

Electronic Supplementary Appendix

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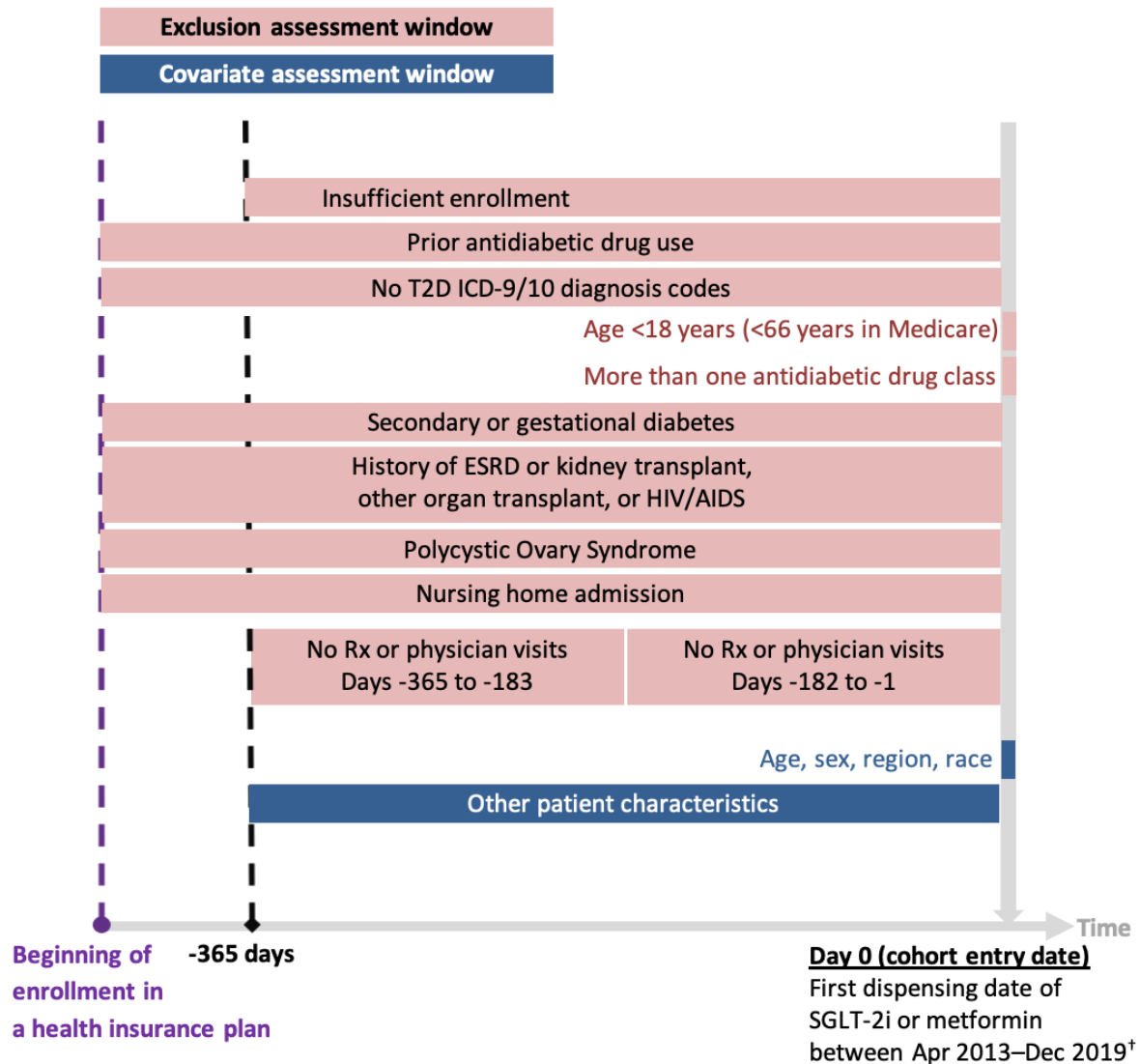
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Figure S1. Study design diagram



T2D: type 2 diabetes; ESRD: end-stage renal disease; HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome; Rx: prescription.

[†] Data range: Clinformatics (Apr 2013–Dec 2019) / MarketScan and Medicare (Apr 2013–Dec 2018)

Table S1. Baseline patient characteristics

Category of patient characteristics	Variable(s)
Demographics	Age, sex, geographic region*, Medicare Advantage**, race***
Lifestyle risk factors	Obesity or overweight, smoking
Claims-measured proxies of diabetes severity and duration	Diabetic nephropathy, diabetic neuropathy, diabetic retinopathy
Risk factors for prognosis of diabetes	CVD†, CKD
Other comorbidities	Hyperlipidemia, hypertension, COPD, malignant neoplasm
Physician specialties††	Cardiologist visits, endocrinologist visits, internist visits, nurse practitioner or physician assistant visits
Healthcare utilization as proxy for overall health status and care intensity, and claims-measured proxies of socioeconomic status ¹	Any recent hospitalizations [#] , average days of hospitalizations, number of ED visits, number of office visits, number of HbA1c test orders, ratio of the number of brand name versus generic drug use ^{##} , number of unique medications, copay for pharmacy cost, preventive healthcare service [§]
Concomitant medications	ACE inhibitors or ARBs Antithrombotic medications Beta blockers Calcium channel blockers Loop diuretics Statin Thiazides
Laboratory results**	HbA1c (%) ^{§§} , eGFR (mL/min/1.73m ²) [¶] , LDL (mg/dl), HDL (mg/dl), total cholesterol (mg/dl), triglyceride (mg/dl)

CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department; HbA1c: hemoglobin A1c; ACE inhibitors: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers.

* Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)

South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)

Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)

West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

** Available for Clinformatics and MarketScan databases.

*** Available for Clinformatics and Medicare databases.

† Defined as history of myocardial infarction, stable or unstable angina, other ischemic heart disease, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

†† Defined as specialist visits occurred within 7 days prior to cohort entry.

Defined as any hospitalizations occurred within 30 days prior to cohort entry.

Added 1 to both numerator and denominator, then log-transformed.

§ Defined as administration of bone mineral density test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu vaccine, or pneumococcal vaccine.

§§ Measured 180 days prior to or on cohort entry.

¶ Estimated using the quadratic GFR equation: $GFR = \exp(1.911 + \frac{5.249}{\text{Serum creatinine}} - \frac{2.114}{\text{Serum creatinine}^2} - 0.00686 * \text{Age} - 0.205 \text{ (if female)})$. If serum creatinine <0.8 mg/dL, use 0.8 for serum creatinine.

¹ Gopalakrishnan, C. et al. Evaluation of Socioeconomic Status Indicators for Confounding Adjustment in Observational Studies of Medication Use. Clin. Pharmacol. Ther. 105, 1513–1521 (2019).

Table S2. [Clinformatics] Patient characteristics and standardized differences at the time of first-line SGLT-2i or metformin initiation (2013-2019). Values are number (percentage) unless otherwise specified.

Baseline characteristics	Apr2013-Dec2014			Jan2015-Jun2016			Jul2016-Dec2017			Jan2018-Dec2019		
	SGLT-2i (n=329)	Metformin (n=48,790)	SD	SGLT-2i (n=488)	Metformin (n=46,792)	SD	SGLT-2i (n=714)	Metformin (n=49,318)	SD	SGLT-2i (n=1,054)	Metformin (n=68,287)	SD
Demographics												
Age (mean, std.dev)	54.20 (10.24)	59.72 (12.49)	-0.48	57.32 (11.50)	60.43 (12.66)	-0.26	58.84 (11.12)	60.45 (12.59)	-0.14	61.31 (12.36)	61.31 (12.60)	0.00
Gender (Male)	149 (45.3)	25264 (51.8)	-0.13	268 (54.9)	24264 (51.9)	0.06	353 (49.4)	25701 (52.1)	-0.05	602 (57.1)	36623 (53.6)	0.07
Region*												
Northeast	30 (9.1)	5382 (11.0)	-0.06	48 (9.8)	5843 (12.5)	-0.08	71 (9.9)	5110 (10.4)	-0.01	115 (10.9)	7373 (10.8)	0.00
South	186 (56.5)	22401 (45.9)	0.21	270 (55.3)	20433 (43.7)	0.23	386 (54.1)	23483 (47.6)	0.13	558 (52.9)	32653 (47.8)	0.10
Midwest	70 (21.3)	10480 (21.5)	0.00	98 (20.1)	9529 (20.4)	-0.01	162 (22.7)	10554 (21.4)	0.03	217 (20.6)	14231 (20.8)	-0.01
West	43 (13.1)	10527 (21.6)	-0.23	72 (14.8)	10987 (23.5)	-0.22	95 (13.3)	10171 (20.6)	-0.20	164 (15.6)	14030 (20.5)	-0.13
Medicare Advantage	34 (10.3)	19464 (39.9)	-0.73	143 (29.3)	21070 (45.0)	-0.33	234 (32.8)	22379 (45.4)	-0.26	516 (49.0)	34359 (50.3)	-0.03
Race (White)	244 (74.2)	31142 (63.8)	0.22	298 (61.1)	27498 (58.8)	0.05	452 (63.3)	29104 (59.0)	0.09	574 (54.5)	36738 (53.8)	0.01
Life-style risk factors												
Obesity or Overweight	114 (34.7)	13696 (28.1)	0.14	181 (37.1)	16002 (34.2)	0.06	350 (49.0)	21193 (43.0)	0.12	541 (51.3)	34634 (50.7)	0.01
Smoking	25 (7.6)	6022 (12.3)	-0.16	52 (10.7)	6663 (14.2)	-0.11	134 (18.8)	9276 (18.8)	0.00	248 (23.5)	14629 (21.4)	0.05
Comorbidities												
Diabetic Nephropathy	10 (3.0)	1460 (3.0)	0.00	25 (5.1)	2346 (5.0)	0.00	57 (8.0)	2374 (4.8)	0.13	115 (10.9)	3933 (5.8)	0.19
Diabetic Neuropathy	29 (8.8)	2170 (4.4)	0.18	40 (8.2)	3101 (6.6)	0.06	68 (9.5)	2998 (6.1)	0.13	117 (11.1)	4344 (6.4)	0.17
Diabetic Retinopathy	4 (1.2)	518 (1.1)	0.01	7 (1.4)	588 (1.3)	0.02	10 (1.4)	509 (1.0)	0.03	36 (3.4)	926 (1.4)	0.14
CVD**	45 (13.7)	10368 (21.3)	-0.20	95 (19.5)	10049 (21.5)	-0.05	172 (24.1)	10573 (21.4)	0.06	380 (36.1)	16071 (23.5)	0.28
Hyperlipidemia	245 (74.5)	35008 (71.8)	0.06	364 (74.6)	32017 (68.4)	0.14	510 (71.4)	32453 (65.8)	0.12	764 (72.5)	47117 (69.0)	0.08
Hypertension	227 (69.0)	33168 (68.0)	0.02	349 (71.5)	31615 (67.6)	0.09	513 (71.8)	33242 (67.4)	0.10	809 (76.8)	47121 (69.0)	0.18
CKD	11 (3.3)	2571 (5.3)	-0.09	25 (5.1)	3342 (7.1)	-0.08	57 (8.0)	3362 (6.8)	0.04	126 (12.0)	5274 (7.7)	0.14
COPD	18 (5.5)	4018 (8.2)	-0.11	27 (5.5)	3897 (8.3)	-0.11	69 (9.7)	4293 (8.7)	0.03	119 (11.3)	6736 (9.9)	0.05
History of Malignant Neoplasm	15 (4.6)	3570 (7.3)	-0.12	38 (7.8)	3402 (7.3)	0.02	49 (6.9)	3569 (7.2)	-0.01	91 (8.6)	5191 (7.6)	0.04
Physician specialties†												
Cardiologists	7 (2.1)	2152 (4.4)	-0.13	16 (3.3)	2045 (4.4)	-0.06	17 (2.4)	2477 (5.0)	-0.14	68 (6.5)	3579 (5.2)	0.05
Endocrinologists	15 (4.6)	1046 (2.1)	0.13	9 (1.8)	988 (2.1)	-0.02	19 (2.7)	960 (1.9)	0.05	41 (3.9)	1349 (2.0)	0.11
Internists	136 (41.3)	33260 (68.2)	-0.56	204 (41.8)	31874 (68.1)	-0.55	292 (40.9)	34507 (70.0)	-0.61	480 (45.5)	48214 (70.6)	-0.53
Nurse practitioners or physician assistants	8 (2.4)	980 (2.0)	0.03	2 (0.4)	1303 (2.8)	-0.19	11 (1.5)	1796 (3.6)	-0.13	22 (2.1)	3529 (5.2)	-0.17
Healthcare utilization												
Any recent hospitalization††	2 (0.6)	1599 (3.3)	-0.19	6 (1.2)	1421 (3.0)	-0.13	5 (0.7)	1628 (3.3)	-0.19	33 (3.1)	2497 (3.7)	-0.03
Average length of hospitalization (mean, std.dev)	0.28 (2.23)	0.51 (2.51)	-0.10	0.35 (2.08)	0.42 (2.09)	-0.03	0.30 (1.34)	0.48 (2.87)	-0.08	0.45 (1.58)	0.50 (2.45)	-0.02
Number of ED visits (mean, Std.dev)	0.82 (2.38)	0.89 (2.42)	-0.03	0.94 (2.56)	0.86 (2.30)	0.03	0.93 (2.55)	0.92 (2.43)	0.00	0.92 (2.32)	0.91 (2.41)	0.00
Number of office visits (mean, std.dev)	9.46 (8.07)	9.73 (9.50)	-0.03	10.32 (8.70)	9.22 (8.87)	0.12	10.80 (10.02)	9.27 (9.25)	0.16	11.55 (9.92)	9.69 (9.43)	0.19
Number of HbA1c tests ordered (mean, std.dev)	1.80 (1.14)	1.53 (1.05)	0.25	1.87 (1.12)	1.55 (1.05)	0.30	1.86 (1.18)	1.55 (1.02)	0.28	1.93 (1.16)	1.59 (1.04)	0.31
Brand/Generic ratio# (mean, std.dev)	-1.34 (1.24)	-1.64 (1.24)	0.24	-1.49 (1.21)	-1.75 (1.22)	0.21	-1.67 (1.23)	-1.90 (1.20)	0.19	-1.80 (1.21)	-1.99 (1.15)	0.16
Number of unique medications (mean, std.dev)	8.52 (6.62)	9.54 (7.35)	-0.15	8.96 (7.25)	9.11 (7.42)	-0.02	9.32 (8.09)	9.37 (7.48)	-0.01	11.19 (9.38)	9.99 (7.85)	0.14
Copay for pharmacy cost (\$, mean, std.dev)	331.39 (405.73)	385.78 (576.46)	-0.11	373.93 (616.64)	342.40 (610.83)	0.05	378.07 (796.77)	306.81 (592.10)	0.10	375.74 (611.63)	295.25 (556.32)	0.14
Preventive healthcare service###	223 (67.8)	35038 (71.8)	-0.09	342 (70.1)	33650 (71.9)	-0.04	519 (72.7)	35746 (72.5)	0.00	799 (75.8)	50306 (73.7)	0.05
Concomitant medications												
ACE inhibitors or ARBs	138 (41.9)	26909 (55.2)	-0.27	236 (48.4)	25980 (55.5)	-0.14	349 (48.9)	27503 (55.8)	-0.14	557 (52.8)	38788 (56.8)	-0.08
Antithrombotic medications	26 (7.9)	5268 (10.8)	-0.10	50 (10.2)	5067 (10.8)	-0.02	70 (9.8)	5658 (11.5)	-0.05	234 (22.2)	8835 (12.9)	0.25
Beta blockers	60 (18.2)	14079 (28.9)	-0.25	120 (24.6)	13074 (27.9)	-0.08	173 (24.2)	13764 (27.9)	-0.08	353 (33.5)	20333 (29.8)	0.08
Calcium channel blockers	48 (14.6)	10829 (22.2)	-0.20	100 (20.5)	10405 (22.2)	-0.04	131 (18.3)	11311 (22.9)	-0.11	256 (24.3)	16716 (24.5)	0.00
Loop diuretics	18 (5.5)	3588 (7.4)	-0.08	23 (4.7)	3291 (7.0)	-0.10	59 (8.3)	3622 (7.3)	0.03	131 (12.4)	5382 (7.9)	0.15
Statin	128 (38.9)	25977 (53.2)	-0.29	211 (43.2)	24830 (53.1)	-0.20	332 (46.5)	26767 (54.3)	-0.16	559 (53.0)	38904 (57.0)	-0.08
Thiazides	30 (9.1)	6312 (12.9)	-0.12	55 (11.3)	5882 (12.6)	-0.04	69 (9.7)	6568 (13.3)	-0.11	111 (10.5)	9632 (14.1)	-0.11
Laboratory values												

HbA1c [§] (%; mean, std.dev)	8.04 (2.03)	7.27 (1.49)	0.43	7.84 (1.77)	7.29 (1.53)	0.33	7.62 (1.68)	7.32 (1.55)	0.19	7.56 (1.61)	7.33 (1.59)	0.15
Missing	189 (57.4)	29783 (61.0)	-0.07	242 (49.6)	25605 (54.7)	-0.10	367 (51.4)	25445 (51.6)	0.00	566 (53.7)	36874 (54.0)	-0.01
eGFR [¶] (mL/min/1.73m ² ; mean, std.dev)	101.76 (16.66)	97.75 (17.03)	0.24	99.06 (18.56)	96.74 (17.23)	0.13	96.48 (18.27)	96.77 (17.32)	-0.02	93.60 (20.02)	95.61 (17.49)	-0.11
Missing	177 (53.8)	27174 (55.7)	-0.04	227 (46.5)	24164 (51.6)	-0.10	351 (49.2)	24182 (49.0)	0.00	536 (50.9)	35711 (52.3)	-0.03
LDL (mg/dl; mean, std.dev)	101.15 (38.65)	100.44 (40.50)	0.02	93.93 (37.19)	98.74 (40.76)	-0.12	96.22 (41.95)	99.79 (40.19)	-0.09	89.43 (40.80)	98.66 (40.62)	-0.23
Missing	190 (57.8)	29551 (60.6)	-0.06	258 (52.9)	26146 (55.9)	-0.06	383 (53.6)	26573 (53.9)	0.00	603 (57.2)	39311 (57.6)	-0.01
HDL (mg/dl; mean, std.dev)	46.61 (12.98)	46.96 (13.82)	-0.03	45.79 (13.90)	46.85 (14.28)	-0.07	46.93 (14.06)	46.92 (14.04)	0.00	46.46 (14.20)	46.15 (13.21)	0.02
Missing	189 (57.4)	29680 (60.8)	-0.07	260 (53.3)	26894 (57.5)	-0.08	390 (54.6)	27505 (55.8)	-0.02	613 (58.2)	40390 (59.1)	-0.02
Total cholesterol (mg/dl; mean, std.dev)	188.23 (45.86)	186.99 (44.28)	0.03	179.88 (48.51)	185.66 (45.72)	-0.12	182.52 (44.09)	185.99 (44.77)	-0.08	175.47 (43.06)	182.90 (45.37)	-0.17
Missing	187 (56.8)	29466 (60.4)	-0.07	257 (52.7)	26530 (56.7)	-0.08	385 (53.9)	26964 (54.7)	-0.02	606 (57.5)	39694 (58.1)	-0.01
Triglyceride (mg/dl; mean, std.dev)	184.85 (136.23)	182.08 (158.01)	0.02	201.83 (313.61)	182.58 (155.25)	0.08	183.52 (128.82)	183.97 (166.15)	0.00	189.48 (183.04)	182.21 (158.54)	0.04
Missing	188 (57.1)	29586 (60.6)	-0.07	259 (53.1)	26814 (57.3)	-0.09	385 (53.9)	27206 (55.2)	-0.02	607 (57.6)	39866 (58.4)	-0.02

SD: standardized difference; std.dev: standard deviation; HbA1c: hemoglobin A1c; CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department.

* Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)

South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)

Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)

West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

** Defined as a history of myocardial infarction, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

† Defined as specialist visits occurred within 7 days prior to cohort entry.

†† Defined as hospitalization occurred within 30 days prior to cohort entry.

Added 1 to both numerator and denominator, then log-transformed.

Defined as administration of bone mineral density (BMD) test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu vaccine, or pneumococcal vaccine.

§ Measured 180 days prior to or on cohort entry.

¶ Estimated using the quadratic GFR equation: $GFR = \exp(1.911 + \frac{5.249}{\text{Serum creatinine}} - \frac{2.114}{\text{Serum creatinine}^2} - 0.00686 * \text{Age} - 0.205 \text{ (if female)})$. If serum creatinine <0.8 mg/dL, use 0.8 for serum creatinine.

Table S3. [MarketScan] Patient characteristics and standardized differences at the time of first-line SGLT-2i or metformin initiation (2013-2018). Values are number (percentage) unless otherwise specified.

Baseline characteristics	Apr2013-Dec2014			Jan2015-Jun2016			Jul2016-Dec2017			Jan2018-Dec2018		
	SGLT-2i (n=1,187)	Metformin (n=102,754)	SD	SGLT-2i (n=1,434)	Metformin (n=79,538)	SD	SGLT-2i (n=1,007)	Metformin (n=66,111)	SD	SGLT-2i (n=524)	Metformin (n=35,097)	SD
Demographics												
Age (mean, std.dev)	54.14 (9.54)	55.90 (11.24)	-0.17	53.54 (9.51)	55.21 (11.00)	-0.16	54.44 (9.85)	54.96 (10.90)	-0.05	53.47 (10.01)	53.57 (10.38)	-0.01
Gender (Male)	587 (49.5)	52968 (51.5)	-0.04	718 (50.1)	40833 (51.3)	-0.03	507 (50.3)	34477 (52.2)	-0.04	298 (56.9)	18873 (53.8)	0.06
Region*												
Northeast	226 (19.0)	18623 (18.1)	0.02	277 (19.3)	14173 (17.8)	0.04	178 (17.7)	11088 (16.8)	0.02	128 (24.4)	6181 (17.6)	0.17
South	651 (54.8)	41888 (40.8)	0.28	832 (58.0)	38188 (48.0)	0.20	619 (61.5)	33574 (50.8)	0.22	276 (52.7)	16710 (47.6)	0.10
Midwest	188 (15.8)	24342 (23.7)	-0.20	201 (14.0)	16673 (21.0)	-0.18	117 (11.6)	13035 (19.7)	-0.22	79 (15.1)	7434 (21.2)	-0.16
West	122 (10.3)	17901 (17.4)	-0.21	124 (8.6)	10504 (13.2)	-0.15	93 (9.2)	8414 (12.7)	-0.11	41 (7.8)	4772 (13.6)	-0.19
Medicare Advantage	117 (9.9)	19049 (18.5)	-0.25	121 (8.4)	12178 (15.3)	-0.21	103 (10.2)	8904 (13.5)	-0.10	43 (8.2)	2994 (8.5)	-0.01
Race (White)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Life-style risk factors												
Obesity or Overweight	308 (25.9)	22009 (21.4)	0.11	487 (34.0)	25630 (32.2)	0.04	412 (40.9)	26923 (40.7)	0.00	238 (45.4)	16039 (45.7)	-0.01
Smoking	66 (5.6)	7774 (7.6)	-0.08	116 (8.1)	7773 (9.8)	-0.06	83 (8.2)	7417 (11.2)	-0.10	55 (10.5)	4161 (11.9)	-0.04
Comorbidities												
Diabetic Nephropathy	19 (1.6)	1065 (1.0)	0.05	27 (1.9)	1117 (1.4)	0.04	26 (2.6)	1328 (2.0)	0.04	16 (3.1)	793 (2.3)	0.05
Diabetic Neuropathy	54 (4.5)	2547 (2.5)	0.11	80 (5.6)	2063 (2.6)	0.15	52 (5.2)	1909 (2.9)	0.12	28 (5.3)	1016 (2.9)	0.12
Diabetic Retinopathy	20 (1.7)	714 (0.7)	0.09	24 (1.7)	471 (0.6)	0.10	3 (0.3)	231 (0.3)	-0.01	10 (1.9)	226 (0.6)	0.11
CVD**	177 (14.9)	16211 (15.8)	-0.02	218 (15.2)	12107 (15.2)	0.00	176 (17.5)	9645 (14.6)	0.08	102 (19.5)	4572 (13.0)	0.18
Hyperlipidemia	807 (68.0)	62520 (60.8)	0.15	958 (66.8)	48955 (61.5)	0.11	573 (56.9)	35751 (54.1)	0.06	337 (64.3)	20402 (58.1)	0.13
Hypertension	732 (61.7)	59591 (58.0)	0.08	939 (65.5)	48935 (61.5)	0.08	647 (64.3)	40875 (61.8)	0.05	339 (64.7)	20988 (59.8)	0.10
CKD	24 (2.0)	1989 (1.9)	0.01	43 (3.0)	1800 (2.3)	0.05	26 (2.6)	1701 (2.6)	0.00	12 (2.3)	796 (2.3)	0.00
COPD	52 (4.4)	5012 (4.9)	-0.02	59 (4.1)	3946 (5.0)	-0.04	45 (4.5)	3060 (4.6)	-0.01	18 (3.4)	1371 (3.9)	-0.03
History of Malignant Neoplasm	55 (4.6)	6288 (6.1)	-0.07	62 (4.3)	4781 (6.0)	-0.08	55 (5.5)	3931 (5.9)	-0.02	29 (5.5)	1906 (5.4)	0.00
Physician specialties†												
Cardiologists	21 (1.8)	3029 (2.9)	-0.08	29 (2.0)	2529 (3.2)	-0.07	34 (3.4)	2142 (3.2)	0.01	26 (5.0)	1116 (3.2)	0.09
Endocrinologists	53 (4.5)	2173 (2.1)	0.13	40 (2.8)	1849 (2.3)	0.03	33 (3.3)	1583 (2.4)	0.05	19 (3.6)	760 (2.2)	0.09
Internists	580 (48.9)	64101 (62.4)	-0.27	663 (46.2)	51593 (64.9)	-0.38	453 (45.0)	43648 (66.0)	-0.43	238 (45.4)	22162 (63.1)	-0.36
Nurse practitioners or physician assistants	18 (1.5)	2662 (2.6)	-0.08	36 (2.5)	2848 (3.6)	-0.06	46 (4.6)	3160 (4.8)	-0.01	24 (4.6)	2174 (6.2)	-0.07
Healthcare utilization												
Any recent hospitalization††	13 (1.1)	2832 (2.8)	-0.12	8 (0.6)	2121 (2.7)	-0.17	10 (1.0)	1843 (2.8)	-0.13	10 (1.9)	1042 (3.0)	-0.07
Average length of hospitalization (mean, std.dev)	0.12 (0.63)	0.12 (0.51)	0.00	0.09 (0.39)	0.12 (0.49)	-0.05	0.10 (0.46)	0.11 (0.50)	-0.03	0.07 (0.30)	0.10 (0.44)	-0.09
Number of ED visits (mean, Std.dev)	0.49 (1.06)	0.52 (1.21)	-0.03	0.50 (1.08)	0.56 (1.35)	-0.04	0.50 (1.07)	0.56 (1.37)	-0.06	0.55 (1.35)	0.57 (1.28)	-0.01
Number of office visits (mean, std.dev)	11.71 (10.59)	10.36 (10.78)	0.13	11.52 (11.05)	10.35 (10.76)	0.11	11.85 (11.74)	10.38 (10.88)	0.13	11.13 (10.97)	10.27 (11.11)	0.08
Number of HbA1c tests ordered (mean, std.dev)	1.56 (1.13)	1.27 (1.04)	0.27	1.57 (1.09)	1.31 (1.02)	0.25	1.58 (1.11)	1.32 (0.99)	0.25	1.56 (1.17)	1.35 (0.97)	0.19
Brand/Generic ratio# (mean, std.dev)	-1.28 (1.20)	-1.46 (1.18)	0.16	-1.47 (1.20)	-1.65 (1.15)	0.15	-1.62 (1.20)	-1.79 (1.14)	0.14	-1.64 (1.17)	-1.86 (1.11)	0.20
Number of unique medications (mean, std.dev)	10.26 (8.23)	9.25 (7.09)	0.13	9.51 (7.68)	9.30 (7.23)	0.03	9.71 (7.60)	9.32 (7.25)	0.05	9.07 (7.74)	9.16 (7.24)	-0.01
Copay for pharmacy cost (\$, mean, std.dev)	271.76 (375.89)	246.81 (343.90)	0.07	234.99 (344.73)	206.07 (393.21)	0.08	205.19 (318.81)	182.64 (360.46)	0.07	165.76 (270.54)	159.62 (356.63)	0.02
Preventive healthcare service###	808 (68.1)	68093 (66.3)	0.04	943 (65.8)	52410 (65.9)	0.00	669 (66.4)	44267 (67.0)	-0.01	331 (63.2)	23526 (67.0)	-0.08
Concomitant medications												
ACE inhibitors or ARBs	556 (46.8)	56032 (54.5)	-0.15	714 (49.8)	43385 (54.5)	-0.10	506 (50.2)	35725 (54.0)	-0.08	254 (48.5)	18567 (52.9)	-0.09
Antithrombotic medications	120 (10.1)	10025 (9.8)	0.01	110 (7.7)	7717 (9.7)	-0.07	120 (11.9)	6772 (10.2)	0.05	70 (13.4)	3423 (9.8)	0.11
Beta blockers	269 (22.7)	27348 (26.6)	-0.09	327 (22.8)	20425 (25.7)	-0.07	242 (24.0)	16665 (25.2)	-0.03	127 (24.2)	8106 (23.1)	0.03
Calcium channel blockers	208 (17.5)	20923 (20.4)	-0.07	260 (18.1)	16889 (21.2)	-0.08	227 (22.5)	14333 (21.7)	0.02	106 (20.2)	7453 (21.2)	-0.02
Loop diuretics	79 (6.7)	6097 (5.9)	0.03	100 (7.0)	4633 (5.8)	0.05	75 (7.4)	3802 (5.8)	0.07	29 (5.5)	1655 (4.7)	0.04
Statin	501 (42.2)	52086 (50.7)	-0.17	619 (43.2)	39423 (49.6)	-0.13	444 (44.1)	32297 (48.9)	-0.10	240 (45.8)	17000 (48.4)	-0.05
Thiazides	110 (9.3)	13338 (13.0)	-0.12	151 (10.5)	10305 (13.0)	-0.08	101 (10.0)	8778 (13.3)	-0.10	51 (9.7)	4654 (13.3)	-0.11

Laboratory values												
HbA1c [§] (%; mean, std.dev)	7.76 (2.02)	7.42 (1.57)	0.19	7.49 (1.46)	7.34 (1.57)	0.10	7.41 (1.72)	7.35 (1.55)	0.04	8.36 (2.38)	7.16 (1.41)	0.61
Missing	1101 (92.8)	95874 (93.3)	-0.02	1323 (92.3)	73434 (92.3)	0.00	929 (92.3)	61114 (92.4)	-0.01	499 (95.2)	33916 (96.6)	-0.07
eGFR [¶] (mL/min/1.73m ² ; mean, std.dev)	100.54 (17.70)	100.25 (15.65)	0.02	100.16 (19.68)	99.81 (15.66)	0.02	104.66 (15.87)	99.79 (16.03)	0.30	100.21 (18.60)	101.07 (15.55)	-0.05
Missing	1097 (92.4)	96319 (93.7)	-0.05	1306 (91.1)	72827 (91.6)	-0.02	920 (91.4)	60458 (91.4)	0.00	494 (94.3)	33754 (96.2)	-0.09
LDL (mg/dl; mean, std.dev)	97.11 (49.48)	97.90 (45.72)	-0.02	104.30 (38.39)	103.79 (41.02)	0.01	101.37 (37.49)	105.26 (41.22)	-0.10	85.22 (48.29)	104.54 (39.82)	-0.44
Missing	1097 (92.4)	95364 (92.8)	-0.01	1323 (92.3)	73200 (92.0)	0.01	929 (92.3)	60934 (92.2)	0.00	497 (94.8)	33830 (96.4)	-0.08
HDL (mg/dl; mean, std.dev)	45.68 (17.07)	45.29 (93.05)	0.01	46.02 (11.22)	46.25 (14.28)	-0.02	45.44 (13.82)	46.93 (64.58)	-0.03	44.19 (12.77)	46.02 (13.09)	-0.14
Missing	1099 (92.6)	95731 (93.2)	-0.02	1330 (92.7)	73443 (92.3)	0.02	929 (92.3)	60894 (92.1)	0.01	497 (94.8)	33830 (96.4)	-0.08
Total cholesterol (mg/dl; mean, std.dev)	182.02 (59.98)	178.11 (61.90)	0.06	187.16 (41.10)	189.82 (46.09)	-0.06	181.54 (48.74)	190.30 (46.51)	-0.18	183.85 (43.39)	186.69 (41.44)	-0.07
Missing	1097 (92.4)	95906 (93.3)	-0.04	1329 (92.7)	73420 (92.3)	0.01	927 (92.1)	60899 (92.1)	0.00	497 (94.8)	33821 (96.4)	-0.07
Triglyceride (mg/dl; mean, std.dev)	173.12 (111.47)	174.07 (154.87)	-0.01	164.62 (93.73)	184.51 (163.93)	-0.15	165.50 (124.01)	184.15 (190.02)	-0.12	249.30 (228.27)	181.38 (161.61)	0.34
Missing	1098 (92.5)	95882 (93.3)	-0.03	1328 (92.6)	73526 (92.4)	0.01	927 (92.1)	60946 (92.2)	0.00	497 (94.8)	33840 (96.4)	-0.08

SD: standardized difference; std.dev: standard deviation; HbA1c: hemoglobin A1c; CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department.

* Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)

South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)

Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)

West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

** Defined as a history of myocardial infarction, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

† Defined as specialist visits occurred within 7 days prior to cohort entry.

†† Defined as hospitalization occurred within 30 days prior to cohort entry.

Added 1 to both numerator and denominator, then log-transformed.

Defined as administration of bone mineral density (BMD) test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu vaccine, or pneumococcal vaccine.

§ Measured 180 days prior to or on cohort entry.

¶ Estimated using the quadratic GFR equation: $GFR = \exp(1.911 + \frac{5.249}{Serum\ creatinine} - \frac{2.114}{Serum\ creatinine^2} - 0.00686 * Age - 0.205 (if\ female))$. If serum creatinine <0.8 mg/dL, use 0.8 for serum creatinine.

Table S4. [Medicare] Patient characteristics and standardized differences at the time of first-line SGLT-2i and metformin initiation (2013-2018). Values are number (percentage) unless otherwise specified.

Baseline characteristics	Apr2013-Dec2014			Jan2015-Jun2016			Jul2016-Dec2017			Jan2018-Dec2018		
	SGLT-2i (n=359)	Metformin (n=119,599)	SD	SGLT-2i (n=843)	Metformin (n=101,812)	SD	SGLT-2i (n=669)	Metformin (n=58,218)	SD	SGLT-2i (n=505)	Metformin (n=34,032)	SD
Demographics												
Age (mean, std.dev)	71.81 (5.41)	73.02 (5.99)	-0.21	71.78 (5.54)	72.98 (5.89)	-0.21	71.68 (5.51)	73.23 (5.99)	-0.27	72.81 (6.14)	73.04 (5.92)	-0.04
Gender (Male)	186 (51.8)	53960 (45.1)	0.13	451 (53.5)	47858 (47.0)	0.13	355 (53.1)	28291 (48.6)	0.09	279 (55.2)	16995 (49.9)	0.11
Region*												
Northeast	86 (24.0)	21140 (17.7)	0.16	211 (25.0)	20266 (19.9)	0.12	153 (22.9)	11912 (20.5)	0.06	102 (20.2)	6713 (19.7)	0.01
South	145 (40.4)	49533 (41.4)	-0.02	368 (43.7)	41663 (40.9)	0.06	285 (42.6)	23510 (40.4)	0.05	194 (38.4)	13267 (39.0)	-0.01
Midwest	66 (18.4)	28104 (23.5)	-0.13	110 (13.0)	21954 (21.6)	-0.23	97 (14.5)	12361 (21.2)	-0.18	81 (16.0)	7653 (22.5)	-0.16
West	62 (17.3)	20822 (17.4)	0.00	154 (18.3)	17929 (17.6)	0.02	134 (20.0)	10435 (17.9)	0.05	128 (25.3)	6399 (18.8)	0.16
Medicare Advantage	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Race (White)	301 (83.8)	99119 (82.9)	0.03	716 (84.9)	85001 (83.5)	0.04	545 (81.5)	48398 (83.1)	-0.04	417 (82.6)	28450 (83.6)	-0.03
Life-style risk factors												
Obesity or Overweight	102 (28.4)	27262 (22.8)	0.13	310 (36.8)	29852 (29.3)	0.16	269 (40.2)	22063 (37.9)	0.05	236 (46.7)	15775 (46.4)	0.01
Smoking	60 (16.7)	20226 (16.9)	-0.01	172 (20.4)	20351 (20.0)	0.01	162 (24.2)	13783 (23.7)	0.01	117 (23.2)	8759 (25.7)	-0.06
Comorbidities												
Diabetic Nephropathy	16 (4.5)	2199 (1.8)	0.15	44 (5.2)	2674 (2.6)	0.13	52 (7.8)	3446 (5.9)	0.07	58 (11.5)	2574 (7.6)	0.13
Diabetic Neuropathy	55 (15.3)	6753 (5.6)	0.32	97 (11.5)	6534 (6.4)	0.18	86 (12.9)	5331 (9.2)	0.12	86 (17.0)	3221 (9.5)	0.22
Diabetic Retinopathy	14 (3.9)	1789 (1.5)	0.15	25 (3.0)	1434 (1.4)	0.11	15 (2.2)	1036 (1.8)	0.03	30 (5.9)	811 (2.4)	0.18
CVD**	184 (51.3)	49978 (41.8)	0.19	395 (46.9)	42098 (41.3)	0.11	337 (50.4)	25678 (44.1)	0.13	289 (57.2)	15103 (44.4)	0.26
Hyperlipidemia	317 (88.3)	100952 (84.4)	0.11	717 (85.1)	84699 (83.2)	0.05	563 (84.2)	47396 (81.4)	0.07	430 (85.1)	28883 (84.9)	0.01
Hypertension	317 (88.3)	100961 (84.4)	0.11	753 (89.3)	86502 (85.0)	0.13	596 (89.1)	50359 (86.5)	0.08	448 (88.7)	29411 (86.4)	0.07
CKD	36 (10.0)	8857 (7.4)	0.09	113 (13.4)	8655 (8.5)	0.16	104 (15.5)	6272 (10.8)	0.14	105 (20.8)	4176 (12.3)	0.23
COPD	60 (16.7)	18737 (15.7)	0.03	133 (15.8)	15465 (15.2)	0.02	110 (16.4)	9083 (15.6)	0.02	78 (15.4)	5386 (15.8)	-0.01
History of Malignant Neoplasm	62 (17.3)	17625 (14.7)	0.07	147 (17.4)	15149 (14.9)	0.07	98 (14.6)	8870 (15.2)	-0.02	84 (16.6)	5212 (15.3)	0.04
Physician specialties†												
Cardiologists	24 (6.7)	9275 (7.8)	-0.04	45 (5.3)	7319 (7.2)	-0.08	49 (7.3)	4068 (7.0)	0.01	53 (10.5)	2448 (7.2)	0.12
Endocrinologists	10 (2.8)	2852 (2.4)	0.03	47 (5.6)	2660 (2.6)	0.15	29 (4.3)	1673 (2.9)	0.08	25 (5.0)	977 (2.9)	0.11
Internists	162 (45.1)	76305 (63.8)	-0.38	387 (45.9)	66298 (65.1)	-0.39	319 (47.7)	37630 (64.6)	-0.35	222 (44.0)	21715 (63.8)	-0.41
Nurse practitioners or physician assistants	16 (4.5)	9235 (7.7)	-0.14	40 (4.7)	9105 (8.9)	-0.17	50 (7.5)	5876 (10.1)	-0.09	47 (9.3)	4209 (12.4)	-0.10
Healthcare utilization												
Any recent hospitalization††	6 (1.7)	6607 (5.5)	-0.21	20 (2.4)	5148 (5.1)	-0.14	14 (2.1)	2690 (4.6)	-0.14	13 (2.6)	1794 (5.3)	-0.14
Average length of hospitalization (mean, std.dev)	0.67 (2.17)	0.79 (2.58)	-0.05	0.73 (2.50)	0.76 (2.48)	-0.01	0.72 (2.12)	0.78 (2.47)	-0.02	0.64 (2.01)	0.80 (2.44)	-0.07
Number of ED visits (mean, Std.dev)	0.45 (1.15)	0.47 (1.10)	-0.02	0.42 (0.95)	0.47 (1.12)	-0.05	0.41 (1.07)	0.49 (1.14)	-0.07	0.44 (0.89)	0.51 (1.18)	-0.07
Number of office visits (mean, std.dev)	11.22 (8.30)	9.26 (7.26)	0.25	10.98 (8.00)	9.29 (7.16)	0.22	11.09 (7.71)	9.71 (7.20)	0.18	11.83 (8.56)	9.78 (7.29)	0.26
Number of HbA1c tests ordered (mean, std.dev)	2.07 (1.32)	1.75 (1.13)	0.26	2.10 (1.25)	1.84 (1.13)	0.23	2.16 (1.23)	2.06 (1.11)	0.08	2.22 (1.28)	2.11 (1.10)	0.09
Brand/Generic ratio# (mean, std.dev)	-1.31 (1.15)	-1.72 (1.19)	0.35	-1.56 (1.16)	-1.91 (1.15)	0.30	-1.86 (1.19)	-2.08 (1.12)	0.19	-1.95 (1.16)	-2.21 (1.08)	0.23
Number of unique medications (mean, std.dev)	12.97 (8.78)	11.76 (7.77)	0.15	12.68 (8.68)	11.77 (7.81)	0.11	12.85 (8.99)	11.77 (7.76)	0.13	13.35 (8.86)	12.16 (8.08)	0.14
Copay for pharmacy cost (\$, mean, std.dev)	494.04 (586.60)	433.79 (612.31)	0.10	528.92 (673.23)	435.57 (661.47)	0.14	505.94 (748.85)	433.66 (669.16)	0.10	512.75 (756.37)	425.59 (668.98)	0.12
Preventive healthcare service###	299 (83.3)	100829 (84.3)	-0.03	727 (86.2)	87098 (85.5)	0.02	559 (83.6)	50585 (86.9)	-0.09	440 (87.1)	29945 (88.0)	-0.03
Concomitant medications												
ACE inhibitors or ARBs	212 (59.1)	75557 (63.2)	-0.08	508 (60.3)	64968 (63.8)	-0.07	416 (62.2)	37894 (65.1)	-0.06	304 (60.2)	22161 (65.1)	-0.10
Antithrombotic medications	95 (26.5)	25963 (21.7)	0.11	201 (23.8)	21924 (21.5)	0.06	181 (27.1)	13654 (23.5)	0.08	159 (31.5)	8201 (24.1)	0.17
Beta blockers	159 (44.3)	54428 (45.5)	-0.02	370 (43.9)	45801 (45.0)	-0.02	304 (45.4)	27087 (46.5)	-0.02	247 (48.9)	15647 (46.0)	0.06
Calcium channel blockers	106 (29.5)	38089 (31.8)	-0.05	260 (30.8)	32041 (31.5)	-0.01	204 (30.5)	18653 (32.0)	-0.03	143 (28.3)	10946 (32.2)	-0.08
Loop diuretics	52 (14.5)	17521 (14.6)	0.00	154 (18.3)	14636 (14.4)	0.11	97 (14.5)	9153 (15.7)	-0.03	96 (19.0)	5412 (15.9)	0.08
Statin	211 (58.8)	79524 (66.5)	-0.16	506 (60.0)	68630 (67.4)	-0.15	440 (65.8)	40820 (70.1)	-0.09	326 (64.6)	24189 (71.1)	-0.14
Thiazides	59 (16.4)	21141 (17.7)	-0.03	109 (12.9)	17566 (17.3)	-0.12	107 (16.0)	9826 (16.9)	-0.02	78 (15.4)	5704 (16.8)	-0.04

SD: standardized difference; std.dev: standard deviation; HbA1c: hemoglobin A1c; CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department.

* Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)

South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)

Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)

West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

** Defined as a history of myocardial infarction, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

† Defined as specialist visits occurred within 7 days prior to cohort entry.

†† Defined as hospitalization occurred within 30 days prior to cohort entry.

Added 1 to both numerator and denominator, then log-transformed.

Defined as administration of bone mineral density (BMD) test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu vaccine, or pneumococcal vaccine.

Table S5. [Sensitivity analysis] Patient characteristics and standardized differences at the time of first-line SGLT-2i and metformin initiation (2013-2019). Values are percentage (%) unless otherwise specified.

	Apr2013- Dec2014			Jan2015- Jun2016			Jul2016- Dec2017			Jan2018- Dec2019			Linear trend (P)
Baseline characteristics	SGLT-2i (n=1,223)	Metformin (n=167,168)	SD	SGLT2-i (n=1,934)	Metformin (n=177,793)	SD	SGLT2-i (n=1,563)	Metformin (n=126,291)	SD	SGLT2-i (n=1,286)	Metformin (n=91,801)	SD	
Demographics													
Age (mean, std.dev)	56.90 (9.17)	62.71 (10.18)	-0.22	60.91 (8.63)	65.22 (9.30)	-0.20	61.05 (9.28)	63.16 (10.04)	-0.13	63.02 (10.79)	62.52 (10.87)	0.01	0.056
Gender (Male)	47.51	49.69	-0.03	52.33	49.65	0.07	51.31	51.34	0.01	57.62	53.42	0.09	0.319
Region*													
Northeast	17.91	16.65	0.04	21.72	18.47	0.08	19.39	17.18	0.06	17.42	15.24	0.05	0.907
South	53.31	41.89	0.15	50.10	42.42	0.13	53.29	45.03	0.15	48.83	44.94	0.09	0.261
Midwest	16.35	23.06	-0.16	14.79	21.83	-0.19	13.76	21.20	-0.20	17.42	20.94	-0.09	0.486
West	12.43	18.39	-0.09	13.39	17.28	-0.07	13.56	16.59	-0.07	16.33	18.88	-0.09	0.811
Medicare Advantage	10.07	25.77	-0.42	14.12	26.88	-0.26	18.54	25.62	-0.16	37.03	35.66	0.03	0.005
Race (White)	78.36	76.17	0.10	79.55	77.25	0.07	71.03	74.28	-0.06	66.67	66.54	-0.01	0.185
Life-style risk factors													
Obesity or Overweight	26.66	23.17	0.09	34.80	30.87	0.10	42.48	39.80	0.05	49.30	48.08	0.03	0.082
Smoking	7.69	11.46	-0.05	12.46	15.14	-0.03	15.48	16.77	-0.02	20.06	19.12	0.02	0.032
Comorbidities													
Diabetic Nephropathy	2.04	1.68	0.07	3.57	2.71	0.08	5.12	4.03	0.06	10.03	5.43	0.16	0.315
Diabetic Neuropathy	5.15	3.68	0.14	7.19	5.02	0.13	7.93	5.64	0.11	10.34	5.98	0.15	0.850
Diabetic Retinopathy	1.14	0.90	0.04	1.60	1.01	0.06	0.96	0.91	0.01	3.27	1.30	0.13	0.475
CVD**	19.87	25.63	0.02	27.25	29.45	0.05	29.62	26.82	0.11	40.12	25.81	0.30	0.085
Hyperlipidemia	72.53	70.70	0.15	73.32	73.47	0.06	69.16	66.47	0.10	75.43	70.30	0.10	0.67
Hypertension	67.05	69.37	0.08	74.72	74.53	0.10	73.90	72.54	0.06	77.99	71.78	0.13	0.493
CKD	3.68	4.51	0.04	6.98	6.33	0.07	8.06	6.60	0.07	13.53	7.65	0.16	0.106
COPD	7.11	9.16	0.01	8.74	10.77	-0.02	9.98	9.47	0.04	11.51	9.62	0.05	0.277
History of Malignant Neoplasm	6.87	9.40	-0.01	9.72	10.71	0.02	8.77	9.76	-0.02	10.26	8.97	0.04	0.439
Physician specialties†													
Cardiologists	2.78	4.88	-0.06	3.67	5.48	-0.06	4.73	5.15	-0.01	7.31	5.19	0.08	0.079
Endocrinologists	4.25	2.25	0.09	3.46	2.47	0.07	3.26	2.52	0.04	4.28	2.28	0.11	0.935
Internists	48.65	65.30	-0.37	47.72	66.93	-0.40	46.32	67.86	-0.44	47.12	68.65	-0.45	0.038
Nurse practitioners or physician assistants	1.88	4.25	-0.10	2.9	5.94	-0.14	4.41	6.15	-0.07	4.51	6.91	-0.12	0.986
Healthcare utilization													
Any recent hospitalization††	0.98	3.78	-0.19	1.34	3.93	-0.14	1.15	3.53	-0.15	2.80	3.78	-0.05	0.116
Avg. length of hospitalizations (mean, std.dev)	0.22 (1.44)	0.41 (1.75)	-0.04	0.37 (1.73)	0.48 (1.96)	-0.02	0.30 (1.25)	0.41 (1.69)	-0.07	0.41 (1.47)	0.44 (1.99)	-0.05	0.524
Number of ED visits (mean, Std.dev)	0.57 (1.54)	0.58 (1.52)	0.00	0.53 (1.33)	0.57 (1.48)	-0.03	0.63 (1.83)	0.62 (1.66)	-0.02	0.77 (2.06)	0.72 (1.98)	0.01	0.758
Number of office visits (mean, std.dev)	11.59 (10.09)	10.06 (9.72)	0.18	11.39 (10.25)	9.78 (8.97)	0.17	11.78 (10.88)	10.03 (9.56)	0.18	11.89 (10.47)	10.06 (9.65)	0.19	0.396
Number of HbA1c test orders (mean, std.dev)	1.64 (1.16)	1.46 (1.07)	0.25	1.74 (1.16)	1.59 (1.08)	0.21	1.77 (1.17)	1.62 (1.04)	0.16	1.84 (1.19)	1.65 (1.04)	0.16	0.050
Brand/Generic ratio# (mean, std.dev)	-1.29 (1.21)	-1.61 (1.20)	0.23	-1.53 (1.19)	-1.79 (1.17)	0.22	-1.69 (1.19)	-1.92 (1.15)	0.19	-1.86 (1.17)	-2.02 (1.12)	0.15	0.022
Number of unique medications (mean, std.dev)	10.78 (8.33)	10.29 (7.38)	0.15	10.81 (7.98)	10.58 (7.52)	0.07	10.75 (8.01)	10.27 (7.39)	0.09	11.72 (9.29)	10.36 (7.67)	0.15	0.975
Copay for pharmacy cost (\$, mean, std.dev)	324.97 (440.00)	347.34 (513.62)	0.05	354.02 (489.98)	344.92 (561.58)	0.10	362.75 (661.33)	309.74 (546.57)	0.11	386.49 (655.31)	300.11 (540.61)	0.13	0.025
Preventive healthcare service###	70.24	73.46	0.00	75.44	76.68	0.03	72.04	75.54	-0.06	75.97	75.55	0.00	0.733
Concomitant medications													
ACE inhibitors or ARBs	64.24	63.52	-0.10	61.60	63.88	-0.08	61.41	65.86	-0.11	62.05	66.34	-0.06	0.436
Antithrombotic medications	29.80	22.22	0.02	26.18	22.42	0.01	29.88	24.88	0.04	33.66	25.14	0.20	0.181
Beta blockers	51.66	46.63	-0.07	47.18	46.19	-0.02	47.53	48.46	-0.05	52.15	47.63	0.10	0.185
Calcium channel blockers	33.11	32.67	-0.06	32.13	32.21	-0.02	30.59	33.05	-0.02	30.36	32.45	-0.03	0.314
Loop diuretics	19.21	15.02	0.04	19.28	15.05	0.06	17.65	16.66	0.03	22.11	16.63	0.11	0.337
Statin	61.59	67.58	-0.19	59.72	68.14	-0.16	67.53	71.30	-0.10	65.68	72.74	-0.08	0.008
Thiazides	11.28	14.86	-0.05	11.89	15.09	-0.08	11.20	14.66	-0.10	12.05	14.76	-0.09	0.182
Laboratory values													

HbA1c [§] (%; mean, std.dev)	7.34 (1.80)	7.38 (1.54)	0.01	7.37 (1.41)	7.31 (1.53)	0.06	7.46 (1.77)	7.33 (1.53)	0.08	7.59 (1.62)	7.27 (1.52)	0.20	0.053
Missing	87.31	83.64	0.02	82.79	79.36	-0.03	76.63	76.64	-0.01	69.18	68.84	0.00	0.785
eGFR [¶] (mL/min/1.73m ² ; mean, std.dev)	101.24 (17.21)	99.27 (16.20)	0.14	99.92 (17.20)	98.53 (16.12)	0.08	101.58 (16.42)	98.25 (16.52)	0.20	93.73 (19.73)	97.02 (16.74)	-0.18	0.355
Missing	85.91	82.36	-0.01	81.33	77.93	-0.04	75.04	75.18	-0.01	67.34	67.74	-0.02	0.946
LDL (mg/dl; mean, std.dev)	104.45 (47.26)	98.17 (44.15)	0.13	103.07 (41.01)	101.94 (40.90)	0.00	98.62 (39.96)	103.09 (40.78)	-0.11	90.53 (39.88)	100.66 (40.12)	-0.25	<.001
Missing	86.57	83.09	0.01	83.49	79.69	-0.01	77.50	77.44	0.00	71.82	71.24	0.00	0.811
HDL (mg/dl; mean, std.dev)	46.29 (15.45)	45.90 (87.99)	-0.02	45.35 (12.31)	46.51 (14.26)	-0.09	45.75 (14.42)	47.14 (57.43)	-0.04	45.23 (13.48)	46.07 (13.14)	-0.07	0.602
Missing	86.29	83.42	-0.01	83.49	80.42	-0.03	77.94	78.16	-0.01	72.02	72.34	-0.02	0.954
Total cholesterol (mg/dl; mean, std.dev)	187.62 (56.66)	179.65 (58.22)	0.12	186.99 (42.80)	188.19 (45.64)	-0.05	178.58 (50.03)	188.40 (45.84)	-0.20	175.38 (40.28)	183.86 (43.73)	-0.20	0.065
Missing	86.19	83.44	-0.01	83.49	80.14	-0.02	77.42	77.77	-0.01	71.92	71.67	0.00	0.322
Triglyceride (mg/dl; mean, std.dev)	172.37 (101.81)	176.49 (154.38)	-0.03	171.74 (123.90)	183.40 (158.43)	-0.07	170.56 (132.48)	183.28 (180.34)	-0.08	191.84 (184.30)	181.40 (153.83)	0.07	0.446
Missing	86.38	83.47	-0.01	83.56	80.45	-0.03	77.42	78.01	-0.02	71.92	71.84	-0.01	0.824

SD: standardized difference; std.dev: standard deviation; HbA1c: hemoglobin A1c; CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department.

* Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)

South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)

Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)

West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

** Defined as a history of myocardial infarction, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

† Defined as specialist visits occurred within 7 days prior to cohort entry.

†† Defined as hospitalization occurred within 30 days prior to cohort entry.

Added 1 to both numerator and denominator, then log-transformed.

Defined as administration of bone mineral density (BMD) test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu vaccine, or pneumococcal vaccine.

§ Measured 180 days prior to or on cohort entry.

¶ Estimated using the quadratic GFR equation: $GFR = \exp(1.911 + \frac{5.249}{Serum\ creatinine} - \frac{2.114}{Serum\ creatinine^2} - 0.00686 * Age - 0.205 (if\ female))$. If serum creatinine <0.8 mg/dL, use 0.8 for serum creatinine.

Figure S2. [Sensitivity analysis] Trends of standardized differences (SDs) of selected patient characteristics, comparing first-line SGLT-2i versus metformin.

