Reviews in Cardiovascular Medicine

IMR Press

TREATMENT UPDATE

Cardiorenal Outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME Trials: A Systematic Review

Aaron Y. Kluger[1,2,*], Kristen M. Tecson[1,2,3], Clay M. Barbin[4,5], Andy Y. Lee[4,5], Edgar V. Lerma[6], Zachary P. Rosol[4,5], Janani Rangaswami[7,8], Norman E. Lepor[9,10], Michael E. Cobble[11] and Peter A. McCullough[1,3,4,5]

[1] *Baylor Heart and Vascular Institute, Dallas, TX, 75226*

[2] *Baylor Scott & White Research Institute, Dallas, TX, 75226*

[3] *Texas A & M College of Medicine Health Science Center, Dallas, TX, 75226*

[4] *Baylor University Medical Center, Dallas, TX, 75226*

[5] *Baylor Heart and Vascular Hospital, Dallas, TX, 75226*

[6] *UIC/Advocate Christ Medical Center, Oak Lawn, IL, 60453*

[7] *Einstein Medical Center, Philadelphia, PA, 19141*

[8] *Sidney Kimmel College of Thomas Jefferson University, Philadelphia, PA, 19107*

[9] *David Geffen School of Medicine at UCLA, Los Angeles, CA, 90095*

[10] *Cedars-Sinai Medical Center, Los Angeles, CA, 90048*

[11] *University of Utah School of Medicine, Salt Lake City, UT, 84132*

*Correspondence to Aaron Y. Kluger: aaron.kluger@bswhealth.org

DOI: 10.31083/j.rcm.2018.02.907

In this systematic review, we sought to summarize the 3 recent sodium-glucose cotransporter 2 inhibitor (SGLT2i) trials (Dapagliflozin Effect on CardiovasculAR Events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, and Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME)) and to explore the potential causes for their different results. We found that the major adverse cardiovascular event rates per 1000 patient-years for drug and placebo, as well as the corresponding relative risk reductions, were 22.6, 24.2, 7%; 26.9, 31.5, 14%; 37.4, 43.9, 14% for DECLARE-TIMI 58, CANVAS, and EMPA-REG OUTCOME, respectively. DECLARE-TIMI 58 had the fewest cardiorenal events (across treatment and control arms) and EMPA-REG OUTCOME the most. DECLARE-TIMI 58 used alternative inclusion criterion for baseline renal function (creatinine clearance $\geq$ 60 mL/min) compared to the other trials (estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m^2 body-surface area). Therefore, the DECLARE-TIMI 58 study cohort had higher eGFR (mean eGFR 85.2 mL/min/1.73 m^2 compared to 76.5 and 74 in CANVAS and EMPA-REG OUTCOME, respectively); this may have caused the difference in results. Additionally contributing to the high event rate in EMPA-REG OUTCOME was the requirement of prior confirmed cardiovascular disease (CVD), resulting in 99.2% of patients with CVD compared to only 65.6% and 40.6% in CANVAS and DECLARE-TIMI 58, respectively (which did not require CVD). In conclusion, there is a need for large-scale studies of SGLT2i with matching inclusion/exclusion criteria and appropriate endpoints to ensure a truly direct comparison of the drugs.

Keywords

SGLT-2 inhibitor; empagliflozin; canagliflozin; dapagliflozin; ertugliflozin; sotagliflozin; CANVAS; EMPA-REG OUTCOME; DECLARE-TIMI 58

1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with cardiovascular disease (CVD) and is an independent risk factor for heart failure (HF) with preserved and reduced ejection fraction; the HF hospitalization rate is approximately 4 times higher for patients with T2DM than for nondiabetic patients (World Health Organization , 2016; Mozaffarian et al., 2016; Fitchett et al., 2017; Lloyd-Jones et al., 2002; Owan et al., 2006; Zelniker et al., 2018). T2DM is also a risk factor for chronic kidney disease (CKD) and end-stage renal disease (Jha et al., 2013; Kastarinen et al., 2010). In addition to its cardiorenal risk, T2DM is associated with foot ulcers and other non-healing lower extremity wounds, deep tissue osteomyelitis, metabolic bone disease, anemia, pancreatitis, and diabetic ketoacidosis (Armstrong et al., 2017; Gilbert and Pratley, 2015; Thomas et al., 2006).

Many T2DM medications have significant adverse events. Subcutaneous insulin is associated with more than a 6-fold increased risk of proliferative retinopathy (Penman et al., 2016). Thiazolidinediones are linked to edema and increased risk for HF hos-

pitalization and/or cardiovascular (CV) death (Kaul et al., 2010; Home et al., 2009; Lincoff et al., 2007). Oral sulfonylureas are mechanistically associated with hypoglycemia, myocardial infarction (MI), stroke, and CV death (Douros et al., 2018; Powell et al., 2018). Compared to newer antidiabetic medications, sulfonylureas are associated with more CV events (O'Brien et al., 2018). Glucagon-like peptide-1 agonists were initially associated with pancreatitis and dipeptidyl peptidase-4 (DPP-4) inhibitors with HF, but further analyses challenged these associations (Li et al., 2014; Scirica et al., 2013; Kaneko and Narukawa, 2017).

The 2008 United States Food and Drug Administration (FDA) anti-hyperglycemic medication guidelines required that new drugs not increase the risk for MI, stroke, or CV death as evaluated in cardiovascular outcomes trials (CVOTs); however, it did not mention HF, CKD, or other organ system diseases despite their associations with T2DM (McMurray et al., 2014; Zannad et al., 2016). Four sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been approved by the FDA based on this guidance: canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro); a fifth, sotagliflozin (Zynquista) is in clinical development. SGLT2i represent a promising new class for the treatment of patients with T2DM and established CVD, as demonstrated by the 2018 American College of Cardiology Expert Consensus Decision (Writing et al., 2018).

Three of the approved SGLT2i (canagliflozin, empagliflozin, dapagliflozin) have been surveilled for CV effects in large randomized clinical trials (Zinman et al., 2015; Neal et al., 2013; Wiviott et al., 2018). The sponsors of these clinical trials were free to make decisions about the populations to be studied, including the presence and severity of baseline heart and kidney disease. The 3 SGLT2i differ in the minimum recommended eGFR for use due to expected reduced pharmacodynamic response with diminishing eGFR (Scheen, 2015; Scheen A, 2015). This led the sponsors to draw separate lower renal function bounds for inclusion into the trials; 2 used the estimated glomerular filtration rate (eGFR) bounds and 1 used creatinine clearance (CrCl).

This systematic review will explore the 3 SGLT2i trials and demonstrate how non-standard inclusion criteria, renal function equations, and event definitions may have caused the different results of the trials.

2. Methods

This systematic review was conducted according to PRISMA guidelines (Moher et al., 2009). We searched ClinicalTrials.gov for the terms (*sglt2 inhibitor* OR *canagliflozin* OR *dapagliflozin* OR *empagliflozin* OR *ertugliflozin* OR *sotagliflozin*) AND cardiovascular. Our search strategy included any trials from January 1, 2012 to November 30, 2018 and filtered for completed interventional trials. Randomized clinical trials were included if they were in English, completed by November 30, 2018, and studied cardiovascular and renal outcomes; we reviewed these trials' original methodology and results papers.

As some results were not present in all trials, we relied on imaging analysis software to estimate the cumulative incidence at 3 years from the Kaplan-Meier (KM) estimate curves (Mitchell et al., 2018). When the KM curves desired for this analysis were not provided, we used the event rate per 1000 patient-years to calculate a ratio for the desired endpoint and applied this ratio to the known composite cumulative incidence to estimate the individual cumulative incidence for the desired outcome. For example, the dapagliflozin KM curve for the composite of HHF or CV death was provided (thus its cumulative incidence was calculable); the curve for HHF alone was not. The HHF event rate was 6.2% and the HHF or CV death event rate was 12.2%; we calculated 0.062 / 0.122 = 0.5082 and multiplied the composite cumulative incidence by this ratio, yielding the HHF cumulative incidence. Additionally, some p-values were not provided, so we calculated them from the hazard ratio (HR) and 95% confidence interval (CI) (Altman and Bland, 2011). Finally, we calculated the relative risk reduction percentages from the HR.

3. Results

30 relevant clinical trials were screened and assessed for eligibility. After applying inclusion/exclusion criteria, 3 randomized clinical trials with 34,322 adult patients were ultimately included.

3.1. The EMPA-REG OUTCOME Trial

The first SGLT2i trial to focus on CV and renal outcomes, the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) randomized double-blind controlled trial assigned 7020 patients with T2DM and CVD to 10mg or 25mg of empagliflozin daily or placebo over a 3.1 year mean and median follow-up period (Zinman et al., 2015). Empagliflozin is recommended for patients with eGFR $\geq$ 45 mL/min/1.73 m^2 body-surface area; patients in this trial were required to have eGFR > 30 mL/min/1.73 m^2 (Mozaffarian et al., 2016; Drugs.com, 2018). Investigators used the Modification of Diet in Renal Disease (MDRD) equation to calculate eGFR. 99.2% of patients had established CVD; the mean eGFR was 74 ± 21 mL/min/1.73 m^2 1819 (25.9%) patients had eGFR < 60 mL/min/1.73 m^2 and 5201 (74.1%) patients had eGFR > 60 mL/min/1.73 m^2 (Zinman et al., 2015, 2014). Duration of T2DM was 17.9% < 5 years, 25.1% 5-10 years, and 57% > 10 years in the empagliflozin patients compared to 18.1% < 5 years, 24.5% 5-10 years, and 57.4% > 10 years in the placebo patients.

The primary endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) occurred in 10.5% of empagliflozin patients compared to 12.1% of placebo patients (rate per 1000 patient-years = 37.4 vs. 43.9, respectively; HR = 0.86, 95% CI = 0.74-0.99, p = 0.04). HF hospitalization (HHF) occurred in 2.7% of empagliflozin patients compared to 4.1% of placebo patients (rate per 1000 patient-years = 9.4 vs. 14.5, HR = 0.65, 95% CI = 0.50-0.85, $p = 0.002$). HHF or CV death (excluding fatal stroke) occurred in 5.7% of empagliflozin patients compared to 8.5% of placebo patients (rate per 1000 patient-years = 19.7 vs. 30.1, HR = 0.66, 95% CI = 0.55-0.79, $p < 0.001$).

The 3-year cumulative incidence for the primary endpoint was 10.5% of empagliflozin patients compared to 11.5% of placebo patients; HHF cumulative incidence was 2.8% of empagliflozin patients compared to 3.7% of placebo patients; HHF or CV death cumulative incidence was 5.9% of empagliflozin patients compared to 7.8% of placebo patients.

The investigators studied renal outcomes as well as CV end-

points. The primary composite renal outcome was defined as a doubling of serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73 m^2 initiation of renal-replacement therapy (RRT), or renal death (Wanner et al., 2016). It occurred in 1.7% of empagliflozin patients compared to 3.1% of placebo patients (rate per 1000 patient-years = 6.3 vs. 11.5, HR = 0.54, 95% CI = 0.40-0.75, $p < 0.001$).

3.2. The CANVAS Program

The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program combined the CANVAS and CANVAS-Renal (CANVAS-R) study cohorts into a randomized double-blind controlled trial, assigning 10,142 T2DM patients to daily canagliflozin (100 mg with optional increase to 300 mg) or placebo over a 2.4 year median follow-up period (188.2 week mean follow-up period) (Neal et al., 2013). Unlike EMPA-REG OUTCOME, CANVAS patients were not required to have a history of CVD. Patients aged ≥ 50 years with at least 2 CVD risk factors (but no established CVD) were included in the study. Canagliflozin is recommended for patients with eGFR ≥ 45 mL/min/1.73 m^2 body-surface area and contraindicated for patients with moderate to severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2); study patients were required to have eGFR > 30 mL/min/1.73 m^2 (Mozaffarian et al., 2016; Drugs.com, 2018). Investigators used the MDRD equation to calculate eGFR. 65.6% of patients had established CVD; the mean eGFR was 76.5 ± 20.5 mL/min/1.73 m^2; 2039 (20.1%) patients had eGFR < 60 and 8101 (79.9%) patients had eGFR > 60 mL/min/1.73 m^2(Mozaffarian et al., 2016; Neal et al., 2013; Neuen et al., 2018). Median duration of T2DM was 13.5 ± 7.7 years in the canagliflozin patients compared to 13.7 ± 7.8 years in the placebo patients.

The primary endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) rate per 1000 patient-years was 26.9 for canagliflozin patients compared to 31.5 for placebo patients (HR = 0.86, 95% CI = 0.75-0.97, $p = 0.08$). The HHF rate was 5.5 for canagliflozin patients compared to 8.7 for placebo patients (HR = 0.67, 95% CI = 0.52-0.87, $p = 0.02$). The HHF or CV death rate was 16.3 for canagliflozin patients compared to 20.8 for placebo patients (HR = 0.78, 95% CI = 0.67-0.91, $p = 0.0015$).

The 3-year cumulative incidence for the primary endpoint was 7.4% of canagliflozin patients compared to 9.1% of placebo patients; HHF cumulative incidence was 1.5% of canagliflozin patients compared to 2.7% of placebo patients; HHF or CV death cumulative incidence was 4.1% of canagliflozin patients compared to 6.1% of placebo patients.

The primary composite renal outcome was defined as a 40% reduction in eGFR sustained for at least 2 consecutive measures, need for RRT (chronic dialysis, sustained eGFR < 15 mL/min/1.73 m^2 or kidney transplantation), or renal death (Neal et al., 2013). It occurred with a rate per 1000 patient-years of 5.5 in empagliflozin patients compared to 9.0 in placebo patients (HR = 0.6, 95% CI = 0.47-0.77, $p < 0.001$).

3.3. The DECLARE-TIMI 58 Trial

The Dapagliflozin Effect on CardiovasculAR Events (DECLARE-TIMI 58) randomized double-blind controlled trial assigned 17,160 T2DM patients to 10 mg of dapagliflozin daily or placebo over a 4.2 year median follow-up period (interquartile range (IQR) = 3.9-4.4) (Wiviott et al., 2018). Consistent with CANVAS but unlike EMPA-REG OUTCOME, patients were not required to have a history of CVD. Males aged ≥ 55 years or females aged ≥ 60 years with ≥ 1 CVD risk factor were included in the trial. Baseline renal function varied significantly from EMPA-REG OUTCOME and CANVAS: dapagliflozin is recommended for patients with eGFR ≥ 60 mL/min/1.73 m^2 body-surface area and contraindicated for patients with eGFR < 30; study patients were required to have CrCl ≥ 60 mL/min, but no minimum eGFR was specified (Drugs.com, 2018; Wiviott et al., 2018).

Investigators used the Cockroft-Gault equation to calculate CrCl as part of the cut-off for exclusion criteria and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate eGFR when reporting the composite renal outcomes. 40.6% of patients had established CVD; the mean eGFR was 85.2 mL/min/1.73 m^2 1265 (7.4%) patients had eGFR < 60 and 15895 (92.6%) patients had eGFR > 60 mL/min/1.73 m^2 (Kosiborod et al., 2017). Median duration of T2DM was 11.0 (IQR = 6.0-16.0) years in the dapagliflozin patients compared to 10.0 (IQR = 6.0-16.0) years in the placebo patients.

The primary safety outcome (composite of CV death, nonfatal MI, or nonfatal stroke) occurred in 8.8% of dapagliflozin patients compared to 9.4% of placebo patients (rate per 1000 patient-years = 22.6 vs. 24.2, HR = 0.93, 95% CI = 0.84-1.03, $p = 0.17$). (Note the lack of statistical significance, presumably due to the low number of events across both arms). HHF occurred in 2.5% of dapagliflozin patients compared to 3.3% of placebo patients (rate per 1000 patient-years = 6.2 vs. 8.5, HR = 0.73, 95% CI = 0.61-0.88, $p = 0.0008$). HHF or CV death occurred in 4.9% of dapagliflozin patients compared to 5.8% of placebo patients (rate per 1000 patient-years = 12.2 vs. 14.7, HR = 0.83, 95% CI = 0.73-0.95, $p = 0.005$).

The 3-year cumulative incidence for the primary safety outcome was 6.5% of dapagliflozin patients compared to 7.1% of placebo patients; HHF cumulative incidence was 1.7% of dapagliflozin patients compared to 2.4% of placebo patients; HHF or CV death cumulative incidence was 3.4% of dapagliflozin patients vs. 4.2% of placebo patients (Drugs.com, 2018; Wiviott et al., 2018).

The primary composite renal outcome was defined as ≥ 40% reduction in eGFR to a threshold < 60 mL/min/1.73 m^2 end-stage renal disease (dialysis ≥ 90 days, sustained eGFR < 15 mL/min/1.73 m^2 or kidney transplantation), or renal/CV death. It occurred in 1.5% of dapagliflozin patients compared to 2.8% of placebo patients (rate per 1000 patient-years = 3.7 vs. 7, HR = 0.53, 95% CI = 0.43-0.66, $p < 0.001$) (Wiviott et al., 2018).

4. Discussion

4.1. Cardiovascular Outcomes

Of the 3 SGLT2i CVOTs, EMPA-REG OUTCOME had the most CV events (in both treatment and control arms) and DECLARE-TIMI 58 the fewest (Figure 1, Figure 2). Additionally, EMPA-REG OUTCOME had the largest relative risk reductions across all CV events and DECLARE-TIMI 58 the smallest (Figure 3). Given that all 3 drugs are in the same class and have

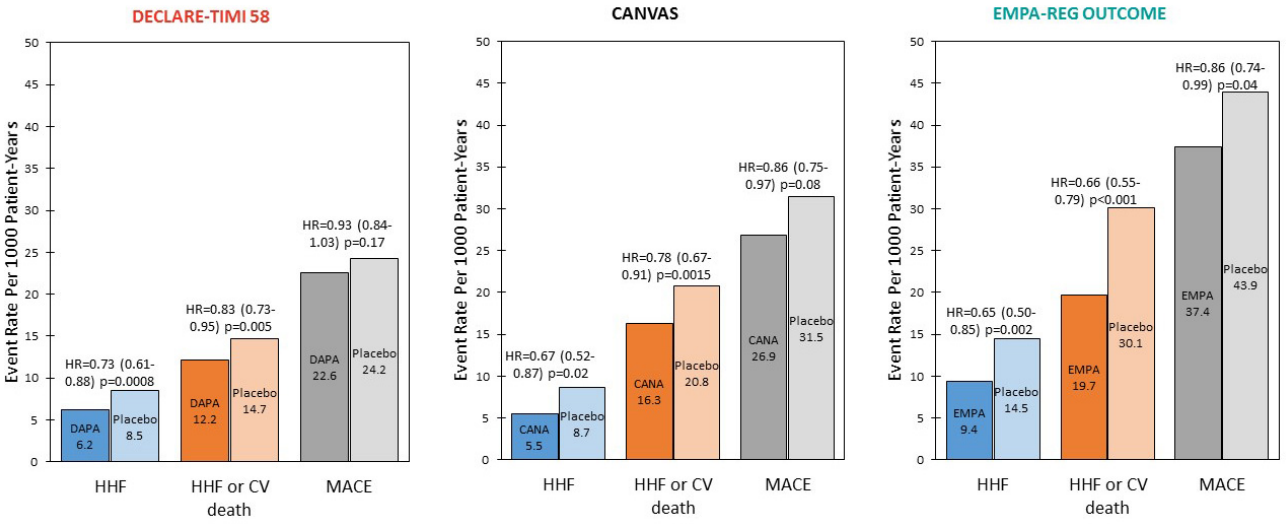

Figure 1. Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) event rates per 1000 patients in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS), and Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trials. Statistical outcomes displayed as hazard ratio (HR) (95% confidence interval) p-value. DAPA=dapagliflozin, CANA = canagliflozin, EMPA = empagliflozin.

similar molecular structures, it is likely that the discrepancies are largely due to study design and selection bias, rather than actual differences between the drugs. Specifically, while CANVAS and EMPA-REG OUTCOME included patients with baseline eGFR > 30 mL/min/1.73 m^2 the DECLARE-TIMI 58 investigators omitted eGFR from the inclusion criteria and instead specified a CrCl ≥ 60 mL/min (Table 1). Additionally, the minimum recommended eGFR for dapagliflozin is ≥ 60 mL/min/1.73 m^2 whereas the cutoff is ≥ 45 for canagliflozin and empagliflozin. These differences resulted in a mean eGFR nearly 10 mL/min/1.73 m^2 higher in DECLARE-TIMI 58 than the other 2 trials (Table 1 and Figure 4). Hence, DECLARE-TIMI 58 patients had more preserved baseline renal function than those in CANVAS and EMPA-REG OUTCOME; given that CKD and decreased eGFR are associated with CV events and mortality, this difference may explain the fewer CV events in DECLARE-TIMI 58 and the lack of a superiority finding (Chang et al., 2013; Sarnak et al., 2003; Werner et al., 2018).

In addition to the inconsistent levels of baseline renal function, varying baseline CV risk in the 3 outcome trials may have further contributed to the different event rates. EMPA-REG OUTCOME required established CVD, while it was merely optional for the other trials, resulting in nearly 100% of EMPA-REG OUTCOME patients having CVD compared to only 40.6% of DECLARE-TIMI 58 and 65.6% of CANVAS patients (Figure 4). Since established CVD is a significant risk factor for future CV events, this may have led to the increased number of events in EMPA-REG OUTCOME and the low number of events in DECLARE-TIMI 58 (Wattanakit et al., 2005). Lastly, some of the event criteria for EMPA-REG OUTCOME were less stringent than those in the other trials; for example CANVAS and DECLARE-TIMI 58 required a 24-hour length-of-stay (LOS) for HHF while EMPA-REG OUTCOME only a 12-hour LOS. This may have further inflated the event rates in EMPA-REG OUTCOME.

These plausible explanations are supported by recent studies. Cavallari and Maddaloni compared the 3 CVOTs and pointed out the differences in baseline CVD (though they did not mention the differences in baseline eGFR) (Cavallari and Maddaloni, 2019). The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2i (CVD-REAL) large-scale (n = 309,056) multinational observational cohort study found no significant differences in CV outcomes between the SGLT2i studied (canagliflozin, dapagliflozin, empagliflozin) (Kosiborod et al., 2017). In the supplemental CVD-REAL 2 trial (n = 470,128), the investigators found no difference in outcomes between patient subgroups (Kosiborod et al., 2018). The CVD-REAL 1 and 2 trials suggest an overall class effect, with no SGLT2i demonstrating significant superiority over the others at reducing CV risk. We suspect that had the 3 CVOTs' inclusion/exclusion criteria been the same, the trials would have produced similar results. Additionally, Zelniker et al. found that SGLT2i reduced the risk of CV outcomes regardless of baseline CVD, but the magnitude of SGLT2i benefit depended on baseline renal function – lower renal function was associated with greater reductions in HHF (Zelniker et al., 2018).

4.2. Renal Outcomes

Similar to the CV events, EMPA-REG OUTCOME had the most renal events (in both treatment and placebo arms) and DECLARE-TIMI 58 (Figure 5) the fewest. We suspect that the difference in renal events is due to differing baseline renal function: DECLARE-TIMI 58 had the highest mean baseline eGFR, so its study population experienced fewer renal events (Table 1). The trials also vary slightly in their definitions of the renal composite outcome (Table 1). For example, EMPA-REG OUTCOME included a doubling of serum creatinine with eGFR < 45 mL/min/1.73 m^2 (this equates to an approximate 40% reduction in eGFR) while the other 2 trials included a 40% reduction in eGFR instead. These alternate definitions may have affected the event rates. It is interesting to

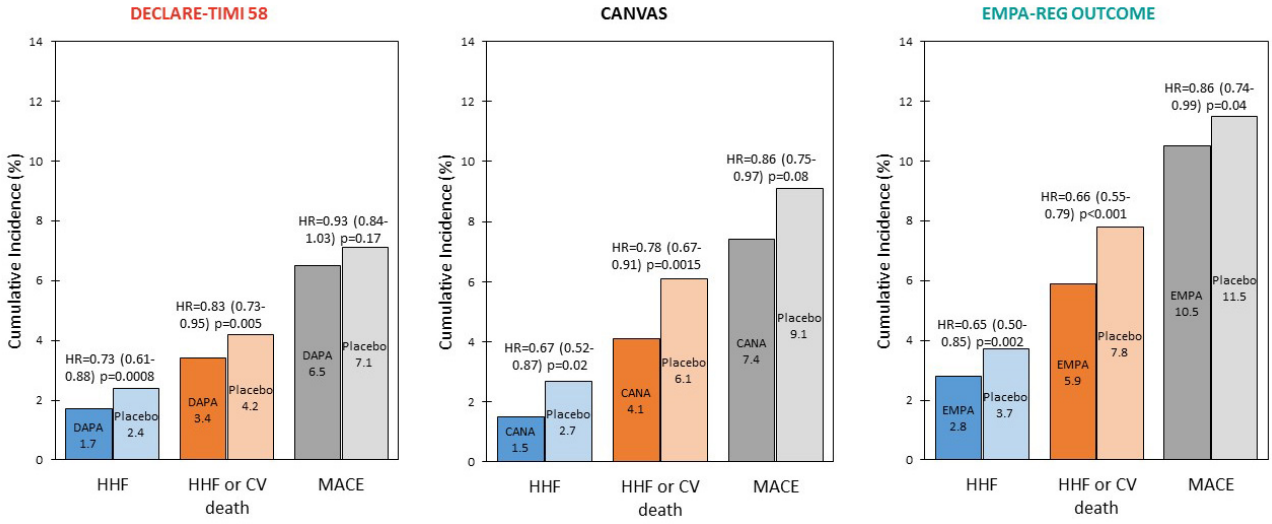

Figure 2. Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) cumulative incidence percentages at 3 years in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS), and Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trials. Statistical outcomes displayed as hazard ratio (HR) (95% confidence interval) p-value. DAPA = dapagliflozin, CANA = canagliflozin, EMPA = empagliflozin.

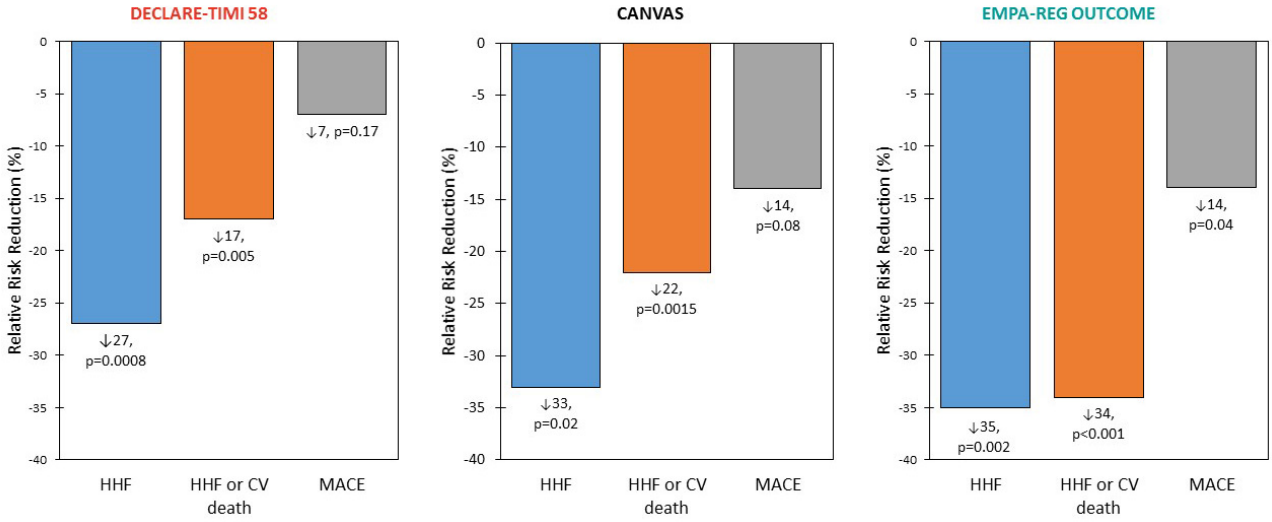

Figure 3. Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) relative risk (RR) reduction percentages in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS), and Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trials. Statistical outcomes displayed as RR reduction percentage, p-value. RR reduction percentages were calculated from hazard ratios.

note that while we would expect the inclusion of CV death to increase the number of composite renal events in DECLARE-TIMI 58 (the other trials only included renal death), this does not seem to have appreciably occurred (Figure 5).

The glomerular filtration estimating equations may have played a role in the disparate results. CANVAS and EMPA-REG OUTCOME used the MDRD equation to calculate eGFR, while DECLARE-TIMI used the CKD-EPI equation. The MDRD equation is valid in patients with a mean measured glomerular filtration rate (GFR) of 40 mL/min/1.73 m^2 but underestimates higher values of measured GFR (≥ 60 mL/min/1.73 m^2) (Stevens et al., 2011). This may lead to misclassification to a lower renal function category and over-diagnosis of CKD. The CKD-EPI equation was developed using a wider range of GFRs than MDRD; it is demonstrably a superior estimate of measured GFR and is more prognostic for clinical events especially at higher values (McCullough et al., 2015). Therefore, the National Kidney Foundation has recommended replacing the MDRD equation with the CKD-EPI equation (Levey et al., 2009; Becker and Vassalotti , 2010). The use of the MDRD equation in CANVAS and EMPA-REG OUTCOME

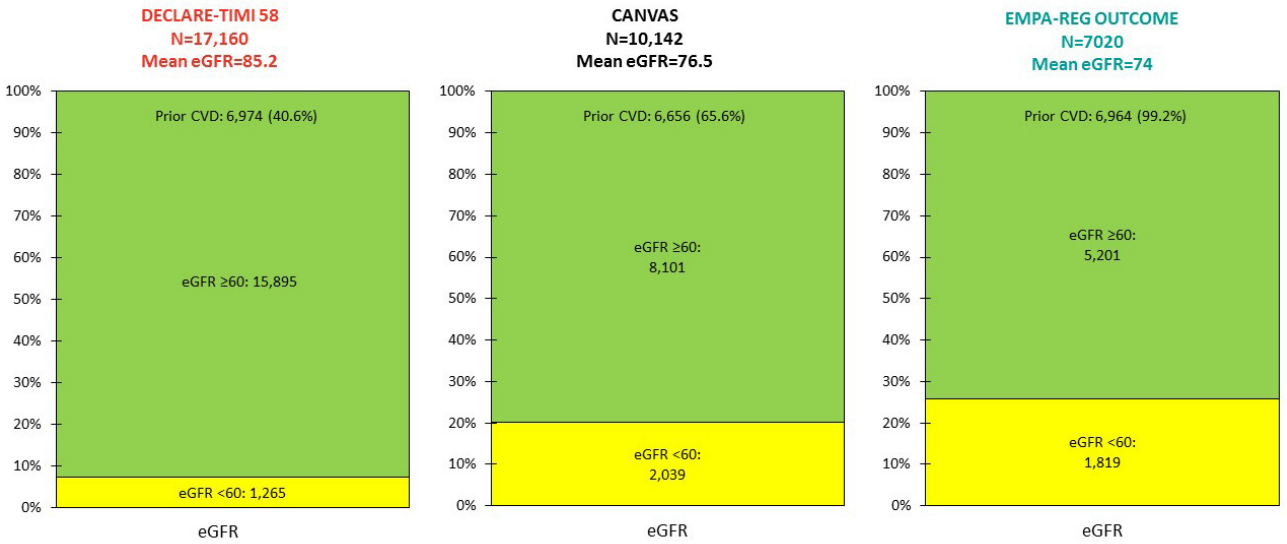

Figure 4. Baseline estimated glomerular filtration rates (eGFRs) and prior cardiovascular disease (CVD) rates in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS), and Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trials. Prior CVD displayed as incidence (percentage).

Table 1. Renal guidelines, entry criteria, and composite outcome definitions in the Canagliflozin Cardiovascular Assessment Study (CANVAS), Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), and Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trials.

	Drug Package Insert	Trial Entry Criteria				Results
Trial	Minimum Recommended eGFR	eGFR Minimum	eGFR Equation	Minimum Creatinine Clearance (mL/min)	Mean eGFR	Composite Renal Outcome
CANVAS	45	30	MDRD	N/A	76.5	≥ 40% reduction in eGFR, RRT (transplant, chronic dialysis, or sustained eGFR < 15), or renal death
DECLARE-TIMI 58	60	N/A	CKD-EPI	60 (Cockroft-Gault equation)	85.2	≥ 40% reduction in eGFR to < 60, ESRD (dialysis ≥ 90 days, transplant or sustained eGFR < 15), or renal/CV death
EMPA-REG OUTCOME	45	30	MDRD	N/A	74	Doubling of serum Cr with eGFR ≤45, RRT, or renal death

eGFR = estimated glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, RRT = renal-replacement therapy, ESRD = end-stage renal disease, Cr = creatinine. All eGFRs are in mL/min/1.73 m^2 body-surface area.

may have systematically underestimated GFR, resulting in more patients with a 40% reduction in eGFR and a subsequent increase in the renal composite event rate. This would not have happened in DECLARE-TIMI 58, which used the more accurate CKD-EPI equation. Further, DECLARE-TIMI 58 used the Cockroft-Gault equation to calculate CrCl for their renal inclusion criterion. This equation has been criticized for being developed using a small patient pool and for being disproportionally affected by body weight; the equation may overestimate GFR in obese patients (Zelniker et al., 2018). Although the utilization of the Cockroft-Gault equation for renal inclusion criterion would not have affected the renal composite event rate (which was based on the CKD-EPI equation), its use highlights the need for consistent methods for evaluating the SGLT2i.

There are other inconsistencies between the 3 CVOTs that need to be reconciled in future analyses. The trials differed in their median follow-up time: 2.4, 3.1, and 4.2 years for CANVAS, DECLARE-TIMI 58, EMPA-REG OUTCOME, respectively. While these would not have affected standardized outcome rates, the absolute rates would be higher in studies with longer

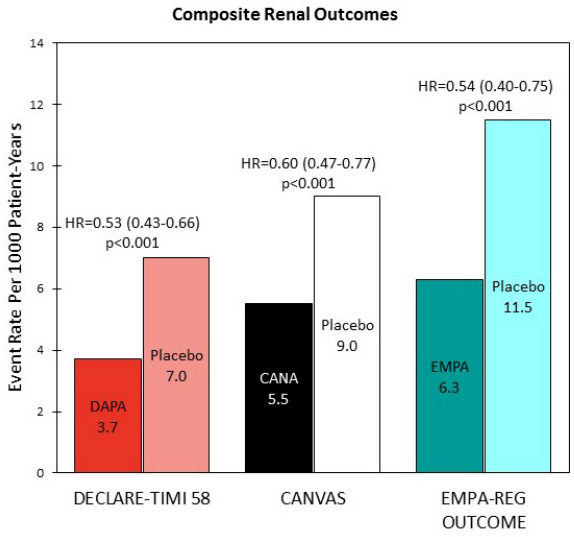

Figure 5. Composite renal outcome rates in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS), and Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trials. Statistical outcomes displayed as hazard ratio (HR) (95% confidence interval), *p*-value. Composite renal outcomes defined as follows: DECLARE-TIMI 58: $\geq$ 40% reduction in estimated glomerular filtration rate (eGFR) to < 60 mL/min/1.73 m^2 body-surface area, end-stage renal disease (dialysis $\geq$ 90 days, transplant or sustained eGFR < 15 mL/min/1.73 m^2), or renal/cardiovascular death; CANVAS: $\geq$ 40% reduction in eGFR, renal replacement therapy (RRT) (transplant, chronic dialysis, or sustained eGFR < 15), or renal death; EMPA-REG OUTCOME: doubling of serum creatinine with eGFR < 45 mL/min/1.72 m^2, RRT, or renal death. DAPA = dapagliflozin, CANA = canagliflozin, EMPA = empagliflozin.

follow-up times. Additionally, baseline T2DM duration differed between the trials, which would have furthered impacted renal function and CV outcomes.

4.3. Other Studies

Multiple large clinical trials are underway examining SGLT2i as treatment for HF and CKD in patients with (and some even without) T2DM (Verma et al., 2018; Clinical Trials, 2018). This includes the eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes (VERTIS-CV) randomized double-blind controlled trial, which has assigned 8238 patients with T2DM and CVD to placebo or ertugliflozin 5 mg or 15 mg added to existing therapy and is expected to end in September 2019 (Cannon et al., 2018; Becker and Vassalotti , 2010; Drugs.com, 2018). 99.9% of patients have established CVD; the mean eGFR is 76.0 ±20.9 mL/min/1.73 m^2 1807 (21.9%) patients have eGFR < 60 mL/min/1.73 m^2 and 6431 (78.1%) have eGFR > 60 mL/min/1.73 m^2. Outcomes are similar to those in the 3 completed CVOTs: composite CV death, nonfatal MI, or nonfatal stroke, composite HHF or CV death, HHF alone, and renal composite: doubling of serum creatinine from baseline, RRT (dialysis or kidney transplant), or renal death. Thus, of the 3 completed CVOTs, EMPA-REG OUTCOME is most similar to VERTIS-CV with regard to baseline eGFR, baseline CVD, and renal composite definition; we therefore expect that VERTIS-CV will have results most similar to EMPA-REG OUTCOME (i.e. higher cardiorenal events across all arms than CANVAS and DECLARE-TIMI 58). The extent to which the populations of SGTL2i CVOTs represent the real-world T2DM population is under study as well. Birkeland et al. explored pre-existing database registries in Germany, the Netherlands, Norway and Sweden and found that DECLARE-TIMI 58 was the most representative of the general T2DM population (59%) compared to CANVAS (34%), EMPA-REG OUTCOME (21%), and VERTIS-CV (17%) (Birkeland et al., 2018). In a similar vein, Wittbrodt et al. studied cross-sectional data from the National Health and Nutrition Examination Survey and found that 39.8% of US adults with T2DM met the eligibility criteria for DECLARE-TIMI 58, compared to 8.8%, 4.1%, and 4.8% for CANVAS, EMPA-REG OUTCOME, and VERTIS-CV, respectively (Wittbrodt et al., 2018). Thus, it is notable that DECLARE-TIMI 58 – the study with the most restrictive inclusion criteria (resulting in patients with the most preserved renal function and lowest baseline CVD rate) – is most representative of the real-world T2DM population.

4.4. Future Studies

We have demonstrated the need for large-scale retrospective studies with consistent baseline eGFR and CVD so that the various SGLT2i can be thoroughly compared, perhaps as a meta-analysis. While CVD-REAL and CVD-REAL 2 provided the foundation for this type of study, the researchers were limited by the available databases and were only able to include eGFR values for patients from some countries (Wattanakit et al., 2005; Cavallari and Maddaloni, 2019). Future studies also need to address how well their study populations represent the general T2DM population. Finally, the effects of dapagliflozin on CV and renal outcomes for patients with baseline eGFR between 30 and 60 mL/min/1.73 m^2 need to be evaluated – perhaps by examining off-label use, given that dapagliflozin is not recommended in patients with eGFR < 60 mL/min/1.73 m^2 (Neuen et al., 2018).

4.5. Limitations

We were primarily limited in that some results (the cumulative incidences, some KM curves, and some p-values) were not present in all trials. We were able to overcome this limitation as described in the Methods section, however.

5. Conclusions

Current and future large-scale cardiorenal outcomes trials must be interpreted in the context of their inclusion criteria, eGFR equations used, and the definitions of their outcomes. Selection of patients according to baseline renal function and CV disease (rather than inherent differences between the SGLT2i) appears to have played a prominent role in the varying CV and renal event rates in the 3 CVOTs completed to date. Future analyses will need to evaluate outcomes in SGLT2i trials across patient populations with similar baseline cardiorenal health.

Strengths and limitations of this study

•This study is the first to contain summary figures for key cardiorenal outcomes of the 3 major SGLT2i trials.

•This study is the first to identify varying inclusion/exclusion criteria as probable explanations for the outcome effect sizes between the 3 major SGLT2i trials, rather than inherent differences between the drugs.

•Some statistical results (e.g. cumulative incidences, p-values) were not present in all 3 trials' original papers, so we used imaging analysis software and calculated ratios to draw conclusions.

Aknowledgement

This work was partially funded by the Baylor Health Care System Foundation (No. 51509).

Conflict of Interest

The authors declare no competing interests.

References

Altman DG, Bland JM. How to obtain the P value from a confidence interval. BMJ. 2011;343:d2304.

Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017;376:2367-2375.

Becker BN; Vassalotti JA. A software upgrade: CKD testing in 2010. Am J Kidney Dis. 2010;55:8-10.

Birkeland KI, Bodegard J, Norhammar A, et al. How Representative are the Patients Included in the CV outcome Trials with SGLT2 Inhibitors of a General Type 2 Diabetes Population? A Large European Observational study. Diabetes Obes Metab. 2018.

Cannon CP, McGuire DK, Pratley R, et al. VERTIS-CV Investigators. Design and baseline characteristics of the eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial (VERTIS-CV). Am Heart J. 2018;206:11-23.

Cavallari I, Maddaloni E. Cardiovascular effects of SGLT-2 inhibitors: What we have learned from cardiovascular outcome trials and what we still need to understand. Diabetes Metab Res Rev. 2019:e3124.

Chang TI, Li S, Chen SC, et al. KEEP Investigators. Risk factors for ESRD in individuals with preserved estimated GFR with and without albuminuria: results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2013;61:S4-11.

Clinical Trials.gov [Internet]. Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease, The VERTIS CV Study (MK-8835-004). C2018.

Douros A, Dell'Aniello S, Yu OHY, et al. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. BMJ. 2018;362:k2693.

Drugs.com: Know More. Be Sure [Internet]. Steglatro. 2018. Available from: https://www.drugs.com/pro/steglatro.html#S5.3.

Drugs.com: Know More. Be Sure [Internet]. Jardiance. c2018. Available from: https://www.drugs.com/pro/jardiance.html.

Drugs.com: Know More. Be Sure [Internet]. Invokana. c2018. Available from: https://www.drugs.com/pro/invokana.html.

Drugs.com: Know More. Be Sure [Internet]. Farxiga. 2018. Available from: https://www.drugs.com/pro/farxiga.html.

Fitchett DH, Udell JA and Inzucchi SE. Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes. Eur J Heart Fail. 2017;19:43-53.

Gilbert MP, Pratley RE. The impact of diabetes and diabetes medications on bone health. Endocr Rev. 2015;36:194-213.

Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373:2125-35.

Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013 Jul 20;382(9888):260-72. doi: 10.1016/S0140-6736(13)60687-X. Epub 2013 May 31. Review. Erratum in: Lancet. 2013;382:208.

Kastarinen M, Juutilainen A, Kastarinen H, et al. Risk factors for end-stage renal disease in a community-based population: 26-year follow-up of 25,821 men and women in eastern Finland. J Intern Med. 2010;267:612-20.

Kaneko M, Narukawa M. Assessment of the Risk of Hospitalization for Heart Failure With Dipeptidyl Peptidase-4 Inhibitors, Saxagliptin, Alogliptin, and Sitagliptin in Patients With Type 2 Diabetes, Using an Alternative Measure to the Hazard Ratio. Ann Pharmacother. 2017;51:570-576.

Kaul S, Bolger AF, Herrington D, et al. American Heart Association; American College Of Cardiology Foundation. Thiazolidinedione drugs and cardiovascular risks: a science advisory from the American Heart Association and American College Of Cardiology Foundation. J Am Coll Cardiol. 2010;55:1885-94.

Kosiborod M, Cavender MA, Fu AZ, et al. CVD-REAL Investigators and Study Group*. Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation. 2017;136:249-259.

Kosiborod M, Lam CSP, Kohsaka S, et al. CVD-REAL Investigators and Study Group. Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL 2 Study. J Am Coll Cardiol. 2018;71:2628-2639.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612.

Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. BMJ. 2014;348:g2366.

Lincoff AM, Wolski K, Nicholls SJ et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. Jama. 2007;298:1180-8.

Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002;106:3068-72.

McCullough PA, Patanker G, Stoler RC. Estimating Renal Filtration, Drug Dosing, and Clinical Outcomes. J Am Coll Cardiol. 2015;65:2724-5.

McMurray JJ, Gerstein HC, Holman RR, et al. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol. 2014;2:843-51.

Mitchell M, Muftakhidinov B, Winchen T [Internet]. Engauge Digitizer Software. c2018.

Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264-269.

Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133:e38-360.

Neal B, Perkovic V, Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin cardiovascular assessment study (CANVAS)–a randomized placebo-controlled trial. Am Heart J. 2013;166:217-223.

Neal B, Perkovic V, Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin cardiovascular assessment study (CANVAS)–a randomized placebo-controlled trial. Am Heart J. 2013;166:217-223.

Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and Renal Outcomes With Canagliflozin According to Baseline Kidney Function. Circulation. 2018;138:1537-1550.

O'Brien MJ, Karam SL, Wallia A, et al. Association of Second-line Antidiabetic Medications With Cardiovascular Events Among

Insured Adults With Type 2 Diabetes. JAMA Netw Open. 2018;1:e186125.
Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. The New England journal of medicine. 2006;355:251-9.
Penman A, Hancock H, Papavasileiou E, et al. Risk Factors for Proliferative Diabetic Retinopathy in African Americans with Type 2 Diabetes. Ophthalmic Epidemiol. 2016;23:88-93.
Powell WR, Christiansen CL, Miller DR. Meta-Analysis of Sulfonylurea Therapy on Long-Term Risk of Mortality and Cardiovascular Events Compared to Other Oral Glucose-Lowering Treatments. Diabetes Ther. 2018;9:1431-1440.
Sarnak MJ, Levey AS, Schoolwerth AC, et al. American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension. 2003;42:1050-65.
Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs. 2015;75:33-59.
Scheen AJ. Pharmacokinetics, Pharmacodynamics and Clinical Use of SGLT2 Inhibitors in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease. Clin Pharmacokinet. 2015;54:691-708.
Scirica BM, Bhatt DL, Braunwald E, et al. SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317-26.
Stevens LA, Li S, Kurella Tamura M, et al. Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) study equations: risk factors for and complications of CKD and mortality in the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2011;57:S9-16.
Thomas MC, Tsalamandris C, MacIsaac RJ, et al. The epidemiology of hemoglobin levels in patients with type 2 diabetes. Am J Kidney Dis. 2006;48:537-45.
Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61:2108-2117.
Wanner C, Inzucchi SE, Lachin JM, et al. EMPA-REG OUTCOME Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375:323-34.
Wattanakit K, Folsom AR, Chambless LE, et al. Risk factors for cardiovascular event recurrence in the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2005;149:606-12.
Werner K, Christensson A, Legrand H, et al. Cystatin C and creatinine-based eGFR levels and their correlation to long-term morbidity and mortality in older adults. Aging Clin Exp Res. 2018.
Wittbrodt ET, Eudicone JM, Bell KF, et al. Eligibility varies among the 4 sodium-glucose cotransporter-2 inhibitor cardiovascular outcomes trials: implications for the general type 2 diabetes US population. Am J Manag Care. 2018;24:S138-S145.
Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Bansilal S, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Gause-Nilsson IA, Langkilde AM, Johansson PA, Sabatine MS. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. Am Heart J. 2018;200:83-89.
Wiviott SD, Raz I, Bonaca MP, et al. DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2018;380:4.
World Health Organization. Global Report on Diabetes [Internet]. c2016. Available from http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1.
Writing Committee, Das SR, Everett BM, et al. 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2018;3200-23.
Zannad F, Stough WG, Lipicky RJ, et al. Assessment of cardiovascular risk of new drugs for the treatment of diabetes mellitus: risk assessment vs. risk aversion. Eur Heart J Cardiovasc Pharmacother. 2016;2:200-5.
Zelniker TA, Braunwald E. Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72:1845-1855.
Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393:31-39.
Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™). Cardiovasc Diabetol. 2014;13:102.
Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. The New England journal of medicine. 2015;373:2117-28.