

# An updated perspective and pooled analysis of cardiovascular outcome trials of GLP-1 receptor agonists and SGLT-2 inhibitors

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## ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT-2) inhibitors reduce major cardiovascular (CV) events in patients with type 2 diabetes mellitus. In this review, we assessed the CV outcome trials of GLP-1 receptor agonists and SGLT-2 inhibitors in terms of their methodological properties and results, and also, using a meta-analytic approach, we calculated and interpreted the pooled analyses. A systematic PubMed search was conducted for CV outcome studies of GLP-1 receptor agonists and SGLT-2 inhibitors with the main outcome of three-point major adverse cardiovascular events (MACE), which is the composite of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke. We pooled the results of each outcome for each group of medications using a fixed effect model. Also, the results of two studies of SGLT-2 inhibitors conducted in patients with heart failure were discussed briefly. We found 12 eligible studies, 7 with GLP-1 agonists (n=56,004) and 5 with SGLT-2 inhibitors (n=46,969). All of the drugs analyzed were non-inferior, and some superior, to placebo in terms of three-point MACE. Pooled analyses demonstrated that GLP-1 receptor agonists, especially those having structural homology for human GLP-1 receptor, and SGLT-2 inhibitors reduced the risk of three-point MACE (by 12% and 10%, respectively), CV mortality (12% and 15%), total mortality (12% and 13%), and to a lesser extent, fatal or non-fatal MI (8% and 9%). While GLP-1 receptor agonists reduced the risk of ischemic stroke by 15%, SGLT-2 inhibitors decreased the risk of hospitalization for heart failure by 32%. GLP-1 agonists and SGLT-2 inhibitors reduced the risk of MACE in patients with type 2 diabetes with established CV disease or those with high risk for CV disease. Also, SGLT-2 inhibitors reduced the risk of hospitalization for heart failure independent of the diabetes status.

**Key words:** glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter-2 inhibitors, cardiovascular outcomes, major cardiovascular events, meta-analysis, mortality, heart failure

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## Introduction

Diabetes mellitus (DM) is one of the major risk factors for cardiovascular (CV) disease, and its prevalence is expected to rise, probably due to lifestyle changes and high prevalence of abdominal obesity (1-5). On the other hand, with the introduction of new anti-diabetics in recent years, there have been rapid and exciting developments in the field of management of DM. Specifically, demonstrating cardiovascular benefits in randomized controlled trials with glucagon-like peptide-1 (GLP-1) receptor

agonists and sodium-glucose co-transporter-2 (SGLT-2) inhibitors created a new era in the management of type 2 DM. Therefore, we aimed to prepare an up-to-date review for CV outcome trials of GLP-1 receptor agonists and SGLT-2 inhibitors by interpreting study characteristics and results of these studies and also giving the pooled estimates for CV outcomes using a meta-analytic approach. We primarily focused on the CV safety trials of GLP-1 receptor agonists and SGLT-2 inhibitors. Further, two studies with SGLT-2 inhibitors conducted in patients with heart failure were briefly discussed.

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## HIGHLIGHTS

- In this review, CV outcome studies of glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT-2) inhibitors were interpreted in detail. The results were also pooled, and showed that GLP-1 receptor agonists, especially those having structural homology for human GLP-1 receptor, and SGLT-2 inhibitors reduced the risk of three-point major adverse cardiovascular (CV) events significantly. Moreover, reduction in CV mortality, total mortality and fatal or non-fatal myocardial infarction was significant. While GLP-1 receptor agonists reduced the risk of ischemic stroke by 15%, SGLT-2 inhibitors decreased the risk of hospitalization for heart failure by 32%.

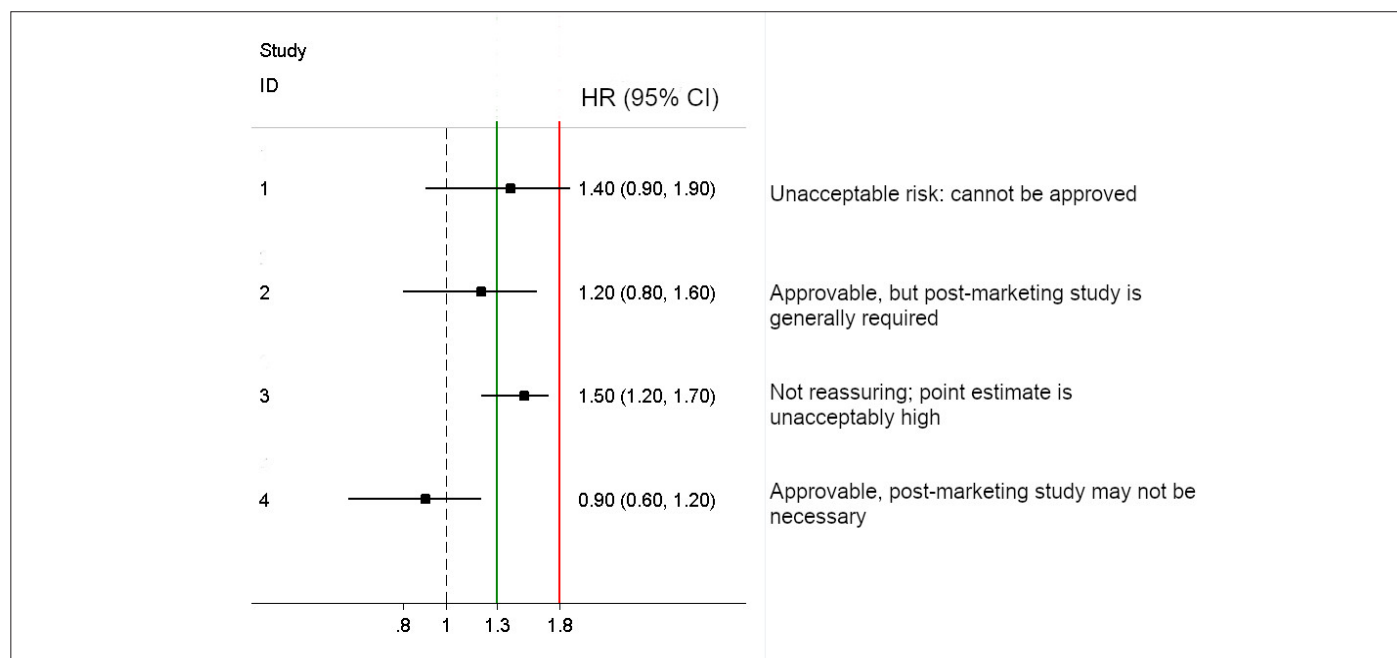
### Background for the need and design of CV outcome trials for new antidiabetic drugs

Intensive glucose control reduces the risk of renal and ocular outcomes (6, 7). However, their effect on reducing major CV events is modest (8). Moreover, despite an improvement in glycemic control, some of the glucose lowering medications increase the risk of CV events (9, 10). This alarming finding led the US Food and Drug Administration (FDA) followed by the European Medicines Agency (EMA) to propose recommendations for pharmaceutical companies emphasizing how to demonstrate that the new drug is not associated with unacceptably high risk of CV events (11, 12). The main points from these recommendations that characterize the studies we discussed here were summarized below:

- Target population: A planned study is recommended to include patients with high risk of CV events, such as patients with advanced disease (for example, having established CV diseases) or having renal impairment, or elderly patients.
- CV outcomes: This should include composite of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke (three-point major adverse CV events [MACE]).
- Non-inferiority margin: Two non-inferiority margins, 1.3 and 1.8, are noteworthy in the FDA and EMA documents (Fig. 1). To get approval, the upper bound of two-sided 95% confidence interval (CI) of the estimated risk ratio should be less than 1.8, which can be obtained by a single large-scale safety trial or meta-analysis of phase 2 and phase 3 trials. If the upper bound of CI is between 1.3 and 1.8, the drug may be approved but post-marketing study is generally required to show that the upper limit is less than 1.3 (Fig. 1, Study number 2). Of note, the upper limit of CI being less than 1.8 alone is not considered reassuring if the point estimates value suggesting a substantial risk, such as 1.5 (Fig. 1, Study number 3). If the pre-marketing study demonstrated that the upper bound of CI is less than 1.3, then post-marketing study *may* not be necessary (Fig. 1, Study number 4).

### Literature search and pooled analysis

We performed a PubMed search for the “CV outcome studies” of GLP-1 agonists and SGLT-2 inhibitors (keywords were given in the Supplemental Appendix). We found seven trials of GLP-1 agonists (n=56,004) (13-19) and 5 trials of SGLT-2 inhibitors (n=46,969) (20-25). In one of the five studies with SGLT-2 inhibitors (the CREDENCE trial) (25), renal outcomes were the primary end-point, but this study was also analyzed as it provided data for CV outcomes. Additionally, two studies with SGLT-2 inhibitors



**Figure 1.** The American Food and Drug Administration's guidance in assessing the cardiovascular safety of new antidiabetic medications. Hazard ratio (HR) and confidence interval (CI) are for the composite outcome of cardiovascular death, non-fatal MI and non-fatal stroke

that were conducted in patients with heart failure were obtained and presented briefly (26, 27).

CV outcome studies were pooled separately for GLP-1 agonists and SGLT-2 inhibitors using a fixed effect meta-analysis. Among the seven GLP-1 agonists, five had structural homology with GLP-1 receptors. Therefore, the results were pooled for each of these subgroups separately, and then consistency of the effect between the subgroups was assessed with a *p* value for interaction.

### Interpretation of CV outcome trials of GLP-1 agonists

Of the seven trials providing CV outcome data of GLP-1 agonists (*n*=56,004; Table 1) (13-19), six molecules were compared to placebo, and with the exception of two drugs, exenatide and lixisenatide, all GLP-1 agonists had a high level of structural homology with human GLP-1 receptors.

In the PIONEER-6 study (17), oral semaglutide and, in the remaining trials, subcutaneous forms of GLP-1 agonists, given once a day (liraglutide and lixisenatide) or once a week (semaglutide, exenatide, albiglutide, and dulaglutide), were compared with placebo.

### Study populations

All of the studies included participants with established CV diseases or a high-risk population for CV diseases, as it is recommended in the regulatory agencies' guidance. The ELIXA and HARMONY trials had different patient profiles than other trials: The ELIXA trial included only patients with acute coronary syndrome (19), and the HARMONY trial included only patients with established CV diseases (16). The details of the inclusion and exclusion criteria were summarized in the Supplemental S-Table 1.

As GLP-1 agonists have been shown to lead to thyroid C-cell hyperplasia in experimental models (28), patients with high calcitonin levels at baseline were excluded in all trials except the HARMONY trial. On the other hand, personal or family history of thyroid medullary carcinoma or multiple endocrine neoplasia type-II, and severe renal disease were among the exclusion criteria in all the studies.

These studies have set different age cut-offs for eligibility. Except PIONEER-6 trial (17), all the studies used a cut-off value for minimum HbA1c and the EXSCEL, REWIND, and ELIXA trials used an upper limit of HbA1c ( $\leq 10\%$ ,  $\leq 9.5\%$ , and  $\leq 11\%$ , respectively) (Supplemental S-Table 1) (15, 18, 19).

### Study design and analysis

All studies were designed as randomized, double-blind, and placebo-controlled trials. The SUSTAIN-6 trial was designed to test only for non-inferiority (superiority was not prespecified), the HARMONY trial tested only for superiority, and other trials tested first for non-inferiority and then (if non-inferiority was obtained) for superiority. Non-inferiority margin was 1.8 in the SUSTAIN-6 and PIONEER-6 trials, but 1.3 in other trials testing non-inferiority. The number of the participants was relatively lower in the SUSTAIN-6 and PIONEER-6 trials, probably due to a

more lenient non-inferiority margin (Table 1). All of the studies have a power of  $\geq 85\%$  (mostly 90%) to test the primary hypothesis. The primary outcome was the three-point MACE in all trials except ELIXA, which included hospitalization for unstable angina pectoris in addition to the three-point MACE.

### Baseline characteristics

Baseline characteristics are given in Table 1. Briefly, the mean age was between 60 and 66 years, and most of the patients were male. Mean body mass index was between 30 and 33 kg/m<sup>2</sup>, indicating that approximately half of the patients were obese. As a requirement of the protocol, all patients in the HARMONY trial had a history of established CV disease. The proportion of the participants with established CV diseases at baseline was the lowest (approximately 31%) in the REWIND trial, and more than two-thirds in other trials. The mean duration of DM was approximately 9 years in the ELIXA trial, and between 11 and 15 years in other trials. More than 70% of the patients were on lipid-lowering treatment at baseline, and antiplatelet use varied between 54% and 94% in all studies. Statin and antiplatelet use were the highest in the ELIXA and HARMONY trials, which was expected because these two trials included only patients with established CV disease. More than two-thirds of the patients were on biguanide treatment at baseline, and use of insulin differed substantially between the trials.

### Follow-up and CV outcomes

The median follow-up duration was the highest in the REWIND trial (5.4 years) and the lowest in the PIONEER-6 trial (15.9 months) (Table 2).

The incidence rate of the primary outcome seems to be consistent with the baseline risk: the lowest in the REWIND trial (2.35 vs. 2.66 per 100-person-years in the treatment group and placebo group, respectively), which has the lowest proportion of established CV disease at baseline, and the highest in the ELIXA trial (6.4 vs. 6.3 100-person-years in the treatment group and placebo group, respectively), which included only patients with acute coronary syndrome. Of note, primary outcome in the ELIXA trial included hospitalizations for unstable angina pectoris in addition to the three-component MACE. However, among the four components, hospitalizations for unstable angina pectoris constituted only 2.2% in the lixisenatide group and 2.5% in the placebo group, suggesting that the inclusion of hospitalization for unstable angina may not markedly change the incidence of three-point MACE. The HARMONY trial, which included only patients with established CV disease at baseline, has the second highest incidence rate for the primary outcome (4.57 vs. 5.87 per 100-person-year in the albiglutide and placebo groups, respectively).

### The primary outcome

In all of the six non-inferiority trials, GLP-1 agonists were non-inferior to placebo (Table 2). Liraglutide, albiglutide, and dulaglutide were also superior to placebo in reducing the primary outcomes. Moreover, there was a trend for superiority with

**Table 1. Study design and baseline characteristics of the cardiovascular outcome trials of GLP-1 receptor agonists**

	<b>ELIXA (19)</b>	<b>LEADER (13)</b>	<b>SUSTAIN-6 (14)</b>	<b>EXSCEL (15)</b>	<b>HARMONY Outcomes (16)</b>	<b>PIONEER-6 (17)</b>	<b>REWIND (18)</b>
Study agent and dosage	Lixisenatide SC 10–20 mcg once daily vs. placebo	Liraglutide SC 1.8 mg or max tolerated dose once daily vs. placebo	Semaglutide SC 0.5–1 mg once weekly vs. placebo	Exenatide SC 2 mg once weekly vs. placebo	Albiglutide SC 30–50 mg (based on glycemic response or tolerability) once weekly vs. placebo	Semaglutide Oral (target dose 14 mg) once daily vs. placebo	Dulaglutide SC 1.5 mg once weekly vs. placebo
Hypothesis testing	Non-inferiority → superiority	Non-inferiority → superiority	Non-inferiority	Non-inferiority → superiority	Non-inferiority → superiority	Non-inferiority → superiority	Superiority
Non-inferiority margin	1.3	1.3	1.8	1.3	1.3	1.8	NA
Power of the trial	96% for non-inferiority 90% for superiority	90%	90%	85%	90%	90%	%90
Sample size	6068	9340	3297	14752	9463	3183	9901
Primary outcomes	CV death / MI /stroke/ hospitalization for UAP	CV death / MI /stroke (including silent MI)	CV death / MI /stroke (including silent MI)	CV death /MI / stroke	CV death /MI / stroke	CV death /MI / stroke	CV death /MI / stroke
Age	59.9±9.7 vs. 60.6±9.6	64.2±7.2 vs. 64.4±7.2	0.5 mg: 64.6±7.3 vs. 64.8±7.6 1 mg: 64.7±7.1 vs. 64.6±7.4	62.0 (56.0-68.0) vs. 62.0 (56.0-68.0)	64.1±8.7 vs. 64.2±8.7	66±7 vs. 66±7	66.2±6.5 vs. 66.2±6.5
Male, %	69.6 vs. 69.1	65 vs. 64	0.5 mg: 59.9 vs. 58.5 1 mg: 63.0 vs. 61.5	62 vs. 62	70 vs. 69	68.1 vs. 68.6	53.4 vs. 53.9
Previous CVD (%)	History at randomization: MI: 22.1 vs. 22.1 PCI: 66.8 vs. 67.6 Coronary bypass: 8.2 vs. 8.5 Stroke: 6.2 vs. 4.7	82.1 vs. 80.6 (including stage 3 renal failure)	83.0 (including stage 3 renal failure). 72.2% only CVD	73.3 vs. 72.9	100 CAD 70 vs. 71 Heart failure: 20 vs. 20 Stroke: 17 vs. 18 PAD: 25 vs. 24 (values are not mutually exclusive)	84.9 vs. 84.5 (including stage 3 renal failure)	31.5 vs. 31.4
Duration of diabetes (years)	9.2±8.2 vs. 9.4±8.3	12.8±8.0 vs. 12.9±8.1	0.5 mg: 14.3±8.2 vs. 14.0±8.5 1 mg: 14.1±8.2 vs. 13.2±7.4	12.0 (7.0-17.0) vs. 12.0 (7.0-18.0)	14.1±8.6 vs. 14.2±8.9	14.7±8.5 vs. 15.1±8.5	10.5±7.3 vs. 10.6±7.2
HbA1c % (GLP1 agonist vs. placebo)	7.7±1.3 vs. 7.6±1.3	8.7 vs. 8.7	0.5 mg: 8.7±1.4 vs. 8.7±1.5 1 mg: 8.7±1.5 vs. 8.7±1.5	8.0 (7.3-8.9) vs. 8.0 (7.3-8.9)	8.76±1.5 vs. 8.72±1.5	8.2±1.6 vs. 8.2±1.6	7.3±1.1 vs. 7.4±1.1
BMI. kg/m <sup>2</sup>	30.1±5.6 vs. 30.2±5.8	32.5±6.3 vs. 32.5±6.3	0.5 mg: 32.7 vs. 32.9 1 mg: 32.9 vs. 32.7	31.8 (28.2-36.2) vs. 31.7 (28.2-36.1)	32.3±5.9 vs. 32.3±5.9	32.3±6.6 vs. 32.3±6.4	32.3±5.7 vs. 32.3±5.8

**Table 1. Study design and baseline characteristics of the cardiovascular outcome trials of GLP-1 receptor agonists (Continue)**

	ELIXA (19)	LEADER (13)	SUSTAIN-6 (14)	EXSCEL (15)	HARMONY Outcomes (16)	PIONEER-6 (17)	REWIND (18)
eGFR, mL/min/1.73 m <sup>2</sup>	76.7±21.3 vs. 75.2±21.4	21.4% vs. 20.0% had eGFR <60	0.5 mg: 27.7% vs. 26.1% 1 mg: 23.6% vs. 23.5% had eGFR<60	76.6 (61.3-92.0) vs. 76.0 (61.0-92.0)	79.1±25.6 vs. 78.9±25.4	74±21 vs. 74±21	75.3 (61.6-91.8) vs. 74.7 (61.2-90.6)
<b>Treatment on admission, %</b>							
- Statin or lipid lowering	93.3 vs. 92.2	72.9 vs. 71.4	0.5 mg: 72.6 vs. 71.6 1 mg: 72.9 vs. 73.9	74.3 vs. 72.7	84 vs. 84	Lipid lowering: 84.0 vs. 86.4	66.3 vs. 66.0
- Antiplatelet	ASA: 94.4	68.7 vs. 66.8	(ASA) 0.5 mg: 61.6 vs. 63.3 1 mg: 65.9 vs. 64.8	(ASA) 64.1 vs. 63.1	(ASA) 77 vs. 77 (P2Y12 inh) 26 vs. 26	78.4 vs. 80.3	53.8 vs. 54.1
- Biguanid	67.2 vs. 65.4	76 vs. 77	0.5 mg: 74.7 vs. 71.1 1 mg: 72.3 vs. 74.8	76.4 vs. 76.8	73 vs. 74	76.7 vs. 78.0	81.3 vs. 81.1
- Insulin	39.2 vs. 39.0	43.7 vs. 45.6	0.5 mg: 58.0 vs. 58.0 1 mg: 58.0 vs. 58.1	46.2 vs. 46.5	60 vs. 58	61 vs. 60	24.0 vs. 23.7
- SGLT-2 on admission	-	-	-	-	-	10.4 vs. 8.8	0.1% (among all Pts)
- SGLT-2 last visit.	-	2.1 vs. 2.8	0.5 mg: 2.5 vs. 4.9 1 mg: 2.8 vs. 6.4	6.5 vs. 9.4	9.7 vs. 10.8	3.1 vs. 7.0	5.3 vs. 7.3
Discontinuation of the study drug, %	Permanent discontinuation: 27.5 vs. 24.0	Due to Any adverse effect: 9.5 vs. 7.3 Serious adverse effect: 4.1 vs. 5.2 Severe adverse effect: 3.5 vs. 4.0 Nausea: 1.6 vs. 0.4	Premature discontinuation: 0.5 mg: 19.9 vs. 18.3 1 mg: 22.6 vs. 19.3	Premature discontinuation: 43.0 vs. 45.2	Premature discontinuation: 24 vs. 27	Due to any adverse effects: 11.6 vs. 6.5	26.8 vs. 28.9

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). ACS - acute coronary syndrome, AE - adverse event, ASA - acetyl salicylic acid, BMI - body mass index, CAD - coronary artery disease, CV - cardiovascular, CVD - cardiovascular disease, eGFR - estimated glomerular filtration rate, GLP1 - glucagon-like peptide-1, HbA1c - glycated hemoglobin, MI - myocardial infarction, NA - Not applicable, PAD - peripheral artery disease, PCI - percutaneous coronary intervention, Pts - patients, SC - subcutaneous, SGLT2 - sodium-glucose co-transporter 2, UAP - unstable angina pectoris

exenatide (p=0.06). Although subcutaneous semaglutide was also found superior to placebo, this finding should be interpreted cautiously as superiority test was not prespecified in the SUSTAIN-6 trial. Oral semaglutide was not found to be superior to placebo in the PIONEER-6 trial. However, the point estimate of the risk reduction in the SUSTAIN-6 trial and the PIONEER-6 trial were consistent with those obtained for other GLP-1 agonists that were superior to placebo, thereby suggesting that the negative result of the PIONEER-6 study might be due to low power,

and the benefit of semaglutide might be irrespective of the route of administration. Moreover, a combined analysis revealed that semaglutide reduced the risk of three-point MACE significantly [Hazard ratio (HR) 0.76, 95% CI 0.62–0.92] (29).

In our pooled analysis, we found that GLP-1 receptor agonists decreased the risk of the three-point MACE by 12% (HR 0.88, 95% CI 0.84–0.93; p<0.001; Fig. 2; Table 3). However, significant heterogeneity of the treatment effect was observed between the subgroups based on structural homology for

**Table 2. Follow-up and outcomes of the cardiovascular outcome trials of GLP-1 receptor agonists**

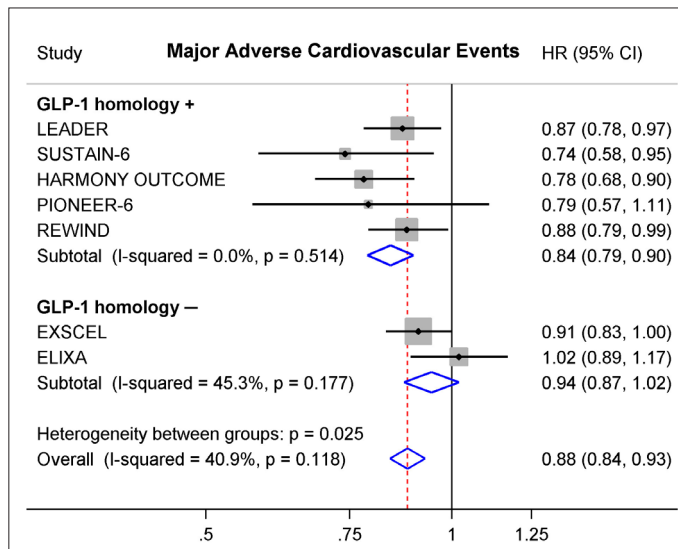
	<b>ELIXA (19)</b>	<b>LEADER (13)</b>	<b>SUSTAIN-6 (14)</b>	<b>EXSCEL (15)</b>	<b>HARMONY Outcomes (16)</b>	<b>PIONEER-6 (17)</b>	<b>REWIND (18)</b>
Comparisons	Lixisenatide vs. placebo	Liraglutide vs. placebo	Semaglutide vs. placebo	Exenatide vs. placebo	Albiglutide vs. placebo	Semaglutide oral vs. placebo	Dulaglutide vs. placebo
Follow-up duration (median)	25 months	3.8 years	2.1 years	3.2 years (IQR 2.2-4.4)	1.6 years (IQR 1.3-2.0)	15.9 months (range 0.4-20)	5.4 years (5.1-5.9)
<b>Primary outcome</b>							
Incidence rate for primary outcome per 100 patient-year	6.4 vs. 6.3 (includes hospitalization for UAP)	3.4 vs. 3.9	3.24 vs. 4.44	3.7 vs. 4.0	4.57 vs. 5.87	2.9 vs. 3.7	2.35 vs. 2.66
Hazard ratio (95% CI) for primary outcome	1.02 (0.89–1.17) (includes hospitalization for UAP) $P<0.001$ for non-inferiority, $P=0.81$ for superiority	0.87 (0.78–0.97) $P<0.001$ for non-inferiority, $P=0.01$ for superiority	0.74 (0.58–0.95) $P<0.001$ for non-inferiority, $P=0.02$ for superiority (superiority not prespecified)	0.91 (0.83-1.00) $P<0.001$ for non-inferiority, $P=0.06$ for superiority	0.78 (0.68–0.90) $P<0.0001$ for non-inferiority, $P<0.0006$ for superiority.	0.79 (0.57–1.11) $P<0.001$ for non-inferiority, $P=0.17$ for superiority.	0.88 (0.79–0.99), $P=0.026$ for superiority
<b>Secondary outcomes [given as incidence rate per 100 patient-year and hazard ratio (95% confidence interval)]</b>							
Total mortality	3.1 vs. 3.3 0.94 (0.78-1.13) $P=0.50$	2.1 vs. 2.5 0.85 (0.74-0.97) $P=0.02^*$	1.82 vs. 1.76 1.05 (0.74-1.50) $P=0.79$	2.0 vs. 2.3 0.86 (0.77-0.97)*	2.44 vs. 2.56 0.95 (0.79-1.16) $P=0.644$	1.1 vs. 2.2 0.51 (0.31-0.84)*	2.06 vs. 2.29 0.90 (0.80-1.01) $P=0.067$
CV mortality	2.3 vs. 2.4 0.98 (0.78-1.22) $P=0.85$	1.2 vs. 1.6 0.78 (0.66-0.93) $P=0.007^*$	1.29 vs. 1.35 0.98 (0.65-1.48) $P=0.92$	1.4 vs. 1.5 0.88 (0.76-1.02)	1.61 vs. 1.72 0.93 (0.73-1.19) $P=0.578$	0.7 vs. 1.4 0.49 (0.27-0.92)*	1.22 vs. 1.34 0.91 (0.78-1.06) <sup>‡</sup> $P=0.21$
All MIs	4.2 vs. 4.1 1.03 (0.87-1.22) $P=0.71$	1.6 vs. 1.9 0.86 (0.73-1.00) $P=0.046^*$	1.52 vs. 1.80 0.85 (0.58-1.23) $P=0.38$	2.1 vs. 2.1 0.97 (0.85-1.10)	2.43 vs. 3.26 0.75 (0.61-0.90) $P=0.003^*$	Not reported	0.87 vs. 0.91 0.96 (0.79-1.15) $P=0.96$
Non-fatal MI	Not reported	1.6 vs. 1.8 0.88 (0.75-1.03) $P=0.11$	1.40 vs. 1.92 0.74 (0.51-1.08) $P=0.12$	Not reported	Not reported	1.8 vs. 1.5 1.18 (0.73-1.90)	0.80 vs. 0.84 0.96 (0.79-1.16) $P=0.65$
Fatal/non-fatal stroke	1.0 vs. 0.9 1.12 (0.79-1.58) $P=0.54$	1.0 vs. 1.1 0.86 (0.71-1.06) $P=0.16$	Not reported	0.8 vs. 0.9 0.85 (0.70-1.03)	1.25 vs. 1.45 0.86 (0.66-1.14) $P=0.300$		0.61 vs. 0.81 0.76 (0.62-0.94) $P=0.01^*$
Non-fatal stroke	Not reported	0.9 vs. 1.0 0.89 (0.72-1.11) $P=0.30$	0.80 vs. 1.31 0.61 (0.38-0.99) $P=0.04^*$	Not reported		0.6 vs. 0.8 0.74 (0.35-1.57)	0.52 vs. 0.69 0.76 (0.61-0.95) $P=0.017^*$
Hospitalization for HF	1.8 vs. 1.9 0.96 (0.75-1.23) $P=0.75$	1.2 vs. 1.4 0.87 (0.73-1.05) $P=0.14$	1.76 vs. 1.61 1.11 (0.77-1.61) $P=0.57$	0.9 vs. 1.0 0.94 (0.78-1.13)	Not reported	1.0 vs. 1.2 0.86 (0.48-1.55)	HF requiring hospital admission or urgent visit: 0.83 vs. 0.89 0.93 (0.77-1.12) $P=0.46$

\*Analysis was not based on a prespecified hierarchical test, therefore the result is exploratory, †: Includes deaths of unknown cause  
BMI - body mass index, CAD - coronary artery disease, CV - cardiovascular, CVD - cardiovascular disease, DM - diabetes mellitus, eGFR - estimated glomerular filtration rate, GLP1 - glucagon-like peptide-1, HbA1c - glycated hemoglobin, HF - heart failure, MI - myocardial infarction, PAD - peripheral artery disease, Pts - patients

human GLP-1 receptor: drugs with structural homology significantly reduced the primary outcome (HR 0.84, 95% CI 0.79–0.90,  $p<0.001$ ), but the reduction was not prominent with

other GLP-1 receptor agonists [exenatide and lixisenatide; HR 0.94, 95% CI 0.87–1.02;  $p=0.139$ ;  $p$  value for interaction (for the heterogeneity of the treatment effect between the sub-





**Figure 2.** Effect of GLP-1 receptor agonists on the composite of CV death, non-fatal MI, and non-fatal stroke.

groups)=0.025]. This might be due to ELIXA trial as it included only patients with recent acute coronary syndromes and had a higher rate of discontinuation. Also, it might be due to class effect (i.e., degree of structural homology with GLP-1 receptors) or play of chance. As the data were obtained from study-level subgroup analysis, this finding should also be interpreted with caution. Moreover, the primary outcome of the ELIXA trial included hospitalization for unstable angina in addition to three-point MACE. Despite this difference, we preferred to include this trial into the analysis, as the frequency of hospitalizations for unstable angina was low.

### Secondary outcomes

Some GLP-1 agonists were favored for some secondary outcomes (Table 2). Specifically, there was a significant decrease in total mortality with liraglutide, exenatide, and oral semaglutide and in CV mortality with liraglutide and oral semaglutide. None of them decreased non-fatal MI, but fatal or non-fatal MI was decreased with liraglutide (p=0.046) and albiglutide (of note, HARMONY trial did not provide the risk of non-fatal MI or non-fatal stroke with albiglutide). While non-fatal stroke was decreased with subcutaneous semaglutide and dulaglutide, fatal or non-fatal stroke was decreased only with dulaglutide. None of them reduced the risk of hospitalization for heart failure. However, all these findings should be considered hypothesis-generating rather than definitive. Only the EXSCEL trial pre-specified hierarchical tests for these outcomes after superiority analysis. However, as the superiority was not observed in this trial, these secondary analyses should be considered as exploratory findings, as well.

Our pooled analysis for the secondary outcomes demonstrated that while the reduction in CV death (p=0.001; p-interaction for heterogeneity between the subgroups of GLP-1 receptor homology 0.466), total mortality (p<0.001; p-interaction 0.945), non-fatal stroke (p=0.002), and fatal or non-fatal stroke (p = 0.002; p-interac-

tion = 0.339) were statistically significant, the risk of non-fatal MI (p=0.092) and hospitalization for heart failure (p=0.123; p-interaction=0.743) were similar between the GLP-1 receptor agonists and placebo (Fig. 3, Table 3). Also, the risk of fatal or non-fatal MI was reduced significantly, especially with the drugs with GLP-1 receptor homology (p=0.03; p-interaction=0.058).

### Subgroup analyses

Each trial assessed whether the main effect of the study medication was similar between several subgroups. In these subgroup analyses, some patients seem to benefit more from GLP-1 agonists compared to placebo, but as the findings were not consistent across the seven trials, they might be due to chance.

### Other effects and safety

GLP-1 agonists lead to a slight decrease in HbA1c, low-density lipoprotein (LDL) cholesterol and body weight and an increase in heart rate (1–4 beat per minute). Although they may increase amylase and lipase levels, no concerning effect was observed for pancreatitis. Subcutaneous semaglutide increased the risk of proliferative retinopathy but in the early period of the study, possibly due to the rapid decline in blood glucose levels. Therefore, in the subsequent trial with oral semaglutide (PIONEER-6), patients with proliferative retinopathy or maculopathy requiring acute treatment were excluded, eventually demonstrating that the risk increase was not significant in this group of patients (7.1% vs 6.3% with semaglutide and placebo, respectively). No concern for malignancy was observed, but a longer follow-up is required to assess the risk.

GLP-1 agonists are also found to be safe agents in terms of hypoglycemic effect, which were usually less common or similar to placebo. In the PIONEER-6 trial, severe hypoglycemia was observed more with placebo, but all the events occurred with the concomitant use of insulin or sulfonylureas.

### Interpretation of CV outcome trials of SGLT-2 inhibitors

Five trials (with empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) that assessing the three-point MACE with SGLT-2 inhibitors were obtained (n=46,969; Table 4) (20-25, 30, 31). Also, two studies [with dapagliflozin (26) and empagliflozin (27)] conducted in patients with heart failure were reached.

All of the four drugs are used orally. There are some differences in the inclusion and exclusion criteria including cut-off values for age, HbA1c, and eGFR (Supplemental S-Table 2).

### Study population

The EMPA-REG OUTCOME (20) and VERTIS-CV (23, 24, 30) trials included only patients with established CV diseases; however, the CANVAS (21) and DECLARE TIMI-58 (22) trials included both patients with established CV diseases and those having risk factors for atherosclerotic vascular diseases (Supplemental S-Table 2). The CREDENCE trial was primarily conducted to assess renal outcomes, and the presence of established CV was not an inclusion criterion. However, 50% of the patients in the

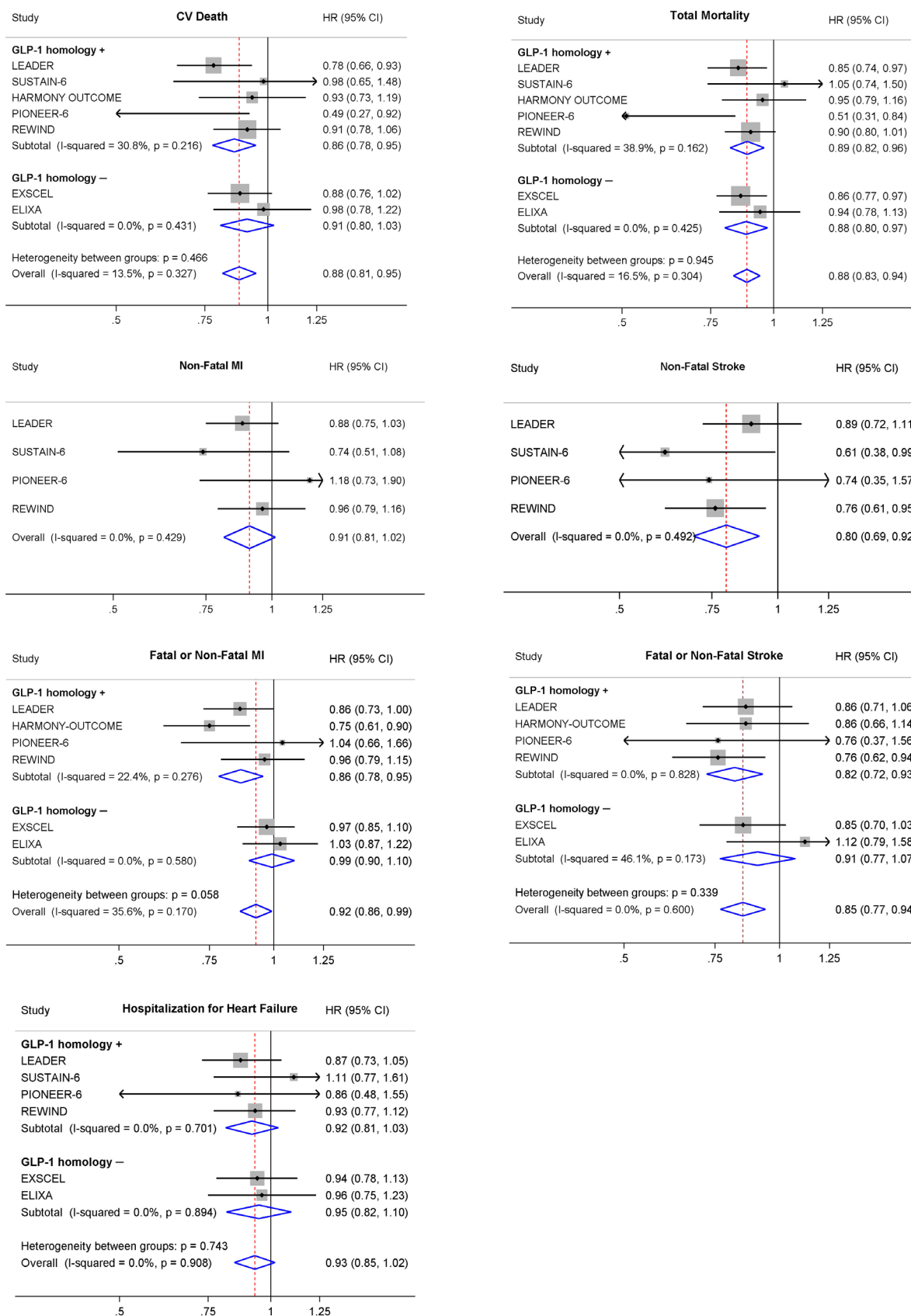


Figure 3. Effect of GLP-1 receptor agonists on each component of the primary outcome and some selected CV outcomes.



**Table 3. Results of the pooled analyses of GLP-1 receptor agonists and SGLT-2 inhibitors**

	GLP-1 receptor agonists	P	SGLT-2 inhibitors	P
Studies	ELIXA (19) LEADER (13) SUSTAIN-6 (14) EXSCEL (15) HARMONY Outcomes (16) PIONEER-6 (17) REWIND (18)		EMPA-REG OUTCOME (20) CANVAS Program (21, 31) DECLARE TIMI-58 (22) VERTIS-CV (25) CREDESCENCE (30)	
Number of patients	56,004		46,969	
3-point MACE	0.88 (0.84-0.93)	<0.001*	0.90 (0.85-0.96)	<0.001
CV mortality	0.88 (0.81-0.95)	0.001	0.85 (0.78-0.93)	<0.001
Total mortality	0.88 (0.83-0.94)	<0.001	0.87 (0.81-0.93)	<0.001
Non-fatal MI	0.91 (0.81-1.02)	0.092	0.91 (0.81-1.02)	0.092
Fatal or non-fatal MI	0.92 (0.86-0.99)	0.030**	0.91 (0.84-0.99)	0.034
Non-fatal stroke	0.80 (0.69-0.92)	0.002	0.98 (0.85-1.13)	0.756
Fatal or non-fatal stroke	0.85 (0.77-0.94)	0.002	0.98 (0.88-1.09)	0.723
Hospitalization for heart failure	0.93 (0.85-1.02)	0.123	0.68 (0.61-0.76)	<0.001

The risk of outcomes was given as HR (95% CI).  
 \*P value for interaction is 0.025 in fixed effect model, favoring those with GLP-1 receptor homology  
 \*\*P value for interaction is 0.058, the trend favoring those with GLP-1 receptor homology  
 CV - cardiovascular; MACE - major adverse cardiovascular events; MI - myocardial infarction

CREDESCENCE trial had established CV diseases at baseline, which is higher than that in the DECLARE TIMI-58 trial. Recent CV events within 2 months (EMPA-REG OUTCOME and DECLARE TIMI-58 trials) or 3 months (CANVAS, VERTIS-CV and CREDESCENCE trials) were exclusion criteria in all studies. Patients on corticosteroid treatment were excluded in the CANVAS, DECLARE TIMI-58, and VERTIS-CV trials, possibly due to the concern of bone fractures that have been reported with some SGLT-2 inhibitors (32, 33). In contrast to the studies with GLP-1 agonists, calcitonin levels, history of thyroid medullary carcinoma, or multiple endocrine neoplasia were not among the exclusion criteria.

Age cut-off for eligibility was markedly different for each study. All of the studies had baseline lower and upper limits of HbA1c criteria for eligibility (Supplemental S-Table 2).

### Study design and analysis

All of these studies were randomized, double-blind, placebo-controlled trials, and except the CREDESCENCE trial, all tested the non-inferiority hypothesis for the three-point MACE. The non-inferiority margin was 1.3 in all studies. Superiority hypothesis was also tested in these studies, however, they applied different hierarchical test steps, which may affect the interpretation of secondary outcomes. In the CREDESCENCE trial, the three-point MACE was tested for superiority as a secondary outcome.

The EMPA-REG OUTCOME, CANVAS, and VERTIS-CV trials had three arms (low-dose, high-dose, and placebo), but low- and high-dose data were pooled during the analysis.

The power was ≥90% in these trials, and the number of the enrolled participants was markedly different across the studies.

### Baseline characteristics

Baseline characteristics are presented in Table 4. Briefly, the mean age was approximately 63–64 years with a male predominance. Established CV diseases were present in all patients in the EMPA-REG OUTCOME and VERTIS-CV trials; meanwhile 65.6%, 40.6%, and 50.4% of the patients in the CANVAS, DECLARE TIMI-58 and CREDESCENCE trials had had established CV disease at baseline, respectively. As in the trials with GLP-1 agonists, approximately half of the study populations had obesity (mean body mass index was between 31 and 32 kg/m<sup>2</sup>). As a renal outcome study, the mean estimated glomerular filtration rate was lower in the CREDESCENCE trial compared to the other trials.

More than half of the patients had DM with a duration of more than 10 years, and it was the highest in the CREDESCENCE trial. Statin use at baseline was the highest in the VERTIS-CV trial (82%), followed by the CREDESCENCE trial (69%). Approximately three-fourths of the patients were on statins (or ezetimibe) in other trials. Antiplatelet medication at baseline was the highest in the EMPA-REG OUTCOME (83% acetylsalicylic acid and 11% clopidogrel) and VERTIS-CV (antiplatelet 85%) trials due to their inclusion of patients with established CV disease only.

### Follow-up and CV outcomes

The range of median follow-up duration of the studies was between 2.4 years (CANVAS trial) and 4.2 years (DECLARE TIMI-58 trial) (Table 5). The CREDESCENCE trial was stopped early due to pre-specified efficacy criteria for early cessation reached at the interim analysis, with median follow-up of 2.62 years (range, 0.02–4.53).

As in the trials with GLP-1 agonists, the incidence rates were generally consistent with the baseline risk (or the presence of

**Table 4. Study design and baseline characteristics of the cardiovascular outcome trials of SGLT-2 inhibitors**

	<b>EMPA-REG OUTCOME (20)</b>	<b>CANVAS Program (21, 31)</b>	<b>DECLARE TIMI 58 (22)</b>	<b>CREDENCE (25)</b>	<b>VERTIS-CV (30)</b>
Study agent and dosage	Empagliflozin 10 mg; 20 mg p.o. once daily vs. placebo	Canagliflozin 100 mg; 300 mg p.o. once daily vs. placebo	Dapagliflozin 10 mg p.o. once daily vs. placebo	Canagliflozin 100 mg p.o. once daily vs. placebo	Ertugliflozin 5 mg; 15 mg p.o. once daily vs. placebo
Randomization	1:1:1 (Analyzed as pooled Empagliflozin vs. placebo)	CANVAS: 1:1:1 100:300:placebo CANVAS-R 100 (optional increase to 300): placebo	1:1	1:1	1:1:1 Analyzed as pooled ertugliflozin vs. placebo
Hypothesis testing	Non-inferiority → superiority	Non-inferiority → superiority	Non-inferiority → superiority	Superiority for renal outcome Three-point MACE is the third secondary outcome in the hierarchical test procedure	Non-inferiority → superiority
Non-inferiority margin	1.3	1.3	1.3	NA	1.3
Power of the trial	90%	90%	99% (assuming hazard ratio of 0.85)	90% for superiority	~96% for non-inferiority (assuming HR of 1.00)
Sample size	7020	10142	17160	4401	8246
Primary outcomes	CV death/MI/stroke (exclude silent MI)	CV death/MI/stroke (including silent MI)	CV death/MI/stroke	ESRD/doubling creatinine/death from renal or cardiac causes	CV death/MI/stroke
Age, years	63.1±8.6 vs. 63.2±8.8	63.2±8.3 vs. 63.4±8.2	63.9±6.8 vs. 64.0±6.8	62.9±9.2 vs. 63.2±9.2	64.4±8.1 vs. 64.4±8.0
Male, %	71.2 vs. 72.0	64.9 vs. 63.3	63.1 vs. 62.1	65.4 vs. 66.7	70.3 vs. 69.3
Previous CVD, %	100	64.8 vs. 66.7	40.5 vs. 40.8	50.5 vs. 50.3	100
Duration of diabetes, years	>10 years: 57.0 vs. 57.4 >5-10 years: 25.1 vs. 24.5	13.5±7.7 vs. 13.7±7.8	11.0 (6.0-16.0) vs. 10.0 (6.0 vs. 16.0)	15.5±8.7 vs. 16.0±8.6	12.9±8.3 vs. 13.1±8.4
HbA1c, %	8.1±0.9 vs. 8.1±0.8	8.2±0.9 vs. 8.2±0.9	8.3±1.2 vs. 8.3±1.2	8.3±1.3 vs. 8.3±1.3	8.2±1.0 vs. 8.2±0.9
BMI, kg/m <sup>2</sup>	30.6±5.3 vs. 30.7±5.2	31.9±5.9 vs. 32.0±6.0	32.1±6.0 vs. 32.0±6.1	31.4±6.2 vs. 31.3±6.2	31.9±5.4 vs. 32.0±5.5
eGFR mL/min/1.73 m <sup>2</sup>	74.2±21.6 vs. 73.8±21.1	76.7±20.3 vs. 76.2±20.8	85.4±15.8 vs. 85.1±16.0	56.3±18.2 vs. 56.0±18.3	76.1±20.9 vs. 75.7±20.8
<b>Treatment on admission, %</b>					
-Statins	77.4 vs. 76.0	74.7 vs. 75.2	Statin or ezetimibe: 74.9 vs. 75.0	69.8 vs. 68.1	Statin: 81.9 vs. 81.6
Ezetimibe: 3.2 vs. 4.2					
-Antiplatelets	ASA: 82.7 vs. 82.6 Clopidogrel: 10.5 vs. 10.7	Antithrombotic: 73.0 vs. 74.4	61.1 vs. 61.1	Including anticoagulants: 60.9 vs. 58.3	84.5 vs. 84.9
-Biguanid	73.8 vs. 74.3	76.7 vs. 77.7	81.8 vs. 82.2	57.9 vs. 57.7	75.8 vs. 77.3
-Insulin	48.0 vs. 48.6	49.9 vs. 50.7	41.6 vs. 40.2	65.9 vs. 65.1	46.5 vs. 48.9
GLP-1 agonists on admission	2.7 vs. 3.0	3.8 vs. 4.3	4.6 vs. 4.1	4.0 vs. 4.3	3.5 vs. 3.1
GLP-1 agonists on last visit	1.4 vs. 2.4	-	-	-	4.9 vs. 5.6
Discontinuation of the study drug	23.4 vs. 29.3	29.2 vs. 29.9	21.1 vs. 25.1	24.7 vs. 29.9	23.5 vs. 27.9

Continuous variables are expressed as mean ± standard deviation or median (interquartile range).

ACS - acute coronary syndrome, AE - adverse event, ASA - acetyl salicylic acid, BMI - body mass index, CAD - coronary artery disease, CV - cardiovascular, CVD - cardiovascular disease, eGFR - estimated glomerular filtration rate, ESRD - end-stage kidney disease, GLP1 - glucagon-like peptide-1, HbA1c - glycated hemoglobin, MI - myocardial infarction, NA - not applicable, PAD - peripheral artery disease, PCI - percutaneous coronary intervention, Pts - patients, SC - subcutaneous, SGLT2 - sodium-glucose co-transporter 2, UAP - unstable angina pectoris

**Table 5. Follow-up and outcomes of the cardiovascular outcome trials of SGLT-2 inhibitors**

	<b>EMPA-REG OUTCOME (20)</b>	<b>CANVAS Program (21, 31)</b>	<b>DECLARE TIMI-58 (22)</b>	<b>CREDESCENCE (25)</b>	<b>VERTIS-CV (30)</b>
Comparisons	Empagliflozin vs. placebo	Canagliflozin vs. placebo	Dapagliflozin vs. placebo	Canagliflozin vs. placebo	Ertugliflozin vs. placebo
Follow-up duration (median) (years)	3.2 (2.2-3.6) vs. 3.1 (2.2-3.5)	2.4	4.2 (3.9-4.4)	2.62 (range 0.02-4.53)	3.0
Primary outcome					
Incidence rate for primary outcome per 100 patient-year	3.74 vs. 4.39	2.69 vs. 3.15	2.26 vs. 2.42	3.87 vs. 4.87	3.9 vs. 4.0
Hazard ratio (95% CI) for the three-point MACE	0.86 (0.74–0.99) <i>P</i> <0.001 for non-inferiority; and <i>P</i> =0.04 for superiority	0.86 (0.75–0.97) <i>P</i> <0.001 for non-inferiority, and <i>P</i> =0.02 for superiority	0.93 (0.84–1.03) <i>P</i> <0.001 for non-inferiority; and <i>P</i> =0.17 for superiority	0.80 (0.67–0.95) <i>P</i> =0.01 for superiority	0.97 (0.85–1.11), <i>P</i> <0.001 value for non-inferiority <i>P</i> for superiority non-significant (not reported)
<b>Secondary outcomes [given as incidence rate per 100 patient-year and hazard ratio (95% confidence interval)]</b>					
Total mortality	1.94 vs. 2.86 0.68 (0.57-0.82) <i>P</i> <0.001*	1.73 vs. 1.95 0.87 (0.74-1.01)	1.51 vs. 1.64 0.93 (0.82-1.04)	0.83 (0.68-1.02)	0.93 (0.80-1.08)
CV mortality	1.24 vs. 2.02 0.62 (0.49-0.77) <i>P</i> <0.001*	1.16 vs. 1.28 0.87 (0.72-1.06)	0.70 vs. 0.71 0.98 (0.82-1.17)	0.78 (0.61-1.00) * ( <i>P</i> =0.05)	0.92 (0.77-1.11)
Fatal/non-fatal MI	1.68 vs. 1.93 0.87 (0.70-1.09) (excluding silent MI) <i>P</i> =0.23	1.12 vs. 1.26 0.89 (0.73-1.09) (including silent MI)	1.17 vs. 1.32 0.89 (0.77-1.01)	0.86 (0.64-1.16)	1.04 (0.86-1.26)
Non-fatal MI	1.60 vs. 1.85 0.87 (0.70-1.09) (excluding silent MI) <i>P</i> =0.22	0.97 vs. 1.16 0.85 (0.69-1.05)		0.81 (0.59-1.10)	1.0 (0.86-1.27)
Fatal/non-fatal stroke	1.23 vs. 1.05 1.18 (0.89-1.56) <i>P</i> =0.26	0.79 vs. 0.96 0.87 (0.69-1.09)	0.69 vs. 0.68 1.01 (0.84-1.21)	0.77 (0.55-1.08)	1.06 (0.82-1.37)
Non-fatal stroke	1.12 vs. 0.91 1.24 (0.92-1.67) <i>P</i> =0.16	0.71 vs. 0.84 0.90 (0.71-1.15)		0.80 (0.56-1.15)	1.0 (0.76-1.32)
Hospitalization for HF	0.94 vs. 1.45 0.65 (0.50-0.85) <i>P</i> =0.002*	0.55 vs. 0.87 0.67 (0.52-0.87)	0.62 vs. 0.85 0.73 (0.61-0.88)	0.61 (0.47-0.80) ( <i>P</i> <0.001)	0.70 (0.54-0.90)

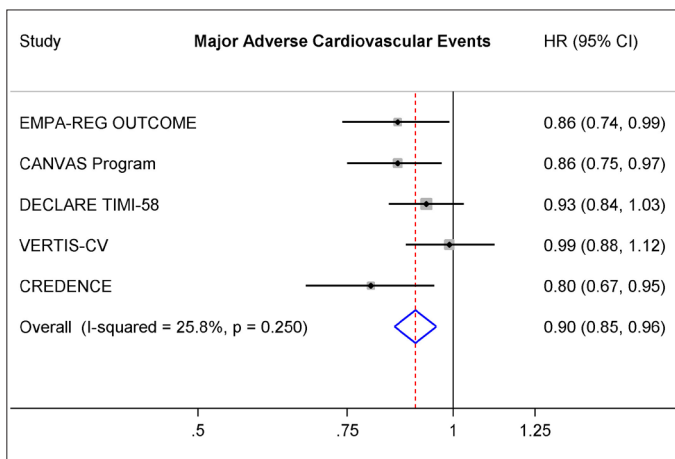
\*Not considered significant due to hierarchical test procedure.

BMI - body mass index, CAD - coronary artery disease, CV - cardiovascular, CVD - cardiovascular disease, DM - diabetes mellitus, ESRD - end-stage kidney disease, eGFR - estimated glomerular filtration rate, HbA1c - glycated hemoglobin, HF - heart failure, MI - myocardial infarction, PAD - peripheral artery disease, Pts - patients, SGLT2 - sodium-glucose co-transporter 2, UT - urinary tract

established CV diseases at baseline), which is the highest in the EMPA-REG OUTCOME (3.74 vs. 4.39 per 100-person years) and VERTIS-CV (3.9 vs. 4.0 per 100-person-years) trials; the lowest in the DECLARE TIMI-58 trial (2.26 vs. 2.42 per 100-person years); and at intermediate level in the CANVAS trial (2.69 vs. 3.15 per 100-person years) (Table 5). Although the presence of CV disease at baseline was not an inclusion criteria, the incidence rate in the CREDESCENCE study (3.87 vs. 4.87 per 100-person-years) was similar to that in the EMPA-REG OUTCOME and VERTIS-CV trials, which might be explained, at least in part, by enrolling

more patients with chronic kidney disease.

All of the four CV non-inferiority trials met the non-inferiority criteria (Table 5). Both empagliflozin and canagliflozin were superior to placebo in terms of the primary safety outcome of the three-point MACE and provided consistent risk reduction [HR and 95% CI 0.86 (0.74–0.99) with empagliflozin; 0.86 (0.75–0.97) with canagliflozin in the CANVAS Program, and 0.80 (0.67–0.95) with canagliflozin in the CREDESCENCE trial]. On the other hand, dapagliflozin [HR 0.93 (0.84–1.03)] and ertugliflozin [HR 0.97 (0.85–1.11)] were not found to be superior to placebo possibly



**Figure 4.** Effect of SGLT-2 inhibitors on the composite of CV death, non-fatal MI, and non-fatal stroke (intention-to-treat population)

due to several factors, such as methodological differences, statin use at baseline (highest in the VERTIS-CV), play of chance, or drug-specific effect.

There are some other differences between the results of these studies that would be better to mention with some caution, as all of them are exploratory analyses. The reduction in the primary outcome with empagliflozin seems to be driven primarily by the reduction in CV mortality. Total mortality was also decreased with empagliflozin (Table 5). For other components of the primary outcome, there was a non-significant decrease in non-fatal MI (excluding silent MI) and a non-significant increase in non-fatal stroke. Of note, HR for non-significant decrease in non-fatal MI was consistent with the decrease in the primary outcome (0.87, 95% CI 0.70–1.09 vs. 0.86, 95% CI 0.74–0.99, respectively), thus suggesting that the non-significant result for non-fatal MI might be caused by a type-II error (false negative result) due to low number of event. The non-significant trend for increased non-fatal stroke in the EMPA-REG OUTCOME trial was not observed in the other three trials. In a further analysis of the EMPA-REG OUTCOME trial, non-significant increase in stroke has been attributed to the events occurring 90 days after the last intake of empagliflozin (34). In the CANVAS trial, the estimate of risk reduction for each component was similar to that obtained for the primary end-point, suggesting that each component contributed similarly to the reduction in the primary outcome.

One of the most important findings obtained from SGLT-2 inhibitors is the significant reduction in the hospitalization for heart failure that is observed in all studies, and this result determines the population that benefited from SGLT-2 inhibitors most.

In our pooled analyses (Fig. 4, 5, Table 3), SGLT-2 inhibitors significantly reduced the three-point MACE (HR 0.90, 95% CI 0.85–0.96;  $p < 0.001$ ), CV death (HR 0.85, 95% CI 0.78–0.93;  $p < 0.001$ ), total mortality (HR 0.87, 95% CI 0.81–0.93;  $p < 0.001$ ), and fatal or non-fatal MI (HR 0.91, 95% CI 0.84–0.99;  $p = 0.034$ ). The most impressive result was the reduction in the hospitalization for heart failure (HR 0.68, 95% CI 0.61–0.76;  $p < 0.001$ ). On the other hand, the risk of non-fatal MI ( $p = 0.092$ ), non-fatal stroke, and

fatal or non-fatal stroke was similar for SGLT-2 inhibitors and placebo groups.

Subgroup analyses provided inconsistent results between the studies: the results seemed to be better for patients aged  $\geq 65$  years or HbA1c levels of  $< 8.5\%$  with empagliflozin; participants on diuretics or beta-blockers with canagliflozin (CANVAS Program); those with DM of  $\geq 10$  years with dapagliflozin; and similar in all subgroups with ertugliflozin. Because of the inconsistencies and the nature of subgroup analyses, these results can be explained by chance.

The EMPA-REG OUTCOME, CANVAS, and VERTIS-CV trials had three arms, and randomized patients to low-dose, high-dose, and placebo groups. In our analyses, the reduction in the primary outcome with low and high doses of empagliflozin and ertugliflozin were consistent ( $p$  values for interaction were 0.923 and 0.245 for empagliflozin and ertugliflozin, respectively), which suggest that the reduction in the primary outcome is independent of the dose, and dose should be based on the glycemic control and side effects but not on the CV benefit. We could not analyze the data for low and high-dose of canagliflozin as we could not obtain the necessary data.

#### Other effects and safety

SGLT-2 inhibitors led to a modest decrease in HbA1c level (less than that obtained with GLP-1 agonists), and in systolic and diastolic blood pressure without increasing heart rate. The risk of severe hypoglycemia was not increased. Compared with placebo, the frequency of serious adverse effects was less common with empagliflozin, canagliflozin and dapagliflozin, but similar with ertugliflozin. Moreover, the frequency of serious adverse effects leading to discontinuation of study medication was significantly higher with empagliflozin and dapagliflozin, there was a trend for being higher with canagliflozin (CANVAS Program), and similar with ertugliflozin.

SGLT-2 inhibitors slightly increased LDL and high-density lipoprotein (HDL) cholesterol levels. However, CANVAS study showed that LDL/HDL cholesterol ratio did not change. Moreover, a small study showed that dapagliflozin reduced small-dense LDL cholesterol and increased large-buoyant LDL cholesterol and HDL-2 cholesterol subtypes, which provide a favorable metabolic profile (35). Therefore, an increase in LDL cholesterol with SGLT-2 inhibitors (at least for some SGLT-2 inhibitors) may not pose a high risk for CV events.

In the CANVAS trial, canagliflozin increased the risk of amputation, especially in patients with a history of amputation, but with unknown cause. However, the CREDESCENCE trial did not report any increase in the risk of amputation. The FDA issued a black-box warning on canagliflozin in 2017 due to this concern, but recently retracted, and instead included it in the Warning and Precautions section of the prescribing information. The warning was removed in consideration of the benefit of canagliflozin for CV and renal outcomes, and the risk of amputation was lower, but still increased, than previously observed.

In contrast to other trials, an increased risk of bone fracture was observed with canagliflozin in the CANVAS Program, which

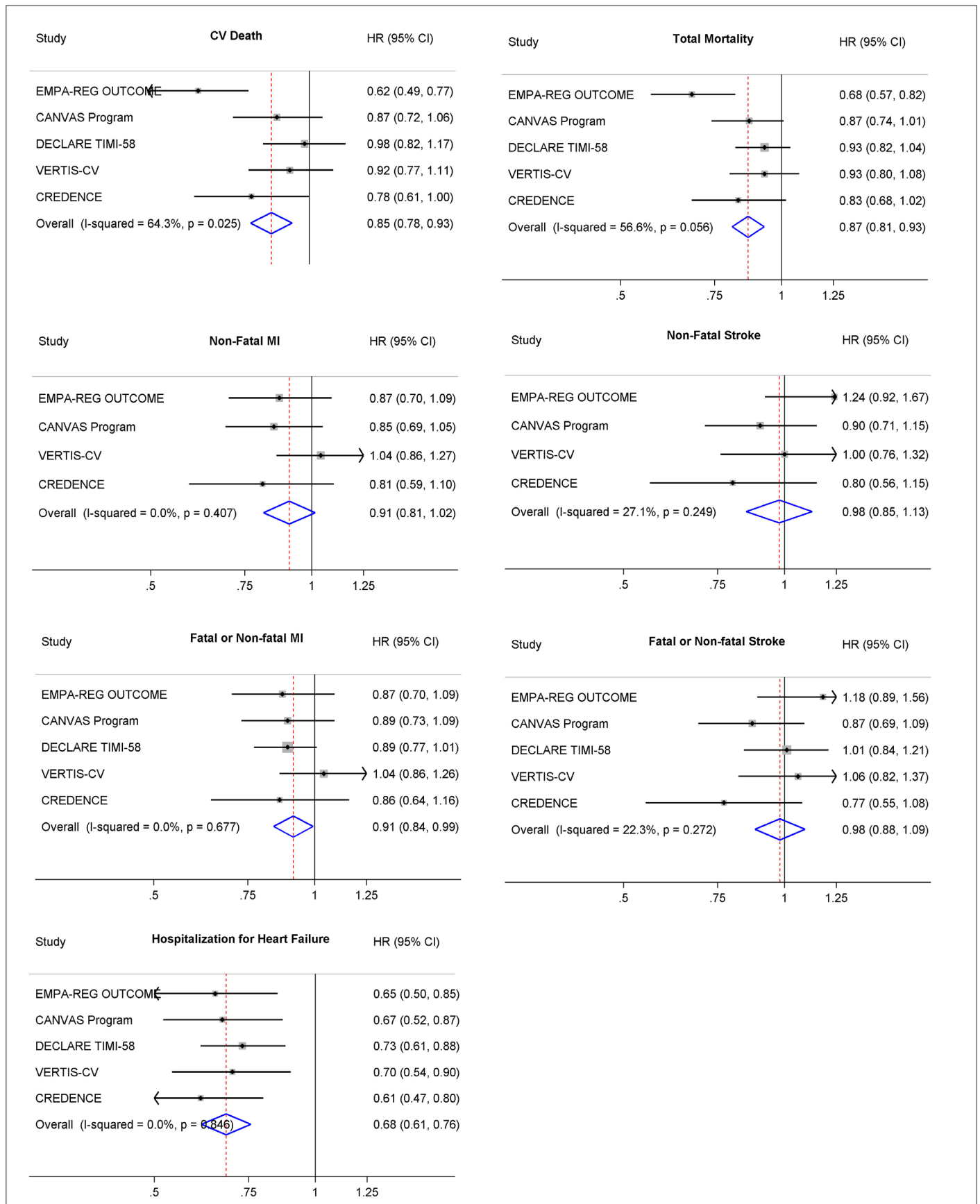


Figure 5. Effect of SGLT-2 inhibitors on each component of the primary outcome and some selected CV outcomes.



was also observed in another earlier study with canagliflozin (33). The CANVAS Program composed of two similar randomized trials, CANVAS and CANVAS-R. Interestingly, despite the similar characteristics of these studies, an increased risk of fracture was observed only in the CANVAS but not in the CANVAS-R, which is difficult to explain. Moreover, the risk of fracture was not increased in the CREDENCE trial, as well.

One of the most important drawbacks of SGLT-2 inhibitors is that all of them increase the risk of mycotic genital infections probably due to glycosuric effect, and it is higher in women than in men. SGLT-2 inhibitors may increase the risk of diabetic ketoacidosis compared to placebo, but the risk is too low.

### **SGLT-2 inhibitors in the treatment of heart failure**

All of the CV outcome studies with SGLT-2 inhibitors demonstrated substantial and consistent reduction in the risk of hospitalization for heart failure. Two studies were specifically conducted in patients with heart failure to assess the risk reduction: DAPA-HF (26) and EMPEROR-Reduced (27). Both studies compared SGLT-2 inhibitors (10 mg dapagliflozin in DAPA-HF, and 10 mg empagliflozin in EMPEROR-Reduced) with placebo in patients with NYHA II-IV heart failure with ejection fraction of less than 40%. The primary outcome was slightly different: composite of worsening of heart failure (defined as hospitalization or urgent visit requiring intravenous treatment for heart failure) or CV death in DAPA-HF, and composite of hospitalization for heart failure or CV death in EMPEROR-Reduced. The mean age was 66 vs. 67 years and the mean ejection fraction was 31% vs. 27% in DAPA-HF and EMPEROR-Reduced, respectively. The proportion of patients with NYHA IV heart failure was less than 1% in both studies, and approximately 67% and 75% of the patients in DAPA-HF and EMPEROR-Reduced trials had NYHA II heart failure, respectively. The use of contemporary CV medication was high in both studies. The median follow-up duration was 18.2 months (range 0–27.8) in DAPA-HF and 16 months in the EMPEROR-Reduced. A similar reduction in the primary outcome was observed in both trials: HR (95% CI) values were 0.74 (0.65–0.85) and 0.75 (0.65–0.86) in DAPA-HF and EMPEROR-Reduced, respectively ( $p$  values <0.001). Recent meta-analysis of DAPA-HF and EMPEROR-Reduced trials demonstrated that these drugs reduced the risk of total mortality (HR and 95% CI, 0.87 and 0.77–0.98), cardiovascular mortality (HR and 95% CI, 0.86 and 0.76–0.98), and composite of hospitalization for heart failure or CV death (HR and 95% CI 0.74 and 0.68–0.82) in patients with heart failure with reduced ejection fraction (36). The benefit was observed regardless of the presence of DM. Reductions in the composite outcome were consistent in most of the subgroups, but the effect seemed to decrease in patients with NYHA III-IV, in white patients, and those enrolled in Europe.

### **Guidelines for GLP-1 agonists and SGLT-2 inhibitors**

In the algorithm given in the 2019 European Society of Cardiology and European Association for the Study of Diabetes Guidelines (37), the first and the main factor in selecting the

appropriate drug in patients with diabetes mellitus is the presence or absence of established CV disease or high/very high-risk characteristics. In the presence of any of these risks, it is recommended to initiate either SGLT-2 inhibitors or GLP-1 agonists with proven CV benefit. On the other hand, in the American Diabetes Association (ADA) guidelines (38), metformin and lifestyle changes are recommended in the first step, followed by the addition of GLP-1 agonists or SGLT-2 inhibitors to the treatment in the presence of established CV diseases or high-risk characteristics for CV diseases. Another difference between the guidelines is that ADA prioritizes GLP-1 agonists for patients with established CV disease, and SGLT-2 inhibitors for those with heart failure or chronic kidney diseases predominates. Therefore, even if the algorithms are slightly different, both recommend GLP-1 agonists or SGLT-2 inhibitors for diabetic patients who have established CV diseases or high-risk characteristics for the development of CV diseases.

### **Limitations**

In this review, we aimed to provide an up-to-date information only for the CV outcome trials of GLP-1 agonists and SGLT-2 inhibitors, focusing on the three-point MACE, its components, and total mortality. Therefore, other trials and outcomes such as glycemic control, metabolic parameters, and ocular and renal outcomes were not given in detail.

In order to obtain the CV outcome trials of GLP-1 agonists and SGLT-2 inhibitors, we searched the PubMed, then summarized and compared the results of each trial, and provided the pooled results. Our aim was to evaluate the data with a wide perspective. However, we do not consider our review as a classical systematic review and meta-analysis, as stringent rules, such as screening multiple databases with more than one researcher, was not applied. Further, a pooled analysis was performed using the study-level data, not individual participant data. In the absence of the individual data, pooling may be misleading, especially for subgroup analysis, which is the common limitation of all study-level meta-analyses.

### **Future perspective and conclusion**

Several studies with SGLT-2 inhibitors are ongoing in heart failure patients with preserved ejection fraction (dapagliflozin: PRESERVED-HF; empagliflozin: EMPEROR-Preserved), which are expected to be completed in 2021. We will see whether SGLT-2 inhibitors will also be beneficial in these patients for whom limited medical options are available. Some other studies are ongoing or planned in patients with acute heart failure or acute MI patients with reduced ejection fraction as well.

In conclusion, in agreement with the individual study data and several meta-analyses, our pooled analysis demonstrated that both GLP-1 agonists and SGLT-2 inhibitors are effective in reducing CV events in diabetic patients with established CV disease or those with high-risk factors for CV disease. The SGLT-2 inhibitors markedly reduce the risk of hospitalization for heart failure even in patients without DM at baseline. Importantly, these benefits are obtained on top of the contemporary medications. Thus, they are

more than anti-diabetics and might be described as CV risk-reducing medications. Therefore, they will change the practice of not only endocrinologists but also cardiologists and internal medicine specialists. It is not known whether the benefit will be generalizable to patients with relatively lower risk for CV disease, as they have not been tested in these groups.

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**Supplemental Appendix**  
**Supplement to “An updated perspective and pooled analysis of Cardiovascular outcome trials of GLP-1 receptor agonists and SGLT-2 inhibitors”**

**Keywords for PubMed search for GLP-1 receptor agonists**

"Glucagon-like peptide-1 receptor agonist"[Title/Abstract] OR "GLP-1 agonist"[Title/Abstract] OR "GLP-1 receptor agonist"[Title/Abstract] OR Exenatide[Title/Abstract] OR lixisenatide[Title/Abstract] OR Dulaglutide[Title/Abstract] OR liraglutide[Title/Abstract] OR semaglutide[Title/Abstract] OR lixisenatide[Title/Abstract] OR albiglutide[Title/Abstract] AND ("cardiovascular outcome"[Title/Abstract] OR cardiovascular[Title/Abstract] OR outcome[Title/Abstract] OR safety[Title/Abstract])

**Keywords for PubMed search for SGLT-2 inhibitors**

"SGLT-2 inhibitors"[Title/Abstract] OR gliflozin\*[Title/Abstract] OR Canagliflozin[Title/Abstract] OR Dapagliflozin[Title/Abstract] OR Empagliflozin[Title/Abstract] OR Ertugliflozin[Title/Abstract] OR Ipragliflozin[Title/Abstract] AND ("cardiovascular outcome"[Title/Abstract] OR cardiovascular[Title/Abstract] OR outcome[Title/Abstract] OR safety[Title/Abstract])

<b>S-Table 1. Inclusion and exclusion criteria of the of the trials of GLP-1 receptor agonists included in the pooled analysis</b>							
	<b>ELIXA</b>	<b>LEADER</b>	<b>SUSTAIN-6</b>	<b>EXSCEL</b>	<b>HARMONY</b>	<b>PIONEER-6</b>	<b>REWIND</b>
Publication year	2015	2016	2016	2017	2018	2019	2019
Comparison	Lixisenatide vs. placebo	Liraglutide vs. placebo	Semaglutide vs. placebo	Exenatide vs. placebo	Albiglutide vs. placebo	Oral semaglutide vs. placebo	Dulaglutide vs. placebo
<b>Inclusion criteria</b>							
Presence of CVD	≥30 years old with ACS (including UAP) within 180 days.	≥50 years old with established CVD (including NYHA II–III, and eGFR < 60 mL/min/1.73 m <sup>2</sup> for Modification in Diet in Renal Disease formula) or < 60 mL/min for Cockcroft-Gault formula OR ≥60 years old with high-risk criteria for CV disease (any of the following): - Microalbuminuria / proteinuria. - Hypertensive LVH hypertrophy (based on ECG or imaging). - LV systolic or diastolic dysfunction. - ABI < 0.9	Similar to the LEADER study	≥18 years old Pts with any level of CV risk (recruitment was restricted so as to had approximately 70% of participants with a history of CV events)	≥40 years old AND established CVD	Similar to the LEADER study	≥50 years old with established CVD OR ≥55 years old with subclinical vascular disease (including eGFR < 60 ml/min/1.73 m <sup>2</sup> ) OR ≥60 years old and having ≥2 of the following risk factors - Current tobacco user - LDL-C ≥130 mg/dL - HDL-C < 50 mg/dL or - Triglycerides ≥200 mg/dL - BP ≥140/95 mmHg or taking medication for hypertension - Waist-to-hip ratio >1 and 0.8 for men and women, respectively.
HbA1C (%) criteria	≥5.5 and ≤11.0	≥7.0	≥7.0	≥6.5 and ≤10.0	>7.0	No restriction for HbA1c for eligibility	≥6.5 and ≤9.5 Allows recruitment of Pts not taking glucose lowering medication at baseline BMI ≥23 kg/m <sup>2</sup> 100% adherence in the run-in period

**S-Table 1. Inclusion and exclusion criteria of the of the trials of GLP-1 receptor agonists included in the pooled analysis (Continue)**

ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	PIONEER-6	REWIND
<b>Selected exclusion criteria</b>						
<ul style="list-style-type: none"> <li>- Type 1 DM</li> <li>- History of ketoacidosis within 6-month</li> <li>- Planned revascularization within 90-d - PCI within 15-d</li> <li>- History of pancreatitis.</li> <li>- Familial medullary thyroid cancer (or genetic predisposition)</li> <li>- History of gastrointestinal disease associated with prolonged nausea or vomiting</li> <li>- Calcitonin &gt; 20 ng/L</li> <li>- eGFR &lt; 30 ml/min/1.73 m<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Type 1 DM - Calcitonin ≥50 ng/L</li> <li>- ACS or cerebrovascular event <i>within</i> 14 d</li> <li>- Planned revascularization - NYHA IV</li> <li>- Renal replacement therapy</li> <li>- End-stage liver disease - Malignancy</li> <li>- Thyroid medullary cancer</li> <li>- MEN type-II or familial medullary thyroid cancer</li> </ul>	<ul style="list-style-type: none"> <li>Similar to the LEADER study, except;</li> <li>- ACS or cerebrovascular event <i>within</i> 90 d</li> <li>- Malignancy <i>within</i> 5 year</li> <li><i>ALSO</i></li> <li>History of chronic pancreatitis or idiopathic acute pancreatitis</li> </ul>	<ul style="list-style-type: none"> <li>- Type 1 DM</li> <li>- History of ketoacidosis</li> <li>- Planned revascularization</li> <li>- End-stage renal disease or eGFR &lt; 30 ml/min/1.73 m<sup>2</sup></li> <li>- Gastroparesis</li> <li>- Personal or family history of thyroid medullary cancer or MEN-II</li> <li>- Calcitonin ≥40 ng/L</li> <li>- History of pancreatitis</li> </ul>	<ul style="list-style-type: none"> <li>- Planned revascularization</li> <li>- Spontaneous MI within 30-d, or ischemic stroke within 90-d</li> <li>- Renal replacement therapy or eGFR &lt; 30 ml/min/1.73 m<sup>2</sup></li> <li>- Severe gastroparesis requiring treatment within 6-month</li> <li>- History of pancreatitis</li> <li>- Personal or family history of thyroid medullary cancer</li> <li>- MEN-II (Calcitonin level was not used as an exclusion criterion)</li> <li>- History of pancreatitis</li> </ul>	<ul style="list-style-type: none"> <li>Similar to the LEADER study, except;</li> <li>- ACS or cerebrovascular event <i>within</i> 2 months</li> <li>- Malignancy <i>within</i> 5 year (except basal or squamous cell carcinoma of skin. or carcinoma in situ)</li> <li>- History of chronic pancreatitis or idiopathic acute pancreatitis</li> <li>- Proliferative retinopathy or maculopathy requiring acute treatment</li> <li>- History of surgery affecting absorption</li> </ul>	<ul style="list-style-type: none"> <li>- ACS or cerebrovascular event <i>within</i> 2 months</li> <li>- Planned revascularization</li> <li>- eGFR &lt; 15 ml/min/1.73 m<sup>2</sup> or on chronic dialysis</li> <li>- Severe gastroparesis or gastric bypass surgery</li> <li>- History of chronic, acute or idiopathic pancreatitis</li> <li>- Severe hepatic dysfunction</li> <li>- Personal or family history of thyroid medullary cancer or MEN-II</li> <li>- Calcitonin &gt; 20 ng/L</li> <li>- Malignancy <i>within</i> 5 year (except basal or squamous cell carcinoma of skin. or carcinoma in situ)</li> </ul>
<p>ACS - acute coronary syndrome, ABI - ankle brachial index, BP - blood pressure, BMI - body mass index, CAD - coronary artery disease, CV - cardiovascular, CVD - cardiovascular disease, DM - diabetes mellitus, eGFR - estimated glomerular filtration rate, GLP1 - Glucagon-like peptide-1, HbA1c - glycated hemoglobin, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, LV - left ventricular, LVH - left ventricular hypertrophy, MEN - multiple endocrine neoplasia, NYHA- New York Heart Association, PAD - peripheral artery disease, PCI - percutaneous coronary intervention, TIA - transient ischemic attack, UAP - unstable angina pectoris</p>						



**S-Table 2. Inclusion and exclusion criteria of the of the trials of the SGLT-2 inhibitors included in the pooled analysis**

	<b>EMPA-REG OUTCOME</b>	<b>CANVAS Program</b>	<b>DECLARE TIMI-58</b>	<b>CREDESCENCE</b>	<b>VERTIS-CV</b>
Publication year	2015	2017	2018	2019	2020
Comparison	Empagliflozin vs. placebo	Canagliflozin vs. placebo	Dapagliflozin 10 mg vs. placebo	Canagliflozin vs. placebo	Ertugliflozin vs. placebo
Inclusion criteria	- Age $\geq 18$ years and body - BMI $\leq 45$ kg/m <sup>2</sup>	- HbA1c $\geq 7.0\%$ and $\leq 10.5\%$	Age $\geq 40$ years - HbA1c $\geq 6.5\%$ and $< 12\%$ - Creatinine clearance $\geq 60$ mL/min (Cockcroft-Gault equation)	- Age $\geq 30$ years - HbA1c 6.5%–12.0% - eGFR 30–90 mL/min/1.73 m <sup>2</sup> and albuminuria - Being on a stable maximum or tolerable dose of ACEI or ARB within 4 weeks of randomization	- Age $\geq 40$ years - HbA1c 7%–10.5% - BMI $\geq 18$ kg/m <sup>2</sup>
Presence of CVD	Established CVD	$\geq 30$ years old and a history of symptomatic ASCVD OR $\geq 50$ years old and having $\geq 2$ CV risk factors given below - Duration of DM $\geq 10$ years - Systolic BP $> 140$ mm Hg while on antihypertensive medication - Current smoking - Micro/macroalbuminuria - HDL-C $< 1$ mmol/L (38.7 mg/dL)	Established CVD OR Age $\geq 55$ years in men and $\geq 60$ years in women AND any of the following risk factors - LDL-C $> 130$ mg/dL within 12 months or on LLT given for the same LDL-C criterion - Systolic BP $> 140$ mm Hg AND diastolic BP $> 90$ mm Hg or being on antihypertensive therapy - Current tobacco use ( $\geq 5$ cigarettes/day for $\geq 1$ year)	Presence of CVD is not an inclusion criteria except established chronic kidney disease	Established CVD
HbA1c (%)	For drug-naïve patients: $\geq 7$ and $\leq 9$ For Pts with background treatment: $\geq 7$ and $\leq 10$	$\geq 7.0$ and $\leq 10.5$	$\geq 6.5$ and $< 12$	6.5–12.0 (6.5–10.5 in Germany)	7–10.5
Selected exclusion criteria	- Uncontrolled hyperglycemia ( $> 240$ mg/dL) - Planned cardiac surgery or revascularization within 3 months - ACS, stroke or TIA within 2 - months - eGFR $< 30$ mL/min/1.73 m <sup>2</sup> (MDRD) - Liver enzymes $> 3 \times$ ULN - Gastrointestinal surgery that may induce malabsorption	- Current use of corticosteroid - eGFR $< 30$ mL/min/1.73 m <sup>2</sup> - History of ketoacidosis - History of severe hypoglycemia within 6 months - MI, UAP, revascularization, cerebrovascular event within 3 months - Planned revascularization - NYHA class IV	- Being on corticosteroid treatment - Acute CV events (including ACS, TIA, stroke, revascularization, decompensated HF and sustained VT) within 8 weeks - Systolic BP $> 180$ mm Hg or Diastolic BP $> 100$ mm Hg at randomization - History of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time - Other malignancies within 5 years (excluding successfully treated non-melanoma skin cancer)	History of ketoacidosis - Uncontrolled HT ( $\geq 180/100$ mm Hg) - MI, revascularization or cerebrovascular events within 12 weeks before randomization, or planned revascularization - NYHA IV - ECG abnormalities that may require urgent diagnostic or therapeutic intervention - Significant liver disease - ALT $> 2 \times$ , bilirubin $> 1.5 \times$ ULN	- Experiencing CV events or vascular intervention between the screening visit and randomization - CV surgery within 3 months of the screening visit - Planned revascularization or CV surgery - NYHA IV (and NYHA III after protocol amendment) - Systolic BP $> 160/90$ mm Hg (Pts were allowed to be reassessed after antihypertensive treatment for eligibility)

**S-Table 2. Inclusion and exclusion criteria of the of the trials of the SGLT-2 inhibitors included in the pooled analysis (Continue)**

<b>EMPA-REG OUTCOME</b>	<b>CANVAS Program</b>	<b>DECLARE TIMI-58</b>	<b>CREDESCENCE</b>	<b>VERTIS-CV</b>
<ul style="list-style-type: none"> <li>- Cancer &lt; 5 years</li> <li>- Premenopausal women who were nursing, pregnant or not practicing an acceptable contraception</li> </ul>	<ul style="list-style-type: none"> <li>- Clinically active liver disease or hepatitis B/C with increased enzyme levels</li> <li>- ALT &gt;2xULN or bilirubin &gt;1.5 x ULN</li> <li>- Malignancy &lt; 5 years (except squamous or basal cell cancer of skin or carcinoma in situ)</li> <li>- Planned major surgery within 3 months</li> <li>- Pregnant or breastfeeding or planning to become pregnant</li> </ul>	<ul style="list-style-type: none"> <li>- Chronic cystitis and/or recurrent urinary tract infection (<math>\geq 3</math> in the last year)</li> <li>- Pregnant or breastfeeding</li> <li>- AST/ALT/total bilirubin &gt; 2.5xULN</li> <li>- eGFR &lt; 60 mL/min (Cockcroft-Gault equation)</li> </ul>	<ul style="list-style-type: none"> <li>- History of malignancy within 5 years, except squamous or basal cell carcinoma of skin or cervical carcinoma in situ.</li> <li>- Major surgery within 12 weeks</li> <li>- Atraumatic amputation within 12 months, or critical ischemia, osteomyelitis or gangrene of the lower extremity within 6 months (added after the study has started)</li> <li>- Use of mineralocorticoid receptor antagonist</li> <li>-</li> </ul>	<ul style="list-style-type: none"> <li>- Clinically significant ECG at the screening visit that requires further evaluation or intervention.</li> <li>- History of type 1 DM or ketoacidosis</li> <li>- Patients has active obstructive uropathy or indwelling urinary catheter</li> <li>- Malignancy within 5 years (except adequately treated basal cell or squamous cell cancer or cervical carcinoma in situ)</li> <li>- &gt;2 alcoholic drinks/day or &gt;14 /week, or engages in binge drinking</li> <li>- Clinically significant malabsorption</li> <li>- History of <math>\geq 1</math> severe hypoglycemic episodes within 6 months or between screening visit and randomization</li> <li>- Triglycerides &gt;600 mg/dL (can be reassessed for eligibility after treatment)</li> <li>- Patients undergone bariatric surgery within 12 months; or &gt;12 months and is not weight-stable</li> <li>- eGFR &lt; 30 mL/min/1.73 m<sup>2</sup> (MDRD)</li> <li>- AST or ALT &gt;2xULN, total bilirubin &gt;1.5x ULN</li> <li>- Active liver disease (except non-alcoholic hepatic steatosis) - Being on or likely to require treatment for <math>\geq 14</math> days of corticosteroids</li> </ul>
<p>ACS - acute coronary syndrome, ACEI - angiotensin converting enzyme inhibitor, ABI - ankle brachial index, ALT - alanine transferase, ARB - angiotensin receptor blocker, AST - aspartate transferase, BP - blood pressure, BMI - body mass index, CAD - coronary artery disease, CT - computed tomographic, CV - cardiovascular, CVD - cardiovascular disease, DM - diabetes mellitus, eGFR - estimated glomerular filtration rate, HbA1c - glycated hemoglobin, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, LLT - lipid-lowering therapy, NYHA - New York Heart Association, PAD - peripheral artery disease, PCI - percutaneous coronary intervention, TIA - transient ischemic attack, UAP: unstable angina pectoris, ULN - upper limit of normal</p>				