

Supplementary Online Content

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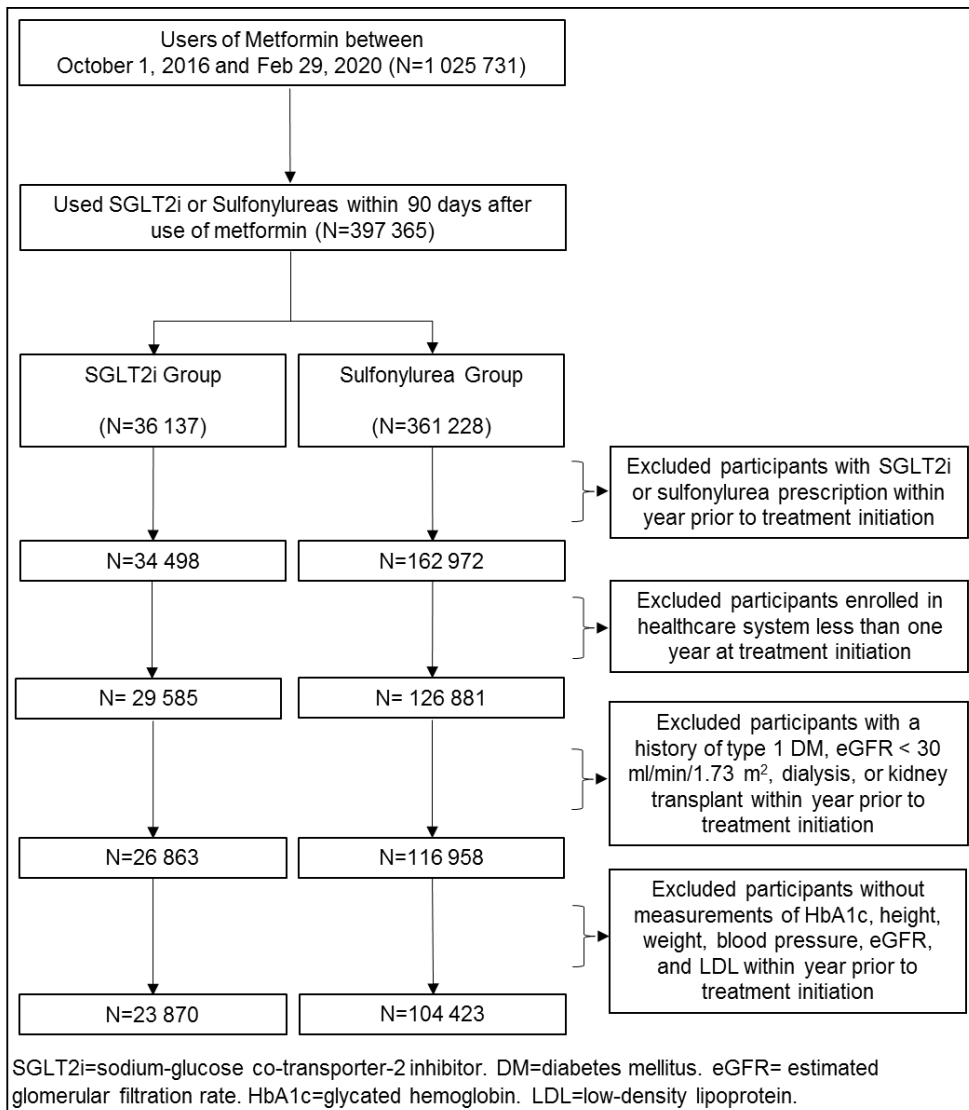
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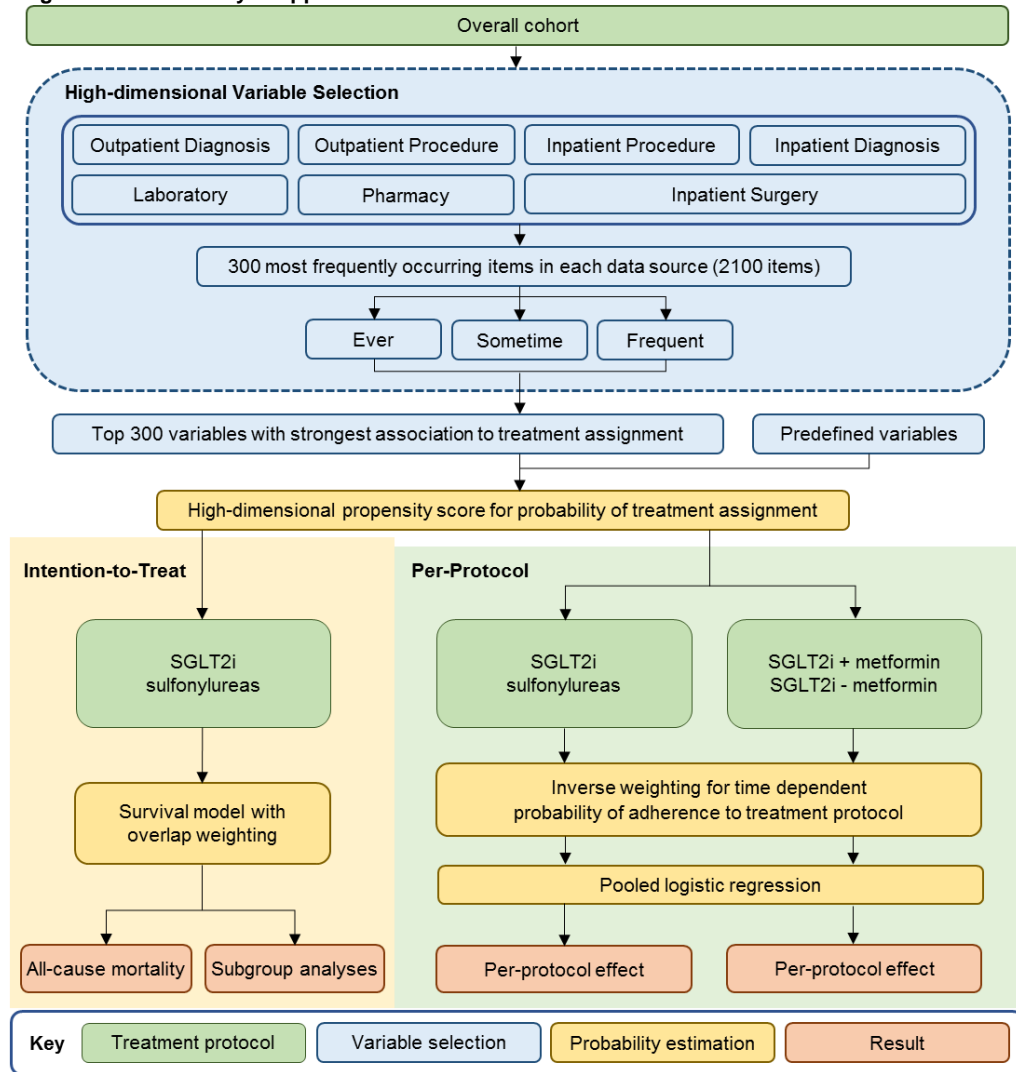
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Cohort flow

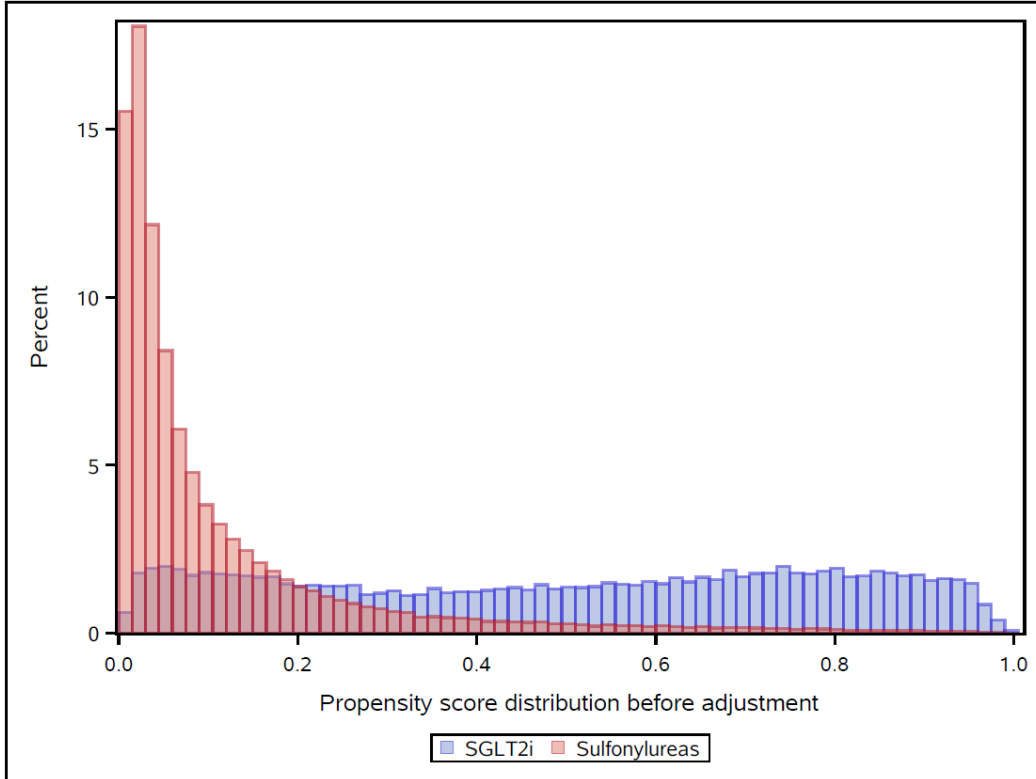


eFigure 2. Overall analytic approach flowchart

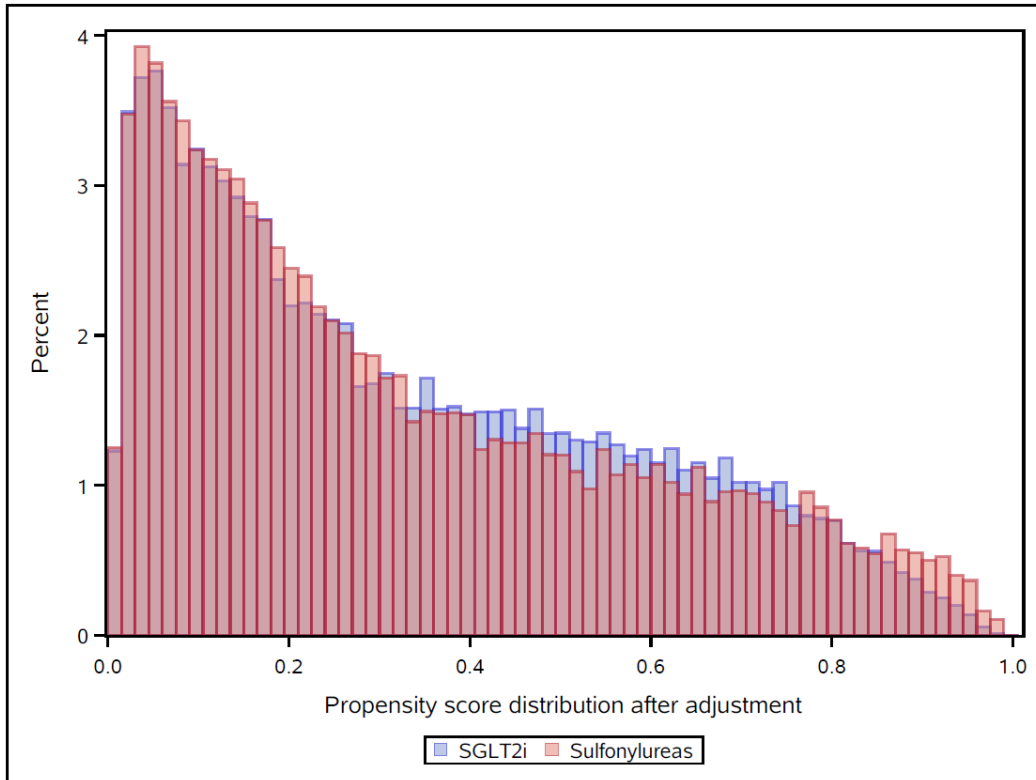


eFigure 3. Propensity score distribution of the SGLT2i and sulfonyleurea arms

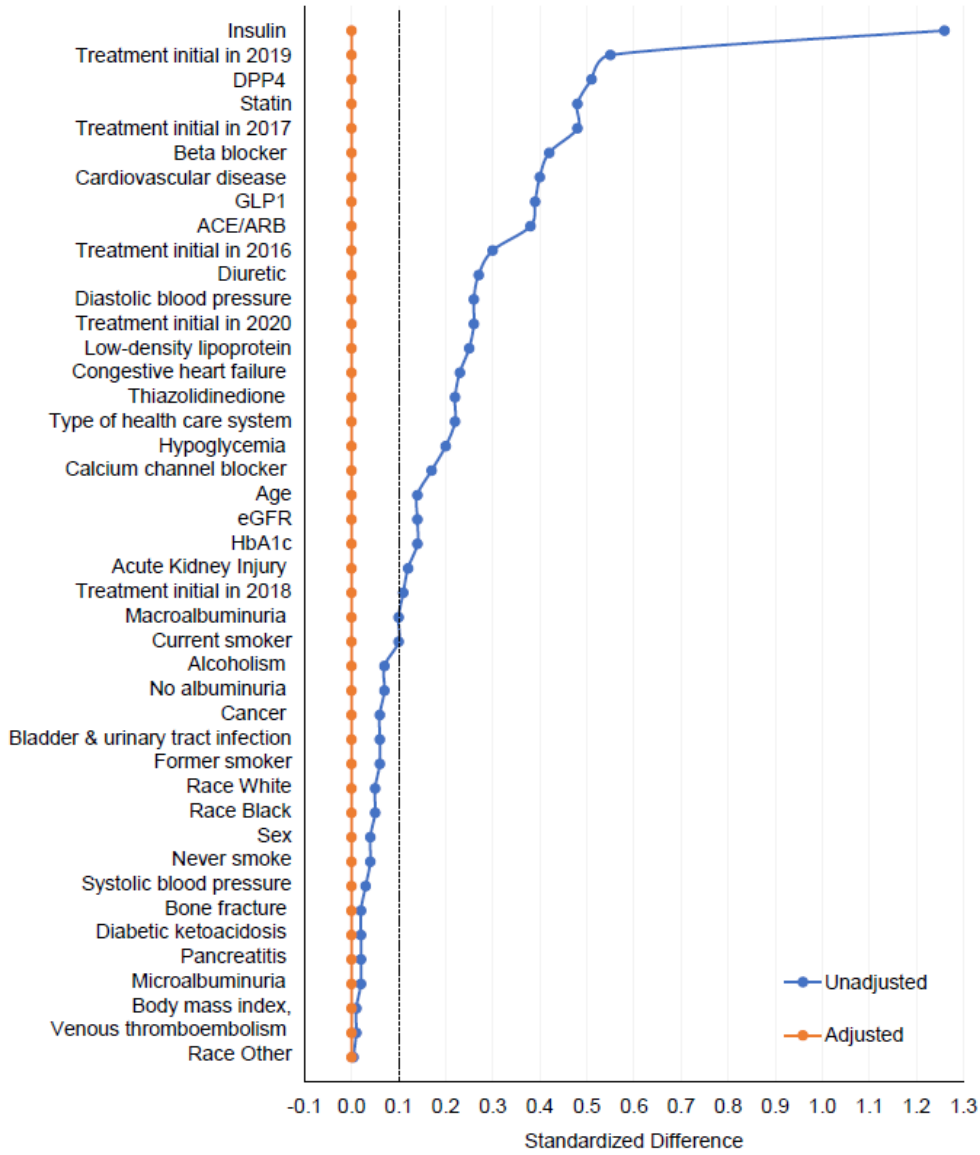
eFigure 3a. Propensity score distribution of the SGLT2i and sulfonyleurea arms before adjustment



eFigure 3b. Propensity score distribution of the SGLT2i and sulfonylurea arms after adjustment



eFigure 4. Standardized differences between the SGLT2i and sulfonylurea arms before and after adjustment



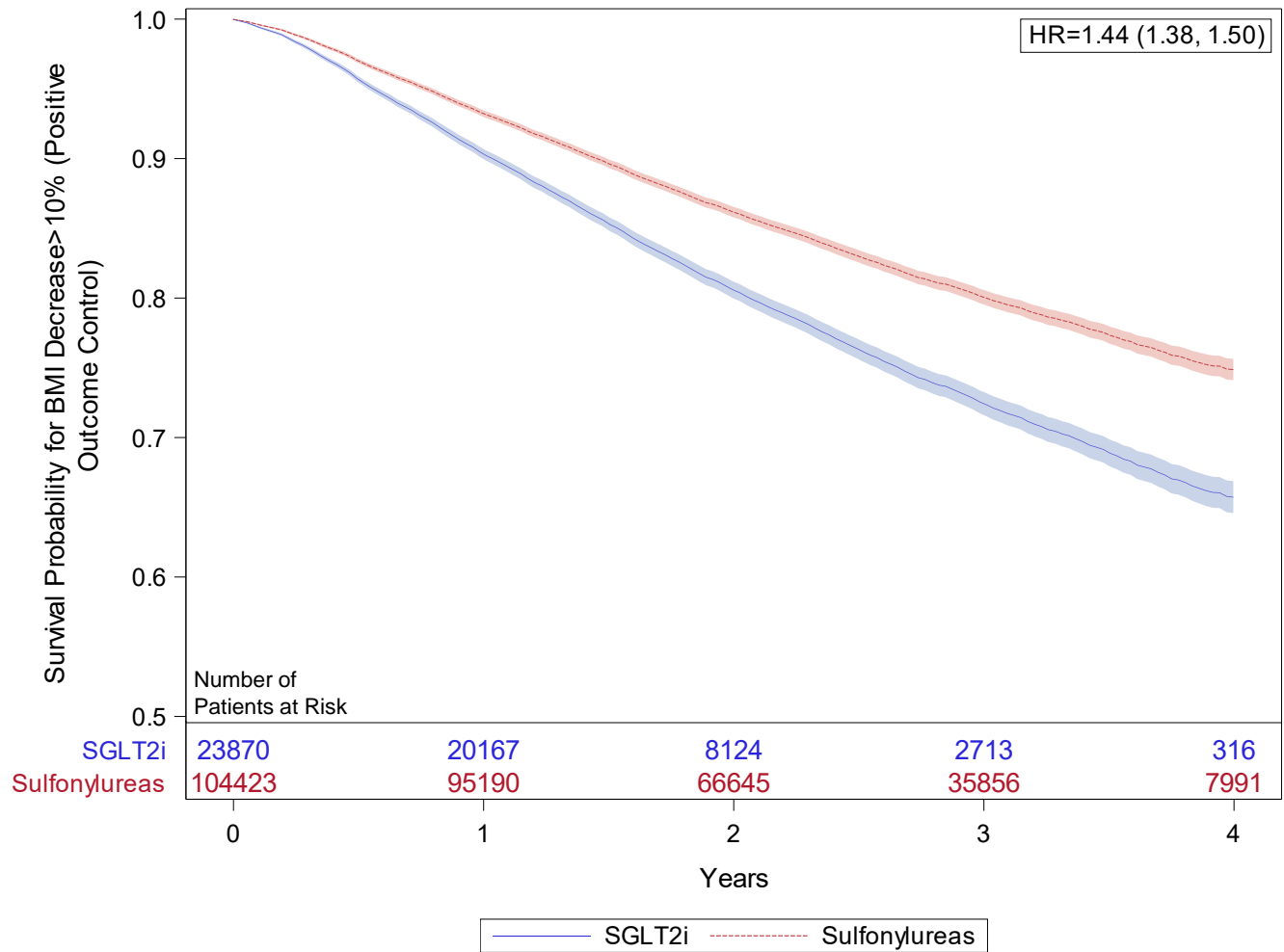
eFigure 5. Adjusted survival probability [for negative and positive outcome controls](#)

eFigure 5a. for chronic lower respiratory disease (negative outcome control). Survival probability in SGLT2i (blue) and sulfonylureas (red) arms, according to an intention-to-treat analysis. Light colored bands represent the 95% confidence interval for each treatment.

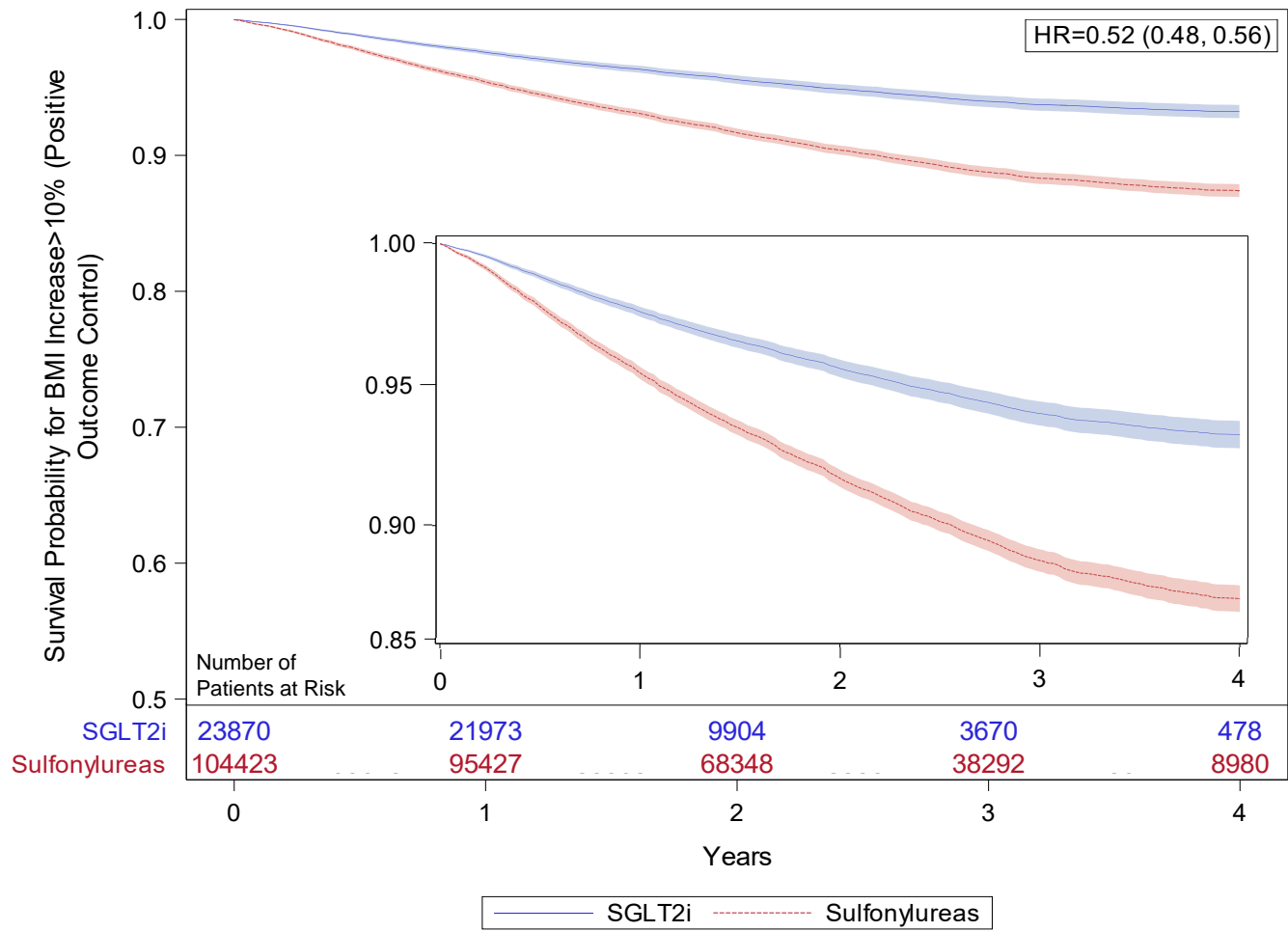
eFigure 5b. Adjusted survival probability for BMI decrease >10% (positive outcome control). Survival probability in SGLT2i (blue) and sulfonylureas (red) arms, according to an intention-to-treat analysis. Light colored bands represent the 95% confidence interval for each treatment.

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eFigure 5c. Adjusted survival probability for BMI increase >10% (positive outcome control). Survival probability in SGLT2i (blue) and sulfonylureas (red) arms, according to an intention-to-treat analysis. Light colored bands represent the 95% confidence interval for each treatment.



eTable 1. Distribution of medications within each antihyperglycemic class at treatment initiation

| SGLT2i | | Sulfonylureas | |
|-------------------|---------------|----------------------|---------------|
| Medication | n (%) | Medication | n (%) |
| Empagliflozin | 23816 (99.77) | Glipizide | 94856 (90.84) |
| Canagliflozin | 38 (0.16) | Glimepiride | 9124 (8.74) |
| Dapagliflozin | 16 (0.07) | Glyburide | 443 (0.42) |

Table 2. Demographic and health characteristics of the unadjusted cohort

| Baseline Characteristics | Overall cohort, no. (%) (n=128293) | SGLT2i, no. (%) (n=23 870 [18.61%]) | Sulfonylurea, no. (%) (n=104 423 [81.39%]) | Absolute standardized difference |
|---|------------------------------------|-------------------------------------|--|----------------------------------|
| Age, mean (SD), years | 63.84 (10.67) | 65.00 (9.28) | 63.57 (10.94) | 0.14 |
| Race | | | | |
| White | 95926 (74.77) | 18283 (76.59) | 77643 (74.35) | 0.05 |
| Black | 25413 (19.81) | 4312 (18.06) | 21101 (20.21) | 0.05 |
| Other | 6954 (5.42) | 1275 (5.34) | 5679 (5.44) | 0.004 |
| Sex | | | | 0.04 |
| Male | 121856 (94.98) | 22825 (95.62) | 99031 (94.84) | |
| Female | 6437 (5.02) | 1045 (4.38) | 5392 (5.16) | |
| eGFR, mean (SD), mL/min/1.73 m ² | 80.31 (19.79) | 78.15 (18.38) | 80.81 (20.07) | 0.14 |
| eGFR status | | | | |
| ≥ 90 mL/min/1.73 m ² | 42905 (33.44) | 6596 (27.63) | 36309 (34.77) | 0.15 |
| ≥ 60 to < 90 mL/min/1.73 m ² | 63674 (49.63) | 12928 (54.16) | 50746 (48.60) | 0.11 |
| ≥ 45 to < 60 mL/min/1.73 m ² | 16623 (12.96) | 3812 (15.97) | 12811 (12.27) | 0.11 |
| 30 to < 45 mL/min/1.73 m ² | 5091 (3.97) | 534 (2.24) | 4557 (4.36) | 0.12 |
| HbA1c, mean (SD), % | 8.77 (1.84) | 8.58 (1.47) | 8.82 (1.91) | 0.14 |
| Body mass index, mean (SD), kg/m ² | 33.14 (6.58) | 34.54 (6.59) | 32.83 (6.54) | 0.01 |
| Low-density lipoprotein, mean (SD), mg/dL | 87.82 (40.12) | 79.95 (35.44) | 89.62 (40.90) | 0.25 |
| Systolic blood pressure, mean (SD), mmHg | 132.58 (16.66) | 132.22 (16.53) | 132.67 (16.69) | 0.03 |
| Diastolic blood pressure, mean (SD), mmHg | 77.13 (10.29) | 74.95 (9.99) | 77.63 (10.29) | 0.26 |
| Congestive heart failure | 7862 (6.13) | 2653 (11.11) | 5209 (4.99) | 0.23 |
| Alcoholism | 7730 (6.03) | 1118 (4.68) | 6612 (6.33) | 0.07 |
| Bone fracture | 1311 (1.02) | 277 (1.16) | 1034 (0.99) | 0.02 |
| Cancer | 23446 (18.28) | 4863 (20.37) | 18583 (17.80) | 0.06 |
| Cardiovascular disease | 30296 (23.61) | 9066 (37.98) | 21230 (20.33) | 0.40 |
| Diabetic ketoacidosis | 305 (0.24) | 75 (0.31) | 230 (0.22) | 0.02 |
| Hypoglycemia | 1723 (1.34) | 908 (3.80) | 815 (0.78) | 0.20 |
| Pancreatitis | 1367 (1.07) | 300 (1.26) | 1067 (1.02) | 0.02 |
| Bladder & urinary tract infection | 3303 (2.57) | 453 (1.90) | 2850 (2.73) | 0.06 |
| Venous thromboembolism | 690 (0.54) | 150 (0.63) | 540 (0.52) | 0.01 |
| Acute Kidney Injury | 8842 (6.89) | 2296 (9.62) | 6546 (6.27) | 0.12 |
| Albuminuria ^a | | | | |
| No albuminuria | 76121 (59.33) | 13481 (56.48) | 62640 (59.99) | 0.07 |
| Microalbuminuria | 44545 (34.72) | 8481 (35.53) | 36064 (34.54) | 0.02 |
| Macroalbuminuria | 7627 (5.94) | 1908 (7.99) | 5719 (5.48) | 0.10 |
| Insulin | 31818 (24.80) | 16093 (67.42) | 15725 (15.06) | 1.26 |
| DPP4 | 10176 (7.93) | 4290 (17.97) | 5886 (5.64) | 0.51 |
| GLP1 | 4801 (3.74) | 3499 (14.66) | 1302 (1.25) | 0.39 |
| Thiazolidinedione | 2799 (2.18) | 1286 (5.39) | 1513 (1.45) | 0.22 |
| ACE/ARB | 70989 (55.33) | 16781 (70.30) | 54208 (51.91) | 0.38 |
| Calcium channel blocker | 32153 (25.06) | 7425 (31.11) | 24728 (23.68) | 0.17 |
| Beta blocker | 47107 (36.72) | 12679 (53.12) | 34428 (32.97) | 0.42 |
| Diuretic | 45576 (35.52) | 10983 (46.01) | 34593 (33.13) | 0.27 |
| Statin | 88781 (69.20) | 20385 (85.40) | 68396 (65.50) | 0.48 |
| Type of health care system | | | | 0.22 |
| Outpatient clinic | 79769 (62.18) | 12294 (51.50) | 67475 (64.62) | |
| Hospital system | 48524 (37.82) | 11576 (48.50) | 36948 (35.38) | |
| Year of treatment initial | | | | |
| 2016 | 8517 (6.64) | 379 (1.59) | 8138 (7.79) | 0.30 |
| 2017 | 39915 (31.11) | 3490 (14.62) | 36425 (34.88) | 0.48 |
| 2018 | 37619 (29.32) | 6038 (25.30) | 31581 (30.24) | 0.11 |
| 2019 | 37442 (29.18) | 11920 (49.94) | 25522 (24.44) | 0.55 |

| | | | | |
|--|---------------|---------------|---------------|------|
| 2020 | 4800 (3.74) | 2043 (8.56) | 2757 (2.64) | 0.26 |
| Smoking status | | | | |
| Never | 68740 (53.59) | 13131 (55.01) | 55609 (53.25) | 0.04 |
| Former | 31121 (24.26) | 6260 (26.23) | 24861 (23.81) | 0.06 |
| Current | 28432 (22.16) | 4479 (18.76) | 23953 (22.94) | 0.10 |
| Follow up, mean (SD), years | 2.57 (1.00) | 2.04 (0.86) | 2.70 (0.99) | 0.71 |
| Abbreviations: SGLT2i, sodium-glucose co-transporter-2 inhibitor; SD, standard deviation; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; DPP4, dipeptidyl peptidase-4 inhibitor; GLP1, glucagon-like peptide-1 receptor agonist; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin-receptor blockers. | | | | |
| * No albuminuria defined as albumin to creatinine ratio < 30 mg/g, microalbuminuria defined as albumin to creatinine ratio from 30 to < 300 mg/g, and macroalbuminuria defined as albumin to creatinine ratio of ≥ 300 mg/g. | | | | |

eTable 3. Intention-to-treat hazard ratios, death rates, and event reductions in the overall cohort and in subgroups

| Analyses | Adjusted hazard ratio (95%CI) | Adjusted death rate in SGLT2i per 1000 person-years | Adjusted death rate in sulfonylurea per 1000 person-years | Event reduction per 1000 person-years |
|----------------------------------|-------------------------------|---|---|---------------------------------------|
| Overall | 0.81 (0.75, 0.87) | 23.01 (21.48, 24.8) | 28.23 (27.1, 29.42) | -5.15 (-7.16, -3.02) |
| Age | | | | |
| ≤65 | 0.85 (0.73, 0.99) | 12.31 (10.7, 14.11) | 14.49 (13.19, 15.93) | -2.17 (-4.32, -0.29) |
| >65 | 0.81 (0.74, 0.88) | 31.58 (29.19, 33.87) | 38.69 (36.53, 40.15) | -7.05 (-9.71, -3.99) |
| CVD | | | | |
| No | 0.81 (0.75, 0.88) | 23.13 (21.65, 24.49) | 28.06 (27.02, 29.47) | -4.95 (-6.90, -3.31) |
| Yes | 0.85 (0.75, 0.97) | 21.4 (19.1, 23.88) | 24.98 (23.34, 26.94) | -3.59 (-6.14, -0.89) |
| eGFR, mL/min/1.73 m ² | | | | |
| ≥90 | 0.79 (0.67, 0.94) | 14.01 (11.86, 16.85) | 17.81 (15.98, 19.12) | -3.74 (-6.2, -0.68) |
| ≥60-<90 | 0.86 (0.78, 0.96) | 24.6 (22.51, 26.75) | 28.17 (26.47, 29.66) | -3.51 (-6.19, -0.99) |
| ≥45-<60 | 0.78 (0.66, 0.91) | 32.78 (28.37, 37.2) | 41.72 (38.13, 45.18) | -9.18 (-13.53, -2.91) |
| ≥30-<45 | 0.71 (0.5, 1.00) | 47.63 (32.64, 62.88) | 64.67 (54.6, 75.96) | -18.27 (-33.34, -1.1) |
| Albuminuria status ^a | | | | |
| No albuminuria | 0.88 (0.79, 0.98) | 19.75 (17.93, 21.65) | 22.4 (21.15, 23.62) | -2.71 (-4.69, -0.79) |
| Micro-albuminuria | 0.79 (0.7, 0.89) | 26.88 (24.19, 29.38) | 33.36 (31.26, 35.72) | -6.69 (-10.02, -3.48) |
| Macro-albuminuria | 0.68 (0.53, 0.85) | 33.63 (27.11, 40.67) | 48.44 (41.35, 54.32) | -14.70 (-23.04, -5.97) |
| BMI, kg/m ² | | | | |
| >18.5- ≤25 | 0.69 (0.54, 0.87) | 42.05 (32.97, 50.44) | 59.27 (52.27, 65.78) | -17.40 (-28.04, -7.58) |
| >25- ≤30 | 0.84 (0.73, 0.97) | 26.07 (23.2, 29.02) | 30.64 (28.22, 33.16) | -4.64 (-7.8, -1.15) |
| >30 | 0.84 (0.77, 0.92) | 20.86 (19.4, 22.49) | 24.67 (23.3, 26.08) | -3.73 (-5.56, -1.95) |
| Insulin | | | | |
| No | 0.84 (0.75, 0.95) | 18.58 (16.37, 20.56) | 21.84 (20.83, 23.08) | -3.36 (-5.45, -0.71) |
| Yes | 0.79 (0.72, 0.87) | 26.92 (25.17, 29.09) | 33.54 (31.64, 35.8) | -6.57 (-9.4, -3.9) |
| ACE/ARB | | | | |
| No | 0.85 (0.75, 0.97) | 21.4 (19.1, 23.88) | 24.98 (23.34, 26.94) | -3.59 (-6.14, -0.89) |
| Yes | 0.79 (0.73, 0.87) | 24.04 (22.31, 26.21) | 29.88 (28.18, 31.65) | -5.81 (-7.84, -3.66) |
| Diuretic | | | | |
| No | 0.86 (0.78, 0.96) | 18.97 (17, 20.71) | 21.97 (20.74, 23.21) | -3.10 (-5.17, -0.67) |
| Yes | 0.77 (0.70, 0.86) | 28.94 (26.74, 31.69) | 37.2 (34.83, 39.82) | -8.26 (-11.24, -4.79) |

Abbreviations: SGLT2i, sodium-glucose co-transporter-2 inhibitor; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; BMI, body mass index; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin-receptor blockers.

^a Albuminuria status defined as: no albuminuria (albumin to creatinine ratios ≤ 30 mg/g), microalbuminuria (>30 to ≤ 300 mg/g), and macroalbuminuria (>300 mg/g).

eTable 4. Adherence rate, estimated event rate, adjusted hazard ratio, and estimated event reduction for all-cause mortality based on per-protocol analyses for continued use of SGLT2i or sulfonylureas

| Treatment groups | Adherence rate ^a | Estimated event rate per 1000 person-years | Adjusted hazard ratio (95% CI) | Event reduction per 1000 person-years (95% CI) |
|--------------------------|-----------------------------|--|--------------------------------|--|
| SGLT2i (N=23870) | 51.80% | 21.18 (18.84, 24.08) | 0.66 (0.60, 0.74) | -10.10 (-12.97, -7.24) |
| Sulfonylureas (N=104423) | 39.69% | 32.22 (27.91, 35.47) | | |

Abbreviations: SGLT2i, sodium-glucose co-transporter-2 inhibitor; CI, confidence interval.
^a Adherence rate based on proportion of participants in the treatment group adherence to the protocol at the end of follow up, after adjustment of baseline characteristics

eTable 5. Adherence rate, estimated event rate, adjusted hazard ratio, and estimated event reduction for all-cause mortality based on per-protocol analyses for continued use of SGLT2i with and without metformin

| Treatment groups | Adherence rate ^a | Estimated event rate per 1000 person-years | Adjusted hazard ratio (95% CI) | Event reduction per 1000 person-years (95% CI) |
|--|-----------------------------|--|--------------------------------|--|
| SGLT2i with metformin (N=22542) | 36.28% | 18.48 (16.01, 22.09) | 0.70 (0.50, 0.97) | -7.62 (-17.12, -0.48) |
| SGLT2i without metformin (N=1328) | 25.57% | 26.26 (18.48, 36.40) | | |
| Abbreviations: SGLT2i, sodium-glucose co-transporter-2 inhibitor; CI, confidence interval. | | | | |
| ^a Adherence rate based on proportion of participants in the treatment group adherence to the protocol at the end of follow up, after adjustment of baseline characteristics | | | | |