

## ONLINE-ONLY SUPPLEMENTAL MATERIAL

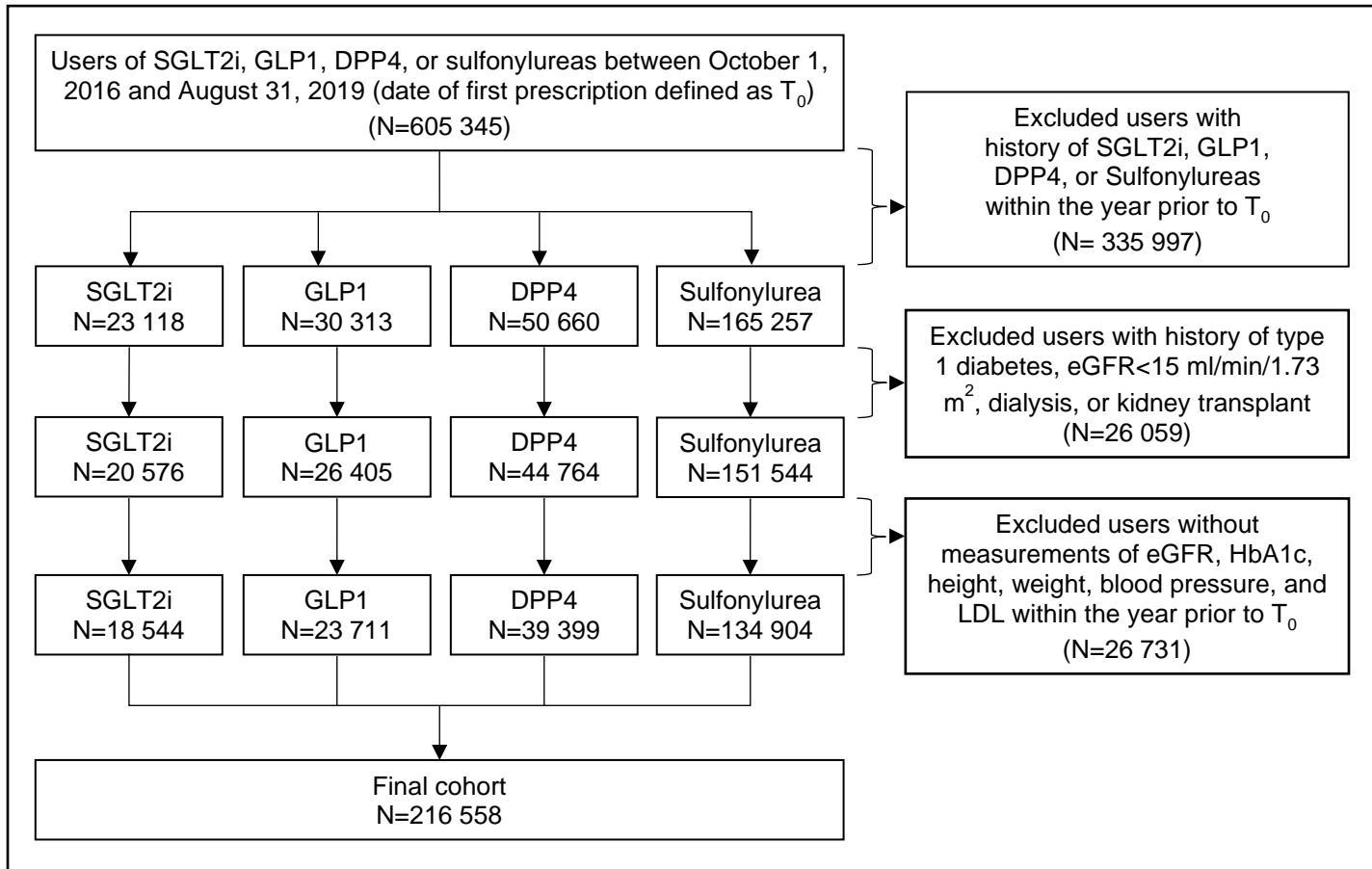
### **Comparative Effectiveness of SGLT2 Inhibitors, GLP-1 Receptor Agonists, DPP4 Inhibitors and Sulfonylureas on Risk of Kidney Outcomes: emulation of a target trial using healthcare databases**

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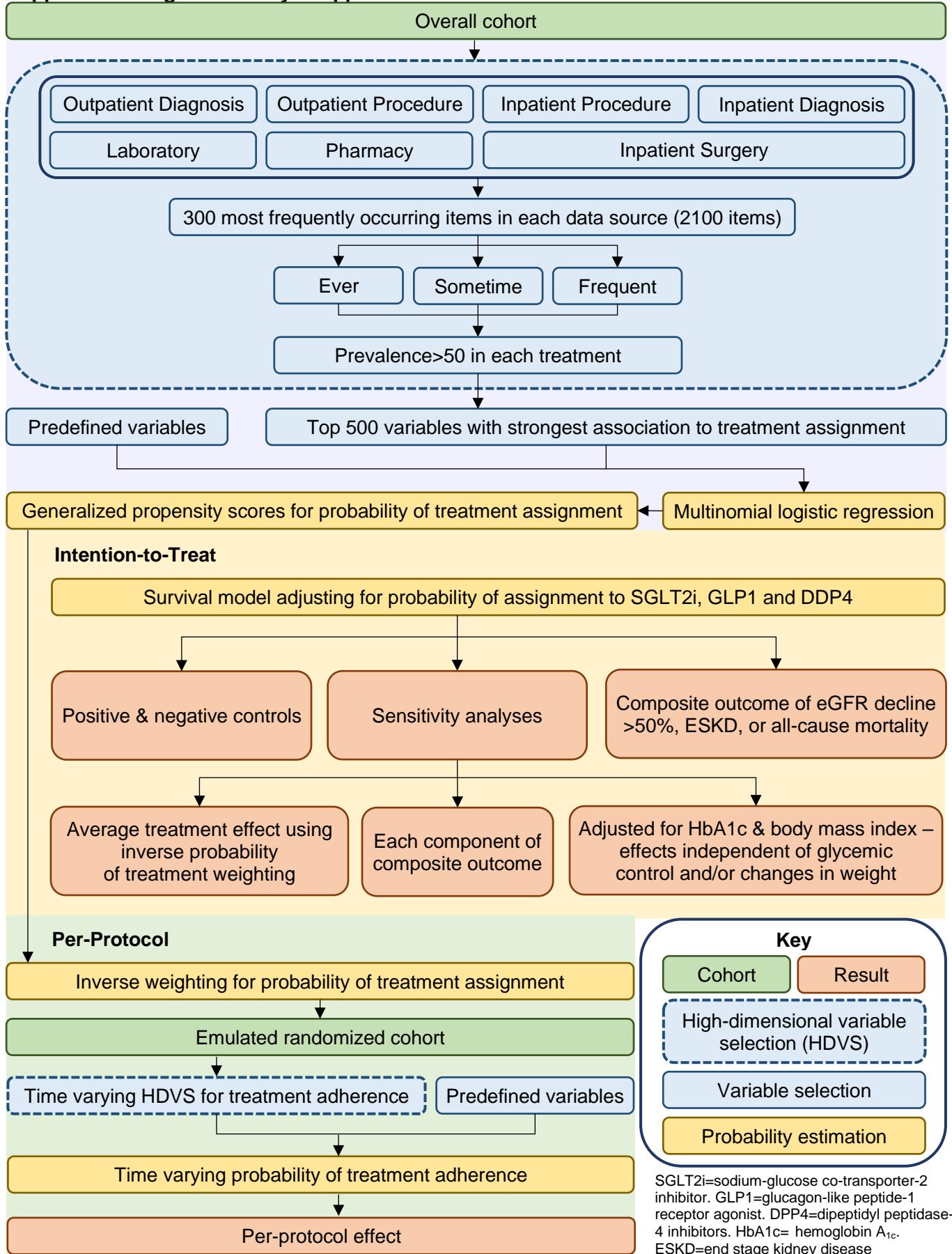
## SUPPLEMENTAL FIGURES

**Supplemental Figure 1. Cohort construction flowchart**

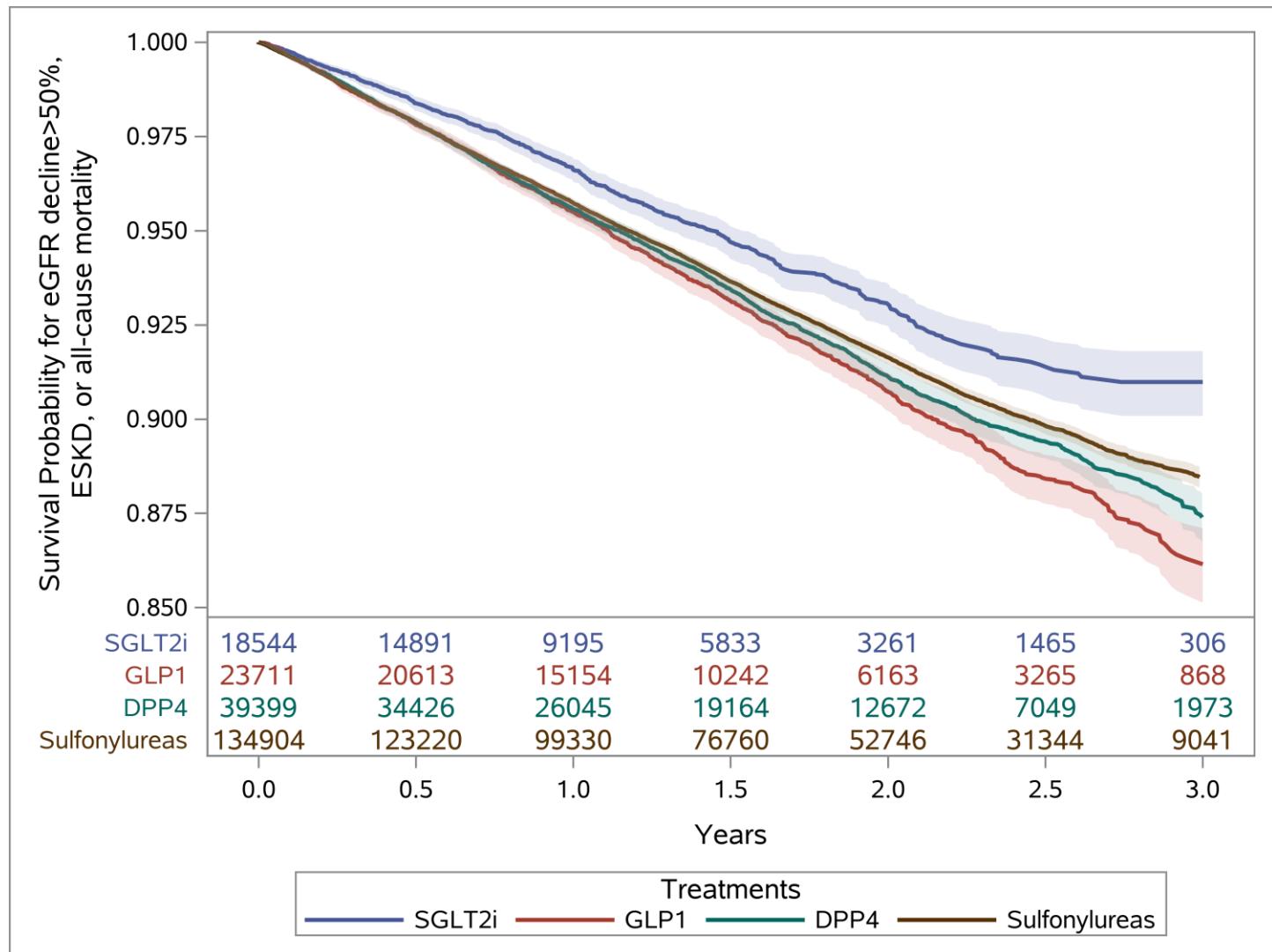


SGLT2i=sodium-glucose co-transporter-2 inhibitor. GLP1=glucagon-like peptide-1. DPP4=dipeptidyl peptidase-4. eGFR=estimated glomerular filtration rate. HbA1c=hemoglobin A<sub>1c</sub>. LDL=low-density lipoprotein.

**Supplemental Figure 2. Analytic approach flowchart**

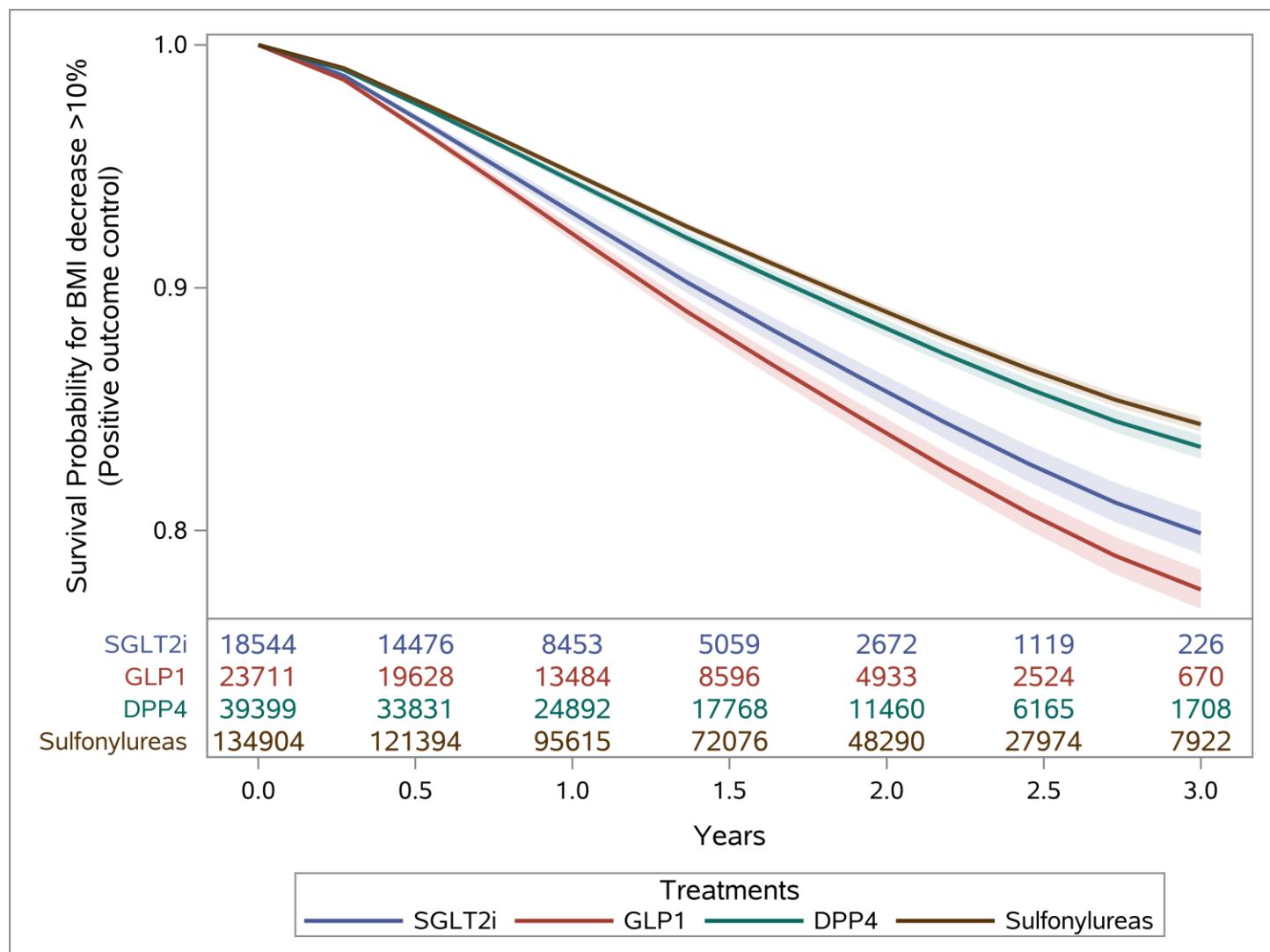


**Supplemental Figure 3. Unadjusted survival probability for the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality in SGLT2i (blue), GLP1 (red), DPP4 (green) and sulfonylureas (brown) arms. Light colored bands represent the 95% confidence interval for each treatment. Number of patients at risk in each arm is indicated in the bottom of the figure.**



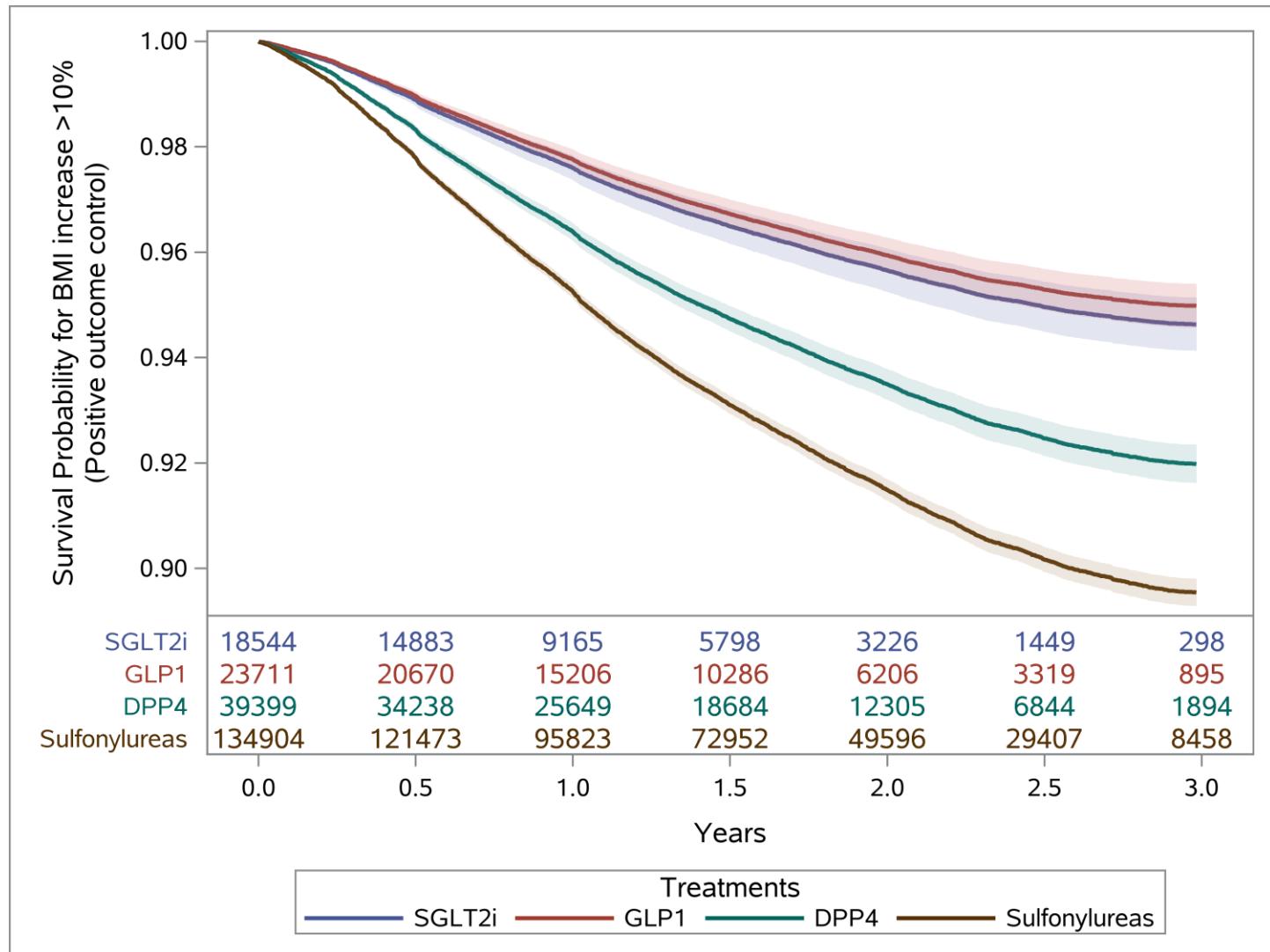
SGLT2i=sodium-glucose co-transporter-2 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist.  
DPP4=dipeptidyl peptidase-4 inhibitor. eGFR=estimated glomerular filtration rate. ESKD=end stage kidney disease.

**Supplemental Figure 4A. Adjusted intention-to-treat survival probability for BMI decrease >10% (positive outcome control). Survival probability in SGLT2i (blue), GLP1 (red), DPP4 (green) a3A3nd sulfonylureas (brown) arms, according to an intention-to-treat analysis. Light colored bands represent the 95% confidence interval for each treatment. Number of patients at risk in each arm is indicated in the bottom of the figure.**



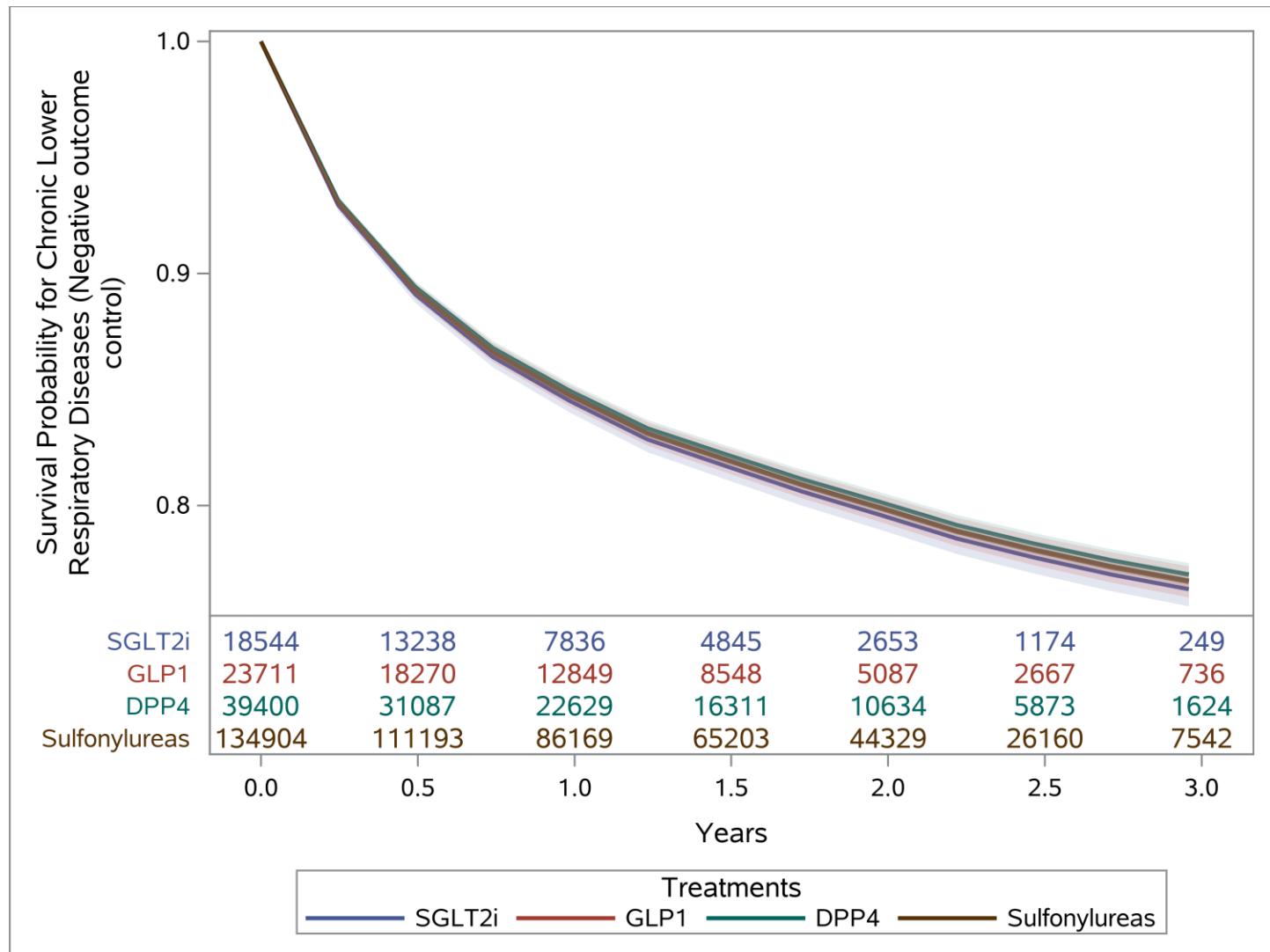
SGLT2i=sodium-glucose co-transporter-2 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist.  
DPP4=dipeptidyl peptidase-4 inhibitor. BMI=body mass index.

**Supplemental Figure 4B. Adjusted intention-to-treat survival probability for BMI increase >10% (positive outcome control) in SGLT2i (blue), GLP1 (red), DPP4 (green) and sulfonylureas (brown) arms, according to an intention-to-treat analysis. Light colored bands represent the 95% confidence interval for each treatment. Number of patients at risk in each arm is indicated in the bottom of the figure.**



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

**Figure 4C. Adjusted intention-to-treat survival probability for chronic lower respiratory diseases (negative outcome control). Survival probability in SGLT2i (blue), GLP1 (red), DPP4 (green) and sulfonylureas (brown) arms, according to an intention-to-treat analysis. Light colored bands represent the 95% confidence interval for each treatment. Number of patients at risk in each arm is indicated in the bottom of the figure.**



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

## SUPPLEMENTAL TABLES

**Supplemental Table 1. Protocol for the target trial**

Protocol Components	Target Trial Protocol
Cohort inclusion criteria	Patients with type 2 diabetes mellitus and no prior use of SGLT2i, GLP1, DPP4 or sulfonylureas within the past year.
Cohort exclusion criteria	History of type 1 diabetes or advanced chronic kidney disease (eGFR<15 mL/min/1.73 m <sup>2</sup> , dialysis or kidney transplant).
Treatment assignment	Participants will be randomly assigned to one of four treatment arms at the time of enrollment and will be notified of the group they are in.
Treatment initiation	Initiation of only one second line diabetes medication (SGLT2i, GLP1, DPP4 or sulfonylureas).
Treatment strategy	Participants will be required to use the assigned medication during follow-up. Participants who experience adverse events or contraindications will be switched to other diabetes medications. Upon evidence of lack of efficacy in blood sugar control, switching medication or co-prescription will be allowed. The participants' physician will guide treatment.
Follow-up	Follow-up begins after treatment assignment. Cohort participants will be followed until occurrence of outcome, administrative end of follow-up (November 30, 2019), or death. Patients will have health conditions and outcomes evaluated/ascertained every 90 days. Any procedures or events occurring between visits will be recorded at next visit.
Outcome	Composite outcome of eGFR decline >50%, ESKD, or all-cause mortality.
Analysis plan to estimate causal contrasts of interest	Estimate intention-to-treat effect.
	Estimate the per-protocol effect of continued use of the assigned medication. Discontinuation of assigned antihyperglycemic will be accounted for through generalized propensity score.

SGLT2i=sodium-glucose co-transporter-2 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist. DPP4=dipeptidyl peptidase-4 inhibitor. eGFR=estimated glomerular filtration rate. ESKD=end stage kidney disease.

**Supplemental Table 2.** Distribution of medications within each antihyperglycemic class at T<sub>0</sub>

SGLT2i		GLP1		DPP4		Sulfonylureas	
Medication	n (%)	Medication	n (%)	Medication	n (%)	Medication	n (%)
Empagliflozin	18 441 (99.45)	Liraglutide	13 347 (56.29)	Saxagliptin	28 978 (73.55)	Glipizide	122 122 (90.53)
Canagliflozin	70 (0.38)	Dulaglutide	5250 (22.14)	Alogliptin	9165 (23.26)	Glimepiride	12 201 (9.04)
Dapagliflozin	27 (0.15)	Semaglutide	3058 (12.90)	Sitagliptin	676 (1.72)	Glyburide	581 (0.43)
Ertugliflozin	6 (0.03)	Albiglutide	1052 (4.44)	Linagliptin	580 (1.47)		
		Exenatide	1003 (4.23)				

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

**Supplemental Table 3.** Crude number of events, person-years of follow up, and crude event rates in the overall cohort and according to treatment arm.

	Overall cohort	SGLT2i	GLP1	DPP4	Sulfonylureas
<b>Composite outcome</b>					
Number of events (%)	14 612 (6.75)	753 (4.06)	1588 (6.70)	2662 (6.76)	9609 (7.12)
Total person-years of follow-up	337 818.40	21 653.84	33 252.53	58 974.79	223 937.24
Unadjusted event rate per 1000 person-years (95% CI)	43.25 (42.56, 43.96)	34.77 (32.33, 37.35)	47.76 (45.44, 50.16)	45.14 (43.44, 46.89)	42.91 (42.06, 43.78)
<b>eGFR decline &gt;50%</b>					
Number of events (%)	7760 (3.58)	491 (2.65)	1043 (4.40)	1376 (3.49)	4850 (3.60)
Total person-years of follow-up	338 397.85	21 661.58	33 353.63	59 102.14	224 280.51
Unadjusted event rate per 1000 person-years (95% CI)	22.93 (22.42, 23.45)	22.67 (20.71, 24.76)	31.27 (29.40, 33.23)	23.28 (22.07, 24.55)	21.62 (21.02, 22.24)
<b>ESKD</b>					
Number of events (%)	2662 (1.23)	88 (0.47)	401 (1.69)	579 (1.47)	1594 (1.18)
Total person-years of follow-up	342 967.37	21 972.31	33 893.27	60 121.87	226 979.92
Unadjusted event rate per 1000 person-years (95% CI)	7.76 (7.47, 8.06)	4.01 (3.21, 4.93)	11.83 (10.70, 13.05)	9.63 (8.86, 10.45)	7.02 (6.68, 7.38)
<b>All-cause mortality</b>					
Number of events (%)	7132 (3.29)	282 (1.52)	510 (2.15)	1301 (3.30)	5039 (3.74)
Total person-years of follow-up	344 796.00	22 032.85	34 197.51	60 207.60	228 358.04
Unadjusted event rate per 1000 person-years (95% CI)	20.68 (20.21, 21.17)	12.80 (11.35, 14.38)	14.91 (13.65, 16.27)	21.61 (20.45, 22.82)	22.07 (21.46, 22.68)
<b>Composite outcome in per-protocol analysis</b>					
Number of events (%)	10 898 (5.03)	575 (3.10)	1253 (5.28)	2024 (5.14)	7046 (5.22)
Total person-years of follow-up	264 019.79	18 643.33	27 897.17	47 266.97	170 212.31
Unadjusted event rate per 1000 person-years (95% CI)	41.28 (40.51, 42.06)	30.84 (28.37, 33.47)	44.91 (42.46, 47.47)	42.82 (40.98, 44.73)	41.40 (40.43, 42.37)

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

**Supplemental Table 4.** Key characteristics after adjustment for propensity scores

Cohort characteristics	SGLT2i	GLP1	DPP4	Sulfonylureas
Age, years	65.41 (3.65)	65.23 (3.65)	65.46 (3.65)	65.62 (3.65)
Race				
White	155 827.83 (71.96)	155 661.22 (71.88)	155 826.28 (71.96)	155 840.56 (71.96)
Black	38 479.68 (17.77)	38 708.31 (17.87)	38 502.59 (17.78)	38 500.89 (17.78)
Other	22 250.49 (10.27)	22 188.47 (10.25)	22 229.13 (10.26)	22 216.55 (10.26)
Sex				
Male	204 478.80 (94.42)	204 535.22 (94.45)	204 670.91 (94.51)	204 642.95 (94.50)
Female	12 079.20 (5.58)	12 022.78 (5.55)	11 887.09 (5.49)	11 915.05 (5.50)
eGFR, mL/min/1.73 m <sup>2</sup>	75.12 (7.01)	75.17 (7.01)	75.04 (7.01)	74.98 (7.01)
HbA1c, %	8.58 (0.50)	8.60 (0.50)	8.57 (0.50)	8.56 (0.50)
Body mass index, kg/m <sup>2</sup>	33.19 (2.44)	33.26 (2.44)	33.15 (2.44)	33.12 (2.44)
Low-density lipoprotein, mg/dL	87.89 (6.80)	88.23 (6.80)	87.89 (6.80)	87.85 (6.80)
Systolic blood pressure, mmHg	132.95 (0.90)	133.00 (0.90)	132.95 (0.90)	132.93 (0.90)
Diastolic blood pressure, mmHg	76.37 (2.59)	76.51 (2.59)	76.36 (2.59)	76.33 (2.59)
Congestive heart failure	16 449.54 (7.60)	16 542.30 (7.64)	16 277.94 (7.49)	16 121.73 (7.44)
Cardiovascular disease	54 788.85 (25.30)	53 400.22 (24.66)	54 551.06 (25.19)	54 446.74 (25.14)
Albuminuria*	57 946.30 (26.76)	57 711.17 (26.65)	57 912.19 (26.74)	57 901.14 (26.74)
Metformin use <sup>†</sup>	103 471.66 (47.78)	102 712.04 (47.43)	103 423.54 (47.76)	103 429.75 (47.76)
Insulin use <sup>†</sup>	56 877.73 (26.26)	55 124.96 (25.46)	56 728.13 (26.20)	56 472.65 (26.08)
Ace/arb use <sup>†</sup>	91 645.47 (42.32)	90 867.73 (41.96)	91 496.84 (42.25)	91 443.03 (42.23)
Calcium channel blocker use <sup>†</sup>	44 305.87 (20.46)	44 090.86 (20.36)	44 288.81 (20.45)	44 287.97 (20.45)
Beta blocker use <sup>†</sup>	66 277.87 (30.61)	65 671.16 (30.32)	66 038.22 (30.49)	65 851.72 (30.41)
Diuretic use <sup>†</sup>	62 551.74 (28.88)	62 582.48 (28.90)	62 363.05 (28.80)	62 186.54 (28.72)
Statin use <sup>†</sup>	114 193.23 (52.73)	112 947.59 (52.16)	114 109.84 (52.69)	114 156.40 (52.71)
Smoking status				
Never	101 276.47 (46.77)	100 982.63 (46.63)	101 426.23 (46.84)	101 558.56 (46.90)
Former	67 033.72 (30.95)	66 885.65 (30.89)	67 055.96 (30.96)	67 068.85 (30.97)
Current	48 247.81 (22.28)	48 689.72 (22.48)	48 075.81 (22.20)	47 930.59 (22.13)

Data are mean (SD), or n (%). SGLT2i=sodium-glucose co-transporter-2 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist. DPP4=dipeptidyl peptidase-4 inhibitor. SD=standard deviation, eGFR=estimated glomerular filtration rate. HbA1c= hemoglobin A<sub>1c</sub>. Ace/arb=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers.

\* With positive albuminuria test or micro-albumin to creatinine ratio >30

† Use defined as more than 90 days prescription within one year before T<sub>0</sub>

**Supplemental Table 5.** Positive and negative outcome controls for the intention-to-treat effect in the overall cohort based on pair-wise treatment comparisons

Analysis	SGLT2i vs. SU HR (95% CI)	GLP1 vs. SU HR (95% CI)	DPP4 vs. SU HR (95% CI)	SGLT2i vs. DPP4 HR (95% CI)	GLP1 vs. DPP4 HR (95% CI)	SGLT2i vs. GLP1 HR (95% CI)
Positive controls						
BMI decrease >10%	1.32 (1.25, 1.40)	1.50 (1.43, 1.57)	1.07 (1.03, 1.11)	1.24 (1.17, 1.31)	1.41 (1.34, 1.48)	0.88 (0.84, 0.94)
BMI increase >10%	0.50 (0.45, 0.56)	0.47 (0.42, 0.52)	0.76 (0.72, 0.80)	0.66 (0.59, 0.74)	0.62 (0.56, 0.68)	1.07 (0.95, 1.21)
Negative control						
Chronic lower respiratory diseases	1.02 (0.98, 1.06)	1.00 (0.97, 1.04)	0.99 (0.96, 1.01)	1.03 (0.99, 1.08)	1.02 (0.98, 1.06)	1.02 (0.97, 1.06)

CI=confidence interval. HR=hazard ratio. SGLT2i=sodium-glucose co-transporter-2 inhibitor. SU=sulfonylureas. GLP1=glucagon-like peptide-1 receptor agonist. DPP4=dipeptidyl peptidase-4 inhibitor.

**Supplemental Table 6.** Adjusted event rates in each treatment arm of the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality

	SGLT2i	GLP1	DPP4	Sulfonylureas
<b>Intention-to-treat analyses</b> <b>Event rate per 1000 person-years (95% CI)</b>				
Overall cohort (n=216 558)				
eGFR				
≥90 (n=60 794)	19.64 (16.25, 23.90)	20.13 (17.24, 23.74)	22.37 (19.91, 25.20)	26.65 (24.19, 29.19)
≥60 to <90 (n=97 748)	23.81 (21.13, 27.02)	24.42 (21.90, 27.38)	30.50 (27.90, 33.40)	34.40 (31.68, 37.22)
≥45 to <60 (n=34 303)	33.69 (28.53, 40.14)	36.23 (31.69, 41.67)	46.07 (41.63, 51.02)	49.91 (45.49, 54.60)
<45 (n=23 713)	52.44 (37.65, 71.64)	61.99 (55.52, 69.08)	76.31 (69.90, 83.15)	80.91 (74.97, 87.21)
Current Metformin use*				
Yes (n=142 586)	23.64 (21.29, 26.38)	25.11 (22.99, 27.54)	30.58 (28.72, 32.59)	33.87 (32.06, 35.68)
No (n=73 972)	33.52 (29.69, 37.93)	33.01 (30.25, 36.07)	42.74 (39.91, 45.80)	47.76 (44.87, 50.63)
Cardiovascular disease				
Yes (n=54 389)	34.39 (30.82, 38.66)	38.52 (34.83, 42.67)	45.87 (42.08, 49.84)	51.50 (47.73, 55.31)
No (n=162 169)	24.16 (21.73, 26.92)	23.58 (21.82, 25.52)	29.69 (28.10, 31.41)	32.25 (30.75, 33.75)
Body mass index				
>30 (n=142 180)	24.63 (22.33, 27.34)	26.50 (24.55, 28.66)	31.23 (29.12, 33.48)	33.88 (31.74, 35.96)
>25 to ≤30 (n=57 085)	28.36 (24.15, 33.21)	25.59 (22.17, 29.68)	34.75 (31.97, 37.79)	38.41 (35.93, 40.91)
≤25 (n=17 293)	49.02 (37.79, 62.96)	46.22 (36.19, 60.54)	66.04 (60.05, 72.87)	66.30 (61.88, 70.96)
Age				
>65 (n=124 641)	32.59 (29.74, 35.94)	32.30 (29.95, 34.89)	40.70 (38.40, 43.13)	45.16 (42.85, 47.52)
≤65 (n=91 917)	18.50 (15.97, 21.53)	21.23 (18.94, 23.97)	26.72 (24.38, 29.39)	29.15 (26.93, 31.43)
<b>Per-protocol analysis†</b> <b>Event rate per 1000 person-years (95% CI)</b>				
Overall cohort (n=216 558)	22.67 (19.13, 26.84)	25.57 (21.17, 30.32)	35.71 (33.56, 38.23)	39.72 (37.58, 42.16)

eGFR=estimated glomerular filtration rate. ESKD=end stage kidney disease. CI=confidence interval. SGLT2i=sodium-glucose co-transporter-2 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist. DPP4=dipeptidyl peptidase-4 inhibitor.

\* Current use defined as having a metformin prescription within 90 days before or at T<sub>0</sub>

† Protocol defined as maintaining use of the assigned antihyperglycemic medication throughout duration in cohort

**Supplemental Table 7.** Sensitivity analyses for the intention-to-treat effect in the overall cohort of pair-wise treatment comparisons on the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality, unless otherwise specified

	<b>SGLT2i vs. SU HR (95% CI)</b>	<b>GLP1 vs. SU HR (95% CI)</b>	<b>DPP4 vs. SU HR (95% CI)</b>	<b>SGLT2i vs. DPP4 HR (95% CI)</b>	<b>GLP1 vs. DPP4 HR (95% CI)</b>	<b>SGLT2i vs. GLP1 HR (95% CI)</b>
Average treatment effect from IPTW	0.62 (0.52, 0.74)	0.74 (0.62, 0.88)	0.91 (0.86, 0.96)	0.68 (0.58, 0.82)	0.81 (0.68, 0.97)	0.84 (0.66, 1.07)
Outcome						
eGFR decline >50%	0.66 (0.60, 0.74)	0.76 (0.69, 0.83)	0.91 (0.85, 0.97)	0.73 (0.66, 0.82)	0.84 (0.76, 0.92)	0.87 (0.78, 0.98)
ESKD	0.65 (0.52, 0.81)	0.72 (0.62, 0.84)	1.06 (0.95, 1.17)	0.61 (0.49, 0.77)	0.68 (0.59, 0.79)	0.90 (0.72, 1.14)
eGFR decline >50% or ESKD	0.67 (0.61, 0.75)	0.77 (0.71, 0.85)	0.92 (0.87, 0.98)	0.73 (0.66, 0.81)	0.84 (0.77, 0.92)	0.87 (0.78, 0.97)
All-cause mortality	0.69 (0.61, 0.79)	0.60 (0.54, 0.67)	0.87 (0.82, 0.93)	0.79 (0.70, 0.91)	0.69 (0.61, 0.78)	1.15 (0.99, 1.34)
Additional adjustments						
Time-dependent HbA1c spline	0.69 (0.64, 0.76)	0.71 (0.66, 0.76)	0.90 (0.86, 0.95)	0.77 (0.70, 0.84)	0.78 (0.73, 0.84)	0.98 (0.90, 1.08)
Time-dependent BMI spline	0.68 (0.62, 0.74)	0.72 (0.67, 0.78)	0.90 (0.86, 0.94)	0.76 (0.69, 0.83)	0.81 (0.75, 0.87)	0.94 (0.86, 1.03)
Time-dependent HbA1c and BMI spline	0.69 (0.63, 0.75)	0.72 (0.67, 0.77)	0.90 (0.86, 0.95)	0.77 (0.70, 0.84)	0.80 (0.74, 0.86)	0.96 (0.87, 1.05)

eGFR=estimated glomerular filtration rate. ESKD=end stage kidney disease. HR=hazard ratio. CI=confidence interval. SGLT2i=sodium-glucose co-transporter-2 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist. DPP4=dipeptidyl peptidase-4 inhibitor. SU=sulfonylureas. IPTW=inverse probability of treatment weighting. HbA1c= hemoglobin A<sub>1c</sub>. BMI=body mass index