

SUPPLEMENTAL MATERIAL

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

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Supplemental Table S1: Risk of Bias Assessment

| Study | Random sequence generation | Allocation sequence concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data addressed | Selective reporting |
|---|----------------------------|---------------------------------|--|--------------------------------|-----------------------------------|---------------------|
| <i>Diabetes at high-risk for ASCVD trials</i> | | | | | | |
| EMPA-REG Outcome | Low | Low | Low | Low | Low | Low |
| CANVAS Program | Low | Low | Low | Low | Low | Low |
| DECLARE-TIMI 58 | Low | Low | Low | Low | Low | Low |
| VERTIS CV | Low | Low | Low | Low | Low | Low |
| <i>Heart failure trials</i> | | | | | | |
| EMPEROR-Reduced | Low | Low | Low | Low | Low | Low |
| DAPA-HF | Low | Low | Low | Low | Low | Low |
| EMPEROR-Preserved | Low | Low | Low | Low | Low | Low |
| DELIVER | Low | Low | Low | Low | Low | Low |
| <i>Chronic kidney disease trials</i> | | | | | | |
| CREDESCENCE | Low | Low | Low | Low | Low | Low |
| DAPA-CKD | Low | Low | Low | Low | Low | Low |
| EMPA-KIDNEY | Low | Low | Low | Low | Low | Low |

Supplemental Table S2: Definition of Established Atherosclerotic Cardiovascular Disease Across Studies

| Study | Definition |
|---|--|
| Diabetes at high risk for ASCVD trials | |
| EMPA-REG Outcome | Trial protocol-defined as any of the following: <ul style="list-style-type: none"> • History of MI • Evidence of multivessel CAD (i.e. ≥ 2 major coronary arteries or left main) defined as follows: stenosis $\geq 50\%$, or prior coronary revascularization, or combination of revascularization in one major coronary artery with residual stenosis $\geq 50\%$ in another • Evidence of single-vessel CAD ($\geq 50\%$ stenosis) not revascularized with either a positive stress test for ischemia or recent (≤ 12 months) hospitalization for unstable angina • Unstable angina with evidence of single-vessel or multi-vessel CAD • History of stroke • Occlusive PAD defined as: limb revascularization, limb or foot amputation, angiographic or hemodynamically significant stenosis in 1 limb ($\geq 50\%$) or ABI < 0.9 |
| CANVAS Program | Trial protocol-defined as any of the following: <ul style="list-style-type: none"> • Prior stroke • Prior MI • Hospital admission for unstable angina • Coronary revascularization • Peripheral revascularization • Documented hemodynamically significant carotid or peripheral vascular disease • Amputation secondary to vascular disease |
| DECLARE-TIMI 58 | Trial protocol-defined as any of the following: <ul style="list-style-type: none"> • Ischemic heart disease – documented MI, coronary revascularization, or $\geq 50\%$ stenosis in 2 coronary artery territories (or bypass graft) • Cerebrovascular disease – documented ischemic stroke, carotid stenting or endarterectomy • Peripheral arterial disease – prior peripheral intervention, lower extremity amputation, or intermittent claudication with ABI < 0.90 |
| VERTIS CV | Trial protocol-defined as any of the following: <ul style="list-style-type: none"> • Ischemic heart disease – documented prior MI or coronary revascularization • Ischemic cerebrovascular disease – documented ischemic stroke or carotid revascularization • Peripheral arterial disease – angiographically documented peripheral vascular disease, ABI < 0.85 with symptoms of claudication or amputation, peripheral bypass or peripheral angioplasty of the extremities |

| Heart failure trials | |
|--------------------------------------|--|
| EMPEROR-Reduced | Established ASCVD term was derived based on presence of CAD, PAD or cerebrovascular disease defined as follows: <ul style="list-style-type: none"> • CAD was defined history of myocardial infarction (MI), prior coronary revascularization (PCI/CABG), documented history of CAD or acute coronary syndrome during the past 6 months. • Cerebrovascular disease was defined as a history of stroke or transient ischemic attack or cerebrovascular disease other than stroke or TIA • Peripheral artery disease was defined as peripheral artery occlusive disease or prior lower limb amputation |
| DAPA-HF | Established ASCVD term derived as follows: prior MI, prior ischemic stroke, history of CAD, history of angina, history of abdominal aortic aneurysm, history of carotid stenosis, history of PAD, previous PCI, previous CABG, previous vascular stent, previous carotid stenting |
| EMPEROR-Preserved | Established ASCVD term was derived based on presence of CAD, PAD or cerebrovascular disease fined as follows: <ul style="list-style-type: none"> • CAD was defined history of myocardial infarction (MI), prior coronary revascularization (PCI/CABG), documented history of CAD or acute coronary syndrome during the past 6 months. • Cerebrovascular disease was defined as a history of stroke or transient ischemic attack or cerebrovascular disease other than stroke or TIA • Peripheral artery disease was defined as peripheral artery occlusive disease or prior lower limb amputation |
| DELIVER | Established ASCVD term derived as follows: prior MI, prior ischemic stroke, history of CAD, history of angina, history of abdominal aortic aneurysm, history of carotid stenosis, history of PAD, previous PCI, previous CABG, previous vascular stent, previous carotid stenting |
| Chronic kidney disease trials | |
| CREDESCENCE | Established ASCVD term was derived as presence of any CAD, PAD or cerebrovascular disease on baseline medical history. |
| DAPA-CKD | Established ASCVD term was derived by the presence of any of the following on the patient’s medical history: <ul style="list-style-type: none"> • CAD – angina pectoris, coronary artery stenosis, coronary revascularization (PCI/CABG), or MI • Cerebrovascular disease – carotid artery stenosis, carotid revascularization, carotid stent insertion, cerebral artery stent insertion, cerebral revascularization, ischemic stroke, or TIA • PAD – aortic aneurysm, history of PAD, peripheral artery stenting, peripheral revascularization |
| EMPA-KIDNEY | Established ASCVD term was derived as prior MI, PAD, stroke or TIA on baseline medical history |

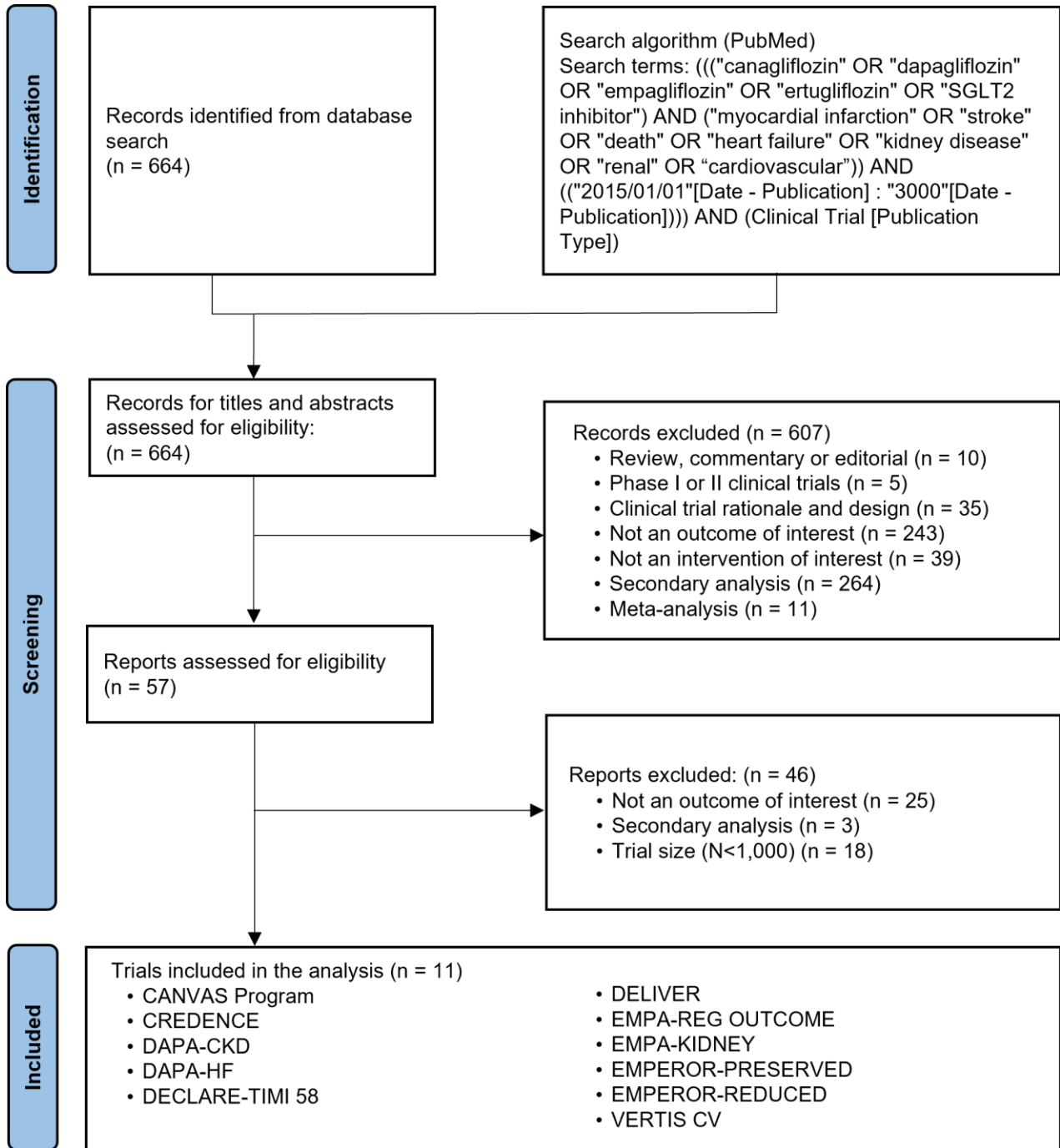
Supplemental Table S3: Availability of Subgroup Data Across Individual Trials

| | Established ASCVD at baseline | History of Myocardial Infarction | Diabetes at baseline | History of Heart Failure | Estimated glomerular filtration rate (dichotomous and KDIGO stages) | Albuminuria | KDIGO Risk Groups |
|-------------------|---|----------------------------------|----------------------|--------------------------|---|---------------|-------------------|
| | <i>Diabetes at high risk for ASCVD trials</i> | | | | | | |
| EMPA-REG Outcome | ✓ | ✓ | ✓ | ✓** | ✓ | ✓ | ✓ |
| CANVAS Program | ✓ | ✓ | ✓ | ✓** | ✓ | ✓ | ✓ |
| DECLARE-TIMI 58 | ✓ | ✓ | ✓ | ✓** | ✓ | ✓ | ✓ |
| VERTIS CV | ✓ | ✓ | ✓ | ✓** | ✓ | ✓ | ✓ |
| | <i>Heart failure trials</i> | | | | | | |
| EMPEROR-Reduced | ✓* | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| DAPA-HF | ✓* | ✓ | ✓ | ✓ | ✓ | Not available | Not available |
| EMPEROR-Preserved | ✓* | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| DELIVER | ✓* | ✓ | ✓ | ✓ | ✓ | Not available | Not available |
| | <i>Chronic kidney disease trials</i> | | | | | | |
| CREDESCENCE | ✓* | ✓ | ✓ | ✓** | ✓ | ✓ | ✓ |
| DAPA-CKD | ✓* | ✓ | ✓ | ✓** | ✓ | ✓ | ✓ |
| EMPA-KIDNEY | ✓* | ✓ | ✓ | ✓** | ✓ | ✓ | ✓ |

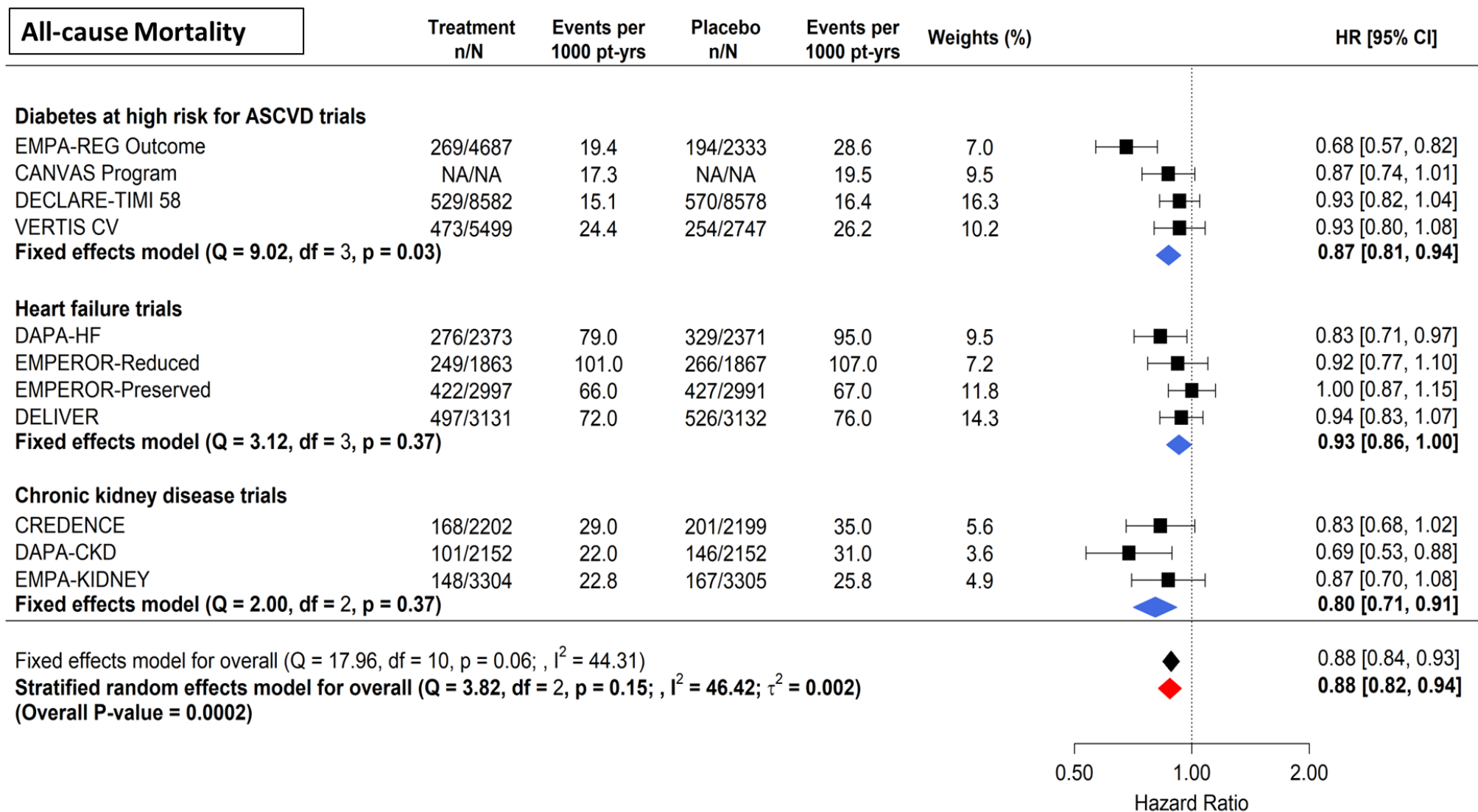
*Established ASCVD was protocol-defined in the trials of patients with diabetes at high risk for ASCVD and derived from the medical history for heart failure and chronic kidney disease trials.

**History of heart failure was protocol-defined in the trials of patients with established heart failure and captured by the medical history for the diabetes at high risk for ASCVD and chronic kidney disease trials.

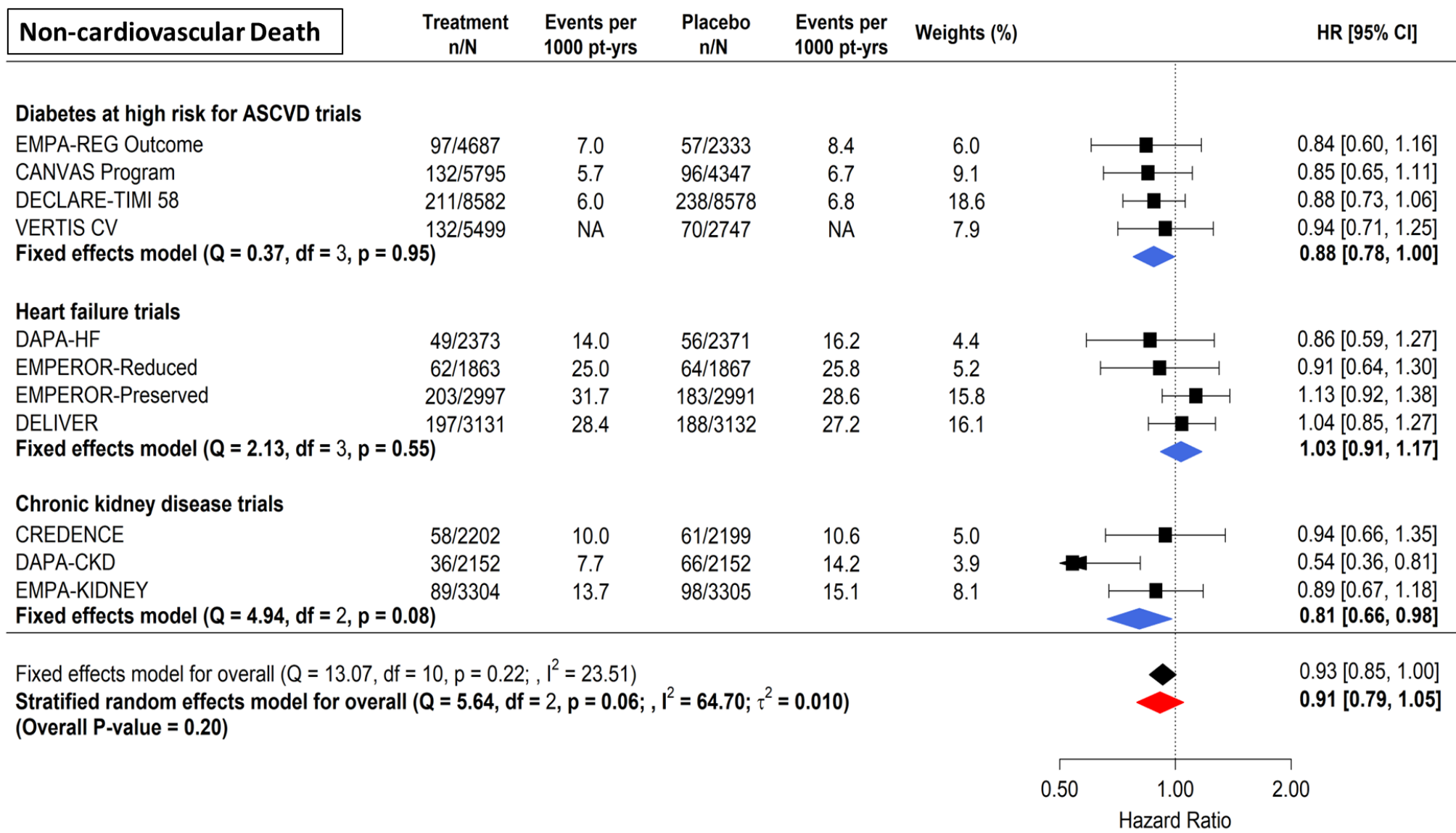
Supplemental Figure S1: PRISMA Diagram



Supplemental Figure S2: Overall Effect of SGL2i on All-Cause Mortality

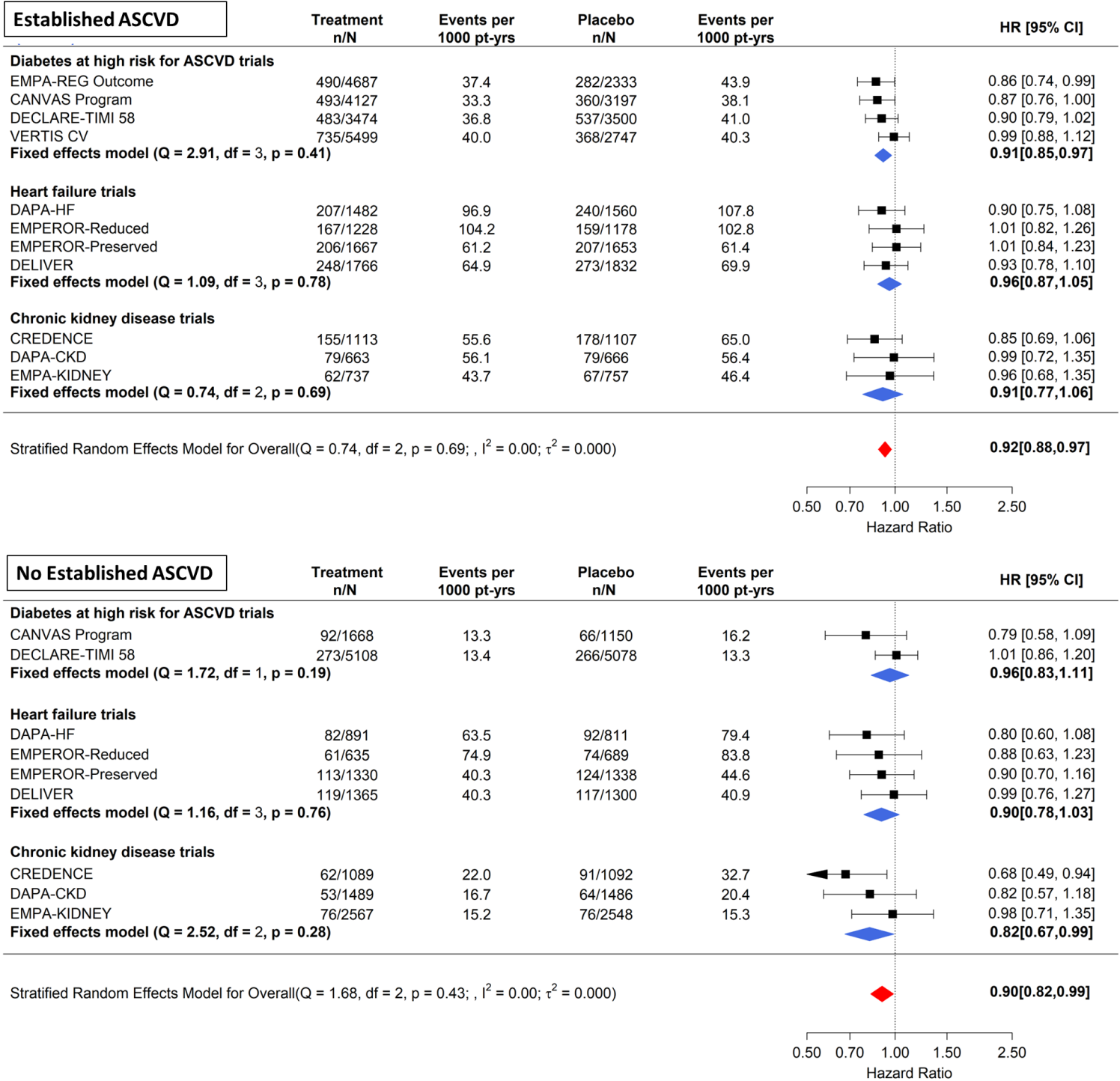


Supplemental Figure S3: Overall Effect of SGLT2i on Non-cardiovascular Death

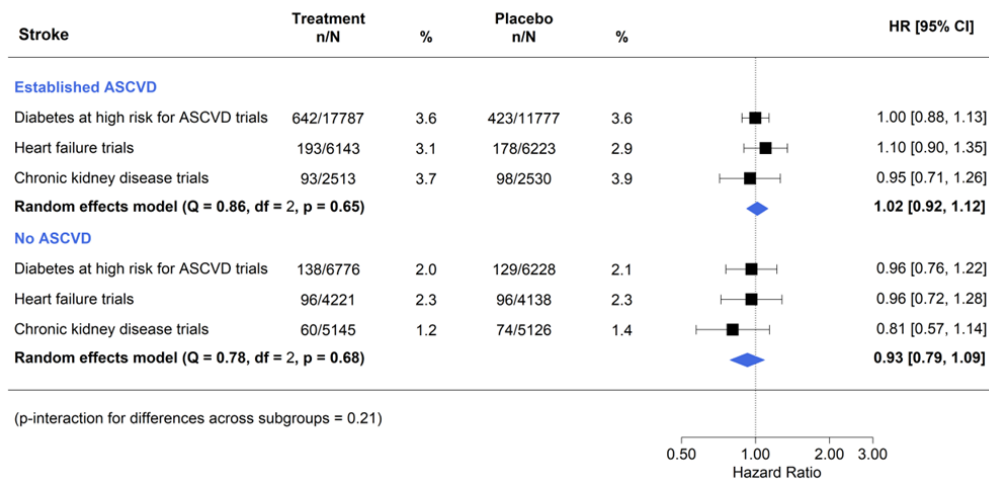
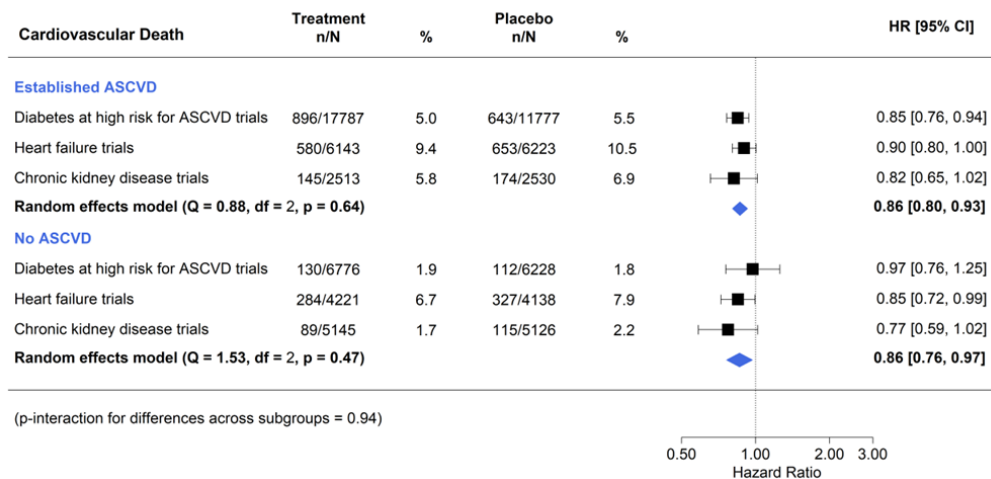
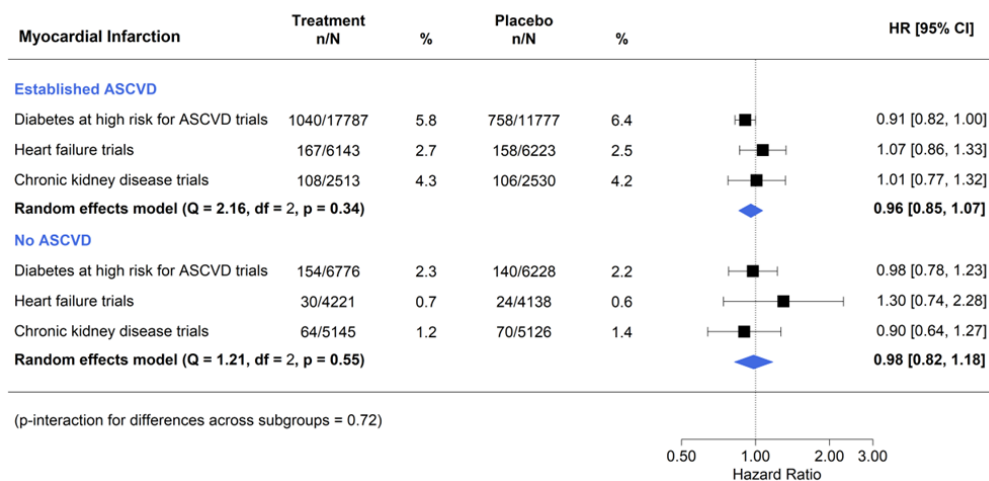
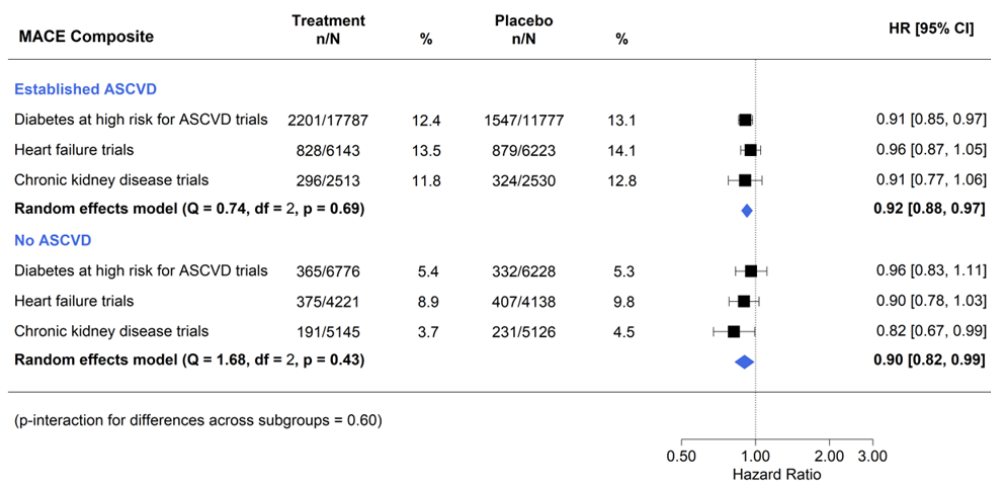


Supplemental Figure S4: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Events Stratified by Established ASCVD (Individual Trial Level)

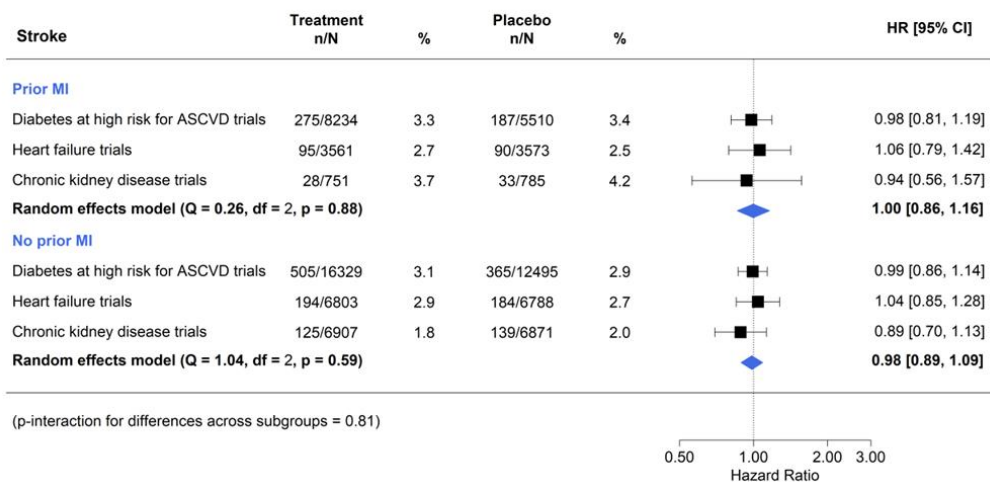
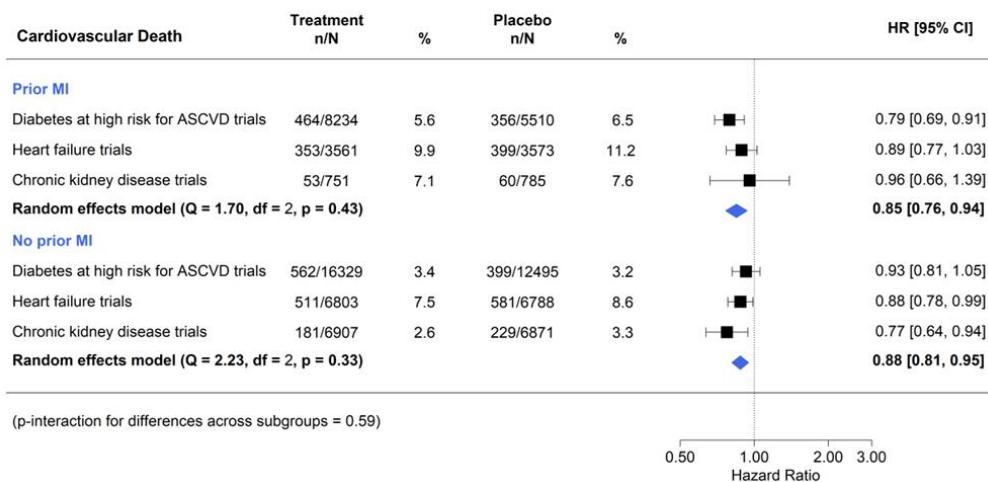
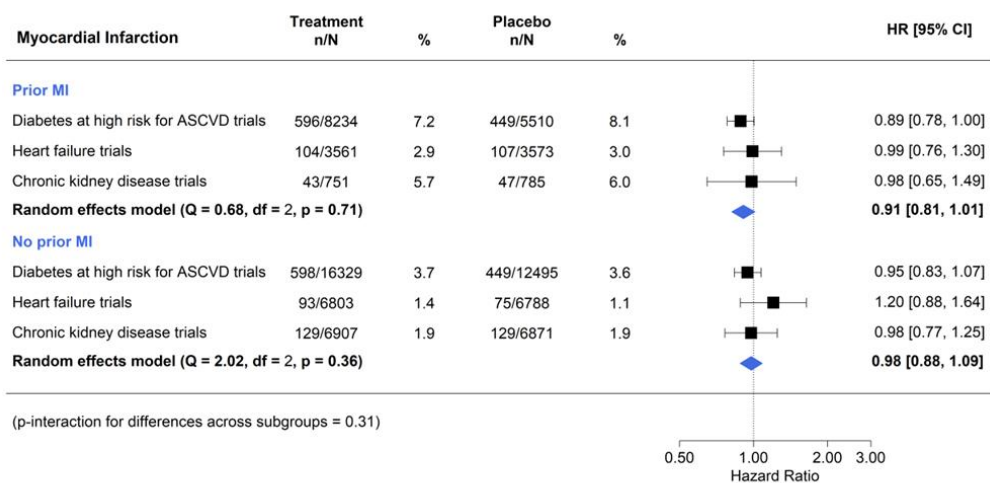
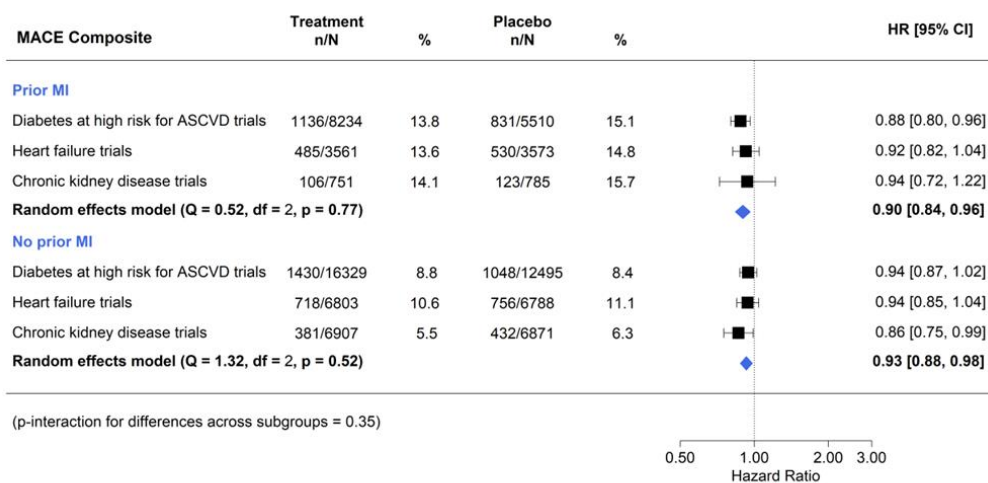
Major Adverse Cardiovascular Events Composite



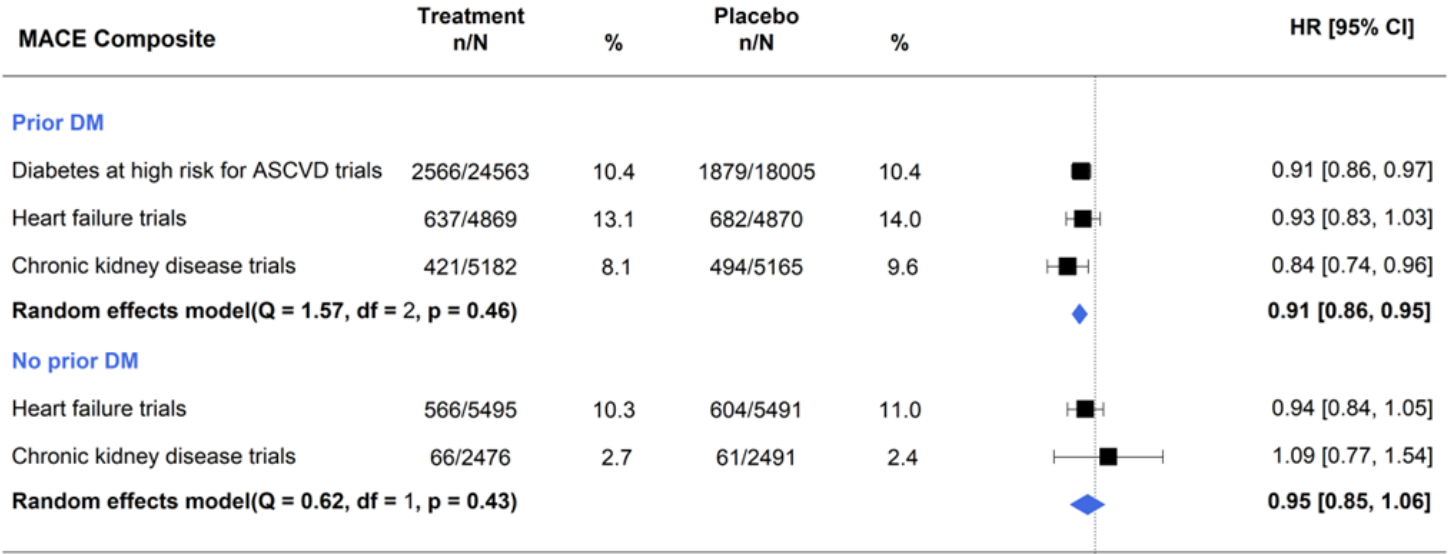
Supplemental Figure S5: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Events Composite and the Individual Components by Established Atherosclerotic Cardiovascular Disease at Baseline



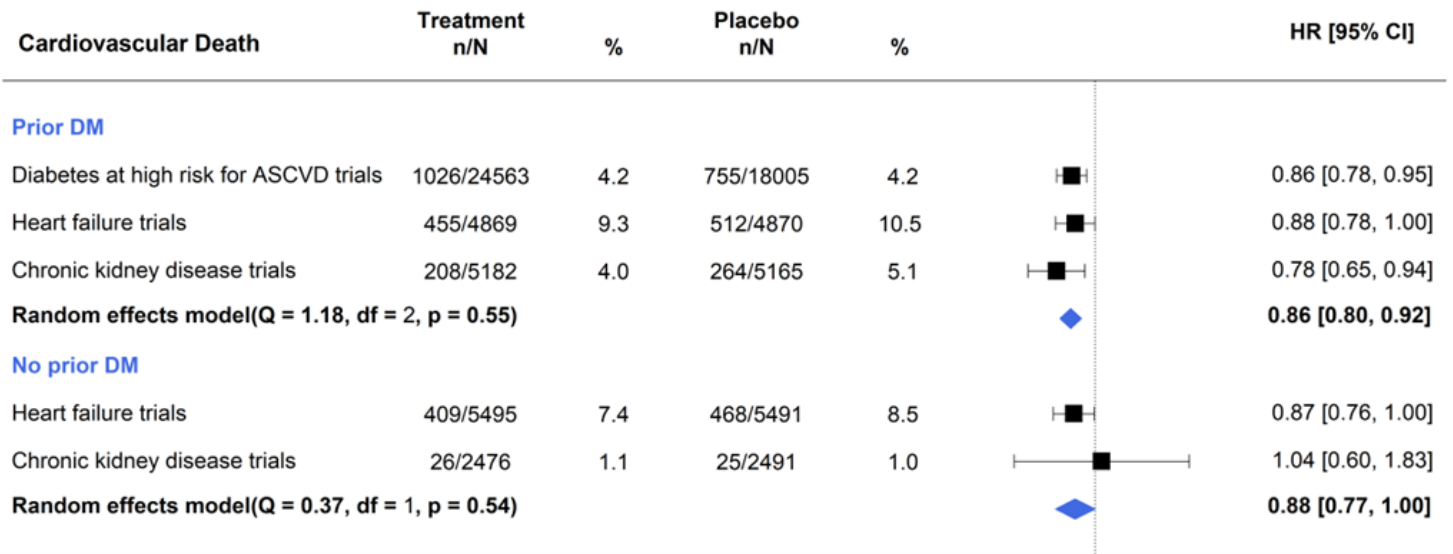
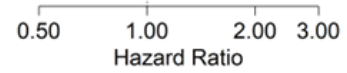
Supplemental Figure S6: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Events Composite and the Individual Components by History of Myocardial Infarction



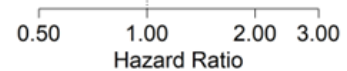
Supplemental Figure S7: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Event Composite and Cardiovascular Death by Diabetes Status



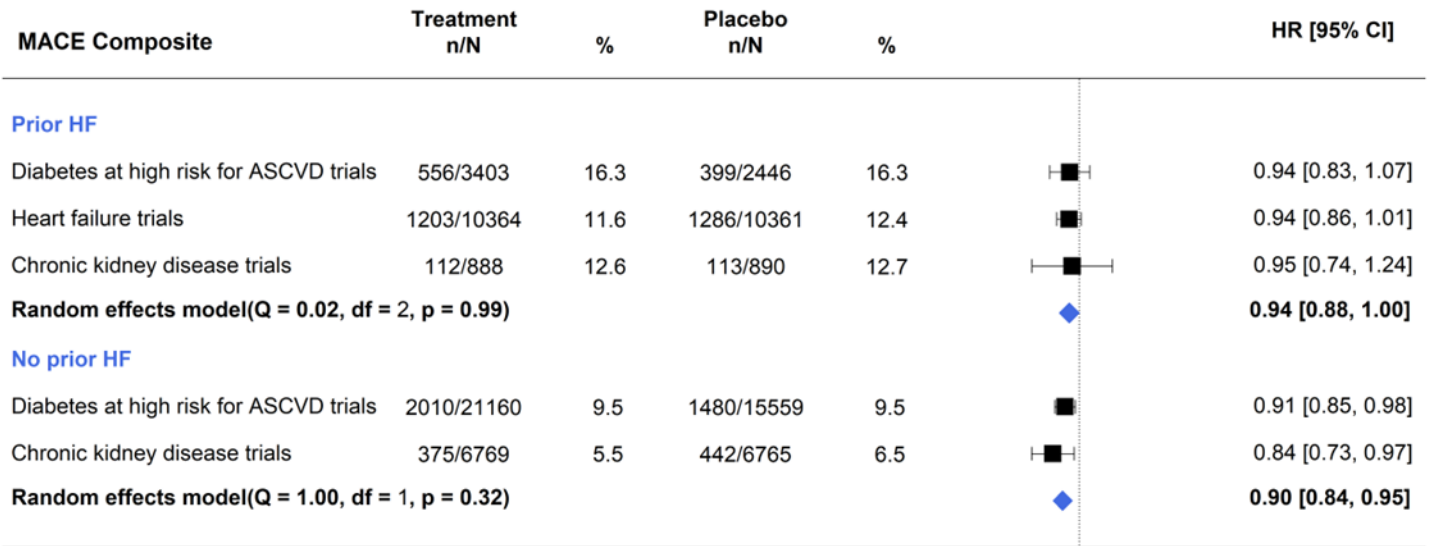
(p-interaction for differences across subgroups = 0.40)



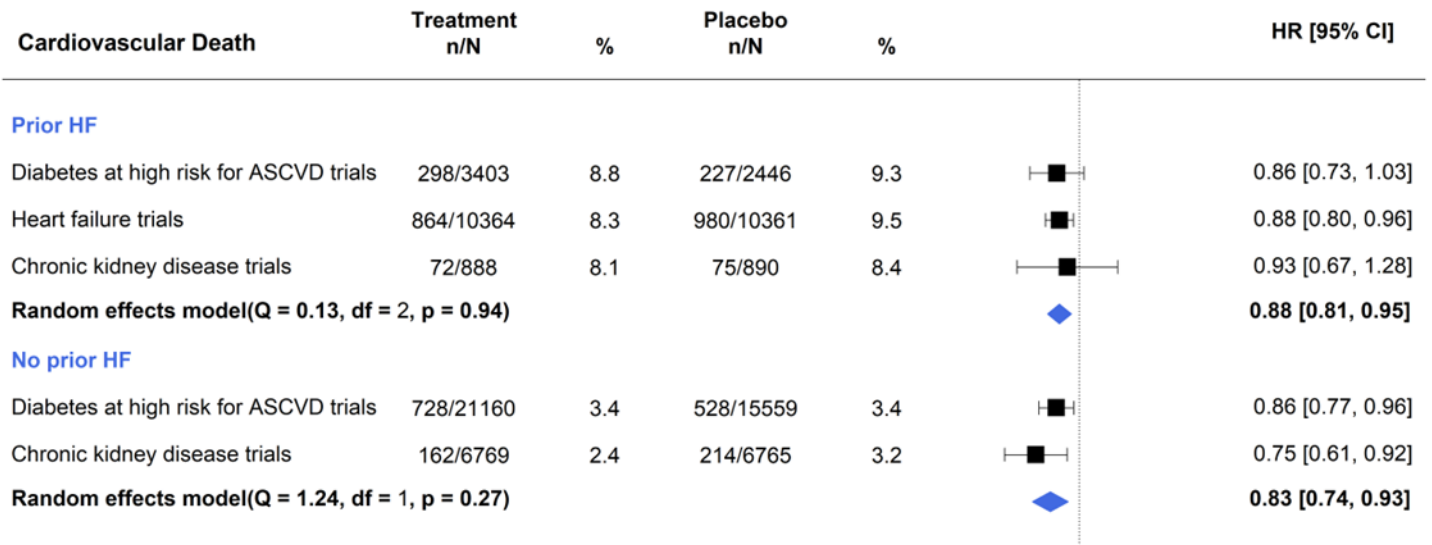
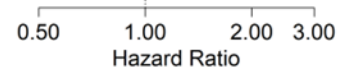
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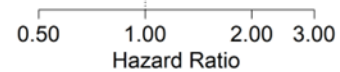
Supplemental Figure S8: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Event Composite and Cardiovascular Death by Prior Heart Failure Status



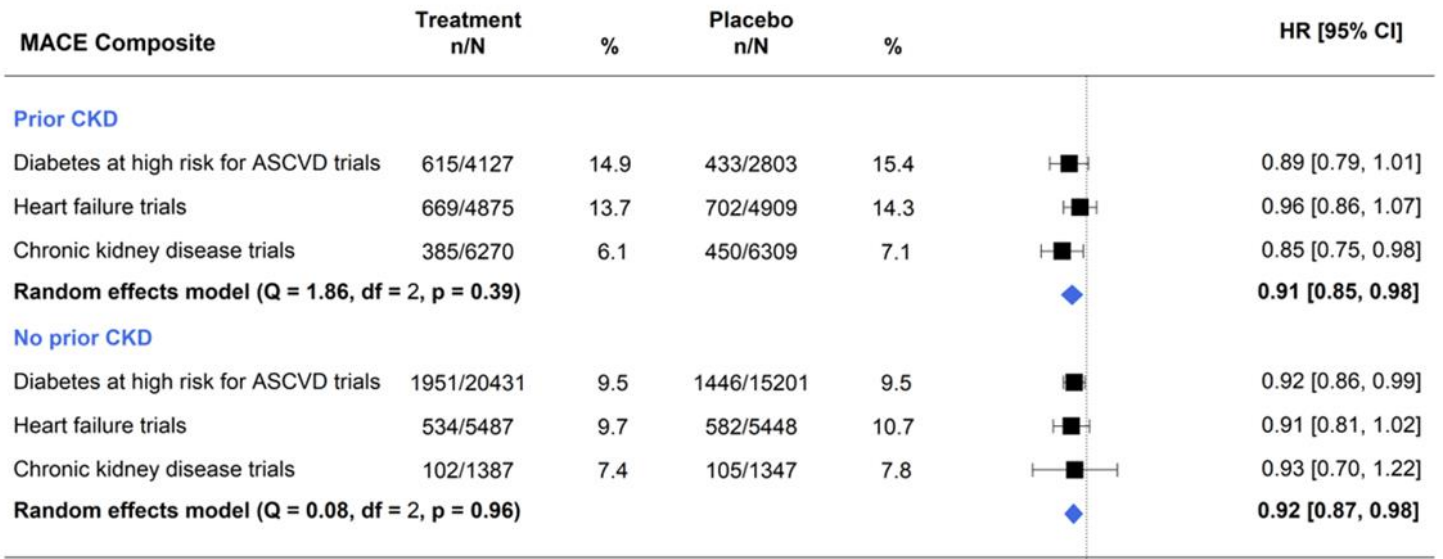
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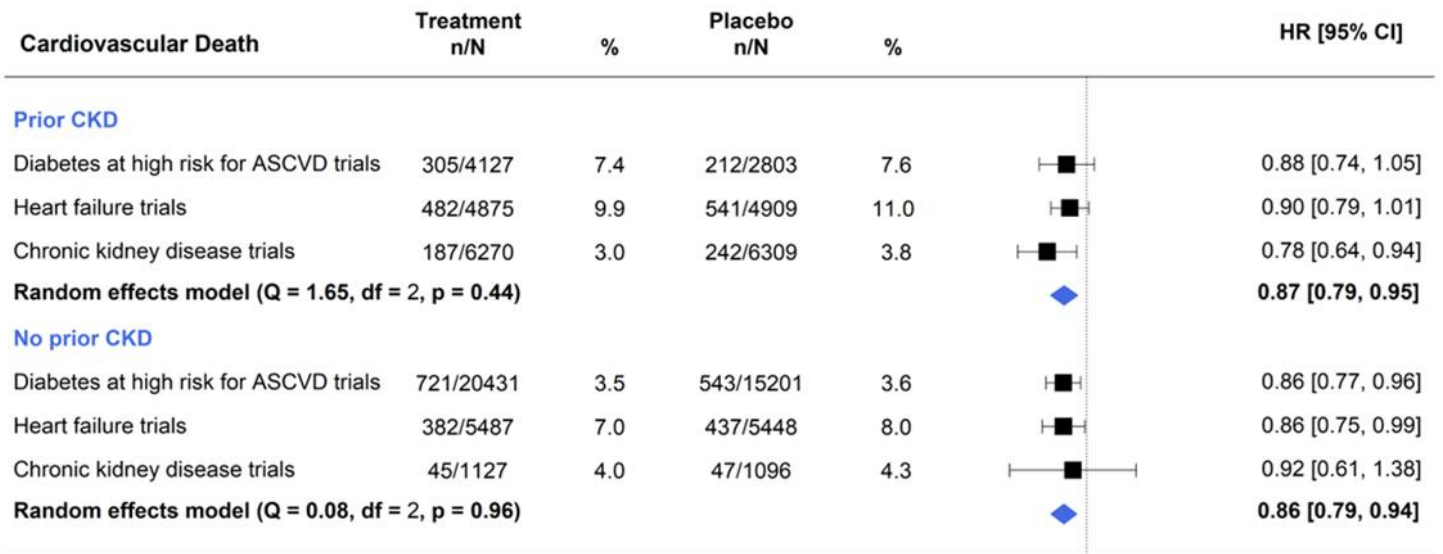
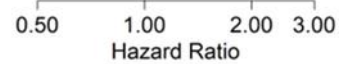
(p-interaction for differences across subgroups = 0.32)



Supplemental Figure S9: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Event Composite and Cardiovascular Death by Estimated Glomerular Filtration Rate (Dichotomous)



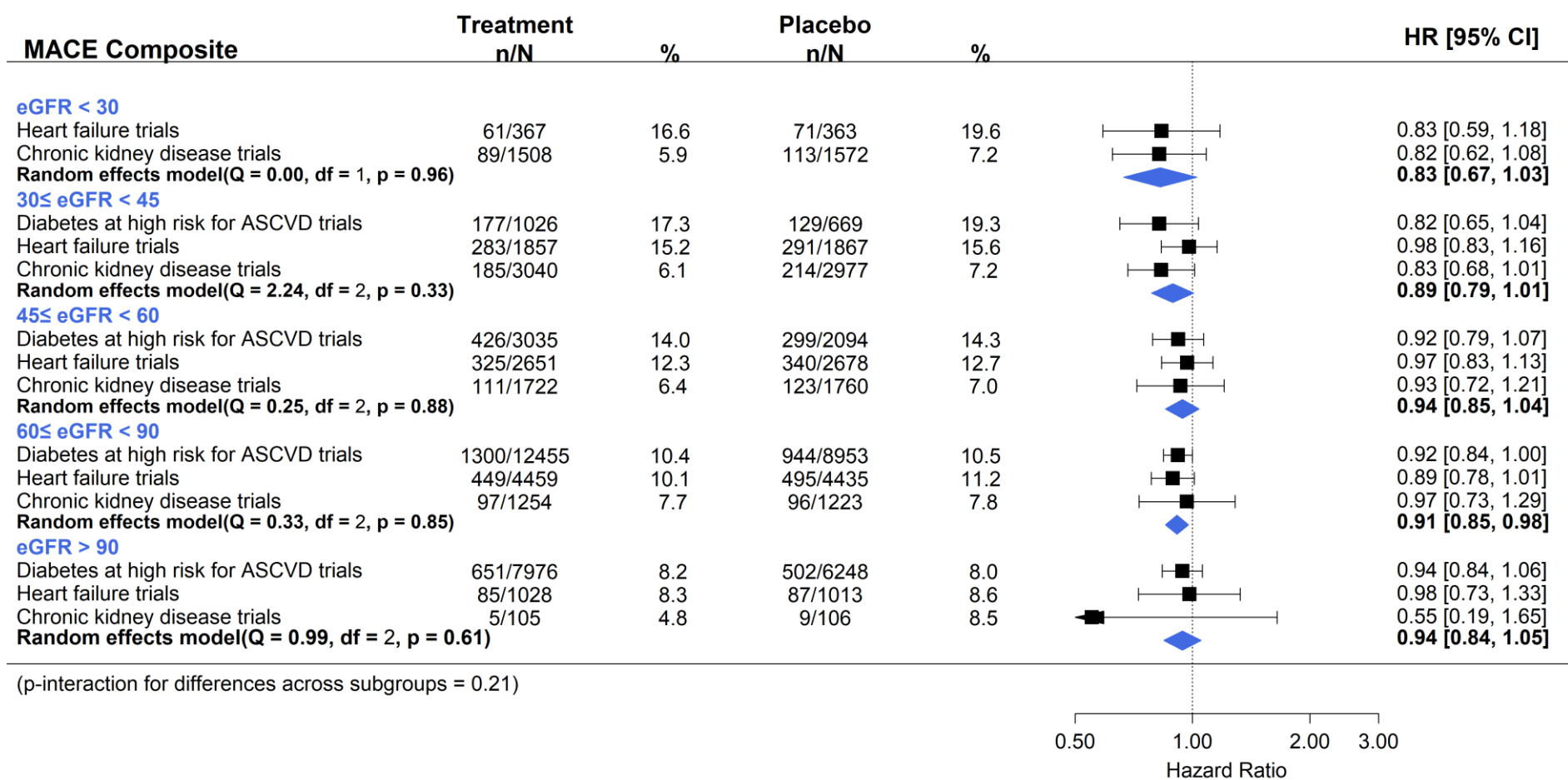
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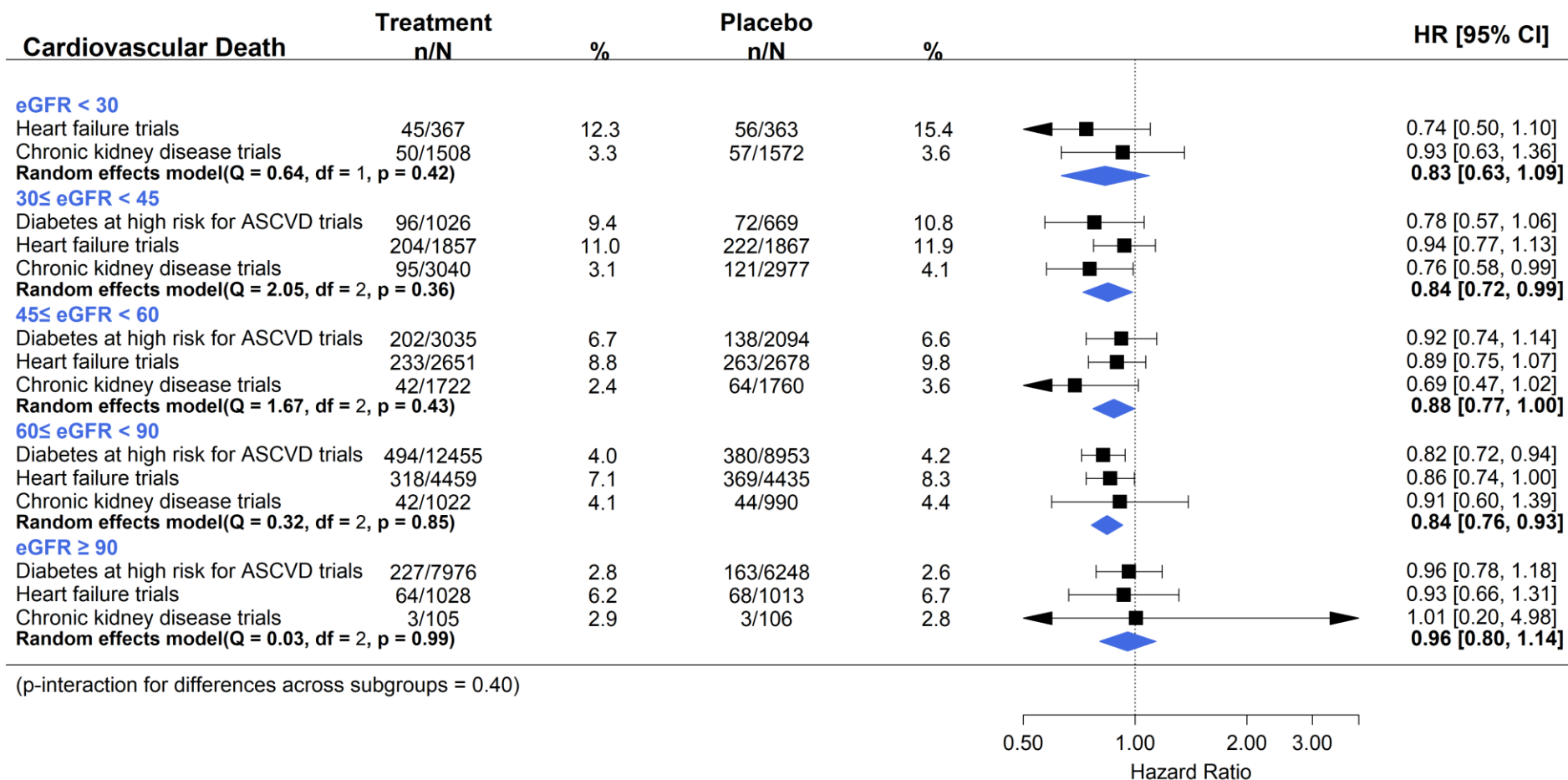
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Supplemental Figure S10: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Event Composite by KDIGO Chronic Kidney Disease Stages

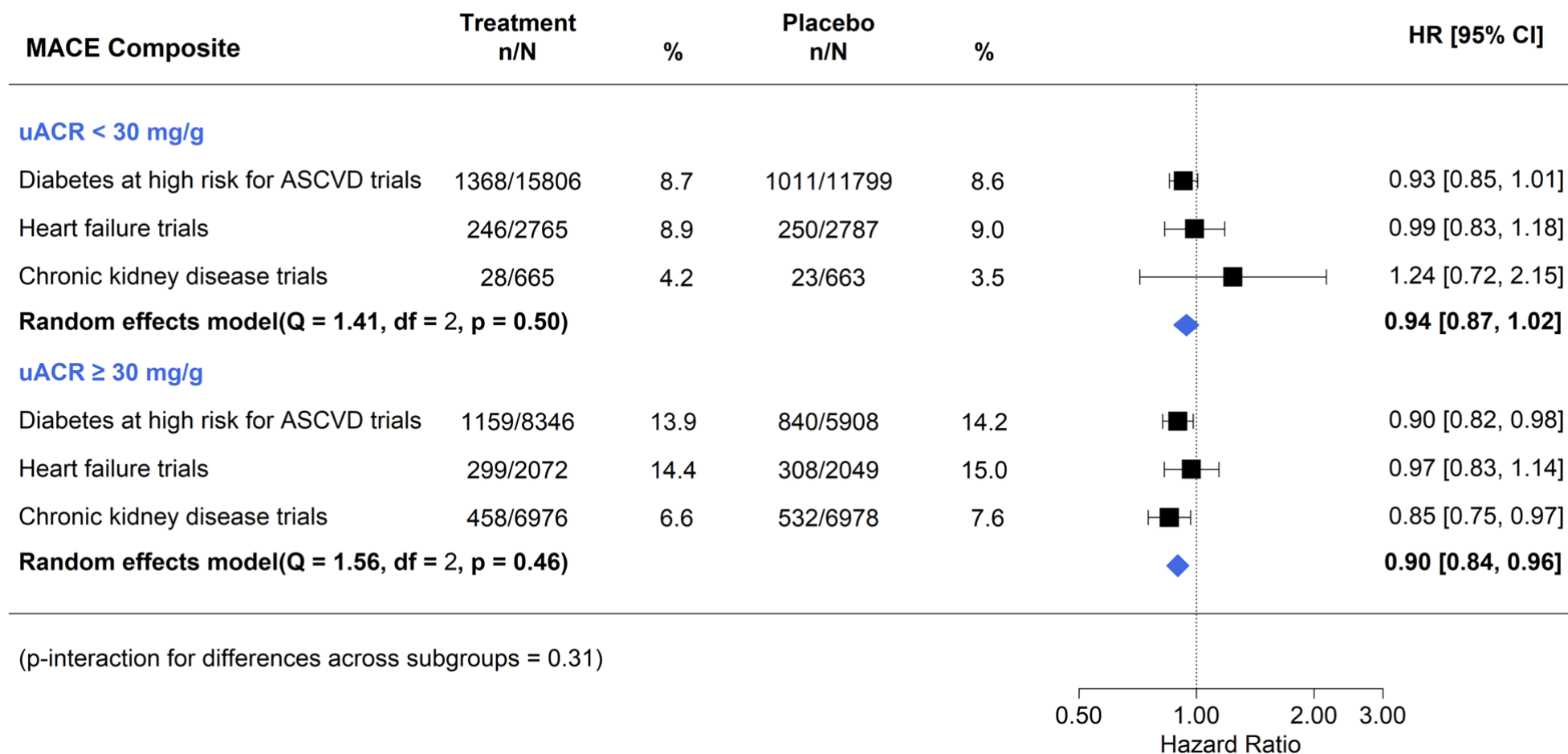


Supplemental Figure S11: Treatment Effect of SGLT2i on Cardiovascular Death by KDIGO Chronic Kidney Disease Stages

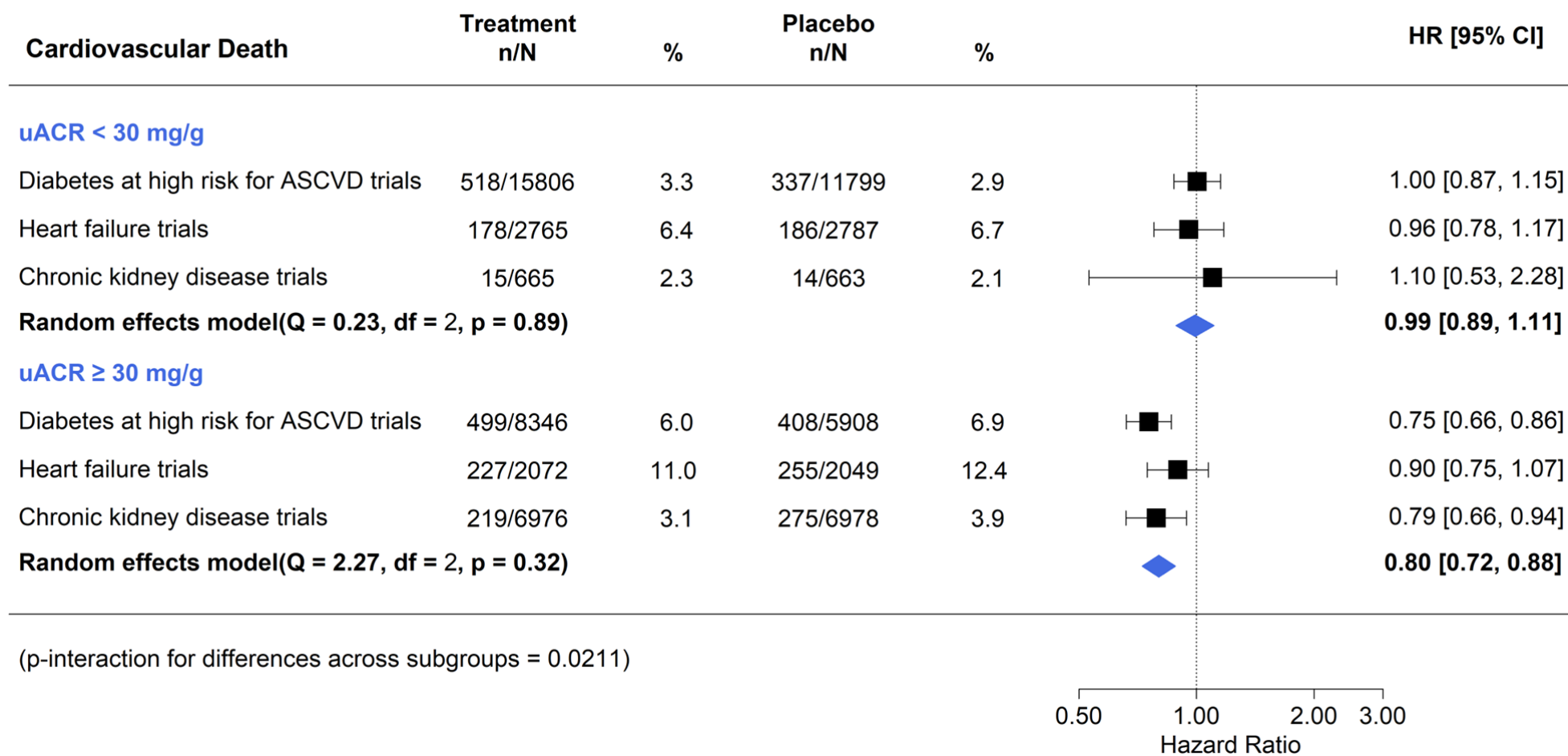


(p-interaction for differences across subgroups = 0.40)

Supplemental Figure S12: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Event Composite by Albuminuria

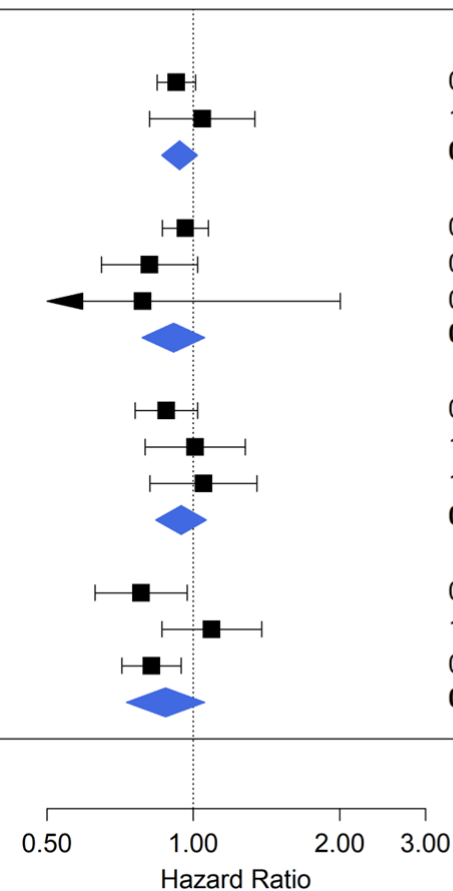


Supplemental Figure S13: Treatment Effect of SGLT2i on Cardiovascular Death by Albuminuria



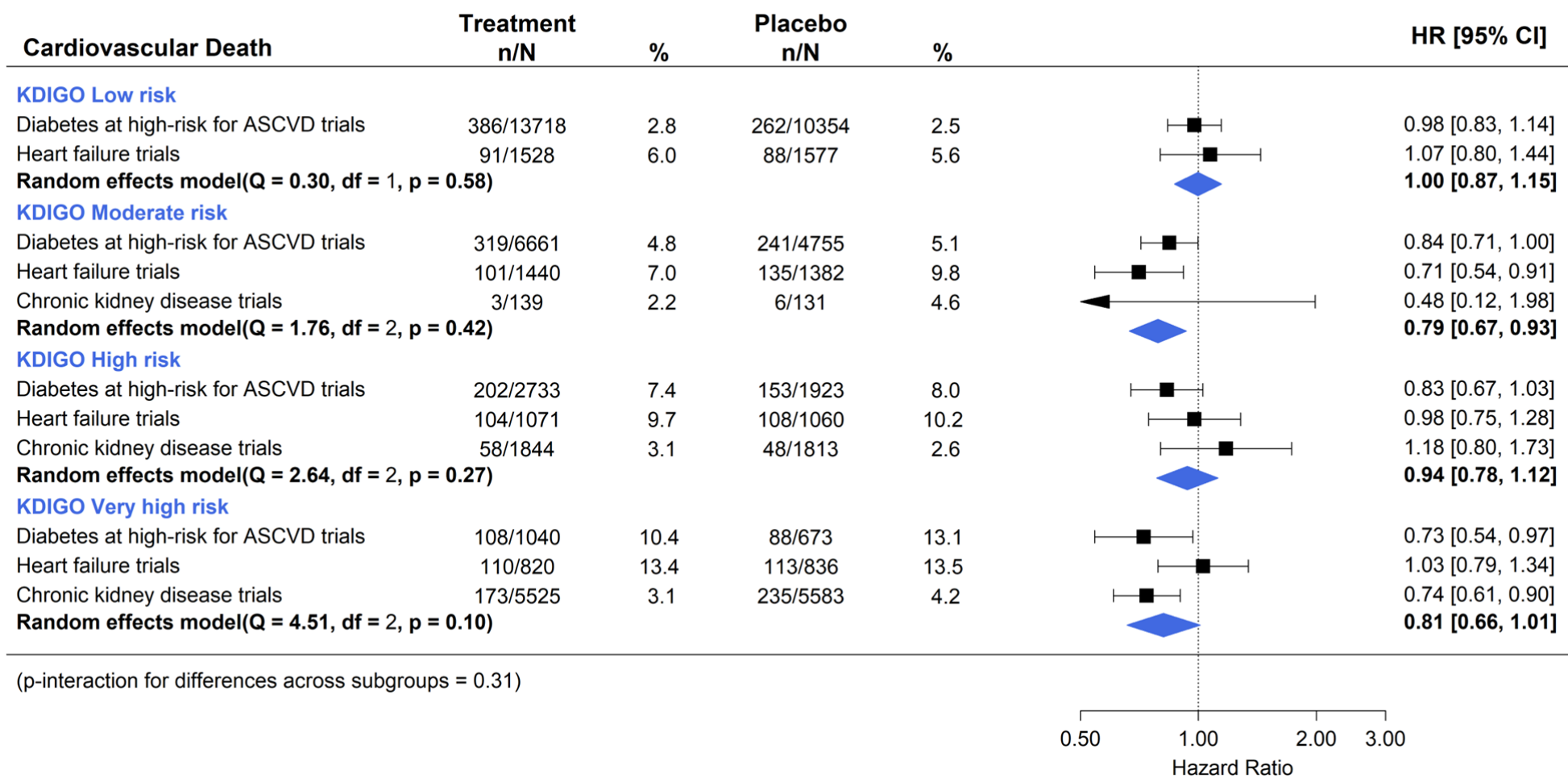
Supplemental Figure S14: Treatment Effect of SGLT2i on Major Adverse Cardiovascular Events Composite by KDIGO Risk Groups

| MACE Composite | Treatment n/N | % | Placebo n/N | % | HR [95% CI] |
|---|------------------|------|----------------|------|-------------------|
| KDIGO Low risk | | | | | |
| Diabetes at high-risk for ASCVD trials | 1106/13718 | 8.1 | 836/10354 | 8.1 | 0.92 [0.84, 1.01] |
| Heart failure trials | 125/1528 | 8.2 | 124/1577 | 7.9 | 1.04 [0.81, 1.34] |
| Random effects model(Q = 0.81, df = 1, p = 0.37) | | | | | |
| KDIGO Moderate risk | | | | | |
| Diabetes at high-risk for ASCVD trials | 802/6661 | 12.0 | 550/4755 | 11.6 | 0.96 [0.86, 1.07] |
| Heart failure trials | 140/1440 | 9.7 | 163/1382 | 11.8 | 0.81 [0.65, 1.02] |
| Chronic kidney disease trials | 11/279 | 3.9 | 12/246 | 4.9 | 0.79 [0.31, 2.00] |
| Random effects model(Q = 1.86, df = 2, p = 0.39) | | | | | |
| KDIGO High risk | | | | | |
| Diabetes at high-risk for ASCVD trials | 420/2733 | 15.4 | 314/1923 | 16.3 | 0.88 [0.76, 1.02] |
| Heart failure trials | 137/1071 | 12.8 | 136/1060 | 12.8 | 1.01 [0.80, 1.28] |
| Chronic kidney disease trials | 125/1844 | 6.8 | 116/1813 | 6.4 | 1.05 [0.81, 1.35] |
| Random effects model(Q = 1.84, df = 2, p = 0.40) | | | | | |
| KDIGO Very high risk | | | | | |
| Diabetes at high-risk for ASCVD trials | 198/1040 | 19.0 | 151/673 | 22.4 | 0.78 [0.63, 0.97] |
| Heart failure trials | 145/820 | 17.7 | 139/836 | 16.6 | 1.09 [0.86, 1.38] |
| Chronic kidney disease trials | 351/5525 | 6.4 | 427/5583 | 7.6 | 0.82 [0.71, 0.94] |
| Random effects model(Q = 5.09, df = 2, p = 0.08) | | | | | |



(p-interaction for differences across subgroups = 0.35)

Supplemental Figure S15: Treatment Effect of SGLT2i on Cardiovascular Death by KDIGO Risk Groups



(p-interaction for differences across subgroups = 0.31)