

SUPPLEMENTARY DATA

**Supplementary Table S1.** Total participant-years of exposure by drug and by region in the placebo arm.

	All	Western Europe	Eastern Europe	North America	Latin America	Asia Pacific
<b>All SGLT2i</b>	732	250	98	315	30	39
<b>dapagliflozin only</b>	314	165	54	43	22	31
<b>canagliflozin only</b>	211	12	3	196	0	0.3
<b>empagliflozin only</b>	101	32	35	25	4.6	4.6
<b>Multiple*</b>	106	41	7	51	3.9	3.4

Calculated as time from first known SGLT2i use to last known SGLT2i use, regardless of gaps. ACM, all-cause mortality; SGLT2i, sodium-glucose co-transporter-2 inhibitor. \*Multiple includes subjects who took more than one SGLT2i over the course of the trial.

**Supplementary Table S2.** Calendar year of SGLT2i initiation by drug in the placebo arm.

	2012	2013	2014	2015	2016	2017*	No time info
<b>All SGLT2i</b>	1	25	125	267	322	43	3
<b>Dapagliflozin</b>	1	15	61	143	145	19	1
<b>Canagliflozin</b>	0	7	60	92	41	10	1
<b>Empagliflozin</b>	0	2	14	60	157	21	2

Values are numbers of subjects. SGLT2i, sodium-glucose co-transporter-2 inhibitor. \*EXSCEL ended in April 2017

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**Supplementary Table S3.** Events, follow-up duration, incidence rates, and hazard ratios for SGLT2i use and dapagliflozin use on all MACE in propensity-matched cohorts, using Poisson multiple regression.

Study design		n	Events	Participant-years of follow-up	Incidence rate (events/100 participant-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio <sup>†</sup> (95% CI)	Nominal p-values (adjusted)
<b>Propensity-matched</b>	No SGLT2i	709	73	1178	6.20			
	SGLT2i	709	36	947	3.80	0.62 (0.39-0.98)	0.64 (0.41-1.02)	0.06
	No dapagliflozin*	353	30	575	5.21			
	Dapagliflozin	353	14	461	3.04	0.58 (0.30-1.15)	0.58 (0.29-1.15)	0.12
<b>Full population</b>	No SGLT2i	6595	1107	22,598	4.90			
	SGLT2i	783	41	1030	3.98	0.83 (0.57-1.20)	0.96 (0.66-1.40)	0.85
	Dapagliflozin	383	18	500	3.60	0.75 (0.43-1.31)	0.92 (0.53-1.61)	0.77
<b>Time-dependent SGLT2i use</b>	No SGLT2i	6595	1135	24,583	4.62			
	SGLT2i	783	41	1030	3.98	0.86 (0.60-1.24)	0.90 (0.62-1.30)	0.57
	Dapagliflozin	383	18	500	3.60	0.77 (0.44-1.34)	0.88 (0.50-1.52)	0.64

MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose co-transporter-2 inhibitor. \*Cohort of non-SGLT2i users matched to dapagliflozin users. <sup>†</sup>Adjustment for: duration of diabetes, age, sex, history of CVD, prior heart failure, prior microalbuminuria, prior macroalbuminuria, baseline eGFR, and baseline HbA<sub>1c</sub>.

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**Supplementary Table S4.** Break-down of events and incidence rates for MACE and ACM in the propensity-matched SGLT2i cohort, by drug.

<b>Time-to-first adjudicated event</b>	<b>SGLT2i used</b>	<b>n</b>	<b>Events</b>	<b>Participant-years of follow-up</b>	<b>Incidence rate (events/ 100 participant-years)</b>
<b>MACE</b>	Any SGLT2i	709	28	822	3.41
	Dapagliflozin	353	12	435	2.76
	Empagliflozin	224	6	183	3.27
	Canagliflozin	189	10	304	3.29
<b>ACM</b>	Any SGLT2i	709	14	871	1.61
	Dapagliflozin	353	8	459	1.74
	Empagliflozin	224	1	193	0.52
	Canagliflozin	189	6	320	1.88

Note that subjects taking more than one SGLT2i during follow-up are included in the row for each SGLT2i taken. 27 subjects took dapagliflozin and empagliflozin, 5 received dapagliflozin and canagliflozin, 23 received empagliflozin and canagliflozin, and one has recorded use of all three SGLT2i. No MACE events and one ACM occurred in subjects receiving more than one SGLT2i during follow-up in the propensity-matched SGLT2i cohort.

ACM, all-cause mortality; MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

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**Supplementary Table S5.** Events, follow-up duration, incidence rates, and hazard ratios for SGLT2i use on first MACE in participants with or without prior cardiovascular disease in the propensity-matched cohorts.

	Propensity-matched cohort	n	Events	Participant-years of follow-up	Incidence rate (events/100 participant-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio <sup>#</sup> (95% CI)	Nominal p-values (adjusted)
<b>No prior CV disease</b>	No SGLT2i	239	11	402	2.74			
	SGLT2i	247	2	312	0.64	0.23 (0.05-1.05)	0.11 (0.02-0.74)	0.02
	No dapagliflozin <sup>*</sup>	133	4	226	1.77			
	Dapagliflozin	133	0	164	-	- <sup>†</sup>	- <sup>†</sup>	- <sup>†</sup>
<b>Prior CV disease</b>	No SGLT2i	470	33	588	5.62			
	SGLT2i	462	26	510	5.09	0.96 (0.57-1.63)	0.95 (0.56-1.62)	0.86
	No dapagliflozin <sup>*</sup>	220	18	259	6.96			
	Dapagliflozin	220	11	245	4.50	0.67 (0.31-1.43)	0.69 (0.32-1.49)	0.34

CV, cardiovascular; MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose co-transporter-2 inhibitor. <sup>\*</sup>Cohort of non-SGLT2i users matched to dapagliflozin users. <sup>†</sup>Hazard ratio cannot be calculated due to lack of events in dapagliflozin arm. P-value for interaction between prior CVD status and SGLT2i use: unadjusted analysis: 0.09, adjusted analysis: 0.07. <sup>#</sup>Adjustment for: duration of diabetes, age, sex, history of CVD, prior heart failure, prior microalbuminuria, prior macroalbuminuria, baseline eGFR, and baseline HbA<sub>1c</sub>.

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**Supplementary Table S6.** Events, follow-up duration, incidence rates, and hazard ratios for SGLT2i use on ACM in participants with or without prior cardiovascular disease in the propensity-matched cohorts.

	Propensity-matched cohort	n	Events	Participant-years of follow-up	Incidence rate (events/100 participant-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio <sup>#</sup> (95% CI)	Nominal p-values (adjusted)
<b>No prior CV disease</b>	No SGLT2i	239	12	429	2.80			
	SGLT2i	247	1	319	0.31	0.12 (0.01-0.91)	0.10 (0.01-0.80)	0.03
	No dapagliflozin <sup>*</sup>	133	2	240	0.83			
	Dapagliflozin	133	0	167	-	<sup>†</sup>	<sup>†</sup>	<sup>†</sup>
<b>Prior CV disease</b>	No SGLT2i	470	25	679	3.68			
	SGLT2i	462	13	553	2.35	0.64 (0.32-1.25)	0.67 (0.34-1.33)	0.26
	No dapagliflozin <sup>*</sup>	220	11	298	3.69			
	Dapagliflozin	220	7	265	2.65	0.71 (0.27-1.90)	0.80 (0.29-2.19)	0.66

ACM, all-cause mortality; CV, cardiovascular; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

<sup>\*</sup>Cohort of non-SGLT2i users matched to dapagliflozin users. <sup>†</sup>Hazard ratio cannot be calculated due to lack of events in dapagliflozin arm. P-value for interaction between prior CVD status and SGLT2i use: unadjusted analysis: 0.11, adjusted analysis: 0.07.<sup>#</sup>Adjustment for: duration of diabetes, age, sex, history of CVD, prior heart failure, prior microalbuminuria, prior macroalbuminuria, baseline eGFR, and baseline HbA<sub>1c</sub>.

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**Supplementary Table S7.** Events, follow-up duration, incidence rates, and hazard ratios for SGLT2i use and dapagliflozin use on exploratory outcomes in the propensity-matched cohorts.

Outcome	Propensity-matched cohort	n	Events	Participant-years of follow-up	Incidence rate (events/100 participant-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio <sup>#</sup> (95% CI)	Nominal p-values (adjusted)
<b>CV death</b>	No SGLT2i	709	17	1108	1.53			
	SGLT2i	709	10	871	1.15	0.73 (0.33-1.60)	0.78 (0.35-1.72)	0.53
	No dapagliflozin*	353	13	538	2.42			
	Dapagliflozin	353	6	432	1.39	0.57 (0.21-1.53)	0.59 (0.21-1.60)	0.30
<b>Non-fatal myocardial infarction</b>	No SGLT2i	709	26	1014	2.56			
	SGLT2i	709	16	831	1.92	0.81 (0.42-1.53)	0.81 (0.43-1.55)	0.81
	No dapagliflozin*	353	13	488	2.66			
	Dapagliflozin	353	5	415	1.20	0.46 (0.16-1.31)	0.40 (0.14-1.16)	0.09
<b>Non-fatal stroke</b>	No SGLT2i	709	10	1045	0.96			
	SGLT2i	709	8	852	0.94	0.91 (0.35-2.33)	1.03 (0.40-2.66)	0.96
	No dapagliflozin*	353	1	510	0.20			
	Dapagliflozin	353	3	418	0.72	– <sup>†</sup>	– <sup>†</sup>	– <sup>†</sup>
<b>Hospitalization for heart failure</b>	No SGLT2i	709	15	1043	1.44			
	SGLT2i	709	7	851	0.82	0.58 (0.23-1.44)	0.63 (0.25-1.58)	0.33
	No dapagliflozin*	353	5	508	0.98			
	Dapagliflozin	353	1	422	0.24	0.29 (0.03-2.64)	0.21 (0.02-2.14)	0.19
<b>PAD/PVD</b>	No SGLT2i	709	17	1083	1.57			
	SGLT2i	709	14	893	1.57	0.91 (0.44-1.85)	0.89 (0.44-1.83)	0.76
	No dapagliflozin*	353	5	532	1.43			

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	Dapagliflozin	353	9	425	2.11	1.93 (0.64-5.79)	1.86 (0.61-5.70)	0.28
<b>Diabetic eye complications<sup>‡</sup></b>	No SGLT2i	709	12	1085	1.11			
	SGLT2i	709	13	889	1.46	1.28 (0.57-2.87)	1.30 (0.58-2.92)	0.53
	No dapagliflozin <sup>*</sup>	353	7	512	1.37			
	Dapagliflozin	353	5	433	1.15	0.82 (0.26-2.64)	0.88 (0.27-2.89)	0.83
<b>Amputation (traumatic or non-traumatic)</b>	No SGLT2i	709	6	1118	0.54			
	SGLT2i	709	6	925	0.65	1.12 (0.36-3.50)	1.16 (0.37-3.70)	0.80
	No dapagliflozin <sup>*</sup>	353	1	545	0.18			
	Dapagliflozin	353	4	446	0.90	- <sup>†</sup>	- <sup>†</sup>	- <sup>†</sup>

CV: cardiovascular; PAD: peripheral artery disease; PVD: peripheral vascular disease; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UACR: urinary albumin-to-creatinine ratio. <sup>\*</sup>Cohort of non-SGLT2i users matched to dapagliflozin users. <sup>†</sup>Hazard ratios and p-values not reported in cases with five or fewer total events. <sup>‡</sup>Includes retinopathy, blindness due to diabetes, and other diabetic eye disease. <sup>#</sup>Adjustment for: duration of diabetes, age, sex, history of CVD, prior heart failure, prior microalbuminuria, prior macroalbuminuria, baseline eGFR, and baseline HbA<sub>1c</sub>.

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**Supplementary Table S8.** Events, follow-up duration, incidence rates, and hazard ratios for SGLT2i use on first MACE in the full placebo arm population.

Study design		n	Events	Participant-years of follow-up	Incidence rate (events/100 participant-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio <sup>†</sup> (95% CI)	Nominal p-values (adjusted)
<b>Full population</b>	No SGLT2i	6595	847	19,760	4.29			
	SGLT2i*	783	31	895	3.46	0.82 (0.57-1.18)	0.95 (0.66-1.38)	0.80
	Dapagliflozin	384	13	441	2.94	0.72 (0.42-1.26)	0.89 (0.51-1.55)	0.68
<b>Time-dependent SGLT2i use</b>	No SGLT2i	6595	873	21,709	4.02			
	SGLT2i	783	31	895	3.46	0.85 (0.59-1.22)	0.88 (0.61-1.27)	0.48
	Dapagliflozin	384	13	441	2.94	0.72 (0.42-1.26)	0.82 (0.47-1.44)	0.50

Median follow-up time for all-cause mortality was 3.2 years for No SGLT2i use and 1.1 years for both SGLT2i use and dapagliflozin use. MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose co-transporter-2 inhibitor. \*79 of 783 SGLT2i users had first MACE event before SGLT2i initiation, and thus contributed no events or follow-up time to the SGLT2i group. †Adjustment for: duration of diabetes, age, sex, history of CVD, prior heart failure, prior microalbuminuria, prior macroalbuminuria, baseline eGFR, and baseline HbA<sub>1c</sub>.

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**Supplementary Table S9.** Events, follow-up duration, incidence rates, and hazard ratios for SGLT2i use on ACM in the full placebo arm population.

Study design		n	Events	Participant-years of follow-up	Incidence rate (events/100 participant-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio <sup>†</sup> (95% CI)	Nomial p-values (adjusted)
Full population	No SGLT2i	6595	568	21,897	2.59			
	SGLT2i	783	16	948	1.69	0.85 (0.51-1.40)	0.98 (0.58-1.65)	0.95
	Dapagliflozin	384	8	467	1.71	0.90 (0.44-1.81)	1.11 (0.55-2.25)	0.76
Time-dependent SGLT2i use	No SGLT2i	6595	568	23,926	2.38			
	SGLT2i	783	16	948	1.69	0.58 (0.35-0.95)	0.62 (0.37-1.04)	0.07
	Dapagliflozin	384	8	467	1.71	0.61 (0.30-1.24)	0.73 (0.36-1.49)	0.39

ACM, all-cause mortality; SGLT2i, sodium-glucose co-transporter-2 inhibitor. <sup>†</sup> Adjustment for: duration of diabetes, age, sex, history of CVD, prior heart failure, prior microalbuminuria, prior macroalbuminuria, baseline eGFR, and baseline HbA<sub>1c</sub>.

**Supplementary Table S10.** MMRM-estimated slope in subjects in the propensity-matched SGLT2i cohort, by drug.

SGLT2i used	eGFR slope (standard error)
Any SGLT2i	+0.87 (0.37)
Canagliflozin	-0.03 (0.55)
Dapagliflozin	+1.17 (0.53)
Empagliflozin	+2.78 (0.72)

eGFR, estimated glomerular filtration rate; MMRM, mixed-model repeated measurement.

**Supplementary Table S11.** Results of MMRM analysis for eGFR slope in the full placebo arm population.

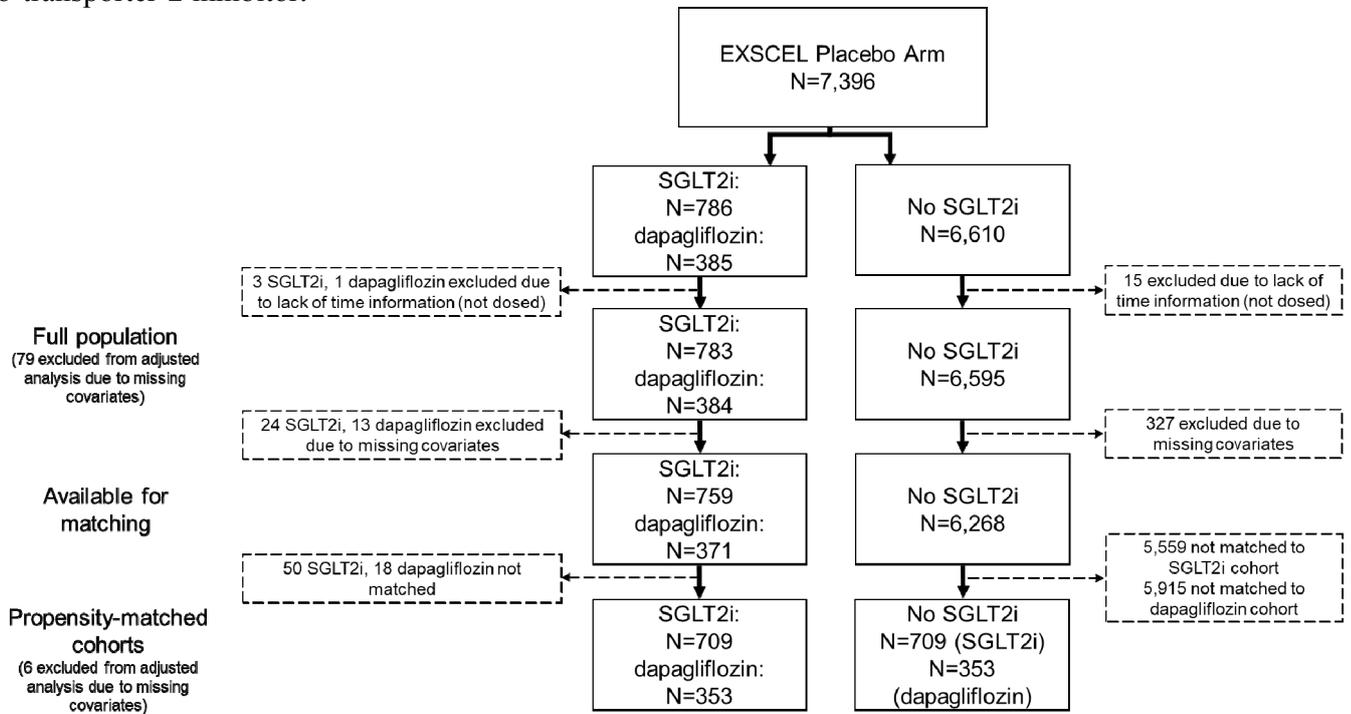
Propensity-matched cohort	eGFR slope (standard error)	Treatment effect (95% CI)	p-value
No SGLT2i	-0.89 (0.05)		
SGLT2i	+0.14 (0.16)	+1.03 (0.68-1.38)	<0.001
No dapagliflozin	-0.90 (0.05)		
Dapagliflozin	+0.38 (0.25)	+1.28 (0.76-1.80)	<0.001

eGFR, estimated glomerular filtration rate; MMRM, mixed-model repeated measurement.

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**Supplementary Figure S1.** Subject flow chart for analysis.

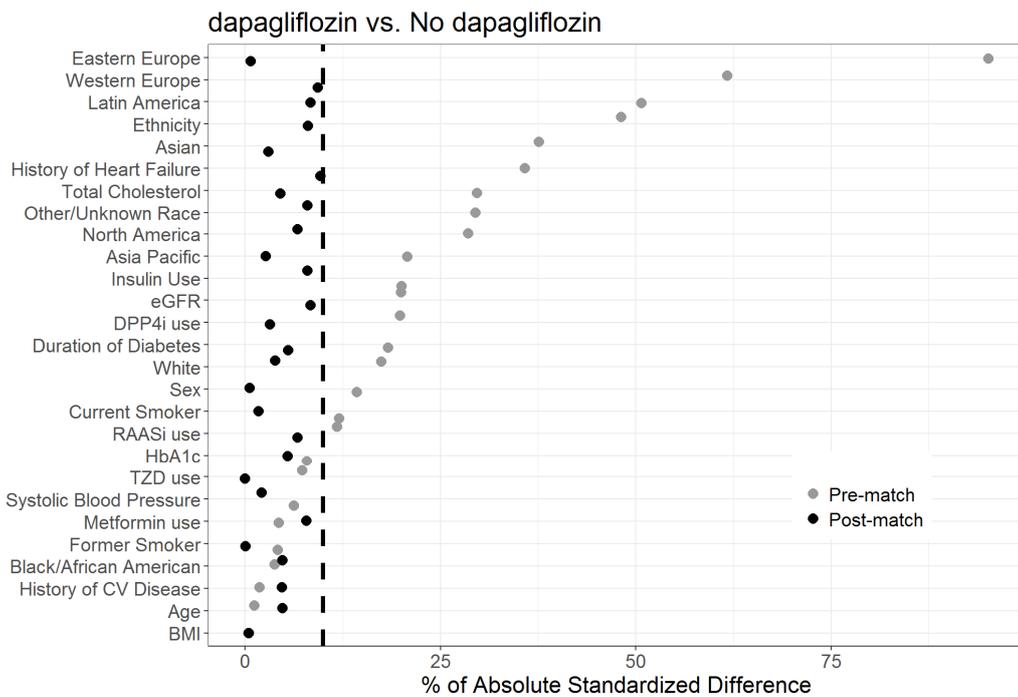
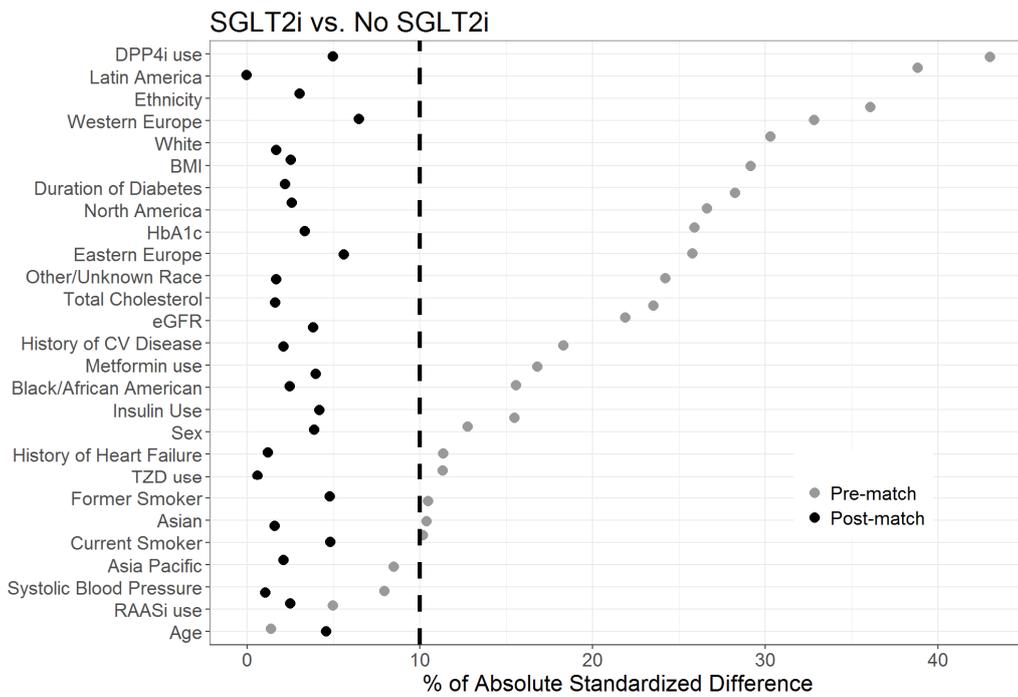
Subjects were excluded from the full population analysis if they were randomized but not dosed. Subjects were excluded from matching if covariates required for matching were missing (no available measurements prior to time of SGLT2i initiation/matching). A large number of non-SGLT2i users were excluded from the propensity-matched cohorts due to the 1:1 matching ratio. SGLT2i, sodium-glucose co-transporter-2 inhibitor.



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**Supplementary Figure S2.** Balance of confounders before and after propensity matching for SGLT2i use (top) and dapagliflozin use (bottom).

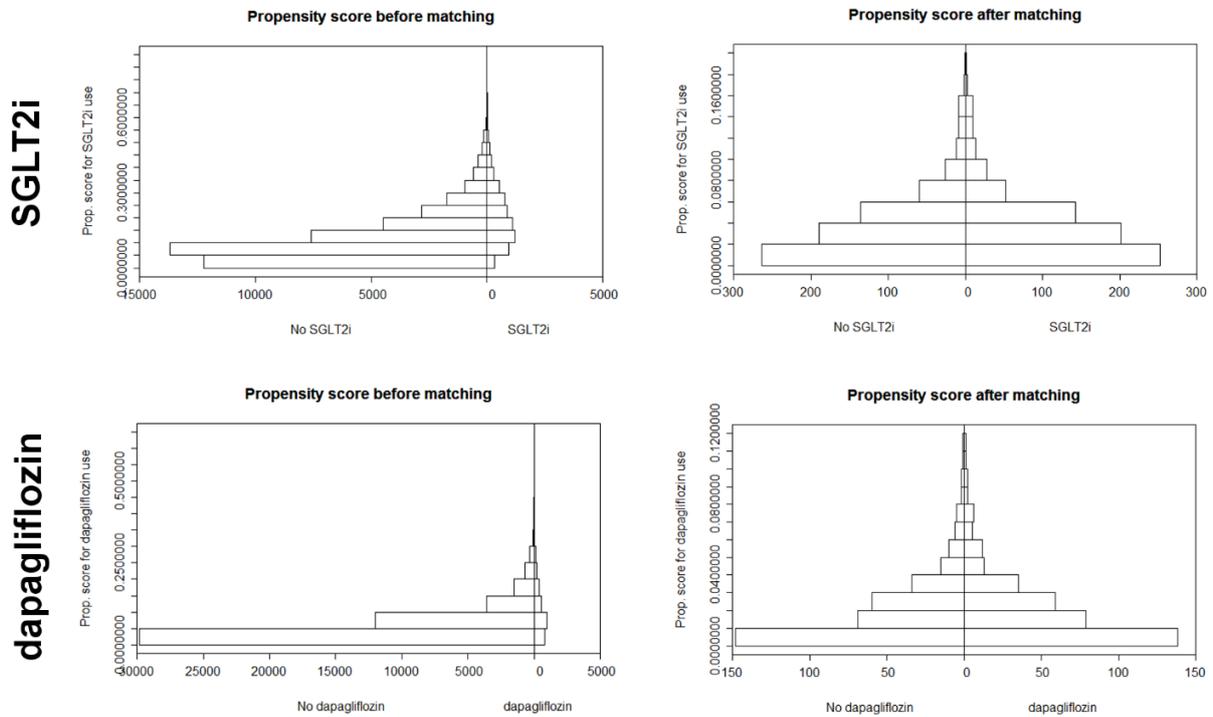
Shown as absolute value of standardized difference. A standardized difference of less than 10% (dashed line) was required for all covariates to accept match. Gray = before matching; black = after matching. CV, cardiovascular; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose co-transporter-2 inhibitor; TZD, thiazolidinedione.



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**Supplementary Figure S3.** Propensity score distributions before (left) and after (right) matching for SGLT2i (top) and dapagliflozin (bottom).

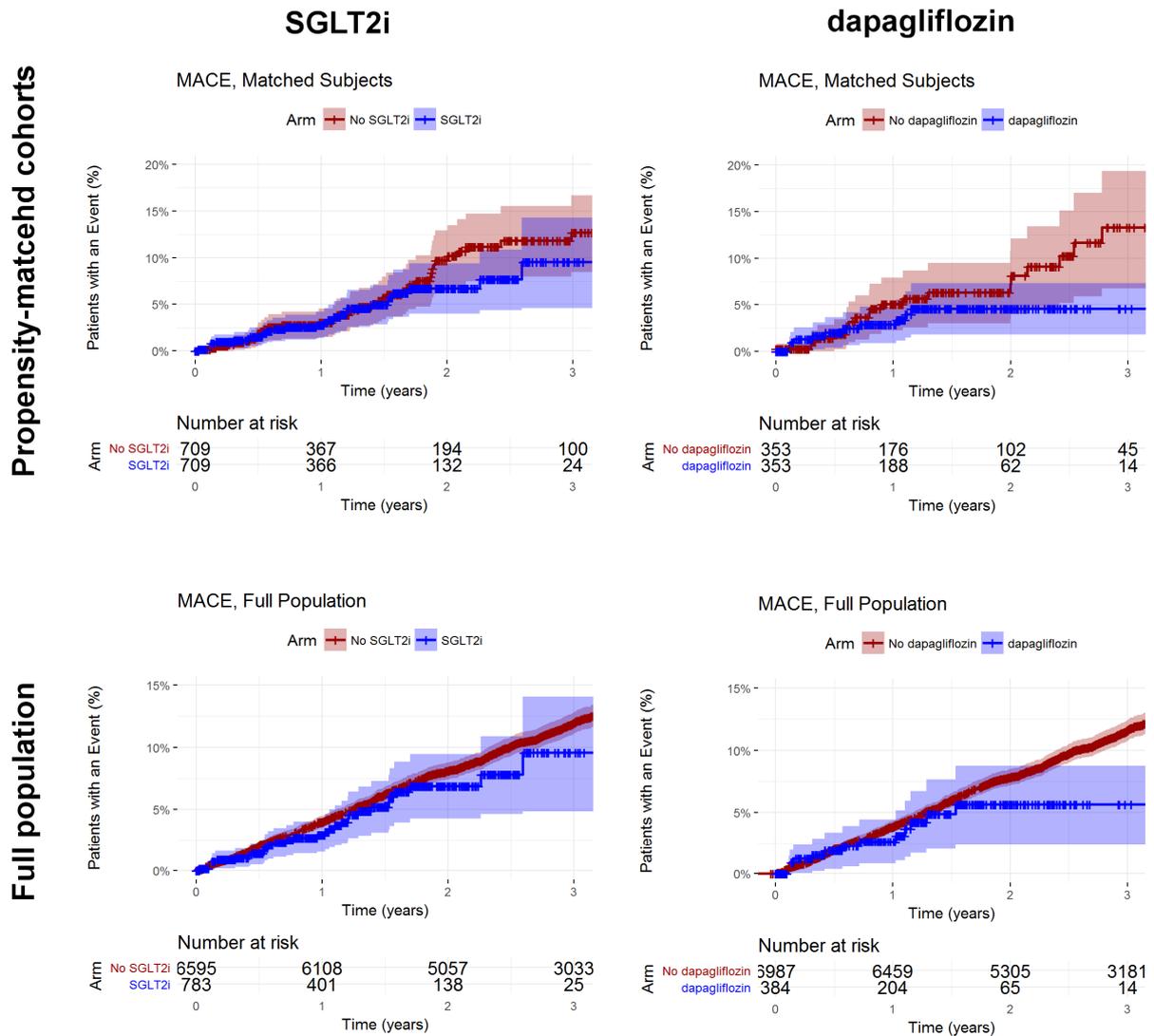
In each plot, controls are on the left and SGLT2i/dapagliflozin users on the right. After matching, the p-values in a chi-squared omnibus test for balance were 0.994 and 0.972 for SGLT2i and dapagliflozin, respectively. Subjects with missing covariates required for matching are excluded. Prop., propensity; SGLT2i, sodium-glucose co-transporter-2 inhibitor.



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**Supplementary Figure S4.** Kaplan-Meier curves for MACE.

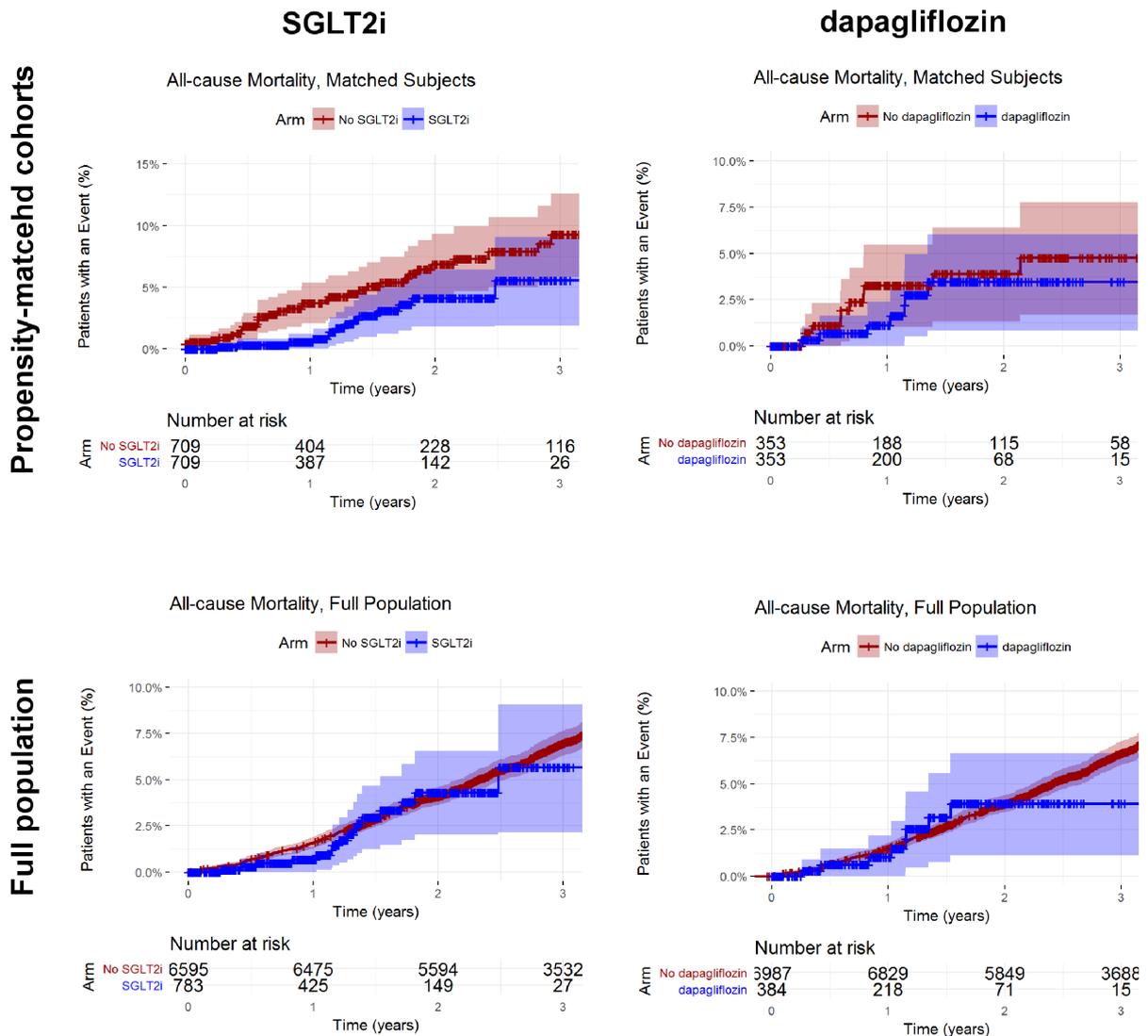
Shown as percentage of subjects with an event. Propensity-matched cohorts: top; full population: bottom; SGLT2i: left; dapagliflozin: right. Control: red; treatment: blue. Subjects at risk at each year are shown in the risk tables below. Crosses indicate events or censoring. Note difference in control arm event curves for cohorts matched to SGLT2i use and dapagliflozin use. MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose co-transporter-2 inhibitor.



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**Supplementary Figure S5.** Kaplan-Meier curves for ACM.

Shown as percentage of subjects with an event. Propensity-matched cohorts: top; full population: bottom; SGLT2i: left; dapagliflozin: right. Control: red; treatment: blue. Subjects at risk at each year are shown in the risk tables below. Crosses indicate events or censoring. Note difference in control arm event curves for cohorts matched to SGLT2i use and dapagliflozin use, and median SGLT2i treatment duration of 9.2 months. Median follow-up time in the full population, starting from trial baseline for controls and SGLT2i initiation for SGLT2i users, was 3.2 years for non-SGLT2i users and non-dapagliflozin users and 1.1 years for SGLT2i users and dapagliflozin users. ACM, all-cause mortality; SGLT2i, sodium-glucose co-transporter-2 inhibitor.



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**Supplementary Figure S6.** Geometric mean ( $\pm$  standard error) eGFR in full population for SGLT2i use (top) and dapagliflozin use (bottom).

Time measured from beginning of SGLT2i/dapagliflozin use for SGLT2i users and from trial baseline for controls. Note median SGLT2i treatment duration of 9.2 months. eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

