or lixisenatide or adlyxin or Lyxumia or dulaglutide or Trulicity or semaglutide or Ozempic
#35 76-#34-#34-#34-#34
#36 #29 OR #35
#37 #36 AND #19

#38 (cohort or longitudinal or prospective or retrospective or observational):ti,ab,kw
#39 registr*
#40 FDA Adverse Event Reporting System or FAER?
#41 {OR #38-#40}
#42 #37 AND #41 in Trials

PubMed (Publisher Supplied)
Date of search: 2 October 2018

#1 Search (((((((sodium-glucose co?transporter 2 inhibit*[Title/Abstract] OR sodium glucose cotransporter 2 inhibit*[Title/Abstract] OR sodium-glucose cotransporter-2 inhibit*[Title/Abstract])) OR (SGLT-2 inhibit*[Title/Abstract] OR SGLT-2i*[Title/Abstract] OR SGLT2i[Title/Abstract] OR SGLT2[Title/Abstract])) OR Gliflozin*[Title/Abstract]) OR (Canagliflozin*[Title/Abstract] OR Invokana[Title/Abstract] OR Sulisent[Title/Abstract] OR Prominad[Title/Abstract])) OR (Dapagliflozin*[Title/Abstract] OR Forxiga[Title/Abstract] OR Farxiga[Title/Abstract])) OR (Empagliflozin*[Title/Abstract] OR Jardiance[Title/Abstract])) OR (Ertugliflozin*[Title/Abstract] OR Steglatro[Title/Abstract])

#2 Search ((((GLP-1 agonist*[Title/Abstract] OR GLP?1R[Title/Abstract] OR GLP-1RA[Title/Abstract] OR GLP-1 RA[Title/Abstract])) OR (Glucagon-like peptide-1 receptor agonist*[Title/Abstract] OR GLP-1 receptor agonist*[Title/Abstract])) OR incretin mimetic*[Title/Abstract]) OR (exenatide[Title/Abstract] OR Byetta[Title/Abstract] OR Bydureon[Title/Abstract] OR liraglutide[Title/Abstract] OR Victoza[Title/Abstract] OR lixisenatide[Title/Abstract] OR adlyxin[Title/Abstract] OR Lyxumia[Title/Abstract] OR dulaglutide[Title/Abstract] OR Trulicity[Title/Abstract] OR semaglutide[Title/Abstract] OR Ozempic[Title/Abstract])

#3 Search #1 OR #2

#4 Search ((((((((((side-effect*[Title/Abstract] OR side effect*[Title/Abstract])) OR (adverse outcome*[Title/Abstract] OR adverse event*[Title/Abstract] OR adverse effect*[Title/Abstract] OR adverse reaction*[Title/Abstract])) OR serious event*[Title/Abstract]) OR (complication*[Title/Abstract] OR harm*[Title/Abstract] OR toxicit*[Title/Abstract])) OR (safe[Title/Abstract] OR safety[Title/Abstract])) OR yellow card*[Title/Abstract]) OR (hypoglycemia[Title/Abstract] OR hypoglycaemia[Title/Abstract])) OR (amputation*[Title/Abstract] OR infection*[Title/Abstract] OR injur*[Title/Abstract])) OR pancreatitis[Title/Abstract]) OR (ketoacidosis[Title/Abstract] OR lactic acidosis[Title/Abstract])) OR retinopathy[Title/Abstract]) OR (kidney[Title/Abstract] OR renal[Title/Abstract])

#5 Search #3 AND #4

#6 Search medline[sb]

#7 Search #5 NOT #6

#8 Search (((cohort[Title/Abstract] OR longitudinal[Title/Abstract] OR prospective[Title/Abstract] OR retrospective[Title/Abstract] OR observational[Title/Abstract])) OR (FDA Adverse Event Reporting System[Title/Abstract] OR FAER*[Title/Abstract])) OR registr*[Title/Abstract]

#9 Search #7 AND #8

Appendix F. Critical Appraisal Criteria for Randomized Clinical Trials

Domain	Specific Criteria Assessed
Bias arising in the randomization process or due to confounding	• Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics • Eligibility criteria specified
Bias due to departures from intended interventions	• Adequate adherence to treatment
Bias from missing data	• Outcome data are reasonably complete and comparable between groups • Missing data are unlikely to bias results (imputation or completers analysis)
Bias in measurement of outcomes	• Blinding of outcome assessors, providers, patients • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups
Bias in reporting results selectively	• No evidence that measures, analyses, or subgroup analyses are selectively reported

Appendix G. Serious Cases (Deaths) Reported in the FDA Adverse Events Reporting System

Appendix G Table 1. Serious Cases (Deaths) Reported in the FDA Adverse Events Reporting System for Glucagon-Like Peptide-1 (GLP-1) Agonists, by Medication

Medication	FDA Approval Year	Serious cases (deaths)	Hypo-glycemia	Amputation	Acute Pancreatitis	Diabetic Retinopathy	Renal Harms	Pancreatic Carcinoma	Breast Cancer	Bile Duct and Gallbladder Disease	Cardiac failure	Anaphylactic reactions
Exenatide (Byetta)	2005	11,853 (1,462)	263 (21)	Leg amputation 3 (0) Toe amputation 5 (0)	820 (59)	19 (3)	Acute renal failure*: 376 (60) Renal impairment: 90 (5)	1,133 (741)	71 (3)	Bile duct cancer 18 (10) Gallbladder disorder 62 (10)	44 (10)	50 (1) Anaphylactic shock 20 (0)
Exenatide extended-release (Bydureon)	2012	2,943 (159)	59 (3)	Leg amputation 1 (0) Toe amputation 2 (0)	57 (3)	1 (0)	Acute renal failure: 76 (7) Renal impairment: 23 (0)	74 (33)	10 (0)	Bile duct cancer 1 (0) Gallbladder disorder 5 (1)	9 (2)	31 (0) Anaphylactic shock 8 (0)
Liraglutide** (Victoza)	2009	8,246 (724)	92 (8)	Leg amputation 3 (0) Toe amputation 8 (0)	558 (17)	12 (0)	Acute renal failure: 233 (24) Renal impairment: 38 (2)	725 (362)	37 (0)	Bile duct cancer 12 (4) Gallbladder disorder 29 (4)	30 (4)	19 (0) Anaphylactic shock 6 (1)
Albiglutide (Tanzeum)	2014	448 (16)	6 (0)	Leg amputation 1 (0) Toe amputation 1 (0)	17 (0)	3 (0)	Acute renal failure: 10 (0) Renal impairment: 10 (0)	1 (0)	1 (0)	Bile duct cancer 0 Gallbladder disorder 1(0)	5 (0)†	1 (0) Anaphylactic shock 0
Dulaglutide (Trulicity)	2014	2,698 (151)	52 (1)	Leg amputation 1 (0) Toe amputation 0 (0)	68 (0)	5 (0)	Acute renal failure: 70 (1) Renal impairment: 21 (0)	43 (7)	8 (0)	Bile duct cancer 3 (0) Gallbladder disorder 5 (0)	22 (6)	17 (1) Anaphylactic shock 4 (1)
Lixisenatide (Adlyxin)	2016	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	Acute renal failure: 0 (0) Renal impairment: 0 (0)	0 (0)	0 (0)	Bile duct cancer 0 (0) Gallbladder disorder	0 (0)	0 (0) Anaphylactic shock 0 (0)
Semiglutide (Ozempic)	2017	32 (2)	1 (0)	Leg amputation 0 (0) Toe amputation 0 (0)	2 (0)	0 (0)	Acute renal failure: 2 (0) Renal impairment: 0 (0)	0 (0)	0 (0)	Bile duct cancer 0 (0) Gallbladder disorder 1 (0)	0 (0)	0 (0) Anaphylactic shock 0 (0)

Abbreviations: AERS = Adverse Event Reporting System; FDA = US Food and Drug Administration; GLP-1 = Glucagon-Like Peptide-1

Notes:
* Reported as acute kidney injury in FDA AERS
† Congestive, not reported for other categories

Appendix G Table 2. Serious Cases (Deaths) Reported in the FDA Adverse Events Reporting System for Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors, by Medication

Medication	FDA Approval Year	Serious cases (deaths)	Hypo-glycemia	Lower limb amputation	Genitourinary infections	Other Genitourinary harms	Acute Pancreatitis	Renal harms	Fracture	Cardiac failure	Diabetic Keto-acidosis	Gangrene	Anaphylactic reactions
Canagliflozin (Invokana)	2013	9,874 (241)	70 (1)	Leg amputations 320 (7) Toe amputations 888 (4)	Genital infection: 3 (1) Balanitis: 1 (0) Vulvovaginal mycotic infection: 37 (0) UTI: 594 (10)	Phimosis: 11 (0) Circumcision: 1 (0)	64 (2)	Acute renal failure: 1,150 (44) Renal impairment: 117 (1)	11 (0)	14 (0)	2,482 (43)	354 (1)	13 (0) Anaphylactic shock: 2 (0)
Dapagliflozin (Farxiga)	2014	1,026 (58)	7 (0)	Leg amputations 1 (1) Toe amputations 9 (0)	Genital infection: 2 (0) Balanitis: 0 (0) Vulvovaginal mycotic infection: 11 (0) UTI: 71 (2)	Phimosis: 0 (0) Circumcision: 0 (0)	21 (0)	Acute renal failure: 68 (3) Renal impairment: 21 (1)	3 (1)	5 (3)	266 (2)	0 (0)	3 (0) Anaphylactic shock: 3 (1)
Empagliflozin (Jardiance)	2014	2,661 (100)	29 (1)	Leg amputation 13 (0) Toe amputation 35 (0)	Genital infection: 4 (0) Balanitis: 8 (0) Vulvovaginal mycotic infection: 37 (0) UTI: 107 (4)	Phimosis: 8 (0) Circumcision: 1 (0)	20 (3)	Acute renal failure: 79 (0) Renal impairment: 24 (0)	3 (0)	16 (3)	806 (8)	9 (0)	5 (0) Anaphylactic shock: 3 (0)
Ertugliflozin (Steglatro)	2017	3 (0)	0 (0)	0 (0)	Genital infection: 0 (0) Balanitis: 0 (0) Vulvovaginal mycotic infection: 0 (0) UTI: 1 (0)	Phimosis: 0 (0) Circumcision: 0 (0)	0 (0)	Acute renal failure: 0 (0) Renal impairment: 0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0) Anaphylactic shock: 0 (0)

Abbreviations: AERS = Adverse Event Reporting System; FDA = US Food and Drug Administration; SGLT-2 = Sodium-Glucose Cotransporter-2

Notes:
* Reported as acute kidney injury in FDA AERS

Appendix H. Detailed Quality Assessment Results for Randomized Controlled Trials

Study	Bias arising in the randomization process or due to confounding	Bias due to departures from intended interventions: Adequate adherence to treatment	Bias from missing data:	Bias in measurement of outcomes	Bias in reporting results selectively	Funding source	Other important threats to validity	Overall quality
DECLARE-TIMI 58 Wiviott, 2018[21]	**Valid random assignment:** Yes **Allocation concealed:** Yes **Balance in BL characteristics:** Yes **Eligibility criteria specified:** Yes	Uncertain. If adherence defined in terms of discontinuation, 79% of IG patients and 75% of CG patients were adherent. The proportion of total time receiving assigned treatment is not reported.	**Attrition and differential follow-up:** 21% of IG patients and 25% of CG patients discontinued study medication, vital status known for nearly all patients in both groups **Handling of missing data:** Completers only, no imputation performed	**Measurements: equal, reliable, valid:** Likely **Blinding of 1) outcomes assessors:** Yes **2) providers:** Yes **3) patients:** Yes	Not detected	Industry	Patients participating in run-in period could be excluded from randomization at the investigator's discretion; 8,538/25,698 (33.2%) were excluded in this way.	Good
Harmony Outcomes Hernandez, 2018[17]	**Valid random assignment:** Yes **Allocation concealed:** Yes **Balance in BL characteristics:** Yes **Eligibility criteria specified:** Yes	Yes. If adherence defined in terms of discontinuation, 76% of IG patients and 73% of CG patients were adherent. If defined as a proportion of total time receiving assigned treatment, 87% of IG patients and 85% of CG patients were adherent.	**Attrition and differential follow-up:** 24% of IG patients and 27% of CG patients discontinued study medication, vital status known for 99.7% of patients in both groups **Handling of missing data:** Completers only, no imputation performed	**Measurements: equal, reliable, valid:** Likely. A study-specific questionnaire was used to collect information on diabetes mgmt., but it wasn't relevant to the primary analysis. **Blinding of 1) outcomes assessors:** Yes **2) providers:** Yes **3) patients:** Yes	Not detected	Industry	None identified	Good
CANVAS Neal, 2017[22]	**Valid random assignment:** Yes **Allocation concealed:** Yes **Balance in BL characteristics:** Yes **Eligibility criteria specified:** Yes	If adherence is defined in terms of discontinuation, there was 29.2% discontinuation in SGLT-2 group, 29.9% in placebo group, which are acceptable. If adherence is defined as time on treatment as a proportion of time of follow-up, SGLT-2 patients were adherent 79.8% of the time, and placebo patients were adherent 78.5% of the time.	**Attrition and differential follow-up:** Overall %: 4% IG%: 3.9% CG%: 4.2% **Handling of missing data:** Multiple imputation	**Measurements: equal, reliable, valid:** Likely **Blinding of 1) outcomes assessors:** Yes **2) providers:** Yes **3) patients:** Yes	Not detected	Industry	Counts of primary-outcome events not provided, and can't be estimated from reported data. Analyses of outcomes employed sequential testing, and non-significant findings for all-cause and CVD mortality are not considered meaningful.	Good

Study	Bias arising in the randomization process or due to confounding	Bias due to departures from intended interventions: Adequate adherence to treatment	Bias from missing data:	Bias in measurement of outcomes	Bias in reporting results selectively	Funding source	Other important threats to validity	Overall quality
EXSCEL Holman, 2017[18]	**Valid random assignment:** Yes **Allocation concealed:** Yes **Balance in BL characteristics:** Yes **Eligibility criteria specified:** Yes	If adherence is defined in terms of discontinuation, this is uncertain (43% discontinuation in GLP-1 group, 45.2% in placebo group). If defined as the proportion of time patients received the trial regimen relative to the time they'd be expected to do so, GLP-1 patients were adherent 76% of the time, as were 75% of placebo patients; these appear adequate.	**Attrition and differential follow-up:** Overall %: 3.8% IG%: 3.6% CG%: 4.1% **Handling of missing data:** Not reported	**Measurements: equal, reliable, valid:** Likely. **Blinding of** **1) outcomes assessors:** Yes **2) providers:** Not reported **3) patients:** Yes	Not detected	Industry	None identified	Good
LEADER Marso, 2016[20]	**Valid random assignment:** Yes **Allocation concealed:** Yes **Balance in BL characteristics:** Yes **Eligibility criteria specified:** Yes	Uncertain. Discontinuation rates not reported. Mean % of trial time in which patients received assigned treatment: 84% for GLP-1, 83% for placebo. AE leading to discontinuation significantly higher in GLP-1 (9.5%) vs placebo (7.3%).	**Attrition and differential follow-up:** Overall %: 3.2% IG%: 3.0% CG%: 3.4% **Handling of missing data:** LOCF for medication and medical history data. First/last days of relevant month/year used to impute missing date information.	**Measurements: equal, reliable, valid:** Likely **Blinding of** **1) outcomes assessors:** Yes **2) providers:** Yes **3) patients:** Yes	Not detected	Industry, with some government support	None identified	Good
SUSTAIN-6 Marso, 2016[19]	**Valid random assignment:** Yes **Allocation concealed:** Yes **Balance in BL characteristics:** Mostly, duration of diabetes significantly shorter in placebo patients, and analyses didn't adjust for this variable, but it's unclear that the difference is clinically meaningful (13.6 years in placebo pts vs 14.2 years in GLP1 patients). Otherwise yes. **Eligibility criteria specified:** Yes	Yes. If adherence is defined in terms of discontinuation, there was 21.2% discontinuation in GLP-1 group and 18.8% in placebo group. If defined as the proportion of time patients received their assigned regimen, GLP-1 patients were adherent 86.5% of the time, as were 89.5% of placebo patients.	**Attrition and differential follow-up:** Overall %: 2% IG%: 1.5% CG%: 2.4% **Handling of missing data:** Not reported	**Measurements: equal, reliable, valid:** Likely **Blinding of** **1) outcomes assessors:** Mostly. Not blinded on peripheral revascularization outcome **2) providers:** Not reported **3) patients:** Yes	Not detected	Industry	None identified	Good

Study	Bias arising in the randomization process or due to confounding	Bias due to departures from intended interventions: Adequate adherence to treatment	Bias from missing data:	Bias in measurement of outcomes	Bias in reporting results selectively	Funding source	Other important threats to validity	Overall quality
ELIXA Pfeffer, 2015[9] #60	**Valid random assignment:** Yes **Allocation concealed:** Yes **Balance in BL characteristics:** Uncertain. GLP-1 group at baseline was significantly younger, higher eGFR, higher A1c, less history of stroke. Differences may not be clinically meaningful, but primary outcome analyses didn't adjust for these variables **Eligibility criteria specified:** Yes	Uncertain. If adherence is defined in terms of discontinuation, the rates aren't excessive, but are significantly higher in the GLP-1 group (27.5%) vs placebo (24.0%). Compliance in terms of medication taken vs medication dispensed was studied, but the data are not presented.	**Attrition and differential follow-up:** Overall %: 3.8% IG%: 3.7% CG%: 3.9% **Handling of missing data:** In general, only data from completers used.	**Measurements: equal, reliable, valid:** Likely **Blinding of** **1) outcomes assessors:** Yes **2) providers:** Yes **3) patients:** Yes	Not detected	Industry	None identified	Fair
EMPAREG-OUTCOME Zinman, 2015[23] Fitchett, 2016[31] Inzucchi, 2018[33] Wanner, 2016[32]	**Valid random assignment:** Yes **Allocation concealed:** Yes **Balance in BL characteristics:** Uncertain. Renal outcomes paper reports that HDL-C and peripheral artery disease prevalence are higher in SGLT-2 patients with lower eGFR, and analyses don't control for these variables. These differences are not apparent when the study groups aren't stratified by eGFR. **Eligibility criteria specified:** Yes	If adherence is defined in terms of discontinuation, yes; there was 23.4% discontinuation in SGLT-2 groups and 29.3% in placebo group, though no test for significance of difference was reported. Investigators assessed compliance in terms of taking all prescribed tablets, but these data are not provided.	**Attrition and differential follow-up:** Overall %: 3% IG%: 3.1% (weighted mean of 2 groups) CG%: 2.9% **Handling of missing data:** Completers only, no imputation performed for primary analysis	**Measurements: equal, reliable, valid:** Likely **Blinding of** **1) outcomes assessors:** Yes **2) providers:** Yes **3) patients:** Yes	Not detected	Industry	A higher % of placebo patients received other cardiovascular medications during the trial. Sequential testing of primary and secondary outcomes was used, giving priority to non-inferiority testing, but the primary outcome and primary outcome and hospitalization for unstable angina were assessed	Fair+

Abbreviations: AE = adverse event; BL = baseline; CANVAS = Canagliflozin Cardiovascular Assessment Study; CG = control group; CVD = cardiovascular disease; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; eGFR = estimated glomerular filtration rate; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG OUTCOME = (Empagliflozin) Cardiovascular Outcome Event Trial; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; GLP-1 = Glucagon-like peptide-1; A1c = hemoglobin A1c; HDL = high-density lipoprotein; IG = intervention group; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LOCF = last observation carried forward; SLGT-2 = Sodium-glucose Cotransporter-2 inhibitor; SUSTAIN-6 = Trail to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes