Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
eFigure 1. Flow Diagram for Empagliflozin vs Liraglutide Cohort

103,425 initiators of Empagliflozin or Liraglutide in Medicare between August 2014 – September 2018, and 12 months of continuous enrollment prior to cohort entry

18,243 excluded:
- 3,472 initiating other SGLT2i on or prior to cohort entry date
- 2,647 initiating other GLP-1RA on or prior to cohort entry date
- 86 patients aged<65 years
- 210 Patients without a diagnosis of type 2 diabetes (T2D)
- 4,993 Patients with a diagnosis of type 1 or secondary diabetes
- 5,899 Patients with malignancy, ESRD, HIV, or transplant anytime prior to cohort entry
- 936 Patients with a nursing home admission

85,182 T2D patients ≥66 years old initiating Empagliflozin or Liraglutide (35,744 Empagliflozin initiators and 49,438 Liraglutide initiators)

42,396 T2D patients with CVD\(^b\) initiating Empagliflozin or Liraglutide

42,725 T2D patients without CVD\(^b\) initiating Empagliflozin or Liraglutide

22,924 1:1 PS-matched T2D patients with CVD\(^b\) initiating Empagliflozin or Liraglutide

22,864 1:1 PS-matched T2D patients without CVD\(^b\) initiating Empagliflozin or Liraglutide

45,788 1:1 PS-matched T2D patients initiating Empagliflozin or Liraglutide

SGLT2i: sodium-glucose cotransporter 2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; CVD: cardiovascular disease; PS: propensity score; T2D: type 2 diabetes

\(^a\) 61 patients did not begin follow-up since they were not alive on the beginning of follow-up (one day after cohort entry)

\(^b\) Defined as history of myocardial infarction, angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic stroke, peripheral arterial disease or surgery, lower extremity amputation.
eFigure 2. Flow Diagram for Empagliflozin vs Sitagliptin Cohort

264,594 initiators of Empagliflozin or Sitagliptin in Medicare between August 2014 – September 2018, and 12 months of continuous enrollment prior to cohort entry

40,325 excluded:
- 4,172 initiating other SGLT2i on or prior to cohort entry date
- 6,295 initiating other GLP-1RA on or prior to cohort entry date
- 198 patients aged <65 years
- 654 Patients without a diagnosis of type 2 diabetes (T2D)
- 9,782 Patients with a diagnosis of type 1 or secondary diabetes
- 15,661 Patients with malignancy, ESRD, HIV, or transplant anytime prior to cohort entry
- 3,563 Patients with a nursing home admission

224,269 T2D patients ≥66 years old initiating Empagliflozin or Sitagliptin (25,300 Empagliflozin initiators and 198,969 Sitagliptin initiators)

264,594 initiators of Empagliflozin or Sitagliptin in Medicare between August 2014 – September 2018, and 12 months of continuous enrollment prior to cohort entry

40,325 excluded:
- 4,172 initiating other SGLT2i on or prior to cohort entry date
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- 3,563 Patients with a nursing home admission

224,269 T2D patients ≥66 years old initiating Empagliflozin or Sitagliptin (25,300 Empagliflozin initiators and 198,969 Sitagliptin initiators)

109,359 T2D patients with CVD* initiating Empagliflozin or Sitagliptin

114,819 T2D patients without CVD* initiating Empagliflozin or Sitagliptin

23,006 1:1 PS-matched T2D patients with CVD* initiating Empagliflozin or Sitagliptin

22,618 1:1 PS-matched T2D patients without CVD* initiating Empagliflozin or Sitagliptin

45,624 1:1 PS-matched T2D patients initiating Empagliflozin or Sitagliptin

SGLT2i: sodium-glucose cotransporter 2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; CVD: cardiovascular disease; PS: propensity score; T2D: type 2 diabetes

* 91 patients did not begin follow-up since they were not alive on the beginning of follow-up (one day after cohort entry)

* Defined as history of myocardial infarction, angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic stroke, peripheral arterial disease or surgery, lower extremity amputation

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### eFigure 3. Hazard Ratios and Rate Differences for 1:1 PS-Matched Initiators of Empagliflozin vs GLP-1RA Across Patient Subgroups

| Outcomes (subgroups) | Empagliflozin Events (N) | GLP-1RA Events (N) | HR (95% CI) | Empagliflozin vs. GLP-1RA | p-value for homogeneity | RD/1000PY (95% CI) | Empagliflozin vs. GLP-1RA | p-value for homogeneity |
|----------------------|--------------------------|--------------------|-------------|---------------------------|------------------------|----------------------|---------------------------|------------------------|
| **Modified MACE**    |                          |                    |             |                           |                        |                      |                           |                        |
| Age<75               | 338 (22,844)             | 353 (22,844)       | 0.90 (0.77, 1.04) |                          | 0.95                   | -2.6 (-6.1, 0.9)    |                          | 0.98                   |
| Age>=75              | 229 (8,935)              | 232 (8,935)        | 0.93 (0.77, 1.11) |                          |                        | -3.0 (-10.1, 4.7)  |                          |                        |
| Male                 | 323 (16,248)             | 340 (16,248)       | 0.87 (0.75, 1.02) |                          | 0.96                   | -4.3 (-9.0, 0.5)    |                          | 0.93                   |
| Female               | 255 (15,567)             | 254 (15,567)       | 0.96 (0.81, 1.15) |                          |                        | -1.0 (-5.7, 3.7)   |                          |                        |
| ASCVD +              | 390 (15,062)             | 394 (15,062)       | 0.92 (0.80, 1.06) |                          | 0.54                   | -3.6 (-9.6, 2.3)    |                          | 0.28                   |
| ASCVD -              | 195 (16,626)             | 186 (16,626)       | 0.99 (0.81, 1.21) |                          |                        | -0.2 (-3.7, 3.4)   |                          |                        |
| HF +                 | 151 (4,088)              | 156 (4,088)        | 0.89 (0.71, 1.12) |                          | 0.52                   | -8.0 (-22.9, 6.8)  |                          | 0.33                   |
| HF -                 | 430 (27,621)             | 417 (27,621)       | 0.97 (0.84, 1.11) |                          |                        | -0.8 (-4.1, 2.4)   |                          |                        |
| CKD +                | 143 (5,502)              | 170 (5,502)        | 0.82 (0.66, 1.03) |                          | 0.19                   | -9.5 (-20.2, 1.2)  |                          | 0.11                   |
| CKD -                | 444 (26,276)             | 421 (26,276)       | 0.98 (0.86, 1.12) |                          |                        | -0.6 (-4.01, 2.8)  |                          |                        |
| **HHF (specific)**   |                          |                    |             |                           |                        |                      |                           |                        |
| Age<75               | 82 (22,844)              | 127 (22,844)       | 0.60 (0.46, 0.80) |                          | 0.24                   | -3.5 (-5.5, -1.6)  |                          | 0.88                   |
| Age>=75              | 77 (8,935)               | 96 (8,935)         | 0.75 (0.56, 1.01) |                          |                        | -4.4 (-9.2, 0.3)   |                          |                        |
| Male                 | 77 (16,248)              | 133 (16,248)       | 0.53 (0.40, 0.70) |                          | 0.10                   | -6.1 (-8.8, -3.4)  |                          | 0.10                   |
| Female               | 81 (15,567)              | 104 (15,567)       | 0.75 (0.56, 1.00) |                          |                        | -2.8 (-5.7, 0.0)   |                          |                        |
| ASCVD +              | 128 (15,062)             | 186 (15,062)       | 0.64 (0.51, 0.80) |                          | 0.59                   | -7.6 (-11.5, -3.9) |                          | 0.00                   |
| ASCVD -              | 34 (16,626)              | 44 (16,626)        | 0.73 (0.46, 1.14) |                          |                        | -1.1 (-2.8, 0.5)   |                          |                        |
| HF +                 | 96 (4,088)               | 131 (4,088)        | 0.67 (0.52, 0.88) |                          | 0.90                   | -19.6 (-32.6, -6.8) |                          | <0.00                  |
| HF -                 | 66 (27,621)              | 90 (27,621)        | 0.68 (0.50, 0.94) |                          |                        | -1.6 (-3.0, -0.3)  |                          |                        |
| CKD +                | 72 (5,502)               | 106 (5,502)        | 0.66 (0.49, 0.89) |                          | 0.94                   | -11.2 (-19.4, -3.2) |                          | 0.03                   |
| CKD -                | 97 (26,276)              | 138 (26,276)       | 0.65 (0.50, 0.84) |                          |                        | -3.0 (-4.8, -1.2)  |                          |                        |
eFigure 4. Hazard Ratios and Rate Differences for 1:1 PS-Matched Initiators of Empagliflozin vs DPP-4 Inhibitor Across Patient Subgroups

| Outcomes (Subgroups) | Empagliflozin Events (N) | DPP-4i Events (N) | HR (95% CI) | Empagliflozin vs. DPP-4i | p-value for homogeneity | RD/1000PY (95% CI) | Regliflozin vs. DPP-4i | p-value for homogeneity |
|----------------------|--------------------------|-------------------|-------------|--------------------------|-------------------------|-----------------------|------------------------|-------------------------|
| **Modified MACE**    |                          |                   |             |                          |                         |                       |                        |                         |
| Age<75               | 238 (16,992)             | 339 (16,992)      | 0.71 (0.60, 0.84) | -                       | 0.52                    | -8.8 (-13.1, -4.6)  | -                      | 0.24                    |
| Age>=75              | 148 (6,279)              | 201 (6,279)       | 0.77 (0.63, 0.96) | -                       |                         | -11.9 (-21.7, -2.1) | -                      |                         |
| Male                 | 237 (12,474)             | 358 (12,474)      | 0.66 (0.56, 0.78) | -                       | 0.71                    | -15.0 (-21.0, -9.2) | -                      | 0.26                    |
| Female               | 150 (10,853)             | 233 (10,853)      | 0.69 (0.56, 0.85) | -                       |                         | -10.4 (-16.1, -4.7) | -                      |                         |
| ASCVD +              | 260 (11,273)             | 377 (11,273)      | 0.69 (0.59, 0.81) | -                       | 0.77                    | -16.6 (-23.7, -9.5) | -                      | 0.04                    |
| ASCVD -              | 130 (12,041)             | 200 (12,041)      | 0.67 (0.53, 0.83) | -                       |                         | -8.4 (-13.0, -3.9)  | -                      |                         |
| HF +                 | 100 (3,099)              | 153 (3,099)       | 0.67 (0.52, 0.86) | -                       | 0.84                    | -28.5 (-45.8, -11.5) | -                      | 0.04                    |
| HF -                 | 291 (20,213)             | 442 (20,213)      | 0.68 (0.59, 0.79) | -                       |                         | -10.7 (-14.8, -6.7) | -                      |                         |
| CKD +                | 101 (3,757)              | 125 (3,757)       | 0.84 (0.64, 1.09) | -                       | 0.25                    | -8.8 (-22.1, 4.5)   | -                      | 0.89                    |
| CKD -                | 290 (19,519)             | 419 (19,519)      | 0.70 (0.61, 0.82) | -                       |                         | -9.8 (-14.0, -5.7)  | -                      |                         |
| **HHF (specific)**   |                          |                   |             |                          |                         |                       |                        |                         |
| Age<75               | 64 (16,992)              | 170 (16,992)      | 0.38 (0.29, 0.51) | -                       | 0.00                    | -9.5 (-12.2, -6.8)  | -                      | 0.23                    |
| Age>=75              | 53 (6,279)               | 92 (6,279)        | 0.61 (0.43, 0.85) | -                       |                         | -9.5 (-15.7, -3.2)  | -                      |                         |
| Male                 | 62 (12,474)              | 157 (12,474)      | 0.39 (0.29, 0.53) | -                       | 0.19                    | -11.7 (-15.3, -8.2) | -                      | 0.08                    |
| Female               | 52 (10,853)              | 106 (10,853)      | 0.53 (0.38, 0.73) | -                       |                         | -7.2 (-11.0, -3.6)  | -                      |                         |
| ASCVD +              | 97 (11,273)              | 218 (11,273)      | 0.45 (0.35, 0.57) | -                       | 0.87                    | -17.3 (-22.4, -12.4) | -                      | 0.00                    |
| ASCVD -              | 20 (12,041)              | 48 (12,041)       | 0.43 (0.25, 0.72) | -                       |                         | -3.5 (-5.6, -1.5)   | -                      |                         |
| HF +                 | 69 (3,099)               | 136 (3,099)       | 0.51 (0.38, 0.67) | -                       | 0.79                    | -37.3 (-53.2, -21.9) | -                      | 0.00                    |
| HF -                 | 46 (20,213)              | 100 (20,213)      | 0.48 (0.34, 0.68) | -                       |                         | -3.9 (-5.8, -2.2)   | -                      |                         |
| CKD +                | 46 (3,757)               | 94 (3,757)        | 0.50 (0.35, 0.72) | -                       | 0.82                    | -20.6 (-31.3, -10.3) | -                      | <0.00                   |
| CKD -                | 68 (19,519)              | 144 (19,519)      | 0.48 (0.36, 0.64) | -                       |                         | -5.9 (-8.2, -3.7)   | -                      |                         |

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eFigure 5. Bias Analyses

| Modified MACE outcome<sup>a</sup> | Hospitalization for heart failure |
|----------------------------------|----------------------------------|
| **Empagliflozin vs. Liraglutide** |                                  |
| Empagliflozin vs. Liraglutide: RR<sub>obs</sub>=0.90 | Empagliflozin vs. Liraglutide: RR<sub>obs</sub>=0.66 |
| ![Graph](image1.png) | ![Graph](image2.png) |
| Empagliflozin vs. Sitagliptin |                                  |
| Empagliflozin vs. Sitagliptin: RR<sub>obs</sub>=0.68 | Empagliflozin vs. Sitagliptin: RR<sub>obs</sub>=0.45 |
| ![Graph](image3.png) | ![Graph](image4.png) |

HbA1c: Hemoglobin A1c; MACE: Major Adverse Cardiovascular Events; RR<sub>obs</sub>: Observed relative risk; RR<sub>CD</sub>: Relative risk between confounder (HbA1c) and primary cardiovascular outcomes

<sup>a</sup> Hospitalization for myocardial infarction, or ischemic or hemorrhagic stroke; all-cause mortality

Using the observed residual difference in HbA1c between initiators of empagliflozin vs. liraglutide and the observed exposure relative risk (RR<sub>obs</sub>) = 0.90 and 0.66 for the composite cardiovascular outcome, and HHF respectively (0.68 and 0.45 respectively for sitagliptin comparison), the graphs plot the changes in "true" or fully adjusted relative risk (RR) for a range of associations between the observed HbA1c and the outcome (RR<sub>CD</sub>). RR<sub>CD</sub> values were obtained from literature (Gerstein HC, Swedberg K, Carlsson J, et al. The Hemoglobin A1c Level as a Progressive Risk Factor for Cardiovascular Death, Hospitalization for Heart Failure, or Death in Patients With Chronic Heart Failure: An Analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Arch Intern Med. 2008;168(15):1699-1704) and mean HbA1c among empagliflozin vs. comparators were also obtained from prior studies on trial-enrolled participants (Gargle HE, White K, McAdam-Marx C. SGLT2 inhibitors or GLP-1 receptor agonists as second-line therapy in type 2 diabetes: patient selection and perspectives. Vasc Health Risk Manag. 2016;12:239-249. Published 2016 Jun 4. doi:10.2147/VHRM.S83088). Overall, fully adjusted effect estimates were fairly robust even under extreme scenarios of the association between a 1-unit increase in HbA1c and the primary cardiovascular outcomes.
| Characteristic | Empagliflozin | Liraglutide | ASD | Empagliflozin | Sitagliptin | ASD |
|---------------|--------------|-------------|-----|--------------|------------|-----|
| N=35,721      | N=49,400     | ASD         | N=25,285 | N=198,893 | ASD |
| Age, years (Mean, SD) | 72.4(5.34) | 71.4(4.87) | 0.193 | 71.9(5.03) | 74.2(6.60) | 0.388 |
| Age categories |              |             |       |              |            |     |
| 66-69 | 12,903 (36.1%) | 21,377 (43.3%) | 0.147 | 9,898 (39.1%) | 58,350 (29.3%) | 0.208 |
| 70-74 | 12,164 (34.1%) | 16,499 (33.4%) | 0.014 | 8,744 (34.6%) | 58,610 (29.5%) | 0.11 |
| 75-79 | 6,719 (18.8%) | 7,911 (16.0%) | 0.074 | 4,448 (17.6%) | 40,621 (20.4%) | 0.072 |
| 80-84 | 2,740 (7.7%) | 2,685 (5.4%) | 0.09 | 1,590 (6.3%) | 23,717 (11.9%) | 0.197 |
| ≥85 | 1,195 (3.3%) | 928 (1.9%) | 0.092 | 605 (2.4%) | 17,595 (8.8%) | 0.283 |
| Gender - Female | 16,753 (46.9%) | 27,793 (56.3%) | 0.188 | 11,556 (45.7%) | 111,998 (56.3%) | 0.213 |
| Geographic region |              |             |       |              |            |     |
| Northeast | 6,747 (18.9%) | 7,719 (15.6%) | 0.086 | 4,492 (17.8%) | 36,958 (18.6%) | 0.021 |
| South | 15,114 (42.3%) | 21,515 (43.6%) | 0.025 | 10,815 (42.8%) | 84,458 (42.5%) | 0.006 |
| Midwest | 6,648 (18.6%) | 11,786 (23.9%) | 0.129 | 4,930 (19.5%) | 42,886 (21.6%) | 0.051 |
| West | 7,212 (20.2%) | 8,380 (17.0%) | 0.083 | 5,048 (20.0%) | 34,591 (17.4%) | 0.066 |

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|                          | Column 1 | Column 2 | Column 3 | Column 4 | Column 5 | Column 6 | Column 7 |
|--------------------------|----------|----------|----------|----------|----------|----------|----------|
| **African American/Black** | 2,508 (7.0%) | 3,797 (7.7%) | 0.025 | 1,649 (6.5%) | 20,936 (10.5%) | 0.144 |
| **Asian**                | 1,452 (4.1%) | 871 (1.8%) | 0.137 | 679 (2.7%) | 8,916 (4.5%) | 0.097 |
| **Hispanic**             | 1,123 (3.1%) | 1,066 (2.2%) | 0.061 | 630 (2.5%) | 7,951 (4.0%) | 0.085 |
| **White**                | 28,681 (80.3%) | 41,685 (84.4%) | 0.107 | 21,083 (83.4%) | 152,221 (76.5%) | 0.172 |
| **Other or unknown**     | 1,957 (5.5%) | 1,981 (4.0%) | 0.069 | 1,244 (4.9%) | 8,869 (4.5%) | 0.022 |
| **Combined comorbidity score, Mean, (SD)** | 1.4(1.95) | 1.7(2.15) | 0.132 | 1.4(1.96) | 1.5(2.25) | 0.051 |
| **Frailty Score, Mean, (SD)** | 0.2(0.05) | 0.2(0.06) | 0.23 | 0.2(0.05) | 0.2(0.06) | 0.17 |
| **Frailty Score: (Categories)** |           |           |          |          |          |          |
| 0.00 - 0.09              | 739 (2.1%) | 555 (1.1%) | 0.075 | 513 (2.0%) | 3,234 (1.6%) | 0.03 |
| 0.10 - 0.19              | 23,958 (67.1%) | 29,238 (59.2%) | 0.164 | 16,847 (66.6%) | 121,336 (61.0%) | 0.117 |
| ≥ 0.20                   | 11,024 (30.9%) | 19,607 (39.7%) | 0.186 | 7,925 (31.3%) | 74,323 (37.4%) | 0.127 |
| **Overweight**           | 3,962 (11.1%) | 3,779 (7.6%) | 0.118 | 2,665 (10.5%) | 16,741 (8.4%) | 0.073 |
| **Obesity**              | 12,415 (34.8%) | 22,892 (46.3%) | 0.238 | 10,074 (39.8%) | 52,895 (26.6%) | 0.284 |
| **Smoking**              | 7,886 (22.1%) | 11,573 (23.4%) | 0.032 | 5,912 (23.4%) | 42,063 (21.1%) | 0.054 |
| **Alcohol abuse or dependence** | 399 (1.1%) | 515 (1.0%) | 0.007 | 309 (1.2%) | 2,485 (1.2%) | 0.002 |
| Condition                                      | 2017 Cases | 2018 Cases | P-value | 2017 Cases | 2018 Cases | P-value |
|------------------------------------------------|------------|------------|---------|------------|------------|---------|
| Drug abuse or dependence                       | 596 (1.7%) | 1,021 (2.1%) | 0.029   | 428 (1.7%) | 3,523 (1.8%) | 0.006   |
| Diabetic nephropathy                           | 5,478 (15.3%) | 10,300 (20.9%) | 0.144   | 4,006 (15.8%) | 29,580 (14.9%) | 0.027   |
| Diabetic retinopathy                           | 4,953 (13.9%) | 7,879 (15.9%) | 0.059   | 3,711 (14.7%) | 23,539 (11.8%) | 0.084   |
| Diabetes with other ophthalmic manifestations  | 3,635 (10.2%) | 6,177 (12.5%) | 0.073   | 2,445 (9.7%) | 25,307 (12.7%) | 0.097   |
| Diabetic neuropathy                            | 9,843 (27.6%) | 15,928 (32.2%) | 0.103   | 7,399 (29.3%) | 48,179 (24.2%) | 0.114   |
| Diabetes with peripheral circulatory disorders | 466 (1.3%) | 1,749 (3.5%) | 0.146   | 288 (1.1%) | 7,619 (3.8%) | 0.174   |
| Diabetic foot                                  | 1,045 (2.9%) | 2,011 (4.1%) | 0.062   | 812 (3.2%) | 6,201 (3.1%) | 0.005   |
| Infection of lower extremities (cellulitis or osteomyelitis) | 1,941 (5.4%) | 3,215 (6.5%) | 0.045   | 1,384 (5.5%) | 11,240 (5.7%) | 0.008   |
| Lower-limb amputations                         | 201 (0.6%) | 392 (0.8%) | 0.028   | 165 (0.7%) | 1,221 (0.6%) | 0.005   |
| Erectile dysfunction                           | 1,788 (5.0%) | 2,064 (4.2%) | 0.04    | 1,363 (5.4%) | 6,799 (3.4%) | 0.096   |
| Hypoglycemia                                   | 3,630 (10.2%) | 5,292 (10.7%) | 0.018   | 2,793 (11.0%) | 17,486 (8.8%) | 0.075   |
| Hyperglycemia                                  | 17,441 (48.8%) | 20,633 (41.8%) | 0.142   | 12,776 (50.5%) | 64,896 (32.6%) | 0.369   |
| Diabetic ketoacidosis                          | 93 (0.3%) | 198 (0.4%) | 0.024   | 70 (0.3%) | 799 (0.4%) | 0.021   |
| Hyperosmolar hyperglycemic nonketotic syndrome | 347 (1.0%) | 488 (1.0%) | 0.002   | 262 (1.0%) | 1,676 (0.8%) | 0.02    |
| Category                                                                 | Observed | Expected | p-value | Observed | Expected | p-value |
|-------------------------------------------------------------------------|----------|----------|---------|----------|----------|---------|
| **Diabetes with other complications**                                    | 4,106    | 5,645    | 0.002   | 3,023    | 17,206   | 0.109   |
| **Diabetes mellitus without mention of complications**                   | 33,606   | 47,097   | 0.056   | 23,711   | 190,808  | 0.098   |
| **Number of anti-DM medications on cohort entry, Mean, (SD)**            | 1.6(0.96)| 1.4(0.95)| 0.14    | 1.4(0.91)| 1.2(0.79)| 0.14    |
| **No use of anti-DM medications in prior 365 days**                      | 1,355    | 2,562    | 0.067   | 1,213    | 21,489   | 0.225   |
| **Initiation of empagliflozin or comparator monotherapy**                | 1,051    | 2,328    | 0.092   | 1,043    | 14,137   | 0.13    |
| **DUAL therapy with metformin**                                          | 4,089    | 4,158    | 0.101   | 3,740    | 32,553   | 0.043   |
| **Metformin (any use)**                                                  | 28,427   | 34,165   | 0.24    | 19,881   | 152,356  | 0.049   |
| **Metformin (concurrent use)**                                           | 22,663   | 25,840   | 0.227   | 16,011   | 123,027  | 0.03    |
| **Metformin (past use)**                                                 | 5,764    | 8,325    | 0.019   | 3,870    | 29,329   | 0.016   |
| **Sulfonylureas - 2nd generation (any use)**                            | 16,507   | 21,987   | 0.034   | 10,724   | 93,931   | 0.097   |
| Category                                      | Concurrent Use (%) | Total Use (%) | p-value | Concurrent Use (%) | Total Use (%) | p-value |
|----------------------------------------------|---------------------|---------------|---------|---------------------|---------------|---------|
| Sulfonylureas - 2nd generation (concurrent use) | 12,603 (35.3%)      | 16,105 (32.6%) | 0.057   | 8,167 (32.3%)       | 73,079 (36.7%) | 0.094   |
| Sulfonylureas - 2nd generation (past use)    | 3,904 (10.9%)       | 5,882 (11.9%)  | 0.031   | 2,557 (10.1%)       | 20,852 (10.5%) | 0.012   |
| Thiazolidinediones (any use)                 | 3,935 (11.0%)       | 4,883 (9.9%)   | 0.037   | 2,727 (10.8%)       | 15,469 (7.8%)  | 0.104   |
| Thiazolidinediones (concurrent use)          | 2,686 (7.5%)        | 3,255 (6.6%)   | 0.036   | 1,912 (7.6%)        | 10,258 (5.2%)  | 0.099   |
| Thiazolidinediones (past use)                | 1,249 (3.5%)        | 1,628 (3.3%)   | 0.011   | 815 (3.2%)          | 5,211 (2.6%)   | 0.036   |
| DPP4i (any use)                              | 14,999 (42.0%)      | 14,459 (29.3%) | 0.268   | 4,901 (19.4%)       | 6,442 (3.2%)   | 0.527   |
| DPP4i (concurrent use)                       | 11,343 (31.8%)      | 8,573 (17.4%)  | 0.339   | 3,222 (12.7%)       | 2,464 (1.2%)   | 0.463   |
| DPP4i (past use)                             | 3,656 (10.2%)       | 5,886 (11.9%)  | 0.054   | 1,679 (6.6%)        | 3,978 (2.0%)   | 0.23    |
| Insulins (any use)                           | 8,401 (23.5%)       | 21,635 (43.8%) | 0.439   | 7,982 (31.6%)       | 30,931 (15.6%) | 0.384   |
| Insulins (concurrent use)                    | 6,376 (17.8%)       | 16,648 (33.7%) | 0.368   | 6,129 (24.2%)       | 22,017 (11.1%) | 0.351   |
| Insulins (past use)                          | 2,025 (5.7%)        | 4,987 (10.1%)  | 0.165   | 1,853 (7.3%)        | 8,915 (4.5%)   | 0.121   |
| Long term use of insulin                     | 5,794 (16.2%)       | 13,041 (26.4%) | 0.251   | 5,622 (22.2%)       | 20,314 (10.2%) | 0.33    |
| Miscellaneous anti-DM medications            | 1,114 (3.1%)        | 1,520 (3.1%)   | 0.002   | 631 (2.5%)          | 4,821 (2.4%)   | 0.005   |
| Condition                                      | Case 1 | Control 1 | p-value | Case 2 | Control 2 | p-value |
|------------------------------------------------|--------|-----------|---------|--------|-----------|---------|
| Hypertension                                  | 32,773 (91.7%) | 45,694 (92.5%) | 0.028   | 23,254 (92.0%) | 181,038 (91.0%) | 0.034   |
| Hyperlipidemia                                | 30,997 (86.8%) | 43,450 (88.0%) | 0.036   | 21,942 (86.8%) | 170,358 (85.7%) | 0.033   |
| Acute MI                                      | 987 (2.8%) | 1,172 (2.4%) | 0.025   | 724 (2.9%) | 5,563 (2.8%) | 0.004   |
| MI sequelae/old MI                            | 2,245 (6.3%) | 3,000 (6.1%) | 0.009   | 1,758 (7.0%) | 11,491 (5.8%) | 0.048   |
| Stable angina                                 | 3,146 (8.8%) | 3,406 (6.9%) | 0.071   | 2,297 (9.1%) | 12,605 (6.3%) | 0.103   |
| Acute coronary syndrome/unstable angina       | 1,438 (4.0%) | 1,628 (3.3%) | 0.039   | 1,066 (4.2%) | 6,368 (3.2%) | 0.054   |
| Coronary atherosclerosis                      | 12,981 (36.3%) | 16,726 (33.9%) | 0.052   | 9,590 (37.9%) | 63,054 (31.7%) | 0.131   |
| Coronary procedure                            | 1,158 (3.2%) | 1,129 (2.3%) | 0.058   | 918 (3.6%) | 4,549 (2.3%) | 0.079   |
| History of coronary procedure                 | 5,202 (14.6%) | 6,359 (12.9%) | 0.049   | 3,951 (15.6%) | 22,959 (11.5%) | 0.119   |
| Congestive heart failure                      | 4,514 (12.6%) | 7,395 (15.0%) | 0.068   | 3,389 (13.4%) | 29,429 (14.8%) | 0.04    |
| Cardiomyopathy                                | 1,594 (4.5%) | 2,329 (4.7%) | 0.012   | 1,213 (4.8%) | 9,340 (4.7%) | 0.005   |
| Atrial fibrillation                           | 4,698 (13.2%) | 6,308 (12.8%) | 0.011   | 3,504 (13.9%) | 27,635 (13.9%) | 0.001   |
| Cardiac conduction disorders                  | 2,385 (6.7%) | 3,234 (6.5%) | 0.005   | 1,736 (6.9%) | 13,407 (6.7%) | 0.005   |
| Other cardiac dysrhythmia                     | 5,275 (14.8%) | 7,042 (14.3%) | 0.015   | 3,820 (15.1%) | 31,513 (15.8%) | 0.02    |
| Valve disorders                               | 5,236 (14.7%) | 6,713 (13.6%) | 0.031   | 3,707 (14.7%) | 29,620 (14.9%) | 0.007   |
| Condition                                      | Cases 1 (4.6%) | Cases 2 (9.8%) | p-value | Cases 1 (4.6%) | Cases 2 (9.8%) | p-value |
|-----------------------------------------------|----------------|----------------|---------|----------------|----------------|---------|
| Other cardiovascular disease                  | 6,570 (18.4%)  | 8,025 (16.2%)  | 0.057   | 4,915 (19.4%)  | 30,947 (15.6%) | 0.102   |
| Ischemic stroke                               | 4,582 (12.8%)  | 5,963 (12.1%)  | 0.023   | 3,227 (12.8%)  | 26,047 (13.1%) | 0.01    |
| Transient ischemic attack                     | 983 (2.8%)     | 1,350 (2.7%)   | 0.001   | 677 (2.7%)     | 6,557 (3.3%)   | 0.036   |
| Other cerebrovascular conditions              | 2,711 (7.6%)   | 4,048 (8.2%)   | 0.022   | 1,976 (7.8%)   | 19,347 (9.7%)  | 0.068   |
| PAD and generalized/unspecified atherosclerosis | 4,948 (13.9%) | 7,153 (14.5%)  | 0.018   | 3,420 (13.5%)  | 29,521 (14.8%) | 0.038   |
| Acute Kidney Injury                           | 1,267 (3.5%)   | 3,073 (6.2%)   | 0.124   | 877 (3.5%)     | 13,748 (6.9%)  | 0.156   |
| Chronic kidney disease                        | 5,736 (16.1%)  | 13,074 (26.5%) | 0.256   | 4,040 (16.0%)  | 43,471 (21.9%) | 0.151   |
| Chronic kidney disease Stage 1-2              | 1,661 (4.6%)   | 2,615 (5.3%)   | 0.03    | 1,176 (4.7%)   | 9,039 (4.5%)   | 0.005   |
| Chronic kidney disease Stage 3-4              | 3,729 (10.4%)  | 9,996 (20.2%)  | 0.274   | 2,616 (10.3%)  | 31,070 (15.6%) | 0.157   |
| Chronic kidney disease unspecified            | 1,963 (5.5%)   | 5,528 (11.2%)  | 0.207   | 1,392 (5.5%)   | 18,661 (9.4%)  | 0.148   |
| Hypertensive nephropathy                      | 2,776 (7.8%)   | 6,801 (13.8%)  | 0.194   | 1,962 (7.8%)   | 22,936 (11.5%) | 0.128   |
| Proteinuria                                   | 2,083 (5.8%)   | 3,858 (7.8%)   | 0.079   | 1,570 (6.2%)   | 10,801 (5.4%)  | 0.033   |
| Condition                                      | Cases 1 | Cases 2 | P-value | Cases 1 | Cases 2 | P-value |
|-----------------------------------------------|---------|---------|---------|---------|---------|---------|
| Miscellaneous renal disease                  | 3,498 (9.8%) | 7,072 (14.3%) | 0.139   | 2,488 (9.8%) | 26,206 (13.2%) | 0.105   |
| Urinary tract infection                       | 5,233 (14.6%) | 9,144 (18.5%) | 0.104   | 3,525 (13.9%) | 38,472 (19.3%) | 0.145   |
| Kidney and urinary stone                      | 1,731 (4.8%) | 2,576 (5.2%) | 0.017   | 1,228 (4.9%) | 9,054 (4.6%) | 0.014   |
| Disorders of electrolyte                      | 2,510 (7.0%) | 4,662 (9.4%) | 0.088   | 1,704 (6.7%) | 20,569 (10.3%) | 0.129   |
| Disorders of fluid balance                    | 1,227 (3.4%) | 2,133 (4.3%) | 0.046   | 842 (3.3%) | 10,444 (5.3%) | 0.095   |
| Edema                                         | 4,530 (12.7%) | 8,494 (17.2%) | 0.127   | 3,354 (13.3%) | 28,501 (14.3%) | 0.031   |
| COPD                                          | 4,442 (12.4%) | 7,222 (14.6%) | 0.064   | 3,143 (12.4%) | 29,206 (14.7%) | 0.066   |
| Asthma                                        | 3,253 (9.1%) | 5,457 (11.0%) | 0.064   | 2,355 (9.3%) | 18,789 (9.4%) | 0.005   |
| Obstructive sleep apnea                       | 6,129 (17.2%) | 11,910 (24.1%) | 0.172   | 5,161 (20.4%) | 26,007 (13.1%) | 0.197   |
| Pneumonia                                     | 1,682 (4.7%) | 2,664 (5.4%) | 0.031   | 1,221 (4.8%) | 12,066 (6.1%) | 0.055   |
| Osteoarthritis                                | 10,818 (30.3%) | 16,119 (32.6%) | 0.051   | 7,798 (30.8%) | 58,638 (29.5%) | 0.03    |
| Osteoporosis without fractures                | 2,639 (7.4%) | 3,611 (7.3%) | 0.003   | 1,662 (6.6%) | 17,671 (8.9%) | 0.087   |
| Fractures                                     | 743 (2.1%) | 1,215 (2.5%) | 0.025   | 536 (2.1%) | 4,459 (2.2%) | 0.008   |
| Falls                                         | 1,836 (5.1%) | 2,791 (5.6%) | 0.023   | 1,298 (5.1%) | 11,933 (6.0%) | 0.038   |
| Hypothyroidism                                | 8,915 (25.0%) | 13,549 (27.4%) | 0.056   | 6,314 (25.0%) | 49,778 (25.0%) | 0.001   |
| Condition                                      | Mean (95% CI)  | Mean (95% CI)  | p-value | Mean (95% CI)  | Mean (95% CI)  | p-value |
|------------------------------------------------|----------------|----------------|---------|----------------|----------------|---------|
| Hyperthyroidism and other thyroid gland disorders | 3,490 (9.8%)   | 4,669 (9.5%)   | 0.011   | 2,582 (10.2%)  | 15,173 (7.6%)  | 0.091   |
| Non-alcoholic steatohepatitis/ fatty liver disease | 1,995 (5.6%)   | 2,761 (5.6%)   | 0       | 1,502 (5.9%)   | 8,352 (4.2%)   | 0.079   |
| Liver disease                                  | 1,546 (4.3%)   | 1,966 (4.0%)   | 0.017   | 1,070 (4.2%)   | 8,349 (4.2%)   | 0.002   |
| Depression                                     | 5,147 (14.4%)  | 9,799 (19.8%)  | 0.144   | 3,903 (15.4%)  | 31,453 (15.8%) | 0.01    |
| Anxiety and sleep disorders                    | 7,317 (20.5%)  | 11,651 (23.6%) | 0.075   | 5,345 (21.1%)  | 40,584 (20.4%) | 0.018   |
| Dementia                                       | 1,637 (4.6%)   | 2,048 (4.1%)   | 0.021   | 1,036 (4.1%)   | 15,087 (7.6%)  | 0.149   |
| Psychosis                                      | 249 (0.7%)     | 463 (0.9%)     | 0.027   | 152 (0.6%)     | 3,458 (1.7%)   | 0.106   |
| Delirium                                       | 357 (1.0%)     | 523 (1.1%)     | 0.006   | 237 (0.9%)     | 3,247 (1.6%)   | 0.062   |
| ACEi and ARBs                                  | 28,377 (79.4%) | 39,703 (80.4%) | 0.023   | 20,047 (79.3%) | 153,612 (77.2%)| 0.05    |
| Beta blockers                                  | 17,862 (50.0%) | 25,087 (50.8%) | 0.016   | 12,840 (50.8%) | 96,207 (48.4%) | 0.048   |
| Calcium channel blockers                       | 12,183 (34.1%) | 17,281 (35.0%) | 0.018   | 8,435 (33.4%)  | 72,879 (36.6%) | 0.069   |
| Nitrates and other antianginal agents          | 3,728 (10.4%)  | 5,106 (10.3%)  | 0.003   | 2,678 (10.6%)  | 19,544 (9.8%)  | 0.025   |
| Thiazide and thiazide-like diuretics           | 5,509 (15.4%)  | 8,780 (17.8%)  | 0.063   | 4,135 (16.4%)  | 32,402 (16.3%) | 0.002   |

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| Drug Class                                           | Count 1 | Count 2 | p-Value | Count 3 | Count 4 |
|-----------------------------------------------------|---------|---------|---------|---------|---------|
| Loop diuretics                                      | 6,010 (16.8%) | 12,687 (25.7%) | 0.218 | 4,676 (18.5%) | 41,271 (20.8%) |
| MRA (potassium-sparing diuretics)                   | 1,757 (4.9%) | 3,176 (6.4%) | 0.065 | 1,375 (5.4%) | 9,627 (4.8%) |
| Other potassium -sparing diuretics and antihypertensive medications | 3,456 (9.7%) | 6,078 (12.3%) | 0.084 | 2,442 (9.7%) | 23,516 (11.8%) |
| Digoxin                                             | 904 (2.5%) | 1,122 (2.3%) | 0.017 | 633 (2.5%) | 6,195 (3.1%) |
| Entresto                                            | 182 (0.5%) | 101 (0.2%) | 0.051 | 140 (0.6%) | 326 (0.2%) |
| Antiarrhythmics                                      | 893 (2.5%) | 1,312 (2.7%) | 0.01 | 680 (2.7%) | 5,382 (2.7%) |
| Anticoagulants (oral)                               | 3,763 (10.5%) | 5,476 (11.1%) | 0.018 | 2,782 (11.0%) | 22,140 (11.1%) |
| Anticoagulants (injectables)                        | 190 (0.5%) | 389 (0.8%) | 0.032 | 163 (0.6%) | 1,428 (0.7%) |
| Antiplatelet agents                                 | 5,537 (15.5%) | 6,850 (13.9%) | 0.046 | 3,990 (15.8%) | 27,455 (13.8%) |
| Statins                                             | 28,925 (81.0%) | 39,299 (79.6%) | 0.036 | 20,465 (80.9%) | 151,259 (76.1%) |
| PCSK9 inhibitors and other-lipid lowering agents    | 6,737 (18.9%) | 9,278 (18.8%) | 0.002 | 4,693 (18.6%) | 31,124 (15.6%) |
| COPD & asthma medications                           | 7,153 (20.0%) | 11,358 (23.0%) | 0.072 | 5,079 (20.1%) | 39,632 (19.9%) |
| Category                      | Internist (-365 days to CED) | Internist (-30 days to CED) | Internist (-365 days to -31 days before CED) |
|------------------------------|------------------------------|-----------------------------|----------------------------------------------|
| Corticosteroids (oral)       | 6,211 (17.4%)                | 9,441 (19.1%)               | 4,420 (17.5%)                               |
| Antiosteoporosis agents      | 1,698 (4.8%)                 | 2,142 (4.3%)                | 977 (3.9%)                                  |
| NSAIDs                       | 8,881 (24.9%)                | 12,822 (26.0%)              | 6,151 (24.3%)                               |
| Opioids                      | 11,480 (32.1%)               | 19,949 (40.4%)              | 8,501 (33.6%)                               |
| Gabapentinoids               | 6,196 (17.3%)                | 11,206 (22.7%)              | 4,586 (18.1%)                               |
| UTI antibiotics              | 8,040 (22.5%)                | 13,581 (27.5%)              | 5,622 (22.2%)                               |
| Antidepressants              | 9,614 (26.9%)                | 17,841 (36.1%)              | 7,300 (28.9%)                               |
| Anxiolytics/ hypnotics       | 2,671 (7.5%)                 | 4,289 (8.7%)                | 1,912 (7.6%)                                |
| Benzodiazepines              | 4,786 (13.4%)                | 7,637 (15.5%)               | 3,458 (13.7%)                               |
| Antipsychotics               | 776 (2.2%)                   | 1,296 (2.6%)                | 542 (2.1%)                                  |
| Antiparkinsonian medications | 1,149 (3.2%)                 | 2,403 (4.9%)                | 836 (3.3%)                                  |
| Dementia medications         | 987 (2.8%)                   | 1,207 (2.4%)                | 565 (2.2%)                                  |
| Internist (-365 days to CED) | 31,975 (89.5%)               | 44,006 (89.1%)              | 22,650 (89.6%)                              |
| Internist (-30 days to CED)  | 22,375 (62.6%)               | 29,402 (59.5%)              | 15,418 (61.0%)                              |
| Internist (-365 days to -31 days before CED) | 31,211 (87.4%) | 43,006 (87.1%) | 22,089 (87.4%) |
|                         | Internist (Number of visits), mean, (SD) | Endocrinologist (-365 days to CED) | Endocrinologist (-30 days to CED) | Endocrinologist (-365 days to -31 days before CED) | Endocrinologist (Number of visits), mean, (SD) | Cardiologist (-365 days to CED) | Cardiologist (-30 days to CED) | Cardiologist (-365 days to -31 days before CED) | Cardiologist (Number of visits), mean, (SD) | Nephrologist (-365 days to CED) |
|-------------------------|------------------------------------------|------------------------------------|-----------------------------------|-----------------------------------------------------|----------------------------------------------|--------------------------------|-------------------------------|-----------------------------------------------|--------------------------------|-----------------------------|
| Internist (Number of visits), mean, (SD) | 15.2(18.25) | 15.8(20.11) | 0.03 | 14.8(18.20) | 15.5(18.68) | 0.04 |
| Endocrinologist (-365 days to CED) | 7,877 (22.1%) | 13,474 (27.3%) | 0.121 | 6,569 (26.0%) | 24,636 (12.4%) | 0.35 |
| Endocrinologist (-30 days to CED) | 5,706 (16.0%) | 9,439 (19.1%) | 0.082 | 4,818 (19.1%) | 15,372 (7.7%) | 0.337 |
| Endocrinologist (-365 days to -31 days before CED) | 6,329 (17.7%) | 10,360 (21.0%) | 0.082 | 5,404 (21.4%) | 18,964 (9.5%) | 0.332 |
| Endocrinologist (Number of visits), mean, (SD) | 2.0(7.35) | 2.3(7.28) | 0.042 | 2.4(8.08) | 1.0(4.81) | 0.216 |
| Cardiologist (-365 days to CED) | 18,190 (50.9%) | 24,446 (49.5%) | 0.029 | 13,244 (52.4%) | 94,034 (47.3%) | 0.102 |
| Cardiologist (-30 days to CED) | 5,999 (16.8%) | 6,457 (13.1%) | 0.105 | 4,405 (17.4%) | 30,628 (15.4%) | 0.055 |
| Cardiologist (-365 days to -31 days before CED) | 17,244 (48.3%) | 23,330 (47.2%) | 0.021 | 12,573 (49.7%) | 87,110 (43.8%) | 0.119 |
| Cardiologist (Number of visits), mean, (SD) | 4.6(9.56) | 4.1(9.13) | 0.05 | 4.8(9.67) | 4.1(9.10) | 0.072 |
| Nephrologist (-365 days to CED) | 1,739 (4.9%) | 5,507 (11.1%) | 0.233 | 1,222 (4.8%) | 16,207 (8.1%) | 0.135 |

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| Nephrologist (-30 days to CED) | 440 (1.2%) | 1,391 (2.8%) | 0.113 | 331 (1.3%) | 5,827 (2.9%) | 0.113 |
| Nephrologist (-365 days to -31 days before CED) | 1,632 (4.6%) | 5,208 (10.5%) | 0.227 | 1,139 (4.5%) | 13,964 (7.0%) | 0.108 |
| Nephrologist (Number of visits), mean, (SD) | 0.3(2.31) | 0.6(3.15) | 0.121 | 0.3(2.41) | 0.5(3.01) | 0.072 |
| Electrocardiogram | 18,863 (52.8%) | 25,299 (51.2%) | 0.032 | 13,419 (53.1%) | 102,299 (51.4%) | 0.033 |
| Electrocardiogram (Number of tests), mean, (SD) | 1.5(2.39) | 1.4(2.47) | 0.006 | 1.5(2.46) | 1.5(2.61) | 0.008 |
| ECG & Other cardiac imaging | 10,995 (30.8%) | 14,958 (30.3%) | 0.011 | 7,926 (31.3%) | 58,455 (29.4%) | 0.043 |
| ECG & Other cardiac imaging (Number of tests), mean, (SD) | 0.8(1.57) | 0.8(1.54) | 0.009 | 0.8(1.63) | 0.7(1.52) | 0.057 |
| Cardiovascular stress test | 5,454 (15.3%) | 7,390 (15.0%) | 0.009 | 4,001 (15.8%) | 25,046 (12.6%) | 0.093 |
| HbA1c test order | 34,726 (97.2%) | 47,912 (97.0%) | 0.014 | 24,641 (97.5%) | 190,117 (95.6%) | 0.102 |
| HbA1c test order (Number of tests), mean, (SD) | 2.8(1.32) | 2.9(1.36) | 0.045 | 2.9(1.31) | 2.6(1.34) | 0.177 |
| Glucose test and monitoring | 12,345 (34.6%) | 18,568 (37.6%) | 0.063 | 8,922 (35.3%) | 64,557 (32.5%) | 0.06 |
| Test Category                                      | Number of Tests | Mean (SD) | Number of Tests | Mean (SD) | Number of Tests | Mean (SD) | p Value |
|---------------------------------------------------|-----------------|-----------|-----------------|-----------|-----------------|-----------|---------|
| Glucose test and monitoring (Number of tests)     | 0.9(1.85)       | 1.0(1.95) | 0.9(1.90)       | 0.8(2.27) | 0.049           |
| Microalbuminuria/proteinuria test order           | 23,247 (65.1%)  | 32,539 (65.9%) | 16,673 (65.9%) | 116,088 (58.4%) | 0.157 |
| Microalbuminuria/proteinuria test order (Number   | 1.0(1.06)       | 1.1(1.14) | 1.0(1.06)       | 0.9(1.04) | 0.125           |
| Metabolic or renal/creatinine panel test order    | 34,885 (97.7%)  | 48,137 (97.4%) | 24,689 (97.6%) | 192,777 (96.9%) | 0.044 |
| Metabolic or renal/creatinine panel test order    | 3.4(2.23)       | 3.6(2.57) | 3.4(2.25)       | 3.4(2.46) | 0.008           |
| Lipid test order                                  | 32,873 (92.0%)  | 44,685 (90.5%) | 23,242 (91.9%) | 177,378 (89.2%) | 0.094 |
| Lipid test order (Number of tests), mean, (SD)    | 2.2(1.55)       | 2.1(1.58) | 2.1(1.58)       | 2.0(1.50) | 0.109           |
| Uric acid test order                              | 5,027 (14.1%)   | 7,482 (15.1%) | 3,482 (13.8%)  | 27,476 (13.8%) | 0.011 |
| Vitamin D test order                              | 11,536 (32.3%)  | 16,783 (34.0%) | 8,022 (31.7%)  | 61,213 (30.8%) | 0.02  |
| PTH test order                                    | 2,086 (5.8%)    | 5,269 (10.7%) | 1,538 (6.1%)   | 13,944 (7.0%) | 0.038 |
|                                | Mean (SD)   | Mean (SD)   | Mean (SD)   | Mean (SD)   | Mean (SD)   |
|--------------------------------|-------------|-------------|-------------|-------------|-------------|
| Hospitalization event (Number of), mean, (SD) | 0.2(0.53)   | 0.2(0.57)   | 0.051       | 0.2(0.54)   | 0.3(0.69)   | 0.131       |
| LOS (-365 days to -31 days before CED), mean, (SD) | 0.8(3.72)   | 0.9(3.62)   | 0.04        | 0.8(3.27)   | 1.0(4.73)   | 0.062       |
| LOS (-30 days to CED), mean, (SD) | 0.1(0.99)   | 0.1(0.92)   | 0.002       | 0.1(0.98)   | 0.5(2.41)   | 0.192       |
| ED event (Number of), mean, (SD) | 0.7(1.66)   | 0.8(1.89)   | 0.075       | 0.7(1.73)   | 0.9(2.08)   | 0.108       |
| Distinct medications ALL, mean, (SD) | 13.2(5.77)  | 14.8(6.11)  | 0.262       | 13.3(5.75)  | 12.8(5.87)  | 0.098       |
| Distinct medications all BRAND, mean, (SD) | 3.1(1.95)   | 3.6(2.17)   | 0.215       | 3.0(1.96)   | 2.7(1.90)   | 0.17        |
| Cost Total ($), mean, (SD) | 11835.8(14020.42) | 13441.0(16301.11) | 0.106       | 12513.0(32756.46) | 10769.7(15528.41) | 0.068       |
| Cost inpatient ($), mean, (SD) | 2075.3(7897.58) | 2238.2(7952.80) | 0.021       | 2177.9(8119.74) | 2884.4(9725.25) | 0.079       |
| Cost outpatient ($), mean, (SD) | 1937.3(4627.23) | 2329.2(7898.34) | 0.061       | 2112.4(5230.43) | 1863.9(4294.26) | 0.052       |
| Cost pharmacy for DM medications ($), mean, (SD) | 3307.0(4102.80) | 3928.6(4413.29) | 0.146       | 3588.9(5267.34) | 1355.5(2287.93) | 0.55        |
| Cost pharmacy for non-DM medications ($), mean, (SD) | 4381.4(6583.45) | 3664.3(7154.91) | 0.104 | 3597.3(29226.04) | 3152.7(7068.80) | 0.021 |
| Cost pharmacy ($), mean, (SD) | 905.3(943.58) | 982.4(1001.04) | 0.079 | 989.8(1766.09) | 587.5(729.96) | 0.298 |
| Cost home healthcare ($), mean, (SD) | 322.3(1743.58) | 448.0(2186.89) | 0.064 | 288.7(1591.43) | 590.5(2368.16) | 0.15 |
| Flu vaccine | 22,607 (63.3%) | 31,825 (64.4%) | 0.024 | 16,256 (64.3%) | 118,837 (59.7%) | 0.094 |
| Pneumococcal vaccine | 7,956 (22.3%) | 11,641 (23.6%) | 0.031 | 5,747 (22.7%) | 41,225 (20.7%) | 0.049 |
| Breast mammography or magnetic resonance imaging | 7,968 (22.3%) | 13,538 (27.4%) | 0.118 | 5,651 (22.3%) | 45,268 (22.8%) | 0.01 |
| Prostate examination or PSA | 10,433 (29.2%) | 11,082 (22.4%) | 0.155 | 7,420 (29.3%) | 44,367 (22.3%) | 0.161 |
| Colonoscopy | 3,708 (10.4%) | 5,359 (10.8%) | 0.015 | 2,839 (11.2%) | 18,179 (9.1%) | 0.069 |
| Pap smear | 1,703 (4.8%) | 2,801 (5.7%) | 0.041 | 1,195 (4.7%) | 8,953 (4.5%) | 0.011 |
| Bone mineral density | 2,986 (8.4%) | 4,577 (9.3%) | 0.032 | 2,043 (8.1%) | 16,408 (8.2%) | 0.006 |

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: betab lockers; CCB: calcium channel blockers; CED: cohort entry date; COPD: chronic obstructive pulmonary diseases; DM: diabetes mellitus; DPP4i: dipeptidyl peptidase-4 inhibitors; MRA: mineralocorticoid receptor antagonists; PAD: peripheral arterial diseases; PSA: prostate surface antigen; SD: standard deviation; ASD: standardized mean differences;

*Includes American Indian/Alaskan Native or unknown.
**eTable 2. Follow-up Time and Censoring Reason for Primary Outcomes Between 1:1 PS-Matched Initiators of Empagliflozin vs Liraglutide or Sitagliptin**

| Overall population | Empagliflozin | Liraglutide |
|--------------------|---------------|-------------|
| **Modified MACE**  |               |             |
| Follow-up, mean (SD), days | 242 (227) | 250 (232) | 233 (221) |
| Follow-up, median (25th, 75th IQR), days | 153 [88, 308] | 163 [88, 324] | 148 [88, 292] |
| Censoring reasons (%): | | | |
| Treatment discontinuation | 48.8 | 46.6 | 51.0 |
| End of study - 12/31/2018 | 36.2 | 37.3 | 31.0 |
| Treatment switching | 8.3 | 9.4 | 7.4 |
| Disenrollment | 4.6 | 4.7 | 4.4 |
| Composite CV outcome | 2.0 | 2.0 | 2.0 |
| All-cause mortality | 0 | 0 | 0 |

| HHF outcome | Empagliflozin | Liraglutide |
|-------------|---------------|-------------|
| Follow-up, mean (SD), days | 242 (227) | 250 (232) | 233 (221) |
| Follow-up, median (25th, 75th IQR), days | 157 [88, 321] | 157 [88, 315] | 157 [88, 327] |
| Censoring reasons (%): | | | |
| Treatment discontinuation | 49.1 | 46.9 | 51.2 |
| End of study - 12/31/2018 | 36.4 | 37.5 | 35.3 |
| Treatment switching | 8.4 | 9.4 | 7.4 |
| Disenrollment | 4.6 | 4.8 | 4.5 |
| HHF outcome | 0.7 | 0.6 | 0.8 |
| All-cause mortality | 0.8 | 0.8 | 0.8 |

| Overall population | Empagliflozin | Sitagliptin |
|--------------------|---------------|-------------|
| **Modified MACE**  |               |             |
| Follow-up, mean (SD), days | 234 (210) | 229 (207) | 239 (212) |
| Follow-up, median (25th, 75th IQR), days | 155 [88, 312] | 151 [88, 302] | 158 [88, 322] |
| Censoring reasons (%): | | | |
| Treatment discontinuation | 42.4 | 42.1 | 42.8 |
| End of study - 12/31/2018 | 44.1 | 43.1 | 45.0 |
| Treatment switching | 7.0 | 8.5 | 5.7 |
| Disenrollment | 4.3 | 4.0 | 4.6 |
| Composite CV outcome | 2.1 | 1.7 | 2.5 |
| All-cause mortality | 0 | 0 | 0 |

| HHF outcome | Empagliflozin | Sitagliptin |
|-------------|---------------|-------------|
| Follow-up, mean (SD), days | 234 (210) | 229 (207) | 239 (212) |
Follow-up, median (25th, 75th IQR), days | 155 [88, 313] | 151 [88, 303] | 159 [88, 322]  
--- | --- | --- | ---  
Censoring reasons (%): | | |  
Treatment discontinuation | 42.6 | 43.1 | 42.2  
End of study - 12/31/2018 | 44.3 | 43.3 | 45.3  
Treatment switching | 7.1 | 8.5 | 5.8  
Disenrollment | 4.3 | 4.0 | 4.6  
HHF outcome development | 0.8 | 0.5 | 1.1  
All-cause mortality | 0.8 | 0.7 | 1.0  

PS: propensity-score; MACE: major adverse cardiovascular events; SD: standard deviation; IQR: interquartile range; HHF: hospitalization for heart failure

*a Censoring was outcome-specific. The table reports follow-up and censoring information specific to the primary outcomes. Censoring reasons specific to other study outcomes may include minor variations.
### Table 3. Sensitivity Analyses for 1:1 PS-Matched Initiators of Empagliflozin vs Liraglutide or Sitagliptin

| Sensitivity analyses | Comparison                          | Primary outcomes                                      | Empagliflozin   | Comparator   | Empagliflozin vs. Comparator |
|---------------------|-------------------------------------|-------------------------------------------------------|----------------|-------------|-----------------------------|
|                     |                                     |                                                       | N events       | N events    | HR (95% CI)                 | RD/1000PY (95% CI) |
|                     |                                     |                                                       | (IR/1000 PY)   | (IR/1000 PY)|                            |                 |
| Metformin at baseline | Empagliflozin vs. Liraglutide       | Modified MACE outcome<sup>a</sup>                     | 314 (17680)    | 301 (17680)| 0.97 (0.83, 1.14)           | -0.53 (-4.64, 3.56) |
|                     |                                     | Hospitalization for heart failure (specific)         | 81 (17680)     | 131 (17680)| 0.56 (0.43, 0.75)           | -4.77 (-7.23, -2.38) |
|                     | Empagliflozin vs. Sitagliptin       | Modified MACE outcome<sup>a</sup>                     | 277 (18266)    | 417 (18266)| 0.68 (0.59, 0.79)           | -11.03 (-15.46, -6.64) |
|                     |                                     | Hospitalization for heart failure (specific)         | 74 (18266)     | 167 (18266)| 0.46 (0.35, 0.60)           | -7.60 (-10.22, -5.05) |
| No insulin at baseline | Empagliflozin vs. Liraglutide       | Modified MACE outcome<sup>a</sup>                     | 242 (13882)    | 224 (13882)| 0.98 (0.82, 1.17)           | -0.27 (-4.72, 4.16)  |
|                     |                                     | Hospitalization for heart failure (specific)         | 62 (13882)     | 90 (13882) | 0.61 (0.44, 0.85)           | -3.64 (-6.25, -1.12) |
|                     | Empagliflozin vs. Sitagliptin       | Modified MACE outcome<sup>a</sup>                     | 226 (15634)    | 321 (15634)| 0.74 (0.62, 0.88)           | -8.01 (-12.60, -3.44) |
|                     |                                     | Hospitalization for heart failure (specific)         | 47 (15634)     | 130 (15634)| 0.38 (0.27, 0.53)           | -7.82 (-10.46, -5.29) |
|                  | Empagliflozin vs. Liraglutide | Empagliflozin vs. Sitagliptin | Empagliflozin vs. Liraglutide | Empagliflozin vs. Sitagliptin |
|------------------|-------------------------------|------------------------------|-------------------------------|-------------------------------|
| ITT 730 days     |                               |                               |                               |                               |
| Modified MACE outcome<sup>a</sup> | 911 (22906)              | 949 (22906)                  | 0.95 (0.87, 1.05)             | -1.64 (-4.92, 1.63)          |
|                  |                               |                               |                               |                               |
| Hospitalization for heart failure (specific) | 285 (22906)              | 403 (22906)                  | 0.70 (0.60, 0.82)             | -4.64 (-6.63, -2.66)         |
|                  |                               |                               |                               |                               |
| Hospitalization for heart failure (specific) | 774 (22822)              | 914 (22822)                  | 0.83 (0.76, 0.92)             | -6.62 (-10.15, -3.10)        |
|                  |                               |                               |                               |                               |
| Hospitalization for heart failure (specific) | 245 (22822)              | 394 (22822)                  | 0.61 (0.52, 0.72)             | -6.70 (-8.88, -4.55)         |
| Exposure risk period 30 days |                               |                               |                               |                               |
| Modified MACE outcome<sup>a</sup> | 358 (22894)              | 319 (22894)                  | 0.97 (0.83, 1.12)             | -0.94 (-5.23, 3.31)          |
|                  |                               |                               |                               |                               |
| Hospitalization for heart failure (specific) | 89 (22894)              | 138 (22894)                  | 0.54 (0.42, 0.71)             | -5.53 (-8.10, -3.05)         |
|                  |                               |                               |                               |                               |
| Hospitalization for heart failure (specific) | 302 (22812)              | 466 (22812)                  | 0.67 (0.58, 0.78)             | -11.91 (-16.34, -7.52)       |
|                  |                               |                               |                               |                               |
| Hospitalization for heart failure (specific) | 83 (22812)              | 221 (22812)                  | 0.39 (0.30, 0.50)             | -10.65 (-13.45, -7.93)       |

PS: propensity score; IR: Incidence rate; PY: person-years; HR: hazard ratio; CI: confidence intervals; RD: rate difference.

<sup>a</sup> Hospitalization for myocardial infarction, or ischemic or hemorrhagic stroke, all-cause mortality.
**eTable 4. Number of Events, Incidence Rates, and Treatment Effect Estimates for 1:1 PS-Matched Initiators of Empagliflozin vs GLP-1RA or DPP-4 Inhibitor in the Overall Population**

| Primary outcomes          | Empagliflozin N events (IR/1,000 PY) | Comparator N events (IR/1,000 PY) | Empagliflozin vs. comparator HR (95% CI) | RD/1,000PY (95% CI) |
|---------------------------|-------------------------------------|-----------------------------------|------------------------------------------|-------------------|
| Empagliflozin vs. GLP-1RA (N of matched pairs = 31,716) |                                     |                                   |                                          |                   |
| Modified MACE outcome⁴    | 582 (28.0)                          | 577 (29.6)                        | 0.94 (0.84, 1.06)                        | -1.55 (-4.88, 1.76) |
| Hospitalization for heart failure (specific) | 161 (7.7)                            | 225 (11.5)                        | 0.66 (0.54, 0.81)                        | -3.79 (-5.73, -1.88) |
| Hospitalization for heart failure (broad) | 794 (38.6)                            | 906 (47.0)                        | 0.82 (0.74, 0.90)                        | -8.46 (-12.54, -4.40) |
| Empagliflozin vs. DPP-4i (N of matched pairs = 23,309) |                                     |                                   |                                          |                   |
| Modified MACE outcome⁴    | 388 (26.6)                          | 581 (38.8)                        | 0.68 (0.60, 0.78)                        | -12.21 (-16.34, -8.10) |
| Hospitalization for heart failure (specific) | 119 (8.1)                            | 238 (15.8)                        | 0.51 (0.41, 0.64)                        | -7.71 (-10.23, -5.24) |
| Hospitalization for heart failure (broad) | 586 (40.5)                            | 861 (58.3)                        | 0.69 (0.62, 0.77)                        | -17.85 (-22.96, -12.77) |

PS: propensity score; GLP-1RA: glucagon-like peptide-1 receptor agonists; DPP-4i: dipeptidyl peptidase-4 inhibitors; IR: Incidence rate; PY: person-years; HR: hazard ratio; CI: confidence intervals; RD: rate difference; CVD: cardiovascular disease.

⁴ Hospitalization for myocardial infarction, or ischemic or hemorrhagic stroke, all-cause mortality.