SUPPLEMENTAL MATERIAL

Table S1. Distribution of antihyperglycemics at treatment initiation.

Medication class	Medication names	Distribution at treatment initiation
SGLT2i	Empagliflozin	36638 (14.91%)
Biguanide	Metformin	58873 (23.96%)
Insulin	Insulin	33563 (13.66%)
Sulfonylureas	Glyburide, Glipizide, Glimepiride	56568 (23.03%)
DPP4	Alogliptin, Sitagliptin, Saxagliptin, Linagliptin	31744 (12.92%)
GLP1	Liraglutide, Exenatide, Semaglutide, Dulaglutide, Lixisenatide,	15646 (6.37%)
Thiazolidinediones	Pioglitazone, Rosiglitazone	10428 (4.24%)
Alpha-glucosidase inhibitors	Miglitol, Acarbose	1902 (0.77%)
Meglitinides	Nateglinide, Repaglinide	283 (0.12%)
Amylin analogues	Pramlintide	18 (0.01%)

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

Table S2. Unadjusted rate of eGFR dip>10% and dip> 30% in SGLT2i and the other antihyperglycemics group.

	Unadjusted rate of eGFR dip>10% per 100 patients (95% Confidence interval)		Unadjusted rate of eGFR dip>30% per 100 patients (95% Confidence interval)	
	SGLT2i	**Other antihyperglycemics**	**SGLT2i**	**Other antihyperglycemics**
Overall cohort	44.16 (43.66, 44.67)	30.37 (30.17, 30.56)	6.35 (6.10, 6.60)	4.12 (4.03, 4.20)
Race-White	43.03 (42.44, 43.62)	29.7 (29.47, 29.94)	5.97 (5.70, 6.26)	3.94 (3.84, 4.04)
Race-Black	49.31 (47.97, 50.66)	31.42 (30.96, 31.88)	7.80 (7.11, 8.55)	4.15 (3.96, 4.36)
Race-Other	45.02 (43.51, 46.53)	32.69 (32.10, 33.29)	6.95 (6.22, 7.76)	5.16 (4.88, 5.44)
eGFR≥90 mL/min/1.73 m^2	30.77 (29.88, 31.68)	22.72 (22.38, 23.06)	3.38 (3.04, 3.75)	2.39 (2.27, 2.52)
90>eGFR≥60 mL/min/1.73 m^2	47.42 (46.72, 48.11)	31.09 (30.8, 31.38)	6.34 (6.01, 6.69)	3.58 (3.46, 3.70)
60>eGFR≥45 mL/min/1.73 m^2	54.14 (52.86, 55.41)	34.67 (34.18, 35.17)	10.66 (9.9, 11.48)	5.65 (5.42, 5.89)
45>eGFR≥30 mL/min/1.73 m^2	60.26 (56.73, 63.70)	42.00 (41.29, 42.72)	12.72 (10.53, 15.3)	9.38 (8.96, 9.81)
No albuminuria (≤30 mg/g)	38.46 (37.67, 39.26)	26.20 (25.91, 26.49)	4.13 (3.82, 4.47)	2.59 (2.49, 2.70)
Microalbuminuria (>30- ≤300 mg/g)	45.98 (45.26, 46.69)	31.57 (31.28, 31.85)	7.02 (6.66, 7.39)	4.54 (4.42, 4.67)
Macroalbuminuria (>300 mg/g)	57.58 (55.96, 59.18)	43.65 (42.94, 44.37)	11.76 (10.75, 12.85)	9.08 (8.68, 9.50)
Congestive heart failure *	56.21 (54.54, 57.86)	43.33 (42.48, 44.19)	12.21 (11.15, 13.35)	9.69 (9.19, 10.21)
Acute Kidney Injury *	55.24 (53.48, 56.98)	44.84 (44.13, 45.55)	13.09 (11.95, 14.33)	11.50 (11.05, 11.96)
ACE/ARB *	45.86 (45.25, 46.47)	31.89 (31.63, 32.16)	7.01 (6.71, 7.33)	4.74 (4.62, 4.86)
Loop diuretics *	54.94 (53.68, 56.20)	40.93 (40.32, 41.54)	11.09 (10.32, 11.91)	8.51 (8.17, 8.86)
Non-loop diuretics *	48.52 (47.53, 49.51)	31.90 (31.50, 32.31)	7.77 (7.25, 8.32)	4.29 (4.12, 4.47)

SGLT2i=sodium-glucose co-transporter-2 inhibitor. eGFR=estimated glomerular filtration rate. HbA1c=glycated hemoglobin. ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers.

* Within patients with history of the disease or used the medication

Table S3. Adjusted rates of eGFR dip>10% in SGLT2i and the other antihyperglycemics group

	Adjusted odds ratio (95% confidence interval)	Adjusted rate per 100 patients (95% confidence interval)		Excess rate per 100 patients associated with SGLT2i (95% confidence interval)
		SGLT2i	Other antihyperglycemics	
Overall cohort	1.54 (1.47, 1.61)	40.65 (40.11, 41.19)	30.79 (30.59, 30.98)	9.86 (8.83, 11.00)
Race-White	1.48 (1.41, 1.57)	39.10 (38.49, 39.72)	30.19 (29.96, 30.43)	8.91 (7.77, 10.01)
Race-Black	1.93 (1.72, 2.18)	47.22 (45.7, 48.74)	31.62 (31.17, 32.08)	15.60 (12.81, 18.65)
Race-Other	1.45 (1.26, 1.66)	41.65 (40.05, 43.27)	33.05 (32.46, 33.65)	8.40 (5.38, 11.88)
eGFR≥90 mL/min/1.73 m^2	1.28 (1.16, 1.41)	27.30 (26.36, 28.26)	22.71 (22.37, 23.05)	4.59 (2.75, 6.51)
90>eGFR≥60 mL/min/1.73 m^2	1.62 (1.53, 1.72)	43.00 (42.26, 43.74)	31.76 (31.47, 32.05)	11.28 (9.78, 12.64)
60>eGFR≥45 mL/min/1.73 m^2	1.63 (1.47, 1.81)	47.14 (45.79, 48.50)	35.3 (34.81, 35.80)	11.84 (9.06, 14.75)
45>eGFR≥30 mL/min/1.73 m^2	1.49 (1.13, 1.95)	52.03 (48.26, 55.79)	42.21 (41.5, 42.93)	9.78 (3.35, 16.55)
No albuminuria (≤30 mg/g)	1.43 (1.33, 1.54)	33.96 (33.14, 34.80)	26.43 (26.14, 26.72)	7.53 (5.99, 9.20)
Microalbuminuria (>30- ≤300 mg/g)	1.63 (1.53, 1.74)	43.49 (42.73, 44.26)	32.05 (31.76, 32.33)	11.44 (9.94, 12.91)
Macroalbuminuria (>300 mg/g)	1.48 (1.29, 1.7)	53.60 (51.85, 55.34)	43.83 (43.11, 44.54)	9.77 (6.40, 13.09)
Congestive heart failure *	1.41 (1.22, 1.62)	52.02 (50.27, 53.77)	43.55 (42.7, 44.4)	8.47 (5.18, 1.76)
Acute Kidney Injury *	1.30 (1.11, 1.54)	51.81 (49.9, 53.72)	45.20 (44.49, 45.9)	6.61 (2.96, 11.04)
ACE/ARB *	1.57 (1.50, 1.66)	42.95 (42.31, 43.6)	32.35 (32.09, 32.62)	10.60 (9.27, 11.90)
Loop diuretics *	1.45 (1.30, 1.61)	50.53 (49.20, 51.86)	41.38 (40.78, 41.99)	9.15 (6.52, 12.01)
Non-loop diuretics *	1.66 (1.53, 1.81)	44.40 (43.35, 45.46)	32.44 (32.04, 32.84)	11.96 (9.76, 13.87)

SGLT2i=sodium-glucose co-transporter-2 inhibitor. eGFR=estimated glomerular filtration rate. HbA1c=glycated hemoglobin. ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers. Model adjusted for covariates measured at treatment initiation.
***** Within patients with history of the disease or used the medication

Adjusted rates of eGFR dip>30% in SGLT2i and the other antihyperglycemics group

	Adjusted odds ratio (95% confidence interval)	Adjusted rate per 100 patients (95% confidence interval)		Excess rate per 100 patients associated with SGLT2i (95% confidence interval)
		SGLT2i	Other antihyperglycemics	
Overall cohort	1.28 (1.17, 1.41)	5.40 (5.16, 5.66)	4.26 (4.17, 4.34)	1.15 (0.70, 1.62)

Race-White	1.22 (1.09, 1.37)	4.93 (4.66, 5.21)	4.07 (3.97, 4.17)	0.86 (0.39, 1.36)
Race-Black	1.95 (1.55, 2.47)	8.10 (7.31, 8.97)	4.32 (4.12, 4.52)	3.80 (2.03, 5.63)
Race-Other	0.97 (0.77, 1.21)	5.17 (4.49, 5.95)	5.34 (5.07, 5.64)	-0.17 (-1.20, 1.02)
eGFR≥90 mL/min/1.73 m²	1.18 (0.92, 1.51)	2.91 (2.57, 3.29)	2.48 (2.36, 2.61)	0.43 (-0.24, 1.16)
90>eGFR≥60 mL/min/1.73 m²	1.36 (1.20, 1.53)	5.03 (4.71, 5.36)	3.76 (3.64, 3.88)	1.27 (0.72, 1.81)
60>eGFR≥45 mL/min/1.73 m²	1.39 (1.18, 1.64)	7.97 (7.26, 8.73)	5.85 (5.62, 6.1)	2.11 (0.97, 3.37)
45>eGFR≥30 mL/min/1.73 m²	1.3 (0.84, 2.01)	11.94 (9.7, 14.61)	9.46 (9.04, 9.89)	2.48 (-1.67, 6.98)
No albuminuria (≤30 mg/g)	1.19 (0.99, 1.43)	3.15 (2.85, 3.47)	2.65 (2.55, 2.76)	0.49 (-0.02, 1.10)
Microalbuminuria (>30- ≤300 mg/g)	1.35 (1.19, 1.53)	6.24 (5.88, 6.62)	4.71 (4.58, 4.84)	1.53 (0.84, 2.28)
Macroalbuminuria (>300 mg/g)	1.13 (0.92, 1.39)	10.18 (9.17, 11.29)	9.1 (8.7, 9.53)	1.08 (-0.67, 2.99)
Congestive heart failure *	1.30 (1.04, 1.63)	12.29 (11.19, 13.49)	9.71 (9.21, 10.23)	2.58 (0.23, 5.00)
Acute Kidney Injury *	1.00 (0.77, 1.29)	11.68 (10.51, 12.96)	11.72 (11.27, 12.18)	-0.04 (-2.36, 3.09)
ACE/ARB *	1.29 (1.16, 1.43)	6.22 (5.92, 6.54)	4.90 (4.78, 5.03)	1.32 (0.69, 1.97)
Loop diuretics *	1.18 (0.99, 1.40)	10.19 (9.41, 11.02)	8.79 (8.44, 9.14)	1.40 (-0.09, 3.24)
Non-loop diuretics *	1.46 (1.25, 1.71)	6.31 (5.81, 6.84)	4.41 (4.24, 4.59)	1.90 (1.13, 2.77)

SGLT2i=sodium-glucose co-transporter-2 inhibitor. eGFR=estimated glomerular filtration rate. HbA1c=glycated hemoglobin. ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers. Model adjusted for covariates measured at treatment initiation.

***** Within patients with history of the disease or used the medication

Table S4. Risk of composite cardiovascular and kidney outcomes associated with SGLT2i (vs. other antihyperglycemics) based on mediation analyses.

	Mediator	Hazard ratio of total effect accounted for mediator (95% confidence interval)	Hazard ratio independent of the mediator (95% confidence interval)	Magnitude of effect abrogated by the mediator (95% confidence interval)
Composite cardiovascular outcome *	**eGFR Dip>10%**	0.92 (0.84, 0.99)	0.88 (0.81, 0.92)	-3.78 (-5.44, -2.22)
	eGFR Dip>30%		0.90 (0.82, 0.98)	-1.18 (-2.22, -0.62)
Composite Kidney outcome †	**eGFR Dip>10%**	0.78 (0.71, 0.87)	0.73 (0.65, 0.82)	-4.76 (-6.85, -3.17)
	eGFR Dip>30%		0.76 (0.68, 0.86)	-1.66 (-3.01, -0.87)

Mediation analyses based on inverse odds ratio-weighting for causal mediation analysis and adjusted for covariates measured at treatment initiation.

The total effect accounted for eGFR dipping as the mediator. The hazard ratio independent of mediator represent the effect which was not mediated by eGFR dip. The magnitude of effect abrogated by the mediator was estimated from the difference between hazard ratios independent of eGFR dip and the hazard ratios for the total effect.

* Composite cardiovascular outcome was defined as non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure or all-cause mortality

† Composite kidney outcome was defined as eGFR decline>50%, ESKD or all-cause mortality

Table S5. Risk of composite cardiovascular and kidney outcomes associated with SGLT2i by predicted probability of SGLT2i related eGFR dip.

Outcomes	Group based on probability of eGFR dip	Adjusted hazard ratio (95% confidence interval)	Event rate difference per 100 patient-years (95% confidence interval)
Composite cardiovascular outcome *	High probability of dip>10%	0.92 (0.85. 0.99)	-0.60 (-1.24, -0.05)
	Low probability of dip>10%	0.84 (0.77, 0.93)	-1.30 (-2.04, -0.58)
	High probability of dip>30%	0.89 (0.82, 0.97)	-0.95 (-1.65, -0.22)
	Low probability of dip>30%	0.89 (0.82, 0.97)	-0.88 (-1.48, -0.24)
Composite kidney outcome †	High probability of dip>10%	0.72 (0.65, 0.79)	-0.86 (-1.41, -0.31)
	Low probability of dip>10%	0.62 (0.55, 0.69)	-1.67 (-2.27, -1.03)
	High probability of dip>30%	0.70 (0.62, 0.78)	-0.83 (-1.52, -0.05)
	Low probability of dip>30%	0.66 (0.60, 0.73)	-1.48 (-1.96, -0.92)

High and low probability of eGFR dip categorized based on probability of eGFR dipping associated with SGLT2i above or below the average, which are 11.64% for dip>10% and 1.92% for dip>30%. Model adjusted for covariates measured at treatment initiation.

* Composite cardiovascular outcome was defined as non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure or all-cause mortality

† Composite kidney outcome was defined as eGFR decline>50%, ESKD or all-cause mortality

Table S6. Characteristics associated with discontinuation among SGLT2i users.

	Prevalence (%)	Discontinuation rate per 100 patients * (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
eGFR dip category			
No dip or dip≤10% (reference)	20454 (55.84)	22.10 (21.53, 22.67)	1.00
10%< dip≤ 30%	13850 (37.81)	20.12 (19.46, 20.79)	0.83 (0.78, 0.87)
Dip> 30%	2326 (6.35)	29.58 (27.72, 31.43)	1.23 (1.11, 1.36)
Adverse events			
Bone fracture	263 (0.72)	25.10 (19.86, 30.33)	1.07 (0.80, 1.39)
Amputation	40 (0.11)	45.00 (29.58, 60.42)	2.85 (1.44, 5.66)
Diabetic ketoacidosis	38 (0.10)	31.58 (16.80, 46.36)	1.49 (0.73, 3.02)
Hypoglycemia	820 (2.24)	26.46 (23.44, 29.48)	1.07 (0.91, 1.26)
Pancreatitis	295 (0.81)	27.46 (22.37, 32.55)	1.24 (0.94, 1.62)
Bladder & urinary tract infections	521 (1.42)	45.11 (40.83, 49.38)	2.58 (2.15, 3.10)
Venous thromboembolism	141 (0.38)	24.82 (17.69, 31.95)	1.08 (0.73, 1.62)
Hospitalization not related to adverse events	2326 (6.35)	29.58 (27.72, 31.43)	1.50 (1.33, 1.69)
Increased HbA1c	8413 (22.97)	30.81 (29.82, 31.80)	1.90 (1.80, 2.02)

Characteristics were evaluated within 6 months after treatment initiation. Model adjusted for covariates measured at treatment initiation.

* Discontinuation rate per 100 patients within those with the characteristics

Table S7. Risk of composite cardiovascular and kidney outcomes associated with SGLT2i continuation vs. discontinuation by eGFR dipping category.

Outcomes	Group	Adjusted hazard ratio (95% confidence interval)	Adjusted event rate per 100 patient-years in those who continue SGLT2i (95% confidence interval)	Adjusted event rate per 100 patient-years in those who discontinue SGLT2i (95% confidence interval)	Event rate difference per 100 patient-years (95% confidence interval)
Composite cardiovascular outcome *	**Overall**	0.80 (0.72, 0.88)	5.28 (5.01, 5.59)	6.58 (6.05, 7.16)	-1.31 (-1.89, -0.74)
	No dip or dip≤10%	0.76 (0.66, 0.88)	4.41 (4.05, 4.76)	5.76 (5.09, 6.53)	-1.34 (-2.18, -0.58)
	Dip> 10%	0.84 (0.73, 0.97)	6.43 (5.92, 6.97)	7.61 (6.74, 8.54)	-1.16 (-2.22, -0.20)
	Dip> 30%	0.73 (0.55, 0.97)	8.50 (7.00, 10.06)	11.63 (9.17, 14.45)	-3.06 (-5.81, -0.24)
Composite kidney outcome †	**Overall**	0.72 (0.63, 0.82)	2.76 (2.52, 2.98)	3.81 (3.37, 4.20)	-1.06 (-1.47, -0.59)
	No dip or dip≤10%	0.74 (0.60, 0.91)	1.92 (1.67, 2.15)	2.62 (2.09, 3.10)	-0.68 (-1.18, -0.16)
	Dip> 10%	0.71 (0.61, 0.84)	3.85 (3.45, 4.29)	5.32 (4.59, 6.09)	-1.50 (-2.27, -0.71)
	Dip> 30%	0.70 (0.52, 0.93)	8.22 (6.82, 9.88)	11.66 (9.14, 14.34)	-3.38 (-6.42, -0.72)

Model adjusted for both covariates measured at treatment initiation and characteristics evaluated within 6 months after treatment initiation.

* Composite cardiovascular outcome was defined as non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure or all-cause mortality

† Composite kidney outcome was defined as eGFR decline>50%, ESKD or all-cause mortality

Figure S1. Cohort construction flow.

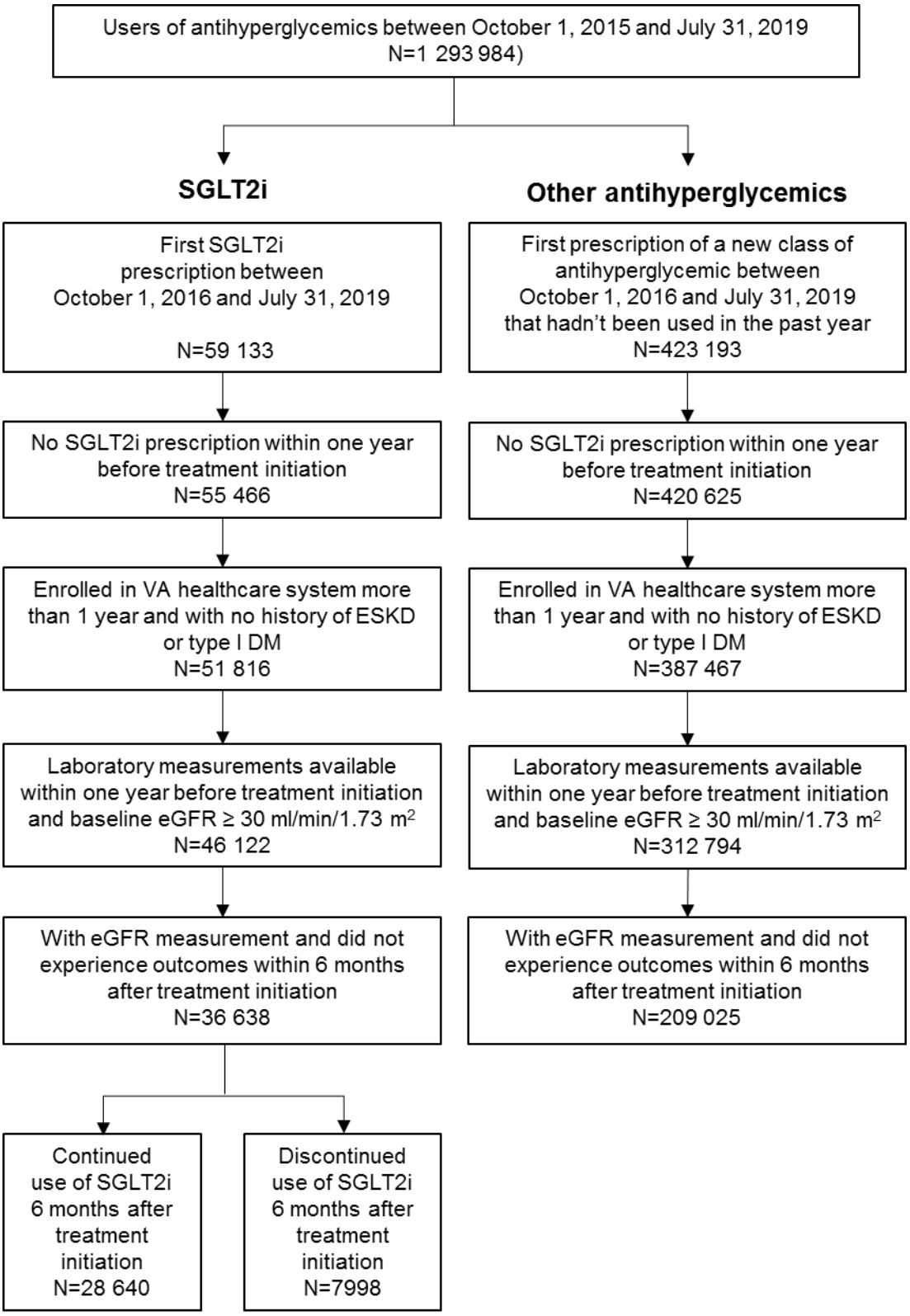


Figure S2. Study timeline.

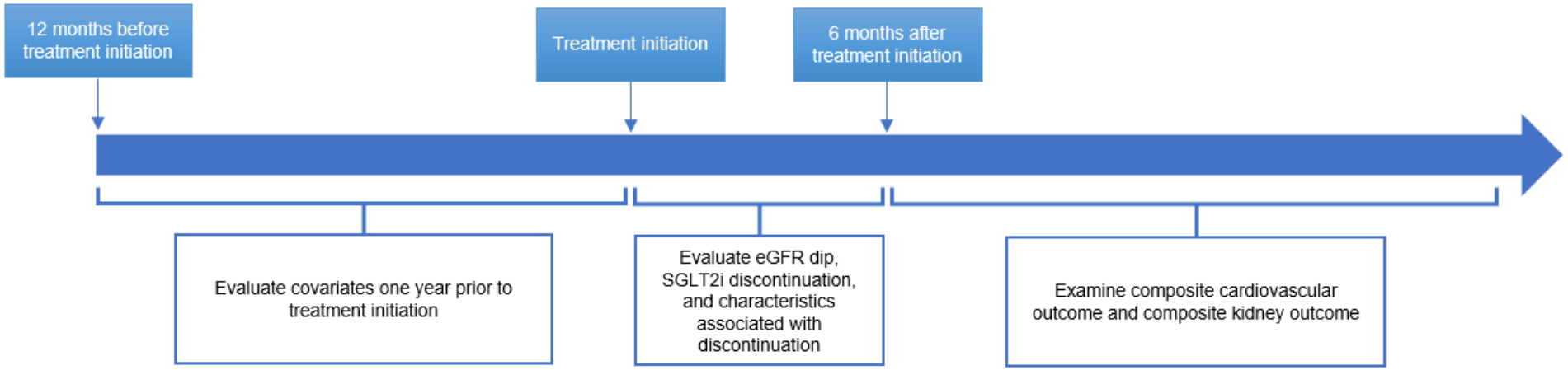


Figure S3. Analytic approach flowchart.

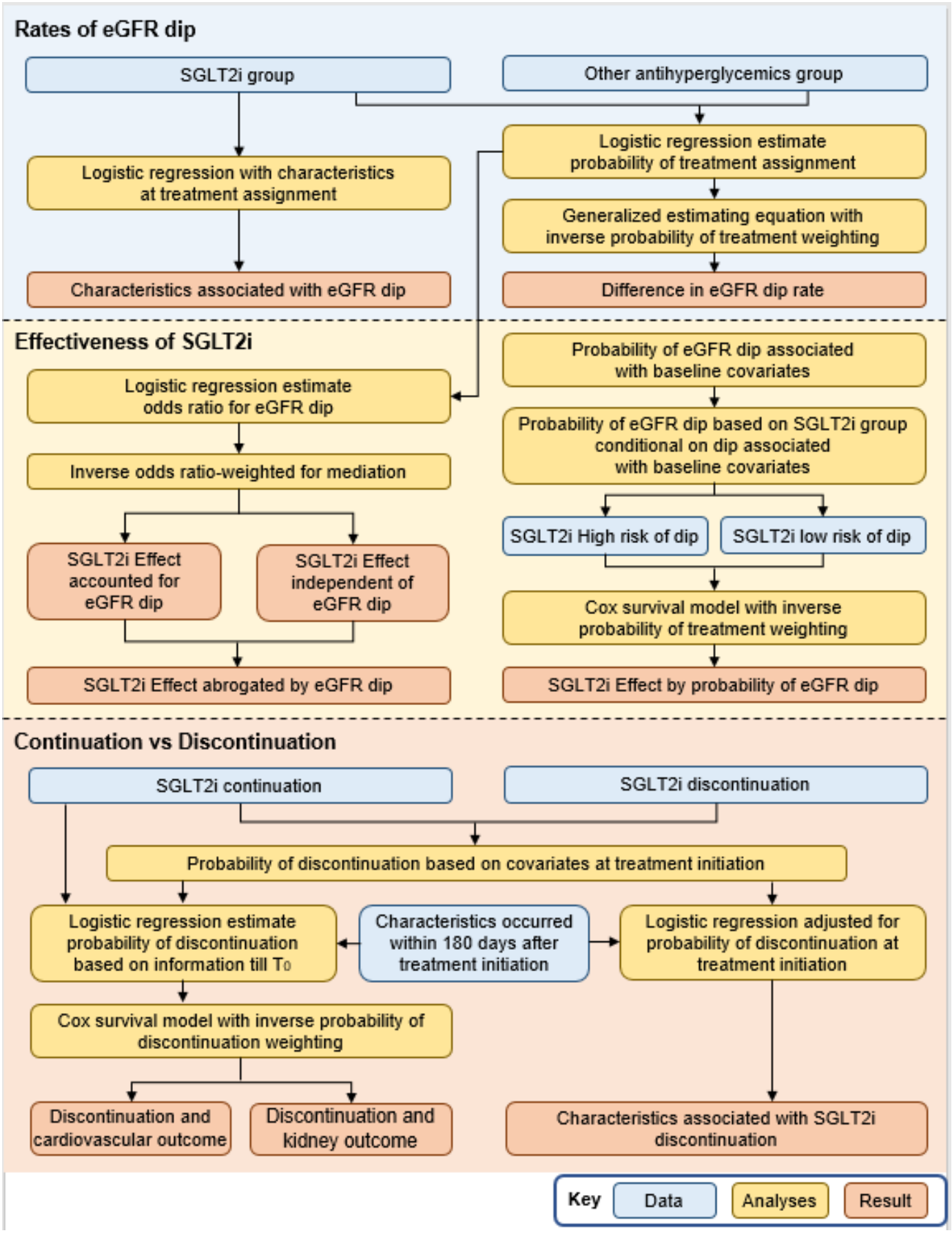
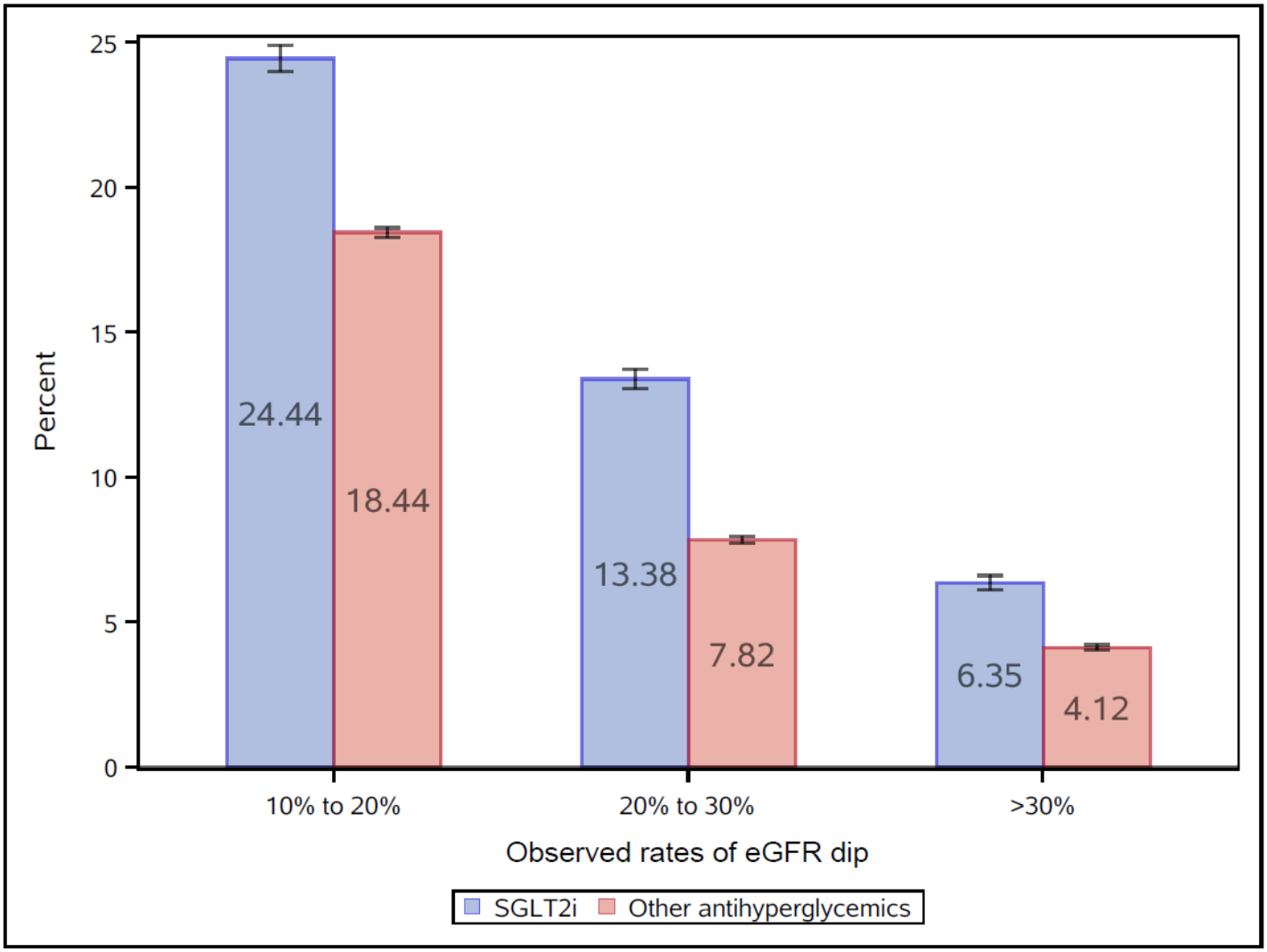


Figure S4. Rates of eGFR dip in the first 6 months among users of SGLT2i and other antihyperglycemics.



Observed rates of eGFR dip >10 to 20%, >20 to 30% and >30% in the SGLT2i group (blue) and the other antihyperglycemics group (red).

Figure S5a. Propensity score distribution in the SGLT2i and other antihyperglycemics groups before weighting

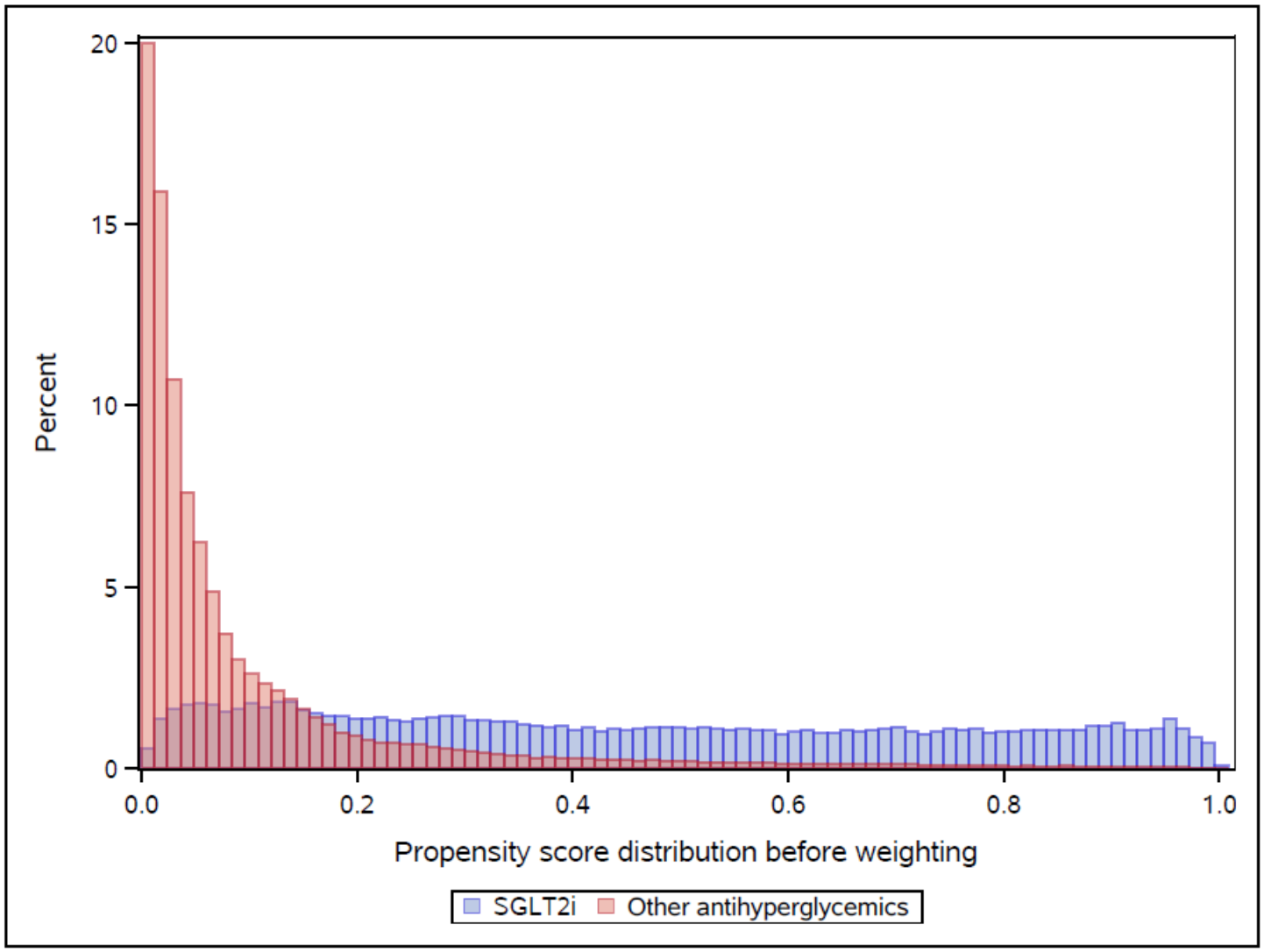


Figure S5b. Propensity score distribution in the SGLT2i and other antihyperglycemics groups after weighting.

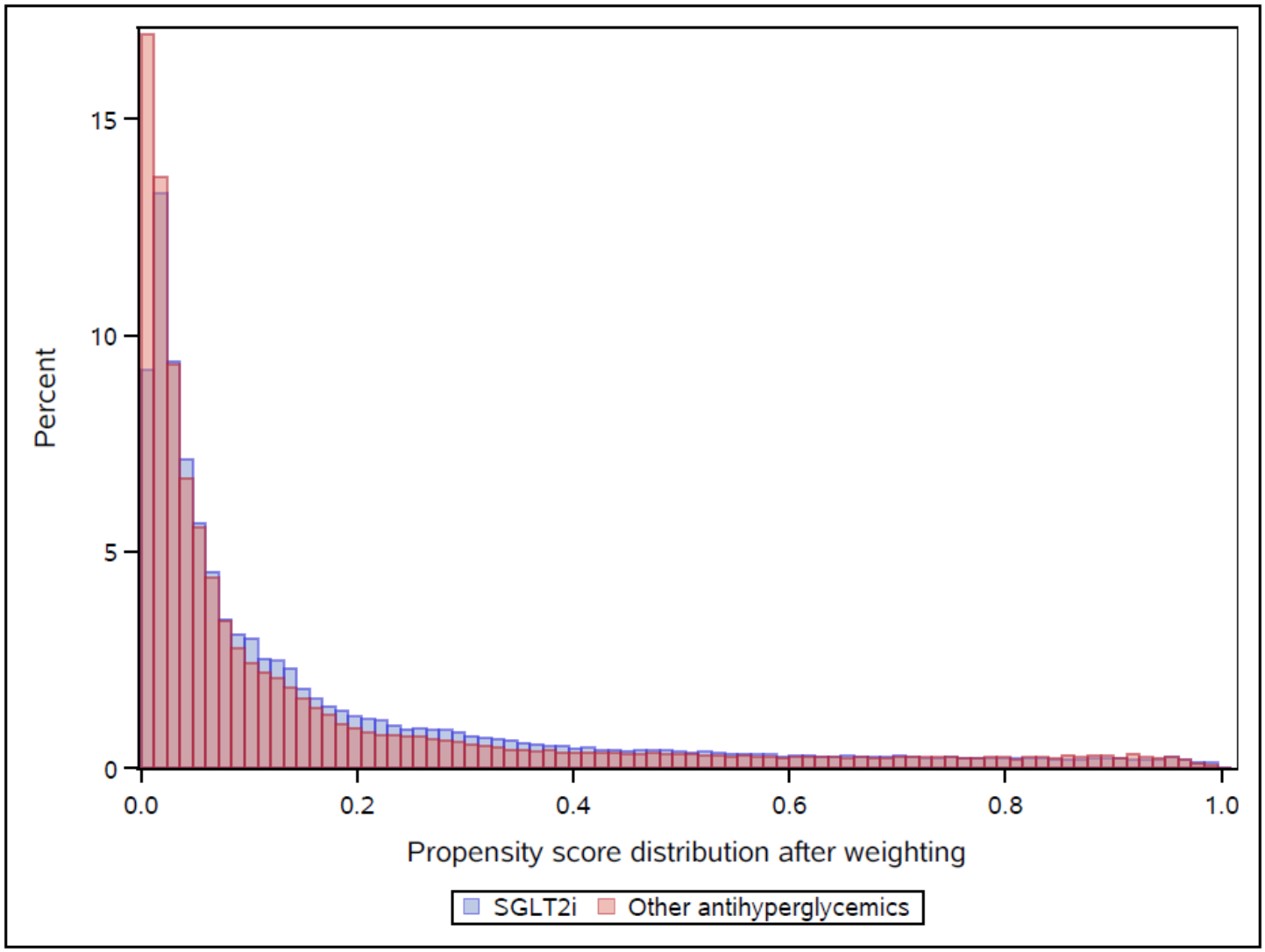


Figure S6a. Propensity score distribution before weighting for those who continued and those who discontinued SGLT2i treatment in the first 6 months.

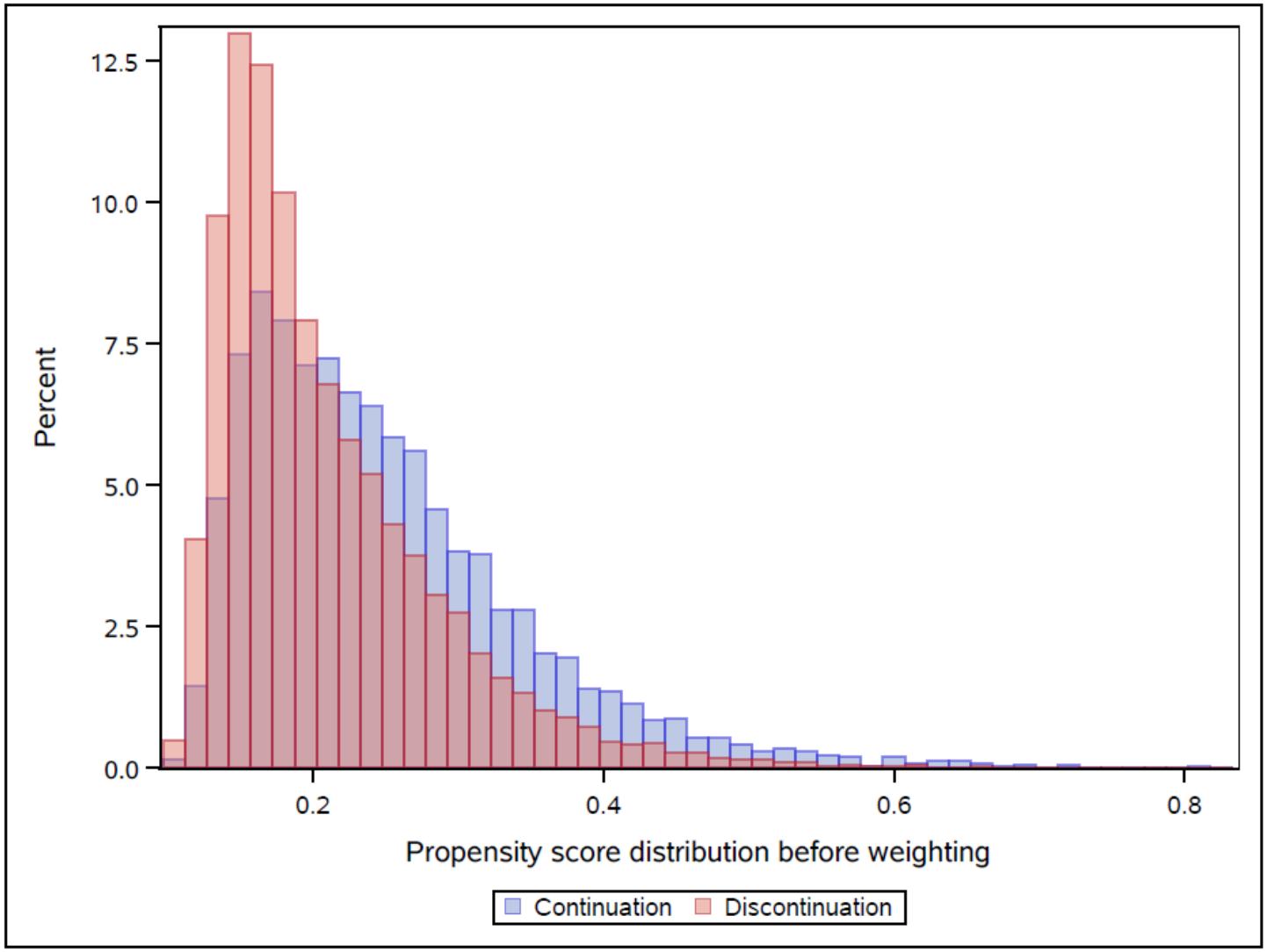


Figure S6b. Propensity score distribution after weighting for those who continued and those who discontinued SGLT2i treatment in the first 6 months.

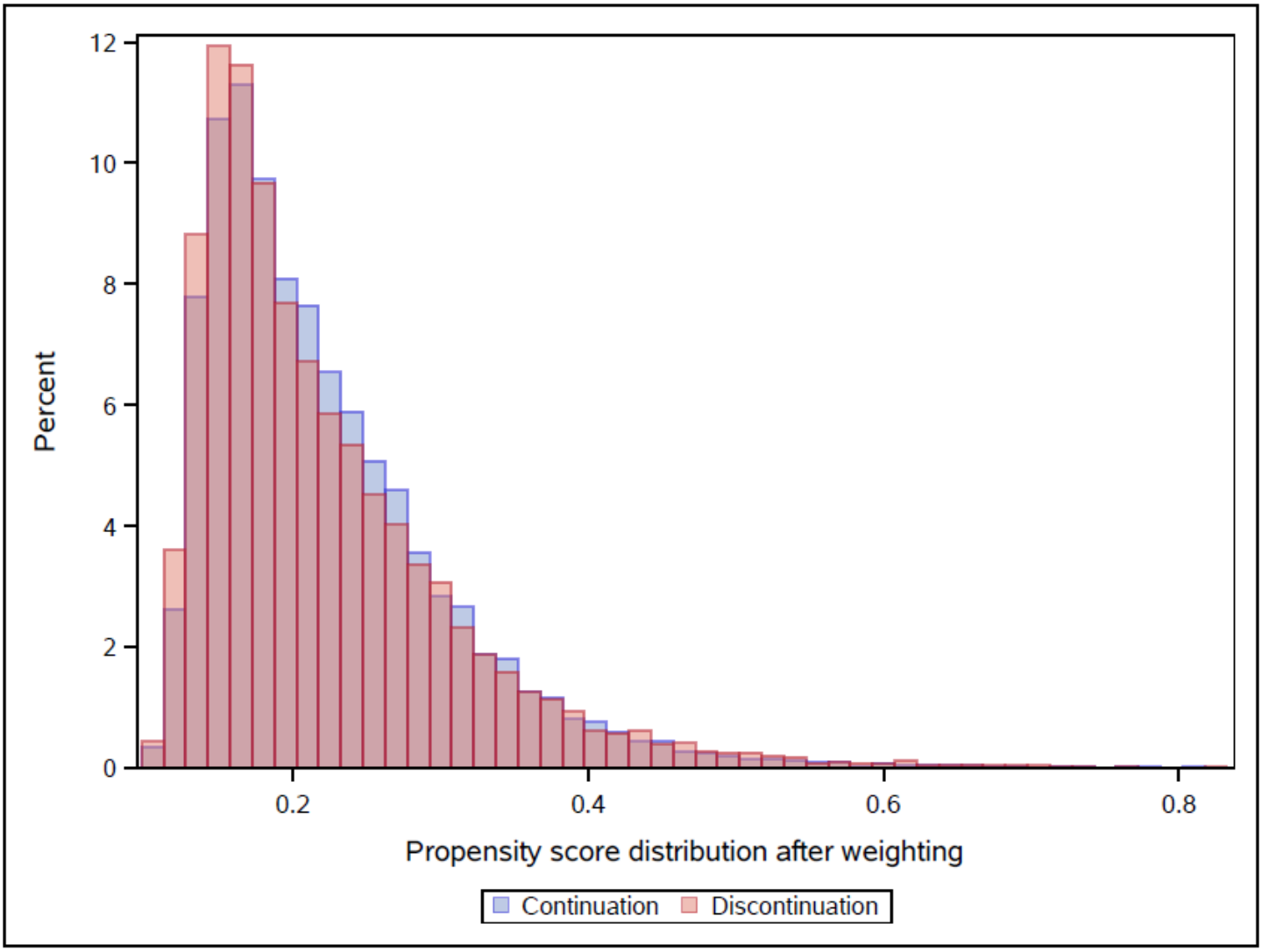
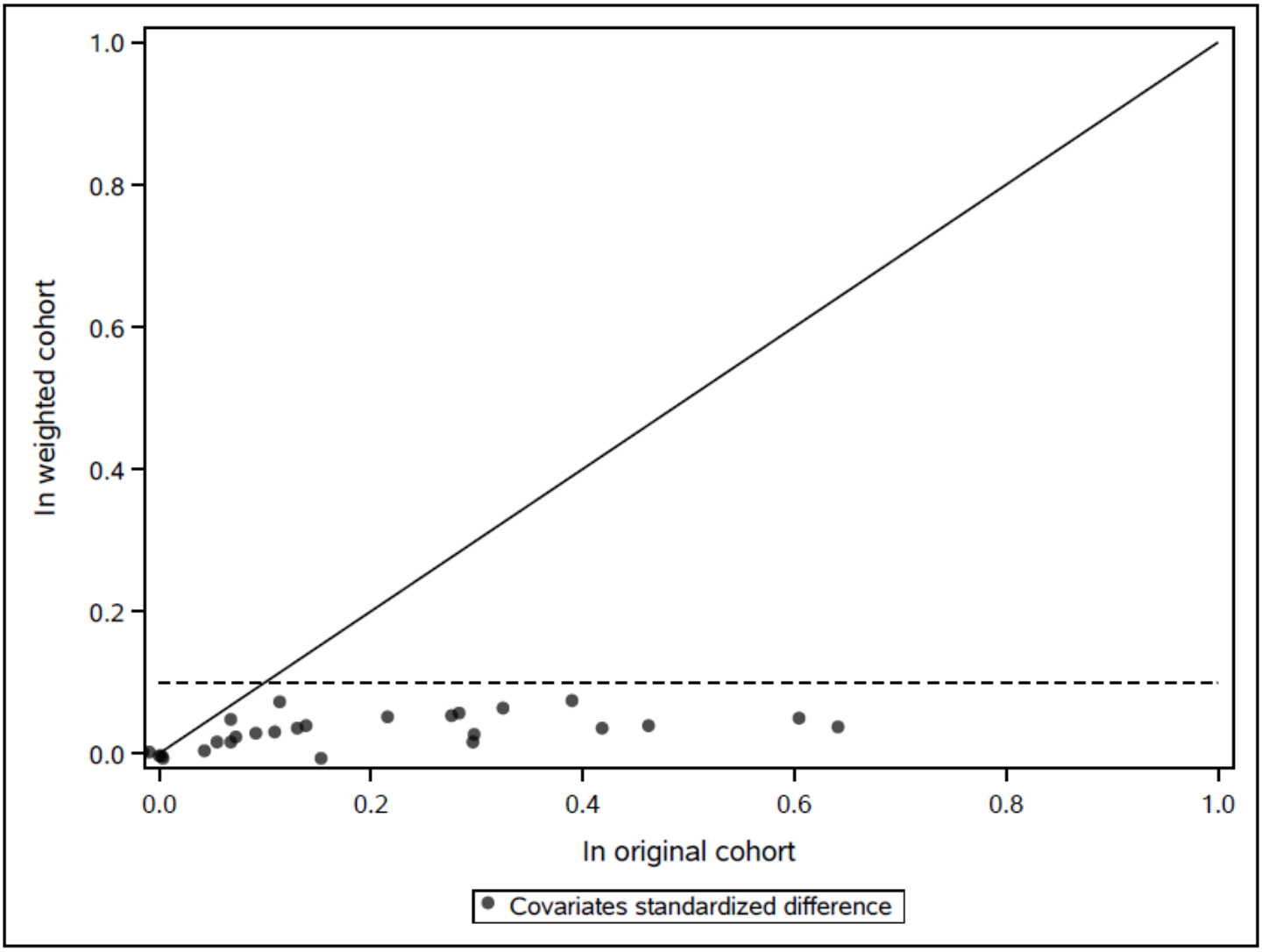
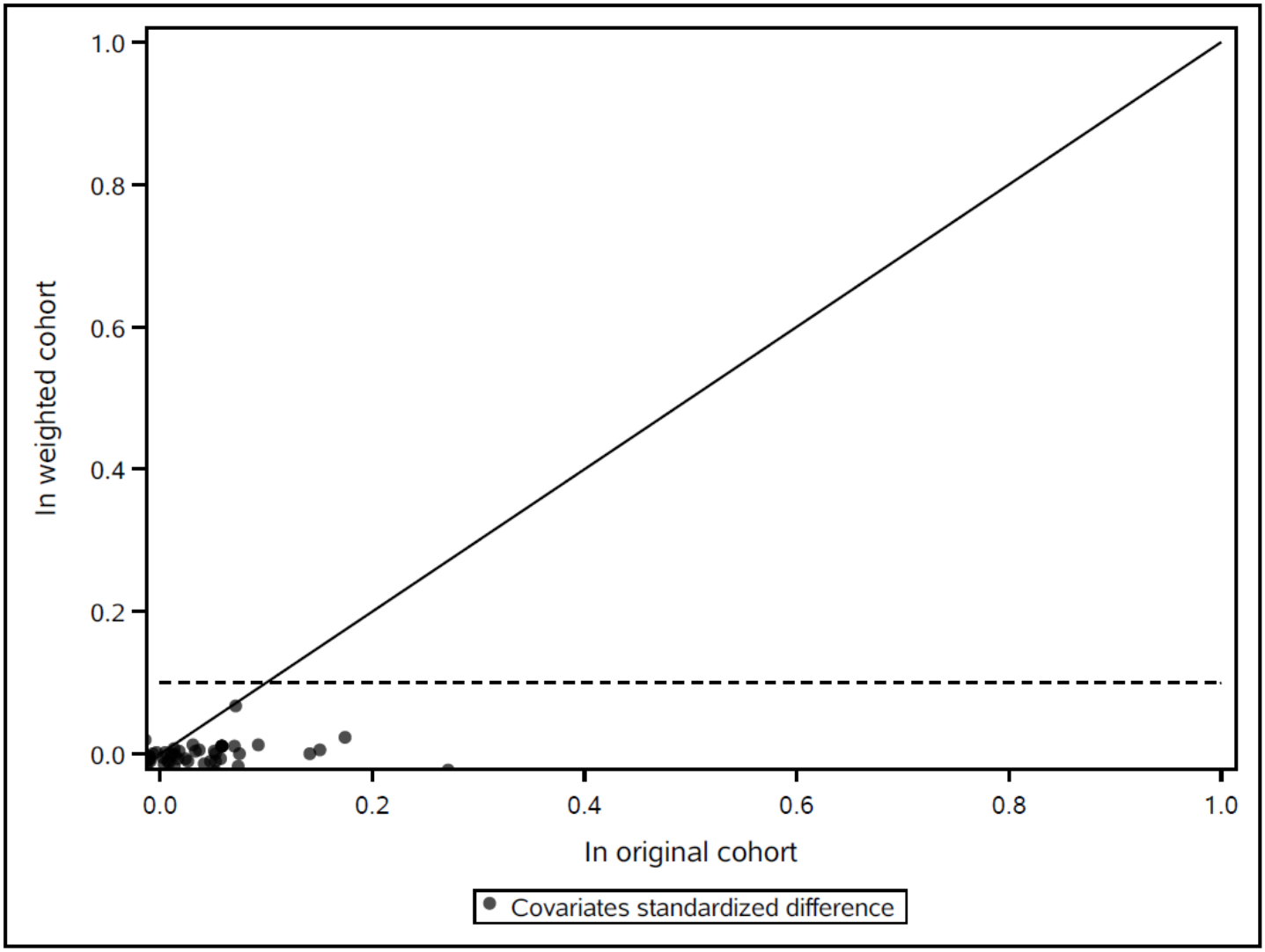


Figure S7a. Standardized difference of covariates between the treatment groups (SGLT2i and other antihyperglycemics) in the original cohort and the weighted cohort.



Standardized difference below 0.1 (below the dashed line) indicated the covariate is well balanced in the weighted cohort.

Figure S7b. Standardized difference of covariates between those who continued and those who discontinued SGLT2i treatment in the first 6 months in the original cohort and the weighted cohort.



Standardized difference below 0.1 (below the dashed line) indicated the covariate is well balanced in the weighted cohort.