SUPPLEMENTAL MATERIAL

Table S1. Electronic Search Terms.

1	canagliflozin.mp. or Canagliflozin/
2	dapagliflozin.mp.
3	empagliflozin.mp.
4	ertugliflozin.mp.
5	type 2 diabetes mellitus.mp. or Diabetes Mellitus, Type 2/
6	Diabetes Mellitus, Type 2/ or T2DM.mp.
7	Coronary Disease/ or Cardiovascular Diseases/ or Myocardial Infarction/ or cardiovascular mortality.mp
8	Acute Coronary Syndrome/
9	heart failure.mp. or Heart Failure/
10	Stroke/
11	Mortality/
12	1 or 2 or 3 or 4
13	5 or 6
14	7 or 8 or 9 or 10 or 11
15	12 and 13 and 14
16.	Limit 15 human
EN	IBASE via OVID
1	canagliflozin.mp. or Canagliflozin/
2	dapagliflozin.mp.
3	empagliflozin.mp.
4	ertugliflozin.mp.
5	type 2 diabetes mellitus.mp. or Diabetes Mellitus, Type 2/
6	Diabetes Mellitus, Type 2/ or T2DM.mp.
7	Coronary Disease/ or Cardiovascular Diseases/ or Myocardial Infarction/ or cardiovascular mortality.mp
8	Acute Coronary Syndrome/
9	heart failure.mp. or Heart Failure/
10	Stroke/
11	Mortality/
12	1 or 2 or 3 or 4
13	5 or 6
14	
15	12 and 13 and 14
16.	Limit 15 human
10.	

Table S2. Risk of Bias Assessment.

	Sequence generation	Allocation sequence concealment	Blinding of participants and	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
			personnel			
EMPA-REG	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CANVAS Program	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DECLARE-TIMI 58	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CREDENCE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk



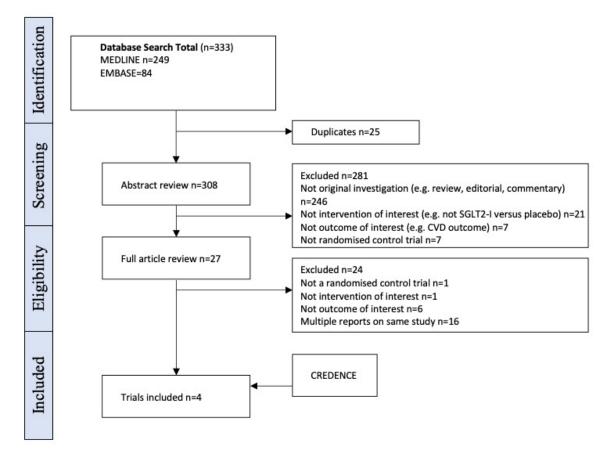


Figure S2A. Effects of SGLT2 inhibition on MACE, CV death, total MI and total stroke for patients with (secondary prevention) and without (primary prevention) cardiovascular disease at baseline.

: Event			
Litter			
4687	2333		0.86 (0.74, 0.99
5795	4347		0.86 (0.75, 0.97
8582	8578		0.93 (0.84, 1.03
2202	2199		0.80 (0.67, 0.95
= 0.0%, p =	= 0.477)	\diamond	0.88 (0.82, 0.94
n 4687	2333		0.86 (0.74, 0.99
			0.82 (0.72, 0.95
3474			0.90 (0.79, 1.02
1113	1107	_ _	0.85 (0.69, 1.06
= 0.0%, p =	0.813)	\diamond	0.86 (0.80, 0.93
2039	1447		0.98 (0.74, 1.30
5108	5078		1.01 (0.86, 1.20
1089	1092	— — ——————————————————————————————————	0.68 (0.49, 0.93
= 57.6%, p	= 0.094)	\diamond	0.94 (0.82, 1.07
4687	2333	_	0.62 (0.49, 0.77
		_	0.87 (0.72, 1.06
			0.98 (0.82, 1.17
			0.78 (0.61, 1.00
		\diamond	0.83 (0.75, 0.92
n			
4687	2333	_ _	0.62 (0.49, 0.77
3756	2900	_ _	0.86 (0.70, 1.06
3474	3500		0.94 (0.76, 1.18
1113	1107		0.79 (0.58, 1.07
		$\overline{\diamond}$	0.80 (0.71, 0.90
2039	1447		0.93 (0.60, 1.43
5108	5078		1.06 (0.79, 1.42
1089	1092		0.75 (0.48, 1.16
= 0.0%, p =	= 0.439)		0.95 (0.77, 1.17
fatal and no	on-fatal)		
4687	2333		0.87 (0.70, 1.09
			0.89 (0.73, 1.09
			0.89 (0.77, 1.01
			0.86 (0.64, 1.16
		$\overline{\diamond}$	0.88 (0.80, 0.97
'n			
4687	2333		0.87 (0.70, 1.09
3756	2900		0.82 (0.66, 1.01
3474	3500		0.87 (0.74, 1.02
1113	1107		0.93 (0.66, 1.32
= 0.0%, p =	= 0.937)	\diamond	0.86 (0.78, 0.96
		_	
2039	1447		1.38 (0.84, 2.26
			0.94 (0.73, 1.21
1089 - 40.1% p			0.69 (0.38, 1.21
- 40.1%, p	- 0.169)		0.97 (0.78, 1.19
atal)			
4687	2333		1.18 (0.89, 1.56
5795	4347	_ _	0.87 (0.69, 1.09
8582	8578		1.01 (0.84, 1.21
2202	2199	_ _	0.77 (0.55, 1.07
	= 0.189)	\diamond	0.96 (0.86, 1.09
n			
4687	2333		1.18 (0.89, 1.56
3756	2900		0.82 (0.63, 1.06
3474	3500		0.97 (0.76, 1.22
1113 = 19.3%, р	1107 = 0.294)		0.87 (0.58, 1.31 0.96 (0.83, 1.10
		1	2100 (2100) 1.11
2039	1447		1 07 /0 66 4 7
			1.07 (0.66, 1.71
			1.09 (0.82, 1.45
			0.60 (0.33, 1.07
- 39.0%, p	- 0.190)		0.99 (0.79, 1.25
	4687 5795 8582 2202 = 0.0%, p = 0.0%, p = 2039 5108 = 57.6%, p 4687 5795 8582 2202 = 70.7%, p 4687 3756 3474 1113 = 59.6%, p 2039 5108 1089 = 0.0%, p = fatal and nc 4687 5795 8582 2202 = 0.0%, p = fatal and nc 4687 3756 3474 1113 = 0.0%, p = fatal and nc fatal and nc	4687 2333 5795 4347 8582 8578 2202 2199 = 0.0%, p = 0.477) n 4687 2333 3756 2900 3474 3500 1113 1107 = 0.0%, p = 0.813) 2039 2039 1447 5108 5078 1089 1092 = 57.6%, p = 0.094) 4687 2333 3756 2900 3474 3500 1113 1107 = 59.6%, p = 0.017) n 4687 2333 3756 2900 3474 3500 1113 1107 = 59.6%, p = 0.060) 2039 2039 1447 5108 5078 2020 2199 = 0.0%, p = 0.996) n n 4687 2333 3756 2900 3474 3500 1113 1107 = 0.0%, p = 0.937) <t< td=""><td>4687 2333 5795 4347 882 8578 2202 2199 200%, $p = 0.477$) \bullet her 2333 3756 2900 2039 1447 5108 5078 1089 1092 $= 70.7\%$, $p = 0.094$) \bullet 4687 2333 5795 4347 8682 8578 22022 2199 $= 70.7\%$, $p = 0.017$) \bullet n 4687 2333 3756 2900 \bullet 3474 3500 \bullet 1113 1107 \bullet 57.6%, $p = 0.017$) \bullet \bullet n 4687 2333 \bullet 576 578 \bullet \bullet 1113 1107 \bullet \bullet 2039 1447 \bullet \bullet 61687 2333 \bullet \bullet 7766 2900</td></t<>	4687 2333 5795 4347 882 8578 2202 2199 200% , $p = 0.477$) \bullet her 2333 3756 2900 2039 1447 5108 5078 1089 1092 $= 70.7\%$, $p = 0.094$) \bullet 4687 2333 5795 4347 8682 8578 22022 2199 $= 70.7\%$, $p = 0.017$) \bullet n 4687 2333 3756 2900 \bullet 3474 3500 \bullet 1113 1107 \bullet 57.6% , $p = 0.017$) \bullet \bullet n 4687 2333 \bullet 576 578 \bullet \bullet 1113 1107 \bullet \bullet 2039 1447 \bullet \bullet 61687 2333 \bullet \bullet 7766 2900

Figure S2B. Effects of SGLT2 inhibition on HF hospitalization, CV death/HF hospitalization and all cause mortality for patients with (secondary prevention) and without (primary prevention) cardiovascular disease at baseline

STUDY Inter HF hospitalization	rvention (n	,		Hazard Ratio (95% CI)
Overall				
EMPA-REG	4687	2333		0.65 (0.50, 0.85
CANVAS	5795	4347		0.67 (0.52, 0.87
DECLARE-TIMI	8582	8578		0.73 (0.61, 0.88
CREDENCE	2202	2199		
Subtotal (I-squared				0.61 (0.47, 0.80 0.68 (0.60, 0.76
Subtotal (I-Squared	= 0.0%, p	- 0.720)	\sim	0.00 (0.00, 0.70
Secondary prevention	on			
EMPA-REG	4687	2333	_ 	0.65 (0.50, 0.85
CANVAS	3756	2900	_	0.68 (0.51, 0.90
DECLARE-TIMI	3474	3500		0.78 (0.63, 0.97
CREDENCE	1113	1107		0.61 (0.44, 0.84
Subtotal (I-squared	= 0.0%, p		\diamond	0.69 (0.61, 0.79
Primary prevention				
CANVAS	2039	1447	e	0.64 (0.35, 1.15
DECLARE-TIMI	5108	5078		0.64 (0.46, 0.88
CREDENCE	1089	1092		0.61 (0.38, 0.95
Subtotal (I-squared			\sim	0.63 (0.50, 0.80
CV death/ HF hospitali	080			C2 6
Overall			_ [
EMPA-REG	4687	2333		0.66 (0.55, 0.79
CANVAS	5795	4347		0.78 (0.67, 0.91
DECLARE-TIMI	8582	8578		0.83 (0.73, 0.95
CREDENCE	2202	2199		0.69 (0.57, 0.83
Subtotal (I-squared			\diamond	0.76 (0.70, 0.82
_				
Secondary prevention EMPA-REG		0000		0.66 /0 EE 0.70
	4687	2333		0.66 (0.55, 0.79
CANVAS	3756	2900		0.77 (0.65, 0.92
DECLARE-TIMI	3474	3500		0.83 (0.71, 0.98
CREDENCE	1113	1107		0.66 (0.52, 0.83
Subtotal (I-squared	= 34.8%,	o = 0.203)	\diamond	0.74 (0.68, 0.81
Primary prevention				
CANVAS	2039	1447	_	0.83 (0.58, 1.19
DECLARE-TIMI	5108	5078		0.84 (0.67, 1.04
CREDENCE	1089	1092		
Subtotal (I-squared			\sim	0.74 (0.53, 1.02 0.81 (0.69, 0.96
All Cause Mortality	0107010	0.010)	~	0.01 (0.00) 0.00
Overall			_ 1	
EMPA-REG	4687	2333		0.68 (0.57, 0.82
CANVAS	5795	4347		0.87 (0.74, 1.01
DECLARE-TIMI	8582	8578		0.93 (0.82, 1.04
CREDENCE	2202	2199		0.83 (0.68, 1.02
Subtotal (I-squared	= 63.1%, p	o = 0.044)	\diamond	0.85 (0.79, 0.92
Secondary preventio	on			
EMPA-REG	4687	2333		0.68 (0.57, 0.82
CANVAS	3756	2900		0.89 (0.75, 1.07
DECLARE-TIMI	3474	3500		0.92 (0.79, 1.08
CREDENCE	1113	1107		0.79 (0.61, 1.02
Subtotal (I-squared	= 57.2%, p	o = 0.071)	\diamond	0.83 (0.75, 0.94
Primary prevention				
CANVAS	2039	1447	_ _	0.79 (0.58, 1.07
DECLARE-TIMI	5108	5078		0.94 (0.78, 1.12
CREDENCE	1089	1092		0.89 (0.63, 1.26
Subtotal (I-squared			$\overline{\diamond}$	0.90 (0.78, 1.03

Figure S2C. Effects of SGLT2 inhibition on non-fatal MI and stroke for patients with (secondary prevention) and without (primary prevention) cardiovascular disease at baseline

STUDY I Non-fatal Myoca		n (n) Placebo (n)		Hazard Ratio (95% C
Overall	ruiai iiiare			
EMPA-REG	4687	2333		0.87 (0.70, 1.09)
CANVAS	5795	4347		0.85 (0.69, 1.05)
CREDENCE	2202	2199		0.81 (0.59, 1.10)
Subtotal (I-squar	red = 0.0%, j	o = 0.935)	\diamond	0.85 (0.74, 0.97)
Secondary preve	ntion			
EMPA-REG	4687	2333		0.87 (0.70, 1.09)
CANVAS	3756	2900		0.79 (0.63, 0.99)
CREDENCE	1113	1107		0.91 (0.63, 1.31)
Subtotal (I-squar	red = 0.0%,	o = 0.755)	\diamond	0.84 (0.73, 0.97)
Primary prevention	on			
CANVAS	2039	1447	_	1.21 (0.73, 2.00)
CREDENCE	1089	1092		0.57 (0.30, 1.04)
Subtotal (I-squar	red = 70.6%,	p = 0.065)	$\langle \rangle$	0.90 (0.61, 1.33)
lon-fatal Stroke Overall				
EMPA-REG	4687	2333		1.24 (0.92, 1.67
CANVAS	5795	4347		0.90 (0.71, 1.15
CREDENCE	2202	2199		0.80 (0.55, 1.14
Subtotal (I-square	d = 50.6%,	o = 0.132)	\diamond	0.97 (0.82, 1.15
Secondary preven	tion			
EMPA-REG	4687	2333		1.24 (0.92, 1.67
CANVAS	3756	2900		0.88 (0.67, 1.16
CREDENCE	1113	1107	_	0.97 (0.62, 1.50
Subtotal (I-square	d = 28.8%,	o = 0.245)	\diamond	1.02 (0.85, 1.22
Primary preventior	ı			
CANVAS	2039	1447		0.97 (0.59, 1.61
CREDENCE	1089	1092		0.54 (0.27, 1.01
Subtotal (I-square	d = 47.9%,	p = 0.166)	\frown	0.78 (0.52, 1.17
		.25	.5 1 2	1

Figure S3A. Effects of SGLT2 inhibition on MACE, CV death, total MI and total stroke for patient with (estimated glomerular filtration rate <60mls/min/1.73m²) and without (estimated glomerular filtration rate >60mls/min/1.73m²) reduced kidney function at baseline, for each included study

Major Adverse Cardia	c Event				
Overall					
EMPA-REG		333		1	0.86 (0.74, 0.9
CANVAS		347			0.86 (0.75, 0.9
		578 199		1	0.93 (0.84, 1.0
CREDENCE Subtotal (I-squared			\diamond		0.88 (0.82, 0.9
eGFR<60 at baselin	e				
EMPA-REG CANVAS		07 29		-	0.88 (0.69, 1.1 0.70 (0.55, 0.9
		59			0.92 (0.69, 1.2
CREDENCE	1308 1	323	-		0.75 (0.60, 0.9
Subtotal (I-squared		.405)	\checkmark		0.80 (0.70, 0.9
GFR>60 at baselin EMPA-REG		726		-	0.84 (0.70, 1.0
CANVAS		417		<u>+</u>	0.92 (0.79, 1.0
		919	-	-	0.95 (0.85, 1.0
CREDENCE Subtotal (I-squared		76 .724)			0.90 (0.66, 1.2 0.92 (0.85, 0.9
CV Death					
Overall	1007 0	222			0.00 (0.10.0.7
EMPA-REG		333			0.62 (0.49, 0.7
CANVAS		347		I	0.87 (0.72, 1.0
DECLARE-TIMI	8582 8	578		-	0.98 (0.82, 1.1
CREDENCE	2202 2	199		-	0.78 (0.61, 1.0
Subtotal (I-squared	= 70.7%, p =	0.017)	\diamond		0.83 (0.75, 0.9
GFR<60 at baselin	e				
EMPA-REG		07		+	0.78 (0.54, 1.1
CANVAS		29		<u> </u>	0.96 (0.69, 1.3
		59		<u> </u>	0.90 (0.57, 1.4
CREDENCE		323			0.74 (0.54, 1.0
Subtotal (I-squared			\diamond	-	0.83 (0.70, 0.9
GFR>60 at baselin EMPA-REG		726			0.53 (0.40, 0.7
CANVAS		417	_	L.	0.84 (0.67, 1.0
DECLARE-TIMI		919			1.00 (0.81, 1.2
CREDENCE		76	-		0.87 (0.56, 1.3
Subtotal (I-squared	= 76.8%, p =	0.005)	\diamond		0.83 (0.73, 0.9
Ayocardial Infarction	(fatal and non-f	'atal)			
Verall EMPA-REG	4687 2	333			0.87 (0.70 4.0
		333			0.87 (0.70, 1.0
CANVAS		347			0.89 (0.73, 1.0
		578			0.89 (0.77, 1.0
CREDENCE Subtotal (I-squared		199 .996)			0.86 (0.64, 1.1 0.88 (0.80, 0.9
			~		
GFR<60 at baselin EMPA-REG		07			0 07 /0 67 4 4
					0.97 (0.67, 1.4
CANVAS		29			0.62 (0.41, 0.9
		59			0.88 (0.58, 1.3
CREDENCE Subtotal (I-squared		323 .426)			0.80 (0.56, 1.1 0.81 (0.67, 0.9
		/	\sim		0.0.1 (0.01, 0.0
GFR>60 at baselin EMPA-REG		726		L	0.83 (0.63, 1.0
CANVAS		417			
					1.01 (0.80, 1.2
		919		I a	0.89 (0.76, 1.0
CREDENCE Subtotal (I-squared		76 688)			1.00 (0.60, 1.6 0.91 (0.82, 1.0
			\sim		0.01 (0.02, 1.0
troke (fatal and non-f overall	atal)				
EMPA-REG	4687 23	333	_		1.18 (0.89, 1.5
CANVAS		347		+-	0.87 (0.69, 1.0
DECLARE-TIMI	8582 8	578	7		1.01 (0.84, 1.2
		199		Ę	0.77 (0.55, 1.0
Subtotal (I-squared		0.109)	<	T	0.96 (0.86, 1.0
GFR<60 at baselin EMPA-REG		07			0.92 (0.58, 1.4
CANVAS	1110 93	29 —	_		0.50 (0.30, 0.8
		59	_		1.23 (0.70, 2.1
CREDENCE Subtotal (I-squared		323 0.078)			0.63 (0.40, 0.9 0.75 (0.59, 0.9
GFR>60 at baselin EMPA-REG	3473 1	726	-		1.34 (0.94, 1.9
		417			1.01 (0.78, 1.3
		919	-	_	0.98 (0.79, 1.1
CREDENCE Subtotal (I-squared		76 .497)	<		1.10 (0.64, 1.9 1.05 (0.91, 1.2
				1	

Figure S3B. Effects of SGLT2 inhibition on HF hospitalization, CV death/HF hospitalization and all cause mortality for patients with (estimated glomerular filtration rate <60mls/min/1.73m²) and without (estimated glomerular filtration rate >60mls/min/1.73m²) reduced kidney function at baseline, for each included study

2333 4347 8578 2199 , p = 0.720)		0.65 (0.50, 0.85) 0.67 (0.52, 0.87) 0.73 (0.61, 0.88)
4347 8578 2199		0.67 (0.52, 0.87)
4347 8578 2199		0.67 (0.52, 0.87)
8578 2199		
, p = 0.720)	\diamond	0.61 (0.47, 0.80)
		0.68 (0.60, 0.76)
607		0.59 (0.39, 0.88)
929		0.57 (0.38, 0.86)
659		0.70 (0.44, 1.12)
1323 , p = 0.915)		0.64 (0.47, 0.88) 0.62 (0.51, 0.75)
1726	_	0.70 (0.49, 1.00)
3417	_ _	0.76 (0.55, 1.06)
7919		0.72 (0.58, 0.87)
876	_	0.55 (0.33, 0.89)
, p = 0.750)	\diamond	0.71 (0.61, 0.82)
2333	_ 	0.66 (0.55, 0.79)
		0.78 (0.67, 0.91)
	=-	0.83 (0.73, 0.95)
2199	————	0.69 (0.57, 0.83)
, p = 0.160)	\diamond	0.76 (0.70, 0.82)
929		0.75 (0.57, 0.98)
		0.78 (0.55, 1.09)
	~	0.68 (0.53, 0.85)
p = 0.772)	\sim	0.72 (0.62, 0.85)
	_	
3417		0.81 (0.66, 0.98)
7919		0.84 (0.73, 0.96)
876		0.73 (0.51, 1.02)
	\diamond	0.82 (0.74, 0.91)
2222		0.68 (0.57, 0.82
		0.87 (0.74, 1.01)
		0.93 (0.82, 1.04)
	~	0.83 (0.68, 1.02) 0.85 (0.79, 0.92)
.,,	•	
007		0.00 /0.50 / 05
		0.80 (0.59, 1.07
		0.90 (0.68, 1.18
		0.91 (0.67, 1.25
		0.76 (0.59, 0.98)
, p = 0.757)	\diamond	0.83 (0.72, 0.96
	— — —	0.62 (0.49, 0.78
3417		0.87 (0.72, 1.04)
7919		0.93 (0.81, 1.05
876		0.98 (0.69, 1.40)
%, p = 0.023)	\diamond	0.86 (0.78, 0.94
25	5 1 2	4
	$\begin{array}{c} 3417\\ 7919\\ 876\\ ,p=0.750) \end{array}$	1726 3417 7919 876 2333 4347 8578 2199 929 659 1323 $p = 0.772)$ 3417 7919 876 $p = 0.747)$ 2333 4347 8578 2199 $6, p = 0.044)$ 607 929 659 1323 4347 8578 2199 $6, p = 0.044)$ 607 929 659 1323 4347 8578 2199 $6, p = 0.044)$ 607 929 659 1323 4347 4578 2199 $6, p = 0.023)$ 4

Figure S3C. Effects of SGLT2 inhibition on non-fatal MI and stroke for patients with (estimated glomerular filtration rate <60mls/min/1.73m²) and without (estimated glomerular filtration rate >60mls/min/1.73m²) reduced kidney function at baseline, for each included study

STUDY	Interventio	on (n) Placebo (n)	Hazard Ratio (95% C
Non-fatal Myoca	rdial Infarc	ion	
Overall			
EMPA-REG	4687	2333 —	0.87 (0.70, 1.09)
CANVAS	5795	4347 —	0.85 (0.69, 1.05)
CREDENCE	2202	2199	0.81 (0.59, 1.10)
Subtotal (I-square	d = 0.0%, p =	0.935) <	0.85 (0.74, 0.97)
eGFR<60 at basel	ine		
CANVAS	1110	929	- 0.55 (0.36, 0.85)
CREDENCE	1308	1323 ———	0.76 (0.52, 1.10)
Subtotal (I-square	d = 19.1%, p	= 0.266)	> 0.66 (0.50, 0.88)
eGFR>60 at basel	ine		
CANVAS	4684	3417	0.99 (0.77, 1.26)
CREDENCE	893	876	0.92 (0.53, 1.62)
Subtotal (I-square	d = 0.0%, p =	0.823)	0.98 (0.78, 1.22)
Non-fatal Stroke			
Overall			1
EMPA-REG	4687	2333	1.24 (0.92, 1.67)
CANVAS	5795	4347	0.90 (0.71, 1.15)
CREDENCE	2202	2199	0.80 (0.55, 1.14)
Subtotal (I-square	d = 50.6%, p	= 0.132)	0.97 (0.82, 1.15)
eGFR<60 at basel	ine		
CANVAS	1110	929	0.57 (0.33, 0.98)
CREDENCE	1308	1323	0.69 (0.43, 1.09)
Subtotal (I-square	d = 0.0%, p	0.601)	> 0.64 (0.45, 0.91)
eGFR>60 at basel	ine		
CANVAS	4684	3417	1.02 (0.77, 1.34)
CREDENCE	893	876	1.02 (0.57, 1.84)
Subtotal (I-square	d = 0.0%, p	0.998)	1.02 (0.79, 1.31)
			1 2 4

Figure S4A. Effects of SGLT2 inhibition on MACE, CV death, total MI and total stroke for patients with and without a history of heart failure at baseline, for each included study

CANVAS DECLARE-TIMI CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI	4687 5795 8582 2202	2333 4347 8578	0.86 (0.74, 0.9 0.86 (0.75, 0.9
EMPA-REG CANVAS DECLARE-TIMI CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI	5795 8582 2202	4347	
CANVAS DECLARE-TIMI CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI	5795 8582 2202	4347	
DECLARE-TIMI CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI	8582 2202		
CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI	2202	0010	- 0.93 (0.84, 1.0
Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI		2100	
HF at baseline CANVAS DECLARE-TIMI	0.0%, p = 0	2199 0.477)	0.80 (0.67, 0.9 0.88 (0.82, 0.9
CANVAS DECLARE-TIMI	0.070, p = 1		V 0.00 (0.02, 0.0
DECLARE-TIMI	803	658	0.80 (0.61, 1.0
			—
CREDENCE	852	872	1.01 (0.81, 1.2
Subtotal (I-squared =	329 0.0%, p = (323 0.431)	0.93 (0.63, 1.3 0.92 (0.79, 1.0
No HF at baseline CANVAS	4992	3689	0.87 (0.76, 1.0
	7730	7706	
	1873	1876	
Subtotal (I-squared =			0.76 (0.62, 0.9 0.88 (0.81, 0.9
			~ · · · · · · · · · · · · · · · · · · ·
CV Death Overall			
	4687	2333	0.62 (0.49, 0.7
CANVAS	5795	4347	0.87 (0.72, 1.0
DECLARE-TIMI	8582	8578	0.98 (0.82, 1.1
	2202	2199	0.78 (0.61, 1.0
Subtotal (I-squared		= 0.017)	0.83 (0.75, 0.9
HF at baseline			
	462	244	0.71 (0.43, 1.1
	803	658	0.72 (0.51, 1.0
	852	872	1.01 (0.73, 1.3
CREDENCE	329	323	1.02 (0.63, 1.6
Subtotal (I-squared	= 0.8%, p =	= 0.388)	0.86 (0.71, 1.0
No HF at baseline			
EMPA-REG	4225	2089	0.60 (0.47, 0.7
CANVAS	4992	3689	0.95 (0.76, 1.2
DECLARE-TIMI	7730	7706	0.97 (0.78, 1.2
CREDENCE	1873	1876	0.70 (0.52, 0.9
Subtotal (I-squared	= 73.1%, p	= 0.011)	0.81 (0.72, 0.9
Myocardial Infarction (f	atal and nor	ı-fatal)	
Overall EMPA-REG	4687	2333	0.87 (0.70, 1.09
	5795	4347	0.89 (0.73, 1.05
	8582	8578	
	2202	2199	0.86 (0.64, 1.16
Subtotal (I-squared =	0.0%, p = (0.996)	0.88 (0.80, 0.97
HF at baseline			
	803	658	1.11 (0.65, 1.89
DECLARE-TIMI	852	872	0.85 (0.61, 1.18
	329	323	1.79 (0.85, 4.02
Subtotal (I-squared =	38.1%, p =	0.199)	0.99 (0.76, 1.29
No HF at baseline			
CANVAS	4992	3689	0.86 (0.69, 1.06
DECLARE-TIMI	7730	7706	
CREDENCE	1873	1876	0.75 (0.54, 1.04
Subtotal (I-squared =	0.0%, p =	0.648)	0.86 (0.77, 0.97
troke (fatal and non-fa	tal)		
Overall	1697	2222	
	4687	2333	1.18 (0.89, 1.5
	5795	4347	0.87 (0.69, 1.0
	3582	8578	
	2202	2199	0.77 (0.55, 1.0
Subtotal (I-squared =	37.1%, p =	0.189)	0.96 (0.86, 1.0
HF at baseline			
	303	658	0.84 (0.51, 1.3
	352	872	1.21 (0.77, 1.9
CREDENCE 3 Subtotal (I-squared =	329 29.4%, p =	323 0.243)	0.59 (0.27, 1.2 0.94 (0.69, 1.2
			0.01 (0.00) 1.2
No HF at baseline CANVAS 4	4992	3689	0.88 (0.68, 1.1
	1992 7730	7706	
CREDENCE 1 Subtotal (I-squared =	1873 0.0%, p = 0	1876 0.677)	0.83 (0.57, 1.2 0.92 (0.80, 1.0
213 B	1996	<i></i>	

Figure S4B. Effects of SGLT2 inhibition on HF hospitalization, CV death/HF hospitalization and all cause mortality for patients with and without a history of heart failure at baseline, for each included study

	vention (i	Placebo (n)	Hazard Ratio (95% C
HF hospitalization			
EMPA-REG	4687	2333	0.65 (0.50, 0.85
CANVAS	5795	4347	0.67 (0.52, 0.87
DECLARE-TIMI	8582	8578	0.73 (0.61, 0.88
CREDENCE	2202	2199	0.61 (0.47, 0.80
Subtotal (I-squared		-	0.68 (0.60, 0.76
Subtotal (I-squared	- 0.0 /0, p	······································	0.00 (0.00, 0.10
HF at baseline EMPA-REG	462	244	0.75 /0.49 1.10
	803	658	0.75 (0.48, 1.19 0.51 (0.33, 0.78
CANVAS			
DECLARE-TIMI	852	872	0.73 (0.55, 0.96
CREDENCE Subtotal (I-squared	329 = 0.0%, p	323 = 0.505)	0.76 (0.47, 1.22 0.69 (0.57, 0.83
No HF at baseline			
EMPA-REG	4225	2089	0.59 (0.43, 0.82
CANVAS	4992	3689	0.39 (0.43, 0.82
DECLARE-TIMI	7730	7706	•
CREDENCE	1873	1876	0.73 (0.58, 0.92 0.54 (0.39, 0.75
Subtotal (I-squared		~	0.67 (0.58, 0.77
V death/ HF bosnital	ization		
CV death/ HF hospital Overall	12811011		
EMPA-REG	4687	2333 —	0.66 (0.55, 0.79
CANVAS	5795	4347	0.78 (0.67, 0.91
DECLARE-TIMI	8582	8578	0.83 (0.73, 0.95
CREDENCE	2202	2199 -	•
			0.69 (0.57, 0.83
Subtotal (I-squared	= 41.9%,	= 0.160)	0.76 (0.70, 0.82
IF at baseline			
EMPA-REG	462	244	0.72 (0.50, 1.04
CANVAS	803	658	0.61 (0.46, 0.80
DECLARE-TIMI	852	872	- 0.79 (0.63, 0.99
CREDENCE	329	323	0.82 (0.57, 1.19
Subtotal (I-squared	= 0.0%, p	= 0.480)	0.73 (0.63, 0.84
No HF at baseline			
EMPA-REG	4225	2089	0.63 (0.51, 0.78
CANVAS	4992	3689	0.87 (0.72, 1.06
DECLARE-TIMI	7730	7706	- 0.84 (0.72, 0.99
CREDENCE	1873	1876	0.64 (0.51, 0.80
Subtotal (I-squared	= 65.2%,	= 0.035)	0.76 (0.69, 0.84
All Cause Mortality			
Overall		-	
EMPA-REG	4687	2333 —	0.68 (0.57, 0.82
CANVAS	5795	4347	0.87 (0.74, 1.0
DECLARE-TIMI	8582	8578 —	0.93 (0.82, 1.04
CREDENCE	2202	2199	0.83 (0.68, 1.02
Subtotal (I-squared		A	0.85 (0.79, 0.92
IF at baseline			
	460	244	0.70 /0.50 4.00
EMPA-REG	462	244	0.79 (0.52, 1.20
CANVAS	803	658	0.70 (0.51, 0.96
DECLARE-TIMI	852	872	0.87 (0.68, 1.12
CREDENCE	329	323	0.94 (0.62, 1.43
Subtotal (I-squared	= 0.0%, p	= 0.655)	0.82 (0.69, 0.96
lo HF at baseline			
EMPA-REG	4225	2089	0.66 (0.51, 0.81
CANVAS	4992	3689 —	0.93 (0.78, 1.11
DECLARE-TIMI	7730	7706 —	0.94 (0.82, 1.07
CREDENCE	1873	1876	0.79 (0.62, 1.00
Subtotal (I-squared	= 62.3%,	= 0.047)	0.87 (0.79, 0.95

Figure S4C. Effects of SGLT2 inhibition on non-fatal MI and stroke for patients with and without a history of heart failure at baseline, for each included study

STUDY	Interventio	n (n) Placebo (n)		Hazard Ratio (95% C
Non-fatal Myocar	rdial Infarcti	ion		
Overall				
EMPA-REG	4687	2333		0.87 (0.70, 1.09)
CANVAS	5795	4347		0.85 (0.69, 1.05)
CREDENCE	2202	2199		0.81 (0.59, 1.10)
Subtotal (I-square	d = 0.0%, p =	= 0.935)	\diamond	0.85 (0.74, 0.97)
HF at baseline				
CANVAS	803	658		1.39 (0.75, 2.56)
CREDENCE	329	323		1.32 (0.59, 3.05)
Subtotal (I-square	d = 0.0%, p =	= 0.921)		1.36 (0.83, 2.23)
No HF at baseline				
CANVAS	4992	3689		0.80 (0.64, 1.00)
CREDENCE	1873	1876		0.74 (0.52, 1.04)
Subtotal (I-square	d = 0.0%, p =	= 0.711)	\diamond	0.78 (0.65, 0.94)
Non-fatal Stroke				
Overall				
EMPA-REG	4687	2333		1.24 (0.92, 1.67)
CANVAS	5795	4347		0.90 (0.71, 1.15)
CREDENCE	2202	2199		0.80 (0.55, 1.14)
Subtotal (I-square	ed = 50.6%, p	= 0.132)	\diamond	0.97 (0.82, 1.15)
HF at baseline				
CANVAS	803	658	_	0.85 (0.49, 1.49)
CREDENCE	329	323	_	0.56 (0.22, 1.30)
Subtotal (I-square	ed = 0.0%, p =	= 0.435)	$\langle \rangle$	0.76 (0.47, 1.21)
No HF at baseline				
CANVAS	4992	3689	_ _	0.92 (0.70, 1.20)
CREDENCE	1873	1876	_	0.86 (0.58, 1.29)
Subtotal (I-square	ed = 0.0%, p =	= 0.784)	\sim	0.90 (0.72, 1.13)
- Contraction - Contraction				
		.25	.5 1 2	4

Figure S5. Sensitivity Analysis for the Outcome of Serious Adverse Events without inclusion of Risk Ratios

Hazard ratio (95% CI)
0.93 (0.87, 1.00) 0.91 (0.87, 0.96) 0.87 (0.79, 0.97) 0.91 (0.88, 0.94)
■ 0.98 (0.54, 1.77) 0.68 (0.49, 0.95) ■ 1.36 (0.65, 2.91) 0.80 (0.61, 1.05)
2.33 (0.76, 7.17) 2.18 (1.10, 4.30) → 10.80 (1.39, 83.65) 2.50 (1.43, 4.38)
■ 1.26 (1.04, 1.52) 1.04 (0.91, 1.18) 0.98 (0.70, 1.37) 1.09 (0.99, 1.21)
 − 1.97 (1.41, 2.75) 1.09 (0.84, 1.40) 1.11 (0.79, 1.56) 1.29 (1.08, 1.53)

Figure S 6. The Effects of SGLT2 inhibition on Major Adverse Cardiac Outcomes for patients depending on Urine Albumin Creatinine Ratio at baseline

				s/1000 t-years			RR (95% CI)	P-heterogeneity
Study	Events	Patients	SGLT2	Placebo				
UACR <30 mg/g								0.23
EMPA-REG	375	4171	30.6	34.5			0.89 (0.72-1.10)	
CANVAS	596	7007	22.1	26.5			0.83 (0.71-0.98)	
Subtotal (I ² =0.0%, P-h	eterogeneit	y=0.61)			•		0.85 (0.75-0.97)	
UACR 30-300 mg/g								
EMPA-REG	248	2013	42.9	48.7		-	0.89 (0.69-1.16)	
CANVAS	272	2266	35.2	35.4			0.98 (0.76-1.25)	
Subtotal (I ² =0.0%, P-h	eterogeneit	y=0.60)			-		0.94 (0.78-1.12)	
UACR >300 mg/g								
EMPA-REG	144	769	62.2	88.9	e		0.69 (0.49-0.96)	
CANVAS	134	760	53.6	72.0			0.75 (0.53-1.06)	
CREDENCE	486	4401	38.7	48.7			0.80 (0.67-0.95)	
Subtotal (I ² =0.0%, P-h	eterogeneit	y=0.74)			•		0.77 (0.67-0.89)	
				0.3	0.5 1	1.5		