# **Supplementary Online Content**

McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol.* Published online October 7, 2020. doi:10.1001/jamacardio.2020.4511

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This supplementary material has been provided by the authors to give readers additional information about their work.

## eAppendix 1. Trial Outcome Definitions That Varied Across Trials

### Kidney composite outcomes

#### **EMPA-REG OUTCOME:**

A post hoc exploratory analysis of a composite of a doubling of the serum creatinine level accompanied by an eGFR  $\leq$ 45 mL/min/1.73 m<sup>2</sup>, the initiation of renal-replacement therapy, or death from renal disease.

### CANVAS and CANVAS-R:

A pre-specified exploratory analysis of the renal composite comprising a 40% reduction in eGFR sustained for at least two consecutive measures, the need for renal-replacement therapy (dialysis or transplantation), or death from renal causes (defined as death with a proximate renal cause).

#### **DECLARE-TIMI 58:**

A pre-specified analysis in the primary analysis hierarchy, comprising the composite of a confirmed, sustained  $\geq$ 40% decrease in eGFR to eGFR<60 mL/min/1.73 m<sup>2</sup> and/or end-stage renal disease (dialysis  $\geq$ 90 days or kidney transplantation or confirmed sustained eGFR <15 mL/min/1.73 m<sup>2</sup>) and/or renal or CV death.

For the present meta-analyses, to align with the other trials, we used a secondary exploratory composite of the above excluding CV death.

### **CREDENCE:**

The primary trial outcome, a composite comprising end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL/min/1.73 m<sup>2</sup>), a doubling of the serum creatinine level, or death from renal or CV causes.

For the present meta-analyses, to align with the other trials, we used a secondary exploratory composite of the above excluding CV death.

### **VERTIS CV:**

A pre-specified analysis in the primary analysis hierarchy, comprising the composite of renal death, dialysis/transplant, or doubling of serum creatinine from baseline.

# eTable 1. Risk of Bias Assessment

	Random sequence generation	Allocation sequence concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting
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
CREDENCE	Low	Low	Low	Low	Low	Low
VERTIS CV	Low	Low	Low	Low	Low	Low

# eTable 2. List of Prespecified Subgroup Analyses by Outcome

Outcomes	Analysis Population	Overall Population	Subgroup	Studies <sup>a</sup>
MACE	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All
			Baseline eGFR level (mL/min/1.73 m²) (<60, 60 to <90, ≥90)	All except CREDENCE
			History of heart failure	All except EMPA-REG OUTCOME
			Baseline A1c (<8.5% vs ≥8.5%)	All except DECLARE-TIMI 58 Note: CANVAS, CREDENCE use 8% as the cutoff
			Baseline albuminuria (<30, 30 to 300, >300)	CANVAS, VERTIS CV
CV Death or HHF	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All
			Baseline eGFR level (mL/min/1.73 m <sup>2</sup> ) (<60, 60 to <90, ≥90)	DECLARE-TIMI 58, VERTIS CV
			History of heart failure	All except CREDENCE
CV Death	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All
			Baseline eGFR level (mL/min/1.73 m <sup>2</sup> ) (<60, 60 to <90, ≥90)	All except CANVAS, CREDENCE
			History of heart failure	All except CREDENCE
			Baseline A1c (<8.5% vs ≥8.5%)	EMPA-REG OUTCOME, VERTIS CV
			Baseline albuminuria (<30, 30 to 300, >300)	CANVAS, VERTIS CV
Renal Composite	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All

			Baseline eGFR level (mL/min/1.73 m <sup>2</sup> ) (<60, 60 to <90, ≥90)	All except CREDENCE
			History of heart failure	DECLARE-TIMI 58, VERTIS CV
			Baseline Albuminuria (<30, 30 to 300, >300)	CANVAS, VERTIS CV
Fatal or non-fatal MI	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All
Fatal or non-fatal Stroke	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All
HHF	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All
All-cause mortality	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All

<sup>a</sup>Data from all studies were included in the meta-analysis of each outcome where possible. However, where data required for conducting the analysis were not available from published literature search, the studies included in the meta-analysis are listed.

A1c, glycated hemoglobin; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; ITT, intent-to-treat; MACE, major adverse cardiovascular event; MI, myocardial infarction

Event	Canagli	flozinª	Canagli	flozin <sup>b</sup>	Dapagli	flozin <sup>c</sup>	Empagli	flozin <sup>d</sup>	Ertugli	flozin <sup>e</sup>
	CANVAS and	CANVAS-R	CREDENCE		DECLARE	DECLARE-TIMI 58		OUTCOME	VERTIS CV	
	Canagliflozin	Placebo	Canagliflozin	Placebo	Dapagliflozin	Placebo	Empagliflozin	Placebo	Ertugliflozin	Placebo
	100 mg and 300 mg	N=4344	100 mg N=2200	N=2197	10 mg N=8574	N=8569	10 mg and 25 mg	N=2333	5 and 15 mg	N=2745
	N=5790						N=4687		N=5493	
	Events/100 yea	irs	Events/100 yea n (%	rs	n (%	6)	n (%	б)	n ('	%)
	6.3	3.4	12.3	11.2						
Amputation	140 (2.4)	47 (1.1)	70 (3.2)	63 (2.9)	123 (1.4)	113 (1.3)	88 (1.9)	43 (1.8)	111 (2.0)	45 (1.6)
Fracture	15.4	11.9	11.8	12.1	457 (5.3)	440 (5.1)	179 (3.8)	91 (3.9)	201 (3.7)	98 (3.6)
FIACIUIE	NA	NA	67 (3.0)	68 (3.1)	457 (5.5)	440 (3.1)	179 (3.6)	91 (3.9)	201 (3.7)	90 (3.0)
Diabetic	0.6	0.3	2.2	0.2	27 (0.3)	12 (0.1)	4 (0.1)	1 (<0.1)	19 (0.3)	2 (0.1)
Ketoacidosis	NA	NA	11 (0.5)	1 (<0.1)	27 (0.3)	12 (0.1)	4 (0.1)	1 (<0.1)	19 (0.3)	2 (0.1)
Genital mycotic infection – male	34.9 <sup>f</sup>	10.8 <sup>f</sup>	NA	NA	76 (0.9) <sup>g</sup>	9 (0.1) <sup>g</sup>	166 (5.0)	25 (1.5)	184 (4.8) <sup>h</sup>	22 (1.2) <sup>h</sup>
Genital mycotic	68.8	17.5	NA	NA	NA	NA	135 (10.0)	17 (2.6)	113 (6.9) <sup>h</sup>	20 (2.4) <sup>h</sup>

# eTable 3. Adverse Events of Special Interest From Cardiovascular and Renal Outcome Trials With SGLT2 Inhibitors

infection – female										
Acute Kidney Injury	3.0	4.1	16.9 86 (3.9)	20.0 98 (4.5)	125 (1.5)	175 (2.0)	45 (1.0)	37 (1.6)	101 (1.8)	60 (2.2)

<sup>a</sup>Data from the integrated analysis of CANVAS and CANVAS-R trials (Neal et al NEJM 2017; 377:644-657) are presented as event rate per 1000 patient years. For amputation, n (%) (the number and percentage of participants with atraumatic lower extremity amputations) are available in Matthews et al. *Diabetologia.* 2019;62:926-38; percentages were calculated using the sum of patients with and without amputation from Table 1 of Matthews et al. 2019 as the denominator (and are provided as overall N's per treatment group here). Fracture refers to all adjudicated fractures; low trauma fracture was the prespecified primary fracture outcome (not shown here) and all fracture was a secondary outcome.

<sup>b</sup>Data from the CREDENCE trial (Perkovic et al. New Engl J Med. 2019;380:2295-2306).

<sup>o</sup>Data from the DECLARE-TIMI 58 trial (Wiviott et al. New Engl J Med. 2019;380:347-57).

<sup>d</sup>Data from the EMPA-REG OUTCOME trial (Zinman et al. *New Engl J Med.* 2015;373:2117-28). The number of patients with lower limb amputations was reported as a post-hoc analysis (Inzucchi et al. *Diabetes Care.* 2018;41:e4-5).

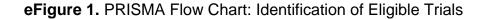
<sup>e</sup>Data from the VERTIS CV trial (Cannon et al. New Engl J Med. 2020; doi: 10.1056/NEJMoa2004967).

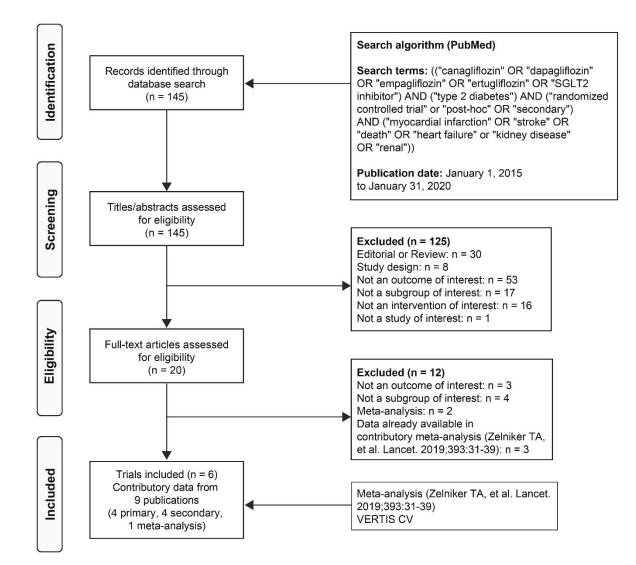
<sup>f</sup>Infection of male genitalia included balanitis, phimosis, and events leading to circumcision.

<sup>g</sup>Data for the overall population (male and female combined).

<sup>h</sup>Included adverse events from a pre-specified Custom MedDRA Query of Preferred Terms associated with genital mycotic infection (GMI). Percentages of GMI for males and females based on total number of males and females, respectively, within each treatment group.

NA, not available





# **eFigure 2.** Meta-Analysis of Effects of SGLT2 Inhibitors on Time to First Event of Cardiovascular Death, Myocardial Infarction, or Stroke (MACE)

## A1c (Panel A), Albuminuria (Panel B), eGFR (Panel C), and History of Heart Failure (Panel D)

A	Trea	tment	Pla	icebo		MACE	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% Cl)
Patients with A1C <8.5%							
EMPA-REG OUTCOME	322/3212	NA	209/1607	NA	13.43	<b>⊢</b> ● - 1	0.76 (0.64-0.90)
CANVAS Program <sup>a</sup>	NA/NA	24.7	NA/NA	26.9	39.63	<b>⊢</b> ● <b> </b> −1	0.94 (0.77-1.15)
<b>CREDENCE</b> <sup>a</sup>	85/1027	31.9	100/1029	38.0	20.20	<b>⊢</b> ● ↓ 1	0.84 (0.63-1.12)
VERTIS CV	438/3419	38.3	216/1730	37.2	26.74	<b>⊢</b> ●1	1.03 (0.88-1.21)
Fixed Effects Model	(Q = 6.81,	df = 3, <i>P</i> = .08; I <sup>2</sup>	= 55.9%)			•	0.90 (0.81-0.99)
Patients with A1C ≥8.5%							
EMPA-REG OUTCOME	168/1475	NA	73/726	NA	31.56	<b>⊢ ● − − −</b>	1.14 (0.86-1.50)
CANVAS Program <sup>b</sup>	NA/NA	28.8	NA/NA	35.3	22.80	<b>⊢</b> •−	0.80 (0.68-0.94)
CREDENCE <sup>b</sup>	131/1174	44.5	168/1169	58.1	11.08	<b>⊢</b> ●−−−	0.76 (0.61-0.96)
VERTIS CV	294/2055	43.0	149/1002	45.5	34.56	<b>⊢</b> ● <b>−</b> 1	0.94 (0.77-1.15)
Fixed Effects Model	(Q = 6.61,	df = 3, <i>P</i> = .09; I <sup>2</sup>	= 54.6%)			•	0.87 (0.78-0.96)
					[		
					0.25	0.5 1	2

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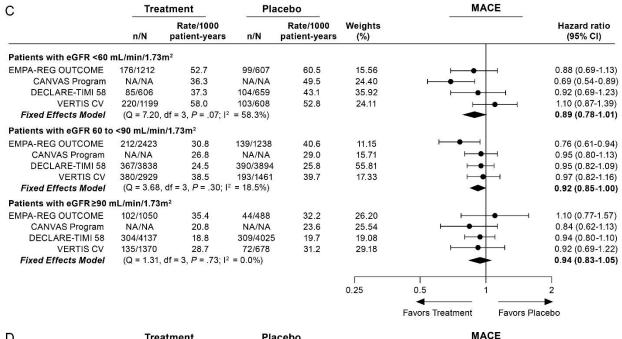
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В	Treat	tment	Pla	icebo		MACE	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% Cl)
Patients with normal alk	ouminuria						
CANVAS Program	NA/4012	22.1	NA/2995	26.5	56.68	<b>⊢_</b> ●	0.83 (0.71-0.98)
VERTIS CV	344/3186	31.8	169/1597	31.1	43.32	· •	1.02 (0.85-1.23)
Fixed Effects Model	(Q = 2.72,	df = 1, <i>P</i> = .10; I <sup>2</sup>	= 63.3%)			-	0.91 (0.80-1.02)
Patients with micro albu	iminuria						
CANVAS Program	NA/1322	35.2	NA/944	35.4	41.21	· ● · ·	0.98 (0.76-1.25)
VERTIS CV	264/1647	48.4	134/845	48.9	58.79	⊢ <b>•</b>	0.99 (0.80-1.22)
Fixed Effects Model	(Q = 0.00,	df = 1, <i>P</i> = .95; I <sup>2</sup>	= 0.0%)			-	0.99 (0.84-1.16)
Patients with macro alb	uminuria						
CANVAS Program	NA/406	53.6	NA/354	72.0	45.41	⊢ <b>−</b> ●−↓	0.75 (0.53-1.06)
VERTIS CV	111/513	72.1	59/242	80.8	54.59	⊢ <b>●</b>	0.89 (0.65-1.23)
Fixed Effects Model	(Q = 0.51,	df = 1, <i>P</i> = .48; I <sup>2</sup>	= 0.0%)				0.82 (0.65-1.04)
					[	1	
					0.25	0.5 1	2

<sup>a</sup>Patients with A1c <8% for CANVAS Program and CREDENCE. <sup>b</sup>Patients with A1c ≥8% for CANVAS Program and CREDENCE.



D	Tre	atment	Pla	icebo		MACE	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% CI)
Patients with history of I	heart failure	•					
CANVAS Program	NA/803	42.2	NA/658	51.4	23.15	<b>⊢</b> • 1	0.80 (0.61-1.05)
<b>DECLARE-TIMI 58</b>	153/852	NA	151/872	NA	33.75	<b>⊢</b>	1.01 (0.81-1.27)
CREDENCE	51/329	62.1	52/323	65.1	11.49	<b>⊢</b>	0.91 (0.62-1.34)
VERTIS CV	211/1286	53.0	107/672	51.5	31.61	<b>⊢</b>	1.03 (0.81-1.29)
Fixed Effects Model	(Q = 2.34	, df = 3, <i>P</i> = .51; l <sup>2</sup>	= 0.0%)			-	0.95 (0.83-1.08)
Patients with no history	of heart fail	ure					
CANVAS Program	NA/4992	24.8	NA/3689	28.3	24.37	<b>⊢</b> ●_+	0.87 (0.76-1.01)
DECLARE-TIMI 58	603/7730	NA	652/7706	NA	41.38	<b>⊢</b> ●- 1	0.92 (0.82-1.02)
CREDENCE	166/1873	34.7	217/1876	45.9	11.99	<b>⊢</b> −−−1	0.76 (0.62-0.93)
VERTIS CV	524/4213	36.5	261/2075	37.1	22.25	<b>⊢</b> •1	0.98 (0.85-1.14)
Fixed Effects Model	(Q = 4.30	, df = 3, <i>P</i> = .23; I <sup>2</sup>	2 = 30.3%)			+	0.90 (0.84-0.96)
					0.25	0.5 1	2

Favors Treatment

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# eFigure 3. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to Cardiovascular (CV) Death

A1c (Panel A), Albuminuria (Panel B), eGFR (Panel C), and History of Heart Failure (Panel D)

	Trea	atment	Pla	acebo		CV	death		
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)				Hazard ratio (95% CI)
Patients with A1C <8.5%									
EMPA-REG OUTCOME	114/3212	NA	96/1607	NA	32.78	<b>⊢_</b> ●i			0.59 (0.45-0.77)
VERTIS CV	206/3419	17.0	107/1730	17.4	67.22		<b>•</b>		0.98 (0.77-1.23)
Fixed Effects Model	(Q = 7.81, c	$df = 1, P = .005; I^2$	= 87.2%)			-	·		0.79 (0.66-0.94)
Patients with A1C ≥8.5%									
EMPA-REG OUTCOME	58/1475	NA	41/726	NA	43.04	<b>⊢</b>	4		0.69 (0.46-1.03)
VERTIS CV	134/2055	18.5	76/1002	21.7	56.96	<b>⊢</b> ●			0.85 (0.64-1.13)
Fixed Effects Model	(Q = 0.69, i	df = 1, <i>P</i> = .41; l <sup>2</sup> =	= 0.0%)			-	-		0.79 (0.63-1.00)
					[	Т	+	1	
					0.25	0.5	1	2	4
							-		
					Favo	rs Treatment		Favors Placebo	

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3	Trea	atment	Pla	acebo		CV death	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% CI)
Patients with normal alb	uminuria						
CANVAS Program	NA/4012	8.6	NA/2995	9.1	52.63		0.91 (0.70-1.19)
VERTIS CV	155/3186	13.7	72/1597	12.6	47.37	<b>⊢ ●</b> 1	1.08 (0.82-1.43)
Fixed Effects Model	(Q = 0.76, d	df = 1, <i>P</i> = .38; I <sup>2</sup> :	= 0.0%)			+	0.99 (0.81-1.20)
Patients with micro albu	minuria						
CANVAS Program	NA/1322	16.0	NA/944	15.8	40.81	<b>⊢</b>	0.98 (0.69-1.41)
VERTIS CV	113/1647	19.3	71/845	24.1	59.19	<b>⊢</b> ● <u></u>	0.80 (0.60-1.08)
Fixed Effects Model	(Q = 0.73, o	df = 1, <i>P</i> = .39; I <sup>2</sup>	= 0.0%)			-	0.87 (0.69-1.09)
Patients with macro albu	uminuria						
CANVAS Program	NA/406	31.3	NA/354	42.6	45.39	<b>⊢−−−</b> +1	0.70 (0.45-1.07)
VERTIS CV	67/513	40.1	39/242	48.8	54.61	⊢ <b>−</b> −−1	0.82 (0.55-1.22)
Fixed Effects Model	(Q = 0.28,	df = 1, <i>P</i> = .60; I <sup>2</sup>	= 0.0%)				0.76 (0.57-1.02)
					0.25		
					0.25	0.5 1 2	4
							F

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NA, not available

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	Trea	atment	Pla	acebo		CV death	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)	2	Hazard ratio (95% CI)
Patients with eGFR <60	mL/min/1.73	m²					
EMPA-REG OUTCOME	75/1212	NA	48/607	NA	22.45	<b>⊢</b> ● ↓ 1	0.78 (0.54-1.12)
DECLARE-TIMI 58	32/606	NA	40/659	NA	39.18	<b>⊢</b>	0.90 (0.57-1.44)
VERTIS CV	111/1199	27.1	64/608	30.8	38.37	<b>⊢</b> ● <u></u> + 1	0.88 (0.64-1.19)
Fixed Effects Model	(Q = 0.32, o	df = 2, <i>P</i> = .85; I <sup>2</sup> =	= 0.0%)			-	0.85 (0.69-1.05)
Patients with eGFR 60 to	o <90 mL/mii	1/1.73m²					
EMPA-REG OUTCOME	69/2425	NA	70/1238	NA	15.18 ⊢		0.49 (0.35-0.68)
DECLARE-TIMI 58	118/3838	NA	124/3894	NA	59.59	<b>⊢</b> ●1	0.96 (0.75-1.24)
VERTIS CV	162/2929	15.5	94/1461	18.2	25.24	<b>⊢</b> ●∔1	0.85 (0.66-1.10)
Fixed Effects Model	(Q = 10.57,	df = 2, <i>P</i> = .005;	l² = 81.1%)			•	0.79 (0.67-0.92)
Patients with eGFR ≥90	mL/min/1.73	m²					
EMPA-REG OUTCOME	28/1050	NA	19/488	NA	33.07	· • • • • • • • • • • • • • • • • • • •	0.70 (0.39-1.25)
DECLARE-TIMI 58	95/4137	NA	85/4025	NA	20.49	<b>⊢ ● −</b> 1	1.08 (0.80-1.44)
VERTIS CV	68/1370	13.9	26/678	10.7	46.43	<b>⊢</b>	1.30 (0.83-2.05)
Fixed Effects Model	(Q = 2.75, d	df = 2, <i>P</i> = .25; l <sup>2</sup> :	= 27.3%)				1.06 (0.84-1.33)
					0.25	0.5 1 2	4

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	Trea	Treatment		Placebo		CV death	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% Cl)
Patients with history of	heart failure						
EMPA-REG OUTCOME	38/462	30.4	27/244	42.6	12.40	⊢ <b>−</b> ●− <u>−</u> −	0.71 (0.43-1.16)
CANVAS Program	NA/803	24.3	NA/658	31.6	25.41	⊢ <b>●</b>	0.72 (0.51-1.02)
DECLARE-TIMI 58	75/852	22.6	74/872	21.8	29.44	<b>⊢</b> +	1.01 (0.73-1.39)
VERTIS CV	116/1286	27.6	64/672	29.2	32.75	<b>⊢</b> ● <b> </b> −1	0.94 (0.69-1.28)
Fixed Effects Model	(Q = 2.86,	df = 3, <i>P</i> = .41; l <sup>2</sup> =	= 0.0%)			-	0.87 (0.73-1.03)
Patients with no history	of heart fail	ure					
EMPA-REG OUTCOME	134/4225	10.6	110/2089	17.9	21.18	<b>⊢_</b> ●	0.60 (0.47-0.77)
CANVAS Program	NA/4992	9.8	NA/3689	9.9	24.75	<b>⊢</b>	0.95 (0.76-1.20)
DECLARE-TIMI 58	170/7730	5.4	175/7706	5.6	27.82	<b>⊢_</b> ∎1	0.97 (0.78-1.20)
VERTIS CV	225/4213	14.8	120/2075	16.0	26.25	⊢ <b>●</b>  -1	0.92 (0.74-1.15)
Fixed Effects Model	(Q = 10.46	, df = 3, <i>P</i> = .02; l <sup>2</sup>	<sup>2</sup> = 71.3%)			•	0.86 (0.77-0.96)
					0.25	0.5 1	2 4

NA, not available

# eFigure 4. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to All-Cause Death

## Overall (Panel A) and by Atherosclerotic Cardiovascular Disease (ASCVD) Status (Panel B)

	Trea	atment	Pla	acebo		All-cause de	ath
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% Cl)
EMPA-REG OUTCOME	269/4687	19.4	194/2333	28.6	14.42 H		0.68 (0.57-0.82)
CANVAS Program	NA/5795	17.3	NA/4347	19.5	19.71	<b>⊢</b> •_•	0.87 (0.74-1.01)
DECLARE-TIMI 58	529/8582	15.1	570/8578	16.4	33.75	⊢•+I	0.93 (0.82-1.04)
CREDENCE	168/2202	29.0	201/2199	35.0	11.60	<b>⊢</b> −●−−−1	0.83 (0.68-1.02)
VERTIS CV	473/5499	24.4	254/2747	26.2	20.53	<b>⊢</b> ● <del> </del> →	0.93 (0.80-1.08)
Fixed Effects Model	(Q = 9.19,	df = 4, <i>P</i> = .06; I <sup>2</sup>	= 56.5%)			-	0.87 (0.81-0.93)
					0.5	1	2
					Favor	s Treatment	Favors Placebo

В

А

	Trea	tment	Pla	icebo		All-cause deat	<u>h</u>
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% Cl)
Patients with ASCVD							
EMPA-REG OUTCOME	269/4687	19.4	194/2333	28.6	18.78	•i	0.68 (0.57-0.82)
CANVAS Program	NA/3756	21.1	NA/2900	23.1	19.67		0.89 (0.75-1.07)
<b>DECLARE-TIMI 58</b>	NA/3474	21.3	NA/3500	23.2	25.41	<b>⊢</b> ● <del> </del> 1	0.92 (0.79-1.08)
CREDENCE	108/1113	37.0	133/1107	46.3	9.40 ⊢		0.79 (0.61-1.02)
VERTIS CV	473/5499	24.4	254/2747	26.2	26.74	<b>⊢</b> ● <del> </del> →	0.93 (0.80-1.08)
Fixed Effects Model	(Q = 8.66,	df = 4, <i>P</i> = .07; I <sup>2</sup>	= 53.8%)			•	0.85 (0.79-0.92)
Patients without ASCVD							
CANVAS Program	NA/2039	11.2	NA/1447	13.4	21.53 H		0.79 (0.58-1.07)
DECLARE-TIMI 58	NA/5108	11.0	NA/5078	11.7	61.67	<b>⊢</b> ● <u> </u>	0.94 (0.78-1.12)
CREDENCE	60/1089	20.9	68/1092	23.7	16.80 ⊢	•	H 0.89 (0.63-1.26)
Fixed Effects Model	(Q = 0.92,	df = 2, <i>P</i> = .63; l <sup>2</sup>	= 0.0%)			-	0.90 (0.78-1.03)
					0.5	1	<b>→</b> <sup>2</sup>
					Favors T	reatment	Favors Placebo

NA, not available

**eFigure 5.** Meta-Analysis of Effects of SGLT2 Inhibitors on Time to the Composite of Hospitalization for Heart Failure (HHF) or Cardiovascular Death (CVD)

Overall (Panel A), and by Atherosclerotic Cardiovascular Disease (ASCVD) Status (Panel B), Baseline eGFR (Panel C), and History of Heart Failure (Panel D).

А

	Treatment		Placebo		HHF/CVD		
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% CI)
EMPA-REG OUTCOME	265/4687	19.7	198/2333	30.1	15.18	<b>⊢</b>	0.66 (0.55-0.79)
CANVAS Program	NA/5795	16.3	NA/4347	20.8	21.24	<b>⊢</b> •1	0.78 (0.67-0.91)
DECLARE-TIMI 58	417/8582	12.2	496/8578	14.7	28.69	⊢●→	0.83 (0.73-0.95)
CREDENCE	179/2202	31.5	253/2199	45.4	14.10	⊢_●	0.69 (0.57-0.83)
VERTIS CV	444/5499	23.4	250/2747	26.6	20.78	<b>⊢</b> ●–↓	0.88 (0.75-1.03)
Fixed Effects Model	(Q = 8.09,	df = 4, <i>P</i> = .09; I <sup>2</sup> =	= 50.6%)			•	0.78 (0.73-0.84)
						1	
				0.	25	0.5 1	2
						◀──────	<b>→</b>

Favors Treatment

Favors Placebo

В

	Treatment		Placebo			HHF/CVD		
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)			Hazard ratio (95% CI)
Patients with ASCVD								
EMPA-REG OUTCOME	265/4687	19.7	198/2333	30.1	18.81	<b>⊢_●</b> 1		0.66 (0.55-0.79)
CANVAS Program	NA/3756	21.0	NA/2900	27.4	20.43	<b>⊢●</b>		0.77 (0.65-0.92)
DECLARE-TIMI 58	272/3474	19.9	325/3500	23.9	23.74	⊢-●	<u> </u>	0.83 (0.71-0.98)
CREDENCE	115/1113	40.2	167/1107	60.3	11.28	<b>⊢</b> −−−1		0.66 (0.52-0.83)
VERTIS CV	444/5499	23.4	250/2747	26.6	25.74	<u> </u>	● <u> </u>	0.88 (0.75-1.03)
Fixed Effects Model	(Q = 8.13, o	df = 4, <i>P</i> = .09; I <sup>2</sup> =	= 50.8%)			•		0.77 (0.72-0.84)
Patients without ASCVD								
CANVAS Program	NA/2039	8.9	NA/1447	9.8	20.37	<b>—</b>		0.83 (0.58-1.19)
DECLARE-TIMI 58	145/5108	7.0	171/5078	8.4	54.41	<b>⊢</b> −●	<b>,</b>	0.84 (0.67-1.04)
CREDENCE	64/1089	22.7	86/1092	30.7	25.23	<b>⊢</b> _●		0.74 (0.54-1.03)
Fixed Effects Model	(Q = 0.42,	df = 2, P = .81; I <sup>2</sup>	= 0.0%)			-	-	0.81 (0.69-0.95)
						1		
				0.	25	0.5	1	2

Favors Treatment Favors Placebo

	Trea	atment	Pla	acebo		HHF/CVD	
×	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% CI)
Patients with eGFR <60	mL/min/1.73	m²					· · · · · · · · · · · · · · · · · · ·
DECLARE-TIMI 58	55/606	NA	81/659	NA	58.95	⊢ <b>−</b> ●−↓1	0.78 (0.55-1.09)
VERTIS CV	141/1199	35.6	92/608	46.5	41.05	<b>⊢</b> ●	0.76 (0.59-1.00)
Fixed Effects Model	(Q = 0.01,	df = 1, <i>P</i> = .91; I <sup>2</sup>	= 0.0%)			-	0.77 (0.62-0.95)
Patients with eGFR 60 to	<90 mL/mii	n/1.73m²					
DECLARE-TIMI 58	199/3838	NA	252/3894	NA	77.96	<b>⊢</b> ●	0.79 (0.66-0.95)
VERTIS CV	222/2929	21.8	126/1461	25.0	22.04	<b>⊢</b> ●+1	0.87 (0.70-1.08)
Fixed Effects Model	(Q = 0.44,	df = 1, <i>P</i> = .51; I <sup>2</sup>	= 0.0%)			•	0.82 (0.71-0.95)
Patients with eGFR ≥90	mL/min/1.73	m²					
DECLARE-TIMI 58	163/4137	NA	163/4025	NA	37.16	<b>⊢</b> • <mark>−</mark> -1	0.96 (0.77-1.19)
VERTIS CV	81/1370	16.9	32/678	13.3	62.84	<b>⊢↓</b> ●−−−1	1.27 (0.84-1.91)
Fixed Effects Model	(Q = 1.40,	df = 1, P = .24; I <sup>2</sup>	= 28.5%)			-	1.02 (0.84-1.24)
					1	T I T	
					0.25	0.5 1 2	4

Favors Treatment

Favors Placebo

D	Trea	atment	Pla	acebo		HHF/CVD	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% Cl)
Patients with history of	heart failure						
EMPA-REG OUTCOME	75/462	63.6	49/244	85.5	13.27	<b>⊢</b>	0.72 (0.50-1.04)
CANVAS Program	NA/803	35.4	NA/658	56.8	23.25	<b>⊢</b> ●	0.61 (0.46-0.80)
DECLARE-TIMI 58	142/852	45.1	172/872	55.5	34.85	<b>⊢</b> ●1	0.79 (0.63-0.99)
VERTIS CV	164/1286	40.1	99/672	47.1	28.63	<b>⊢</b> ● <u>+</u> 1	0.85 (0.66-1.09)
Fixed Effects Model	(Q = 3.36,	df = 3, <i>P</i> = .34; I <sup>2</sup>	= 10.7%)			•	0.75 (0.66-0.86)
Patients with no history	of heart fail	ure					
EMPA-REG OUTCOME	190/4225	15.5	149/2089	24.9	19.45	⊢●→	0.63 (0.51-0.78)
CANVAS Program	NA/4992	13.6	NA/3689	15.2	23.48	⊢●┼	0.87 (0.72-1.06)
DECLARE-TIMI 58	275/7730	8.9	324/7706	10.5	34.63	⊢	0.84 (0.72-0.99)
VERTIS CV	280/4213	18.8	151/2075	20.6	22.44	⊢●┼┤	0.91 (0.75-1.11)
Fixed Effects Model	(Q = 7.41, d	df = 3, <i>P</i> = .06; l <sup>2</sup>	= 59.5%)			•	0.82 (0.74-0.90)
					0.25	0.5 1 2	

Favors Treatment

Favors Placebo

## **eFigure 6.** Meta-Analysis of Effects of SGLT2 Inhibitors on Time to First Event of Kidney-Related Outcomes

## Albuminuria (Panel A) and History of Heart Failure (Panel B)

Treatment		Pla	acebo			Kidney outcomes			
n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)					Hazard ratio (95% CI)
uminuria									
NA/4012	2.6	NA/2995	4.9	48.58		H	• • •		0.50 (0.33-0.77)
64/3186	5.8	35/1597	6.3	51.42				-	0.92 (0.61-1.39)
(Q = 4.09,	df = 1, <i>P</i> = .04; l <sup>2</sup>	<sup>e</sup> = 75.6%)					-		0.68 (0.51-0.92)
ninuria									
NA/1322	9.0	NA/944	8.4	42.05			· · · · · · · · · · · · · · · · · · ·		0.98 (0.60-1.60)
57/1647	10.0	36/845	12.6	57.95			<b>⊢</b> ●	H	0.80 (0.53-1.21)
(Q = 0.38,	df = 1, <i>P</i> = .54; I <sup>2</sup>	<sup>2</sup> = 0.0%)	1000				-	-1	0.87 (0.63-1.20)
minuria									
NA/406	29.4	NA/354	56.6	48.88		⊢	<b>—</b>		0.48 (0.31-0.74)
50/513	31.7	37/242	50.0	51.12			<b>⊢</b>		0.62 (0.41-0.95)
(Q = 0.68,	df = 1, <i>P</i> = .41; I <sup>2</sup>	= 0.0%)					-		0.55 (0.40-0.74)
					[	1	1		
					0.125	0.25	0.5 1		2
						-		-	
	n/N minuria NA/4012 64/3186 (Q = 4.09, ninuria NA/1322 57/1647 (Q = 0.38, minuria NA/406 50/513	Rate/1000 patient-years      minuria      NA/4012    2.6      64/3186    5.8      (Q = 4.09, df = 1, P = .04; I <sup>2</sup> ninuria      NA/1322    9.0      57/1647    10.0      (Q = 0.38, df = 1, P = .54; I <sup>2</sup> minuria      NA/406    29.4      50/513    31.7	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Rate/1000 patient-years    Rate/1000 patient-years    Weights (%)      Iminuria NA/4012    2.6    NA/2995    4.9    48.58      64/3186    5.8    35/1597    6.3    51.42      (Q = 4.09, df = 1, $P = .04; l^2 = 75.6\%$ )    12    57/1647    10.0    36/845    12.6    57.95      (Q = 0.38, df = 1, $P = .54; l^2 = 0.0\%$ )    minuria    NA/406    29.4    NA/354    56.6    48.88    12      NA/406    29.4    NA/354    56.6    48.88    12      (Q = 0.68, df = 1, $P = .41; l^2 = 0.0\%$ )    51.12    10.0    10.0    10.0	Rate/1000 patient-years    Rate/1000 patient-years    Weights (%)      minuria NA/4012    2.6    NA/2995    4.9    48.58      64/3186    5.8    35/1597    6.3    51.42      (Q = 4.09, df = 1, $P = .04; l^2 = 75.6\%$ )         ninuria NA/1322    9.0    NA/944    8.4    42.05      57/1647    10.0    36/845    12.6    57.95      (Q = 0.38, df = 1, $P = .54; l^2 = 0.0\%$ )         minuria (Q = 0.68, df = 1, $P = .41; l^2 = 0.0\%$ )    50.0    51.12	Rate/1000  Rate/1000  Rate/1000  Weights    n/N  patient-years  n/N  patient-years  (%)    minuria  NA/4012  2.6  NA/2995  4.9  48.58    64/3186  5.8  35/1597  6.3  51.42    (Q = 4.09, df = 1, $P = .04$ ; $I^2 = 75.6\%$ )

Favors Treatment

Favors Placebo

В	Trea	Treatment		acebo			Kidney outcomes			
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)					Hazard ratio (95% CI)
Patients with history of I	neart failure									
DECLARE-TIMI 58	27/852	NA	48/872	NA	43.33			•		0.58 (0.36-0.92)
VERTIS CV	53/1286	12.9	40/672	18.8	56.67			•		0.69 (0.46-1.04)
Fixed Effects Model	(Q = 0.30,	df = 1, <i>P</i> = .59; I <sup>2</sup>	= 0.0%)					-	-	0.64 (0.47-0.87)
Patients with no history	of heart fail	ure								
DECLARE-TIMI 58	100/7730	NA	190/7706	NA	60.82			⊢•−		0.52 (0.41-0.66)
VERTIS CV	122/4213	8.2	68/2075	9.3	39.18			H		0.88 (0.66-1.19)
Fixed Effects Model	(Q = 7.35,	df = 1, <i>P</i> = .007; I	<sup>2</sup> = 86.4%)		r	-		-	-	0.64 (0.53-0.77)
					0.1	25	0.25	0.5	1	2
							-			
							Favors	Treatment		Favors Placebo

NA, not available

**eFigure 7.** Meta-Analysis of Effects of SGLT2 Inhibitors on Time to First Event of Myocardial Infarction (MI)

Overall (Panel A) and by Atherosclerotic Cardiovascular Disease (ASCVD) Status (Panel B)

A	Treatment		Treatment Placebo				MI			
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)				Hazard ratio (95% CI)	
EMPA-REG OUTCOME	223/4687	16.8	126/2333	19.3	14.71				0.87 (0.70-1.09)	
CANVAS Program	NA/5795	11.2	NA/4347	12.6	17.95		H H		0.89 (0.73-1.09)	
DECLARE-TIMI 58	393/8582	11.7	441/8578	13.2	39.19		<b>⊢</b> ●-		0.89 (0.77-1.01)	
CREDENCE	83/2202	14.6	95/2199	16.9	8.16	H			0.86 (0.64-1.16)	
VERTIS CV	330/5499	17.7	158/2747	17.0	19.98		<b>⊢</b> ●−1		1.04 (0.86-1.26)	
Fixed Effects Model	(Q = 2.34,	df = 4, <i>P</i> = .67; I <sup>2</sup>	= 0.0%)				•		0.91 (0.84-0.99)	
					0.25	0.5	1	2	4	
					Favors	Treatmen	 1	Favors Plac	ebo	

В

	Trea	tment	Pla	icebo		MI	_	Hazard ratio (95% Cl)
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)			
Patients with ASCVD								
EMPA-REG OUTCOME	223/4687	16.8	126/2333	19.3	17.76	<b>⊢</b> ●∔I		0.87 (0.70-1.09)
CANVAS Program	NA/3756	12.5	NA/2900	16.0	17.05	<b>⊢</b> ●		0.79 (0.63-0.99)
DECLARE-TIMI 58	279/3474	21.0	321/3500	24.1	33.82	⊢ <b>●</b> - i		0.87 (0.74-1.02)
CREDENCE	63/1113	22.2	66/1107	23.6	7.25	<b>⊢</b>		0.93 (0.66-1.32)
VERTIS CV	330/5499	17.7	158/2747	17.0	24.12	<b>⊢</b> •−-+		1.04 (0.86-1.26)
Fixed Effects Model	(Q = 3.80,	df = 4, <i>P</i> = .43; I	2 = 0.0%)			•		0.90 (0.82-0.99)
Patients without ASCVD								
CANVAS Program	NA/2039	5.5	NA/1447	4.4	17.40	⊢ <b>⊢</b> ● −−−		1.21 (0.73-2.00)
DECLARE-TIMI 58	114/5108	5.6	120/5078	5.9	69.21	<b>⊢</b> ● <mark>  −</mark>		0.94 (0.73-1.21)
CREDENCE	20/1089	7.0	29/1092	10.3	13.40 -			0.70 (0.39-1.23)
Fixed Effects Model	(Q = 1.97, e	df = 2, <i>P</i> = .37; I <sup>2</sup>	= 0.0%)			-		0.94 (0.77-1.17)
					0.05			
					0.25	0.5 1	2	4
					-			•

Favors Treatment

Favors Placebo

# eFigure 8. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to First Event of Stroke

Overall (Panel A) and by Atherosclerotic Cardiovascular Disease (ASCVD) Status (Panel B)

	Trea	atment	Pla	acebo		-	Stroke	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)	8		Hazard ratio (95% Cl)
EMPA-REG OUTCOME	164/4687	12.3	69/2333	10.5	14.07		- I	1.18 (0.89-1.56)
CANVAS Program	NA/5795	7.9	NA/4347	9.6	21.20	۲		0.87 (0.69-1.09)
DECLARE-TIMI 58	NA/8582	7.5	NA/8578	7.8	37.94		<b>⊢</b> ● – 1	0.96 (0.81-1.14)
CREDENCE	62/2202	10.9	80/2199	14.2	9.73	H	• +	0.77 (0.55-1.08)
VERTIS CV	185/5499	9.8	87/2747	9.3	17.06			1.06 (0.82-1.37)
Fixed Effects Model	(Q = 5.01, o	df = 4, <i>P</i> = .29; I <sup>2</sup>	= 20.1%)				-	0.96 (0.87-1.07)
					0.25	0.5	1	2
						Favors Treatm	ent	Favors Placebo

	Trea	atment	Pla	acebo		Stroke	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights s (%)		Hazard ratio (95% CI)
Patients with ASCVD							
EMPA-REG OUTCOME	164/4687	12.3	69/2333	10.5	19.11	<b>⊢↓</b> ● − − 1	1.18 (0.89-1.56)
CANVAS Program	NA/3756	8.8	NA/2900	10.4	19.98	<b>⊢</b> ● ↓ →	0.88 (0.67-1.16)
DECLARE-TIMI 58	NA/3474	10.9	NA/3500	11.7	28.68	<b>⊢_</b> ● <mark> </mark>	0.93 (0.74-1.17)
CREDENCE	44/1113	15.4	50/1107	17.7	9.07	⊢ <b>●</b>	0.87 (0.58-1.31)
VERTIS CV	185/5499	9.8	87/2747	9.3	23.17	<b>⊢</b> ↓●I	1.06 (0.82-1.37)
Fixed Effects Model	(Q = 3.16, c	df = 4, <i>P</i> = .53; I <sup>2</sup>	= 0.0%)			-	0.99 (0.87-1.11)
Patients without ASCVD							
CANVAS Program	NA/2039	4.5	NA/1447	5.0	18.89	⊢ <b>−−</b> −	0.97 (0.59-1.61)
DECLARE-TIMI 58	NA/5108	5.2	NA/5078	5.1	66.86	<b>⊢</b>	1.02 (0.78-1.33)
CREDENCE	18/1089	6.3	30/1092	10.7	14.25 <b>—</b>		0.60 (0.34-1.08)
Fixed Effects Model	(Q = 2.69,	df = 2, <i>P</i> = .26; I <sup>2</sup>	= 25.7%)			-	0.94 (0.75-1.17)
					0.25	0.5 1	2
						◀── ──	→

Favors Placebo Favors Treatment

NA, not available

А

В

**eFigure 9.** Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of the Major Adverse Cardiovascular Event (MACE) Composite Without Inclusion of the CREDENCE Trial

Overall (Panel A) and Following a Post Hoc Comparison by Atherosclerotic Cardiovascular Disease (ASCVD) Status (Panel B)

А

	Treatment		Placebo			MACE	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	17.64	<b>⊢</b> ●1	0.86 (0.74-0.99)
CANVAS Program	NA/5795	26.9	NA/4347	31.5	22.59	<b>⊢</b> ●−1	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	35.94	<b>⊢</b> ●- I	0.93 (0.84-1.03)
VERTIS CV	735/5499	40.0	368/2747	40.3	23.83	<b>⊢</b>	0.99 (0.88-1.12)
Fixed Effects Model	(Q = 3.21	, df = 3, P = .36;	l <sup>2</sup> = 6.5%)			*	0.91 (0.86-0.97)
					0.25	0.5 1	2
						← —	

В

	Treatment		Placebo			MACE		
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)			Hazard ratio (95% CI)
Patients with ASCVD								
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	21.05		<b>⊢</b> ●–	0.86 (0.74-0.99)
CANVAS Program	NA/3756	34.1	NA/2900	41.3	23.20		<b>⊢</b> ● →	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	27.31		<b>⊢●</b>	0.90 (0.79-1.02)
VERTIS CV	735/5499	40.0	368/2747	40.3	28.43		<b>⊢</b> ∳(	0.99 (0.88-1.12)
Fixed Effects Model	(Q = 4.32	2, df = 3, <i>P</i> = .23	; 1² = 30.5%)				•	0.90 (0.84-0.96)
Patients without ASCVD								
CANVAS Program	NA/2039	15.8	NA/1447	15.5	25.90		<b>⊢</b>	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	74.10		<b>⊢</b> ∳−-1	1.01 (0.86-1.20)
Fixed Effects Model	(Q = 0.03	, df = 1, <i>P</i> = .86;	l <sup>2</sup> = 0.0%)				-	1.00 (0.87-1.16)
					[	1		1
					0.25	0.5	1	2
						-		

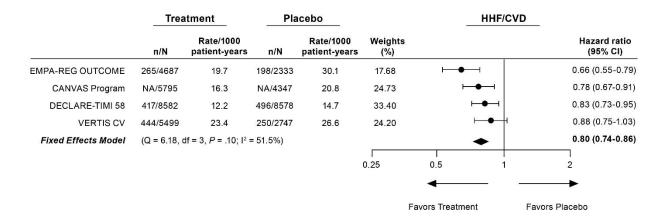
Favors Treatment Favors Placebo

Favors Treatment

Favors Placebo

NA, not available

**eFigure 10.** Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Hospitalization for Heart Failure (HHF) or Cardiovascular Death (CVD) Without Inclusion of the CREDENCE Trial



NA, not available

**eFigure 11.** Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Hospitalization for Heart Failure (HHF) Without Inclusion of the CREDENCE Trial

Overall (Panel A) and Following a Post-Hoc Comparison by Atherosclerotic Cardiovascular Disease (ASCVD) Status (Panel B)

Α							
	Trea	Treatment		Placebo		НН	F
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	19.15	<b>⊢</b> •→	0.65 (0.50-0.85)
CANVAS Program	NA/5795	5.5	NA/4347	8.7	20.36	<b>⊢</b> • • • • •	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	40.15	<b>⊢</b> ●1	0.73 (0.61-0.88)
VERTIS CV	139/5499	7.3	99/2747	10.5	20.34	<b>⊢</b> •−−1	0.70 (0.54-0.90)
Fixed Effects Model	(Q = 0.60,	df = 3, <i>P</i> = .90; l <sup>2</sup>	= 0.0%)			•	0.70 (0.62-0.78)
					0.25	0.5 1	2
						Favors Treatment	Favors Placebo

В	Trea	tment	Pla	icebo		HHF	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% CI)
Patients with ASCVD							
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	22.49	<b>⊢</b> •−i	0.65 (0.50-0.85)
CANVAS Program	NA/3756	7.3	NA/2900	11.3	19.63	<b>⊢</b>	0.68 (0.51-0.90)
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	34.00	<b>⊢_</b> ●(	0.78 (0.63-0.97)
VERTIS CV	139/5499	7.3	99/2747	10.5	23.88	<b>⊢</b>	0.70 (0.54-0.90)
Fixed Effects Model	(Q = 1.26,	df = 3, <i>P</i> = .74; I <sup>2</sup>	= 0.0%)			•	0.71 (0.63-0.81)
Patients without ASCVD							
CANVAS Program	NA/2039	2.6	NA/1447	4.2	22.92 ⊢		0.64 (0.35-1.15)
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	77.08	⊢ <b></b>	0.64 (0.46-0.88)
Fixed Effects Model	(Q = 0.00,	df = 1, <i>P</i> = 1.00; I	<sup>2</sup> = 0.0%)			-	0.64 (0.48-0.85)
					1		
					0.25	0.5 1	2
						← —	
					0.25	4	

Favors Treatment Favors Placebo

NA, not available

**eFigure 12.** Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Kidney-Related Outcomes Without Inclusion of the CREDENCE Trial

	Trea	Treatment		Placebo		Kidney o	utcomes
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)		Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	15.40	<b>⊢</b> −−1	0.54 (0.40-0.75)
CANVAS Program	NA/5795	5.5	NA/4347	9.0	24.97	<b>⊢</b>	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	33.15	<b>⊢</b> I	0.53 (0.43-0.66)
VERTIS CV	175/5499	9.3	108/2747	11.5	26.48	<b>⊢</b> ●	⊣ 0.81 (0.64-1.03)
Fixed Effects Model	(Q = 7.62, d	df = 3, <i>P</i> = .06; l <sup>2</sup>	= 60.6%)			•	0.61 (0.54-0.69)
					0.25	0.5	1 2
						Favors Treatment	Favors Placebo

**eFigure 13.** Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to Cardiovascular (CV) Death Without Inclusion of the CREDENCE Trial

	Treatment		Pla	Placebo		_	CV death	<u> </u>
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)			Hazard ratio (95% CI)
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	17.96	<b>⊢</b>		0.62 (0.49-0.77)
CANVAS Program	NA/5795	11.6	NA/4347	12.8	24.52		<b>⊢</b> ● + I	0.87 (0.72-1.06)
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	29.03		- <b>-</b>	0.98 (0.82-1.17)
VERTIS CV	341/5499	17.6	184/2747	19.0	28.49		<b>⊢</b> ●	0.92 (0.77-1.10)
Fixed Effects Model	(Q = 10.68,	df = 3, <i>P</i> = .01; l <sup>2</sup>	<sup>2</sup> = 71.9%)				•	0.86 (0.78-0.95)
					0.25	0.5	1	2
						Favors Treat	ment	Favors Placebo

NA, not available

**eFigure 14.** Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to All-Cause Death Without Inclusion of the CREDENCE Trial

	Trea	atment	Pla	Placebo			All-cause of	death
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)			Hazard ratio (95% Cl)
EMPA-REG OUTCOME	269/4687	19.4	194/2333	28.6	16.31	) <u> </u>	•	0.68 (0.57-0.82)
CANVAS Program	NA/5795	17.3	NA/4347	19.5	22.29		<b>—</b> •	0.87 (0.74-1.01)
DECLARE-TIMI 58	529/8582	15.1	570/8578	16.4	38.18		<b></b>	0.93 (0.82-1.04)
VERTIS CV	473/5499	24.4	254/2747	26.2	23.22		<b>⊢</b> ●	0.93 (0.80-1.08)
Fixed Effects Model	(Q = 9.00, d	df = 3, <i>P</i> = .03; I <sup>2</sup>	= 66.7%)				•	0.87 (0.81-0.94)
					0.25	0.5	1	2
						Favors Treat	tment	Favors Placebo

**eFigure 15.** Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Myocardial Infarction (MI) Without Inclusion of the CREDENCE Trial

	Treatment		Placebo				МІ	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)			Hazard ratio (95% Cl)
EMPA-REG OUTCOME	223/4687	16.8	126/2333	19.3	16.02	<b>⊢</b> ●		0.87 (0.70-1.09)
CANVAS Program	NA/5795	11.2	NA/4347	12.6	19.55	<b>—</b> •	н –	0.89 (0.73-1.09)
DECLARE-TIMI 58	393/8582	11.7	441/8578	13.2	42.68	<b>—</b>		0.89 (0.77-1.01)
VERTIS CV	330/5499	17.7	158/2747	17.0	21.76	F		1.04 (0.86-1.26)
Fixed Effects Model	(Q = 2.17, d	f = 3, <i>P</i> = .54; l <sup>2</sup> =	= 0.0%)			-	•	0.92 (0.84-1.00)
					0.25	0.5	1	2
						◄		
						Favors Treatment	Favo	ors Placebo

NA, not available

# **eFigure 16.** Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Stroke Without Inclusion of the CREDENCE Trial

	Treatment		Pla	Placebo		Si	Stroke	
	n/N	Rate/1000 patient-years	n/N	Rate/1000 patient-years	Weights (%)			Hazard ratio (95% CI)
EMPA-REG OUTCOME	164/4687	12.3	69/2333	10.5	15.59	F		1.18 (0.89-1.56)
CANVAS Program	NA/5795	7.9	NA/4347	9.6	23.48	<b>⊢</b> ●	+1	0.87 (0.69-1.09)
DECLARE-TIMI 58	NA/8582	7.5	NA/8578	7.8	42.03	<u> </u>	•	0.96 (0.81-1.14)
VERTIS CV	185/5499	9.8	87/2747	9.3	18.90	<u> </u>		1.06 (0.82-1.37)
Fixed Effects Model	(Q = 3.13, c	df = 3, <i>P</i> = .37; I² =	= 4.1%)			-	•	0.99 (0.88-1.10)
					0.25	l 0.5	1	2
						◄		
					F	avors Treatment	Favors	Placebo