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# **Sodium Glucose Co-transporter 2 Inhibitors and Major Adverse Cardiovascular Outcomes: A SMART-C Collaborative Meta-Analysis**

**Running title:** *Patel et al.; SGLT2i and Major Adverse Cardiovascular Outcomes*

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## Abstract

**Background:** Sodium glucose co-transporter 2 inhibitors (SGLT2i) consistently improve heart failure and kidney-related outcomes; however, effects on major adverse cardiovascular events (MACE) across different patient populations are less clear.

**Methods:** This was a collaborative trial-level meta-analysis from the SGLT2i meta-analysis cardio-renal trialists consortium, which includes all phase 3, placebo-controlled, outcomes trials of SGLT2i across three patient populations (diabetes at high risk for atherosclerotic cardiovascular disease [ASCVD], heart failure [HF], or chronic kidney disease [CKD]). The outcomes of interest were MACE (composite of CV death, myocardial infarction [MI], or stroke), individual components of MACE (inclusive of fatal and non-fatal events), all-cause mortality, and death subtypes. Effect estimates for SGLT2i vs. placebo were meta-analyzed across trials and examined across key subgroups (established ASCVD, prior MI, diabetes, prior HF, albuminuria, CKD stages and risk groups).

**Results:** A total of 78,607 patients across 11 trials were included: 42,568 (54.2%), 20,725 (26.4%), and 15,314 (19.5%) were included from trials of patients with diabetes at high risk for ASCVD, HF, or CKD, respectively. SGLT2i reduced the rate of MACE by 9% (HR 0.91 [95%CI 0.87-0.96],  $p < 0.0001$ ) with a consistent effect across all three patient populations ( $I^2 = 0\%$ ) and across all key subgroups. This effect was primarily driven by a reduction in CV death (HR 0.86 [0.81-0.92],  $p < 0.0001$ ), with no significant effect for MI in the overall population (HR 0.95 [0.87-1.04],  $p = 0.29$ ), and no effect on stroke (HR 0.99 [0.91-1.07],  $p = 0.77$ ). The benefit for CV death was driven primarily by reductions in HF death and sudden cardiac death (HR 0.68 [0.46-1.02] and HR 0.86 [0.78-0.95], respectively) and was generally consistent across subgroups, with the possible exception of being more apparent in those with albuminuria ( $P_{int} = 0.02$ ).

**Conclusion:** SGLT2i reduce the risk of MACE across a broad range of patients irrespective of ASCVD, diabetes, kidney function or other major clinical characteristics at baseline. This effect is driven primarily by a reduction of CV death, particularly HF and sudden cardiac death, without a significant effect on MI in the overall population, and no effect on stroke. These data may help inform selection for SGLT2i therapies across the spectrum of cardiovascular-kidney-metabolic disease.

**Key Words:** chronic kidney disease, diabetes, metabolic syndrome, sodium glucose co-transporter 2 inhibitors, meta-analysis

## Non-standard Acronyms and Abbreviations

ASCVD: atherosclerotic cardiovascular disease

KDIGO: Kidney Disease Improving Global Outcomes

MACE: major adverse cardiovascular events

MI: myocardial infarction

SGLT2i: sodium glucose co-transporter 2 inhibitors

SMART-C: SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists Consortium

## Clinical Perspectives

### What is new?

- Sodium glucose co-transporter 2 inhibitors (SGLT2i) reduce the risk of major adverse cardiovascular events (MACE: composite of cardiovascular death, myocardial infarction, or stroke) across a broad range of patient populations and key subgroups.
- The primary benefit of SGLT2i for MACE is driven by a reduction in cardiovascular death, without a clear effect on myocardial infarction or stroke.
- The treatment benefit of SGLT2i for cardiovascular death is mediated primarily by a reduction in the risk of heart failure death and sudden cardiac death.

### What are the clinical implications?

- These data suggest that SGLT2i have beneficial effects on MACE which are consistent irrespective of established atherosclerotic cardiovascular disease or diabetes status at baseline, and across a wide range of kidney function including in the subset of patients with advanced stage chronic kidney disease.
- Collectively, these data may help inform selection of SGLT2i therapy across a broad range of patients encountered in clinical practice.

## Introduction

Sodium glucose co-transporter 2 inhibitors (SGLT2i) have been rigorously examined in several large, randomized, placebo-controlled, clinical outcomes trials that have enrolled a broad range of patient populations including those with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD) or with multiple ASCVD risk factors,<sup>1-4</sup> heart failure across the ejection fraction spectrum,<sup>5-9</sup> and chronic kidney disease across a spectrum of severity.<sup>10-13</sup> While initially developed as glucose-lowering agents for use in patients with diabetes, data from these trials have demonstrated that SGLT2i provide consistent reductions in adverse heart failure and kidney outcomes across the class, irrespective of diabetes status at baseline.<sup>14,15</sup> However, the effects of SGLT2i on major adverse cardiovascular events (MACE) have been more modest, with differences observed between trials. Prior meta-analyses have been relatively underpowered to definitively examine the effects of SGLT2i on individual components of MACE or on subtypes of these components.<sup>16,17</sup> Moreover, ongoing uncertainty exists regarding the effects of SGLT2i on MACE across several important subgroups of patients, including those without ASCVD or diabetes at baseline, as well as those with more advanced stages of chronic kidney disease.

Accordingly, leveraging data from all large-scale, placebo-controlled, CV outcome trials of SGLT2i to date, we conducted a collaborative meta-analysis to examine the effect of SGLT2i on the risk of MACE and its individual components, overall and within clinically relevant subgroups of patients. We also assessed the effect of SGLT2i on death subtypes.

## Methods

### Search strategy and selection criteria

This study was a collaborative trial-level meta-analysis of the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists Consortium (SMART-C). To briefly summarize, SMART-C includes investigators of all large, placebo-controlled, phase 3 outcomes trials of SGLT2i, allowing for sharing of trial data across the consortium as previously described.<sup>15</sup> Each of the included trials was approved by the governing institutional review board or ethics committee at each site and written informed consent was obtained from all participants. We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA) reporting guideline. A systematic literature search of randomized, placebo-controlled CV outcomes trials of SGLT2i between January 1, 2012 and December 28, 2023 was conducted in PubMed (**Figure S1**). In order to restrict to studies of sufficient size and follow-up time to support a rigorous examination of the treatment effect of SGLT2i on cardiovascular events, eligible studies included phase 3 placebo-controlled, double-blind, randomized trials of SGLT2i therapy, which enrolled at least 1,000 participants in each arm, with median follow-up of at least 6 months. Studies with combination SGLT1/2i were excluded from the present analysis. All eligible studies were reviewed independently by 2 authors (S.M.P., Y.M.K.). Risk of bias assessments were also completed independently by two authors (S.M.P., Y.M.K.) using the Cochrane risk-of-bias assessment tool (**Table S1**). All conflicts were resolved by consensus discussion.





## Outcomes

The primary outcome of interest for this meta-analysis was the 3-point MACE composite of CV death, myocardial infarction (MI), and stroke (inclusive of all types). The individual components, inclusive of fatal and non-fatal events for MI and stroke, were also assessed. All-cause mortality (ACM) and subtypes of death (fatal MI, fatal stroke, heart failure death, sudden cardiac death, other CV death, and non-CV death), were also examined. All outcomes were reported at the trial level per standard definitions as described within the trial-specific CEC charters.<sup>1-8,10-12</sup> Each outcome was analyzed as time-to-event, and the trial-specific effect estimates used in the meta-analysis were intention-to-treat.

## Data Analysis

The SMART-C investigators provided the requisite trial-level summary data (hazard ratio and corresponding 95% confidence intervals [CI]) for each included study in this collaborative meta-analysis. Owing to the possibility that treatment effects for some outcomes may vary across the studied populations, trial effect estimates were first meta-analyzed using a fixed-effects model within each of the three primary patient populations (type 2 diabetes at high risk for ASCVD, heart failure and chronic kidney disease), and then pooled as random effects for calculation of the overall effect estimates. A sensitivity analysis was also performed using fixed effects to calculate overall estimates for the main effects. Heterogeneity of estimated treatment effects across the three primary trial populations was assessed using the Cochrane Q statistic and Higgins and Thompson's  $I^2$  and considered to be low if  $I^2$  was <25%, moderate if  $I^2$  was 25-75%, and high if  $I^2$  was  $\geq$ 75%.

Effect modification was examined by random effects meta regression models including an intercept and the subgroup of interest as a moderator using the method of residual maximum

likelihood and Hartung-Knapp adjustment. Pre-defined subgroups of interest in this study included: established ASCVD or not (protocol-defined in some trials, derived post-hoc in others; **Table S2**), diabetes status at baseline, prior MI, history of heart failure (specific pre-defined criteria in the heart failure trials, simple medical history question in the non-heart failure trials), chronic kidney disease (assessed dichotomously as estimated glomerular filtration rate [eGFR]  $<60$  vs.  $\geq 60$  mL/min/1.73 m<sup>2</sup> and categorically by the Kidney Disease Improving Global Outcomes [KDIGO] stages)<sup>18</sup>, albuminuria at baseline ( $<30$  vs.  $\geq 30$  mg/g), and KDIGO risk groups defined by a combination of eGFR and albuminuria.<sup>18</sup> Specifically for the ordered KDIGO stages and risk groups, a linear test-for-trend was used to examine increases or decreases in treatment effect across groups, whereas effect modification for the non-ordinal subgroups was assessed using a Hartung-Knapp test as mentioned above. Data availability for subgroups across trials is presented in **Table S3**.

All reported p values were two-sided, and values  $<0.05$  were considered statistically significant. However, heterogeneity and p-values were interpreted carefully in the context of multiple hypothesis testing. All analyses were performed using Metafor package<sup>19</sup> and R Statistical Software (v4.0.4; R Core Team 2021).

## Results

### Analysis Population Characteristics

A total of 78,607 patients were included across 11 randomized trials of SGLT2i versus placebo, with 42,568 (54.2%), 20,725 (26.4%), and 15,314 (19.5%) included from trials that focused on enrolling patients with diabetes at high risk for ASCVD, patients with established heart failure, or patients with chronic kidney disease, respectively (**Table 1**). The mean age ranged from 62-72 years across trials, with 27,702 (34.4%) patients of female sex and 58,571 (74.5%) of white race; older age and female sex tended to be more prevalent in the heart failure trial populations.

Overall, 62,654 (79.7%) patients had diabetes, 28,352 (36.0%) had heart failure, and 29,237 (37.2%) had an eGFR <60 mL/min/1.73 m<sup>2</sup> at baseline. A total of 46,305 (58.9%) patients had established ASCVD, and 22,414 (28.5%) had prior MI at baseline; both established ASCVD and prior MI were least prevalent among patients enrolled in the chronic kidney disease trials, with otherwise similar prevalence among the diabetes at high risk for ASCVD and heart failure trial populations (**Table 1**).

### Treatment Effect in Overall Population

The median follow-up ranged from 2.4 to 4.2 years, 1.3 to 2.2 years, and 2.0 to 2.6 years for the diabetes at high risk for ASCVD, heart failure, and chronic kidney disease trials, respectively (**Table 1**). A total of 7,976 (10.1%) patients experienced MACE, with 4,148 (5.3%), 2,819 (3.6%) and 2,220 (2.8%) experiencing CV death, MI, and stroke, respectively, during follow-up. Stratifying by trial population, incidence rates of MACE and CV death were highest in the heart failure trials, whereas rates of MI and stroke were highest in the trials of patients with diabetes at high risk for ASCVD (**Figures 1-2**).

SGLT2i reduced the rate of MACE by 9% overall (HR 0.91 [95% CI 0.87-0.96],  $p < 0.0001$ ), with a consistent effect observed across all three trial populations ( $I^2 = 0$ ; **Figure 1**). In terms of the individual components, SGLT2i had the clearest effect on CV death (HR 0.86 [95% CI 0.81-0.92],  $p < 0.0001$ ; **Figure 2**). There was no clear effect on MI in the overall population (HR 0.95 [95% CI 0.87-1.04],  $p = 0.29$ ), and no effect on stroke (HR 0.99 [95% CI 0.91-1.07],  $p = 0.77$ ) (**Figure 2**).

The distribution of CV death subtypes in the placebo arm across trial types are shown in **Figure 3**. In the trials of patients with diabetes at high risk for ASCVD, sudden cardiac death accounted for about half of CV deaths, with fatal MI/stroke accounting for approximately 25% and heart failure deaths just over 10%. In the heart failure trials, sudden cardiac deaths and heart failure deaths together accounted for over 70% of CV deaths, with fatal MI/stroke accounting for approximately 10%. In the chronic kidney disease trials, sudden cardiac deaths accounted for about 40% of the CV deaths, with heart failure deaths and fatal MI/stroke each accounting for 20-25% of CV deaths.

The reduction in CV death was driven primarily by a reduction in heart failure death (HR 0.68 [95% CI 0.46-1.02]) and sudden cardiac death (HR 0.86 [95% CI 0.78-0.95]), with no effect on fatal MI or fatal stroke (**Figure 4**). SGLT2i also reduced all-cause mortality (HR 0.88 [95% CI 0.82-0.94],  $P < 0.001$ ; **Figure S2**), with directional consistency for non-CV death (HR 0.91 [95% CI 0.79-1.05]; **Figure S3**), and with moderate heterogeneity for both across trial types ( $I^2 = 46\%$  and  $65\%$ , respectively). The numerically largest effect on all-cause and non-CV mortality was observed for patients enrolled in the chronic kidney disease trials (HR 0.80 [95% CI 0.71-0.91] and HR 0.81 [95% CI 0.66-0.98], respectively).

### Treatment Effect across Subgroups

Treatment effect of SGLT2i on MACE and CV death by subgroups are presented in **Figure 5A-B**. Incidence rates for MACE were higher among patients with established ASCVD across all 3 trial types (**Figure S4**). SGLT2i consistently reduced the risk of MACE in those with vs. without established ASCVD at baseline (HR 0.92 [95% CI 0.88-0.97] vs. 0.90 [0.82-0.99], p-interaction = 0.60; **Figure 5A and Figures S4-5**). SGLT2i also reduced CV death irrespective of established ASCVD at baseline (HR 0.86 [95% CI 0.80-0.93] vs. 0.86 [0.76-0.97], p-interaction = 0.94; **Figure 5B and Figure S5**). For MI, the effect estimates were similar in those with or without established ASCVD (HR 0.96 [95% CI 0.85-1.07] vs. 0.98 [0.82-1.18], respectively; p-interaction = 0.72; **Figure S5**). Of note, in the dedicated trials of patients with diabetes at high risk for ASCVD (which had the most rigorous definitions for established ASCVD), in the subset with established ASCVD, the HR for the effect of SGLT2i on MI was 0.91 (95% CI 0.82-0.998, p=0.046) (**Figure S5**). These results were consistent when stratifying by history of MI (**Figure 5 and Figure S6**).

The effects of SGLT2i on MACE and CV death were consistent when further stratified by diabetes status, prior heart failure, and eGFR at baseline assessed dichotomously (<60 vs. ≥60 mL/min/1.73 m<sup>2</sup>) (**Figure 5 and Figures S7-9**). Moreover, the effects of SGLT2i on MACE and CV death were consistent across the full spectrum of kidney function, including in participants with eGFR <30 mL/min/1.73 m<sup>2</sup> (HR 0.83 [95% CI 0.67-1.03] and 0.83 [95% CI 0.63-1.09], respectively) (**Figures S10-11**). Stratifying by albuminuria, the effect of SGLT2i on MACE appeared consistent (p-interaction = 0.31) whereas for CV death, there was some evidence that the benefit appeared to be primarily among those with at least some (i.e., ≥30 mg/g) albuminuria (p-interaction = 0.02; **Figure 5 and Figures S12-13**). Assessed across KDIGO risk groups, the

benefit for MACE and CV death was consistent across groups (p-trend = 0.35 and 0.31, respectively; **Figures S14-15**).

## **Discussion**

In this collaborative meta-analysis of approximately 78,000 patients across 11 randomized trials, we examined the treatment effect of SGLT2i on MACE, the individual MACE components, and subtypes of death. Moreover, by leveraging the large sample size and number of events across a broad range of patient populations afforded by this dataset, we further explored heterogeneity of treatment effect across several clinically relevant subgroups. Overall, we observed a 9% reduction in the rate of MACE, an effect that was generally consistent across patient populations including those with or without established ASCVD, diabetes or heart failure at baseline, and across a wide range of kidney function. With regard to the latter, it is notable that there was no attenuation of the benefit of SGLT2i on MACE even in individuals with an eGFR <30 mL/min/1.73 m<sup>2</sup>, a subgroup in whom there was initial doubt regarding the efficacy of this class of medications due to the lesser impact on urinary glucose excretion and thus glycemic control.<sup>20</sup> Collectively, these data provide a comprehensive overview of the anticipated treatment effects of SGLT2i across a wide range of patient populations and may help inform selection of SGLT2i therapies in patients encountered in clinical practice.

### **Treatment Effect on Individual MACE Components**

In terms of the individual MACE components, the benefit of SGLT2i was driven primarily by a reduction in CV death, specifically heart failure death and sudden cardiac death. There was a non-significant 5% lower rate of MI in the overall study populations, suggesting that any benefit of SGLT2i on MI is likely to be small. There was no effect of SGLT2i on the risk of stroke. In

addition to helping refine the expected benefit of SGLT2i, these findings also speak to some limitations of a traditional 3-point MACE composite as a clinical trial endpoint, which is commonly used with the intent of capturing ASCVD-related events. Our findings highlight the heterogeneity in event type that may be captured by such a composite, which becomes particularly relevant when applied across different patient populations where the risk for non-ASCVD-related CV deaths may be greater (e.g., heart failure-related death versus coronary heart disease death). With respect to clinical implications, these data speak to the specific types of MACE events which may be reduced with SGLT2i and may be useful to clinicians to guide decision-making regarding selection of glucose-lowering therapies in patients with diabetes.

### **Treatment Effect on Cardiovascular Death Subtypes**

With respect to subtypes of death, the benefit on CV death appeared driven largely by heart failure and sudden cardiac deaths. Notably, sudden death is not synonymous with arrhythmia, and is often a default adjudication when an unwitnessed out-of-hospital death occurs.<sup>21</sup> Such deaths may encompass both heart failure-related death (including arrhythmia) or fatal ASCVD-related deaths (including fatal MI), that occurred outside of a medical setting. As such, these findings raise the possibility that the salutary effects of SGLT2i on CV death, and thus MACE, could be driven primarily by modification of heart failure-related events. Interestingly, the benefit for CV death appeared to be primarily in those with some degree of albuminuria at baseline, who had approximately double the event rate compared to those without albuminuria. It remains unclear whether this is driven by the fact that albuminuria is an independent risk predictor for adverse outcomes or alternatively indicates that the mechanism of benefit may be related to the nephroprotective effects of SGLT2i. Moreover, given the large number of subgroups tested, it is also conceivable that this finding may represent a play of chance. We

further found a consistent reduction in all-cause mortality with directional consistency also for non-CV death. However, the mechanism of benefit of SGLT2i on non-CV death remains unclear. While other potential salutary effects of SGLT2i on outcomes beyond conventional cardiovascular and kidney endpoints have been reported,<sup>22,23</sup> it is important to note that some of the SGLT2i trials, namely all of the chronic kidney disease trials, were prematurely terminated which may result in an overestimate of the treatment effect in this regard.

### **Potential Differences by Patient Populations and Mechanisms of Benefit**

Although the effect of SGLT2i on MI was not significant in the overall population, these data raise the possibility that there could be a potential benefit among patients clinically felt to be at high risk of future ASCVD events, particularly the subset with definitively established ASCVD at baseline. These observations may be due to differences in baseline risk of the patient populations or perhaps reflect the heterogeneity of the established ASCVD definition across trial types. For example, in the dedicated trials enrolling patients with diabetes at high risk for ASCVD, rigorous definitions for established ASCVD were prospectively applied to ensure selection of a secondary prevention population as necessary to maintain the targeted event rate. In contrast, in the heart failure or chronic kidney disease trials, a retrospective definition was applied to delineate the established ASCVD group, where patients with any indication of coronary, peripheral or cerebrovascular disease in the medical history (e.g., incidentally noted coronary calcification) may have been included. In the case of the latter, these patients would be expected to be lower risk than a traditional secondary prevention population (e.g., those with a prior MI), and thus could be expected to derive lower absolute benefit from such therapies. To that end, there was a 9% reduction in the rate of MI in patients with established ASCVD from the





dedicated trials which required a rigorous pre-specified definition for this group, and this effect was similar in the subset with prior MI from these trials.

Notably, the mechanistic underpinnings underlying the cardiovascular benefits of SGLT2i remain unclear. For MI specifically, it is uncertain whether a treatment benefit would be mediated primarily by direct athero-protective effects, with resultant reduction in the risk of acute plaque rupture or erosion (i.e., type 1 MI), or alternatively, by reduction in the risk of heart failure or progression in kidney disease from various pleiotropic effects, which collectively may have beneficial effects for type 2 MI. We also observed no effect on stroke, which while acknowledged as a heterogeneous entity reflective of a multitude of possible etiologies (both ischemic and hemorrhagic, with the former inclusive of atherosclerosis-related, cardioembolic and small vessel/lacunar subtypes), typically has been shown to benefit from other ASCVD-modifying therapies.<sup>24-27</sup> In addition, in DAPA-MI, which enrolled patients presenting with acute MI but excluded those with pre-existing heart failure or diabetes (i.e., excluding a subset potentially at higher risk for recurrent type 2 MI), there was no effect on the risk of MI.<sup>28</sup> The results of the EMPACT-MI (NCT4509674) study will be further informative in characterizing the treatment effects of SGLT2i on MI.

### **Contextualizing Findings with Prior Data**

Results from prior meta-analyses have demonstrated a robust reduction in the risk of heart failure and kidney outcomes with SGLT2i, with consistency of treatment effect across a multitude of subgroups.<sup>15,29</sup> However, the effects of SGLT2i on MACE have remained less certain. Among the trials specifically designed to enroll patients with diabetes at high risk for ASCVD, a within trial effect on MACE was seen in two of the trials,<sup>1,2</sup> but not in two other trials.<sup>3,4</sup> Pooling data from these four trials, prior meta-analyses demonstrated a reduction in MACE with SGLT2i vs.

placebo restricted to the subset of patients with established ASCVD, with an otherwise neutral effect in the subgroup without ASCVD.<sup>16,17</sup> Our study expands on these prior findings, leveraging the totality of randomized data for SGLT2i across a broader range of patient populations with the more nuanced findings noted above.

### **Limitations**

Several limitations of our study should be acknowledged. Our results should be interpreted in the context of the differences in eligibility criteria, follow-up duration and subgroup definitions (in particular, the definition of established ASCVD) across studies. With only one or two trials of each drug in each disease state, the data do not permit rigorous comparisons of different members of the class. As all included patients are reflective of those enrolled based on diabetes with high risk for ASCVD, heart failure or chronic kidney disease at baseline, absence of one characteristic (e.g., no diabetes) may select for another (e.g., either heart failure or chronic kidney disease) and thus, these findings may not be generalizable to all patients (e.g., a patient without diabetes, heart failure and chronic kidney disease) encountered in clinical practice.

Observations regarding possible heterogeneity of treatment effect in subgroups should be interpreted as hypothesis-generating given the multiple outcomes and subgroups tested.

### **Conclusion**

SGLT2i consistently reduce the risk of MACE across a broad range of patient populations irrespective of ASCVD, diabetes, or kidney function at baseline. This benefit appears to be driven primarily by a reduction in CV death, particularly heart failure death and sudden cardiac death, without a significant effect on MI in the overall population, and no effect on stroke. These

data may help inform the selection of SGLT2i therapies across the spectrum of cardiovascular-kidney-metabolic disease.

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### Supplemental Materials



Tables S1-S3

Figures S1-S15

Circulation

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**Table 1: Baseline Characteristics Across SGLT2 Inhibitor Trials**

	Diabetes at High Risk for ASCVD				Heart Failure				Chronic Kidney Disease		
Characteristics by Trial	EMPA-REG Outcome	CANVAS Program	DECLARE-TIMI 58	VERTIS CV	DAPA-HF	EMPEROR -Reduced	EMPEROR -Preserved	DELIVER	CREDENCE	DAPA-CKD	EMPA-KIDNEY
Participants	7020	10142	17160	8246	4744	3730	5988	6263	4401	4304	6609
Median follow-up, y	3.1	2.4	4.2	3.0	1.5	1.3	2.2	2.3	2.6	2.4	2.0
Age, y	63.1 (8.7)	63.3 (8.3)	63.9 (6.8)	64.4 (8.1)	66.3 (10.9)	66.9 (11.0)	71.9 (9.5)	71.7 (9.6)	63.0 (9.2)	61.8 (12.1)	63.8 (13.9)
Female sex	2004 (28.5)	3633 (35.8)	6422 (37.4)	2477 (30.0)	1109 (23.4)	893 (23.9)	2676 (44.7)	2747 (43.9)	1494 (33.9)	1425 (33.1)	2192 (33.2)
Race											
White	5081 (72.4)	7944 (78.3)	13653 (79.6)	7240 (87.8)	3333 (70.3)	2629 (70.4)	4542 (75.9)	4439 (70.9)	2931 (66.6)	2920 (67.8)	3859 (58.4)
Asian	1517 (21.6)	1284 (12.7)	2303 (13.4)	498 (6.0)	1116 (23.5)	672 (18.0)	824 (13.8)	1274 (20.3)	877 (19.9)	1467 (34.1)	2393 (36.2)
Black	357 (5.1)	336 (3.3)	603 (3.5)	235 (2.8)	226 (4.7)	257 (6.9)	258 (4.3)	159 (2.5)	224 (5.1)	191 (4.4)	262 (4.0)
Other or missing	65 (0.9)	578 (5.7)	601 (3.5)	273 (3.3)	69 (1.5)	172 (4.6)	364 (6.1)	391 (6.2)	369 (8.4)	356 (8.2)	95 (1.4)
Established ASCVD	7020 (100.0)	6656 (65.6)	6974 (40.6)	8246 (100.0)	3042 (64.1)	2406 (64.5)	3320 (55.4)	3598 (57.4)	2220 (50.4)	1329 (30.9)	1494 (22.6)
Diabetes	7020 (100.0)	10142 (100.0)	17160 (100.0)	8246 (100.0)	2139 (45.1)	1856 (49.8)	2938 (49.1)	2806 (44.8)	4401 (100.0)	2906 (67.5)	3040 (46.0)
Prior MI	3273 (46.6)	2956 (29.1)	3584 (20.9)	3931 (47.7)	2092 (44.1)	1623 (43.5)	1780 (29.7)	1639 (26.2)	442 (10.0)	392 (9.1)	702 (10.6)
Prior HF	706 (10.1)	1461 (14.4)	1724 (10.0)	1958 (23.7)	4744 (100.0)	3730 (100.0)	5988 (100.0)	6263 (100.0)	652 (15.0)	468 (11.0)	658 (10.0)
GFR, mL/min/1.73 m <sup>2</sup>	74 (21)	77 (21)	85 (16)	76 (21)	66 (19)	62 (22)	61 (20)	61 (19)	56 (18)	43 (12)	37 (14)
GFR Groups											
>90	1538 (21.9)	2476 (24.4)	8162 (47.6)	2048 (24.8)	621 (13.1)	449 (12.0)	468 (7.8)	503 (8.0)	211 (4.8)	0 (0.0)	46 (0.7)
60-<90	3661 (52.2)	5625 (55.5)	7732 (45.1)	4390 (53.2)	2195 (46.3)	1480 (39.7)	2530 (42.3)	2689 (42.9)	1558 (35.4)	454 (10.5)	465 (7.0)
45-<60	1249 (17.8)	1485 (14.6)	1076 (6.3)	1319 (16.0)	1207 (25.4)	900 (24.1)	1565 (26.1)	1657 (26.5)	1266 (28.8)	1328 (30.9)	888 (13.4)
30-<45	543 (7.7)	526 (5.2)	169 (1.0)	457 (5.5)	695 (14.7)	694 (18.6)	1114 (18.6)	1221 (19.5)	1191 (27.1)	1898 (44.1)	2928 (44.3)
<30	27 (0.4)	28 (0.3)	20 (0.1)	0 (0.0)	24 (0.5)	205 (5.5)	309 (5.2)	192 (3.1)	174 (4.0)	624 (14.5)	2282 (34.5)
UACR, mg/g	17.7 (7.1-72.5)	12.3 (6.7-42.1)	13.1 (6.0-43.6)	19.0 (6.0-68.0)	NA	22.1 (8.0-81.3)	21.0 (8.0-71.6)	NA	927 (463-1833)	949 (477-1885)	329 (49-1069)

UACR Groups											
<30	4171 (60.0)	7007 (69.8)	11644 (69.1)	4783 (58.0)	NA	2078 (56.0)	3474 (58.0)	NA	31 (0.7)	0 (0.0)	1328 (20.1)
30-<300	2013 (29.0)	2266 (22.6)	4030 (23.9)	2492 (30.2)	NA	1236 (33.3)	1860 (31.1)	NA	495 (11.2)	444 (10.3)	1864 (28.2)
≥300	769 (11.0)	760 (7.6)	1169 (6.9)	755 (9.2)	NA	396 (10.7)	629 (10.5)	NA	3875 (88.0)	3859 (89.7)	3417 (51.7)

All values represent n (%) for categorical variables and mean (SD) for continuous variables with the exception of UACR, which is reported as median (25<sup>th</sup> – 75<sup>th</sup> percentile). ASCVD – atherosclerotic cardiovascular disease; HF – heart failure; MI – myocardial infarction; UACR – urine albumin-to-creatinine ratio



# Circulation



## Figure Legends

### Figure 1. Overall Effect of Sodium-Glucose Cotransporter 2 Inhibition on Major Adverse Cardiovascular Events Composite.

The forest plot depicts the treatment effect of SGLT2i on MACE composite at the level of the individual trials, by trial type, and in the overall study population. SGLT2i reduced the rate of MACE by 9% overall with consistency across trial types. Abbreviations: ASCVD – atherosclerotic cardiovascular disease; FE – fixed effects; MACE – major adverse cardiovascular events; RE – random effects; SGLT2i – sodium glucose co-transporter 2 inhibitors.

### Figure 2. Overall Effect of Sodium-Glucose Cotransporter 2 Inhibition on Individual Components.

These forest plots depict the treatment effect of SGLT2i on the individual components of the MACE composite, at the level of the individual trials, by trial type, and in the overall study population. **Panel A** shows the treatment effect on cardiovascular death, **panel B** shows the effect on myocardial infarction, and **panel C** shows the effect on stroke. The benefit of SGLT2i was driven primarily by a reduction in the risk of cardiovascular death, without a clear effect on myocardial infarction or stroke in the overall study population. Abbreviations: ASCVD – atherosclerotic cardiovascular disease; FE – fixed effects; MACE – major adverse cardiovascular events; RE – random effects; SGLT2i – sodium glucose co-transporter 2 inhibitors.

### Figure 3. Cardiovascular Death Subtypes Across Trial Populations (Placebo arms only).

The pie charts show the distribution of subtypes of CV death in the placebo arms of each trial

grouped by trial type. Sudden cardiac death contributed to half of CV deaths in the diabetes at high risk for ASCVD trials, with both sudden cardiac death and heart failure death contributing to three-quarters of all deaths in the heart failure trials, and to just over 60% of all deaths in the chronic kidney disease trials. Fatal MI and stroke each accounted for just over 10% of all deaths in the diabetes at high risk for ASCVD and chronic kidney disease trials but combined accounted for only 10% of all deaths in the heart failure trials. Abbreviations: ASCVD – atherosclerotic cardiovascular disease, CV – cardiovascular, MI – myocardial infarction.

**Figure 4. Overall Effect of Sodium Glucose Cotransporter 2 Inhibition on Subtypes of Cardiovascular Death.**

These forest plots depict the treatment effect of SGLT2i on subtypes of CV death. SGLT2i appeared to have the greatest benefit for heart failure death and sudden cardiac death, without a clear effect on fatal myocardial infarction or fatal stroke. Abbreviations: ASCVD – atherosclerotic cardiovascular disease; RE – random effects; SGLT2i – sodium glucose cotransporter 2 inhibitors.

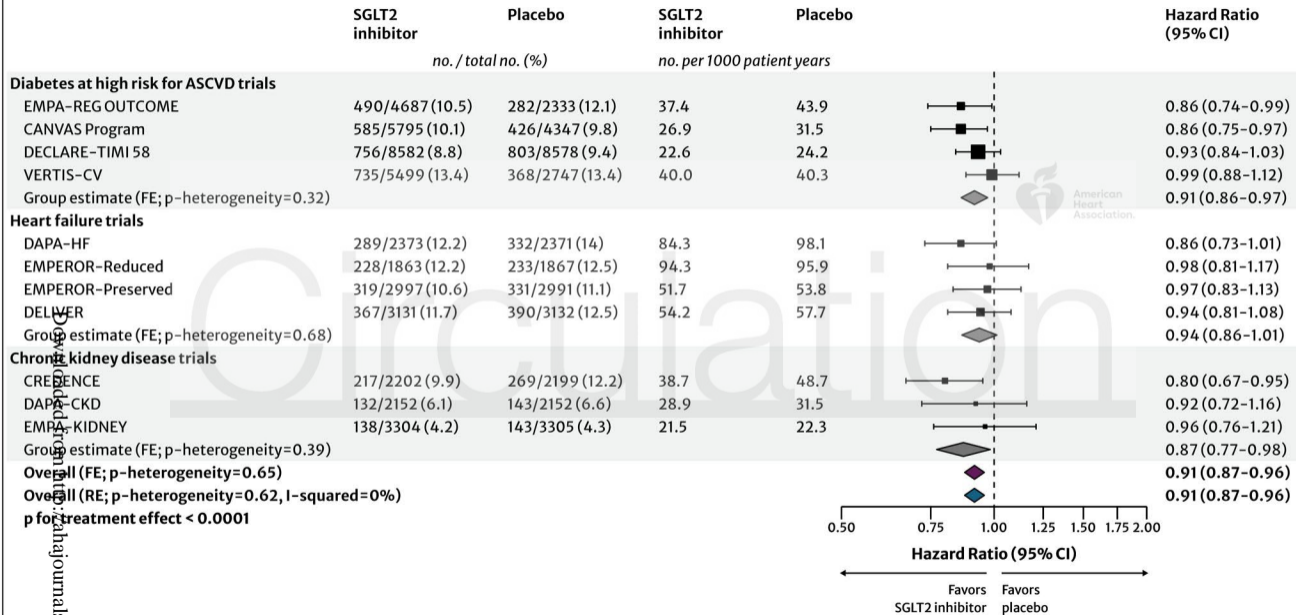
**Figure 5. Overall Effect of Sodium Glucose Cotransporter 2 Inhibition by Subgroups for the Major Adverse Cardiovascular Events Composite and Cardiovascular Death.**

**Panel A** depicts the treatment effect of SGLT2i on the MACE composite across subgroups, and **panel B** depicts the treatment effect on cardiovascular death across subgroups. The treatment effect of SGLT2i on the MACE composite was consistent across all key subgroups. For cardiovascular death, there was also a generally consistent treatment effect except for albuminuria, where the benefit of SGLT2i for cardiovascular death appeared to be primarily

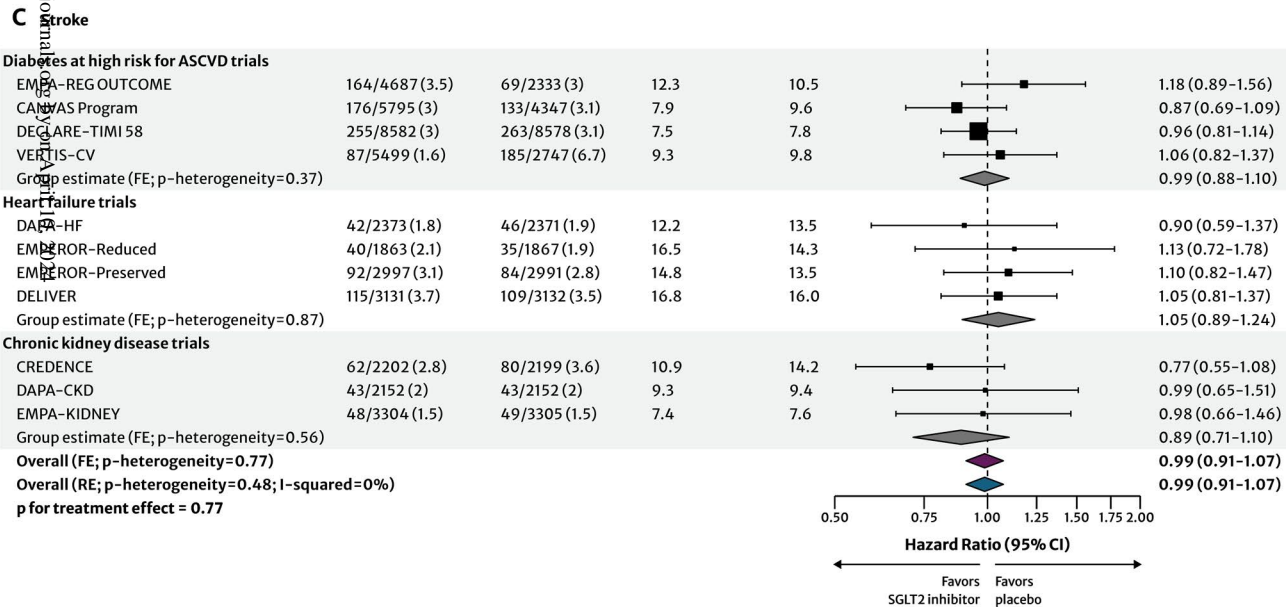
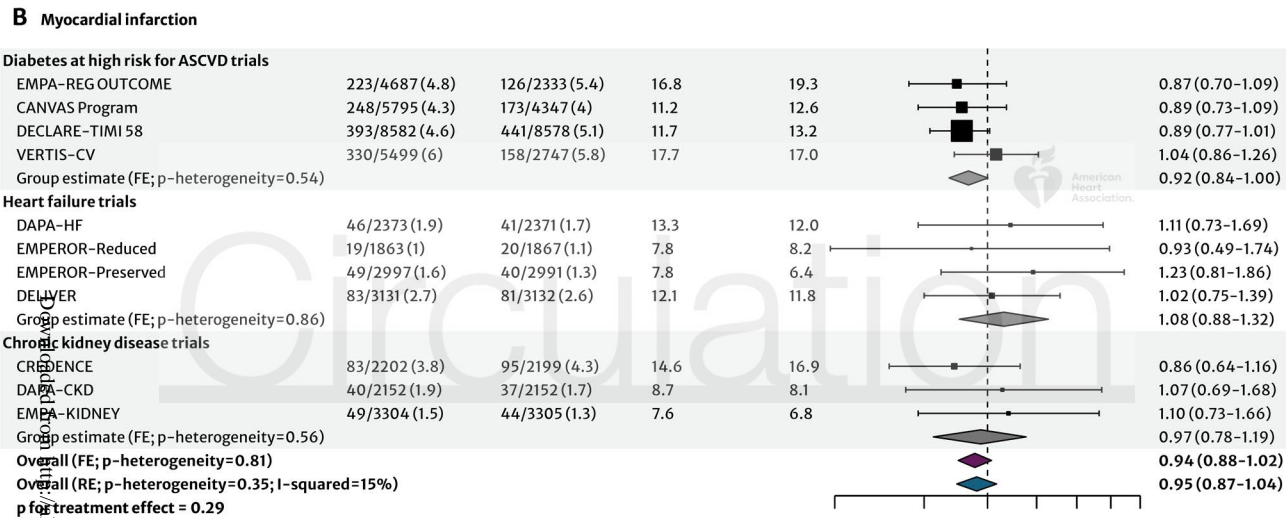
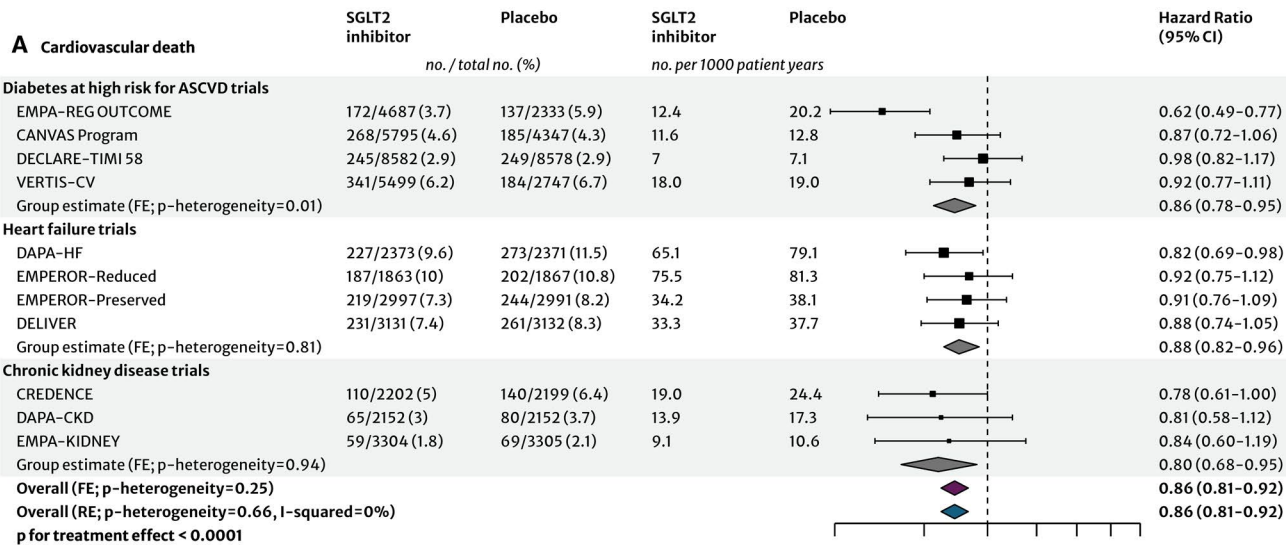
among those with presence of albuminuria at baseline. Abbreviations: ASCVD – atherosclerotic cardiovascular disease; eGFR – estimated glomerular filtration rate; SGLT2i – sodium glucose co-transporter 2 inhibitors; UACR – urine albumin-to-creatinine ratio.



# Circulation

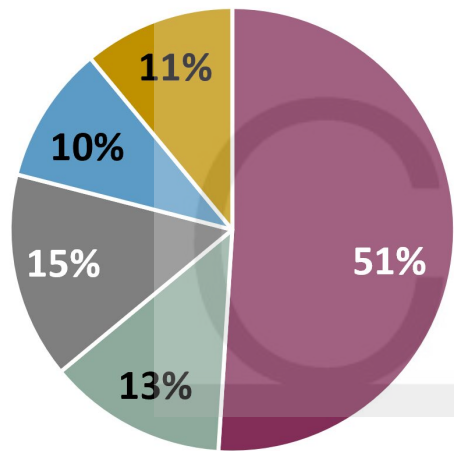


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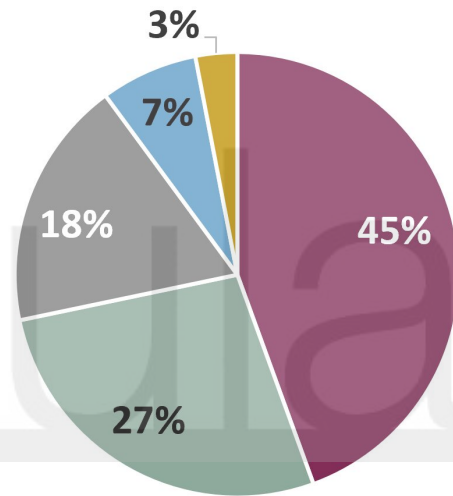


# Distribution of Cardiovascular Death Subtypes Across Trial Populations

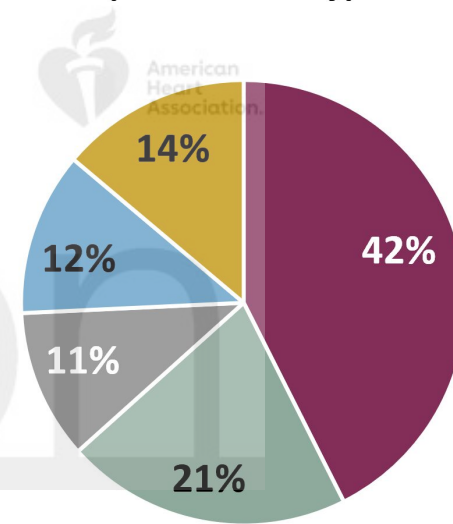
## Diabetes at High Risk for ASCVD Trials (Placebo only)



## Heart Failure Trials (Placebo only)



## Chronic Kidney Disease Trials (Placebo only)



**Sudden Cardiac Death**    **Heart Failure Death**    **Other CV Death**    **Fatal MI**    **Fatal Stroke**

