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Letter

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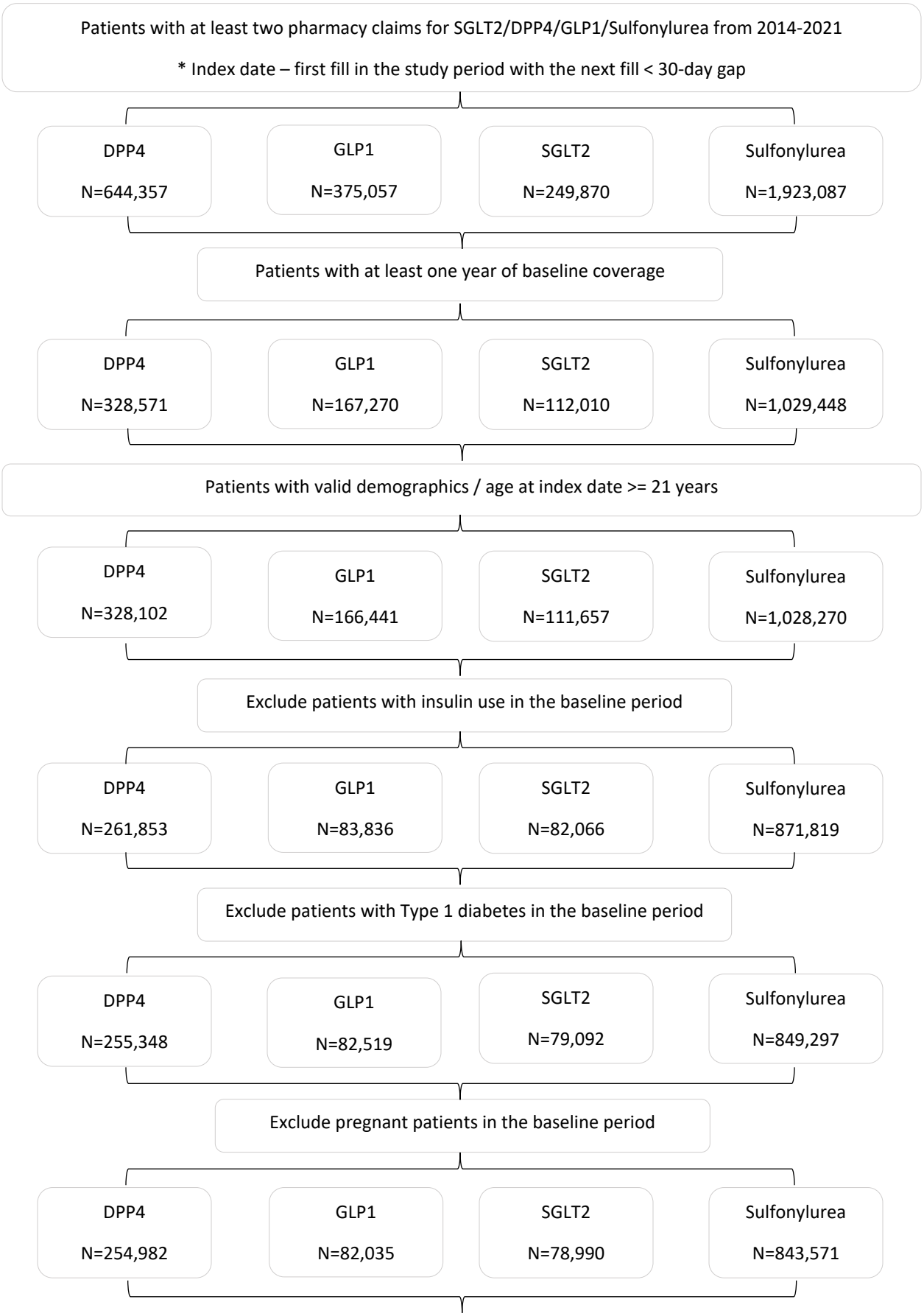
Effectiveness of glucose-lowering medications on cardiovascular outcomes in patients with type 2 diabetes at moderate cardiovascular risk

In the format provided by the authors and unedited

SUPPLEMENTAL MATERIALS

Contents

Figure 1. Cohort build.



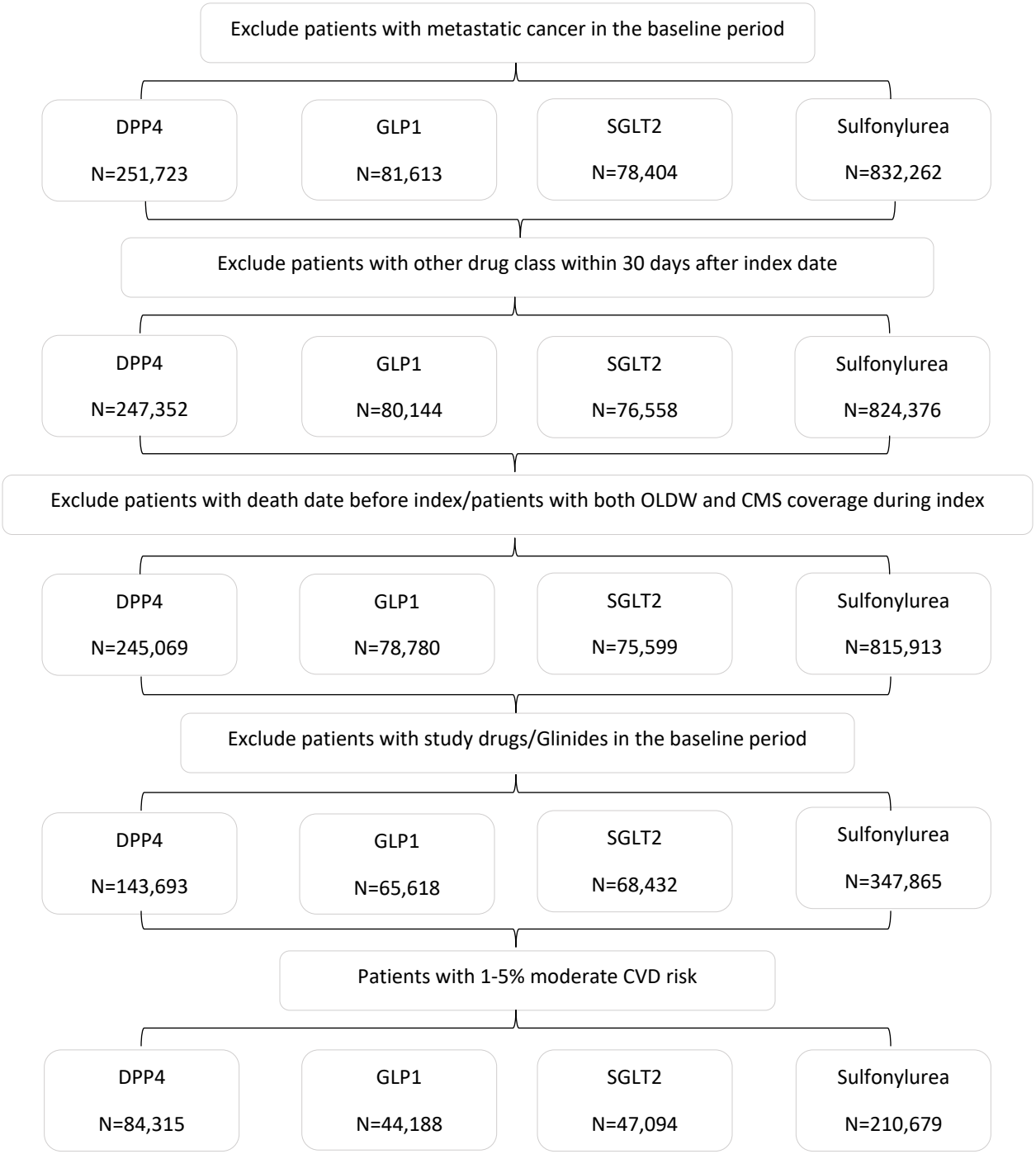

Exclude patients with metastatic cancer in the baseline period
DPP4
N=251,723
GLP1
N=81,613
SGLT2
N=78,404
Sulfonylurea
N=832,262
Exclude patients with other drug class within 30 days after index date
DPP4
N=247,352
GLP1
N=80,144
SGLT2
N=76,558
Sulfonylurea
N=824,376
Exclude patients with death date before index/patients with both OLDW and CMS coverage during index
DPP4
N=245,069
GLP1
N=78,780
SGLT2
N=75,599
Sulfonylurea
N=815,913
Exclude patients with study drugs/Glinides in the baseline period
DPP4
N=143,693
GLP1
N=65,618
SGLT2
N=68,432
Sulfonylurea
N=347,865
Patients with 1-5% moderate CVD risk
DPP4
N=84,315
GLP1
N=44,188
SGLT2
N=47,094
Sulfonylurea
N=210,679

Table 1. Baseline patient characteristics prior to inverse probability of treatment weighting. SMD ≥0.10 are highlighted in bold font.

	DPP4i (N=84,315)	**GLP-1RA** (N=44,188)	**SGLT2i** (N=47,094)	**Sulfonylurea** (N=210,679)	**Total** (N=386,276)	**Largest SMD**
Age, mean (SD)	66.5 (8.2)	61.3 (8.9)	63.5 (8.7)	66.6 (8.0)	65.6 (8.4)	**0.63**
Age group, N (%)						**0.66**
<45	636 (0.8)	626 (1.4)	538 (1.1)	1,894 (0.9)	3,694 (1.0)	
45-49	2,766 (3.3)	3,852 (8.7)	2,527 (5.4)	6,372 (3.0)	15,517 (4.0)	
50-54	5,850 (6.9)	6,967 (15.8)	5,550 (11.8)	13,554 (6.4)	31,921 (8.3)	
55-59	8,003 (9.5)	7,555 (17.1)	6,919 (14.7)	18,405 (8.7)	40,882 (10.6)	
60-64	7,936 (9.4)	6,250 (14.1)	6,357 (13.5)	19,229 (9.1)	39,772 (10.3)	
65-69	23,886 (28.3)	10,037 (22.7)	12,122 (25.7)	64,207 (30.5)	110,252 (28.5)	
70-74	24,381 (28.9)	7,096 (16.1)	9,739 (20.7)	60,918 (28.9)	102,134 (26.4)	
≥75	10,857 (12.9)	1,805 (4.1)	3,342 (7.1)	26,100 (12.4)	42,104 (10.9)	
Sex, N (%)						**0.36**
Female	42,914 (50.9)	27,048 (61.2)	20,427 (43.4)	100,005 (47.5)	190,394 (49.3)	
Male	41,401 (49.1)	17,140 (38.8)	26,667 (56.6)	110,674 (52.5)	195,882 (50.7)	
Race/ethnicity, N (%)						**0.15**
Asian	3,163 (3.8)	679 (1.5)	1,480 (3.1)	6,160 (2.9)	1,1482 (3.0)	
Black	8,803 (10.4)	5,456 (12.3)	4,982 (10.6)	21,245 (10.1)	40,486 (10.5)	
Hispanic	7,290 (8.6)	3,734 (8.5)	4,345 (9.2)	17,796 (8.4)	33,165 (8.6)	
White	62,370 (74.0)	32,792 (74.2)	34,556 (73.4)	159,342 (75.6)	289,060 (74.8)	
Unknown	2,689 (3.2)	1,527 (3.5)	1,731 (3.7)	6,136 (2.9)	12,083 (3.1)	
Region, N (%)						**0.17**
Midwest	19,371 (23.0)	10,696 (24.2)	11,143 (23.7)	60,701 (28.8)	101,911 (26.4)	
Northeast	13,194 (15.6)	4,635 (10.5)	5,714 (12.1)	27,648 (13.1)	51,191 (13.3)	
South	40,312 (47.8)	23,261 (52.6)	23,827 (50.6)	93,633 (44.4)	181,033 (46.9)	
West	11,257 (13.4)	5,559 (12.6)	6,362 (13.5)	28,218 (13.4)	51,396 (13.3)	
Unknown	181 (0.2)	37 (0.1)	48 (0.1)	479 (0.2)	745 (0.2)	

	DPP4i (N=84,315)	**GLP-1RA** (N=44,188)	**SGLT2i** (N=47,094)	**Sulfonylurea** (N=210,679)	**Total** (N=386,276)	**Largest SMD**
Prescriber specialty, N (%)						**0.38**
Cardiology	80 (0.1)	92 (0.2)	328 (0.7)	140 (0.1)	640 (0.2)	
Endocrinology	1,053 (1.2)	2<402 (5.4)	1,299 (2.8)	1,007 (0.5)	5761 (1.5)	
Nephrology	41 (0.0)	19 (0.0)	61 (0.1)	134 (0.1)	255 (0.1)	
Primary care	51,202 (60.7)	21,361 (48.3)	26,264 (55.8)	130,575 (62.0)	229,402 (59.4)	
Others	12,809 (15.2)	7,896 (17.9)	7,139 (15.2)	31,267 (14.8)	59,111 (15.3)	
Unknown	19,130 (22.7)	12,418 (28.1)	12,003 (25.5)	47,556 (22.6)	91,107 (23.6)	
Index year, N (%)						**0.91**
2014	13,515 (16.0)	1,572 (3.6)	2,231 (4.7)	32,032 (15.2)	49,350 (12.8)	
2015	13,367 (15.9)	2,411 (5.5)	4,905 (10.4)	32,125 (15.2)	52,808 (13.7)	
2016	13,409 (15.9)	3,700 (8.4)	4,939 (10.5)	32,669 (15.5)	54,717 (14.2)	
2017	13,372 (15.9)	51,16 (11.6)	6,610 (14.0)	34,141 (16.2)	59,239 (15.3)	
2018	12,498 (14.8)	6,691 (15.1)	6,780 (14.4)	32,200 (15.3)	58,169 (15.1)	
2019	10,622 (12.6)	8,957 (20.3)	9,299 (19.7)	28,152 (13.4)	57,030 (14.8)	
2020	4,223 (5.0)	6,234 (14.1)	5,263 (11.2)	10,304 (4.9)	26,024 (6.7)	
2021	3,309 (3.9)	9,507 (21.5)	7,067 (15.0)	9,056 (4.3)	28,939 (7.5)	
Source data, N (%)						**0.70**
OLDW	34,859 (41.3)	31,536 (71.4)	29,617 (62.9)	81,247 (38.6)	177,259 (45.9)	
Medicare fee-for-service	49,456 (58.7)	12,652 (28.6)	17,477 (37.1)	129,432 (61.4)	209,017 (54.1)	
Comorbidities, N (%)						
Acute MI, months 1-9	157 (0.2)	78 (0.2)	148 (0.3)	377 (0.2)	760 (0.2)	0.03
Acute MI, months 10-12	34 (0.0)	22 (0.0)	48 (0.1)	109 (0.1)	213 (0.1)	0.02
Coronary artery disease (other than acute MI)	12,911 (15.3)	5,791 (13.1)	8,264 (17.5)	31,740 (15.1)	58,706 (15.2)	**0.12**
Acute stroke, months 1-9	85 (0.1)	53 (0.1)	62 (0.1)	257 (0.1)	457 (0.1)	0.01
Acute stroke, months 10-12	21 (0.0)	15 (0.0)	12 (0.0)	70 (0.0)	118 (0.0)	0.01
Cerebrovascular disease (other than acute stroke)	5,401 (6.4)	2,295 (5.2)	2,547 (5.4)	12,201 (5.8)	22,444 (5.8)	0.05
HHF, months 1-9	75 (0.1)	77 (0.2)	104 (0.2)	207 (0.1)	463 (0.1)	0.03

	DPP4i (N=84,315)	**GLP-1RA** (N=44,188)	**SGLT2i** (N=47,094)	**Sulfonylurea** (N=210,679)	**Total** (N=386,276)	**Largest SMD**
HHF, months 10-12	57 (0.1)	27 (0.1)	91 (0.2)	202 (0.1)	377 (0.1)	0.04
Heart failure (other)	1,437 (1.7)	1,170 (2.6)	1,316 (2.8)	3,555 (1.7)	7,478 (1.9)	0.07
Revascularization procedure, months 1-9	923 (1.1)	390 (0.9)	728 (1.5)	2,293 (1.1)	4,334 (1.1)	0.06
Revascularization procedure, months 10-12	466 (0.6)	149 (0.3)	424 (0.9)	1,110 (0.5)	2,149 (0.6)	0.07
Atrial fibrillation/flutter	3,703 (4.4)	1,798 (4.1)	2,051 (4.4)	9,008 (4.3)	16,560 (4.3)	0.02
Hypertension	69,522 (82.5)	34,046 (77.0)	37,941 (80.6)	173,197 (82.2)	314,706 (81.5)	**0.13**
Nephropathy with CKD <stage 3	6,913 (8.2)	2,671 (6.0)	3,203 (6.8)	16,974 (8.1)	29,761 (7.7)	0.08
CKD, stages 3-4	5,035 (6.0)	2,026 (4.6)	1,539 (3.3)	11,446 (5.4)	20,046 (5.2)	**0.13**
CKD stage 5 or ESKD	114 (0.1)	49 (0.1)	24 (0.1)	241 (0.1)	428 (0.1)	0.03
Renal replacement therapy	387 (0.5)	83 (0.2)	75 (0.2)	788 (0.4)	1,333 (0.3)	0.05
Acute kidney injury	2,300 (2.7)	794 (1.8)	662 (1.4)	5,831 (2.8)	9,587 (2.5)	**0.10**
Peripheral vascular disease	5,636 (6.7)	3,014 (6.8)	3,217 (6.8)	13,871 (6.6)	25,738 (6.7)	0.01
Neuropathy	15,431 (18.3)	7,945 (18.0)	7,720 (16.4)	38,909 (18.5)	70,005 (18.1)	0.05
Amputation	265 (0.3)	191 (0.4)	133 (0.3)	785 (0.4)	1,374 (0.4)	0.03
Other lower extremity complication	1,307 (1.6)	659 (1.5)	554 (1.2)	3,552 (1.7)	6,072 (1.6)	0.04
Retinopathy	8,066 (9.6)	3,192 (7.2)	3,881 (8.2)	19,502 (9.3)	34,641 (9.0)	0.08
Treatment for retinopathy	347 (0.4)	164 (0.4)	182 (0.4)	992 (0.5)	1,685 (0.4)	0.02
Blindness	459 (0.5)	179 (0.4)	191 (0.4)	1,220 (0.6)	2,049 (0.5)	0.02
Hyperglycemic crisis	70 (0.1)	16 (0.0)	19 (0.0)	315 (0.1)	420 (0.1)	0.04
Hypoglycemic crisis	81 (0.1)	29 (0.1)	21 (0.0)	246 (0.1)	377 (0.1)	0.03
Obesity	25,509 (30.3)	25,269 (57.2)	18,190 (38.6)	63,077 (29.9)	132,045 (34.2)	**0.57**
Metabolic/bariatric surgery	1,219 (1.4)	1,299 (2.9)	473 (1.0)	2,773 (1.3)	5,764 (1.5)	**0.14**
Pancreatitis	315 (0.4)	108 (0.2)	255 (0.5)	1,302 (0.6)	1,980 (0.5)	0.06
Pancreatic cancer	90 (0.1)	22 (0.0)	64 (0.1)	354 (0.2)	530 (0.1)	0.04
Cancer	8,170 (9.7)	3,027 (6.9)	3,550 (7.5)	19,348 (9.2)	34,095 (8.8)	**0.10**
Smoking (current)	6,837 (8.1)	4,217 (9.5)	4,177 (8.9)	18,489 (8.8)	33,720 (8.7)	0.05

	DPP4i (N=84,315)	**GLP-1RA** (N=44,188)	**SGLT2i** (N=47,094)	**Sulfonylurea** (N=210,679)	**Total** (N=386,276)	**Largest SMD**
Thyroid cancer	359 (0.4)	284 (0.6)	223 (0.5)	658 (0.3)	1,524 (0.4)	0.05
Genitourinary tract infection	4,514 (5.4)	1,886 (4.3)	1,647 (3.5)	10,469 (5.0)	18,516 (4.8)	0.09
Cirrhosis	756 (0.9)	339 (0.8)	346 (0.7)	1,984 (0.9)	3,425 (0.9)	0.02
Dementia	1,246 (1.5)	227 (0.5)	276 (0.6)	2,668 (1.3)	4,417 (1.1)	**0.10**
Falls	3,367 (4.0)	3,935 (8.9)	2,153 (4.6)	7,256 (3.4)	16,711 (4.3)	**0.23**
Urinary incontinence	3,595 (4.3)	2,128 (4.8)	1,343 (2.9)	8,060 (3.8)	15,126 (3.9)	**0.10**
Unplanned hospitalization	6,990 (8.3)	3,138 (7.1)	2,939 (6.2)	18,322 (8.7)	31,389 (8.1)	0.09
Medications, N (%)						
Anti-platelet drug	3,833 (4.5)	1,575 (3.6)	2,613 (5.5)	9,561 (4.5)	17,582 (4.6)	**0.10**
Diuretic	32,753 (38.8)	18,015 (40.8)	17,733 (37.7)	83,697 (39.7)	152,198 (39.4)	0.06
RAAS inhibitor	57,824 (68.6)	26,056 (59.0)	31,536 (67.0)	144,160 (68.4)	259,576 (67.2)	**0.20**
Sacubitril/valsartan	49 (0.1)	63 (0.1)	381 (0.8)	64 (0.0)	557 (0.1)	**0.12**
MRA	1,772 (2.1)	1,751 (4.0)	1,424 (3.0)	4,335 (2.1)	9,282 (2.4)	**0.11**
Beta blocker	28,418 (33.7)	12,585 (28.5)	15,486 (32.9)	71,936 (34.1)	128,425 (33.2)	**0.12**
Calcium channel blocker	22,165 (26.3)	9,983 (22.6)	11,566 (24.6)	54,836 (26.0)	98,550 (25.5)	0.09
Other anti-hypertensive drug	3,887 (4.6)	2,047 (4.6)	1,828 (3.9)	10,804 (5.1)	18,566 (4.8)	0.06
Lipid-lowering medication	60,098 (71.3)	26,146 (59.2)	33,197 (70.5)	143,384 (68.1)	262,825 (68.0)	**0.26**
Oral anti-coagulant	4,257 (5.0)	2,205 (5.0)	2,316 (4.9)	10,388 (4.9)	19,166 (5.0)	0.01
Metformin	69,039 (81.9)	28,140 (63.7)	38,726 (82.2)	167,163 (79.3)	303,068 (78.5)	**0.43**
Thiazolidinedione	4,265 (5.1)	2,006 (4.5)	2,740 (5.8)	8,592 (4.1)	17,603 (4.6)	0.08

Abbreviations: CKD, chronic kidney disease. DPP4i, dipeptidyl peptidase-4 inhibitors. GLP-1RA, glucagon-like peptide-1 receptor agonists. HHF, hospitalization for heart failure. MRA, mineralocorticoid receptor antagonist, RAAS, renin angiotensin aldosterone system. SGLT2i, sodium-glucose cotransporter 2 inhibitors. SMD, standardized mean difference.

Table 2. Standardized mean differences (SMD) for all pairwise comparisons in the unweighted study population. SMD ≥0.10 are highlighted in bold font.

	SU vs. DPP4i	SU vs GLP-1RA	SU vs. SGLT2i	DPP4i vs GLP-1RA	DPP4i vs SGLT2i	GLP-1RA vs SGLT2i	Max SMD
Age	0.02	**0.63**	**0.38**	**0.61**	**0.36**	**0.25**	**0.63**
Age group	0.06	**0.66**	**0.40**	**0.63**	**0.38**	**0.25**	**0.66**
<45							
45-49							
50-54							
55-59							
60-64							
65-69							
70-74							
≥75							
Sex	0.07	**0.28**	0.08	**0.21**	**0.15**	**0.36**	**0.36**
Female							
Male							
Race/ethnicity	0.05	**0.12**	0.06	**0.15**	0.05	0.12	**0.15**
Asian							
Black							
Hispanic							
White							
Unknown							
Region	**0.14**	**0.17**	**0.14**	**0.17**	**0.11**	0.06	**0.17**
Midwest							
Northeast							
South							
West							
Unknown							
Prescriber specialty	0.09	**0.38**	**0.23**	**0.32**	**0.17**	**0.20**	**0.38**

	SU vs. DPP4i	SU vs GLP-1RA	SU vs. SGLT2i	DPP4i vs GLP-1RA	DPP4i vs SGLT2i	GLP-1RA vs SGLT2i	Max SMD
Cardiology							
Endocrinology							
Nephrology							
Primary care							
Other							
Unknown							
Index year	0.04	**0.88**	**0.61**	**0.91**	**0.65**	**0.28**	**0.91**
2014							
2015							
2016							
2017							
2018							
2019							
2020							
2021							
Source data	0.06	**0.70**	**0.50**	**0.64**	**0.44**	**0.18**	**0.70**
Comorbidities							
Acute MI, months 1-9	0.00	0.00	0.03	0.00	0.03	0.03	0.03
Acute MI, months 10-12	0.01	0.00	0.02	0.00	0.02	0.02	0.02
Coronary artery disease (other than acute MI)	0.01	0.06	0.07	0.06	0.06	**0.12**	**0.12**
Acute stroke, months 1-9	0.01	0.00	0.00	0.01	0.01	0.00	0.01
Acute stroke, months 10-12	0.00	0.00	0.00	0.01	0.00	0.00	0.01
Cerebrovascular disease (other than acute stroke)	0.03	0.03	0.02	0.05	0.04	0.01	0.05
HHF, months 1-9	0.00	0.02	0.03	0.02	0.03	0.01	0.03
HHF, months 10-12	0.01	0.01	0.03	0.00	0.03	0.04	0.04
Heart failure (other)	0.00	0.07	0.07	0.06	0.07	0.01	0.07
Revascularization, months 1-9	0.00	0.02	0.04	0.02	0.04	0.06	0.06
Revascularization, months 10-12	0.00	0.03	0.04	0.03	0.04	0.07	0.07

	SU vs. DPP4i	SU vs GLP-1RA	SU vs. SGLT2i	DPP4i vs GLP-1RA	DPP4i vs SGLT2i	GLP-1RA vs SGLT2i	Max SMD
Atrial fibrillation/flutter	0.01	0.01	0.00	0.02	0.00	0.01	0.02
Hypertension	0.01	**0.13**	0.04	**0.13**	0.05	0.09	**0.13**
Nephropathy with CKD <stage 3	0.01	0.08	0.05	0.08	0.05	0.03	0.08
CKD, stages 3-4	0.02	0.04	**0.11**	0.06	**0.13**	0.07	**0.13**
CKD stage 5 or ESKD	0.01	0.00	0.02	0.01	0.03	0.02	0.03
Renal replacement therapy	0.01	0.04	0.04	0.05	0.05	0.01	0.05
Acute kidney injury	0.00	0.07	**0.10**	0.06	0.09	0.03	0.10
Peripheral vascular disease	0.00	0.01	0.01	0.01	0.01	0.00	0.01
Neuropathy	0.00	0.01	0.05	0.01	0.05	0.04	0.05
Amputation	0.01	0.01	0.02	0.02	0.01	0.03	0.03
Other lower extremity complication	0.01	0.02	0.04	0.00	0.03	0.03	0.04
Retinopathy	0.01	0.07	0.04	0.08	0.05	0.04	0.08
Treatment for retinopathy	0.01	0.02	0.01	0.01	0.00	0.00	0.02
Blindness	0.00	0.02	0.02	0.02	0.02	0.00	0.02
Hyperglycemic crisis	0.02	0.04	0.04	0.02	0.02	0.00	0.04
Hypoglycemic crisis	0.01	0.02	0.03	0.01	0.02	0.01	0.03
Obesity	0.01	**0.57**	**0.18**	**0.56**	**0.18**	**0.38**	**0.57**
Bariatric/metabolic surgery	0.01	**0.11**	0.03	**0.10**	0.04	**0.14**	**0.14**
Pancreatitis	0.03	0.06	0.01	0.02	0.02	0.05	0.06
Pancreatic cancer	0.02	0.04	0.01	0.02	0.01	0.03	0.04
Cancer	0.02	0.09	0.06	**0.10**	0.08	0.03	**0.10**
Smoking	0.02	0.03	0.00	0.05	0.03	0.02	0.05
Thyroid cancer	0.02	0.05	0.03	0.03	0.01	0.02	0.05
Genitourinary tract infection	0.02	0.03	0.07	0.05	0.09	0.04	0.09
Cirrhosis	0.00	0.02	0.02	0.01	0.02	0.00	0.02
Dementia	0.02	0.08	0.07	**0.10**	0.09	0.01	**0.10**
Falls	0.03	**0.23**	0.06	**0.20**	0.03	**0.17**	**0.23**
Urinary incontinence	0.02	0.05	0.05	0.03	0.08	**0.10**	**0.10**

	SU vs. DPP4i	SU vs GLP-1RA	SU vs. SGLT2i	DPP4i vs GLP-1RA	DPP4i vs SGLT2i	GLP-1RA vs SGLT2i	Max SMD
Unplanned hospitalization	0.01	0.06	0.09	0.04	0.08	0.03	0.09
Medications							
Anti-platelet drug	0.00	0.05	0.05	0.05	0.05	**0.10**	**0.10**
Diuretic	0.02	0.02	0.04	0.04	0.02	0.06	0.06
RAAS inhibitor	0.00	**0.20**	0.03	**0.20**	0.03	**0.17**	**0.20**
Beta blocker	0.01	**0.12**	0.03	**0.11**	0.02	**0.10**	**0.12**
Calcium channel blocker	0.01	0.08	0.03	0.09	0.04	0.05	0.09
Other anti-hypertensive drug	0.02	0.02	0.06	0.00	0.04	0.04	0.06
Lipid-lowering medication	0.07	**0.19**	0.05	**0.26**	0.02	**0.24**	**0.26**
Oral anti-coagulant	0.01	0.00	0.00	0.00	0.01	0.00	0.01
Metformin	0.06	**0.35**	0.07	**0.42**	0.01	**0.43**	**0.43**
Thiazolidinedione	0.05	0.02	0.08	0.02	0.03	0.06	0.08
Entresto	0.01	0.04	**0.12**	0.03	**0.11**	**0.10**	**0.11**
MRA	0.00	**0.11**	0.06	**0.11**	0.06	0.05	**0.11**

Abbreviations: CKD, chronic kidney disease. DPP4i, dipeptidyl peptidase-4 inhibitors. GLP-1RA, glucagon-like peptide-1 receptor agonists. HHF, hospitalization for heart failure. MI, myocardial infarction. RAAS, renin angiotensin aldosterone system. SGLT2i, sodium-glucose cotransporter 2 inhibitors. SMD, standardized mean difference.

Table 3. Standardized mean differences (SMD) for all pairwise comparisons in the weighted study population.

	SU vs. DPP4i	SU vs GLP-1RA	SU vs. SGLT2i	DPP4i vs GLP-1RA	DPP4i vs SGLT2i	GLP-1RA vs SGLT2i	Max SMD
Age, mean	0.01	0.03	0.03	0.03	0.04	0.00	0.04
Age group	0.01	0.05	0.04	0.06	0.05	0.03	0.06
<45							
45-49							
50-54							
55-59							
60-64							
65-69							
70-74							
≥75							
Sex	0.00	0.00	0.01	0.00	0.01	0.01	0.01
Female							
Male							
Race/ethnicity	0.01	0.04	0.02	0.04	0.02	0.03	0.04
Asian							
Black							
Hispanic							
White							
Unknown							
Region	0.00	0.04	0.02	0.04	0.02	0.03	0.04
Midwest							
Northeast							
South							
West							
Unknown							
Prescriber specialty	0.01	0.02	0.04	0.02	0.03	0.02	0.04

	SU vs. DPP4i	SU vs GLP-1RA	SU vs. SGLT2i	DPP4i vs GLP-1RA	DPP4i vs SGLT2i	GLP-1RA vs SGLT2i	Max SMD
Cardiology							
Endocrinology							
Nephrology							
Primary care							
Other							
Unknown							
Index year	0.01	0.05	0.07	0.05	0.07	0.05	0.07
2014							
2015							
2016							
2017							
2018							
2019							
2020							
2021							
Source data	0.01	0.01	0.02	0.01	0.02	0.01	0.02
Comorbidities							
Acute MI, months 1-9	0.00	0.01	0.00	0.00	0.00	0.00	0.01
Acute MI, months 10-12	0.00	0.01	0.01	0.00	0.00	0.00	0.01
Coronary artery disease (other than MI)	0.00	0.02	0.01	0.02	0.01	0.02	0.02
Acute stroke, months 1-9	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Acute stroke, months 10-12	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Cerebrovascular disease (other than stroke)	0.00	0.00	0.01	0.00	0.01	0.00	0.01
HHF, months 1-9	0.00	0.00	0.00	0.00	0.00	0.01	0.01
HHF, months 10-12	0.00	0.01	0.01	0.01	0.01	0.00	0.01
Heart failure (other)	0.00	0.00	0.00	0.00	0.01	0.00	0.01

	SU vs. DPP4i	SU vs GLP-1RA	SU vs. SGLT2i	DPP4i vs GLP-1RA	DPP4i vs SGLT2i	GLP-1RA vs SGLT2i	Max SMD
Revascularization, months 1-9	0.00	0.01	0.01	0.01	0.01	0.00	0.01
Revascularization, months 10-12	0.00	0.01	0.01	0.00	0.00	0.00	0.01
Atrial fibrillation/flutter	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Hypertension	0.00	0.02	0.01	0.02	0.01	0.03	0.03
Nephropathy with CKD <stage 3	0.00	0.00	0.02	0.00	0.02	0.02	0.02
CKD, stages 3-4	0.00	0.00	0.02	0.00	0.03	0.03	0.03
CKD stage 5 or ESKD	0.00	0.00	0.01	0.00	0.01	0.01	0.01
Renal replacement therapy	0.00	0.00	0.01	0.00	0.01	0.00	0.01
Acute kidney injury	0.00	0.02	0.02	0.02	0.02	0.00	0.02
Peripheral vascular disease	0.00	0.00	0.01	0.00	0.00	0.00	0.01
Neuropathy	0.00	0.01	0.00	0.01	0.00	0.01	0.01
Amputation	0.00	0.00	0.01	0.00	0.01	0.00	0.01
Other lower extremity complication	0.00	0.01	0.01	0.00	0.00	0.00	0.01
Retinopathy	0.00	0.00	0.01	0.00	0.01	0.01	0.01
Treatment for retinopathy	0.00	0.00	0.00	0.00	0.00	0.01	0.01
Blindness	0.00	0.01	0.01	0.01	0.01	0.00	0.01
Hyperglycemic crisis	0.01	0.00	0.01	0.01	0.00	0.01	0.01
Hypoglycemic crisis	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Obesity	0.00	0.03	0.02	0.03	0.02	0.01	0.03
Bariatric/metabolic surgery	0.00	0.00	0.00	0.00	0.00	0.01	0.01
Pancreatitis	0.01	0.01	0.01	0.01	0.00	0.01	0.01
Pancreatic cancer	0.00	0.00	0.00	0.01	0.00	0.01	0.01
Cancer	0.00	0.01	0.00	0.01	0.01	0.01	0.01
Smoking	0.00	0.00	0.01	0.00	0.00	0.00	0.01
Thyroid cancer	0.00	0.01	0.00	0.01	0.00	0.01	0.01

	SU vs. DPP4i	SU vs GLP-1RA	SU vs. SGLT2i	DPP4i vs GLP-1RA	DPP4i vs SGLT2i	GLP-1RA vs SGLT2i	Max SMD
Genitourinary tract infection	0.00	0.01	0.02	0.01	0.01	0.00	0.02
Cirrhosis	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Dementia	0.00	0.01	0.02	0.01	0.02	0.01	0.02
Falls	0.00	0.00	0.01	0.00	0.01	0.01	0.01
Urinary incontinence	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Unplanned hospitalization	0.00	0.02	0.02	0.02	0.01	0.01	0.02
Medications							
Anti-platelet drug	0.00	0.01	0.01	0.01	0.01	0.02	0.02
Diuretic	0.00	0.01	0.01	0.01	0.01	0.01	0.01
RAAS inhibitor	0.00	0.01	0.01	0.01	0.01	0.03	0.03
Beta blocker	0.00	0.01	0.01	0.01	0.01	0.02	0.02
Calcium channel blocker	0.00	0.00	0.01	0.00	0.01	0.01	0.01
Other anti-hypertensive drug	0.00	0.00	0.01	0.00	0.01	0.01	0.01
Lipid-lowering medication	0.00	0.01	0.01	0.01	0.01	0.02	0.02
Oral anti-coagulant	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Metformin	0.00	0.01	0.00	0.01	0.00	0.01	0.01
Thiazolidinedione	0.00	0.02	0.01	0.02	0.01	0.01	0.02
Entresto	0.00	0.01	0.01	0.01	0.01	0.00	0.01
MRA	0.00	0.01	0.00	0.00	0.00	0.01	0.01

Abbreviations: AF, atrial fibrillation/flutter. CKD, chronic kidney disease. DPP4i, dipeptidyl peptidase-4 inhibitors. GLP-1RA, glucagon-like peptide-1 receptor agonists. HHF, hospitalization for heart failure. MI, myocardial infarction. RAAS, renin angiotensin aldosterone system. SGLT2i, sodium-glucose cotransporter 2 inhibitors. SMD, standardized mean difference.

Table 4. Study Outcomes.

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes
Coronary artery bypass grafting surgery, percutaneous coronary intervention, lower extremity revascularization	CABG: Procedure: 36.1x DX: V45.81, 414.02, 414.03, 414.04, 414.05 PCI: DX: V45.82 Procedure: 36.0x, 00.6x (*includes coronary and other*), 00.4x (*includes coronary and other*) LIMB: 39.25, 39.29, 38.08, 38.16, 38.18, 38.38, 38.48, 38.68, 38.88, 39.50, 39.90, 00.55, 84.3, 84.1x	CABG: Procedure: 02100x, 02110x, 02120x, 02130x DX: Z95.1, T82.21x, I25.7x (except I25.75x), I25.810, I25.812 PCI: DX: Z98.61, Z95.5, V45.82 Procedure: 0270x, 0271x, 0272x, 0273x, 02C0x, 02C1x, 02C2x, 02C3x LIMB: 041x, 047x, 04Bx, 04Cx, 04Lx, 04Px, 04Rx (4th letter C-Y, except G, I, O, X)	CABG: 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536, 4110F PCI: 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, 92995, 92996, 92975, 92977
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	I09.81, I11.0, I13.0, I13.2, I50.xx	
Acute myocardial infarction	410.x	I21.x	
Acute stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 430, 431	I63.x, I60.x, I61.x, I69.0x, I69.1x	

Table 5. Independent variables included in the propensity score model.

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
Acute kidney failure	584.xx	N17.0, N17.1, N17.2, N17.8, N17.9		
Atrial fibrillation and flutter	427.31, 427.32	I48.0, I48.1x, I48.2x, I48.91, I48.3, I48.4, I48.92,		
Metabolic/bariatric surgery	V45.86, 43.82, 43.89, 44.38, 44.39, 44.68, 44.95, 44.69, 45.91, 45.51	Z98.84, 0DQ64ZZ, 0DQ60ZZ, 0DB80ZZ, 0D16078, 0D16479, 0DV64CZ, 0D190Z9, 0DB60ZZ	43644, 43645, 43770, 43775, 43842, 43843, 43845, 43846, 43847, S2082, S2085	
Blindness[1]	369.x	H54.x		
Cancer (except non-melanoma skin cancer)[2]	14x.xx, 15x.xx, 160.x-165.x, 170.x-172.x, 174.x-176.x, 179-189.x, 190.x-195.x, 199.xx-208.xx (except 203.x1, 204.x1, 205.x1, 206.x1, 207.x1, 208.x1)	C00.x-C14.x, C15.x-C26.x, C3x.xx, C40.xx-C41.x, C43.x, C4A.xx, C45.x-C49.xx, C50.xxx, C51.x-C58, C60.x-C63.x, C64.x-C68.x, C69.xx-C72.x, C73-C76.x, C7A.xx, C80.xx-C96.x (except C90.x1, C91.x1, C92.x1, C93.x1, C94.x1, C95.x1)		
Cirrhosis	571.2, 571.5, 571.6	K70.3x, K74.3, K74.4, K74.5, K74.6x		
Coronary artery disease (not including hospitalizations for acute MI)	429.2, 410.x, 411.x, 412.x, 413.x, 414.x **excluded hospitalizations for 410.x, if in the first two diagnosis positions*	I20.x, I21.x, I22.x, I23.x, I24x, I25.x **excluded hospitalizations for I21.x, if in the first two diagnosis positions*		
Coronary artery bypass grafting surgery, percutaneous coronary intervention, lower extremity revascularization	CABG: Procedure: 36.1x DX: V45.81, 414.02, 414.03, 414.04, 414.05 PCI: DX: V45.82 Procedure: 36.0x, 00.6x (*includes coronary and other*), 00.4x (*includes coronary and other*) LIMB: 39.25, 39.29, 38.08, 38.16, 38.18, 38.38, 38.48,	CABG: Procedure: 02100x, 02110x, 02120x, 02130x DX: Z95.1, T82.21x, I25.7x (except I25.75x), I25.810, I25.812 PCI: DX: Z98.61, Z95.5, V45.82 Procedure: 0270x, 0271x, 0272x, 0273x, 02C0x, 02C1x, 02C2x, 02C3x LIMB: 041x, 047x, 04Bx, 04Cx, 04Lx, 04Px, 04Rx (4th letter C-Y, except G, I, O, X)	CABG: 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536, 4110F PCI: 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, 92995, 92996, 92975, 92977	

	38.68, 38.88, 39.50, 39.90, 00.55, 84.3, 84.1x			
Cerebrovascular disease (not including hospitalizations for acute stroke)	430, 431, 432.x, 433.xx, 434.xx 435.x, 436, 437.x, 438.xx, V12.54 **excluded hospitalizations for 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 430, 431, if in the first two diagnosis positions*	G45.0, G45.1, G45.2, G45.8, G45.9, G46.x, I60.xx, I61.x, I62.xx, I63.xxx, I65.xx, I66.xx, I67.8x, I67.9, I69.xxx, Z86.73 **excluded hospitalizations for I63.x, I60.x, I61.x, I69.0x, I69.1x, I69.3x, if in the first two diagnosis positions*		
CKD stages 3-4	585.3 (stage 3), 585.4 (stage 4)	N18.3 (stage 3), N18.4 (stage 4)		
CKD stage 5, ESRD	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, V45.11	N18.5, N18.6, I12.0, I13.11, I13.2		
Dementia	046.1x, 290.1x, 290.2x, 290.3, 290.4x, 291.2, 292.82, 294.1x, 294.2x, 331.0, 331.1x, 331.2, 331.6, 331.82, 331.89	A81.0x, F01.5x, F02.8x, F03.9x, F10.27, F10.97, F13.27, F13.97, F18.97, F19.17, F19.27, F19.97, G30.x, G31.0x, G31.1, G31.83, G31.85		
Falls	E88x.x, E987.x	W00.xxxx, W01.xxxx, W03.xxxx, W04.xxxx, W05.xxxx, W06.xxxx, W07.xxxx, W08.xxxx, W09.xxxx, W10.xxxx, W11.xxxx, W12.xxxx, W13.xxxx, W14.xxxx, W15.xxxx, W16.xxxx, W17.xxxx, W18.xxxx, W19.xxxx, Y30.XXXA		
Genitourinary tract infection: Hospitalization/ED visit for UTI (DX1), sepsis with UTI, pyelonephritis, Fournier gangrene[3-6]	UTI: 590.xx, 595.xx, 597.xx, or 599.0x Prostatitis: 601.x Sepsis (038.xx, 790.7, 995.9x, 785.52) + UTI (590.xx, 595.xx, 597.xx, or 599.0x) Pyelo: 590.xx	UTI: N30.xx, N39.0 Prostatitis: N41.x Sepsis (O38.xx, A40.xx, A41.xx, R65.21, R78.81) Pyelo: N10, N15.1 Genital infection: N75.1, N76.0, B37.3, B37.4x		

	Genital infection: 616.x, 112.1, 112.2 FG Men: 608.83* FG Women: 785.4, 616.3, 616.4* + CPT codes 11004, 11006 or ICD-9-PCS 8622 **inpatient claim, or have a hospitalization within 7 days*	FG Men: N49.3* FG Women: N75.1, N76.4, N76.8* + CPT codes 11004, 11006 or ICD-9-PCS 8622 **inpatient claim, or have a hospitalization within 7 days*		
Hyperglycemic crisis	250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23 *DX1 in ED or admission hospital claim*	E10.10, E10.11, E11.10, E11.11, E13.10, E13.11, E11.00, E11.01, E13.00, E13.01 *DX1 in ED or admission hospital claim*		
Hypertension	401.x, 402.xx, 403.xx, 404.xx, 405.xx	I10, I11.x, I12.x, I13.xx, I15.x, I16.x		
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	I09.81, I11.0, I13.0, I13.2, I50.xx		
Hypoglycemic crisis	251.0, 251.1, 251.2, 962.3, 250.8x (for 250.8x: if no concurrent 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1x-707.2x, 707.8, 707.9, 709.3, 730.0x-730.2x, 731.8 on the same date) *DX1 in ED or admission hospital claim*	E10.641, E10.649, E11.641, E11.649, E13.641, E13.649, E16.0, E16.1, E16.2, T38.3X1A, T38.3X1D, T38.3X1S, T38.3X2A, T38.3X2D, T38.3X2S, T38.3X3A, T38.3X3D, T38.3X3S, T38.3X4A, T383X4D, T38.3X4S, T38.3X5A, T383X5D, T38.3X5S *DX1 in ED or admission hospital claim*		
Lower extremity complications: Foot/leg amputation,[1] osteomyelitis, ulcer, [1] Charcot arthropathy[7,8]	Amputation status: V49.7 Osteomyelitis: 730.0x, 730.1x, 730.2, 730.8x, 730.9x	Amputation status: Z89.4x-Z89.6x Osteomyelitis: M01.xx, M86.xx	Amputation procedure: 27590, 27880, 27889, 27888, 27882, 27884, 27886, 28120, 28122, 28124, 28800, 28805, 28810, 28820, or 28825	

	Ulcer: 707.0x, 707.1x, 707.2x, 707.9 Charcot arthropathy: 713.5 Amputation: ICD9 procedure codes 84.10-84.19	Ulcer: L89.5xx, L89.6xxx, L97.2xxx, L97.3xxx, L97.4xxx, L97.5xxx, L97.8xxx, L97.9xxx Charcot arthropathy: M14.6x		
Myocardial infarction	Acute MI: 410.x Old MI: 412.x	Acute MI: I21.x Other MI: I22.x, I23.x, I25.2.x		
Neuropathy	357.2, 337.1, 356.9, 358.1, 458.0, 536.3, 564.5, 596.54, 713.5, 951.0, 951.1, 951.3, 250.6x, 249.6x, 337.0x, 354.x, 355.x	G90.09, G90.8, G90.9, G99.0, G60.9, G73.3, G90.01, I95.1, K31.84, K59.1, N31.9, E08.4x, E09.4x, E10.4x, E11.4x, E13.4x, G56.x, G57.x, H49.x, M14.6x, S04.x		
Obesity	278.00, 278.01, V85.3x, V85.4x	E66.01, E66.09, E66.1, E66.2, E66.8, E66.9, Z68.3x, Z68.4x		
Peripheral vascular disease	442.3, 440.21, 443.81, 443.9, 892.1, 040.0, 444.22, 785.4, 250.7x, 249.7, 707.1x	E08.51, E09.51, E10.51, E11.51, E13.51, E08.59, E09.59, E10.59, E11.59, E13.59, E08.621, E09.621, E10.621, E11.621, E13.621, I72.4, I73.89, I73.9, A48.0, I74.3, I96, E08.52, E09.52, E10.52, E11.52, E13.52, I70.21x, S91.3x, L97.x		
Pneumonia	487.0, 480.x, 481.x 482.x, 483.x, 485.x, 486.x	A01.03, A02.22, A37.01, A37.11, A37.81, A37.91, A50.04, A54.84, B01.2, B05.2, B06.81, B77.81, J09.X1, J13, J14, J17, J84.2, J85.1, J85.2, J95.851, J10.0x, J11.0x, J12.x, J15.x, J16.x, J18.x, J84.11x		
Pancreatitis[9]	577.0	K85.xx		
Pancreatic cancer	157.x	C25.xx History of: Z85.07		
Thyroid cancer	193.x	C73.xx History of: Z85.850		
Retinopathy	362.01, 362.03, 362.04, 362.05, 362.06, 362.07,	H35.9, E08.3x, E09.3x, E10.3x, E11.3x, E13.3x, H35.0x, H35.35x,		

	362.53, 362.81, 362.82, 362.83, 362.02, 379.23, 250.5x, 249.5x, 362.1x, 361.x, 369.x	H35.6x, H35.8x, H33.x, H54.x, H43.1x		
Retinopathy treatment: Intravitreal anti-vascular endothelial growth factor (VEGF) or corticosteroid therapy; focal, grid, panretinal laser photocoagulation[10]	**PDR treatment:** 362.02, 362.16, 362.29, 379.23 in first two diagnosis positions * Exclude 362.35, 362.36, 362.52 in any diagnosis position **PDR surgery:** 361.81, 362.02, 362.16, 362.29, 379.23 in first two diagnosis positions **DME treatment:** 362.07 Diabetes mellitus (250.0x, 250.5x, 362.01-362.06) and macular edema (362.53, 362.83) in first two diagnosis positions * Exclude 362.35, 362.36, 362.52 in any diagnosis position	**PDR treatment:** E11.35x, E13.35x, H35.2x, H43.1x in first two diagnosis positions * Exclude H34.81x, H34.83x, H35.32x in any diagnosis position **PDR surgery:** E11.35x, E13.35x, H33.4x, H35.2x, H43.1x in first two diagnosis positions **DME treatment:** E11.311x, E11.321x, E11.331x, E11.341x, E11.351x, E13.311x, E13.321x, E13.331x, E13.341x, E13.351x in first two diagnosis positions * Exclude H34.81x, H34.83x, H35.32x in any diagnosis position	**PDR treatment:** 67028**, 67228 ** Any drug except corticosteroid (J3301, J3300) * CPT codes are required with the diagnosis codes **PDR surgery:** 67036, 67039, 67040, 67041, 67042, 67113 * CPT codes are required with the diagnosis codes **DME treatment:** 67028, 67210 * CPT codes are required with the diagnosis codes	
Urinary incontinence	625.6, 788.30, 788.31, 788.32, 788.33, 788.34, 788.38, 788.39, 788.91	N39.3, N39.41, N39.42, N39.46, N39.490, N39.492, N39.498, R32, R39.81		
Smoking	305.1, 649.0x, 989.84	F17.xx (except F17.2x1), Z72.0, O99.33x, T65.2x, Z53.01, Z71.6,	4000F, 4001F, 4004F, 99406, 99407, C9801, C9802, G0375, G0376, G0436, G0437, G8402, G8453, G8455, G9276, G9458, G9792	

Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 430, 431	I63.x, I60.x, I61.x, I69.0x, I69.1x, History of: I69.3x		
Renal replacement therapy (dialysis or kidney transplant)	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, 792.5, 996.81, V42.0, V45.1, V45.11, V45.12, V56.x, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8, 39.95, 54.98, 55.53, 55.6, 55.69 *Exclude patients with baseline CKD5 (403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, V45.11)	I12.0, I13.11, I13.2, I95.3, N18.5, N186, R88.0, T81.502x, T81.512x, T81.522x, T81.532x, T81.592x, T85.611x, T85.621x, T85.631x, T85.651x, T85.71x, T86.1, T86.10, T86.11, T86.12, T86.13, T86.19, Y84.1, Z48.22, Z49, Z49.0, Z49.01, Z49.02, Z49.3, Z49.31, Z49.32, Z91.15, Z94.0, Z99.2, 0TT00ZZ, 0TT04ZZ, 0TT10ZZ, 0TT14ZZ, 0TT30ZZ, 0TT34ZZ, 0TT37ZZ, 0TT38ZZ, 0TT40ZZ, 0TT44ZZ, 0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY10Z0, 0TY10Z1, 0TY10Z2, 3E1M39Z, 5A1D00Z, 5A1D60Z Dialysis ICD 10 PCS – 5A1D70Z, 5A1D80Z, 5A1D90Z *Exclude patients with baseline CKD5 (N18.5, N18.6, I12.0, I13.11, I13.2)	50340, 50360, 50365, 50370, 90935, 90937, 90940, 90945, 90947, 90957, 90958, 90959, 90960, 90961, 90962, 90965, 90966, 90969, 90970, 90999, G0257, S9335, 99512 Dialysis CPT – 90921, 90925, 90991, 90992, 90994	0800, 0801, 0802, 0803, 0804, 0805, 0806, 0807, 0808, 0809, 0820, 0821, 0822, 0823, 0824, 0825, 0826, 0827, 0828, 0829, 0830, 0831, 0832, 0833, 0834, 0835, 0836, 0837, 0838, 0839, 0840, 0841, 0842, 0843, 0844, 0845, 0846, 0847, 0848, 0849, 0850, 0851, 0852, 0853, 0854, 0855, 0856, 0857, 0858, 0859, 0880, 0881, 0882, 0883, 0884, 0885, 0886, 0887, 0888, 0889
Mild nephropathy without CKD that is stage 3 or worse	593.9, 586, 250.4x, 249.4x, 580.x, 581.x, 582.x, 583.x, 585.x Excluded patients with the following baseline codes: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, V45.11 585.3, 585.4	E08.21, E08.22, E08.29, E09.21, E09.22, E09.29, E10.21, E10.22, E10.29, E11.21, E11.22, E11.29, E13.21, E13.22, E13.29, N19, N00.x, N03.x, N04.x, N05.x, N18.x Excluded patients with the following baseline codes: N18.5, N18.6, I12.0, I13.11, I13.2 N18.3, N18.4,	Excluded patients with the following baseline codes: 50340, 50360, 50365, 50370, 90935, 90937, 90940, 90945, 90947, 90957, 90958, 90959, 90960, 90961, 90962, 90965, 90966, 90969, 90970, 90999, G0257, S9335, 99512, 90921, 90925, 90991, 90992, 90994	Excluded patients with the following baseline codes: 0800, 0801, 0802, 0803, 0804, 0805, 0806, 0807, 0808, 0809, 0820, 0821, 0822, 0823, 0824, 0825, 0826, 0827, 0828, 0829, 0830, 0831, 0832, 0833, 0834, 0835, 0836, 0837, 0838, 0839, 0840, 0841, 0842, 0843, 0844, 0845, 0846, 0847, 0848, 0849,

	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, 792.5, 996.81, V42.0, V45.1, V45.11, V45.12, V56.x, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8, 39.95, 54.98, 55.53, 55.6, 55.69	I12.0, I13.11, I13.2, I95.3, N18.5, N186, R88.0, T81.502x, T81.512x, T81.522x, T81.532x, T81.592x, T85.611x, T85.621x, T85.631x, T85.651x, T85.71x, T86.1, T86.10, T86.11, T86.12, T86.13, T86.19, Y84.1, Z48.22, Z49, Z49.0, Z49.01, Z49.02, Z49.3, Z49.31, Z49.32, Z91.15, Z94.0, Z99.2, 0TT00ZZ, 0TT04ZZ, 0TT10ZZ, 0TT14ZZ, 0TT30ZZ, 0TT34ZZ, 0TT37ZZ, 0TT38ZZ, 0TT40ZZ, 0TT44ZZ, 0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY10Z0, 0TY10Z1, 0TY10Z2, 3E1M39Z, 5A1D00Z, 5A1D60Z Dialysis ICD 10 PCS – 5A1D70Z, 5A1D80Z, 5A1D90Z		0850, 0851, 0852, 0853, 0854, 0855, 0856, 0857, 0858, 0859, 0880, 0881, 0882, 0883, 0884, 0885, 0886, 0887, 0888, 0889
Screening colonoscopy			00811, 00812, 74263, 81528, 82270, G0104, G0105, G0106, G0120, G0121, G0122, G0327, G0328, G0107, 82270, 82274	
Appendicitis	540.x, 541.x, 542.x, 543.x	K35.x, K36.x, K37.x, K38.x		
Unplanned Hospitalizations	• Source - Readmission Measures Methodology (cms.gov): • Algorithm - 2022 All-Cause Hospital-Wide Measure Updates and Specifications Report: Hospital-Wide Readmission • Code list - 2022 Hospital-Wide Readmission Measure Code Specifications Supplemental File • Codes in each CCS category - HCUP-US Tools and Software Page CCS-Services and Procedures (ahrq.gov)			

Table 6. Medication classes considered as interventions, excluded from analyses, or included as independent variables in the propensity score model.

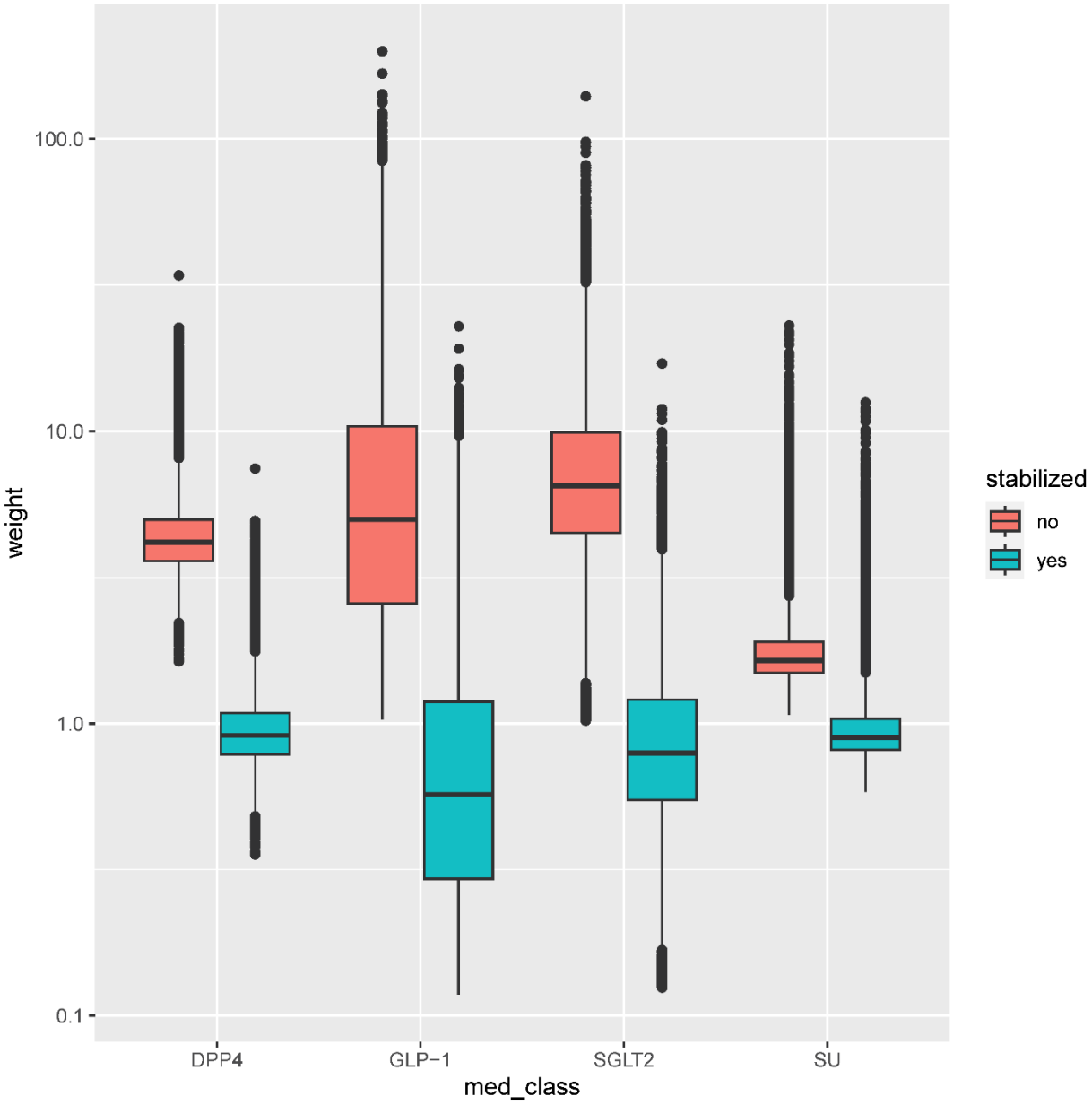
Medication Class	Specific Drugs
Treatment arms	
Sulfonylurea	Glimepiride Glipizide Glyburide
DPP-4 inhibitor	Alogliptin Linagliptin Sitagliptin Saxagliptin
GLP-1 receptor agonist	Exenatide Liraglutide Albiglutide Dulaglutide Semaglutide Lixisenatide
SGLT2 inhibitor	Canagliflozin Empagliflozin Dapagliflozin Ertugliflozin
Other baseline medications included in the propensity score model	
Biguanide	Metformin
Thiazolidinedione	Pioglitazone Rosiglitazone
Anticoagulants	Warfarin (Coumadin, Jantoven) Dabigatran (Pradaxa) Rivaroxaban (Xarelto) Apixaban (Eliquis) Edoxaban (Savaysa) Betrixaban (Bevyxxa)
Antiplatelets	Anagrelide (Agrylin) Cilostazol (Pletal) Clopidogrel (Plavix) Dipyridamole (Aggrenox, Persantine) Prasugrel (Effient) Ticagrelor (Brilinta) Ticlopidine (Ticlid) Vorapaxar (Zontivity) Cangrelor
Statins	Atorvastatin Rosuvastatin Simvastatin Pravastatin Lovastatin Fluvastatin Pitavastatin
Ezetimibe	Ezetimibe
PCSK-9 inhibitors	Alirocumab Evolocumab Inclisiran

RAAS inhibitors	Benazepril Captopril Enalapril Fosinopril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril Azilsartan Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan (without sacubitril) Aliskiren
Sacubitril/valsartan	Sacubitril/valsartan
Diuretics	Bendroflumethiazide Chlorothiazide Chlorthalidone Hydrochlorothiazide Indapamide Methyclothiazide Metolazone Bumetanide Ethacrynate Sodium Ethacrynic acid Furosemide Torsemide Amiloride Triamterene
Mineralocorticoid receptor antagonist (MRA)	Eplerenone Spironolactone
Beta blockers	Atenolol Betaxolol Bisoprolol Metoprolol Tartrate Metoprolol Succinate Nebivolol Nadolol Propranolol Acebutolol Pindolol Timolol Carvedilol Labetalol Esmolol Sotalol
Calcium channel blockers	Amlodipine Felodipine Isradipine Nicardipine

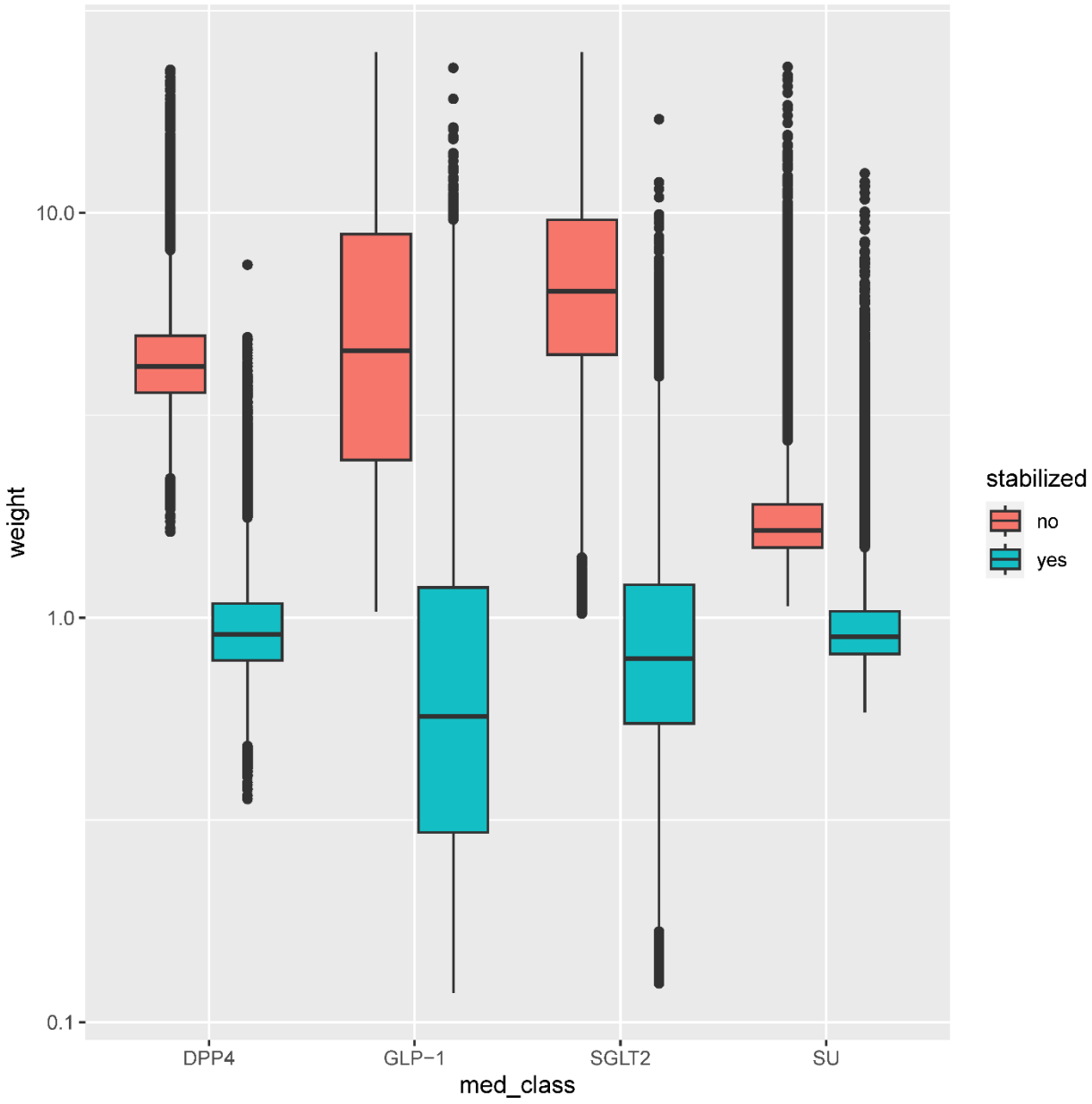
	Nifedipine Nisoldipine Clevidipine Nimodipine Diltiazem Verapamil
Other anti-hypertensives	Doxazosin Prazosin Terazosin Alfuzosin Clonidine Methyldopa Guanfacine Hydralazine Minoxidil Guanethidine Tolazoline Sodium Nitroprusside Phenoxybenzamine Hydrochloride Phentolamine Fenoldopam
Patients treated with the following medications at baseline were excluded from the study	
Glinides	Nateglinide Repaglinide
Basal insulin	NPH Isophane Zinc Glargine Detemir Degludec
Bolus insulin	Regular insulin Beef insulin Pork insulin Aspart Lispro Glulisine

Figure 2. Distribution of original (unstabilized) and stabilized propensity score weights, stratified by drug. Distributions of unstabilized and stabilized weights by treatment group, overall (A) and excluding weights over 25 (B). Sample sizes for each group are: DPP4 inhibitor (N=84,315), GLP-1 receptor agonists (N=44,188), SGLT2 inhibitors (N=47,094), and sulfonylurea (SU) (N=210,679). The box is defined by the 25th and 75th percentiles with the bar in the middle representing the median. Solid vertical lines (whiskers) represent data points within 1.5 times the interquartile range. Any observations beyond are represented as a point.

A



B.


10.0
1.0
0.1
weight
DPP4
GLP−1
SGLT2
SU
med_class
stabilized
no
yes

STATISTICAL ANALYSIS PLAN

Study Title: Second-line Therapies for Patients with Type 2 Diabetes and Moderate Cardiovascular Disease Risk: Cardiovascular Outcomes

Statistical Analysis Plan Authors: Rozalina McCoy, MD MS and Eric Polley, PhD

Analysts: Yihong Deng, PhD, Jeph Herrin, PhD, and Kavya Swarna, MPH

Statistical Analysis Plan Date: September 13, 2022

Update History: SAP was revised in August 2023 based on peer-review feedback and finalized on 10/04/2023. Revised sections are highlighted in yellow.

The purpose of this analysis plan is to provide a detailed description of our methods and decisions, in order to guide our analyst(s). To facilitate replications of our methodology, the information in this document will be included in the final manuscript and supplementary materials.

Table of Contents

1. Study Design

1.1 Study Design

The target trial framework[11] for causal inference will be used for this observational cohort study.

1.2 Data Sources

We will use de-identified administrative claims with linked laboratory results, electronic health record (EHR), and mortality data from the OptumLabs® Data Warehouse (OLDW). OLDW is a de-identified claims dataset comprised of longitudinal health information on enrollees of commercial and Medicare Advantage (MA) health plans, representing a diverse mix of ages, races/ethnicities, incomes, and all 50 U.S. states.[12,13] The claims data in OLDW include medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage enrollees. OptumLabs is a Centers for Medicare and Medicaid Services Qualified entity and for this study will be linked to 100% Medicare FFS (parts A, B, and D) claims by OptumLabs prior to being made available for research use.

1.3 Study Population

In OLDW and linked 100% Medicare FFS data, we will identify adults (≥21 years) who first filled any glucagon-like peptide-1 receptor agonist (GLP-1RA), sodium glucose co-transporter 2 inhibitor (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP-4i), or sulfonylurea (**Table 1**) between 1/1/2014-12/31/2021. The date of the first fill will be used as the index date for each patient. Patients will be required to have a second fill of the study drug class to confirm use and at least 12 months of baseline enrollment with medical and pharmacy coverage prior to the index date to

ascertain baseline covariates. We will allow a 30-day gap between medication fills (between the last day covered by a preceding prescription and the new prescription) to count as continued use.

Exclusion criteria (applied to the baseline 12 months period unless otherwise specified): 1) fill for any study drug during the baseline period; 2) simultaneous (day 0 to day 30 following index date) start of ≥2 study drugs; 3) baseline glinide use (because similar to sulfonylurea); 4) baseline insulin use; 4) type 1 diabetes (defined by presence of any type 1 diabetes codes during the baseline period); 5) baseline pregnancy; 6) baseline metastatic cancer. Patients can enter the cohort only once, the first time they meet eligibility criteria for a treatment arm.

We will then restrict the study population to patients at moderate CVD risk, defined as an annualized risk of experiencing myocardial infarction (MI), stroke, or all-cause mortality of 1-5%. The Annualized Claims-Based Major Adverse Cardiovascular Event Estimator (ACME) was developed and internally validated in the general cohort of adults aged ≥21 years with type 2 diabetes included in OLDW and Medicare FFS data.[14]

Table 1. Glucose-lowering medication classification

Medication Class	**Specific Drugs**
Biguanide	Metformin
Sulfonylurea	Glimepiride Glipizide Glyburide
DPP-4 inhibitor	Alogliptin Linagliptin Sitagliptin Saxagliptin
GLP-1 receptor agonist	Exenatide Liraglutide Albiglutide Dulaglutide Semaglutide Lixisenatide
SGLT2 inhibitor	Canagliflozin Empagliflozin Dapagliflozin Ertugliflozin
Thiazolidinedione	Pioglitazone

Table 1. Glucose-lowering medication classification

Medication Class	Specific Drugs
	Rosiglitazone
Basal insulin	NPH Isophane Zinc Glargine Detemir Degludec
Bolus insulin	Regular insulin Beef insulin Pork insulin Aspart Lispro Glulisine
Other glucose-lowering medications	Pramlintide Acarbose Miglitol
Glinides	Nateglinide Repaglinide
Other baseline medications	
Anticoagulants	Warfarin (Coumadin, Jantoven) Dabigatran (Pradaxa) Rivaroxaban (Xarelto) Apixaban (Eliquis) Edoxaban (Savaysa) Betrixaban (Bevyxxa)
Antiplatelets	Anagrelide (Agrylin) Cilostazol (Pletal) Clopidogrel (Plavix) Dipyridamole (Aggrenox, Persantine) Prasugrel (Effient) Ticagrelor (Brilinta) Ticlopidine (Ticlid) Vorapaxar (Zontivity) Cangrelor
Statins	Atorvastatin Rosuvastatin Simvastatin Pravastatin Lovastatin Fluvastatin Pitavastatin
Ezetimibe	Ezetimibe
PCSK-9 inhibitors	Alirocumab Evolocumab Inclisiran
RAAS inhibitors	Benazepril Captopril Enalapril Fosinopril Lisinopril Moexipril Perindopril Quinapril

Table 1. Glucose-lowering medication classification	
Medication Class	**Specific Drugs**
	Ramipril Trandolapril Azilsartan Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan (without sacubitril) Aliskiren
Sacubitril/valsartan	sacubitril/valsartan
Diuretics	Bendroflumethiazide Chlorothiazide Chlorthalidone Hydeochlorothiazide Indapamide Methyclothiazide Metolazone Bumetanide Ethcrynate Sodium Ethacrynic acid Furosemide Torsemide Amiloride Triamterene
MRA	Eplerenone Spironolactone
Beta blockers	Atenolol Betaxolol Bisoprolol Metoprolol Tartrate Metoprolol Succinate Nebivolol Nadolol Propranalol Acebutolol Pindolol Timolol Carvedilol Labetalol Esmolol Sotalol
Calcium channel blockers	Amlodipine Felodipine Isradipine Nicardipine Nifedipine Nisoldipine Clevidipine Nimodipine Diltiazem

Table 1. Glucose-lowering medication classification	
Medication Class	**Specific Drugs**
	Verapamil
Other anti-hypertensives	Doxazosin Prazosin Terazosin Alfuzosin Clonidine Methyldopa Guanfacine Hydralazine Minoxidil Guanethidine Tolazoline Sodium Nitroprusside Phenoxybenzamine Hydrochloride Phentolamine Fenoldopam

Note: In the original SAP, Sacubitril/valsartan was categorized as a RAAS inhibitor; after peer-review, it was moved to its own medication category. Similarly, Eplerenone and Spironolactone were categorized as diuretics; after peer-review, they were moved to their own medication category.

2. Measurements

2.1 Baseline characteristics

We will record and summarize key baseline characteristics, including socio-demographic, comorbidity, and medication use information by medication class started and overall. Socio-demographic characteristics include age (mean, median, categories: 21-44, 45-54, 55-64, 65-74, ≥75 years), sex, race/ethnicity (White, Black, Hispanic, Asian, unknown), and U.S. region. Age will be analyzed as a continuous variable in the models but reported as a categorical variable in the descriptive tables. Comorbidities recorded during the baseline 12 months will include those listed in **Table 2**. Prescriber specialty of the index drug will be categorized as Cardiologist/ Endocrinologist/ Nephrologist/ Primary Care Physician/ unknown specialty. Baseline medications will be ascertained based on pharmacy claims during the baseline year prior to the index date (metformin; other medications in **Table 1**).

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
Acute kidney failure	584.xx	N17.0, N17.1, N17.2, N17.8, N17.9		
Atrial fibrillation and flutter	427.31, 427.32	I48.0, I48.1x, I48.2x, I48.91, I48.3, I48.4, I48.92,		
Bariatric surgery	V45.86, 43.82, 43.89, 44.38, 44.39, 44.68, 44.95, 44.69, 45.91, 45.51	Z98.84, 0DQ64ZZ, 0DQ60ZZ, 0DB80ZZ, 0D16078, 0D16479, 0DV64CZ, 0D190Z9, 0DB60ZZ	43644, 43645, 43770, 43775, 43842, 43843, 43845, 43846, 43847, S2082, S2085	
Blindness and low vision[1]	369.x	H54.x		
Cancer (except non-melanoma skin cancer) [2]	14x.xx, 15x.xx, 160.x-165.x, 170.x-172.x, 174.x-176.x, 179-189.x, 190.x-195.x, 199.xx-208.xx (except 203.x1, 204.x1, 205.x1, 206.x1, 207.x1, 208.x1)	C00.x-C14.x, C15.x-C26.x, C3x.xx, C40.xx-C41.x, C43.x, C4A.xx, C45.x-C49.xx, C50.xxx, C51.x-C58, C60.x-C63.x, C64.x-C68.x, C69.xx-C72.x, C73-C76.x, C7A.xx, C80.xx-C96.x (except C90.x1, C91.x1, C92.x1, C93.x1, C94.x1, C95.x1)		
Cirrhosis	571.2, 571.5, 571.6	K70.3x, K74.3, K74.4, K74.5, K74.6x		
Coronary artery disease	429.2, 410.x, 411.x, 412.x, 413.x, 414.x	I20.x, I21.x, I22.x, I23.x, I24x, I25.x		

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
Coronary artery bypass grafting surgery, percutaneous coronary intervention, lower extremity revascularization	CABG: Procedure: 36.1x DX: V45.81, 414.02, 414.03, 414.04, 414.05 PCI: DX: V45.82 Procedure: 36.0x, 00.6x (*includes coronary and other*), 00.4x (*includes coronary and other*) LIMB: 39.25, 39.29, 38.08, 38.16, 38.18, 38.38, 38.48, 38.68, 38.88, 39.50, 39.90, 00.55, 84.3, 84.1x	CABG: Procedure: 02100x, 02110x, 02120x, 02130x DX: Z95.1, T82.21x, I25.7x (except I25.75x), I25.810, I25.812 PCI: DX: Z98.61, Z95.5, V45.82 Procedure: 0270x, 0271x, 0272x, 0273x, 02C0x, 02C1x, 02C2x, 02C3x LIMB: 041x, 047x, 04Bx, 04Cx, 04Lx, 04Px, 04Rx (4th letter C-Y, except G, I, O, X)	CABG: 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536, 4110F PCI: 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, 92995, 92996, 92975, 92977	
Cerebrovascular disease	430, 431, 432.x, 433.xx, 434.xx 435.x, 436, 437.x, 438.xx, V12.54	G45.0, G45.1, G45.2, G45.8, G45.9, G46.x, I60.xx, I61.x (except I61.0), I62.xx, I63.xxx, I65.xx, I66.xx, I67.8x (except I67.83, I67.84), I67.9, I69.xxx, Z86.73		
CKD stages 3-4	585.3 (stage 3), 585.4 (stage 4)	N18.3 (stage 3), N18.4 (stage 4)		
CKD stage 5, ESRD	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, V45.11	N18.5, N18.6, I12.0, I13.11, I13.2		

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
Dementia	046.1x, 290.1x, 290.2x, 290.3, 290.4x, 291.2, 292.82, 294.1x, 294.2x, 331.0, 331.1x, 331.2, 331.6, 331.82, 331.89	A81.0x, F01.5x, F02.8x, F03.9x, F10.27, F10.97, F13.27, F13.97, F18.97, F19.17, F19.27, F19.97, G30.x, G31.0x, G31.1, G31.83, G31.85		
Falls	E88x.x, E987.x	W00.xxxx, W01.xxxx, W03.xxxx, W04.xxxx, W05.xxxx, W06.xxxx, W07.xxxx, W08.xxxx, W09.xxxx, W10.xxxx, W11.xxxx, W12.xxxx, W13.xxxx, W14.xxxx, W15.xxxx, W16.xxxx, W17.xxxx, W18.xxxx, W19.xxxx, Y30.XXXA		
Genitourinary tract infection: Hospitalization/ED visit for UTI (DX1), sepsis with UTI, pyelonephritis, Fournier gangrene[3-6]	UTI: 590.xx, 595.xx, 597.xx, or 599.0x Prostatitis: 601.x Sepsis (038.xx, 790.7, 995.9x, 785.52) + UTI (590.xx, 595.xx, 597.xx, or 599.0x) Pyelo: 590.xx Genital infection: 616.x, 112.1, 112.2 FG Men: 608.83* FG Women: 785.4, 616.3, 616.4* + CPT codes 11004, 11006 or ICD-9-PCS 8622 **inpatient claim, or have a hospitalization within 7 days*	UTI: N30.xx, N39.0 Prostatitis: N41.x Sepsis (O38.xx, A40.xx, A41.xx, R65.21, R78.81) Pyelo: N10, N15.1 Genital infection: N75.1, N76.0, B37.3, B37.4x FG Men: N49.3* FG Women: N75.1, N76.4, N76.8* + CPT codes 11004, 11006 or ICD-9-PCS 8622 **inpatient claim, or have a hospitalization within 7 days*		

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
DKA/HHS	250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23 *DX1 in ED or admission hospital claim*	E10.10, E10.11, E11.10, E11.11, E13.10, E13.11, E11.00, E11.01, E13.00, E13.01 *DX1 in ED or admission hospital claim*		
Hyperlipidemia	272.0, 272.1, 272.3, 273.4	E78.xx		
Hypertension	401.x, 402.xx, 403.xx, 404.xx, 405.xx	I10, I11.x, I12.x, I13.xx, I15.x, I16.x		
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	I09.81, I11.0, I13.0, I13.2, I50.xx		
Hypoglycemia	251.0, 251.1, 251.2, 962.3, 250.8x (for 250.8x: if no concurrent 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1x-707.2x, 707.8, 707.9, 709.3, 730.0x-730.2x, 731.8 on the same date) *DX1 in ED or admission hospital claim*	E10.641, E10.649, E11.641, E11.649, E13.641, E13.649, E16.0, E16.1, E16.2, T38.3X1A, T38.3X1D, T38.3X1S, T38.3X2A, T38.3X2D, T38.3X2S, T38.3X3A, T38.3X3D, T38.3X3S, T38.3X4A, T383X4D, T38.3X4S, T38.3X5A, T383X5D, T38.3X5S *DX1 in ED or admission hospital claim*		
Lower extremity complications: Foot/leg amputation,[1] osteomyelitis, ulcer, [1]Charcot arthropathy[7,8]	Amputation status: V49.7 Osteomyelitis: 730.0x, 730.1x, 730.2, 730.8x, 730.9x Ulcer: 707.0x, 707.1x, 707.2x, 707.9 Charcot arthropathy: 713.5	Amputation status: Z89.4x-Z89.6x Osteomyelitis: M01.xx, M86.xx Ulcer: L89.5xx, L89.6xxx, L97.2xxx, L97.3xxx, L97.4xxx, L97.5xxx, L97.8xxx, L97.9xxx Charcot arthropathy: M14.6x	Amputation procedure: 27590, 27880, 27889, 27888, 27882, 27884, 27886, 28120, 28122, 28124, 28800, 28805, 28810, 28820, or 28825	

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
	Amputation: ICD9 procedure codes 84.10-84.19			
Myocardial infarction	Acute MI: 410.x Old MI: 412.x	Acute MI: I21.x Other MI: I22.x, I23.x, I25.2.x		
Metastatic cancer [1,2]	196.xx, 197.xx, 198.xx	C77.xx, C78.xx, C79.xx		
Mild nephropathy	593.9, 586, 250.4x, 249.4x, 580.x, 581.x, 582.x, 583.x, 585.x *Exclude patients with baseline CKD5/ESKD (403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, 792.5, 996.81, V42.0, V45.1, V45.11, V45.12, V56.x, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8, 39.95, 54.98, 55.53, 55.6, 55.69) *Exclude patients with baseline CKD3-4 (585.3 (stage 3), 585.4 (stage 4)	E08.21, E08.22, E08.29, E09.21, E09.22, E09.29, E10.21, E10.22, E10.29, E11.21, E11.22, E11.29, E13.21, E13.22, E13.29, N19, N00.x, N03.x, N04.x, N05.x, N18.x *Exclude patients with baseline CKD5/ESKD (I12.0, I13.11, I13.2, I95.3, N18.5, N18.6, R88.0, T81.502x, T81.512x, T81.522x, T81.532x, T81.592x, T85.611x, T85.621x, T85.631x, T85.651x, T85.71x, T86.1, T86.10, T86.11, T86.12, T86.13, T86.19, Y84.1, Z48.22, Z49, Z49.0, Z49.01, Z49.02, Z49.3, Z49.31, Z49.32, Z91.15, Z94.0, Z99.2, 0TT00ZZ, 0TT04ZZ, 0TT10ZZ, 0TT14ZZ, 0TT30ZZ, 0TT34ZZ, 0TT37ZZ, 0TT38ZZ, 0TT40ZZ, 0TT44ZZ, 0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY10Z0, 0TY10Z1, 0TY10Z2, 3E1M39Z, 5A1D00Z, 5A1D60Z	*Exclude patients with baseline ESKD (50340, 50360, 50365, 50370, 90935, 90937, 90940, 90945, 90947, 90957, 90958, 90959, 90960, 90961, 90962, 90965, 90966, 90969, 90970, 90999, G0257, S9335, 99512 Dialysis CPT – 90921, 90925, 90991, 90992, 90994)	*Exclude patients with baseline ESKD (0800, 0801, 0802, 0803, 0804, 0805, 0806, 0807, 0808, 0809, 0820, 0821, 0822, 0823, 0824, 0825, 0826, 0827, 0828, 0829, 0830, 0831, 0832, 0833, 0834, 0835, 0836, 0837, 0838, 0839, 0840, 0841, 0842, 0843, 0844, 0845, 0846, 0847, 0848, 0849, 0850, 0851, 0852, 0853, 0854, 0855, 0856, 0857, 0858, 0859, 0880, 0881, 0882, 0883, 0884, 0885, 0886, 0887, 0888, 0889)

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
		Dialysis ICD 10 PCS – 5A1D70Z, 5A1D80Z, 5A1D90Z) *Exclude patients with baseline CKD3-4 (N18.3 (stage 3), N18.4 (stage 4)		
Neuropathy	357.2, 337.1, 356.9, 358.1, 458.0, 536.3, 564.5, 596.54, 713.5, 951.0, 951.1, 951.3, 250.6x, 249.6x, 337.0x, 354.x, 355.x	G90.09, G90.8, G90.9, G99.0, G60.9, G73.3, G90.01, I95.1, K31.84, K59.1, N31.9, E08.4x, E09.4x, E10.4x, E11.4x, E13.4x, G56.x, G57.x, H49.x, M14.6x, S04.x		
Obesity	278.00, 278.01, V85.3x, V85.4x	E66.01, E66.09, E66.1, E66.2, E66.8, E66.9, Z68.3x, Z68.4x		
Peripheral vascular disease	442.3, 440.21, 443.81, 443.9, 892.1, 040.0, 444.22, 785.4, 250.7x, 249.7, 707.1x	E08.51, E09.51, E10.51, E11.51, E13.51, E08.59, E09.59, E10.59, E11.59, E13.59, E08.621, E09.621, E10.621, E11.621, E13.621, I72.4, I73.89, I73.9, A48.0, I74.3, I96, E08.52, E09.52, E10.52, E11.52, E13.52, I70.21x, S91.3x, L97.x		
Pneumonia	487.0, 480.x, 481.x 482.x, 483.x, 485.x, 486.x	A01.03, A02.22, A37.01, A37.11, A37.81, A37.91, A50.04, A54.84, B01.2, B05.2, B06.81, B77.81, J09.X1, J13, J14, J17, J84.2, J85.1, J85.2, J95.851, J10.0x, J11.0x, J12.x, J15.x, J16.x, J18.x, J84.11x		
Pancreatitis[9]	577.0	K85.xx		

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
Pancreatic cancer	157.x	C25.xx History of: Z85.07 (f*or baseline comorbidities only, not for outcomes*)		
Thyroid cancer	193.x	C73.xx History of: Z85.850 (f*or baseline comorbidities only, not for outcomes*)		
Pregnancy	630.xx-679.xx, V22.x, V23.x	O00-O9A, Z33.x, Z34.x		
Retinopathy	362.01, 362.03, 362.04, 362.05, 362.06, 362.07, 362.53, 362.81, 362.82, 362.83, 362.02, 379.23, 250.5x, 249.5x, 362.1x, 361.x, 369.x	H35.9, E08.3x, E09.3x, E10.3x, E11.3x, E13.3x, H35.0x, H35.35x, H35.6x, H35.8x, H33.x, H54.x, H43.1x		
Retinopathy treatment: Intravitreal anti-vascular endothelial growth factor (VEGF) or corticosteroid therapy; focal, grid, panretinal laser photocoagulation[10]	**PDR treatment:** 362.02, 362.16, 362.29, 379.23 in first two diagnosis positions * Exclude 362.35, 362.36, 362.52 in any diagnosis position **PDR surgery:** 361.81, 362.02, 362.16, 362.29, 379.23 in first two diagnosis positions **DME treatment:** 362.07	**PDR treatment:** E11.35x, E13.35x, H35.2x, H43.1x in first two diagnosis positions * Exclude H34.81x, H34.83x, H35.32x in any diagnosis position **PDR surgery:** E11.35x, E13.35x, H33.4x, H35.2x, H43.1x in first two diagnosis positions **DME treatment:**	**PDR treatment:** 67028**, 67228 ** Any drug except corticosteroid (J3301, J3300) * CPT codes are required with the diagnosis codes **PDR surgery:** 67036, 67039, 67040, 67041, 67042, 67113 * CPT codes are required with the diagnosis codes **DME treatment:** 67028, 67210	

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
	Diabetes mellitus (250.0x, 250.5x, 362.01-362.06) and macular edema (362.53, 362.83) in first two diagnosis positions * Exclude 362.35, 362.36, 362.52 in any diagnosis position	E11.311x, E11.321x, E11.331x, E11.341x, E11.351x, E13.311x, E13.321x, E13.331x, E13.341x, E13.351x in first two diagnosis positions * Exclude H34.81x, H34.83x, H35.32x in any diagnosis position	* CPT codes are required with the diagnosis codes	
Renal Replacement Therapy (RRT)	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, 792.5, 996.81, V42.0, V45.1, V45.11, V45.12, V56.x, V56.0, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8, 39.95, 54.98, 55.53, 55.6, 55.69 *Exclude patients with baseline CKD5 (403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, V45.11)	I12.0, I13.11, I13.2, I95.3, N18.5, N186, R88.0, T81.502x, T81.512x, T81.522x, T81.532x, T81.592x, T85.611x, T85.621x, T85.631x, T85.651x, T85.71x, T86.1, T86.10, T86.11, T86.12, T86.13, T86.19, Y84.1, Z48.22, Z49, Z49.0, Z49.01, Z49.02, Z49.3, Z49.31, Z49.32, Z91.15, Z94.0, Z99.2, 0TT00ZZ, 0TT04ZZ, 0TT10ZZ, 0TT14ZZ, 0TT30ZZ, 0TT34ZZ, 0TT37ZZ, 0TT38ZZ, 0TT40ZZ, 0TT44ZZ, 0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY10Z0, 0TY10Z1, 0TY10Z2, 3E1M39Z, 5A1D00Z, 5A1D60Z Dialysis ICD 10 PCS – 5A1D70Z, 5A1D80Z, 5A1D90Z *Exclude patients with baseline CKD5 (N18.5, N18.6, I12.0, I13.11, I13.2)	50340, 50360, 50365, 50370, 90935, 90937, 90940, 90945, 90947, 90957, 90958, 90959, 90960, 90961, 90962, 90965, 90966, 90969, 90970, 90999, G0257, S9335, 99512 Dialysis CPT – 90921, 90925, 90991, 90992, 90994	0800, 0801, 0802, 0803, 0804, 0805, 0806, 0807, 0808, 0809, 0820, 0821, 0822, 0823, 0824, 0825, 0826, 0827, 0828, 0829, 0830, 0831, 0832, 0833, 0834, 0835, 0836, 0837, 0838, 0839, 0840, 0841, 0842, 0843, 0844, 0845, 0846, 0847, 0848, 0849, 0850, 0851, 0852, 0853, 0854, 0855, 0856, 0857, 0858, 0859, 0880, 0881, 0882, 0883, 0884, 0885, 0886, 0887, 0888, 0889
Type 2 diabetes	250.x0, 250.x2	E11.xx		

Table 2. Comorbidity code sets

Comorbidity	ICD-9 Codes	ICD-10 codes	CPT codes	Revenue codes
Urinary incontinence	625.6, 788.30, 788.31, 788.32, 788.33, 788.34, 788.38, 788.39, 788.91	N39.3, N39.41, N39.42, N39.46, N39.490, N39.492, N39.498, R32, R39.81		
Smoking	305.1, 649.0x, 989.84	F17.xx (except F17.2x1), Z72.0, O99.33x, T65.2x, Z53.01, Z71.6,	4000F, 4001F, 4004F, 99406, 99407, C9801, C9802, G0375, G0376, G0436, G0437, G8402, G8453, G8455, G9276, G9458, G9792	
Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 430, 431	I63.x, I60.x, I61.x, I69.0x, I69.1x, History of: I69.3x *(for baseline comorbidities only, not for outcomes)*		
Unplanned Hospitalizations	• Source - Readmission Measures Methodology (cms.gov): • Algorithm - 2022 All-Cause Hospital-Wide Measure Updates and Specifications Report: Hospital-Wide Readmission • Code list - 2022 Hospital-Wide Readmission Measure Code Specifications Supplemental File • Codes in each CCS category - HCUP-US Tools and Software Page CCS-Services and Procedures (ahrq.gov)			

2.2 Outcomes

Primary outcome: Time to 3-point MACE (non-fatal MI, non-fatal stroke, all-cause mortality).

Secondary outcomes: Times to first event of each endpoint, as detailed in **Table 3**. Code sets for each of the outcome variables, as well as the baseline characteristic and eligibility criteria variables, are detailed in **Table 2**.

We will use commonly used, published, and previously validated diagnosis and procedure codes to ascertain study outcomes. For MACE (primary outcome), previous evaluations suggest that the performance of the MACE outcome codes are relatively good, with positive predictive values between 88.4% and 94% for myocardial infarction, 85% for ischemic stroke, and 80%-98% for hemorrhagic stroke.[15-19]

Table 3. Study Outcomes. Included are the primary and key secondary endpoints examined in our study. All outcomes will be ascertained using published approaches used by our team and/or others using claims data. Diagnoses in all positions on claims will be considered unless specified otherwise. DX1, primary diagnosis; DX1-2, primary/secondary diagnosis. *Not assessed due to inadequate published data on event rates for all included drug classes. (1) Time to first event; (2) Record of all events with their dates

Primary, Secondary, or Exploratory	**Name of Outcome**	**Specific measure to be used**	**Powered?** Yes or No
Primary	3-point MACE	Non-fatal MI, non-fatal stroke, all-cause mortality (*defined below*) (1)	Yes
Secondary	Expanded MACE	MACE + HF hospitalization, revascularization procedure (*defined below*) (1)	Yes
Secondary	Non-fatal MI	ED visit (DX1) or hospitalization (DX1-2) for MI[20,21] – (1) (2)	Yes
Secondary	Non-fatal stroke	ED visit (DX1) or hospitalization (DX1-2) for stroke[21,22] – (1) (2)	Yes
Secondary	Mortality	All-cause mortality[23] (1)	Yes
Secondary	HF hospitalization	Hospitalization (DX 1) for HF[24] – (1) (2)	Yes
Secondary	Revascularization procedure	Percutaneous coronary intervention, coronary artery bypass graft surgery, peripheral artery revascularization procedures[21] – (1) (2)	Yes

Mortality will be identified based on the Social Security Death Master File and discharge status. Before November 2011, the Social Security Death Master File has complete mortality data.

However, effective on November 1st, 2011, Section 205(r) of the Social Security Act prohibits the Social Security Administration (SSA) from disclosing state death records that SSA receives through its contracts with the states, except in limited circumstances. Thus, if the SSA knows of a death only from the states and not from any of its other sources of death information, which happens roughly one-third of the time, those death data will not appear on the Death Master File.[25] Using discharge status (i.e. in-hospital death), we typically capture an additional 30% of deaths in addition to what has been captured by Death Master File. Therefore, most of the deaths missing from Death Master File should be captured by discharge status, particularly since most deaths occur in an institutional setting. A small proportion of patients who died out of hospital and were not captured by Death Master File could be missing, however, this should be non-differential between treatment groups and should not influence our comparison.

2.3 Study follow-up

For each patient, we will also determine the follow-up time, which will start the day after the first fill date of the study drug (index date). Follow-up will continue until the date of the first occurrence of any the following events (point 4 in **Figure 1**):

(a) Study endpoint: patients will not be right-censored at each endpoint if they are still "at-risk" for other endpoints; instead follow-up will continue for other endpoints, if eligible.

(b) End of insurance coverage (end of patient enrollment with a gap of ≥45 days)

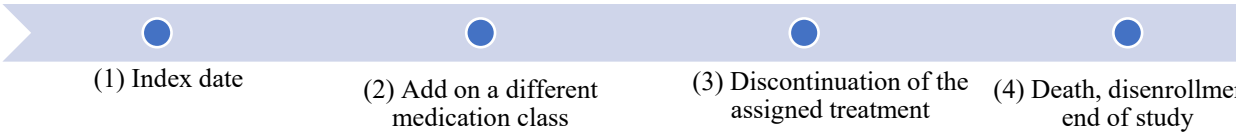
(c) Death

(d) December 31, 2021

Two sensitivity analyses will be performed using an "as treated" approach, censoring patients sooner than for the primary analysis 1) if they discontinue the assigned medication (defined as

not refilling a medication after 30 days of the end of last treatment episode) .and 2) if they discontinue the assigned medication or add a different glucose-lowering medication class, whichever comes first. See **Figure 1**.

Figure 1. Censoring approaches. Main analyses will be conducted using the "intention to treat" approach, censoring at death, disenrollment, or end of the study period (point 4), whichever comes first. As a first sensitivity analysis ("on treatment approach"), patients will be censored when they discontinue the assigned drug (point 3) or at death, disenrollment, or end of the study period (point 4), whichever comes first. As a second sensitivity analysis ("as treated approach"), patients will be censored when they add a different medication class (point 2), discontinue the assigned drug (point 3), or at death, disenrollment, or end of the study period (point 4), whichever comes first.



2.4 Missing data

Patients will be considered to have a condition, comorbidity, outcome, or drug exposure if they have a corresponding claim, and will be considered not having a comorbidity, outcome or drug exposure if they do not have a corresponding claim. Although we will not have missing data in comorbidities, drug use, or outcomes, misclassification may exist. While this is a limitation of using claims data, the algorithms used to define our inclusion/exclusion criteria, outcomes of interest, and important covariates are commonly used and have demonstrated good performance in previous studies. We suspect that any existing residual misclassification will be non-differential between treatment groups and should not meaningfully impact our findings.

We will exclude patients with invalid demographic data during the cohort creation process (e.g., inconsistent birth year or sex) and based on our prior work anticipate <1% of patients being excluded due to this missing or inconsistent data. For race/ethnicity, the categories in the database are non-Hispanic white, non-Hispanic black, Hispanic, Asian, other and

unknown. The other and unknown are combined within OLDW data and used as a separate category in the propensity score model and final model.

3. Statistical Methods

3.1 Main Analyses

Primary analyses will be conducted under an intention-to-treat approach, modified to define "intention" as a patient having two consecutive fills of the assigned drug. This treatment assignment will replace randomized assignment in the target trial, and the date of the first of the two fills will be designated as the "index date" for that patient. Outcome ascertainment will begin on the day after the index date. All patients will continue follow-up and outcome assessments until the planned conclusion of the study (12/31/2021) or end of observation in OLDW. Otherwise, analyses of secondary outcomes would be susceptible to a healthy survivor effect because the only subjects evaluated in the later years would be those who have not yet experienced MACE.

We will estimate multinomial propensity score models using baseline data from 12 months prior to the index date to account for the multiple treatments.[26] Discussions with subject-matter experts on the research team and the Patient Safety Advisory Group (PSAG) will be used to determine an exhaustive list of potential confounders. These experts will be asked to report all potential factors used for determining treatment decisions and potential factors influencing the outcomes in this proposal. The exhaustive list of potential confounders will be evaluated with the available data within the OLDW claims database. The results from these discussions and analyses will be reported as a directed acyclic graph (DAG)[27] and discussed with subject-matter experts during a PSAG meeting.

To address the assumption of consistency of the propensity score model, we will allow for flexible modeling strategies with controls to assess for overfitting. Our proposal is to use the super learner framework[28] with a diverse set of individual prediction algorithms included in the ensemble. The super learner framework allows for flexible estimation of an ensemble predictor with the theoretical properties of cross-validation for model selection to control for overfitting. The framework has been demonstrated to outperform individual algorithms for the estimation of propensity scores.[29,30]

The proposed inverse propensity score weights with multiple treatment groups is unstabilized, as our primary estimand is the population average treatment effect.[31] If weights have extreme values when evaluating the distributions, then the stabilized version using the denominator proposed in Yoshida[32] for the optimal matching stabilized weights with multiple treatments will be used as a sensitivity analysis to avoid large confidence intervals for the effect estimates. The final propensity scores will then be incorporated as weights into time-to-event models. For the final model, we will report model diagnostic and performance statistics, and hazard ratios with 95% confidence intervals. A single model with all treatment groups will be estimated and the omnibus test for at least one treatment group having a different hazard rate will be evaluated. All pairwise effects will be estimated.

We will evaluate the balance between treatment groups by comparing standardized mean differences of baseline covariates.[33] The distribution of the weights between treatment groups will be evaluated graphically to assess overlap. If the propensity score models are unable to appropriately account for confounding by indication, and the variable is highly likely to be associated with the outcome, then the propensity score weighted estimates should not be used for the average treatment effect.

To aid interpretation of results, we will calculate the number needed to treat (NNT) with DPP4i, GLP-1RA, and SGLT2i vs. sulfonylurea to avoid one event at 1, 2 and 3 years.

A single overall omnibus test for the hazard rates all being equal to each other versus at least one different will be conducted at the 0.05 significance level.

3.2 Secondary Analyses

Heterogeneity of treatment effects (HTE) will be evaluated for patient age. The primary model will be used to estimate treatment effects across subgroups (age <65 and ≥65 years), with the targeted parameter for the subgroup analysis being the ratio in the predicted treatment effect for each pairwise comparison between the subgroups.[34] We will estimate multivariable effect prediction models[35,36] to assess for HTE by incorporating the statistical interaction effect between the treatment and age.[37,38] Propensity score weights will be used to emulate randomization according to the target trial framework.

3.3 Sensitivity Analyses

Two sensitivity analyses will be performed using an "as treated" approach, censoring patients sooner than for the primary analysis 1) if they discontinue the assigned medication (defined as not refilling a medication after 30 days of the end of last treatment episode) .and 2) if they discontinue the assigned medication or add a different glucose-lowering medication class, whichever comes first. See **Figure 1**.

We will assess residual confounding by testing a falsification end point that is unlikely to be associated with the studied medications: new diagnosis of pneumonia, hospitalization for appendicitis, and completion of preventive colon cancer screening in the follow-up period. The same propensity score weights from the primary analysis will be used for the falsification

outcome and the pairwise comparisons between treatment groups will be estimated as described in the primary analysis section.

STROBE Statement

	Item No	Recommendation	Page(s)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	12-13
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	12-13
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	13-14
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	14-15 eTables 5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	14-15 eTables 5-6
Bias	9	Describe any efforts to address potential sources of bias	15-17
Study size	10	Explain how the study size was arrived at	13-14 eFig 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	14-16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	15-17
		(*b*) Describe any methods used to examine subgroups and interactions	16-17
		(*c*) Explain how missing data were addressed	n/a

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	17 Ext Fig 1
		(*e*) Describe any sensitivity analyses	16-17 Ext Fig 1
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6 eFig 1
		(b) Give reasons for non-participation at each stage	eFig 1
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-6 eFig 1 Table 1 eTable 2
		(b) Indicate number of participants with missing data for each variable of interest	Table 1 eTable 2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6 Table 2 Figure 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7 Table 2 Figure 1
		(*b*) Report category boundaries when continuous variables were categorized	6-7 Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-7 Table 3 Ext Table 3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-7

			Ext Tables 1-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

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