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 ≤45 mL/min/1.73 m^2, 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 ≥40% decrease in eGFR to eGFR<60 mL/min/1.73 m^2 and/or end-stage renal disease (dialysis ≥90 days or kidney transplantation or confirmed sustained eGFR <15 mL/min/1.73 m^2) 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^2), 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[a]
MACE	CV ITT	Yes	Presence or absence of atherosclerotic cardiovascular disease	All
			Baseline eGFR level (mL/min/1.73 m^2) (<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^2) (<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^2) (<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^2) (<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

[a]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

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

Event	Canagliflozin[a]		Canagliflozin[b]		Dapagliflozin[c]		Empagliflozin[d]		Ertugliflozin[e]	
	CANVAS and CANVAS-R		CREDENCE		DECLARE-TIMI 58		EMPA-REG OUTCOME		VERTIS CV	
	Canagliflozin 100 mg and 300 mg N=5790	Placebo N=4344	Canagliflozin 100 mg N=2200	Placebo N=2197	Dapagliflozin 10 mg N=8574	Placebo N=8569	Empagliflozin 10 mg and 25 mg N=4687	Placebo N=2333	Ertugliflozin 5 and 15 mg N=5493	Placebo N=2745
	Events/1000 patient-years n (%)		Events/1000 patient-years n (%)		n (%)		n (%)		n (%)	
Amputation	6.3 140 (2.4)	3.4 47 (1.1)	12.3 70 (3.2)	11.2 63 (2.9)	123 (1.4)	113 (1.3)	88 (1.9)	43 (1.8)	111 (2.0)	45 (1.6)
Fracture	15.4 NA	11.9 NA	11.8 67 (3.0)	12.1 68 (3.1)	457 (5.3)	440 (5.1)	179 (3.8)	91 (3.9)	201 (3.7)	98 (3.6)
Diabetic Ketoacidosis	0.6 NA	0.3 NA	2.2 11 (0.5)	0.2 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[f]	10.8[f]	NA	NA	76 (0.9)[g]	9 (0.1)[g]	166 (5.0)	25 (1.5)	184 (4.8)[h]	22 (1.2)[h]
Genital mycotic	68.8	17.5	NA	NA	NA	NA	135 (10.0)	17 (2.6)	113 (6.9)[h]	20 (2.4)[h]

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)

[a]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 pre-specified primary fracture outcome (not shown here) and all fracture was a secondary outcome.

[b]Data from the CREDENCE trial (Perkovic et al. *New Engl J Med*. 2019;380:2295-2306).

[c]Data from the DECLARE-TIMI 58 trial (Wiviott et al. *New Engl J Med*. 2019;380:347-57).

[d]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).

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

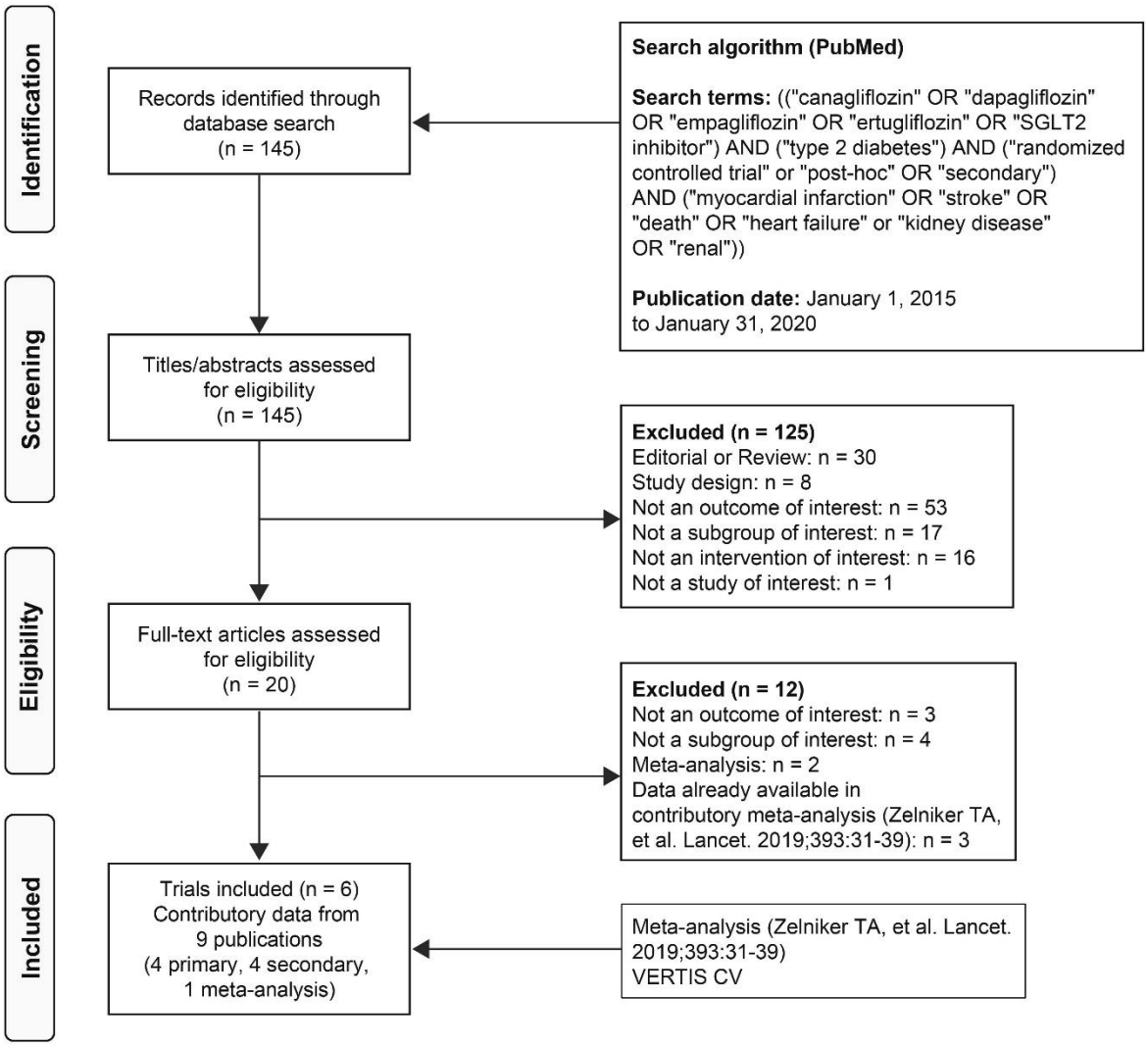
[f]Infection of male genitalia included balanitis, phimosis, and events leading to circumcision.

[g]Data for the overall population (male and female combined).

[h]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.

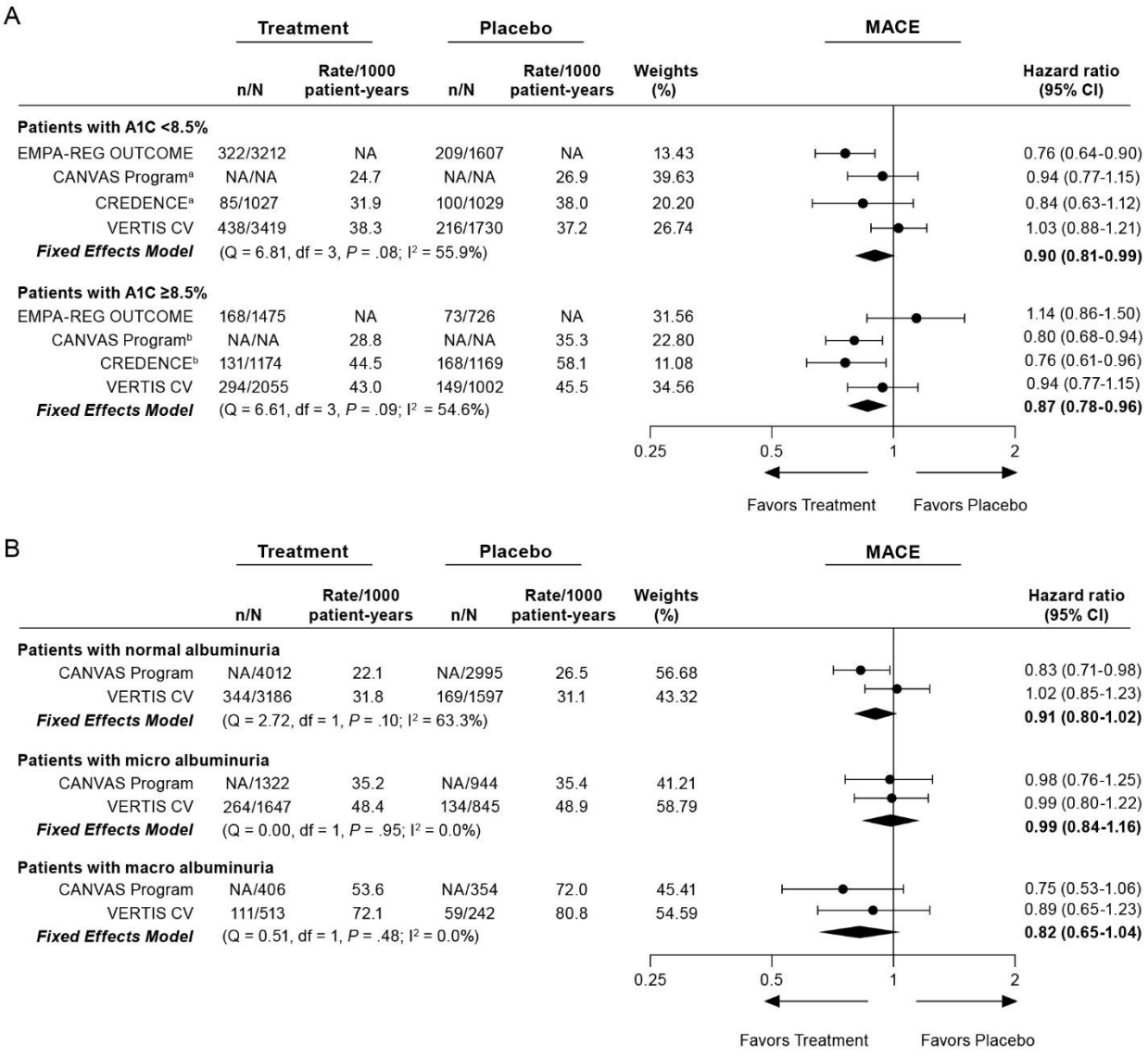
NA, not available

eFigure 1. PRISMA Flow Chart: Identification of Eligible Trials



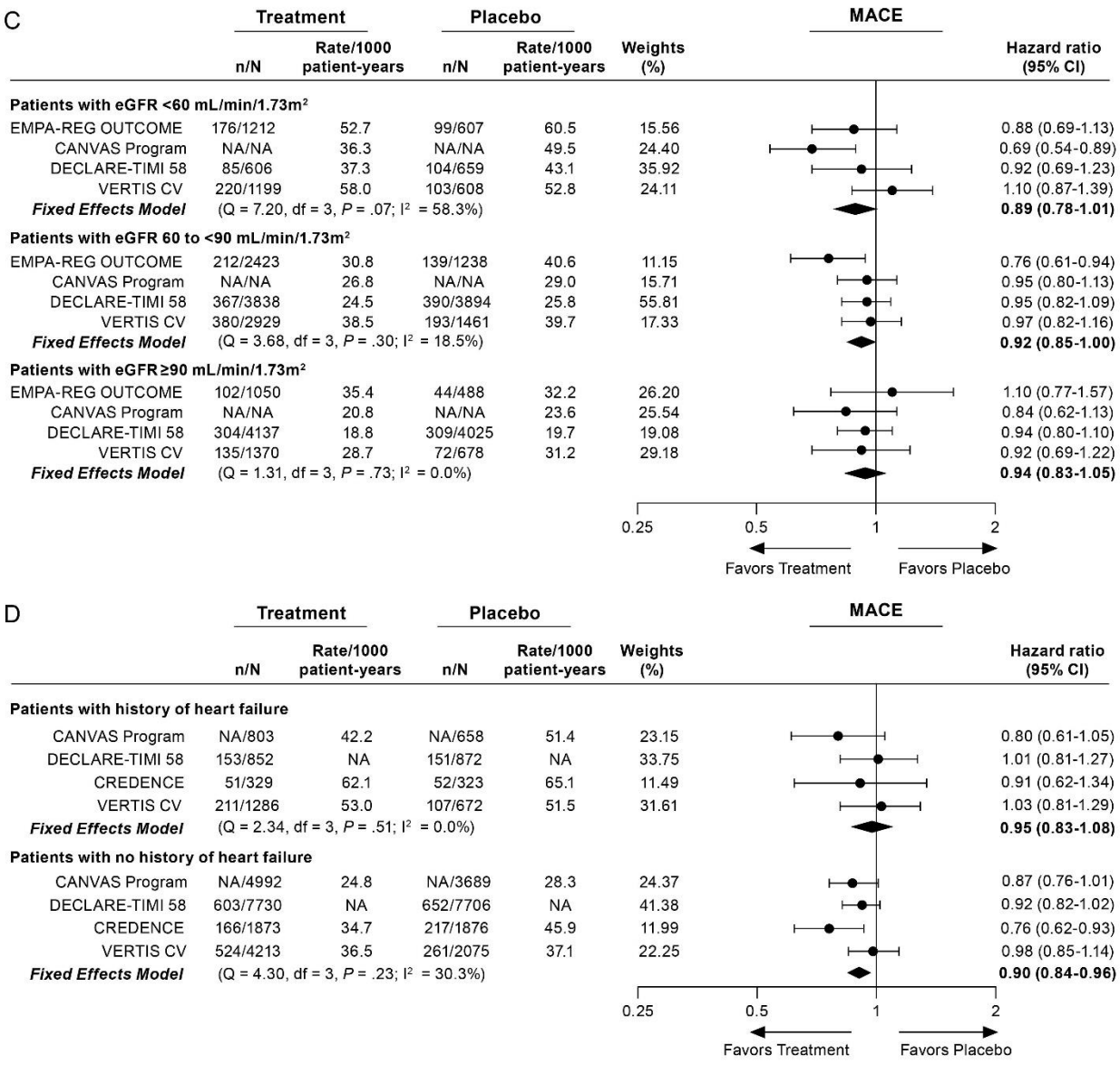
eFigure 2. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to First Event of Cardiovascular Death, Myocardial Infarction, or Stroke (MACE)

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



[a]Patients with A1c <8% for CANVAS Program and CREDENCE.
[b]Patients with A1c ≥8% for CANVAS Program and CREDENCE.

NA, not available



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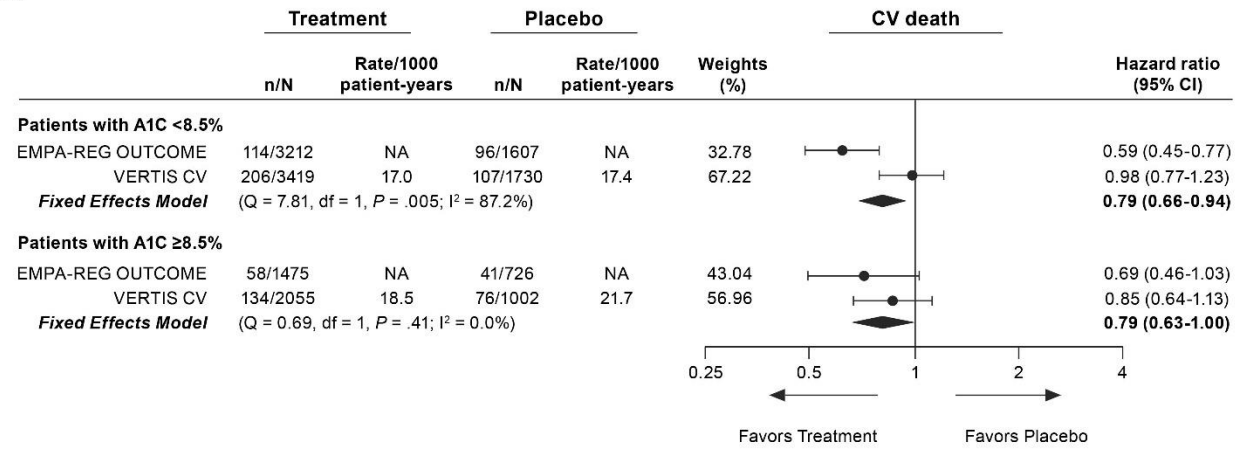
eFigure 3. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to Cardiovascular (CV) Death

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

A



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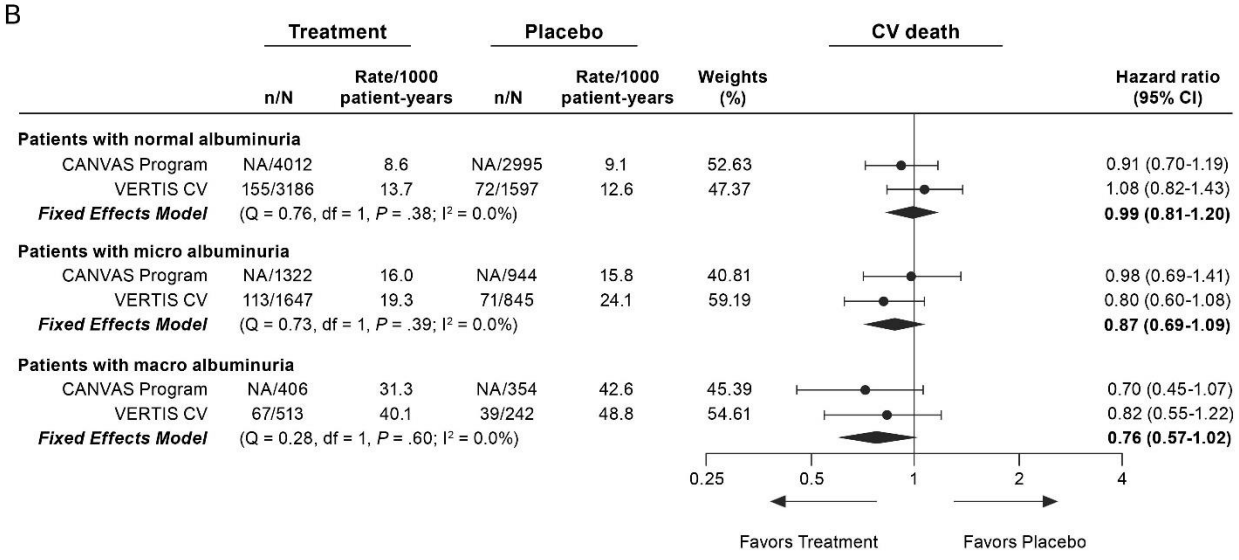

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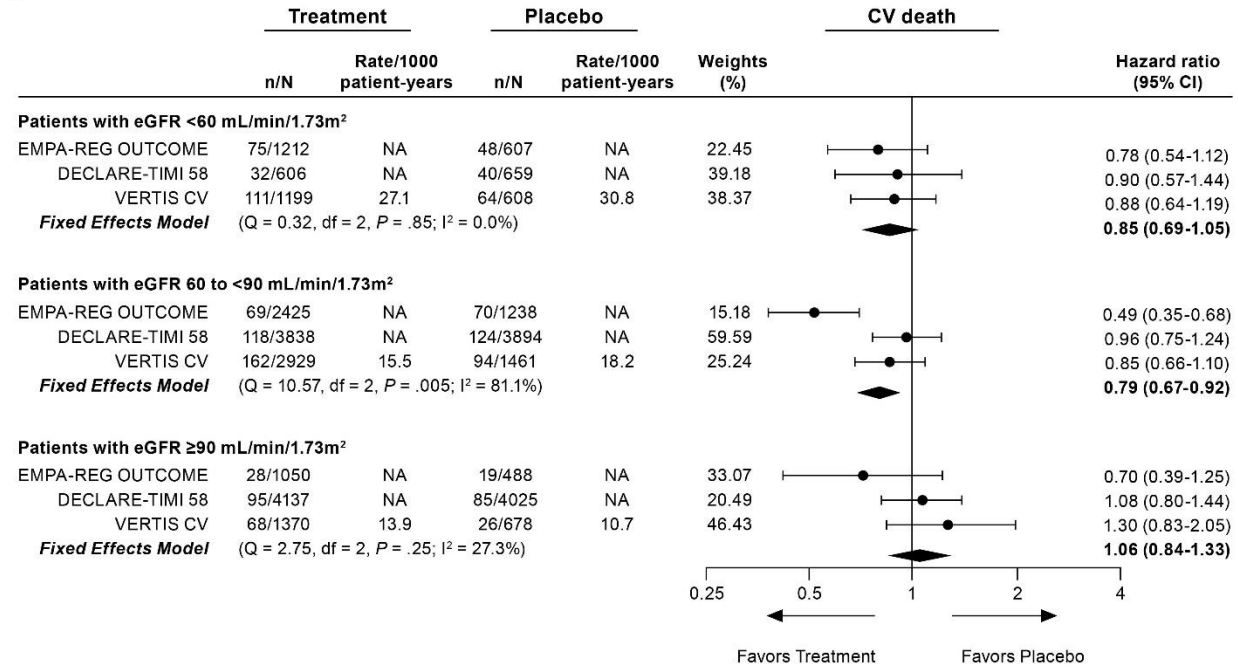
C



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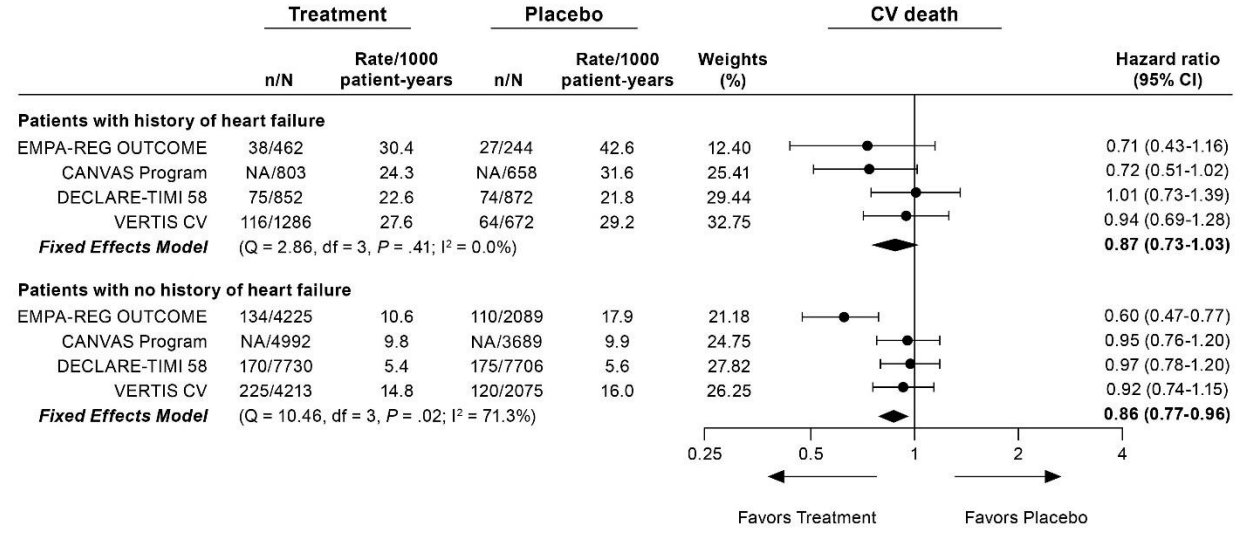

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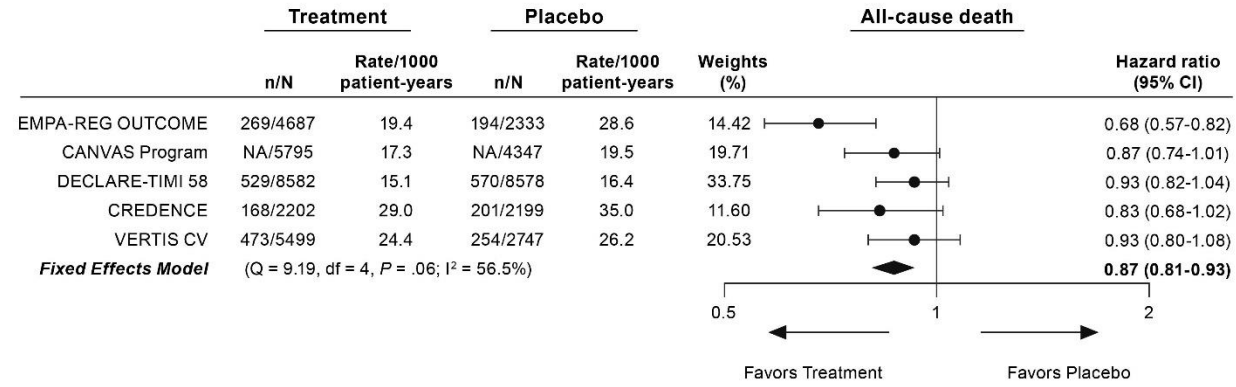
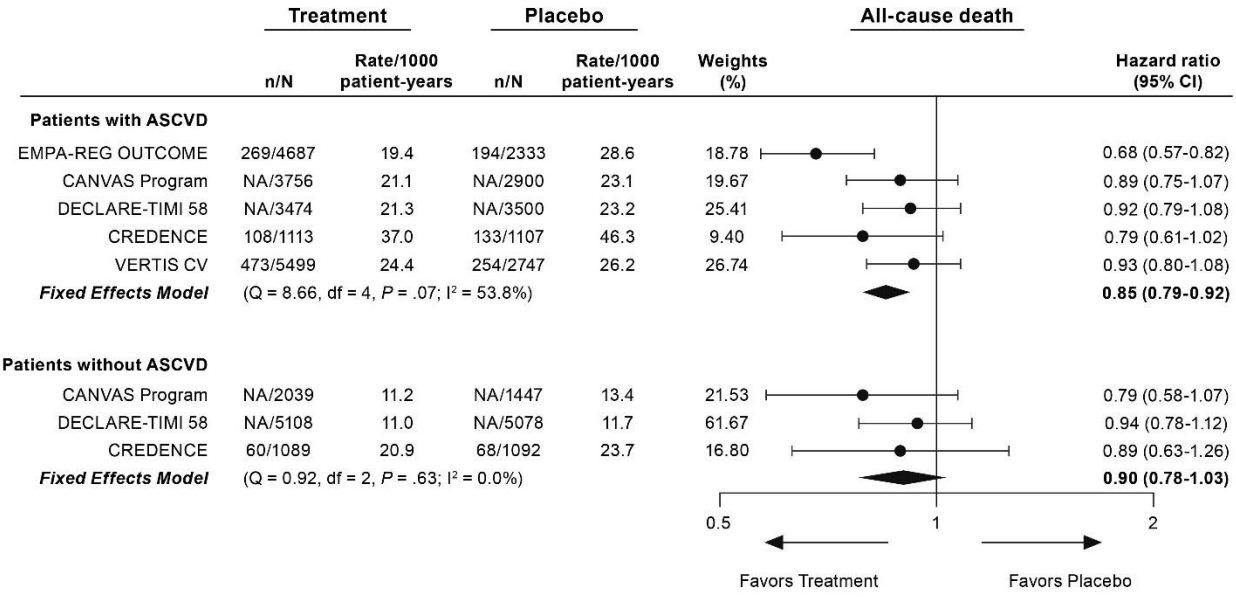
eFigure 4. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to All-Cause Death

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

A



B



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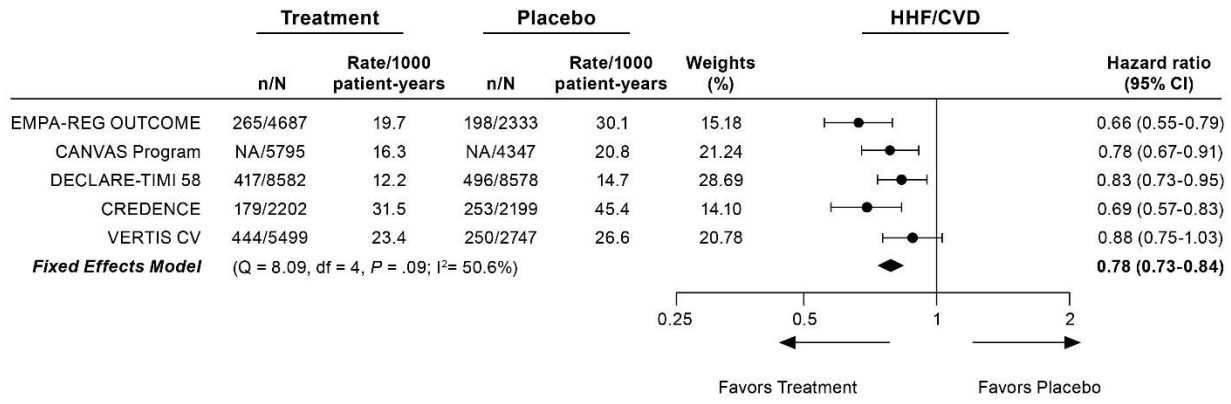
eFigure 5. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to the Composite of Hospitalization for Heart Failure (HHF) or Cardiovascular Death (CVD)

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

A



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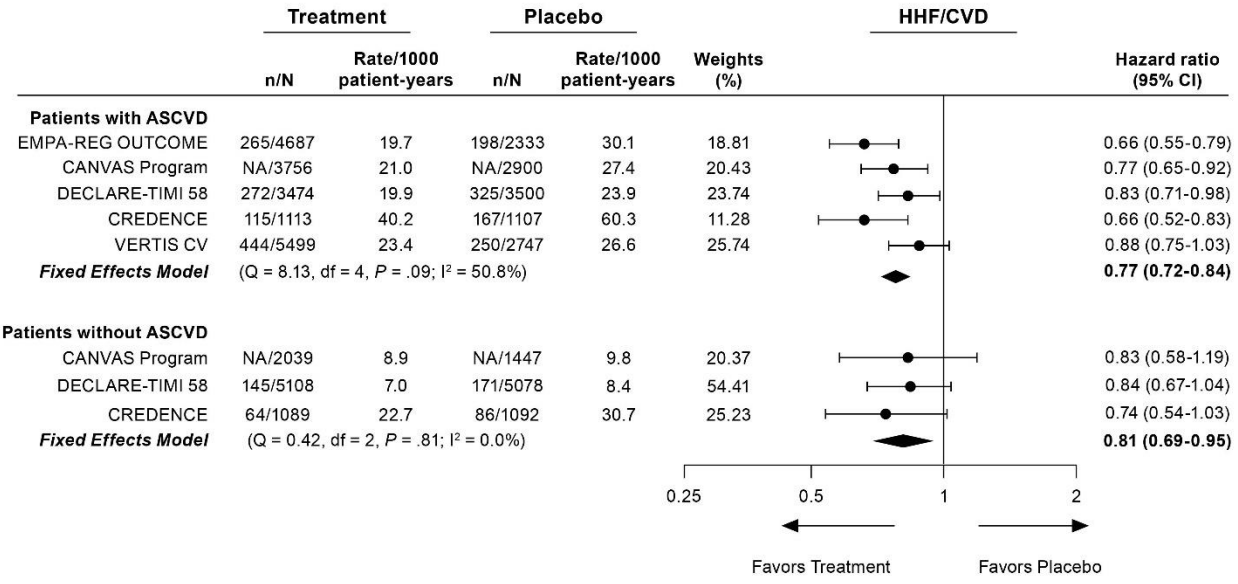

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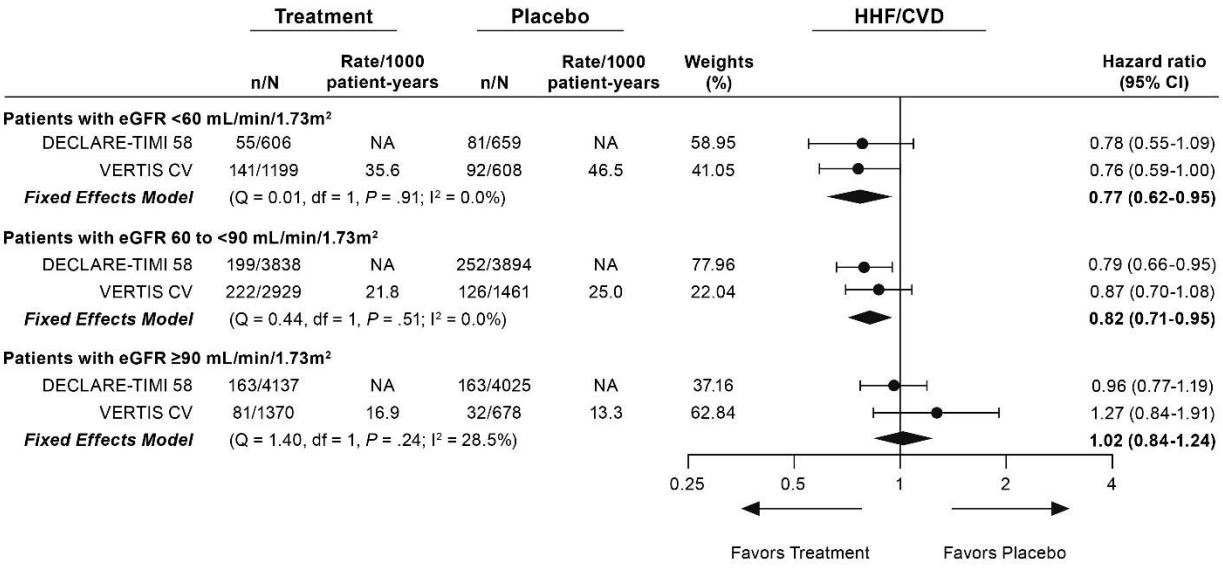

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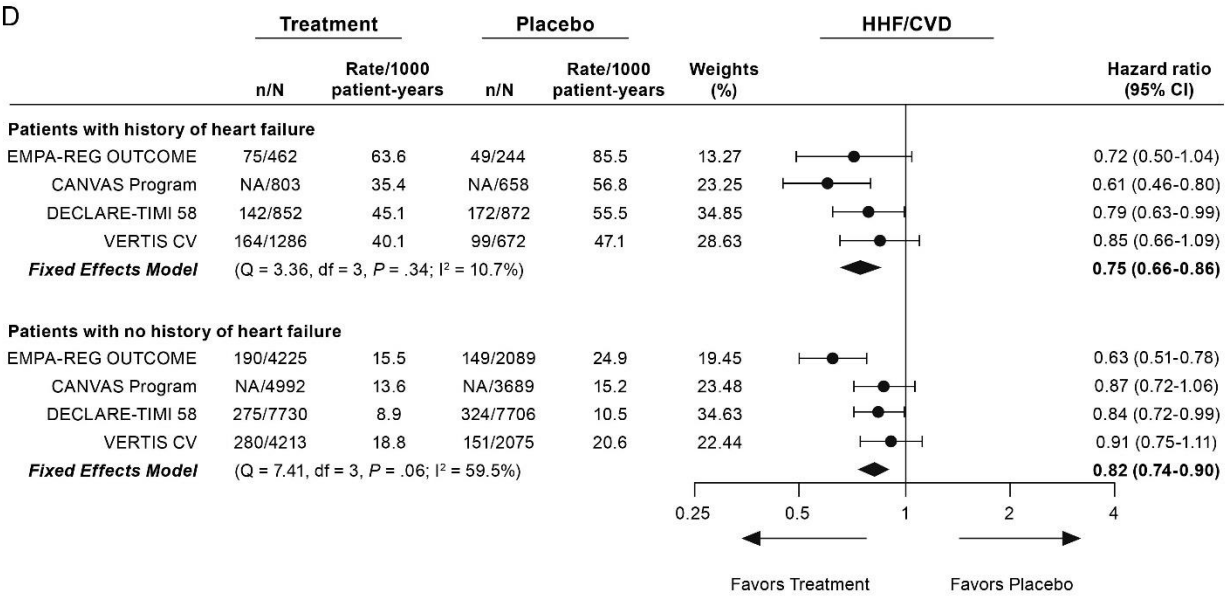
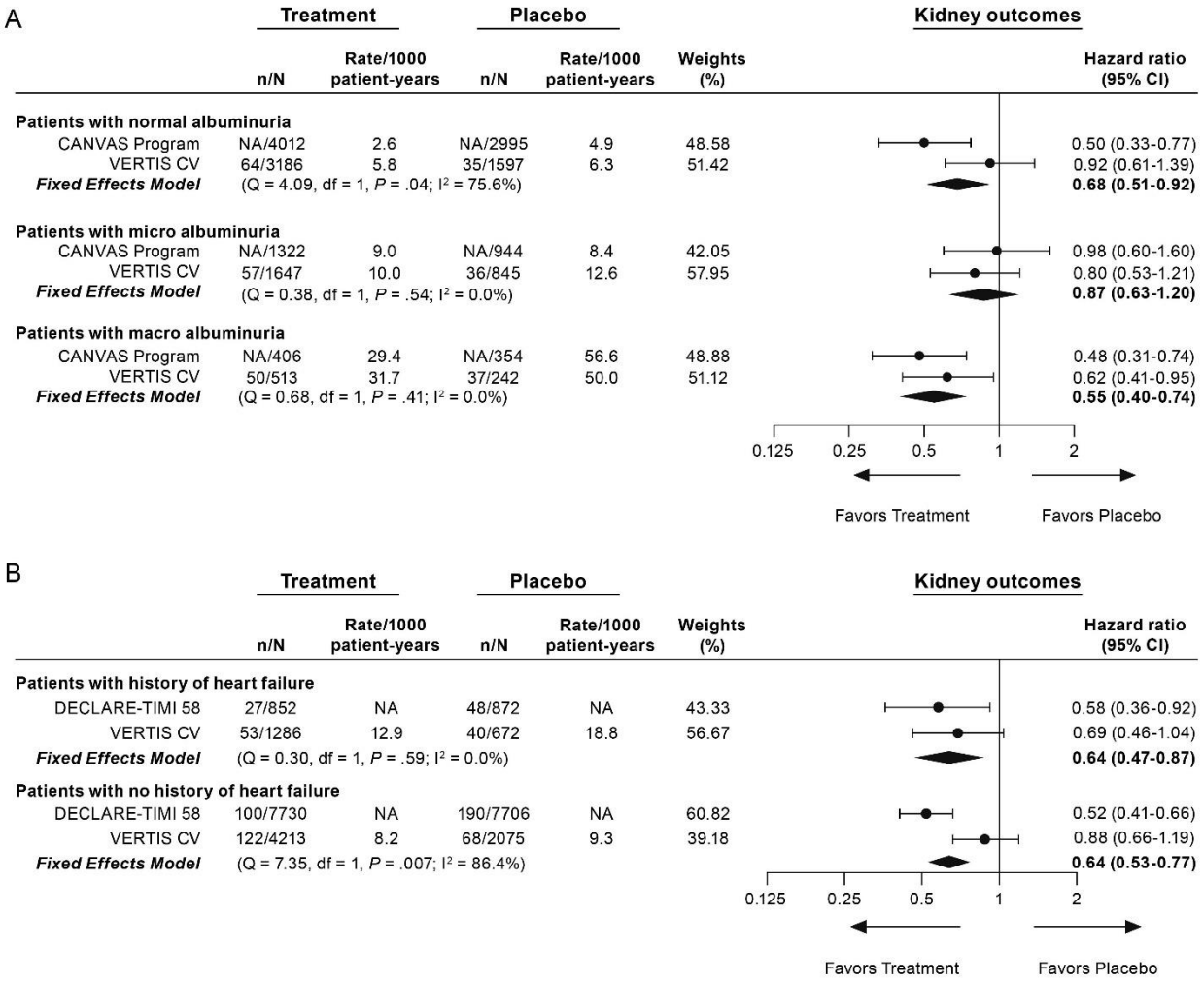


eFigure 6. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to First Event of Kidney-Related Outcomes

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



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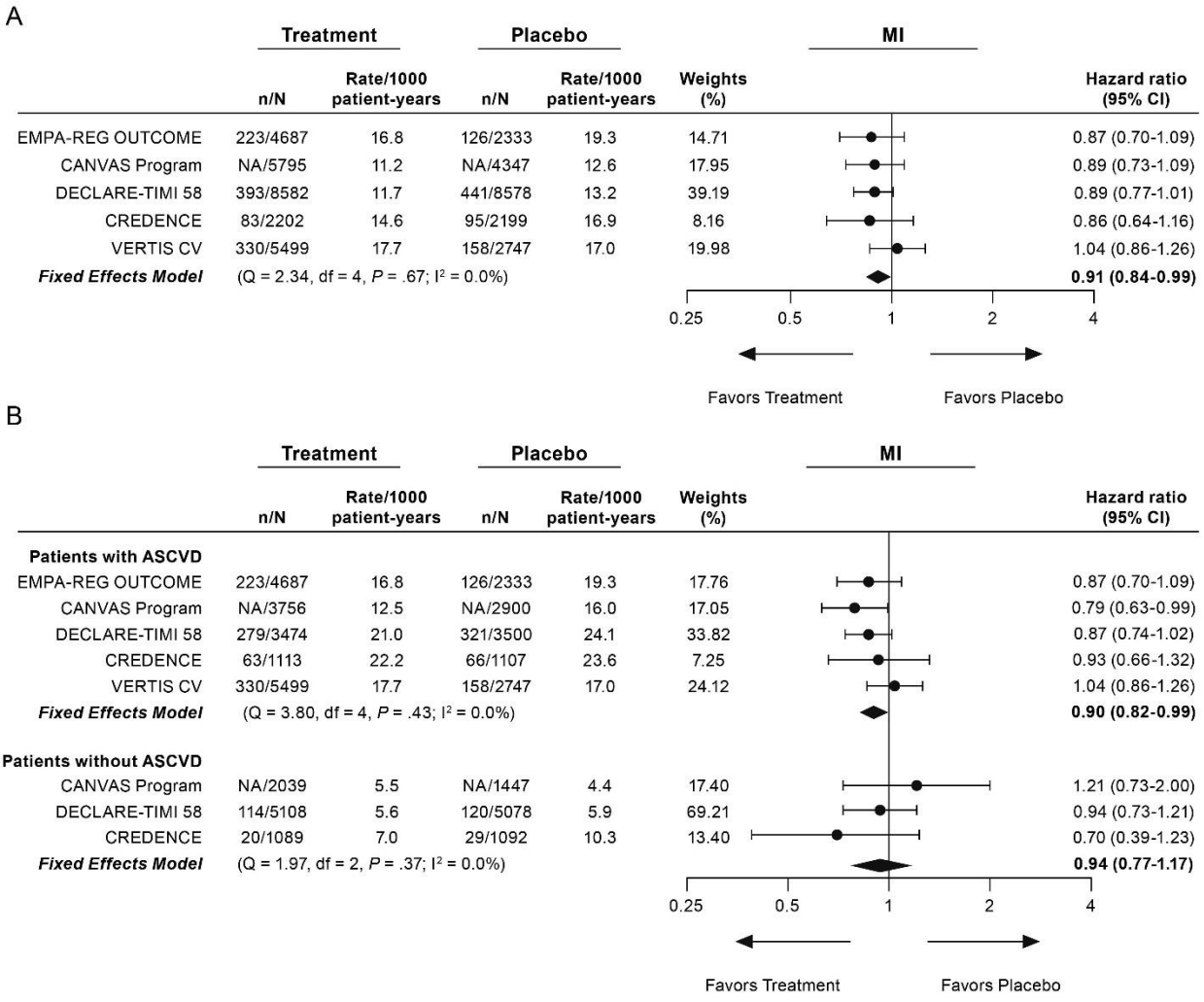
eFigure 7. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to First Event of Myocardial Infarction (MI)

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



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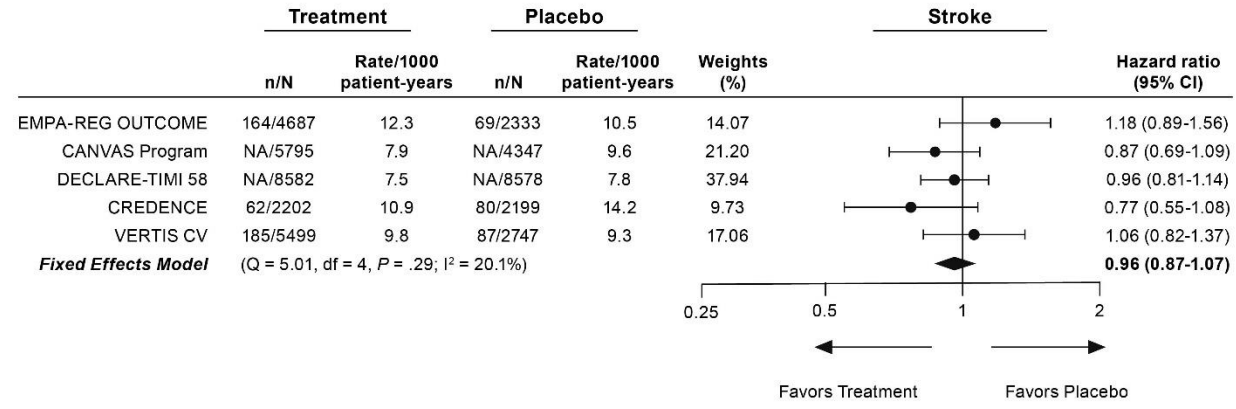
eFigure 8. Meta-Analysis of Effects of SGLT2 Inhibitors on Time to First Event of Stroke

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

A



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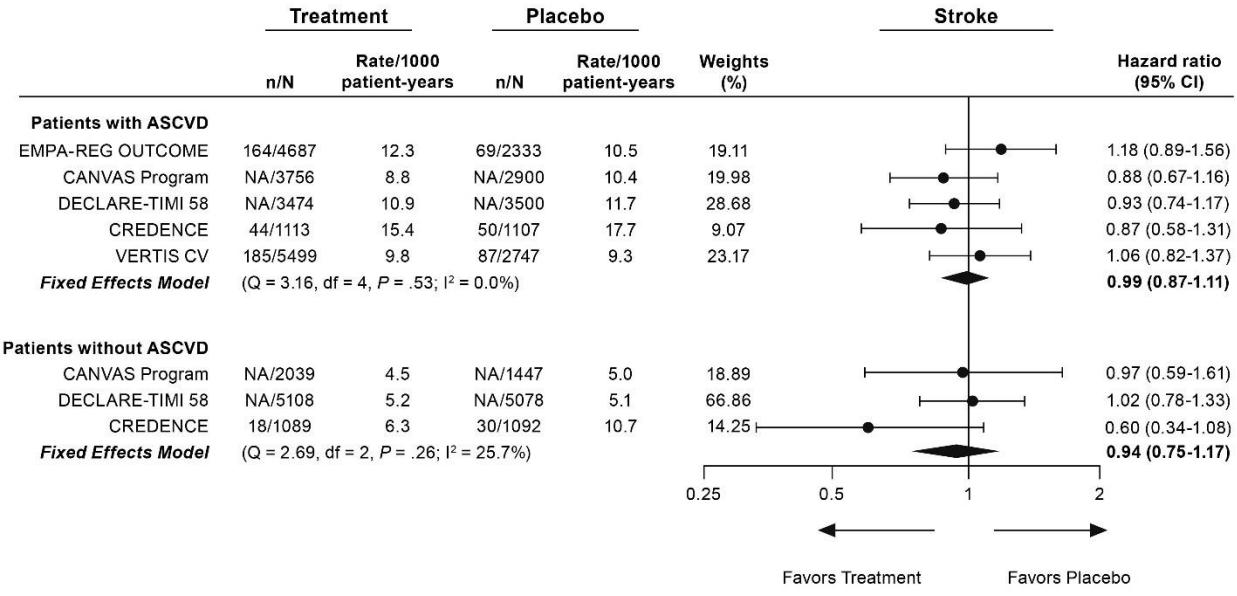

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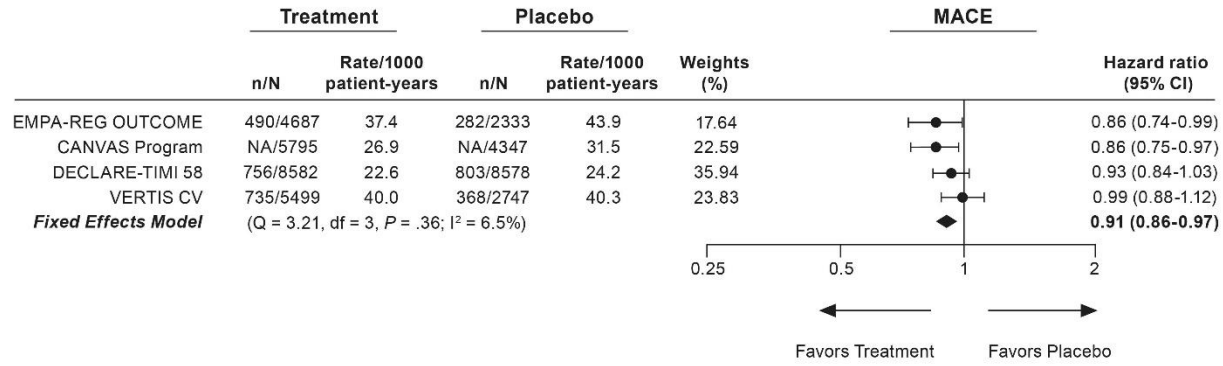
eFigure 9. Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of the Major Adverse Cardiovascular Event (MACE) Composite Without Inclusion of the CREDENCE Trial

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

A



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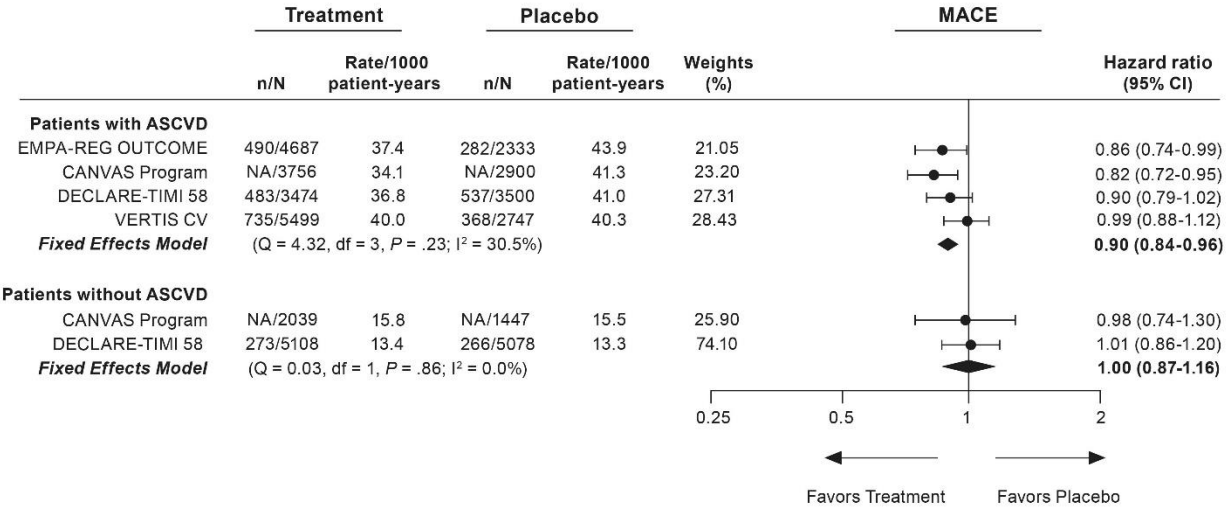

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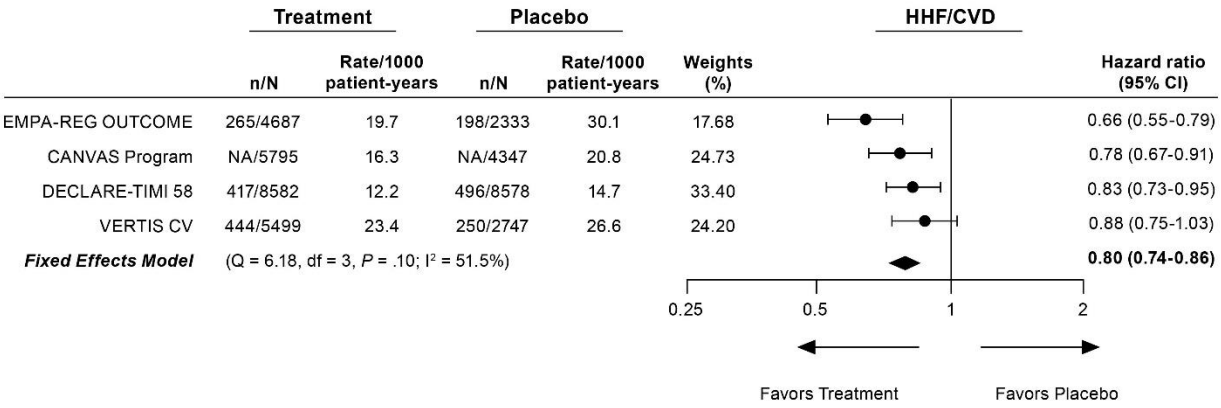
eFigure 10. Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Hospitalization for Heart Failure (HHF) or Cardiovascular Death (CVD) Without Inclusion of the CREDENCE Trial



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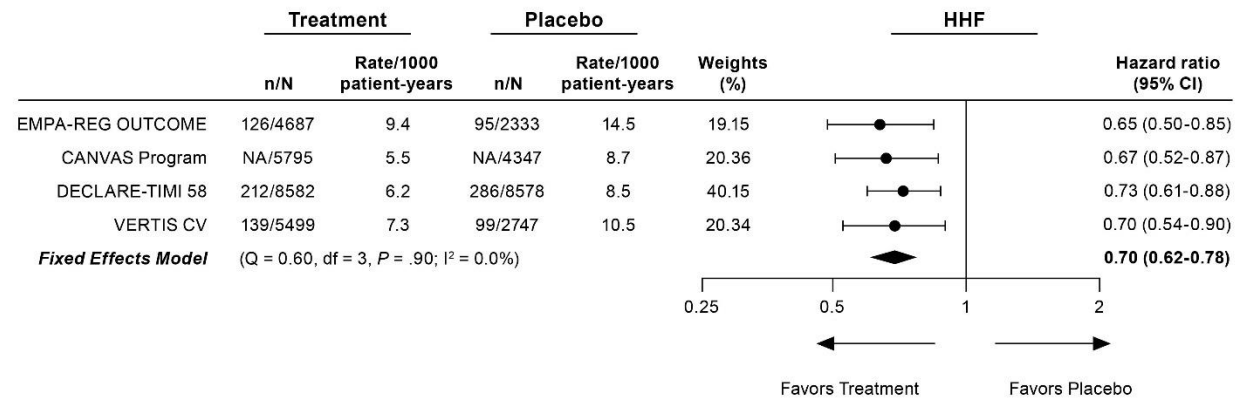
eFigure 11. Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Hospitalization for Heart Failure (HHF) Without Inclusion of the CREDENCE Trial

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

A



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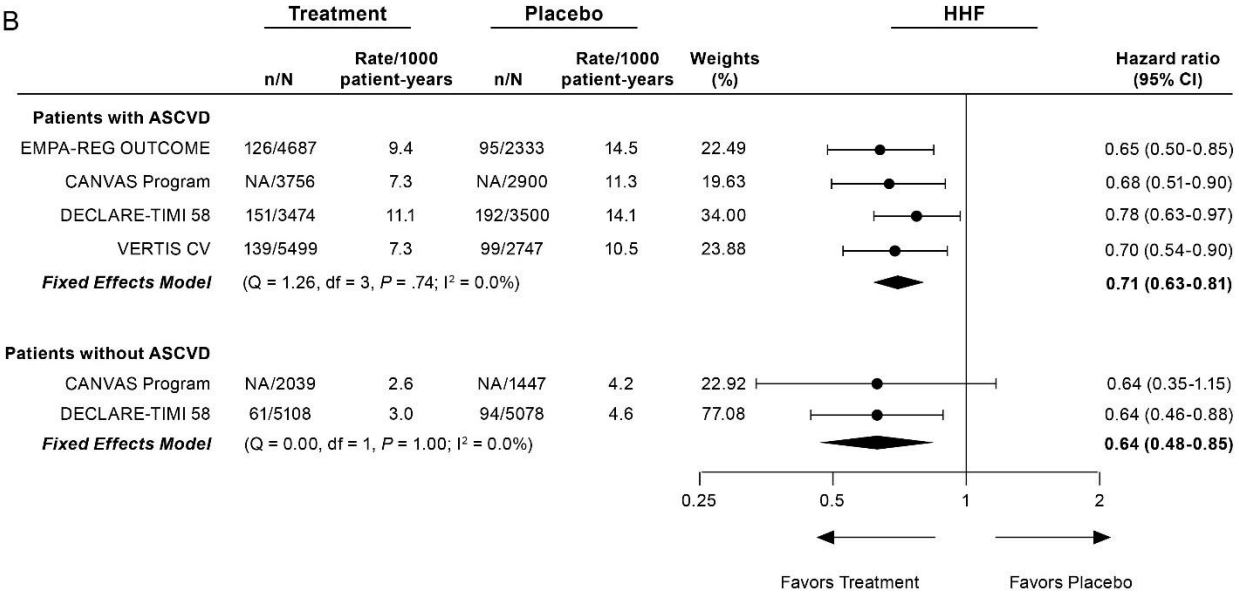

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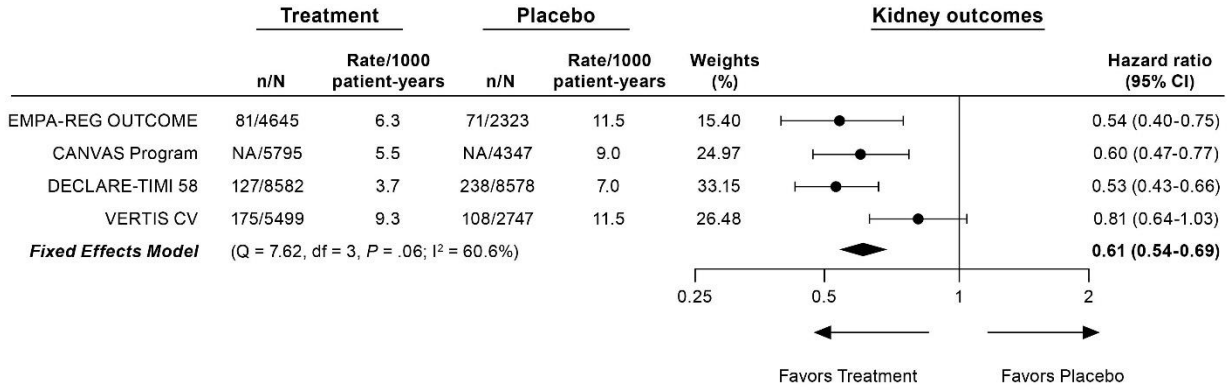
eFigure 12. Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Kidney-Related Outcomes Without Inclusion of the CREDENCE Trial



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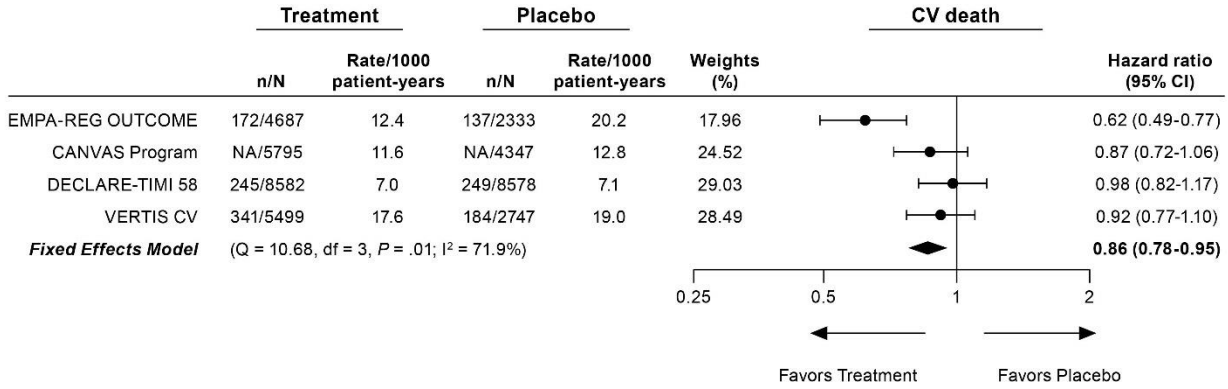
eFigure 13. Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to Cardiovascular (CV) Death Without Inclusion of the CREDENCE Trial



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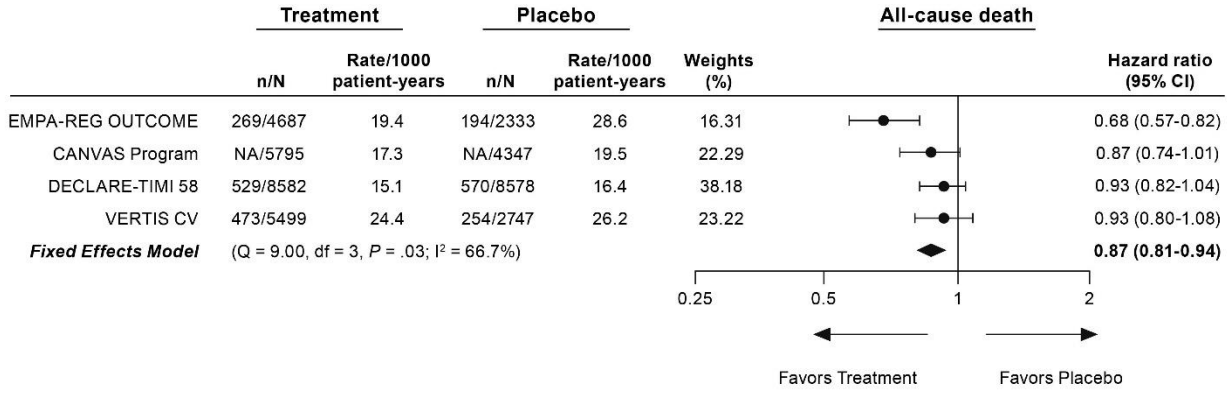

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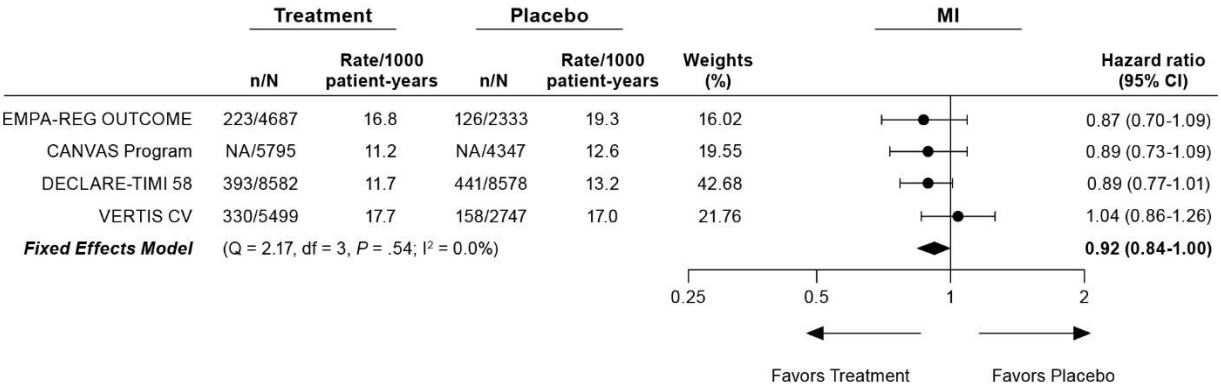

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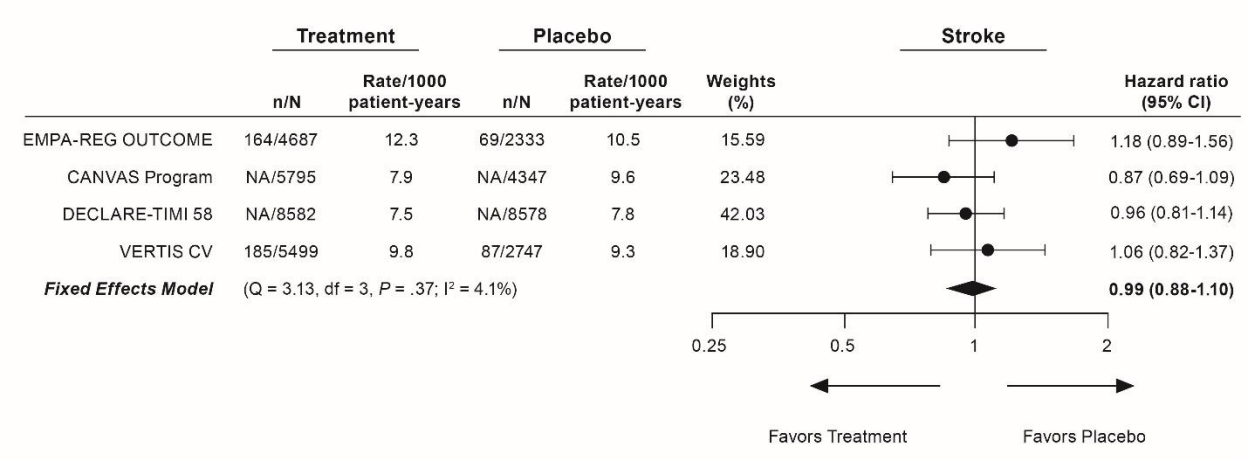
eFigure 16. Sensitivity Analysis of the Effects of SGLT2 Inhibitors on Time to First Event of Stroke Without Inclusion of the CREDENCE Trial



NA, not available