Comparative Effectiveness of the SGLT2 Inhibitor Empagliflozin vs. Other Antihyperglycemics on Risk of Kidney Outcomes

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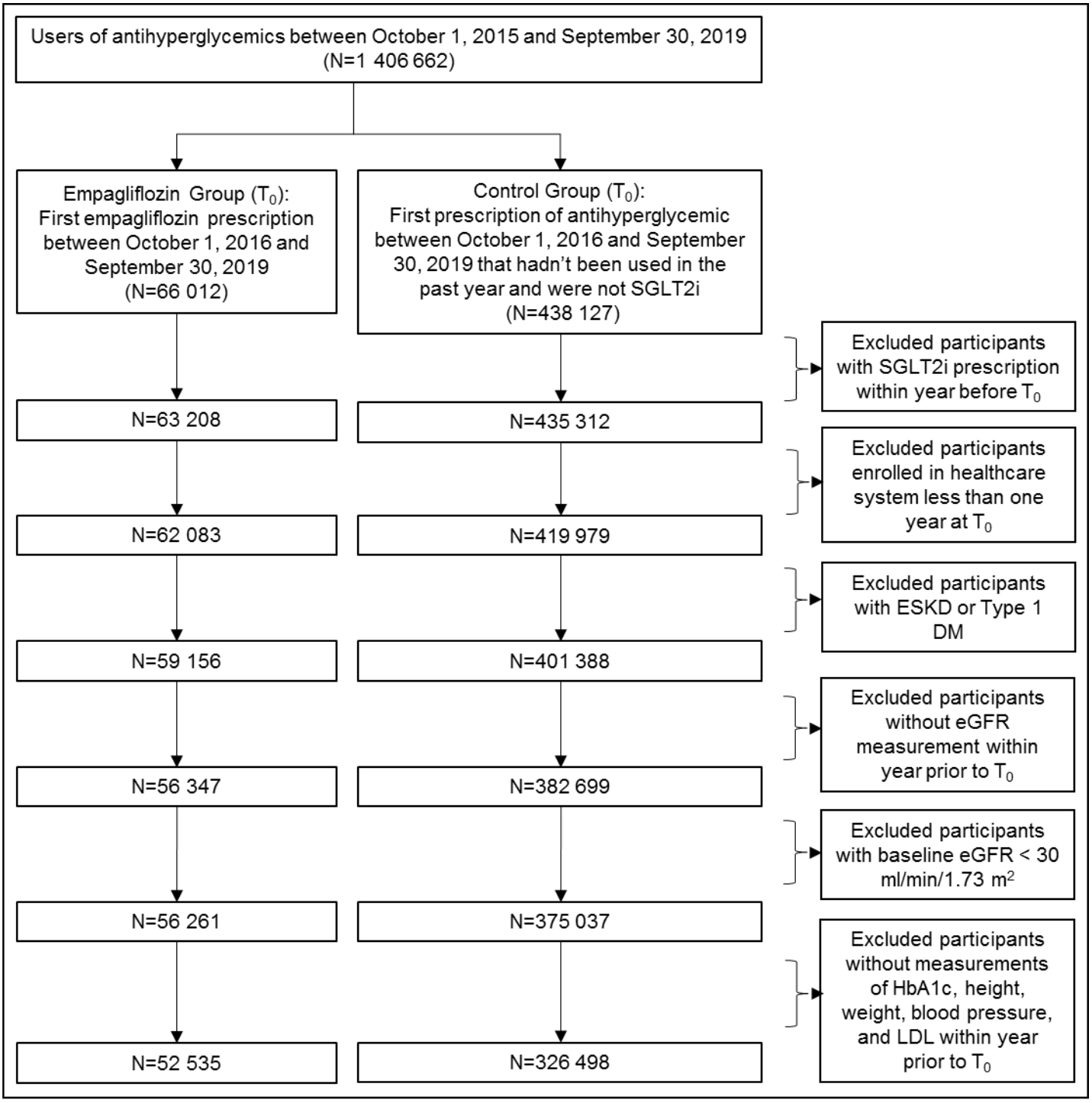
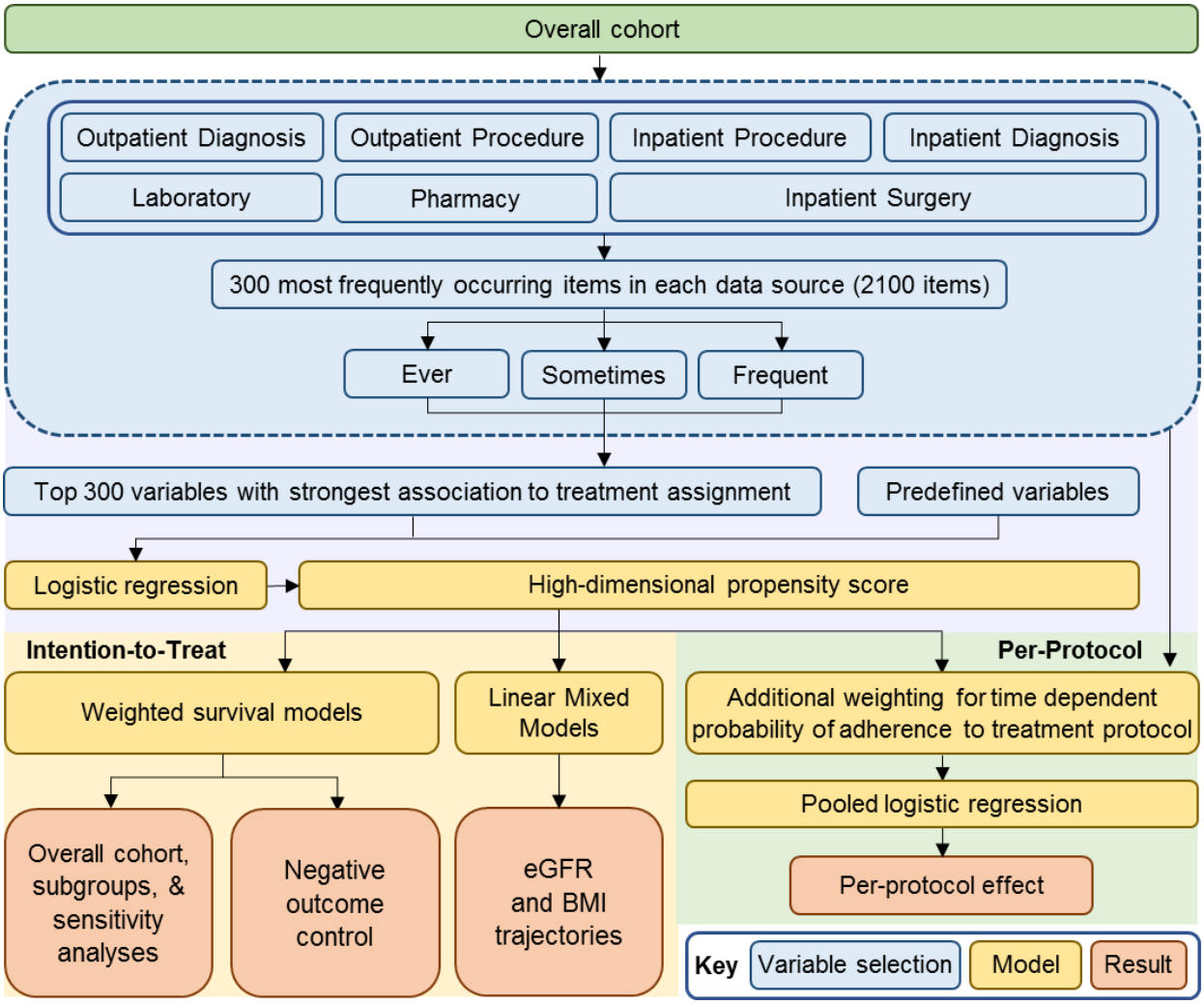
Supplemental Figures

Supplemental Figure 1a: Flowchart for cohort construction



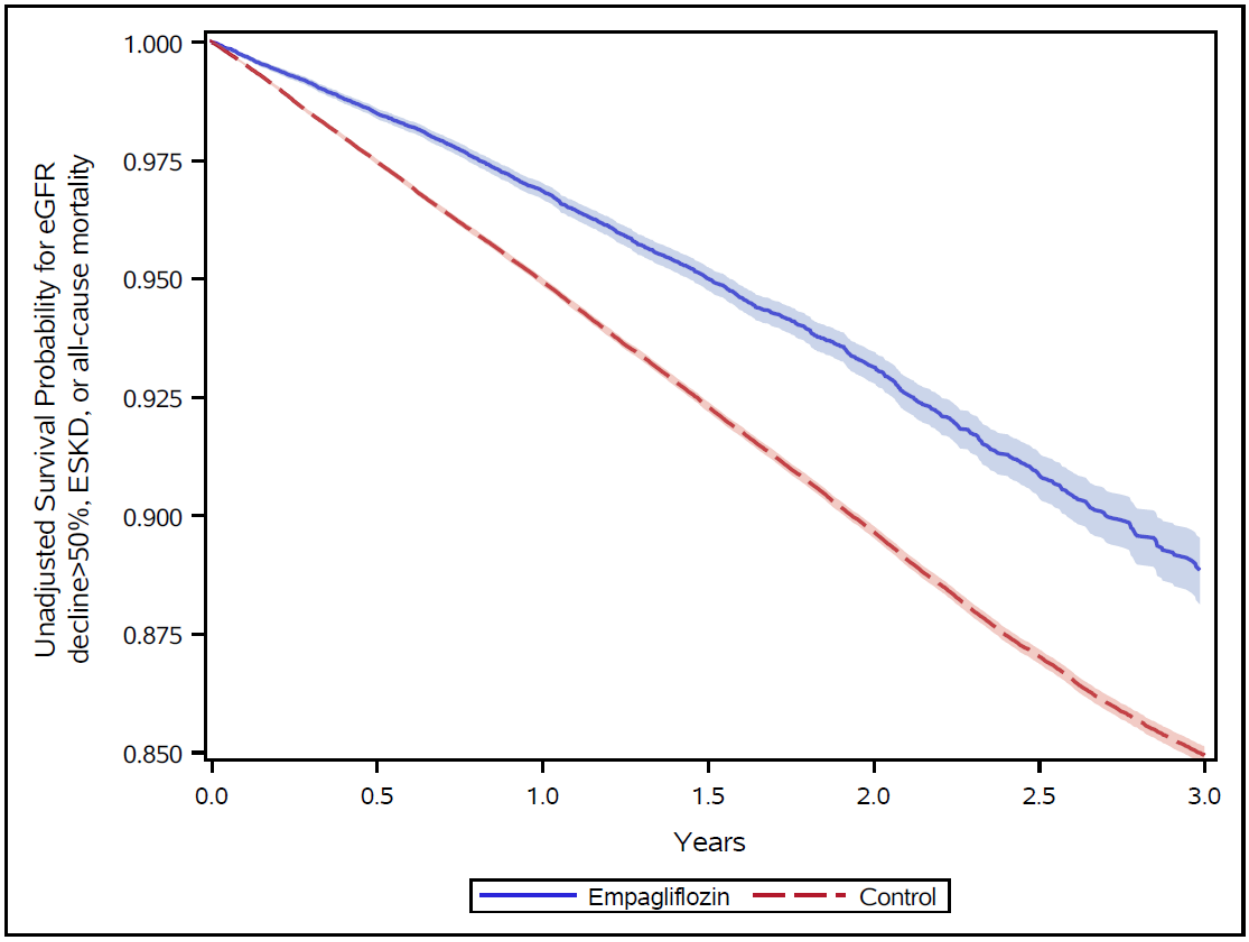
SGLT2i=sodium-glucose co-transporter-2 inhibitor. T_0= time zero. ESKD=end stage kidney disease. DM=diabetes mellitus. eGFR= estimated glomerular filtration rate. HbA1c=glycated hemoglobin. LDL=low-density lipoprotein.

Supplemental Figure 1b: Flowchart for analytic approach



eGFR=estimated glomerular filtration rate. BMI=body mass index.

Supplemental Figure 2: Unadjusted survival probability for major adverse kidney events (MAKE) of estimated glomerular filtration rate (eGFR) decline >50%, end-stage kidney disease (ESKD), or all-cause mortality in the empagliflozin group (blue) and the control group of other non-SGLT2i antihyperglycemics (red) in the original cohort



eGFR=estimated glomerular filtration rate. ESKD=end-stage kidney disease.

Supplemental Tables

Supplemental Table 1. Treatment medications

Medication class	**Medication names**
SGLT2i	Empagliflozin
Biguanide	Metformin
Insulin	Insulin
Sulfonylureas	Glyburide, Glipizide, Glimepiride
DPP4	Alogliptin, Sitagliptin, Saxagliptin, Linagliptin
GLP1	Liraglutide, Exenatide, Semaglutide, Dulaglutide, Lixisenatide,
Thiazolidinediones	Pioglitazone, Rosiglitazone
Alpha-glucosidase inhibitors	Miglitol, Acarbose
Meglitinides	Nateglinide, Repaglinide
Amylin analogues	Pramlintide

SGLT2i=sodium-glucose co-transporter-2 inhibitor. DPP4=dipeptidyl peptidase-4 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist.

Supplemental Table 2. Antihyperglycemic initiated at time zero

Medication class	Original cohort	Weighted cohort
SGLT2i	52 535 (13.86%)	52 535 (49.85%)
Biguanide	97 670 (25.77%)	6087 (5.78%)
Insulin	51 683 (13.64%)	7288 (6.92%)
Sulfonylureas	89 709 (23.67%)	7877 (7.47%)
DPP4	47 166 (12.44%)	8520 (8.08%)
GLP1	21 396 (5.64%)	17 697 (16.79%)
Thiazolidinediones	15 678 (4.14%)	4546 (4.31%)
Alpha-glucosidase inhibitors	2787 (0.74%)	660 (0.63%)
Meglitinides	389 (0.10%)	158 (0.15%)
Amylin analogues	20 (0.01%)	18 (0.02%)

SGLT2i=sodium-glucose co-transporter-2 inhibitor. DPP4=dipeptidyl peptidase-4 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist.

Supplemental Table 3. Baseline characteristics in original cohort

Baseline Characteristics	Overall N=379 033	Empagliflozin N=52 535 (13.86%)	Other non-SGLT2i antihyperglycemics N=326 498 (86.14%)	Absolute standardized difference
Age, years	65.67 (10.65)	65.35 (9.23)	65.72 (10.86)	0.04
Race				
White	265 153 (69.96)	38 697 (73.66)	226 456 (69.36)	0.10
Black	71 717 (18.92)	7 943 (15.12)	63 774 (19.53)	0.12
Other	42 163 (11.12)	5 895 (11.22)	36 268 (11.11)	<0.01
Sex				
Male	359 143 (94.75)	50 172 (95.50)	308 971 (94.63)	0.04
Female	19 890 (5.25)	2 363 (4.50)	17 527 (5.37)	0.04
eGFR, mL/min/1.73 m^2	76.38 (20.88)	77.91 (18.40)	76.14 (21.24)	0.09
eGFR category				
eGFR≥90 mL/min/1.73 m^2	106 517 (28.10)	14 468 (27.54)	92 049 (28.19)	0.01
90>eGFR≥60 mL/min/1.73 m^2	181 141 (47.79)	28 206 (53.69)	152 935 (46.84)	0.14
60>eGFR≥45 mL/min/1.73 m^2	63 027 (16.63)	8 515 (16.21)	54 512 (16.70)	0.01
45>eGFR≥30 mL/min/1.73 m^2	28 348 (7.48)	1 346 (2.56)	27 002 (8.27)	0.25
HbA1c, %	8.68 (1.87)	8.69 (1.40)	8.68 (1.94)	0.01
HbA1c, mmol/mol	71 (15.30)	71 (11.44)	71 (15.87)	0.01
Body mass index, kg/m^2	32.88 (6.55)	34.06 (6.41)	32.69 (6.55)	0.21
Low-density lipoprotein, mg/dL	89.41 (37.13)	81.50 (34.37)	90.68 (37.40)	0.26
Systolic blood pressure, mmHg	132.80 (17.12)	132.19 (16.25)	132.90 (17.25)	0.04
Diastolic blood pressure, mmHg	76.20 (10.42)	75.08 (9.83)	76.38 (10.50)	0.13
Congestive heart failure	27 487 (7.25)	5 320 (10.13)	22 167 (6.79)	0.12
Alcoholism	20 619 (5.44)	2 211 (4.21)	18 408 (5.64)	0.07
Bone fracture	4 663 (1.23)	613 (1.17)	4 050 (1.24)	<0.01
Cancer	73 060 (19.28)	10 627 (20.23)	62 433 (19.12)	0.03
Cardiovascular disease	104 524 (27.58)	21 294 (40.53)	83 230 (25.49)	0.32
Diabetic ketoacidosis	1 336 (0.35)	108 (0.21)	1 228 (0.38)	0.03
Hypoglycemia	7 513 (1.98)	1 730 (3.29)	5 783 (1.77)	0.10
Pancreatitis	4 179 (1.10)	625 (1.19)	3 554 (1.09)	0.01
Bladder & urinary tract infections	12 216 (3.22)	1 077 (2.05)	11 139 (3.41)	0.08
Venous thromboembolism	2 295 (0.61)	325 (0.62)	1 970 (0.60)	<0.01

Acute Kidney Injury	32 677 (8.62)	4 705 (8.96)	27 972 (8.57)	0.01
Albuminuria				
No albuminuria (≤30 mg/g)	161 895 (42.71)	20 827 (39.64)	141 068 (43.21)	0.07
Microalbuminuria (>30-≤300 mg/g)	183 259 (48.35)	26 371 (50.20)	156 888 (48.05)	0.04
Macroalbuminuria (>300 mg/g)	33 879 (8.94)	5 337 (10.16)	28 542 (8.74)	0.05
Metformin *	206 046 (54.36)	42 156 (80.24)	163 890 (50.20)	0.66
Insulin *	111 280 (29.36)	29 011 (55.22)	82 269 (25.20)	0.64
Sulfonylureas *	113 840 (30.03)	24 901 (47.40)	88 939 (27.24)	0.43
DPP4 *	26 607 (7.02)	12 817 (24.40)	13 790 (4.22)	0.60
GLP1 *	10 428 (2.75)	6 557 (12.48)	3 871 (1.19)	0.46
Thiazolidinediones *	9 955 (2.63)	42 77 (8.14)	5 678 (1.74)	0.30
Alpha-glucosidase inhibitors *	3 955 (1.04)	878 (1.67)	3 077 (0.94)	0.06
Meglitinides *	485 (0.13)	165 (0.31)	320 (0.10)	0.04
Amylin analogues *	66 (0.02)	28 (0.05)	38 (0.01)	0.02
Total number of diabetes medications used	1.27 (0.92)	2.30 (0.94)	1.11 (0.81)	1.36
ACE/ARB *	214 631 (56.63)	36 566 (69.60)	178 065 (54.54)	0.31
Calcium channel blockers *	101 581 (26.80)	15 918 (30.30)	85 663 (26.24)	0.09
Beta blockers *	147 767 (38.99)	26 989 (51.37)	120 778 (36.99)	0.29
Diuretics *	140 298 (37.01)	23 003 (43.79)	117 295 (35.93)	0.16
Statins *	262 356 (69.22)	44 515 (84.73)	217 841 (66.72)	0.43
Hospital complexity				
Outpatient clinic	227 402 (60.00)	28 123 (53.53)	199 279 (61.04)	0.15
Health care system	151 631 (40.00)	24 412 (46.47)	127 219 (38.96)	0.15
Year of treatment initial				
2016	27 704 (7.31)	956 (1.82)	26 748 (8.19)	0.30
2017	124 385 (32.82)	8 439 (16.06)	115 946 (35.51)	0.46
2018	125 617 (33.14)	16 957 (32.28)	108 660 (33.28)	0.02
2019	101 327 (26.73)	26 183 (49.84)	75 144 (23.02)	0.58
Smoking status				
Never	172 433 (45.49)	24 389 (46.42)	148 044 (45.34)	0.02
Former	118 451 (31.25)	17 260 (32.85)	101 191 (30.99)	0.04
Current	88 149 (23.26)	10 886 (20.72)	77 263 (23.66)	0.07

All values are mean (SD) or n (proportions [%]), unless specified. SGLT2i=sodium-glucose co-transporter-2 inhibitor. SD=standard

deviation. eGFR=estimated glomerular filtration rate. HbA1c=glycated hemoglobin. DPP4=dipeptidyl peptidase-4 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist. ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers.
* Any prescription within one year before $T_{0.}$

Supplemental Table 4a. Sample size, event rate and results in the overall cohort and in subgroups

Analyses		Weighted sample size *		Event rate per 1000 person-years (95% CI)		HR (95% CI)	Event difference per 1000 person-years (95% CI)
		Empagliflozin	Control	Empagliflozin	Control		
Overall		52 535	52 850	34.80 (33.39, 36.25)	51.18 (49.53, 52.87)	0.68 (0.64, 0.73)	-14.99 (-17.17, -12.66)
eGFR							
≥90 ml/min/1.73m^2		14 468	14 564	24.93 (22.72. 27.30)	35.60 (33.06, 38.29)	0.70 (0.60, 0.82)	-10.22 (-13.84, -6.01)
≥60 to <90 ml/min/1.73m^2		28 206	29 006	34.55 (32.66, 36.53)	52.55 (50.31, 54.86)	0.66 (0.60, 0.73)	-16.56 (-19.70, -13.13)
≥45 to <60 ml/min/1.73m^2		8 515	8 308	50.34 (46.11. 54.86)	64.97 (60.24, 69.97)	0.78 (0.69, 0.89)	-12.94 (-18.59, -6.67)
≥30 to <45 ml/min/1.73m^2		1 346	1 231	59.26 (46.84, 73.96)	83.59 (68.84, 100.60)	0.71 (0.55, 0.92)	-21.22 (-33.72, -5.90)
Albuminuria							
None (≤30 mg/g)		20 827	20 723	21.00 (19.28, 22.82)	32.23 (30.18, 34.37)	0.65 (0.57, 0.75)	-10.44 (-13.08, -7.44)
Microalbuminuria (>30- ≤300 mg/g)		26 371	26 464	38.60 (36.52, 40.76)	53.46 (51.09, 55.92)	0.72 (0.66, 0.79)	-13.59 (-16.72, -10.21)
Macroalbuminuria (>300 mg/g)		5 337	5 444	72.01 (65.57, 78.92)	98.84 (91.54, 106.60)	0.74 (0.62, 0.88)	-22.02 (-32.75, -9.76)
eGFR and Albuminuria							
eGFR≥ 60 ml/min/ 1.73m^2	No albuminuria (≤30 mg/g)	17 906	18 112	19.51 (17.74, 21.41)	31.11 (28.45, 33.96)	0.63 (0.56, 0.71)	-10.78 (-12.76. -8.58)
	Microalbuminuria (>30- ≤300 mg/g)	21 160	21 591	35.27 (33.08, 37.57)	51.06 (47.91, 54.37)	0.70 (0.65, 0.76)	-14.75 (-17.38, -11.94)
	Macroalbuminuria (>300 mg/g)	3 608	3 769	66.95 (59.58, 74.99)	88.05 (77.65, 99.45)	0.77 (0.67, 0.89)	-17.13 (-25.11, -8.21)
eGFR< 60 ml/min/	No albuminuria (≤30 mg/g)	2 921	2 771	30.62 (25.12. 36.97)	44.07 (36.58, 52.64)	0.71 (0.57, 0.88)	-13.66 (-20.51, -5.33)
	Microalbuminuria	5 211	5 020	53.18 (47.60,	69.31 (62.16,	0.77 (0.68, 0.88)	-13.55 (-19.17, -7.28)

1.73m^2	(>30- ≤300 mg/g)			59.22)	77.07)		
	Macroalbuminuria(>300 mg/g)	1 729	1 601	83.94 (71.40, 98.04)	103.10 (87.55, 120.70)	0.82 (0.68, 0.99)	-15.98 (-29.27, -0.91)
CVD							
Yes		21 294	21 410	46.57 (44.04, 49.20)	69.77 (66.74, 72.90)	0.67 (0.61, 0.74)	-19.98 (-23.86, -15.78)
No		31 241	30 242	26.58 (24.99, 28.25)	35.49 (33.69, 37.36)	0.76 (0.69, 0.83)	-8.60 (-11.09, -5.88)
ACE/ARB use							
Yes		36 566	37 452	37.47 (35.72, 39.27)	54.07 (52.07, 56.14)	0.70 (0.64, 0.76)	-15.03 (-17.88, -11.96)
No		15 969	15 355	28.58 (26.28, 31.03)	40.31 (37.62, 43.15)	0.71 (0.63, 0.81)	-10.78 (-14.02, -7.14)
Metformin use							
Yes		42 156	43 953	32.53 (31.01, 34.09)	50.02 (48.24, 51.85)	0.65 (0.60, 0.71)	-15.92 (-18.56, -13.06)
No		10 379	9 838	44.17 (40.62, 47.95)	63.48 (59.19, 68.01)	0.70 (0.63, 0.77)	-17.42 (-21.40, -13.08)
Statin use							
Yes		44 515	45 700	35.71 (34.16, 37.31)	51.79 (50.01, 53.62)	0.69 (0.64, 0.75)	-14.53 (-17.06, -11.82)
No		8 020	7 443	29.79 (26.53, 33.33)	43.92 (39.93, 48.19)	0.68 (0.58, 0.80)	-13.17 (-17.35, -8.37)
Diuretic use							
Yes		23 003	23 492	47.36 (44.88, 49.94)	64.81 (62.03, 67.69)	0.73 (0.67, 0.80)	-15.13 (-18.94, -11.00)
No		29 532	29 106	25.07 (23.49, 26.73)	38.29 (36.39, 40.26)	0.66 (0.60, 0.74)	-12.69 (-15.24, -9.88)
Insulin use							
Yes		29 011	28 320	40.95 (38.92. 43.06)	55.18 (52.87, 57.56)	0.75 (0.68, 0.82)	-12.73 (-16.06, -9.12)
No		23 524	22 073	26.88 (25.02, 28.83)	40.02 (37.76, 42.38)	0.67 (0.60, 0.75)	-11.99 (-14.56, -9.15)
BMI							
>30 kg/m^2		37 933	38 440	32.80 (31.20,	46.87 (45.04,	0.70 (0.65, 0.77)	-13.01 (-15.59, -10.22)

			34.45)	48.76)		
>25 to ≤30 kg/m^2	12 027	11 713	35.88 (32.89, 39.05)	54.66 (51.04, 58.46)	0.66 (0.57, 0.76)	-16.78 (-21.22, -11.75)
≤25 kg/m^2	2 575	2 386	61.34 (52.84, 70.82)	90.83 (80.36, 102.30)	0.68 (0.55, 0.83)	-23.66 (-33.48, -12.04)

HR=hazard ratio. CI=confidence interval. eGFR=estimated glomerular filtration rate. CVD=cardiovascular disease. ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers. BMI=body mass index.

* Sample size based on subgroup specific weighting

Supplemental Table 4b. Sample size, event rate and results for individual components of MAKE

Analyses	Weighted sample size		Event rate per 1000 person-years (95% CI)		HR (95% CI)	Event difference per 1000 person-years (95% CI)
	Empagliflozin	Control	Empagliflozin	Control		
MAKE	52 535	52 850	34.80 (33.39, 36.25)	51.18 (49.53, 52.87)	0.68 (0.64, 0.73)	-14.99 (-17.17, -12.66)
eGFR decline >50%	52 535	52 850	19.51 (18.47, 20.61)	29.45 (18.20, 30.74)	0.72 (0.66, 0.79)	-8.54 (-10.46, -6.45)
ESKD	52 535	52 850	3.63 (3.19, 4.12)	5.34 (4.82, 5.90)	0.69 (0.57, 0.84)	-1.76 (-2.45, -0.91)
All-cause mortality	52 535	52 850	15.11 (14.19, 16.06)	24.67 (23.54, 25.83)	0.61 (0.56, 0.68)	-8.83 (-10.17, -7.37)
eGFR decline >50% or ESKD	52 535	52 850	21.22 (20.13, 22.36)	29.61 (28.36, 30.90)	0.72 (0.66, 0.79)	-8.48 (-10.41, -6.39)

HR=hazard ratio. CI=confidence interval. eGFR=estimated glomerular filtration rate. ESKD=end stage kidney disease

Supplemental Table 5. Sensitivity analyses

Analyses	**HR (95% CI)**
Variable ratio propensity score matching	0.73 (0.69, 0.77)
Controlled for time dependent body mass index	0.71 (0.66, 0.76)
Controlled for time dependent HbA1c	0.73 (0.68, 0.78)
Controlled for both time dependent body mass index and HbA1c	0.72 (0.67, 0.77)
Within patients enrolled in years 2016 and 2017	0.70 (0.64, 0.77)
Within patients enrolled in years 2018 and 2019	0.65 (0.59, 0.72)
Excluded patients with events within 180 days from time zero	0.67 (0.62, 0.73)
eGFR decline>50% based on 2 eGFR separated by at least 30 days	0.61 (0.51, 0.73)
ESKD was defined as dialysis, kidney transplantation, or eGFR less than 15 ml/min/1.73m^2 on 2 separate occasions at least 30 days apart	0.53 (0.36, 0.80)
Traffic related injury (negative control)	1.10 (0.88, 1.38)

HR=hazard ratio. CI=confidence interval. HbA1c=glycated hemoglobin. eGFR=estimated glomerular filtration rate.