#### **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	Blinding of outcome assessment	Incomplete outcome data	Selective reporting					
			personnel		addressed						
Diabetes at high-risk for ASCVD trials											
<b>EMPA-REG Outcome</b>	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					
		Heart	failure trials								
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					
		Chronic kid	ney disease trid	als							
CREDENCE	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	<ul> <li>Trial protocol-defined as any of the following:</li> <li>History of MI</li> <li>Evidence of multivessel CAD (i.e. ≥2 major coronary arteries or left main) defined as follows: stenosis ≥50%, or prior coronary revascularization, or combination of revascularization in one major coronary artery with residual stenosis ≥50% in another</li> <li>Evidence of single-vessel CAD (≥50% stenosis) not revascularized with either a positive stress test for ischemia or recent (≤12 months) hospitalization for unstable angina</li> <li>Unstable angina with evidence of single-vessel or multi-vessel CAD</li> <li>History of stroke</li> <li>Occlusive PAD defined as: limb revascularization, limb or foot amputation, angiographic or hemodynamically significant stenosis in 1 limb (≥50%) or ABI &lt;0.9</li> </ul>
CANVAS Program	<ul> <li>Trial protocol-defined as any of the following:</li> <li>Prior stroke</li> <li>Prior MI</li> <li>Hospital admission for unstable angina</li> <li>Coronary revascularization</li> <li>Peripheral revascularization</li> <li>Documented hemodynamically significant carotid or peripheral vascular disease</li> <li>Amputation secondary to vascular disease</li> </ul>
DECLARE-TIMI 58	<ul> <li>Trial protocol-defined as any of the following:         <ul> <li>Ischemic heart disease – documented MI, coronary revascularization, or ≥50% stenosis in 2 coronary artery territories (or bypass graft)</li> <li>Cerebrovascular disease – documented ischemic stroke, carotid stenting or endarterectomy</li> <li>Peripheral arterial disease – prior peripheral intervention, lower extremity amputation, or intermittent claudication with ABI &lt;0.90</li> </ul> </li> </ul>
VERTIS CV	<ul> <li>Trial protocol-defined as any of the following:</li> <li>Ischemic heart disease – documented prior MI or coronary revascularization</li> <li>Ischemic cerebrovascular disease – documented ischemic stroke or carotid revascularization</li> <li>Peripheral arterial disease – angiographically documented peripheral vascular disease, ABI &lt;0.85 with symptoms of claudication or amputation, peripheral bypass or peripheral angioplasty of the extremities</li> </ul>

	Heart failure trials
EMPEROR-Reduced	<ul> <li>Established ASCVD term was derived based on presence of CAD, PAD or cerebrovascular disease defined as follows:</li> <li>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.</li> <li>Cerebrovascular disease was defined as a history of stroke or transient ischemic attack or cerebrovascular disease other than stroke or TIA</li> <li>Peripheral artery disease was defined as peripheral artery occlusive disease or prior lower limb amputation</li> </ul>
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	<ul> <li>Established ASCVD term was derived based on presence of CAD, PAD or cerebrovascular disease fined as follows:</li> <li>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.</li> <li>Cerebrovascular disease was defined as a history of stroke or transient ischemic attack or cerebrovascular disease other than stroke or TIA</li> <li>Peripheral artery disease was defined as peripheral artery occlusive disease or prior lower limb amputation</li> </ul>
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
CREDENCE	Established ASCVD term was derived as presence of any CAD, PAD or cerebrovascular disease on baseline medical history.
DAPA-CKD	<ul> <li>Established ASCVD term was derived by the presence of any of the following on the patient's medical history:</li> <li>CAD – angina pectoris, coronary artery stenosis, coronary revascularization (PCI/CABG), or MI</li> <li>Cerebrovascular disease – carotid artery stenosis, carotid revascularization, carotid stent insertion, cerebral artery stent insertion, cerebral revascularization, ischemic stroke, or TIA</li> <li>PAD – aortic aneurysm, history of PAD, peripheral artery stenting, peripheral revascularization</li> </ul>
EMPA-KIDNEY	Established ASCVD term was derived as prior MI, PAD, stroke or TIA on baseline medical history

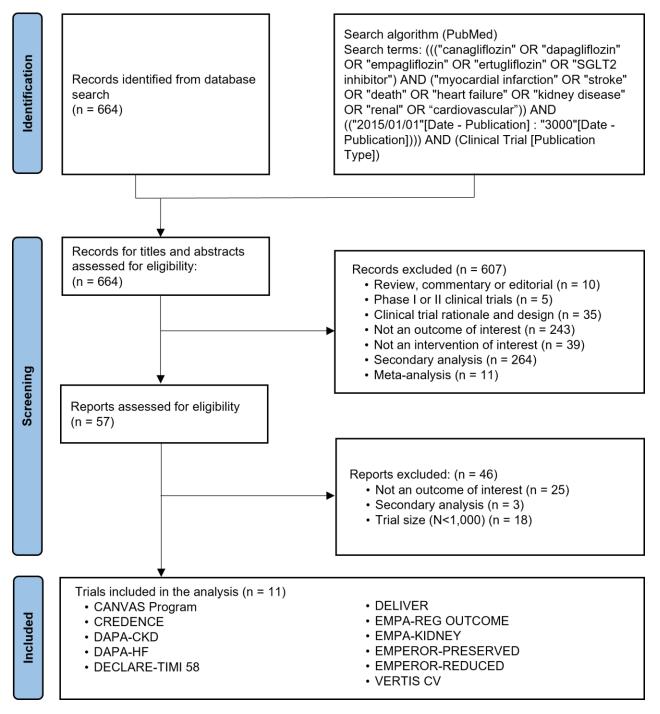
Supplemental Table S3: Availability	of Subgroup Data Across Individual Trials

	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
			Di	abetes at high risl	k for ASCVD trials		
EMPA-REG Outcome	√	$\checkmark$	$\checkmark$	√**	√	$\checkmark$	$\checkmark$
CANVAS Program	√	$\checkmark$	$\checkmark$	<b>√*</b> *	✓	$\checkmark$	$\checkmark$
DECLARE-TIMI 58	$\checkmark$	$\checkmark$	$\checkmark$	<b>√*</b> *	√	$\checkmark$	$\checkmark$
VERTIS CV	$\checkmark$	$\checkmark$	$\checkmark$	<b>√*</b> *	✓	$\checkmark$	$\checkmark$
				Heart failu	ire trials		
EMPEROR-Reduced	√*	$\checkmark$	$\checkmark$	$\checkmark$	✓	$\checkmark$	$\checkmark$
DAPA-HF	√*	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	Not available	Not available
EMPEROR-Preserved	√*	$\checkmark$	$\checkmark$	$\checkmark$	√	$\checkmark$	$\checkmark$
DELIVER	√*	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	Not available	Not available
				Chronic kidney	disease trials		
CREDENCE	√*	$\checkmark$	$\checkmark$	<b>√*</b> *	✓	$\checkmark$	$\checkmark$
DAPA-CKD	√*	$\checkmark$	$\checkmark$	<b>√*</b> *	✓	√	$\checkmark$
EMPA-KIDNEY	√*	$\checkmark$	$\checkmark$	<b>√</b> **	✓	$\checkmark$	$\checkmark$

\*Established ASCVD was protocol-defined in 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

All-cause Mortality	Treatment n/N	Events per 1000 pt-yrs	Placebo n/N	Events per 1000 pt-yrs	Weights (%)		HR [95% CI]
Diabetes at high risk for ASCVD tri	ials						
EMPA-REG Outcome	269/4687	19.4	194/2333	28.6	7.0	<b>⊢-⊞</b> 1	0.68 [0.57, 0.82]
CANVAS Program	NA/NA	17.3	NA/NA	19.5	9.5	· • ·	0.87 [0.74, 1.01]
DECLARE-TIMI 58	529/8582	15.1	570/8578	16.4	16.3	· ■ : ⊢∎∺	0.93 [0.82, 1.04]
VERTIS CV	473/5499	24.4	254/2747	26.2	10.2	<b>∎</b>	0.93 [0.80, 1.08]
Fixed effects model (Q = 9.02, df =		21.1	20 11 21 11	20.2	10.2	•	0.87 [0.81, 0.94]
Heart failure trials							
DAPA-HF	276/2373	79.0	329/2371	95.0	9.5	┝╌╋╌┥	0.83 [0.71, 0.97]
EMPEROR-Reduced	249/1863	101.0	266/1867	107.0	7.2	┝╌┲┊┥	0.92 [0.77, 1.10]
EMPEROR-Preserved	422/2997	66.0	427/2991	67.0	11.8	┝╌╋─┤	1.00 [0.87, 1.15]
DELIVER	497/3131	72.0	526/3132	76.0	14.3	┝╌╋╧┤	0.94 [0.83, 1.07]
Fixed effects model (Q = 3.12, df =	3, <b>p = 0.37</b> )					•	0.93 [0.86, 1.00]
Chronic kidney disease trials							
CREDENCE	168/2202	29.0	201/2199	35.0	5.6	<b>├</b> ── <b>─</b>	0.83 [0.68, 1.02]
DAPA-CKD	101/2152	22.0	146/2152	31.0	3.6	<b>├──■</b> ───┤	0.69 [0.53, 0.88]
EMPA-KIDNEY	148/3304	22.8	167/3305	25.8	4.9	┝──╋──┤	0.87 [0.70, 1.08]
Fixed effects model (Q = 2.00, df =	2, <b>p = 0.37</b> )					<b></b>	0.80 [0.71, 0.91]
Fixed offects model for everall (O = 1	17.06 df = 10 p = 0.06	$(1^2 - 44.24)$					0.88 [0.84, 0.93]
Fixed effects model for overall (Q = 1 Stratified random effects model fo			1 <sup>2</sup> - 46 42: -2	- 0.002)			0.88 [0.82, 0.93]
(Overall P-value = 0.0002)	or overall (Q = 3.82, 01	-2, p = 0.15;	, <b>ι = 40.42;</b> τ	- 0.002)		-	0.00 [0.02, 0.94]
						0 50 1 00	2.00
						0.50 1.00	2.00
						Hazard Ratio	

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

Non-cardiovascular Death	Treatment n/N	Events per 1000 pt-yrs	Placebo n/N	Events per 1000 pt-yrs	Weights (%)		HR [95% CI]
Disbatas at high risk for ASCVD trials							
Diabetes at high risk for ASCVD trials	07/4007	7.0	F7/0000	0.4	0.0		0.94 [0.60, 1.46]
EMPA-REG Outcome	97/4687	7.0	57/2333	8.4	6.0		0.84 [0.60, 1.16]
CANVAS Program	132/5795	5.7	96/4347	6.7	9.1		0.85 [0.65, 1.11]
DECLARE-TIMI 58	211/8582	6.0	238/8578	6.8	18.6		0.88 [0.73, 1.06]
VERTIS CV Fixed effects model (Q = 0.37, df = 3, p =	132/5499 = <b>0 95</b> )	NA	70/2747	NA	7.9		0.94 [0.71, 1.25] <b>0.88 [0.78, 1.00]</b>
The effects model ( $\alpha = 0.57$ , $\alpha = 0, p$	- 0.33)						0.00 [0.70, 1.00]
Heart failure trials							
DAPA-HF	49/2373	14.0	56/2371	16.2	4.4	⊢∎	0.86 [0.59, 1.27]
EMPEROR-Reduced	62/1863	25.0	64/1867	25.8	5.2		0.91 [0.64, 1.30]
EMPEROR-Preserved	203/2997	31.7	183/2991	28.6	15.8	· • • • • • • • • • • • • • • • • • • •	1.13 [0.92, 1.38]
DELIVER	197/3131	28.4	188/3132	27.2	16.1		1.04 [0.85, 1.27]
Fixed effects model (Q = 2.13, df = 3, p =		20.1	100/0102	27.2	10.1		1.03 [0.91, 1.17]
Chronic kidney disease trials							
CREDENCE	58/2202	10.0	61/2199	10.6	5.0	<b>⊢−−−−∎</b>	0.94 [0.66, 1.35]
DAPA-CKD	36/2152	7.7	66/2152	14.2	3.9		0.54 [0.36, 0.81]
EMPA-KIDNEY	89/3304	13.7	98/3305	15.1	8.1		0.89 [0.67, 1.18]
Fixed effects model ( $Q = 4.94$ , df = 2, p =		10.7	00/0000	10.1	0.1		0.81 [0.66, 0.98]
	-						
Fixed effects model for overall (Q = 13.07,	df = 10, p = 0.22	; , I <sup>2</sup> = 23.51)				$\blacklozenge$	0.93 [0.85, 1.00]
Stratified random effects model for over	rall (Q = 5.64, df	= 2, <b>p</b> = <b>0.06</b> ; ,	<b>Ι<sup>2</sup> = 64.70;</b> τ <sup>2</sup>	= 0.010)		-	0.91 [0.79, 1.05]
(Overall P-value = 0.20)							
						0.50 1.00	2.00
						Hazard Ratio	

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

	Major	Adverse Cardio	vascular Event	s Composite		
Established ASCVD	Treatment n/N	Events per 1000 pt-yrs	Placebo n/N	Events per 1000 pt-yrs		HR [95% CI]
Diabetes at high risk for ASCVD t	trials					
EMPA-REG Outcome	490/4687	37.4	282/2333	43.9	⊢∎→	0.86 [0.74, 0.99]
CANVAS Program	493/4127	33.3	360/3197	38.1	⊢∎−	0.87 [0.76, 1.00]
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	<b>⊢∎</b>	0.90 [0.79, 1.02]
VERTIS CV	735/5499	40.0	368/2747	40.3	⊢∎-1	0.99 [0.88, 1.12]
Fixed effects model (Q = 2.91, df	= 3, p = 0.41)				•	0.91[0.85,0.97]
Heart failure trials						
DAPA-HF	207/1482	96.9	240/1560	107.8	┝──ॖॖॖॖॖॖॖॖॖॖ	0.90 [0.75, 1.08]
EMPEROR-Reduced	167/1228	104.2	159/1178	102.8	⊢	1.01 [0.82, 1.26]
EMPEROR-Preserved	206/1667	61.2	207/1653	61.4	⊢_∎(	1.01 [0.84, 1.23]
DELIVER	248/1766	64.9	273/1832	69.9	┝╌╋┊╌┤	0.93 [0.78, 1.10]
Fixed effects model (Q = 1.09, df	<b>=</b> 3, <b>p = 0.78</b> )				<b>•</b>	0.96[0.87,1.05]
Chronic kidney disease trials						
CREDENCE	155/1113	55.6	178/1107	65.0	⊢∎	0.85 [0.69, 1.06]
DAPA-CKD	79/663	56.1	79/666	56.4	⊢	0.99 [0.72, 1.35]
EMPA-KIDNEY	62/737	43.7	67/757	46.4	⊢∎	0.96 [0.68, 1.35]
Fixed effects model (Q = 0.74, df	= 2, p = 0.69)					0.91[0.77,1.06]

Stratified Random Effects Model for Overall(Q = 0.74, df = 2, p = 0.69; ,  $l^2$  = 0.00;  $\tau^2$  = 0.000)

• 0.92[0.88,0.97] 0.50 0.70 1.00 1.50 2.50

Hazard Ratio

No Established ASCVD	Treatment n/N	Events per 1000 pt-yrs	Placebo n/N	Events per 1000 pt-yrs		HR [95% CI]
Diabetes at high risk for ASCVE	) trials					
CANVAS Program	92/1668	13.3	66/1150	16.2	⊢∎	0.79 [0.58, 1.09]
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	<b>⊢</b> − <b>₽</b> −−1	1.01 [0.86, 1.20]
Fixed effects model (Q = 1.72, c	if = 1, p = 0.19)				-	0.96[0.83,1.11]
Heart failure trials						
DAPA-HF	82/891	63.5	92/811	79.4	⊢∎	0.80 [0.60, 1.08]
EMPEROR-Reduced	61/635	74.9	74/689	83.8	⊢──∎∔──┤	0.88 [0.63, 1.23]
EMPEROR-Preserved	113/1330	40.3	124/1338	44.6	⊢−−∎∔−−1	0.90 [0.70, 1.16]
DELIVER	119/1365	40.3	117/1300	40.9	<b>⊢∔</b> {	0.99 [0.76, 1.27]
Fixed effects model (Q = 1.16, c	if = 3, p = 0.76)				-	0.90[0.78,1.03]
Chronic kidney disease trials						
CREDENCE	62/1089	22.0	91/1092	32.7		0.68 [0.49, 0.94]
DAPA-CKD	53/1489	16.7	64/1486	20.4	⊢∎	0.82 [0.57, 1.18]
EMPA-KIDNEY	76/2567	15.2	76/2548	15.3	⊢∎(	0.98 [0.71, 1.35]
Fixed effects model (Q = 2.52, c	if = 2, p = 0.28)					0.82[0.67,0.99]

Stratified Random Effects Model for Overall(Q = 1.68, df = 2, p = 0.43; ,  $I^2 = 0.00$ ;  $\tau^2 = 0.000$ )

0.90[0.82,0.99] 0.50 0.70 1.00 1.50 2.50

Hazard Ratio

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

MACE Composite	Treatment n/N	%	Placebo n/N	%		HR [95% CI]	Myocardial Infarction	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Established ASCVD							Established ASCVD						
Diabetes at high risk for ASCVD trials	2201/17787	12.4	1547/11777	13.1	-	0.91 [0.85, 0.97]	Diabetes at high risk for ASCVD trials	1040/17787	5.8	758/11777	6.4	<b>⊢</b> ∰-	0.91 [0.82, 1.00]
Heart failure trials	828/6143	13.5	879/6223	14.1	H	0.96 [0.87, 1.05]	Heart failure trials	167/6143	2.7	158/6223	2.5	⊢∎	1.07 [0.86, 1.33]
Chronic kidney disease trials	296/2513	11.8	324/2530	12.8	⊢ <b>⊞</b> ∔1	0.91 [0.77, 1.06]	Chronic kidney disease trials	108/2513	4.3	106/2530	4.2	⊢ <b></b>	1.01 [0.77, 1.32]
Random effects model (Q = 0.74, df	= 2, p = 0.69)				•	0.92 [0.88, 0.97]	Random effects model (Q = 2.16, df =	= 2, p = 0.34)				•	0.96 [0.85, 1.07]
No ASCVD							No ASCVD						
Diabetes at high risk for ASCVD trials	365/6776	5.4	332/6228	5.3	H <b>H</b> -1	0.96 [0.83, 1.11]	Diabetes at high risk for ASCVD trials	154/6776	2.3	140/6228	2.2	<b>⊢</b> ∎	0.98 [0.78, 1.23]
Heart failure trials	375/4221	8.9	407/4138	9.8	⊢ <b>⊞</b> -H	0.90 [0.78, 1.03]	Heart failure trials	30/4221	0.7	24/4138	0.6	⊢ ∎	1.30 [0.74, 2.28]
Chronic kidney disease trials	191/5145	3.7	231/5126	4.5	<b>⊢-⊞</b> €	0.82 [0.67, 0.99]	Chronic kidney disease trials	64/5145	1.2	70/5126	1.4	FB	0.90 [0.64, 1.27]
Random effects model (Q = 1.68, df	= 2, p = 0.43)				•	0.90 [0.82, 0.99]	Random effects model (Q = 1.21, df =	= 2, p = 0.55)				-	0.98 [0.82, 1.18]
(p-interaction for differences across su	bgroups = 0.60)						(p-interaction for differences across sub	bgroups = 0.72)					
					0.50 1.00 Hazard Ra	2.00 3.00 atio						0.50 1.00 2.00 Hazard Ratio	3.00

HR [95% CI]

Cardiovascular Death	n/N	%	Placebo n/N	%		HR [95% CI]
Established ASCVD						
Diabetes at high risk for ASCVD trials	896/17787	5.0	643/11777	5.5	HEH	0.85 [0.76, 0.94]
Heart failure trials	580/6143	9.4	653/6223	10.5	⊢ <b>⊞</b> -I	0.90 [0.80, 1.00]
Chronic kidney disease trials	145/2513	5.8	174/2530	6.9	⊢∎	0.82 [0.65, 1.02]
Random effects model (Q = 0.88, df =	= 2, <b>p = 0.64</b> )				•	0.86 [0.80, 0.93]
No ASCVD						
Diabetes at high risk for ASCVD trials	130/6776	1.9	112/6228	1.8	⊢ <b>∎</b> I	0.97 [0.76, 1.25]
Heart failure trials	284/4221	6.7	327/4138	7.9	⊢∎⊣	0.85 [0.72, 0.99]
Chronic kidney disease trials	89/5145	1.7	115/5126	2.2	<b>⊢_∎</b> 1	0.77 [0.59, 1.02]
Random effects model (Q = 1.53, df =	= 2, p = 0.47)				•	0.86 [0.76, 0.97]

Placebo

Treatment

Stroke	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Established ASCVD						
Diabetes at high risk for ASCVD trials	642/17787	3.6	423/11777	3.6	H <b>H</b> H	1.00 [0.88, 1.13]
Heart failure trials	193/6143	3.1	178/6223	2.9	⊢∎⊣	1.10 [0.90, 1.35]
Chronic kidney disease trials	93/2513	3.7	98/2530	3.9	⊢ <b>_</b>	0.95 [0.71, 1.26]
Random effects model (Q = 0.86, df =	= 2, p = 0.65)				•	1.02 [0.92, 1.12]
No ASCVD						
Diabetes at high risk for ASCVD trials	138/6776	2.0	129/6228	2.1	⊢ <b>_</b>	0.96 [0.76, 1.22]
Heart failure trials	96/4221	2.3	96/4138	2.3	⊢ <b>_</b>	0.96 [0.72, 1.28]
Chronic kidney disease trials	60/5145	1.2	74/5126	1.4	⊢∎	0.81 [0.57, 1.14]
Random effects model (Q = 0.78, df =	= 2, p = 0.68)				-	0.93 [0.79, 1.09]

0.50 2.00 3.00 1.00 Hazard Ratio

0.50 1.00 2.00 3.00 Hazard Ratio

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

MACE Composite	Treatment n/N	%	Placebo n/N	%		HR [95% CI]	Myocardial Infarction	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Prior MI							Prior MI						
Diabetes at high risk for ASCVD trials	1136/8234	13.8	831/5510	15.1	H	0.88 [0.80, 0.96]	Diabetes at high risk for ASCVD trials	596/8234	7.2	449/5510	8.1	H <b>H</b> H	0.89 [0.78, 1.00]
Heart failure trials	485/3561	13.6	530/3573	14.8	H	0.92 [0.82, 1.04]	Heart failure trials	104/3561	2.9	107/3573	3.0	⊢	0.99 [0.76, 1.30]
Chronic kidney disease trials	106/751	14.1	123/785	15.7	<b>⊢</b>	0.94 [0.72, 1.22]	Chronic kidney disease trials	43/751	5.7	47/785	6.0	⊢ <b></b> (	0.98 [0.65, 1.49]
Random effects model (Q = 0.52, df =	= 2, p = 0.77)				•	0.90 [0.84, 0.96]	Random effects model (Q = 0.68, df =	= 2, p = 0.71)				•	0.91 [0.81, 1.01]
No prior MI							No prior MI						
Diabetes at high risk for ASCVD trials	1430/16329	8.8	1048/12495	8.4	H <b>200</b> 4	0.94 [0.87, 1.02]	Diabetes at high risk for ASCVD trials	598/16329	3.7	449/12495	3.6	⊦∎⊣	0.95 [0.83, 1.07]
Heart failure trials	718/6803	10.6	756/6788	11.1	+	0.94 [0.85, 1.04]	Heart failure trials	93/6803	1.4	75/6788	1.1	⊢_∎(	1.20 [0.88, 1.64]
Chronic kidney disease trials	381/6907	5.5	432/6871	6.3	H <b>B</b> -1	0.86 [0.75, 0.99]	Chronic kidney disease trials	129/6907	1.9	129/6871	1.9	H	0.98 [0.77, 1.25]
Random effects model (Q = 1.32, df =	= 2, p = 0.52)				٠	0.93 [0.88, 0.98]	Random effects model (Q = 2.02, df =	= 2, p = 0.36)				•	0.98 [0.88, 1.09]
(p-interaction for differences across sub	bgroups = 0.35)						(p-interaction for differences across sul	bgroups = 0.31)					
					0.50 1.00 2 Hazard Ratio	2.00 3.00						0.50 1.00 2.0 Hazard Ratio	0 3.00

Cardiovascular Death	Treatment n/N	%	Placebo n/N	%		HR [95% CI]	Stroke	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Prior MI							Prior MI						
Diabetes at high risk for ASCVD trials	464/8234	5.6	356/5510	6.5	⊢∎⊣	0.79 [0.69, 0.91]	Diabetes at high risk for ASCVD trials	275/8234	3.3	187/5510	3.4	H <b>H</b> H	0.98 [0.81, 1.19]
Heart failure trials	353/3561	9.9	399/3573	11.2	⊢∎⊣	0.89 [0.77, 1.03]	Heart failure trials	95/3561	2.7	90/3573	2.5	<b>⊢</b>	1.06 [0.79, 1.42]
Chronic kidney disease trials	53/751	7.1	60/785	7.6	⊢ <b>−</b>	→ 0.96 [0.66, 1.39]	Chronic kidney disease trials	28/751	3.7	33/785	4.2	⊢ <b></b>	0.94 [0.56, 1.57]
Random effects model (Q = 1.70, df =	= 2, p = 0.43)				•	0.85 [0.76, 0.94]	Random effects model (Q = 0.26, df =	= 2, p = 0.88)				-	1.00 [0.86, 1.16]
No prior MI							No prior MI						
Diabetes at high risk for ASCVD trials	562/16329	3.4	399/12495	3.2	⊢∎⊣	0.93 [0.81, 1.05]	Diabetes at high risk for ASCVD trials	505/16329	3.1	365/12495	2.9	H <b>H</b> H	0.99 [0.86, 1.14]
Heart failure trials	511/6803	7.5	581/6788	8.6	H	0.88 [0.78, 0.99]	Heart failure trials	194/6803	2.9	184/6788	2.7	⊢∎⊣	1.04 [0.85, 1.28]
Chronic kidney disease trials	181/6907	2.6	229/6871	3.3	⊢∎⊣	0.77 [0.64, 0.94]	Chronic kidney disease trials	125/6907	1.8	139/6871	2.0	⊢∎∔	0.89 [0.70, 1.13]
Random effects model (Q = 2.23, df =	= 2, p = 0.33)				٠	0.88 [0.81, 0.95]	Random effects model (Q = 1.04, df =	= 2, p = 0.59)				+	0.98 [0.89, 1.09]
(p-interaction for differences across sul	bgroups = 0.59)						(p-interaction for differences across sub	bgroups = 0.81)					
					0.50 1.00 Hazard	2.00 3.00 I Ratio						0.50 1.00 Hazard Rati	2.00 3.00 io

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

MACE Composite	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Prior DM						
Diabetes at high risk for ASCVD trials	2566/24563	10.4	1879/18005	10.4		0.91 [0.86, 0.97]
Heart failure trials	637/4869	13.1	682/4870	14.0	ŀ <b>I</b>	0.93 [0.83, 1.03]
Chronic kidney disease trials	421/5182	8.1	494/5165	9.6	<b>⊢⊞</b> -1	0.84 [0.74, 0.96]
Random effects model(Q = 1.57, df =	2, <b>p = 0.46</b> )				•	0.91 [0.86, 0.95]
No prior DM						
Heart failure trials	566/5495	10.3	604/5491	11.0	⊦∎H	0.94 [0.84, 1.05]
Chronic kidney disease trials	66/2476	2.7	61/2491	2.4	⊦ <b>≣</b> i	1.09 [0.77, 1.54]
Random effects model(Q = 0.62, df =	1, p = 0.43)				•	0.95 [0.85, 1.06]

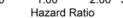


Cardiovascular Death	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Prior DM						
Diabetes at high risk for ASCVD trials	1026/24563	4.2	755/18005	4.2	H <b>a</b> H	0.86 [0.78, 0.95]
Heart failure trials	455/4869	9.3	512/4870	10.5	ŀ <b>₩</b> -I	0.88 [0.78, 1.00]
Chronic kidney disease trials	208/5182	4.0	264/5165	5.1	⊢-■1	0.78 [0.65, 0.94]
Random effects model(Q = 1.18, df =	2, <b>p = 0.55</b> )				•	0.86 [0.80, 0.92]
No prior DM						
Heart failure trials	409/5495	7.4	468/5491	8.5	⊨ <b>⊞</b> -į	0.87 [0.76, 1.00]
Chronic kidney disease trials	26/2476	1.1	25/2491	1.0	<b> </b>	⊣ 1.04 [0.60, 1.83]
Random effects model(Q = 0.37, df =	1, p = 0.54)				•	0.88 [0.77, 1.00]

0.50 1.00 2.00 3.00 Hazard Ratio

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

MACE Composite	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Prior HF						
Diabetes at high risk for ASCVD trials	556/3403	16.3	399/2446	16.3	H	0.94 [0.83, 1.07]
Heart failure trials	1203/10364	11.6	1286/10361	12.4	H	0.94 [0.86, 1.01]
Chronic kidney disease trials	112/888	12.6	113/890	12.7	<b>⊢</b> −−	0.95 [0.74, 1.24]
Random effects model(Q = 0.02, df =	2, <b>p = 0.99</b> )				•	0.94 [0.88, 1.00]
No prior HF						
Diabetes at high risk for ASCVD trials	2010/21160	9.5	1480/15559	9.5	-	0.91 [0.85, 0.98
Chronic kidney disease trials	375/6769	5.5	442/6765	6.5	⊢ <b>⊞</b> -i	0.84 [0.73, 0.97]
Random effects model(Q = 1.00, df =	1, <b>p = 0.32</b> )				•	0.90 [0.84, 0.95]
(p-interaction for differences across sul	ogroups = 0.20)					
	,				0.50 1.00	2.00 3.00



Cardiovascular Death	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Prior HF						
Diabetes at high risk for ASCVD trials	298/3403	8.8	227/2446	9.3	<b>⊢</b> ∎-1	0.86 [0.73, 1.03]
Heart failure trials	864/10364	8.3	980/10361	9.5	H	0.88 [0.80, 0.96]
Chronic kidney disease trials	72/888	8.1	75/890	8.4	<b>⊢</b>	0.93 [0.67, 1.28]
Random effects model(Q = 0.13, df =	2, <b>p = 0.94</b> )				•	0.88 [0.81, 0.95]
No prior HF						
Diabetes at high risk for ASCVD trials	728/21160	3.4	528/15559	3.4	F <b>H</b> -1	0.86 [0.77, 0.96]
Chronic kidney disease trials	162/6769	2.4	214/6765	3.2	F₩1	0.75 [0.61, 0.92]
Random effects model(Q = 1.24, df =						0.83 [0.74, 0.93]

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

MACE Composite	Treatment n/N	%	Placebo n/N	%	- 1	HR [95% CI]
Prior CKD						
Diabetes at high risk for ASCVD trials	615/4127	14.9	433/2803	15.4	H	0.89 [0.79, 1.01]
Heart failure trials	669/4875	13.7	702/4909	14.3	H <b>H</b> H	0.96 [0.86, 1.07]
Chronic kidney disease trials	385/6270	6.1	450/6309	7.1	⊢∎⊣	0.85 [0.75, 0.98]
Random effects model (Q = 1.86, df =	= 2, p = 0.39)				•	0.91 [0.85, 0.98]
No prior CKD						
Diabetes at high risk for ASCVD trials	1951/20431	9.5	1446/15201	9.5	-	0.92 [0.86, 0.99]
Heart failure trials	534/5487	9.7	582/5448	10.7	F <b>E</b>	0.91 [0.81, 1.02]
Chronic kidney disease trials	102/1387	7.4	105/1347	7.8	⊢ <b>∎</b> –1	0.93 [0.70, 1.22]
Random effects model (Q = 0.08, df =	= 2, p = 0.96)				٠	0.92 [0.87, 0.98]

Hazard Ratio

0.50

1.00

Hazard Ratio

2.00 3.00

Cardiovascular Death	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
Prior CKD						
Diabetes at high risk for ASCVD trials	305/4127	7.4	212/2803	7.6	⊢∎∔	0.88 [0.74, 1.05]
Heart failure trials	482/4875	9.9	541/4909	11.0	H	0.90 [0.79, 1.01]
Chronic kidney disease trials	187/6270	3.0	242/6309	3.8	⊢-■	0.78 [0.64, 0.94]
Random effects model (Q = 1.65, df =	= 2, p = 0.44)				•	0.87 [0.79, 0.95]
No prior CKD						
Diabetes at high risk for ASCVD trials	721/20431	3.5	543/15201	3.6	H	0.86 [0.77, 0.96]
Heart failure trials	382/5487	7.0	437/5448	8.0	⊢ <b>∎</b> -	0.86 [0.75, 0.99]
Chronic kidney disease trials	45/1127	4.0	47/1096	4.3	I	0.92 [0.61, 1.38]
Random effects model (Q = 0.08, df =	= 2, p = 0.96)				•	0.86 [0.79, 0.94]

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

	Treatment		Placebo			
MACE Composite	n/N	%	n/N	%		HR [95% CI]
-050 - 22						
eGFR < 30	04/007	10.0	74/000	10.0		0 92 10 50 1 191
Heart failure trials	61/367	16.6	71/363	19.6		0.83 [0.59, 1.18]
Chronic kidney disease trials Random effects model(Q = 0.00, df = 1, p =	89/1508	5.9	113/1572	7.2		0.82 [0.62, 1.08] <b>0.83 [0.67, 1.03]</b>
• • • • •	0.90)					0.83 [0.87, 1.03]
$30 \le \text{eGFR} < 45$	477/4000	47.0	400/000	10.0		0.82 [0.65 1.04]
Diabetes at high risk for ASCVD trials Heart failure trials	177/1026	17.3	129/669	19.3		0.82 [0.65, 1.04]
	283/1857	15.2	291/1867	15.6		0.98 [0.83, 1.16]
Chronic kidney disease trials Random effects model(Q = 2.24, df = 2, p =	185/3040	6.1	214/2977	7.2		0.83 [0.68, 1.01] <b>0.89 [0.79, 1.01]</b>
$45 \le \text{eGFR} < 60$	0.33)					0.03 [0.73, 1.01]
Diabetes at high risk for ASCVD trials	426/3035	14.0	299/2094	14.3	<b>⊢_</b>	0.92 [0.79, 1.07]
Heart failure trials	325/2651	12.3	340/2678	12.7		0.97 [0.83, 1.13]
Chronic kidney disease trials	111/1722	6.4	123/1760	7.0		0.93 [0.72, 1.21]
Random effects model( $Q = 0.25$ , df = 2, p =		0.4	120/11/00	1.0	· 👗 ·	0.94 [0.85, 1.04]
60≤ eGFR < 90	,					
Diabetes at high risk for ASCVD trials	1300/12455	10.4	944/8953	10.5	⊢ <b>⊞</b> -i	0.92 [0.84, 1.00]
Heart failure trials	449/4459	10.1	495/4435	11.2	· —	0.89 [0.78, 1.01]
Chronic kidney disease trials	97/1254	7.7	96/1223	7.8	·	0.97 [0.73, 1.29]
Random effects model( $Q = 0.33$ , df = 2, p =			00/1220	1.0	· · · · · · · · · · · · · · · · · · ·	0.91 [0.85, 0.98]
eGFR > 90					•	• • •
Diabetes at high risk for ASCVD trials	651/7976	8.2	502/6248	8.0	<b>⊢</b> ∎	0.94 [0.84, 1.06]
Heart failure trials	85/1028	8.3	87/1013	8.6		0.98 [0.73, 1.33]
Chronic kidney disease trials	5/105	4.8	9/106	8.5		0.55 [0.19, 1.65]
Random effects model(Q = 0.99, df = 2,	p = 0.61)		0,100	0.0	-	0.94 [0.84, 1.05]
• • •					· · · · · · · · · · · · · · · · · · ·	
(p-interaction for differences across subgro	oups = 0.21)					
					ri	
					0.50 1.00 2.0	00 3.00

Hazard Ratio

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

	Treatment		Placebo			HR [95% CI]
Cardiovascular Death	n/N	%	n/N	%		
eGFR < 30						
Heart failure trials	45/367	12.3	56/363	15.4		0.74 [0.50, 1.10]
Chronic kidney disease trials	50/1508	3.3	57/1572	3.6		0.93 [0.63, 1.36]
Random effects model(Q = 0.64, df = 1,	, p = 0.42)					0.83 [0.63, 1.09]
30≤ eGFR < 45						
Diabetes at high risk for ASCVD trials	96/1026	9.4	72/669	10.8		0.78 [0.57, 1.06]
Heart failure trials	204/1857	11.0	222/1867	11.9	┝──╋┊─┤	0.94 [0.77, 1.13]
Chronic kidney disease trials	95/3040	3.1	121/2977	4.1		0.76 [0.58, 0.99]
Random effects model( $Q = 2.05$ , df = 2,	, p = 0.36)					0.84 [0.72, 0.99]
$45 \le eGFR < 60$	000/0005	- <b>-</b>	100/0001			0.00.00.74.4.441
Diabetes at high risk for ASCVD trials	202/3035	6.7	138/2094	6.6		0.92 [0.74, 1.14]
Heart failure trials	233/2651	8.8	263/2678	9.8		0.89 [0.75, 1.07]
Chronic kidney disease trials Random effects model(Q = 1.67, df = 2,	42/1722	2.4	64/1760	3.6		0.69 [0.47, 1.02] <b>0.88 [0.77, 1.00]</b>
$60 \le eGFR < 90$	, p = 0.43)					0.00 [0.77, 1.00]
Diabetes at high risk for ASCVD trials	404/40455	1.0	200/0052	4.0		0.82 [0.72, 0.94]
Heart failure trials		4.0	380/8953	4.2	┝╼╋╌┥	
Chronic kidney disease trials	318/4459 42/1022	7.1 4.1	369/4435 44/990	8.3 4.4		0.86 [0.74, 1.00] 0.91 [0.60, 1.39]
Random effects model(Q = 0.32, df = 2,		4.1	44/990	4.4		<b>0.84 [0.76, 0.93]</b>
eGFR ≥ 90	, p 0.00)					0.04 [0.7 0, 0.00]
Diabetes at high risk for ASCVD trials	227/7976	2.8	163/6248	2.6		0.96 [0.78, 1.18]
Heart failure trials	64/1028	6.2	68/1013	6.7		0.93 [0.66, 1.31]
Chronic kidney disease trials	3/105	2.9	3/106	2.8		1.01 [0.20, 4.98]
Random effects model( $Q = 0.03$ , df = 2,		2.5	5/100	2.0		0.96 [0.80, 1.14]
(p-interaction for differences across su	(140) bgroups = 0.40					
					· · · · · · · · · · · · · · · · · · ·	
					0.50 1.00 2.00 3.00	
					Hazard Ratio	

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

MACE Composite	Treatment n/N	%	Placebo n/N	%		HR [95% CI]
uACR < 30 mg/g						
Diabetes at high risk for ASCVD trials	1368/15806	8.7	1011/11799	8.6	H	0.93 [0.85, 1.01]
Heart failure trials	246/2765	8.9	250/2787	9.0	├ <b>─₩</b> ─┤	0.99 [0.83, 1.18]
Chronic kidney disease trials	28/665	4.2	23/663	3.5	├	— 1.24 [0.72, 2.15]
Random effects model(Q = 1.41, df =	2, <b>p = 0.50</b> )				•	0.94 [0.87, 1.02]
uACR ≥ 30 mg/g						
Diabetes at high risk for ASCVD trials	1159/8346	13.9	840/5908	14.2	H	0.90 [0.82, 0.98]
Heart failure trials	299/2072	14.4	308/2049	15.0	<b>⊢</b> - <b>H</b>	0.97 [0.83, 1.14]
Chronic kidney disease trials	458/6976	6.6	532/6978	7.6	H- <b></b>	0.85 [0.75, 0.97]
Random effects model(Q = 1.56, df =	2 n = 0.46					0.90 [0.84, 0.96]

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

			%		HR [95% CI]
uACR < 30 mg/g					
Diabetes at high risk for ASCVD trials 518/15	306 3.3	337/11799	2.9	- <b>₩</b> -1	1.00 [0.87, 1.15]
Heart failure trials 178/27	65 6.4	186/2787	6.7	<u>⊢</u>	0.96 [0.78, 1.17]
Chronic kidney disease trials 15/66	5 2.3	14/663	2.1	├	1.10 [0.53, 2.28]
Random effects model(Q = 0.23, df = 2, p = 0.8	39)			<b></b>	0.99 [0.89, 1.11]
uACR ≥ 30 mg/g					
Diabetes at high risk for ASCVD trials 499/83	46 6.0	408/5908	6.9	H <b>H</b> H	0.75 [0.66, 0.86]
Heart failure trials 227/20	72 11.0	255/2049	12.4	<b>⊢⊞</b> 1	0.90 [0.75, 1.07]
Chronic kidney disease trials 219/69	76 3.1	275/6978	3.9	F-₩-1	0.79 [0.66, 0.94]
Random effects model(Q = 2.27, df = $2, p = 0.3$	0.80 [0.72, 0.88]				

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

	Treatment		Placebo			
MACE Composite	n/N	%	n/N	%		HR [95% CI]
KDIGO Low risk						
Diabetes at high-risk for ASCVD trials	1106/13718	8.1	836/10354	8.1	⊢ <b>∎</b> -j	0.92 [0.84, 1.01]
Heart failure trials	125/1528	8.2	124/1577	7.9	_ <b>, ,</b> , _ , _ , _ , _ , _ , _ , _	1.04 [0.81, 1.34]
Random effects model(Q = 0.81, df = 1,   KDIGO Moderate risk	p = 0.37)				•	0.94 [0.86, 1.02]
Diabetes at high-risk for ASCVD trials	802/6661	12.0	550/4755	11.6	<b>⊢</b> ∎-1	0.96 [0.86, 1.07]
leart failure trials	140/1440	9.7	163/1382	11.8	<b>-</b> ∎	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)						0.91 [0.78, 1.06]
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	<b>₽</b> 1	1.01 [0.80, 1.28]
Chronic kidney disease trials	125/1844	6.8	116/1813	6.4	<b>⊢≣</b>	1.05 [0.81, 1.35]
Random effects model(Q = 1.84, df = 2,	p = 0.40)					0.94 [0.84, 1.06]
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)					0.88 [0.73, 1.06]

Hazard Ratio

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

	Treatment		Placebo			
Cardiovascular Death	n/N	%	n/N	%		HR [95% CI]
KDIGO Low risk						
Diabetes at high-risk for ASCVD trials	386/13718	2.8	262/10354	2.5	<b>⊢</b> ∎	0.98 [0.83, 1.14]
leart failure trials	91/1528	6.0	88/1577	5.6	<b>⊢</b>	1.07 [0.80, 1.44]
Random effects model(Q = 0.30, df = 1,	p = 0.58)					1.00 [0.87, 1.15]
KDIGO Moderate risk						
Diabetes at high-risk for ASCVD trials	319/6661	4.8	241/4755	5.1	<b>⊢</b> ∎−-Ì	0.84 [0.71, 1.00]
leart failure trials	101/1440	7.0	135/1382	9.8	<b>⊢</b> ∎1	0.71 [0.54, 0.91]
Chronic kidney disease trials	3/139	2.2	6/131	4.6		0.48 [0.12, 1.98]
Random effects model(Q = 1.76, df = 2, p = 0.42)						0.79 [0.67, 0.93]
KDIGO High risk						
Diabetes at high-risk for ASCVD trials	202/2733	7.4	153/1923	8.0	<u>⊢_∎_</u>	0.83 [0.67, 1.03]
leart failure trials	104/1071	9.7	108/1060	10.2	<b>⊢</b>	0.98 [0.75, 1.28]
Chronic kidney disease trials	58/1844	3.1	48/1813	2.6	}I	1.18 [0.80, 1.73]
Random effects model(Q = 2.64, df = 2,	p = 0.27)					0.94 [0.78, 1.12]
KDIGO Very high risk					-	
Diabetes at high-risk for ASCVD trials	108/1040	10.4	88/673	13.1	⊢	0.73 [0.54, 0.97]
Heart failure trials	110/820	13.4	113/836	13.5	}	1.03 [0.79, 1.34]
Chronic kidney disease trials	173/5525	3.1	235/5583	4.2	<b>⊢</b> ■{	0.74 [0.61, 0.90]
Random effects model(Q = 4.51, df = 2,						0.81 [0.66, 1.01]

Hazard Ratio