**Data Supplement**

The following data supplement includes sensitivity analyses that answer three questions: do imbalances in observed covariates appear between metformin and sulfonylurea users over time; does the distribution of observed covariates change over time; and was the observed difference in risk of CVD events or death between metformin and sulfonylurea users driven by the patients with the longest follow-up times? The first two questions are addressed with Data Supplement Tables 1 and 2. These tables show the distribution of covariates for the cohort at baseline and for those who remain at risk in the cohort at years 1, 2, and 3 in the persistence exposure required (PER) analysis. Data Supplement Table 1 displays the whole cohort, and Data Supplement Table 2 the propensity score matched cohort. No notable imbalances in observed covariates appear between metformin and sulfonylurea users over time. This was also the case for the persistent exposure not required (PENR) analysis results, which were very similar to the PER results shown except as noted here (data available on request). We observed no remarkable changes in cohort characteristics over time, with the exception of fiscal year and the proportion of those identified as white increasing by 8% in both exposure groups over the first three years. The fiscal year of entry limits the follow-up time possible for a patient, effectively censoring the data administratively. Because race is a predictor of persistence on therapy, the trend in the proportion of patients who were white appeared as expected. The PENR results, which do not require persistence on therapy, show no change in the distribution of race over time. Data Supplement Table 3 presents the hazard ratios and rate differences calculated at the end of the first year of follow-up. The results from the entire study period are displayed for comparison. The similarity between the adjusted hazard ratios and the adjusted incident rate differences demonstrates that the analyses over the entire time period were not driven by the patients with the longest follow-up times.

Data supplement Table 1 Full Cohort: Characteristics of all metformin and sulfonylurea users at cohort entry and those who remained in the cohort at year 1, 2 and 3. We detected no remarkable changes in cohort characteristics over time.

Data supplement Table 2 Propensity Score (PS) Matched Cohort: Characteristics of PS matched metformin and sulfonylurea users at cohort entry and those who remain in the cohort at year 1, 2 and 3. We detected no remarkable changes in cohort characteristics over time.

Data Supplement Table 3 Full and Propensity Score (PS) Matched Cohorts: Comparison of hazard ratios and rate differences between 1 year of follow-up and the entire study. Hazard ratios and rate differences were similar when data was truncated at one year, suggesting that the overall result is not driven by a select group of patients who remain in the cohort.

| *Characteristic* | *Metformin* | | | | *Sulfonylurea* | | | |
|---|---|---|---|---|---|---|---|---|
| | ***Baseline N=155,025*** | ***Year 1 N=64,669*** | ***Year 2 N=30,794*** | ***Year 3 N=13,556*** | ***Baseline N=98,665*** | ***Year 1 N=35,373*** | ***Year 2 N=16,882*** | ***Year 3 N=7,467*** |
| **Age,** median (IQR) | 62 (56,71) | 63 (57,72) | 63 (57,72) | 64 (57,72) | 67 (57, 76) | 68 (58, 77) | 69 (58, 77) | 69 (59, 76) |
| **Male** (%) | 95 | 95 | 96 | 96 | 97 | 98 | 98 | 98 |
| **Race,** (%) | | | | | | | | |
| White | 74 | 78 | 81 | 82 | 75 | 80 | 82 | 83 |
| Black | 12 | 10 | 8 | 8 | 13 | 11 | 10 | 9 |
| Hispanic/ Other | 6 | 4 | 4 | 4 | 6 | 5 | 5 | 4 |
| **HbA1c (%),** median (IQR) | 7.0 (6.4, 7.8) | 7.0 (6.4, 7.7) | 6.9 (6.4,7.6) | 6.9 (6.3, 7.6) | 7.3 (6.6, 8.2) | 7.2 (6.6, 8.1) | 7.2 (6.6, 8.0) | 7.2 (6.5, 7.9) |
| **Low Density Lipoprotein (mg/dL),** median (IQR) | 103 (81, 128) | 101 (81, 124) | 101 (81, 124) | 103 (83, 127) | 101 (80,127) | 100 (80,125) | 101 (81,124) | 102 (83,125) |
| **Creatinine (mg/dL)**, median(IQR) | 1.0 (0.9, 1.1) | 1.0 (0.9, 1.1) | 1.0 (0.9, 1.1) | 1.0 (0.9, 1.1) | 1.1 (0.9, 1.2) | 1.1 (0.9, 1.2) | 1.1 (0.9, 1.2) | 1.1 (0.9, 1.2) |
| **Systolic Blood pressure (mm/Hg)**, median (IQR) | 134 (124,144) | 134(124, 143) | 134(124, 144) | 135(124, 145) | 135 (124,146) | 135 (124,146) | 136 (125,146) | 136 (126,147) |
| **Diastolic Blood pressure (mm/Hg),** median (IQR) | 77 (70, 84) | 76 (70, 83) | 76 (70, 82) | 76 (70, 83) | 76 (68, 83) | 76 (68, 82) | 76 (68, 82) | 76 (68, 82) |
| **Body Mass Index (kilograms/meter$^2$),** median(IQR) | 31.9 (28.5,36.2) | 32.0 (28.6,36.1) | 31.9 (28.5,35.9) | 31.8 (28.5,35.7) | 30.2 (26.9,34.2) | 30.3 (27.3,34.2) | 30.2 (27.2,34.0) | 30.2 (27.2,33.8) |
| **Number of Medications** median (IQR) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) | 5 (3, 8) | 5 (3, 7) | 5 (3, 7) |
| **Outpatient visits,** median (IQR) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) | 3 (2, 7) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) |
| **Hospitalized** (%) | 6 | 5 | 5 | 4 | 7 | 6 | 5 | 5 |
| **Baseline Co-morbidities (%) §** | | | | | | | | |
| Myocardial infarction/ coronary disease | 20 | 21 | 21 | 21 | 23 | 25 | 25 | 25 |
| Stroke/Transient ischemic attack/ carotid revascularization | 8 | 8 | 8 | 7 | 9 | 9 | 9 | 8 |
| Peripheral artery disease | 3 | 2 | 2 | 2 | 3 | 3 | 3 | 3 |
| Smoking | 10 | 10 | 9 | 8 | 8 | 8 | 7 | 7 |
| Obstructive pulmonary disease/ Emphysema | 9 | 8 | 8 | 8 | 9 | 9 | 9 | 8 |
| Atrial Fibrillation/ Flutter | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 |
| **Fiscal year** | | | | | | | | |
| 2003 | 13 | 15 | 21 | 33 | 19 | 23 | 29 | 41 |
| 2004 | 17 | 20 | 27 | 42 | 22 | 24 | 30 | 40 |
| 2005 | 21 | 24 | 33 | 25 | 21 | 23 | 27 | 19 |
| 2006 | 24 | 28 | 19 | -- | 21 | 22 | 14 | -- |
| 2007 | 25 | 14 | -- | -- | 17 | 8 | -- | -- |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Use of Medications (%)** | | | | | | | | |
| ACE Inhibitors or ARBs \|\| | 58 | 58 | 58 | 57 | 57 | 58 | 58 | 57 |
| Beta-blockers | 36 | 39 | 39 | 38 | 38 | 41 | 40 | 39 |
| Calcium Channel Blockers | 23 | 25 | 26 | 26 | 25 | 28 | 29 | 29 |
| Other Antihypertensives | 16 | 17 | 17 | 17 | 18 | 19 | 19 | 19 |
| Statin lipid lowering agents | 61 | 65 | 65 | 64 | 55 | 60 | 60 | 58 |
| Other lipid lowering agents | 13 | 13 | 13 | 12 | 11 | 12 | 12 | 12 |
| Anti-arrhythmics | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Anticoagulants | 4 | 5 | 5 | 5 | 6 | 7 | 7 | 7 |
| Antipsychotic medications | 7 | 8 | 7 | 7 | 7 | 7 | 7 | 6 |
| Digoxin | 3 | 4 | 4 | 4 | 6 | 7 | 7 | 7 |
| Thiazide and other diuretics | 33 | 34 | 33 | 32 | 30 | 32 | 32 | 31 |
| Loop Diuretics | 9 | 9 | 9 | 8 | 14 | 14 | 13 | 12 |
| Nitrates | 11 | 12 | 12 | 12 | 14 | 15 | 15 | 16 |
| Aspirin | 17 | 17 | 17 | 18 | 17 | 18 | 17 | 18 |
| Platelet inhibitors | 6 | 7 | 6 | 6 | 8 | 8 | 8 | 7 |

Data Supplement Table 1 Full Cohort: Characteristics of all metformin and sulfonylurea users at cohort entry and those who remain in the cohort at year 1, 2 and 3 in the persistent exposure required analysis. We detected no remarkable changes in cohort characteristics over time.

| ***Characteristic*** | ***Metformin*** | | | | ***Sulfonylurea*** | | | |
|---|---|---|---|---|---|---|---|---|
| | ***Baseline N=80,648*** | ***Year 1 N=33,418*** | ***Year 2 N=16,887*** | ***Year 3 N=7,976*** | ***Baseline N=80, 648*** | ***Year 1 N=29,502*** | ***Year 2 N=14,118*** | ***Year 3 N=6,185*** |
| **Age,** median (IQR) | 65 (57, 74) | 66 (58, 74) | 67 (58, 74) | 67 (58, 74) | 64 (56, 74) | 66 (57, 74) | 67 (58, 74) | 67 (58, 74) |
| **Male** (%) | 97 | 97 | 97 | 98 | 97 | 97 | 98 | 98 |
| **Race,** (%) | | | | | | | | |
| White | 75 | 80 | 82 | 84 | 75 | 79 | 82 | 83 |
| Black | 13 | 10 | 9 | 8 | 13 | 11 | 9 | 9 |
| Hispanic/ Other | 6 | 5 | 5 | 5 | 6 | 5 | 5 | 4 |
| **HbA1c (%),** median (IQR) | 7.2 (6.5, 8.2) | 7.1 (6.5, 7.9) | 7.1 (6.5, 7.8) | 7.0 (6.4, 7.8) | 7.2 (6.6, 8.2) | 7.2 (6.6, 8.0) | 7.2 (6.5, 7.9) | 7.1 (6.5, 7.9) |
| **Low Density Lipoprotein (mg/dL),** median (IQR) | 102(80, 127) | 100 (80, 124) | 100 (80, 124) | 103 (82, 127) | 102 (81, 127) | 101 (81, 125) | 101 (82, 125) | 102 (83, 125) |
| **Creatinine (mg/dL)**, median(IQR) | 1.1 (0.9, 1.2) | 1.0 (0.9, 1.2) | 1.0 (0.9, 1.2) | 1.0 (0.9, 1.2) | 1.0 (0.9, 1.2) | 1.0 (0.9, 1.2) | 1.0 (0.9, 1.2) | 1.0 (0.9, 1.2) |
| **Systolic Blood pressure (mm/Hg)**, median (IQR) | 135 (124,146) | 135 (124,145) | 135 (124,146) | 136 (125,147) | 135 (124,146) | 135 (124,145) | 136 (125,146) | 136 (126,146) |
| **Diastolic Blood pressure (mm/Hg),** median (IQR) | 76 (69, 83) | 76 (68, 82) | 76 (68, 82) | 76 (69, 82) | 76 (69, 83) | 76 (69, 82) | 76 (69, 82) | 76 (69, 82) |
| **Body Mass Index (kilograms/meter$^2$),** median(IQR) | 30.7 (27.4,34.6) | 30.7 (27.6,34.6) | 30.7 (27.6,34.4) | 30.7 (27.7,34.4) | 30.7 (27.5,34.7) | 30.8 (27.7,34.7) | 30.7 (27.7,34.5) | 30.7 (27.8,34.4) |
| **Number of Medications** median (IQR) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) | 5 (3, 7) |
| **Outpatient visits,** median (IQR) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) | 4 (2, 7) |
| **Hospitalized** (%) | 7 | 5 | 5 | 5 | 7 | 5 | 5 | 5 |
| **Baseline Co-morbidities (%) §** | | | | | | | | |
| Myocardial infarction/ coronary disease | 22 | 23 | 23 | 23 | 22 | 24 | 24 | 24 |
| Stroke/Transient ischemic attack/ carotid revascularization | 9 | 9 | 8 | 8 | 9 | 9 | 9 | 8 |
| Peripheral artery disease | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Smoking | 9 | 8 | 8 | 7 | 9 | 9 | 8 | 8 |
| Obstructive pulmonary disease/ Emphysema | 9 | 9 | 8 | 8 | 9 | 9 | 9 | 8 |
| Atrial Fibrillation/ Flutter | 3 | 4 | 4 | 3 | 3 | 4 | 4 | 3 |
| **Fiscal year** | | | | | | | | |
| 2003 | 18 | 20 | 26 | 38 | 17 | 21 | 27 | 39 |
| 2004 | 21 | 23 | 29 | 41 | 21 | 24 | 29 | 41 |
| 2005 | 21 | 24 | 30 | 20 | 21 | 23 | 28 | 20 |
| 2006 | 22 | 24 | 15 | -- | 22 | 23 | 15 | -- |
| 2007 | 18 | 10 | -- | -- | 19 | 9 | -- | -- |
| **Use of Medications (%)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ACE Inhibitors or ARBs \|\| | 57 | 58 | 57 | 56 | 58 | 59 | 58 | 57 |
| Beta-blockers | 37 | 40 | 39 | 38 | 37 | 40 | 40 | 38 |
| Calcium Channel Blockers | 25 | 27 | 27 | 27 | 24 | 27 | 28 | 29 |
| Other Antihypertensives | 17 | 18 | 19 | 19 | 17 | 18 | 18 | 18 |
| Statin lipid lowering agents | 56 | 61 | 62 | 60 | 56 | 61 | 61 | 60 |
| Other lipid lowering agents | 11 | 12 | 12 | 12 | 11 | 13 | 13 | 12 |
| Anti-arrhythmics | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Anticoagulants | 5 | 6 | 6 | 5 | 5 | 6 | 6 | 5 |
| Antipsychotic medications | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| Digoxin | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 5 |
| Thiazide and other diuretics | 30 | 31 | 31 | 31 | 31 | 33 | 32 | 31 |
| Loop Diuretics | 11 | 12 | 11 | 10 | 11 | 11 | 10 | 10 |
| Nitrates | 13 | 14 | 14 | 14 | 13 | 14 | 14 | 15 |
| Aspirin | 17 | 17 | 17 | 18 | 17 | 17 | 17 | 18 |
| Platelet inhibitors | 8 | 8 | 7 | 7 | 7 | 8 | 7 | 7 |

Data Supplement Table 2: Propensity Score (PS) Matched Cohort: Characteristics of PS matched metformin and sulfonylurea users at cohort entry and those who remain in the cohort at year 1, 2 and 3 in the persistent exposure required analysis. We detected no remarkable changes in cohort characteristics over time.

Data Supplement Table 3 Full and Propensity Score (PS) Matched Cohorts: Comparison of hazard ratios and rate differences between 1 year of follow-up and the entire study. Hazard ratios and rate differences were similar when data was truncated at one year, suggesting that the overall result is not driven by a select group of patients who remain in the cohort.

| | ***Full Cohort*** | | ***Propensity matched Cohort*** | |
|---|---|---|---|---|
| | ***Metformin*** | ***Sulfonylurea*** | ***Metformin*** | ***Sulfonylurea*** |
| **Persistent Exposure required* (entire study period)** | ***N=155,025*** | ***N=98,665*** | ***N=80,648*** | ***N=80,648*** |
| **Person Years** | 179,351 | 101,125 | 94,970 | 83,848 |
| Cardiovascular events or death | 1871 | 1844 | 1239 | 1284 |
| Unadjusted rate/1000 person-years, (95%CI) | 10.4 (10.0, 10.9) | 18.2 (17.4, 19.1) | 13.0 (12.3, 13.8) | 15.3 (14.5, 16.2) |
| Adjusted incidence rate difference, (95%CI) † | 2.2 (1.4, 3.0) | | 2.1 (1.0, 3.3) | |
| Adjusted Hazard ratio (95% Confidence Intervals)‡ | Reference | 1.21 (1.13, 1.29) | Reference | 1.16 (1.08, 1.25) |
| **Persistent Exposure required* (cohort truncated 1 year)** | | | | |
| **Person Years** | 100,685 | 57,956 | 51,344 | 47979 |
| Cardiovascular events or death | 1081 | 1087 | 726 | 739 |
| Unadjusted rate/1000 person-years, (95%CI) | 10.7 | 18.8 | 14.1 (13.2, 15.2) | 15.4 (14.3, 16.5) |
| Adjusted incidence rate difference, (95%CI) † | 1.8 (0.7, 3.1) | | 1.3 (-0.3, 3.1) | |
| Adjusted Hazard ratio (95% Confidence Intervals)‡ | Reference | 1.17 (1.07, 1.29) | Reference | 1.09 (0.98, 1.22) |
| **Persistent exposure not required** § (**entire study period)** | | | | |
| **Person Years** | 361,929 | 244,804 | 204,286 | 198,517 |
| Cardiovascular events or death | 4818 | 5572 | 3550 | 3816 |
| Unadjusted rate/1000 person-years | 13.3 (12.9, 13.7) | 22.8 (22.2, 23.4) | 17.4 (16.8, 18.0) | 19.2 (18.6, 19.8) |
| Adjusted incidence rate difference, (95%CI)† | 2.8 (2.1, 3.6) | | 3.5 (2.6, 4.5) | |
| Adjusted Hazard ratio (95% Confidence Intervals)‡ | Reference | 1.21 (1.16, 1.27 ) | Reference | 1.20 (1.15, 1.26) |
| **Persistent exposure not required** § **(cohort truncated 1 year)** | | | | |
| **Person Years** | 142,429 | 89,846 | 74,364 | 73,730 |
| Cardiovascular events or death | 1784 | 2028 | 1199 | 1379 |
| Unadjusted rate/1000 person-years | 12.5 | 22.6 | 16.1 (15.3, 17.0) | 18.7 (17.7, 19.6) |
| Adjusted incidence rate difference, (95%CI)† | 2.8 (1.6, 3.9) | | 3.1 (1.6, 4.7) | |
| Adjusted Hazard ratio (95% Confidence Intervals)‡ | Reference | 1.22 (1.13, 1.31) | Reference | 1.19 (1.10, 1.29) |

***** Primary analysis considers patients persistent on incident regimen until they do not have oral antidiabetic medications for 90 days.

† The adjusted incidence rate difference is the excess in the number of events per 1000 person years of sulfonylurea use compared to the number of events per 1000 person years of metformin use. The adjusted incidence rate difference is calculated as the incidence rate among metformin users*(adjusted Hazard Ratio-1).

‡Cox Proportional Hazards model for time to cardiovascular disease with sandwich variance estimate clustered by VA medical center. Adjusted for age, sex, race, fiscal year of cohort entry, physiologic variables closest to cohort entry (blood pressure, creatinine, glycated hemoglobin [HbA1c], low density lipoprotein levels [LDL] and body mass index [BMI]), indicators of healthcare utilization (number of outpatient visits and active medications, hospitalization during baseline [yes/no]), smoking, selected medications indicative of CVD and presence of co-morbidities (myocardial infarction; obstructive coronary disease or prescription for a long acting nitrate; stroke/ transient ischemic attack; atrial fibrillation/ flutter; mitral/ aortic or rheumatic heart disease; asthma/obstructive pulmonary disease; procedures for carotid/ peripheral artery revascularization or bypass or lower extremity amputation—available in Appendix Table 1). Propensity score matched models also include facility of care. All continuous variables were modeled as third degree polynomials.

§Persistent exposure not required analysis- In which patients remain in their original exposure group, regardless of persistence on drug therapy, until outcome or end of the study.