Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

**EDITORIAL**, see p 260

**BACKGROUND:** Reduction in cardiovascular death and hospitalization for heart failure (HHF) was recently reported with the sodium-glucose cotransporter-2 inhibitor (SGLT-2i) empagliflozin in patients with type 2 diabetes mellitus who have atherosclerotic cardiovascular disease. We compared HHF and death in patients newly initiated on any SGLT-2i versus other glucose-lowering drugs in 6 countries to determine if these benefits are seen in real-world practice and across SGLT-2i class.

**METHODS:** Data were collected via medical claims, primary care/hospital records, and national registries from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom. Propensity score for SGLT-2i initiation was used to match treatment groups. Hazard ratios for HHF, death, and their combination were estimated by country and pooled to determine weighted effect size. Death data were not available for Germany.

**RESULTS:** After propensity matching, there were 309,056 patients newly initiated on either SGLT-2i or other glucose-lowering drugs (154,528 patients in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT-2i class, respectively. Baseline characteristics were balanced between the 2 groups. There were 961 HHF cases during 190,164 person-years follow-up (incidence rate, 0.51/100 person-years). Of 215,622 patients in the United States, Norway, Denmark, Sweden, and the United Kingdom, death occurred in 1,334 (incidence rate, 0.87/100 person-years), and HHF or death in 1983 (incidence rate, 1.38/100 person-years). Use of SGLT-2i, versus other glucose-lowering drugs, was associated with lower rates of HHF (hazard ratio, 0.61; 95% confidence interval, 0.51–0.73; P<0.001); death (hazard ratio, 0.49; 95% confidence interval, 0.41–0.57; P<0.001); and HHF or death (hazard ratio, 0.54; 95% confidence interval, 0.48–0.60; P<0.001) with no significant heterogeneity by country.

**CONCLUSIONS:** In this large multinational study, treatment with SGLT-2i versus other glucose-lowering drugs was associated with a lower risk of HHF and death, suggesting that the benefits seen with empagliflozin in a randomized trial may be a class effect applicable to a broad population of patients with type 2 diabetes mellitus in real-world practice.

**CLINICAL TRIAL REGISTRATION:** URL: http://www.clinicaltrials.gov. Unique identifier: NCT02993614.

Mikhail Kosiborod, MD
Matthew A. Cavender, MD, MPH
Alex Z. Fu, PhD
John P. Wilding, MD, PhD
Kamlesh Khunti, MD, PhD
Reinhard W. Holl, MD, PhD
Anna Norhammar, MD
Kåre I. Birkeland, MD, PhD
Marit Eika Jørgensen, MD, PhD
Marcus Thøressen, PhD
Niki Arya, MSc
Johan Bodegård, MD, PhD
Niklas Hammar, PhD
Peter Fenici, MD, PhD

on behalf of the CVD-REAL Investigators and Study Group*

*See online-only Data Supplement for a list of individuals.

**Correspondence to:** Mikhail Kosiborod, MD, Saint Luke’s Mid America Heart Institute, 4401 Wornall Rd, Kansas City, MO, 64111. E-mail mkosiborod@saint-lukes.org

**Sources of Funding,** see page 257

**Key Words:** canagliflozin ■ dapagliflozin ■ death ■ diabetes mellitus ■ empagliflozin ■ heart failure ■ sodium glucose transporter 2

© 2017 The Authors. Circulation is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited.
Clinical Perspective

What Is New?

- This is the first large real-world study of >300,000 patients with type 2 diabetes mellitus, both with and without established cardiovascular disease, from routine clinical practice across 6 countries, evaluating the outcomes of hospitalization for heart failure (HHF) and all-cause death in patients with type 2 diabetes mellitus with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) versus other glucose-lowering drugs.
- The distribution of exposure time for the various SGLT-2i compounds (for HHF outcome) was 53% for canagliflozin, 42% for dapagliflozin, and 5% for empagliflozin, with substantial intercountry variability.

What Are the Clinical Implications?

- Treatment with SGLT-2i versus other glucose-lowering drugs was associated with a 39% relative risk reduction in HHF, a 51% reduction in all-cause death, and a 46% reduction in the HHF or death composite, consistent with the effects previously reported in a randomized clinical trial of empagliflozin.
- Approximately 87% of patients did not have known cardiovascular disease, suggesting possible cardiovascular benefits for a broad population of patients with type 2 diabetes mellitus.
- The lower rates of HHF and death associated with SGLT-2i treatment are likely class related, as there was no significant heterogeneity across countries, despite geographic variations in the use of specific SGLT-2i (<76% canagliflozin in the United States and >92% dapagliflozin in Europe).

Type 2 diabetes mellitus (T2D) remains a major risk factor for cardiovascular disease (CVD)1,2 and overall mortality,3,4 despite advances in treatment.5-7 Heart failure is an especially common complication of T2D,8-10 with particularly poor outcomes and 5-year survival rates of <25%.11 This highlights the need for novel treatments that not only improve glycemic control, but also reduce the risk of CVD, including heart failure.

Although higher hemoglobin A1c is associated with greater risk of CVD,12 intensive glucose control has failed to reduce the development of heart failure, and cardiovascular-related or all-cause death. However, the EMPA-REG OUTCOME trial (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), a prospective randomized controlled trial in patients with T2D and established atherosclerotic CVD, demonstrated a substantial reduction in cardiovascular death and hospitalization for heart failure (HHF) with the sodium-glucose cotransporter-2 inhibitor (SGLT-2i), empagliflozin,13 within a short follow-up period. The mechanisms of these benefits, although unclear, were almost certainly not attributable to glucose lowering, given a very small difference in hemoglobin A1c levels between empagliflozin- and placebo-treated patients and early separation of the event curves.

Following the EMPA-REG OUTCOMES trial, several critical questions remain, with substantial clinical implications. First, the applicability of findings to real-world clinical practice (where patients receive standard of care with various other glucose-lowering drugs [oGLDs]) is unclear. Second, it is unknown whether the observed benefits are specific to empagliflozin, or represent a class effect. Finally, because EMPA-REG OUTCOME only included patients with established CVD, it remains to be seen if similar benefits can be expected in patients with T2D who have a broader cardiovascular risk profile.

Using data from multiple countries in the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors: NCT02993614), we compared the risk for HHF, death, and the combined end point of HHF or death in patients with T2D who were new users of SGLT-2i versus oGLDs in real-world practice.

METHODS

Data Sources

Deidentified health records across 6 countries (United States, Germany, Sweden, Norway, Denmark, and the United Kingdom) were analyzed. In the United States, Truven Health MarketScan Claims and Encounters and linked Medicare Supplemental and Coordination of Benefits databases were used, which included enrollment and demographic information, inpatient and outpatient medical, and outpatient pharmacy claims from >300 large self-insured US employers and >25 US health plans. In Germany, the Diabetes Prospective Follow-Up initiative is a quality assessment registry for individuals with diabetes mellitus and uses standardized documentation and objective comparison of quality indicators, with 452 centers participating. In Sweden, Norway, and Denmark, mandatory national full-population registries of each respective country were used, with linked Prescribed Drug Registers covering all drugs dispensed, National Patient Registers covering all hospitalizations and specialized outpatient care, and Cause of Death Registers.14-17 In the United Kingdom, records from the Clinical Practice Research Datalink and The Health Improvement Network data sets were used, which included primary care data from >670 general practices linked with hospitalization and mortality registries. Additional details of the individual data sets can be found in the online-only Data Supplement Appendix.

Patient Cohort

Patients with T2D (diagnosis codes in online-only Data Supplement Tables I and II) who were newly started on either SGLT-2i or oGLDs were selected from each data set beginning on the date of first prescription or pharmacy dispensation.
of an SGLT-2i or a new oGLD in each of the countries (start date ranged from November 2012 in the United Kingdom to July 2013 in Sweden). New users were defined as individuals prescribed/filling a prescription (as initial or add-on therapy) for any SGLT-2i (canagliflozin, dapagliflozin, or empagliflozin) or oGLD (any other oral or injectable medication), including fixed-dose combinations, with no issued prescriptions of that medicine class during the preceding year (in Germany, with no prior documentation in the medical record of using that medicine class within the previous 6 months). Additional inclusion criteria were age ≥18 years on the index date (defined as the prescription date for new SGLT-2i or new oGLD), and >1 year data history in the database before the index date. Patients with type 1 or gestational diabetes were excluded. Patients were followed from the index date until the end of the index treatment (for the on-treatment analysis), migration/leaving the practice/database, last date of data collection, outcome date, or censoring date (range from September 2015 in the United States to November 2016 in Sweden).

Outcomes

Primary outcome was HHF assessed in all countries. In the United States, United Kingdom, and Germany, HHF was defined as hospital admissions for heart failure (defined using primary discharge diagnosis codes in the United States,18 primary discharge diagnosis codes and documentation from the electronic health records in the United Kingdom, as defined in the online-only Data Supplement Appendix, and documentation in the electronic health records in Germany). In the Nordic countries (Sweden, Norway, and Denmark), HHF was defined by any hospital visit, in- or outpatient (ie, prognostically equivalent outpatient heart failure [HF] event),19 with a registered primary diagnosis of HF (defined using diagnosis codes for HF events as detailed in the online-only Data Supplement Appendix, and validated independently in all 3 countries).20–22 Secondary outcomes included all-cause death, and a composite of HHF or all-cause death (time-to-first-event), evaluated in the practice/database, last date of data collection, outcome date, or censoring date, respectively within each country.

Statistical Analysis

Baseline characteristics of patients in the SGLT-2i and oGLD groups were analyzed by using descriptive statistics. Categorical variables were described by frequencies and percentages, and continuous variables by using mean (± SD). For continuous variables such as age, the overall mean across all databases was a summary estimate of country-specific means, weighted according to the number of patients in each respective database.

For the SGLT-2i group, the percentage of individual agents and their respective contributions to the overall SGLT-2i exposure time, and for the oGLD group, the percentage of individual drug classes, were summarized by country/geographic region and overall.

A nonparsimonious propensity score was developed (separately within each country) for being initiated on an SGLT-2i to minimize confounding. Variables that may have affected treatment assignment or outcomes were included in the propensity score (online-only Data Supplement Table IV).23 Based on propensity scores, patients receiving SGLT-2i were matched 1:1 with those receiving oGLDs. Nearest-neighbor caliper width of 0.25 multiplied by the SD of the propensity score distribution was used for the matching.23 In Sweden, Norway, and Denmark, an automated balance optimization method using the function Match (in package Matching) in R and a caliper of 0.2 were used for matching. The adequacy of propensity matching was assessed by standardized differences of postmatch patient characteristics. A significant imbalance was considered to be present if a >10% standardized difference was present between the 2 groups after propensity match.24

Incidence analyses of HHF, death, and composite of HHF or death were conducted by treatment group. Only the first episode of each outcome was included, and the crude incidence rate (IR) in each group was calculated as the number of incident events divided by the total number of person-years at risk, and expressed per 100 person-years with 95% confidence interval (CI). Times to first event for the SGLT-2i and oGLD groups were compared using Cox proportional hazards models and presented as hazard ratios (HRs) and 95% CI for each outcome separately within each country.

The primary analysis used an on-treatment approach where patients were followed from the start of an index treatment and censored at the end of that treatment plus a grace period (duration of last issued prescription).

The HRs (95% CI) for each of the end points from each individual country were then pooled together for an overall weighted summary,25 in which random-effects models with inverse variance weighting for each country were implemented.26 Forest plots displaying the country-specific HRs (95% CI) along with the pooled overall HR (95% CI) were produced.

Multiple sensitivity analyses were conducted: first, the HR (95% CI) within each country, and for each outcome, were examined after adjusting the crude propensity-scored estimates for multiple covariates that may have confounded the relationship between treatment and outcome. The adjusted HRs (95% CIs) from each country were pooled and meta-analyzed using the same method as described above. Second, the analyses for each outcome were repeated using intent-to-treat analysis, in which patients were followed after discontinuation of index treatment.27–29 Third, the analyses for HHF were repeated after stepwise removal of specific oGLD classes from the comparator group, to examine whether a specific oGLD class contributed disproportionately to the results. Stepwise elimination was performed in the following sequence: thiazolidinediones, thiazolidinediones+insulin, thiazolidinediones+insulin+sulfonylureas. Fourth, HHF analyses were repeated after excluding patients treated with glucagon-like peptide-1 receptor agonist at baseline from SGLT-2i and oGLD groups. Fifth, primary analyses were repeated separately in the United States and Europe. Finally, the association between treatment with SGLT-2i and oGLD was reexamined separately for patients that had both in- and outpatient hospital visits for...
HF, and those that had only inpatient hospital visits for HF in Sweden (because these could not be separated in Norway and Denmark; and only inpatient HF visits were analyzed in other countries).

For power calculations, see the online-only Data Supplement Appendix. Because of the deidentified nature of patient records, informed consent was not obtained. Analyses of deidentified data were conducted in accordance with local laws and regulations, and received approvals from respective Scientific/Ethics/Data Protection Committees. Country-specific analyses were conducted by independent academic/statistical groups. The meta-analyses were conducted by Statisticon, and validated by the independent academic statisticians at Saint Luke's Mid America Heart Institute.

RESULTS

Study Population

A total of 1392,254 new SGLT-2i or oGLD users were identified; 166,033 SGLT-2i, and 1,226,221 oGLD overall and by country (Figure 1 and online-only Data Supplement Figure I). Before propensity match (online-only Data Supplement Table V) patients initiated on SGLT-2i were younger, less likely to have chronic kidney disease or cardiovascular complications, but more likely to have microvascular disease. Greater proportions of patients initiated on SGLT-2i versus oGLD received statins and antihypertensive drugs, and lower proportions received loop diuretics. Patients on SGLT-2i were more likely to be treated with other glucose-lowering medication classes at baseline. The overlap in propensity scores between groups before and after the propensity match is shown in online-only Data Supplement Figures II and III.

Baseline characteristics were well balanced between groups postmatching overall and by country (Table and online-only Data Supplement Table VI), with standardized differences for most variables being <10% (online-only Data Supplement Figure IV). Pre- and postmatch standardized differences are shown in online-only Data Supplement Table VII. Mean age was 57 years, 44%...
were women, and 13% had established CVD. Overall, 67% of patients received statins, 80% antihypertensive medications, 74% with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and 79% metformin.

The composition of SGLT-2i agents is shown in online-only Data Supplement Table VIII, and the composition of the index medications in the oGLD group is shown in online-only Data Supplement Tables IX and X. The composition of SGLT-2i agents in terms of total exposure time was balanced between canagliflozin and dapagliflozin, with <7% total exposure attributable to empagliflozin for all outcomes (Figure 2).

**SGLT-2i and HHF**

A total of 309,056 patients (154,528 in each group) were identified after propensity matching. Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT-2i class, respectively (Figure 2A through 2C).

Over 190,64 person-years follow-up, there were 961 HHF events (IR, 0.51/100 person-years; online-only Data Supplement Table XI; IR by treatment group in online-only Data Supplement Table XII). Mean duration of follow-up for HHF was 239 days in the SGLT-2i group and 211 days in the oGLD group (online-only Data Supplement Table XIII). Initiation of SGLT-2i versus oGLD was associated with a lower risk of HHF (pooled HR, 0.61; 95% CI, 0.51–0.73; P<0.001; Figure 3A). HRs favored SGLT-2i in each country (P value for heterogeneity 0.17).

**SGLT-2i and All-Cause Death**

A total of 215,622 patients (107,811 in each group) were identified. Canagliflozin, dapagliflozin, and empagliflozin accounted for 42%, 51%, and 7% of SGLT-2i exposure time, respectively (Figure 2A through 2C).

Over 153,990 person-years of follow-up, there were 1334 events (IR, 0.87/100 person-years; online-only Data Supplement Table XI; IR by treatment group in online-only Data Supplement Table XII). Mean duration of follow-up was 271 days in the SGLT-2i group and 251 days in the oGLD group (online-only Data Supplement Table XIII). Initiation of SGLT-2i versus oGLD was associated with a lower risk of death (pooled HR, 0.49; 95% CI, 0.41–0.57; P<0.001; Figure 4A). HRs favored SGLT-2i in each country (P value for heterogeneity 0.09).

**SGLT-2i and Composite Outcome of HHF or Death**

For the composite outcome, the number of patients was identical to the all-cause death analysis. Canagliflozin, dapagliflozin, and empagliflozin accounted for 45%,
Mean duration of follow-up was 253 days in the SGLT-2i group and from 233 days in the oGLD group (online-only Data Supplement Table XIII). Initiation of SGLT-2i versus oGLD was associated with a lower risk of HHF or death \( (pooled \text{ HR}, 0.54; 95\% \text{ CI}, 0.48–0.60; \text{ P}<0.001; \text{ Figure 4D}) \). HRs favored SGLT-2i in each country \( (P \text{ value for heterogeneity} 0.17) \).

### Sensitivity Analyses

For all 3 outcomes, similar results were found after multivariate adjustment (Figures 3B, 4B, and 4E), using an intent-to-treat approach (Figures 3C, 4C, and 4F) and stepwise removal of specific oGLD classes (online-only Data Supplement Figures V and VI). Comparisons within geographic regions yielded similar results (online-only Data Supplement Figure VII). The association between treatment with SGLT-2i versus oGLD and lower risk of HHF was consistent among patients that had both in- and outpatient hospital visits for HF, and those who had only inpatient hospital visits for HF in Sweden (online-only Data Supplement Table XIV).

### DISCUSSION

In this large contemporary analysis of real-world clinical practice across 6 countries, within a well-matched sample of >300 000 patients with T2D and nearly 200 000 patient-years of observation, initiation of SGLT-2i versus oGLDs was associated with a 39% lower incidence of HHF. Since the overwhelming majority of patients did not have established CVD, this suggests that the benefits of SGLT-2i on the prevention of HF may extend to lower-risk patients than those enrolled in randomized trials so far. These findings were unchanged after additional multivariable adjustment, and in multiple sensitivity analyses. Specifically, the results were unchanged after sequential removal of several oGLD classes from the comparator group, suggesting that the differential outcomes observed are unlikely to reflect adverse effects of comparator drugs, but are rather associated with benefit from SGLT-2i. Furthermore, results were consistent across countries, regardless of variability in healthcare systems and use of specific SGLT-2i (predominantly canagliflozin in the United States; dapagliflozin).

**Figure 3 Continued.** of diabetes mellitus, ACE inhibitor or ARB use, β-blocker or α-blocker use, Ca²⁺ channel blocker use, loop diuretic use, thiazide diuretic use). **C.** Intent-to-treat, unadjusted. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; CPRD, Clinical Practice Research Datalink; DPV, Diabetes Patientenverlaufsdokumentation (Diabetes Prospective Follow-Up); HHF, hospitalization for heart failure; oGLD, other glucose-lowering drugs; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; and THIN, The Health Improvement Network.
Figure 4. Hazard ratios and 95% CI for the outcome of all-cause death and composite of hospitalization for heart failure or all-cause death.

A, All-cause death: on treatment, unadjusted. B, All-cause death: on treatment, adjusted (model adjusted for history of heart failure, age, sex, frailty, history of myocardial infarction, history of atrial fibrillation, hypertension, obesity/body mass index, (Continued)
in Europe), suggesting an association with the class rather than any single agent. Importantly, initiation of SGLT-2i versus oGLDs was also associated with a 51% lower rate of all-cause death, and a 46% lower rate of the combined end point of HHF or all-cause death.

Although intensive glucose lowering has, in randomized trials, failed to reduce what are arguably some of the most important outcomes in patients with T2D (all-cause death and incident HF), results from the EMPA-REG OUTCOME trial demonstrated that such benefits are achievable within a short time frame with an SGLT-2i, likely via nonglycemic mechanisms. Ultimately, the main goals of treating patients with T2D are to prolong life and improve quality of life. Given that CVD (including HF) is a leading cause of mortality/morbidity in T2D, the results of the recent cardiovascular outcomes trials suggest that the time has come to shift from the narrow focus on hemoglobin A1c to a more comprehensive focus in which treatments proven to improve important outcomes (especially mortality) are prioritized.

Our findings address several key unanswered questions with regard to the potential role of SGLT-2i in the management of T2D, with important clinical implications. First, our results demonstrate that the effects associated with the use of SGLT-2i in regard to HF and all-cause death are remarkably similar in real-world practice to those seen in the EMPA-REG OUTCOME trial. Second, we found no significant heterogeneity in results across countries, despite geographic variations in the use of specific SGLT-2i, suggesting that the associated lower risks for cardiovascular outcomes are likely class related. Indeed, for all outcomes evaluated, empagliflozin contributed <7% of total exposure time. Third, we evaluated a broader cardiovascular risk population in general practice, where the overwhelming majority (87%) had no established CVD, suggesting that lower-risk patients may derive benefits with SGLT-2i similar to the patients with higher risk. If confirmed by data from ongoing trials (CANVAS10 [Canagliflozin Cardiovascular Assessment Study; NCT01032629]; DECLARE [Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; NCT01730534]; and VERTIS [Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease, The VERTIS CV Study (MK-8835-004); NCT01986881]), this would have substantial impact on clinical practice. In this regard, we see the data produced from carefully conducted, methodologically rigorous, large multicountry epidemiological studies, as complementary to those generated by clinical trials, as they help establish the real-world effectiveness of treatments in a broad population of patients from clinical practice. Indeed, the importance of such studies for a broad range of objectives, including evaluation of treatment effects and outcomes, and their potential for complementing the knowledge gained from clinical trials, is being increasingly recognized,31 and the terminology describing these as real-world evidence has recently been accepted by major international regulatory bodies.32–34

To our knowledge, CVD-REAL is the first large study addressing the real-world effectiveness (rather than efficacy) of SGLT-2i on specific outcomes of HHF and all-cause death across multiple countries. Given that SGLT-2i is a novel class, real-world experience is limited. Single-country data were previously reported with a specific SGLT-2i (dapagliflozin) in Sweden; however, that study was limited by the smaller number of patients, and focused on different outcomes (hypoglycemia and composite of CVD).35 The size of our sample and our ability to pool data from diverse sources allowed us to collect a large number of events, and examine the stability of results across various cardiovascular outcomes, multiple countries (with variable use of specific SGLT-2i), and perform numerous sensitivity analyses.

Our findings should be examined within the context of several potential limitations. First, given the observational nature of the study, and despite robust propensity-matching and multiple sensitivity analyses, a possibility of residual, unmeasured confounding, cannot be excluded. Second, we focused on HHF and all-cause death, and did not examine other events, such as myocardial infarction and stroke. However, HF is arguably the most lethal T2D complication9,36 and is associated with particularly poor survival.11 Third, we did not examine safety. Fourth, despite a large number of patient-years of follow up, SGLT-2i experience in real-world practice is still relatively limited; longer-term follow-up will be required to examine if effects are sustained over time. Fifth, there were differences in the definitions of

Figure 4 Continued. duration of diabetes mellitus, ACE inhibitor or ARB use, β-blocker or α-blocker use, Ca2+ channel blocker use, loop diuretic use, thiazide diuretic use). C, All-cause death: intent-to-treat, unadjusted. D, Hospitalization for heart failure or all-cause death: on treatment, unadjusted. E, Hospitalization for heart failure or all-cause death: on treatment, adjusted (model adjusted for history of heart failure, age, sex, frailty, history of myocardial infarction, history of atrial fibrillation, hypertension, obesity/body mass index, duration of diabetes mellitus, ACE inhibitor or ARB use, β-blocker or α-blocker use, Ca2+ channel blocker use, loop diuretic use, thiazide diuretic use). F, Hospitalization for heart failure or all-cause death: intent-to-treat, unadjusted. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; CPRD, Clinical Practice Research Datalink; DPV, Diabetes Patientenverlaufsdocumentation (Diabetes Prospective Follow-Up); oGDL, other glucose-lowering drugs; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; and THIN, The Health Improvement Network.
HHF across countries; however, the results were consistent across countries and in sensitivity analyses specifically performed to examine these differences. Finally, our study did not address the mechanisms linking the use of SGLT-2i and associated cardiovascular benefits. However, this knowledge gap is being examined by mechanistic investigations across the class.37–39

CONCLUSION
In this large multinational study, treatment with SGLT-2i versus oGLDs was associated with lower rates of HHF and death, suggesting that the benefits previously reported with empagliflozin in the context of a randomized trial may be applicable to a broad population of patients with T2D in real-world practice. The lack of heterogeneity in results across countries, despite geographic variations in the use of specific SGLT-2i, suggests a class effect for SGLT-2i.

ACKNOWLEDGMENTS
The authors acknowledge Betina T. Blak, Sara E. Dempster, Markus F. Scheerer, Karolina Andersson-Sundell, Kelly Bell, Eric T. Wittbrodt, Luis Alberto García Rodríguez, Lucia Cea Soriano, Oscar Fernández Cantero, Ellen Riehle, Brian Murphy, Esther Bollow, Hanne Lavdal Gulseth, Bendix Carstensen, Fengming Tang, Kevin Kennedy, and Sheryl L Windsor for their tireless contribution to the country-level analyses, quality check validation, and results interpretation. Data validation was independently conducted by MAHI, an external academic institution. All authors had access to the full data package and are responsible for data interpretation and conclusions. Additional details on databases and sensitivity analyses are provided in the online-only Data Supplement. Editorial support was provided by Róisín O’Connor and Mark Davies, inScience Communications, Springer Healthcare, and funded by AstraZeneca.

SOURCES OF FUNDING
This work was supported by AstraZeneca.

DISCLOSURES
Dr Kosiborod has served advisory boards for AstraZeneca, Boehringer Ingelheim, Sanofi, Glytec, Novo Nordisk, ZS Pharma, GSK, Amgen, Eisai and Merck (Diabetes); is a consultant for AstraZeneca, Sanofi, and ZS Pharma; and received research grants from AstraZeneca and Boehringer Ingelheim. Dr Cavender received personal fees from Merck and AstraZeneca. Dr Fu received grants from AstraZeneca and Merck; and personal fees from Asclepius Analytics and Complete HEOR Services. Dr Wilding received lecture fees from Astellas, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, Orexigen, Sanofi; and consultancy (Institutional) from AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Orexigen; and grants to institution from Takeda, Novo Nordisk and AstraZeneca. Dr Khunti serves as consultant and speaker for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen and Boehringer Ingelheim; and received grants in support of investigator and investigator initiated trials from AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, Merck Sharp & Dohme and Roche; and served on advisory boards for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen, and Boehringer Ingelheim. Dr Holl received grants from AstraZeneca. Dr Norhammar received personal fees from AstraZeneca for this study; and honoraria for lectures and advisory board meetings for Novo Nordisk, Boehringer Ingelheim, and Lilly. Dr Birkeland received grants to his institution from AstraZeneca for this study. Dr Jørgensen is a shareholder of Novo Nordisk, was employed by Steno Diabetes Center A/S until December 31, 2016, a research hospital working in the Danish National Health Service and owned by Novo Nordisk A/S; received grants from AstraZeneca and for lectures and consulting from Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, and Merck Sharp & Dohme. Dr Thuresson is an employee of Statiscicon who were under contract to AstraZeneca for this study. N. Arya and Drs Bodegard, Hammar, and Fenici are employees of AstraZeneca.

AFFILIATIONS
From Saint Luke’s Mid America Heart Institute and University of Missouri–Kansas City (M.K.); University of North Carolina, Chapel Hill (M.A.C.); Georgetown University Medical Center, Washington, DC (A.Z.F.); University of Liverpool, United Kingdom (J.B.); University of Leeds, United Kingdom (K.I.B.); University of Ulm, Germany (R.W.H.); Karolinska Institutet, Stockholm, Sweden (A.N., N.H.); University of Oslo, Norway (K.I.B.); Oslo University Hospital, Norway (K.I.B.); Steno Diabetes Center, Copenhagen, Gentofte, Denmark (M.E.J.); National Institute of Public Health, Southern Denmark University, Copenhagen (M.E.J.); Statiscicon AB, Uppsala, Sweden (M.T.); AstraZeneca, Gaithersburg, MD (N.A.); AstraZeneca, Oslo, Norway (J.B.); AstraZeneca Gothenburg, Sweden (N.H.); and AstraZeneca, Cambridge, United Kingdom (P.F.).

FOOTNOTES
Received April 28, 2017; accepted May 11, 2017.

REFERENCES
1. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio F, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215–2222. doi: 10.1016/S0140-6736(10)60484-9.
2. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, Narula J, Shor ES, Young JB, Hong Y; American Heart Association CVD-REAL Study
Kosiborod et al

Council on Epidemiology and Prevention; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; Functional Genomics and Translational Biology Interdisciplinary Working Group. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation. 2008;117:2544–2565. doi: 10.1161/CIRCULATIONAHA.107.188965.

3. Di Angelantonio E, Kaptoge S, Wormser D, Willie P, Butterworth AS, Bansal N, O’Keeffe LM, Gao P, Wood AM, Burgess S, Freitag DF, Pennelli L, Peters SA, Hart CL, Håheim LL, Gilmore R, Nordrehaug JG, Pauly BM, Yeap BB, Knuman MW, Nietert PJ, Kauhanen J, Salonen JT, Kallikouri V, Simonis LA, van der Schouw YT, Barrett-Conner E, Selmer R, Crespo CJ, Rodríguez B, Verschuren WM, Salomaa V, Sävståkku D, van der Harst P, Björkeldt C, Wilhelmsen L, Wallace RB, Brenner H, Aumoluy P, Barr EL, Iso H, Onat A, Trevisan M, D’Agostino RB Sr, Cooper C, Kovács M, Velini L, Roussel R, Hu FB, Satô S, Davidson KW, Howard BV, Lehtimäki T, Meisingseth L, Raitakari OT, Nuutinen J, Pyörälä K, Scherjon SA, Harder FM, Proust-A, Meade TW, Casiglia E, Lavor DA, Gallacher J, Nagel D, Franco OH, Assmann G, Dagenais GR, Jukema JW, Sundström J, Woodward MR, Brunner EJ, Khaw KT, Wareham NJ, Whitelaw WA, Njølstad I, Thompson SG, Danesh J; Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality. JAMA. 2015;314:52–60. doi: 10.1001/jama.2015.7008.

4. Kannell WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974;34:29–34.

5. IDF Diabetes Atlas Group. Update of mortality attributable to diabetes for the IDF diabetes atlas: estimates for the year 2011. Diabetes Res Clin Pract. 2013;100:277–279. doi:10.1016/j.diabres.2013.02.005.

6. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387:1513–1530. doi:10.1016/S0140-6736(16)00168-8.

7. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, Wedel H, Clemmets M, Dahlqvist S, Lind M. Excess mortality among persons with type 2 diabetes. N Engl J Med. 2015;373:1720–1732. doi:10.1056/NEJMoa1405341.

8. Cauberghe NM, Rensma SC Jr, Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL. REGISTRY Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherosclerosis for Continued Health (REACH) Registry. Circulation. 2015;132:923–931. doi: 10.1161/CIRCULATIONAHA.114.014796.

9. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen KT, Smith SC Jr, Engel SS, Garg J, Josse R, Kaufman KD, Pencina MJ, Korn S, Lachin JM, McGuire DK, Pencina MJ, Schneeweiss S, Smith SC Jr, Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL. REGISTRY Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherosclerosis for Continued Health (REACH) Registry. Circulation. 2015;132:923–931. doi: 10.1161/CIRCULATIONAHA.114.014796.

10. Wannamethee GR, Shaper AG, Walker M, Whincup PH, Hemingway H, O’Meara ES, Wannamethee SG. The association between cardiovascular disease and type 2 diabetes mellitus on hospitalization for heart failure, cardiovascular events, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128. doi: 10.1056/NEJMoa1405174.

11. Håheim LL, Helgeland J. Agreement between referral information and discharge diagnoses according to Norwegian elective treatment guidelines - a cross-sectional study. BMC Health Serv Res. 2014;14:493. doi: 10.1186/1472-6963-14-493.

12. Rudvoldseng J, Andersson E, Ekbom A, Mahaffey KW, Fulcher G, Gørdh C, Wang S, Lind M, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL. REGISTRY Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherosclerosis for Continued Health (REACH) Registry. Circulation. 2015;132:923–931. doi: 10.1161/CIRCULATIONAHA.114.014796.

13. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen KT, Woerle HJ, Broedel UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128. doi: 10.1056/NEJMoa1405174.
33. European Commission. Directorate-General for Health and Food Safety. STAMP Commission Expert Group. Real world evidence. Brussels, Belgium: European Commission; March 10, 2016. http://ec.europa.eu/health/sites/health/files/committee/stamp/2016-03_stamp44_real_world_evidence_background_paper.pdf. Accessed May 12, 2017.

34. Calif RM, Robb MA, Bindman AB, Briggs JP, Collins FS, Conway PH, Coster TS, Cunningham FE, De Lew N, DeSalvo KB, Dynek C, Dziurawiec VL, Fleurence RL, Frank RG, Gaziano JM, Kaufmann P, Lauer M, Marks PW, McGinnis JM, Richards C, Selby JV, Shulkin DJ, Shuren J, Slavitt AM, Smith SR, Washington BV, White PJ, Woodcock J, Woodson J, Sherman RE. Transforming evidence generation to support health and healthcare decisions. N Engl J Med. 2016;375:2395–2400. doi: 10.1056/NEJMsb1610128.

35. Nyström T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Novel oral glucose-lowering drugs compared to insulin are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycemia in type 2 diabetes patients [published online ahead of print January 24, 2017]. Diabetes Obes Metab. doi:10.1111/dom.12889.

36. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–1326. doi: 10.1056/NEJMoa1307684.

37. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation. 2016;134:752–772. doi: 10.1161/CIRCULATIONAHA.116.021887.

38. Marx N, McGuire DK. Sodium-glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. Eur Heart J. 2016;37:3192–3200. doi: 10.1093/eurheartj/hew110.

39. Sattar N, McLaren J, Kristensen SL, Preiss D, McMurray JJ. SGLT2 Inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? Diabetologia. 2016;59:1333–1339. doi: 10.1007/s00125-016-3956-x.
Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

Mikhail Kosiborod, Matthew A. Cavender, Alex Z. Fu, John P. Wilding, Kamlesh Khunti, Reinhard W. Holl, Anna Norhammar, Kåre I. Birkeland, Marit Eika Jørgensen, Marcus Thuresson, Niki Arya, Johan Bodegård, Niklas Hammar and Peter Fenici on behalf of the CVD-REAL Investigators and Study Group*

_Circulation_. 2017;136:249-259; originally published online May 18, 2017; doi: 10.1161/CIRCULATIONAHA.117.029190

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/136/3/249
Free via Open Access

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2017/05/16/CIRCULATIONAHA.117.029190.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
Table of Contents

CVD-REAL Investigator and Study Group ........................................................................... 4
Characteristics of the databases ......................................................................................... 5
Statistical power calculations ............................................................................................. 8
SUPPLEMENTARY TABLES

Table S1. ICD and Read codes for Type 2 diabetes, Type 1 diabetes and gestational diabetes .......................................................... 9
Table S2. Read codes for history of cardiovascular events ............................................... 17
Table S3. Comparison of post-propensity match baseline characteristics between the US Truven MarketScan mortality subset and US Truven MarketScan total population ................................................................. 36
Table S4. List of variables used to develop propensity score ........................................... 38
Table S5. Baseline characteristics for all countries/databases pre-match .......................... 40
Table S6. Baseline characteristics for all countries/databases post-match ......................... 42
Table S7: Standardized differences in baseline characteristics between SGLT-2 inhibitor and other GLD treatment groups pre- and post-propensity match by country .................................................. 44
Table S8. Composition of SGLT-2 inhibitor class in propensity matched cohorts ............... 48
Table S9. Index glucose-lowering medication classes for patients in the other GLD group: all countries combined (HHF analysis) .................................................................................................. 49
Table S10. Index glucose-lowering medication classes for patients in the other GLD group: all countries combined (all-cause death analysis and HHF or all-cause death analysis) .................................................. 50
Table S11: Number of patients, person-years at risk (on treatment), events and events/100 person-years (incidence rates) for each of the endpoints .......................................................... 51
Table S12. Pooled event rates by treatment groups ............................................................ 52
Table S13. Mean follow-up time (in days) by country and endpoint ................................. 53
Table S14. Sensitivity analyses examining association between treatment with SGLT-2i vs. oGLD and outcomes of HHF in Sweden, among patients with both in- and outpatient hospital visits with primary diagnosis of heart failure, and those with only inpatient hospital visits with the primary diagnosis of heart failure ............................................................................. 54

SUPPLEMENTARY FIGURES

Figure S1: Patient selection flow-charts for each country .............................................. 55
  A. US Truven MarketScan
B. Norway National Registers  
C. Denmark National Registers  
D. Sweden National Registers  
E. UK CPRD/THIN  
F. Germany  

Figure S2: Propensity score distribution by country pre-match  
A. US Truven MarketScan  
B. Norway National Registers  
C. Denmark National Registers  
D. Sweden National Registers  
E. UK CPRD/THIN  
F. Germany  

Figure S3: Propensity score distribution by country post-match  
A. US Truven MarketScan  
B. Norway National Registers  
C. Denmark National Registers  
D. Sweden National Registers  
E. UK CPRD/THIN  
F. Germany  

Figure S4: Standardized differences between SGLT-2 inhibitor and other GLD treatment groups by country  
A. US Truven MarketScan  
B. Norway National Registers  
C. Denmark National Registers  
D. Sweden National Registers  
E. UK CPRD/THIN  
F. Germany  

Figure S5: Stepwise sensitivity analysis (sequentially removing comparators):  
Outcome of hospitalization for heart failure  
A. TZD removed  
B. TZD and insulin removed  
C. TZD, insulin and SU removed  

Figure S6: Outcome of hospitalization for heart failure excluding patients with baseline GLP-1 RAs  

Figure S7: Outcomes of hospitalization for heart failure, all-cause death, and hospitalization for heart failure or all-cause for the SGLT-2 inhibitor versus other GLD treatment groups:  
A. US only  
B. European countries combined  

References for the supplementary appendices
CVD-REAL Investigator and Study Group

Executive Scientific Committee (Academic Members and Investigators):
Mikhail Kosiborod, MD, Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, MO, United States; Matthew A. Cavender, MD MPH, University of North Carolina, Chapel Hill, NC, United States; Alex Z. Fu, PhD, Georgetown University Medical Center, Washington DC, United States; John P. Wilding MD, PhD, University of Liverpool, Liverpool, United Kingdom; Kamlesh Khunti, MD PhD, University of Leicester, Leicester, United Kingdom; Anna Norhammar, MD, Cardiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; Kåre Birkeland, MD PhD, Department of Endocrinology, University of Oslo, Norway; Marit Eika Jørgensen, MD PhD, cand.med, Steno Diabetes Center, Gentofte, Denmark; Reinhard W. Holl MD PhD, Institute of Epidemiology, University of Ulm, Ulm, Germany;

Executive Scientific Committee (AstraZeneca Members):
Niklas Hammar, PhD, Senior Director Epidemiology, AZ Gothenburg, Sweden and Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Study Principal Investigator); Peter Fenici, MD, PhD, Global Medical Affairs Senior Leader, AZ, Academy House, Cambridge, United Kingdom (Study Leader); Niki Arya, MSc, Principal Statistician, Biometrics and Information Sciences, AZ Gaithersburg, MD, United States (Study Statistician); Kyle Nahrebne, MSc, Global Publication Leader, AZ Gaithersburg, MD, United States (Study Publication Leader);

All Members of the Executive Steering Committee have contributed to data interpretation and approved this manuscripts analyses and conclusions. Executive Scientific Committee Academic Members MK, MAC AZF, JPW, KK, AN have also reviewed and input the study protocol and amendment, together with the Executive Scientific Committee AZ Members NH, PF, NA, KN and with the Study Core Team Members, KAS, JB, BTB, SED, KB, MFS. Study meta analyses have been conducted by Niki Arya (AstraZeneca) and Marcus Thuresson (Statisticon).

Study Core Team (AstraZeneca Members):
Karolina Andersson-Sundell, MSc PhD, Assoc. Dir. Epidemiology, MEOR, AZ Gothenburg, Sweden; Johan Bodegård, MD PhD, Medical Evidence Scientific Lead Nordics/Baltic, AZ Oslo, Norway; Betina T. Blak, MSc PhD RWE Scientific Leader, AZ Luton, United Kingdom; Sara E. Dempster, PhD Associate Principal Informatics Scientist, AZ Waltham, MA, United States; Kelly Bell PharmD, MSPhr, HEOR Director, AZ Wilmington, DE, United States; Eric T. Wittbrodt, PharmD, MPH, HEOR Director, AZ Wilmington, DE, United States; Markus F. Scheerer, MSc PhD, Scientific Advisor Diabetes, AZ Wedel, Germany

All Study Core Team Members have contributed to country level analyses and local coordination with databases analysts in their respective country. Study Core Team Members, KAS, JB, BTB, SED, KB, MFS have also reviewed and input the study protocol design and amendments.

External Investigators and Analysts:
Hanne Lovdal Gulseth, MD, PhD, Department of Endocrinology, Oslo University Hospital, Aker, Norway; Bendix Carstensen, PhD, Diabetes Center, Gentofte, Denmark; Marcus Thuresson, PhD Statistician (Study Statistician), Statisticon AB, Uppsala, Sweden; Esther Bollow, Institute of Epidemiology, University of Ulm, Ulm, Germany; Luis Alberto Garcia Rodriguez, MD, CEIFE - Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain; Lucía Cea Soriano, PharmD, PhD, CEIFE – Centro Español de Investigación Farmacoepidemiológica and Department of Preventive Medicine and Public Health, Faculty of Medicine, Complutense University of Madrid, Spain; Oscar Fernández Cantero, CEIFE – Centro Español de Investigación Farmacoepidemiológica; Ellen Riehle, MPH, Senior Research Analyst, Truven Health Analytics, an IBM Company, Ann Arbor, MI; Brian Murphy, MS, Senior Data Analyst, Evidera, Waltham, MA.

All other External Investigators and Analysts Members have contributed to country level data analyses, quality check and validation and results interpretation in their respective country.
Characteristics of the databases

Truven Health MarketScan® Commercial Claims and Encounters (Commercial) and Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) databases comprise enrolment information, demographic information and inpatient medical, outpatient medical and outpatient pharmacy claims data from over 300 large self-insured US employers and over 25 US health plans. These study databases satisfy the conditions set forth in Sections 164.514 (a)-(b)ii of the Health Insurance Portability and Accountability Act of 1996 privacy rule regarding the determination and documentation of statistically de-identified data. Thus, the study did not require external IRB or ethics review. The Truven MarketScan database has been used for comparative effectiveness research since 1989, with over 1100 peer-reviewed publications overall and is considered to be nationally representative in the US for the included patient populations. Truven MarketScan is highly representative of the US commercially insured population aged <65 years, without contributing any specific bias to create differences from the commercially insured population as a whole. Comparisons of age, gender, and region for Truven MarketScan with US Census data (2010) demonstrate close similarities between the two datasets (data on file).

Clinical Practice Research Datalink (CPRD) holds anonymized longitudinal primary care patient records collected from over 670 general practices across the UK, covering >11.3 million patients. It includes diagnoses, issued drug prescriptions, clinical measures taken within the general practice, lab tests and referrals to specialist care. Hospitalisation information and specialist care notes are generally recorded by the general practitioner into the primary care patient records. Of the UK practices included in CPRD, 58% are linked to the Hospital Episode Statistics (HES) dataset with detailed hospitalisation information (excluding drug use) on all hospitalisation episodes in England, and to death certificates from the Office of National Statistics (ONS) to derive estimates of all-cause and cause-specific death. CPRD includes approximately 6.9% of the UK population, and patients are broadly representative of the UK general population. Herrett et al. assesses the representativeness of CPRD by comparing the age and sex distribution within CPRD to the UK Census in 2011. They found that CPRD was broadly representative of the UK population with respect to age and sex. In addition, Herrett et al. published a literature review assessing the validation and validity of diagnoses in CPRD (formerly known as GPRD). They concluded that overall, estimates of validity were high. A detailed description of CPRD can be found in a paper by Williams et al. This generalizability of CPRD to the UK population has resulted in CPRD being used in over 1000 publications.

The Health Improvement Network (THIN) includes data from >580 UK practices, with similar data to CPRD. THIN coverage of the UK population by 2013 was 5.67% and the representativeness of THIN was described by Blak et al. by comparing the distribution of deprivation, morbidities (Quality and Outcomes Framework [QOF] conditions) and demographics to national statistics and national QOF 2006/2007 data. They demonstrated that THIN is representative of the UK population with respect to morbidities, demographics, and mortality rates. Furthermore, in THIN, it was found that between 1990 and 2009 the standardized mortality ratio ranged from 0.81 (95% CI: 0.39–1.49; 1990) to 0.93 (95% CI: 0.48–1.64; 1995). Adjusting for demographics/deprivation, the
2006 THIN death rate was 9.08/1000 population, which is consistent with the national death rate of 9.4/1000 population. When Blak et al. was originally published, THIN included 532 general practices. Currently there are approximately 600 general practices. A description of the development of THIN is described in Bourke et al. Lewis et al validated THIN by comparing drug-disease associations found in the original GPRD practices included in THIN, to drug-disease associations found in the new practices included in THIN. They concluded that: ‘THIN data that are collected outside of the GPRD appear as valid as the data collected as part of the GPRD’. Other validation studies of THIN are also available, and similar to CPRD, THIN has been used for numerous publications (~400 to date; http://www.epic-uk.org/our-data/statistics.shtml), some of which compare THIN data results to external measures, demonstrating similarities.

Some of the general practices providing data to CPRD are also providing data to THIN. Therefore, there is an overlap and a potential to combine the two databases in order to increase patient numbers. A recent study within diabetes has shown that 61% of CPRD patients are also included in THIN. This overlap in patients has been taken into account in the present study so that no individual is double counted. The duplicated practices list between CPRD and THIN was obtained by looking for coincidences of patients by practices between both databases. The parameters used for the match were sex, year of birth, family id, and date and Read code of diabetes. For the analyses all THIN practices were retained and the non-overlapping CPRD HES and ONS linked practices. In CPRD, HHF was identified in linked HES with International Statistical Classification of Diseases and Related Health Problems (ICD-system) 10 codes I50.x and all-cause death was identified in linked ONS death data. HHF and all-cause death was identified in the general practice medical records in THIN. For HHF, free text from THIN was collected within +365 days of event and reviewed to ascertain and validate the cause of hospitalisation and the event date. The reviewers were blinded to the index medication. Patients were selected from THIN and/or CPRD from November 2012 to September 2015 (THIN) and to January 2016 (CPRD). This study was approved by the Scientific Review Committee (SRC) of THIN; protocol approval number: 16THIN027A1. Further, the Independent Scientific Advisory Committee (ISAC) of CPRD approved it; protocol approval number: 16_064RAR.

The Diabetes-Patienten-Verlaufsdokumentation (DPV; or “Diabetes Prospective Follow-up”) initiative involves more than 400 clinical centres predominantly from Germany and Austria, documenting data pertaining to diabetes. Similar to an electronic medical record, relevant data are documented only once and are available for numerous purposes: graphical and tabular description, medical report, treatment plan, diabetes passport, reminder on upcoming visits (watchdog), certification of centers and type 2 diabetes program (DMP) documentation. Every 6 months, anonymized data are sent to the University of Ulm, Germany. Analyses are conducted separately for pediatric and adult patients either anonymised or centre-based after prior written informed consent for regional quality circles. Data of the anonymised DPV registry are used for treatment research in order to investigate practice-oriented questions. A publication list can be found on the website under ‘publications’ (www.d-p-v.eu). Data from this registry have been used extensively in multi-center outcomes.
research, with 452 centers participating. The DPV-initiative is the multicenter benchmark database for patients with diabetes in Germany, includes all levels of diabetes care for the German population of patients with T2D, and has been used in over 370 peer-reviewed publications. The DPV Type 2 diabetes population is consistent with that observed in the national German Health Interview and Examination Surveys when considering the inclusion and exclusion criteria of the CVD-REAL study. In addition, demographic characteristics of the DPV population are consistent with other large data collections of patients with diabetes from Germany, such as the DMP data from Northrhine (https://www.kvno.de/downloads/quali/qualbe_dmp14.pdf) or the DIVE registry (http://www.dive-register.de/).

The National Prescribed Drug Registers in Sweden, Norway and Denmark have full coverage of each country’s population. Patients were followed with regard to outcome in the National Patient Register and National Cause of Death Register. The Swedish national database includes information from linkage of three national Swedish registries held by the Swedish National Board of Health and Welfare, with full coverage of the Swedish population: 1) The Prescribed Drug Register July 1, 2005 to December 2016, covering all drug prescriptions filled using Anatomical Therapeutic Chemical codes; 2) The Cause of Death Register 1961–2015; 3) The National Patient Register covering all hospital admissions and discharge diagnoses in 1987–2015, discharge diagnoses, specialized care and open patient clinic visits in 2001–2015. Diagnoses are recorded according to the International Statistical Classification of Diseases and Related Health Problems (ICD) system. Similarly, the Norwegian national database includes type 2 diabetes patient information from three national Norwegian registries with full coverage of the Norwegian population: the Norwegian Prescription Database (July 2004 to July 2016) covering all filled drug prescriptions using ATC codes; the Norwegian Cause of Death Register (1958 to 2014); and the Norwegian Patient Register covering all hospital out-patient clinic visit and discharge diagnoses and all hospital discharge diagnoses for the years 2008 to July 2016. Diagnoses are recorded according to the ICD-system. Data linkage is performed by the Norwegian Institute of Public Health. The Danish national database also has a similar structure, and includes T2D patient information from three national Danish registries with full coverage of the Danish population: the Prescribed Drug Register (1990 to 2015) covering all filled drug prescriptions using ATC codes; the Cause of Death Register (1952– to 2014); and the National Patient Register covering all open patient clinic visit diagnoses for 2000 to 2015 and all hospital discharge diagnoses for the years 1980 to 2015, and discharge diagnoses and. Diagnoses are recorded according to the ICD-system. All three registers are held by the Statistics Denmark. Data from Statistics Denmark were made available following an application to Statistics Denmark. The Danish study was approved by the Danish Data Protection Agency (Datatilsynet, registration number 2015-41-4148).

Data were anonymised, and the requirement for informed consent was therefore waived according to standard analytical procedures with each database owner.
Statistical power calculations

For the primary outcome (HHF) a risk reduction of 20% for SGLT-2i versus oGLD was considered clinically meaningful. For 85% power to detect a risk reduction of 20% with a two-sided α-level of 0.05 and a 1:1 treatment allocation (SGLT-2i vs. oGLD), a total of 730 events across the matched treatment groups in all the datasets was required. As there were a total of 961 HHF events within the matched cohorts, we had sufficient power to perform the HHF analysis.

Analyses were conducted using R- version 3.2.325,26 in Sweden, Norway and Denmark, STATA version 12.0 (StataCorp LP, College Station, TX, US) in the UK, STATA version 12.0 (StataCorp LP, College Station, TX, US) and SAS version 9.4 (Cary, NC) in the US, and SAS version 9.4 (TS1M1) (Cary, NC, US) in Germany.
**SUPPLEMENTARY TABLES**

Table S1. ICD and Read codes for Type 2 diabetes, Type 1 diabetes and gestational diabetes

| Type 2 diabetes       |
|-----------------------|
| **ICD codes**         |
| ICD-9 250.X0, 250.X2  |
| ICD-10 codes E11 and 024.1 |
| **Read codes**        |
| 66A4.00               | Diabetic on oral treatment |
| 66Ao.00               | Diabetes type 2 review     |
| 66At100               | Type II diabetic dietary review |
| 66At111               | Type 2 diabetic dietary review |
| 66AV.00               | Diabetic on insulin and oral treatment |
| C100100               | Diabetes mellitus, adult onset, no mention of complication |
| C100111               | Maturity onset diabetes   |
| C100112               | Non-insulin dependent diabetes mellitus |
| C101100               | Diabetes mellitus, adult onset, with ketoacidosis |
| C102100               | Diabetes mellitus, adult onset, with hyperosmolar coma |
| C103100               | Diabetes mellitus, adult onset, with ketoacidotic coma |
| C104100               | Diabetes mellitus, adult onset, with renal manifestation |
| C105100               | Diabetes mellitus, adult onset, + ophthalmic manifestation |
| C106100               | Diabetes mellitus, adult onset, + neurological manifestation |
| C107100               | Diabetes mellitus, adult, + peripheral circulatory disorder |
| C107200               | Diabetes mellitus, adult with gangrene |
| C107400               | NIDDM with peripheral circulatory disorder |
| C109.00               | Non-insulin dependent diabetes mellitus |
| C109.11               | NIDDM - Non-insulin dependent diabetes mellitus |
| Code     | Description                                               |
|----------|-----------------------------------------------------------|
| C109.12  | Type 2 diabetes mellitus                                  |
| C109.13  | Type II diabetes mellitus                                 |
| C109000  | Non-insulin-dependent diabetes mellitus with renal comps  |
| C109011  | Type II diabetes mellitus with renal complications        |
| C109012  | Type 2 diabetes mellitus with renal complications         |
| C109100  | Non-insulin-dependent diabetes mellitus with ophthalmic comps |
| C109111  | Type II diabetes mellitus with ophthalmic complications   |
| C109112  | Type 2 diabetes mellitus with ophthalmic complications    |
| C109200  | Non-insulin-dependent diabetes mellitus with neuro comps  |
| C109211  | Type II diabetes mellitus with neurological complications |
| C109212  | Type 2 diabetes mellitus with neurological complications  |
| C109300  | Non-insulin-dependent diabetes mellitus with multiple comps |
| C109400  | Non-insulin dependent diabetes mellitus with ulcer        |
| C109411  | Type II diabetes mellitus with ulcer                      |
| C109412  | Type 2 diabetes mellitus with ulcer                       |
| C109500  | Non-insulin dependent diabetes mellitus with gangrene     |
| C109511  | Type II diabetes mellitus with gangrene                   |
| C109512  | Type 2 diabetes mellitus with gangrene                    |
| C109600  | Non-insulin-dependent diabetes mellitus with retinopathy  |
| C109611  | Type II diabetes mellitus with retinopathy                |
| C109612  | Type 2 diabetes mellitus with retinopathy                 |
| C109700  | Non-insulin dependent diabetes mellitus - poor control    |
| C109711  | Type II diabetes mellitus - poor control                  |
| C109712  | Type 2 diabetes mellitus - poor control                   |
| C109900  | Non-insulin-dependent diabetes mellitus without complication |
| C109A00  | Non-insulin dependent diabetes mellitus with mononeuropathy |
| C109A11  | Type II diabetes mellitus with mononeuropathy              |
| Code     | Description                                                                 |
|----------|-----------------------------------------------------------------------------|
| C109B00  | Non-insulin dependent diabetes mellitus with polyneuropathy                |
| C109B11  | Type II diabetes mellitus with polyneuropathy                              |
| C109C00  | Non-insulin dependent diabetes mellitus with nephropathy                   |
| C109C11  | Type II diabetes mellitus with nephropathy                                 |
| C109C12  | Type 2 diabetes mellitus with nephropathy                                   |
| C109D00  | Non-insulin dependent diabetes mellitus with hypoglycaemic coma             |
| C109D11  | Type II diabetes mellitus with hypoglycaemic coma                           |
| C109D12  | Type 2 diabetes mellitus with hypoglycaemic coma                            |
| C109E00  | Non-insulin dependent diabetes mellitus with diabetic cataract              |
| C109E11  | Type II diabetes mellitus with diabetic cataract                             |
| C109E12  | Type 2 diabetes mellitus with diabetic cataract                              |
| C109F00  | Non-insulin-dependent diabetes mellitus with peripheral angiopathy          |
| C109F11  | Type II diabetes mellitus with peripheral angiopathy                        |
| C109F12  | Type 2 diabetes mellitus with peripheral angiopathy                         |
| C109G00  | Non-insulin dependent diabetes mellitus with arthropathy                    |
| C109G11  | Type II diabetes mellitus with arthropathy                                  |
| C109G12  | Type 2 diabetes mellitus with arthropathy                                   |
| C109H00  | Non-insulin dependent diabetes mellitus with neuropathic arthropathy        |
| C109H11  | Type II diabetes mellitus with neuropathic arthropathy                      |
| C109H12  | Type 2 diabetes mellitus with neuropathic arthropathy                       |
| C109J00  | Insulin treated Type 2 diabetes mellitus                                   |
| C109J11  | Insulin treated non-insulin dependent diabetes mellitus                     |
| C109J12  | Insulin treated Type II diabetes mellitus                                  |
| C109K00  | Hyperosmolar non-ketotic state in type 2 diabetes mellitus                  |
| C10C.11  | Maturity onset diabetes in youth                                            |
| C10D.00  | Diabetes mellitus autosomal dominant type 2                                 |
| C10D.11  | Maturity onset diabetes in youth type 2                                     |
| Code   | Description                                      |
|--------|--------------------------------------------------|
| C10F.00 | Type 2 diabetes mellitus                         |
| C10F.11 | Type II diabetes mellitus                        |
| C10F000 | Type 2 diabetes mellitus with renal complications |
| C10F011 | Type II diabetes mellitus with renal complications |
| C10F100 | Type 2 diabetes mellitus with ophthalmic complications |
| C10F111 | Type II diabetes mellitus with ophthalmic complications |
| C10F200 | Type 2 diabetes mellitus with neurological complications |
| C10F211 | Type II diabetes mellitus with neurological complications |
| C10F300 | Type 2 diabetes mellitus with multiple complications |
| C10F311 | Type II diabetes mellitus with multiple complications |
| C10F400 | Type 2 diabetes mellitus with ulcer              |
| C10F411 | Type II diabetes mellitus with ulcer              |
| C10F500 | Type 2 diabetes mellitus with gangrene           |
| C10F511 | Type II diabetes mellitus with gangrene           |
| C10F600 | Type 2 diabetes mellitus with retinopathy        |
| C10F611 | Type II diabetes mellitus with retinopathy        |
| C10F700 | Type 2 diabetes mellitus - poor control          |
| C10F711 | Type II diabetes mellitus - poor control          |
| C10F900 | Type 2 diabetes mellitus without complication     |
| C10F911 | Type II diabetes mellitus without complication     |
| C10FA00 | Type 2 diabetes mellitus with mononeuropathy      |
| C10FA11 | Type II diabetes mellitus with mononeuropathy      |
| C10FB00 | Type 2 diabetes mellitus with polyneuropathy      |
| C10FB11 | Type II diabetes mellitus with polyneuropathy      |
| C10FC00 | Type 2 diabetes mellitus with nephropathy         |
| C10FC11 | Type II diabetes mellitus with nephropathy         |
| C10FD00 | Type 2 diabetes mellitus with hypoglycaemic coma   |
| ICD Code | Description |
|----------|-------------|
| C10FD11 | Type II diabetes mellitus with hypoglycaemic coma |
| C10FE00 | Type 2 diabetes mellitus with diabetic cataract |
| C10FE11 | Type II diabetes mellitus with diabetic cataract |
| C10FF00 | Type 2 diabetes mellitus with peripheral angiopathy |
| C10FF11 | Type II diabetes mellitus with peripheral angiopathy |
| C10FG00 | Type 2 diabetes mellitus with arthropathy |
| C10FG11 | Type II diabetes mellitus with arthropathy |
| C10FH00 | Type 2 diabetes mellitus with neuropathic arthropathy |
| C10FJ00 | Insulin treated Type 2 diabetes mellitus |
| C10FJ11 | Insulin treated Type II diabetes mellitus |
| C10FK00 | Hyperosmolar non-ketotic state in type 2 diabetes mellitus |
| C10FL00 | Type 2 diabetes mellitus with persistent proteinuria |
| C10FL11 | Type II diabetes mellitus with persistent proteinuria |
| C10FM00 | Type 2 diabetes mellitus with persistent microalbuminuria |
| C10FM11 | Type II diabetes mellitus with persistent microalbuminuria |
| C10FN00 | Type 2 diabetes mellitus with ketoacidosis |
| C10FP00 | Type 2 diabetes mellitus with ketoacidotic coma |
| C10FQ00 | Type 2 diabetes mellitus with exudative maculopathy |
| C10FR00 | Type 2 diabetes mellitus with gastroparesis |
| C10K.00 | Type A insulin resistance |
| C10K000 | Type A insulin resistance without complication |
| C10z100 | Diabetes mellitus, adult onset, + unspecified complication |
| L180600 | Pre-existing diabetes mellitus, non-insulin-dependent |

**Type 1 diabetes**

**ICD codes**

ICD-9 codes 250.x1, 250.X3

ICD-10 codes E10 and O24
| Read codes       | Description                                         |
|------------------|-----------------------------------------------------|
| 66An.00          | Diabetes type 1 review                              |
| C108D11          | Type I diabetes mellitus with nephropathy           |
| 66An.00          | Diabetes type 1 review                              |
| 66A000           | Type I diabetic dietary review                      |
| 66A011           | Type 1 diabetic dietary review                      |
| C100011          | Insulin dependent diabetes mellitus                 |
| C101000          | Diabetes mellitus, juvenile type, with ketoacidosis  |
| C102000          | Diabetes mellitus, juvenile type, with hyperosmolar coma|
| C103000          | Diabetes mellitus, juvenile type, with ketoacidotic coma|
| C104000          | Diabetes mellitus, juvenile type, with renal manifestation|
| C105000          | Diabetes mellitus, juvenile type, + ophthalmic manifestation|
| C106000          | Diabetes mellitus, juvenile, + neurological manifestation|
| C107000          | Diabetes mellitus, juvenile + peripheral circulatory disorder|
| C107300          | IDDM with peripheral circulatory disorder           |
| C108.00          | Insulin dependent diabetes mellitus                 |
| C108.11          | IDDM-Insulin dependent diabetes mellitus            |
| C108.12          | Type 1 diabetes mellitus                            |
| C108.13          | Type I diabetes mellitus                            |
| C108000          | Insulin-dependent diabetes mellitus with renal complications |
| C108011          | Type I diabetes mellitus with renal complications    |
| C108012          | Type 1 diabetes mellitus with renal complications    |
| C108100          | Insulin-dependent diabetes mellitus with ophthalmic comps |
| C108112          | Type 1 diabetes mellitus with ophthalmic complications |
| C108200          | Insulin-dependent diabetes mellitus with neurological comps |
| C108211          | Type I diabetes mellitus with neurological complications |
| C108212          | Type 1 diabetes mellitus with neurological complications |
| Code     | Condition                                      |
|----------|------------------------------------------------|
| C108300  | Insulin dependent diabetes mellitus with multiple complications |
| C108400  | Unstable insulin dependent diabetes mellitus |
| C108411  | Unstable type I diabetes mellitus             |
| C108412  | Unstable type 1 diabetes mellitus             |
| C108500  | Insulin dependent diabetes mellitus with ulcer|
| C108511  | Type I diabetes mellitus with ulcer           |
| C108512  | Type 1 diabetes mellitus with ulcer           |
| C108600  | Insulin dependent diabetes mellitus with gangrene |
| C108700  | Insulin dependent diabetes mellitus with retinopathy |
| C108711  | Type I diabetes mellitus with retinopathy     |
| C108712  | Type 1 diabetes mellitus with retinopathy     |
| C108800  | Insulin dependent diabetes mellitus - poor control |
| C108811  | Type I diabetes mellitus - poor control       |
| C108812  | Type 1 diabetes mellitus - poor control       |
| C108900  | Insulin dependent diabetes maturity onset     |
| C108911  | Type I diabetes mellitus maturity onset       |
| C108912  | Type 1 diabetes mellitus maturity onset       |
| C108A00  | Insulin-dependent diabetes without complication|
| C108A11  | Type I diabetes mellitus without complication |
| C108B00  | Insulin dependent diabetes mellitus with mononeuropathy |
| C108B11  | Type I diabetes mellitus with mononeuropathy  |
| C108C00  | Insulin dependent diabetes mellitus with polyneuropathy |
| C108D00  | Insulin dependent diabetes mellitus with nephropathy |
| C108D11  | Type I diabetes mellitus with nephropathy     |
| C108E00  | Insulin dependent diabetes mellitus with hypoglycaemic coma |
| C108E11  | Type I diabetes mellitus with hypoglycaemic coma |
| C108E12  | Type 1 diabetes mellitus with hypoglycaemic coma |
| Code     | Description                                               |
|----------|-----------------------------------------------------------|
| C108F00  | Insulin dependent diabetes mellitus with diabetic cataract|
| C108F11  | Type 1 diabetes mellitus with diabetic cataract           |
| C108G00  | Insulin dependent diabetes mellitus with peripheral angiopathy|
| C108H00  | Insulin dependent diabetes mellitus with arthropathy      |
| C108H11  | Type 1 diabetes mellitus with arthropathy                 |
| C108J00  | Insulin dependent diabetes mellitus with neuropathic arthropathy|
| C108J11  | Type 1 diabetes mellitus with neuropathic arthropathy     |
| C108J12  | Type 1 diabetes mellitus with neuropathic arthropathy     |
| C10C.12  | Maturity onset diabetes in youth type 1                   |
| C10E.00  | Type 1 diabetes mellitus                                  |
| C10E.11  | Type 1 diabetes mellitus                                  |
| C10E.12  | Insulin dependent diabetes mellitus                        |
| C10E000  | Type 1 diabetes mellitus with renal complications          |
| C10E012  | Insulin-dependent diabetes mellitus with renal complications|
| C10E100  | Type 1 diabetes mellitus with ophthalmic complications     |
| C10E111  | Type 1 diabetes mellitus with ophthalmic complications     |
| C10E112  | Insulin-dependent diabetes mellitus with ophthalmic comp. |
| C10E200  | Type 1 diabetes mellitus with neurological complications   |
| C10E212  | Insulin-dependent diabetes mellitus with neurological comp.|
| C10E300  | Type 1 diabetes mellitus with multiple complications       |
| C10E311  | Type 1 diabetes mellitus with multiple complications       |
| C10E312  | Insulin dependent diabetes mellitus with multiple comp.   |
| C10E400  | Unstable type 1 diabetes mellitus                          |
| C10E411  | Unstable type 1 diabetes mellitus                          |
| C10E412  | Unstable insulin dependent diabetes mellitus               |
| C10E500  | Type 1 diabetes mellitus with ulcer                        |
| C10E511  | Type 1 diabetes mellitus with ulcer                        |
| Code | Description                                      |
|------|--------------------------------------------------|
| C10E512 | Insulin dependent diabetes mellitus with ulcer  |
| C10E600 | Type 1 diabetes mellitus with gangrene          |
| C10E611 | Type I diabetes mellitus with gangrene          |
| C10E700 | Type 1 diabetes mellitus with retinopathy       |
| C10E711 | Type I diabetes mellitus with retinopathy       |
| C10E712 | Insulin dependent diabetes mellitus with retinopathy |
| C10E800 | Type 1 diabetes mellitus - poor control         |
| C10E812 | Insulin dependent diabetes mellitus - poor control |
| C10E900 | Type 1 diabetes mellitus maturity onset         |
| C10E911 | Type I diabetes mellitus maturity onset         |
| C10E912 | Insulin dependent diabetes maturity onset       |
| C10EA00 | Type 1 diabetes mellitus without complication   |
| C10EA11 | Type I diabetes mellitus without complication   |
| C10EA12 | Insulin-dependent diabetes without complication |
| C10EB00 | Type 1 diabetes mellitus with mononeuropathy    |
| C10EC00 | Type 1 diabetes mellitus with polyneuropathy    |
| C10EC11 | Type I diabetes mellitus with polyneuropathy    |
| C10EC12 | Insulin dependent diabetes mellitus with polyneuropathy |
| C10ED00 | Type 1 diabetes mellitus with nephropathy       |
| C10ED12 | Insulin dependent diabetes mellitus with nephropathy |
| C10EE00 | Type 1 diabetes mellitus with hypoglycaemic coma|
| C10EE12 | Insulin dependent diabetes mellitus with hypoglycaemic coma |
| C10EF00 | Type 1 diabetes mellitus with diabetic cataract |
| C10EF12 | Insulin dependent diabetes mellitus with diabetic cataract |
| C10EG00 | Type 1 diabetes mellitus with peripheral angiopathy |
| C10EH00 | Type 1 diabetes mellitus with arthropathy       |
| C10EJ00 | Type 1 diabetes mellitus with neuropathic arthropathy |
| Code    | Description                                      |
|---------|--------------------------------------------------|
| C10EK00 | Type 1 diabetes mellitus with persistent proteinuria |
| C10EL00 | Type 1 diabetes mellitus with persistent microalbuminuria |
| C10EL11 | Type I diabetes mellitus with persistent microalbuminuria |
| C10EM00 | Type 1 diabetes mellitus with ketoacidosis |
| C10EM11 | Type I diabetes mellitus with ketoacidosis |
| C10EN00 | Type 1 diabetes mellitus with ketoacidotic coma |
| C10EN11 | Type I diabetes mellitus with ketoacidotic coma |
| C10EP00 | Type 1 diabetes mellitus with exudative maculopathy |
| C10EP11 | Type I diabetes mellitus with exudative maculopathy |
| C10EQ00 | Type 1 diabetes mellitus with gastroparesis |
| C10z000 | Diabetes mellitus, juvenile type, + unspecified complication |
| L180500 | Pre-existing diabetes mellitus, insulin-dependent |
| 8Hj3.00 | Referral to DAFNE diabetes structured education programme |
| 8Hj4.00 | Referral to DESMOND diabetes structured education programme |
| 8Hj5.00 | Referral to XPERT diabetes structured education programme |
| 8I82.00 | Did not complete DAFNE diabetes structured education program |
| 8I83.00 | Did not complete DESMOND diabetes structured education program |
| 8I84.00 | Did not complete XPERT diabetes structured education program |
| 9NiC.00 | Did not attend DAFNE diabetes structured education programme |
| 9NiD.00 | Did not attend DESMOND diabetes structured education program |
| 9NiE.00 | Did not attend XPERT diabetes structured education programme |
| 9OLG.00 | Attended XPERT diabetes structured education programme |
| 9OLH.00 | Attended DAFNE diabetes structured education programme |
| 9OLJ.00 | DAFNE diabetes structured education programme completed |
| 9OLK.00 | DESMOND diabetes structured education programme completed |
| 9OLL.00 | XPERT diabetes structured education programme completed |

**Gestational Diabetes**
### ICD codes

**ICD-9 codes**

- 648.8

**ICD-10:O24.4**

### Read codes

| Code   | Description                                                                 |
|--------|-----------------------------------------------------------------------------|
| ZC2CB00 | Dietary advice for gestational diabetes                                      |
| ZV13F00 | [V]Personal history of gestational diabetes mellitus                         |
| L180900 | Gestational diabetes mellitus                                                |
| L180811 | Gestational diabetes mellitus                                                |
| 6CE0000 | Gestational diabetes information leaflet given                               |
| 66Ay.00 | Gestational diabetes mellitus annual review                                  |
| 6CE0000 | Gestational diabetes information leaflet given                               |
| Q44B.00 | Syndrome of infant of mother with gestational diabetes                        |
| 66AX.00 | Diabetes: shared care in pregnancy - diabetol and obstet                     |
| 6761.00 | Diabetic pre-pregnancy counselling                                           |
| L180.00 | Diabetes mellitus during pregnancy/childbirth/puerperium                     |
| L180000 | Diabetes mellitus - unspec whether in pregnancy/puerperium                   |
| L180100 | Diabetes mellitus during pregnancy - baby delivered                          |
| L180300 | Diabetes mellitus during pregnancy - baby not yet delivered                   |
| L180800 | Diabetes mellitus arising in pregnancy                                       |
| L180z00 | Diabetes mellitus in pregnancy/childbirth/puerperium NOS                    |
| Code   | Description                                            |
|--------|--------------------------------------------------------|
| G30..00| Acute myocardial infarction                           |
| G30..13| Cardiac rupture following myocardial infarction (MI)  |
| G300.00| Acute anterolateral infarction                        |
| G301.00| Other specified anterior myocardial infarction         |
| G301000| Acute anteroapical infarction                         |
| G30..11| Attack - heart                                        |
| G30..14| Heart attack                                           |
| G30..15| MI - acute myocardial infarction                      |
| G301100| Acute anterosetal infarction                          |
| G301z00| Anterior myocardial infarction NOS                    |
| G302.00| Acute inferolateral infarction                        |
| G303.00| Acute inferoposterior infarction                      |
| G304.00| Posterior myocardial infarction NOS                   |
| G305.00| Lateral myocardial infarction NOS                     |
| G306.00| True posterior myocardial infarction                  |
| G307.00| Acute subendocardial infarction                       |
| G307000| Acute non-Q wave infarction                           |
| G308.00| Inferior myocardial infarction NOS                    |
| G309.00| Acute Q-wave infarct                                  |
| G30B.00| Acute posterolateral myocardial infarction            |
| G30X.00| Acute transmural myocardial infarction of unspecif site|
| G30X000| Acute ST segment elevation myocardial infarction      |
| G30y.00| Other acute myocardial infarction                     |
| G30y000| Acute atrial infarction                               |
| G30y100| Acute papillary muscle infarction                     |
| G30y200| Acute septal infarction                               |
| G30yz00| Other acute myocardial infarction NOS                 |
| G30z.00| Acute myocardial infarction NOS                       |
| G31..00| Other acute and subacute ischaemic heart disease      |
| G311500| Acute coronary syndrome                               |
| G310.00| Postmyocardial infarction syndrome                    |
| Code   | Description                                                                 |
|--------|------------------------------------------------------------------------------|
| G31y100| Microinfarction of heart                                                     |
| G31y200| Subendocardial ischaemia                                                     |
| G35..00| Subsequent myocardial infarction                                             |
| G350.00| Subsequent myocardial infarction of anterior wall                           |
| G351.00| Subsequent myocardial infarction of inferior wall                           |
| G353.00| Subsequent myocardial infarction of other sites                             |
| G35X.00| Subsequent myocardial infarction of unspecified site                        |
| 3232.00| ECG: old myocardial infarction                                               |
| 3235.00| ECG: subendocardial infarct                                                  |
| 323Z.00| ECG: myocardial infarct NOS                                                  |
| 889A.00| Diab mellit insulin-glucose infus acute myocardial infarct                   |
| G307100| Acute non-ST segment elevation myocardial infarction                        |
| G312.00| Coronary thrombosis not resulting in myocardial infarction                   |
| G36..00| Certain current complication follow acute myocardial infarct                 |
| G360.00| Haemopericardium/current comp folow acut myocard infarct                     |
| G364.00| Ruptur chordae tendinae/curr comp fol acute myocard infarct                  |
| G365.00| Rupture papillary muscle/curr comp fol acute myocard infarct                |
| G384.00| Postoperative subendocardial myocardial infarction                           |
| Gyu3100| [X]Other current complicatns following acute myocard infarct                |
| Gyu3400| [X]Acute transmural myocardial infarction of unspecif site                   |

**Unstable Angina**

| Code   | Description                                                                 |
|--------|------------------------------------------------------------------------------|
| G311.11| Crescendo angina                                                            |
| G311.13| Unstable angina                                                             |
| G311.14| Angina at rest                                                              |
| G311100| Unstable angina                                                             |
| G311200| Angina at rest                                                              |
| G311300| Refractory angina                                                           |
| G311400| Worsening angina                                                            |
| G330.00| Angina decubitus                                                            |
| G330000| Nocturnal angina                                                            |
| G330z00| Angina decubitus NOS                                                         |
| G331.00| Prinzmetaf's angina                                                         |
| G331.11| Variant angina pectoris                                                     |
| Code     | Description                                    |
|----------|-----------------------------------------------|
| 14A7.00  | H/O: CVA/stroke                               |
| 14A7.11  | H/O: CVA                                      |
| 14A7.12  | H/O: stroke                                   |
| 14AK.00  | H/O: Stroke in last year                      |
| 662M100  | Stroke 6 month review                         |
| 662M200  | Stroke initial post discharge review          |
| 8HBJ.00  | Stroke / transient ischaemic attack referral  |
| G63..11  | Infarction - precerebral                      |
| G63y000  | Cerebral infarct due to thrombosis of precerebral arteries |
| G63y100  | Cerebral infarction due to embolism of precerebral arteries |
| G64..11  | CVA - cerebral artery occlusion               |
| G64..12  | Infarction - cerebral                         |
| G64..13  | Stroke due to cerebral arterial occlusion     |
| G640.00  | Cerebral thrombosis                           |
| G640000  | Cerebral infarction due to thrombosis of cerebral arteries |
| G641.00  | Cerebral embolism                             |
| G641.11  | Cerebral embolus                              |
| G641000  | Cerebral infarction due to embolism of cerebral arteries |
| G64z.00  | Cerebral infarction NOS                       |
| G64z.11  | Brainstem infarction NOS                      |
| G64z.12  | Cerebellar infarction                         |
| G64z000  | Brainstem infarction                          |
| G64z100  | Wallenberg syndrome                           |
| G64z111  | Lateral medullary syndrome                    |
| G64z200  | Left sided cerebral infarction                |
| G64z300  | Right sided cerebral infarction               |
| G64z400  | Infarction of basal ganglia                   |
| G654.00  | Multiple and bilateral precerebral artery syndromes |
| G66..00  | Stroke and cerebrovascular accident unspecified |
| G66..11  | CVA unspecified                               |
| G66..12  | Stroke unspecified                            |
| G66..13  | CVA - Cerebrovascular accident unspecified    |
| Code   | Description                                                      |
|--------|------------------------------------------------------------------|
| G660.00| Middle cerebral artery syndrome                                  |
| G661.00| Anterior cerebral artery syndrome                                |
| G662.00| Posterior cerebral artery syndrome                               |
| G663.00| Brain stem stroke syndrome                                       |
| G664.00| Cerebellar stroke syndrome                                       |
| G665.00| Pure motor lacunar syndrome                                      |
| G666.00| Pure sensory lacunar syndrome                                    |
| G667.00| Left sided CVA                                                   |
| G668.00| Right sided CVA                                                  |
| G675.00| Moyamoya disease                                                 |
| G676.00| Nonpyogenic venous sinus thrombosis                              |
| G676000| Cerebral infarct due cerebral venous thrombosis, nonpyogenic    |
| G678.00| Cereb autosom dominant arteriop subcort infarcts leukoenceph     |
| G683.00| Sequelae of cerebral infarction                                  |
| G68X.00| Sequelae of stroke, not specified as hemorrhage or infarction    |
| G6W..00| Cerebral infarct due unsp occlust/stenos precerebr arteries      |
| G6X..00| Cerebral infarct due unsp occlus or sten cerebrl art rs          |
| Gyu6300| [X] Cerebral infarct due unsp occlus or sten cerebrl art rs      |
| Gyu6400| [X] Other cerebral infarct                                        |
| Gyu6C00| [X] Sequelae of stroke, not specified as hemorrhage or infarction|
| Gyu6G00| [X] Cerebral infarct due unsp occlus/stenos precerebr arteries   |
| L440.12| Stroke in the puerperium                                         |
| ZLEP.00| Discharge from stroke serv                                       |
| ZV12511| [V] Personal history of stroke                                   |
| ZV12512| [V] Personal history of cerebrovascular accident (CVA)           |

**Hemostroke**

| Code   | Description                                                      |
|--------|------------------------------------------------------------------|
| 7004100| Evacuation of haematoma from temporal lobe of brain              |
| 7004200| Evacuation of haematoma from cerebellum                          |
| 7004300| Evacuation of intracerebral haematoma NEC                        |
| 7008200| Aspiration of haematoma of brain tissue                          |
| G61..00| Intracerebral haemorrhage                                       |
| G61..11| CVA - cerebrovascular accid due to intracerebral haemorrhage    |
| G61..12| Stroke due to intracerebral haemorrhage                         |
| Code    | Description                                      |
|---------|--------------------------------------------------|
| G610.00 | Cortical haemorrhage                             |
| G611.00 | Internal capsule haemorrhage                     |
| G612.00 | Basal nucleus haemorrhage                        |
| G613.00 | Cerebellar haemorrhage                           |
| G614.00 | Pontine haemorrhage                              |
| G615.00 | Bulbar haemorrhage                               |
| G616.00 | External capsule haemorrhage                     |
| G617.00 | Intracerebral haemorrhage, intraventricular      |
| G618.00 | Intracerebral haemorrhage, multiple localized    |
| G619.00 | Lobar cerebral haemorrhage                       |
| G61X.00 | Intracerebral haemorrhage in hemisphere, unspec  |
| G61X000 | Left sided intracerebral haemorrhage, unspec     |
| G61X100 | Right sided intracerebral haemorrhage, unspec    |
| G61Z.00 | Intracerebral haemorrhage NOS                    |
| G681.00 | Sequelae of intracerebral haemorrhage            |
| Gyu6200 | [X]Other intracerebral haemorrhage               |
| Gyu6F00 | [X]Intracerebral haemorrhage in hemisphere, unspec |
| 7017000 | Evacuation of subdural haematoma                 |
| 7034.00 | Drainage of subdural space                       |
| 7034Y00 | Other specified drainage of subdural space       |
| 7034Z00 | Drainage of subdural space NOS                   |
| G621.00 | Subdural haemorrhage - nontraumatic              |
| G622.00 | Subdural haematoma - nontraumatic                |
| G623.00 | Subdural haemorrhage NOS                         |
| S62..13 | Subdural haemorrhage following injury            |
| S622.00 | Closed traumatic subdural haemorrhage            |
| S622000 | Subdural h'ge inj no open intracranial wnd + unspec consc |
| S622100 | Subdural h'ge inj no open intracranial wound+no loss consc |
| S622200 | Subdural h'ge inj no open intracranial wound+<1hr loss consc |
| S622300 | Subdural h'ge inj no open intracran wnd+1-24hr loss consc |
| S622400 | Subdural h'ge inj no open intracranial wnd+>24 LOC +recovery |
| S622500 | Subdural h'ge inj no open intracran wnd+>24hr LOC -restored |
| S622600 | Subdural h'ge inj no open intracran wnd+LOC unspec duration |
| Code       | Description                                                                 |
|------------|-----------------------------------------------------------------------------|
| S62200     | Subdural h'ge inj no open intracran wound+concussion unspec                 |
| S623.00    | Open traumatic subdural haemorrhage                                        |
| S623000    | Subdural h'ge inj + open intracranal wound + unspec consc                   |
| S623100    | Subdural h'ge inj + open intracranial wound+no loss consc                   |
| S623200    | Subdural h'ge inj + open intracranial wound<<1hr loss consc                 |
| S623300    | Subdural h'ge inj + open intracranial wnd+1-24hr loss consc                  |
| S623400    | Subdural h'ge inj + open intracranal wound>>24hr LOC +recovery              |
| S623500    | Subdural h'ge inj + open intracranal wnd>>24hr LOC -restored                |
| S623600    | Subdural h'ge inj + open intracranal wnd+LOC unspec duration                |
| S623z00    | Subdural h'ge inj + open intracranial wnd+concussion unspec                  |
| S628.00    | Traumatic subdural haemorrhage                                              |
| S629.00    | Traumatic subdural haematoma                                                |
| S629000    | Traumatic subdural haematoma without open intracranial wound                |
| S629100    | Traumatic subdural haematoma with open intracranial wound                   |
| G60..00    | Subarachnoid haemorrhage                                                   |
| G601.00    | Subarachnoid haemorrhage from carotid siphon and bifurcation                |
| G602.00    | Subarachnoid haemorrhage from middle cerebral artery                        |
| G603.00    | Subarachnoid haemorrhage from anterior communicating artery                 |
| G604.00    | Subarachnoid haemorrhage from posterior communicating artery                |
| G605.00    | Subarachnoid haemorrhage from basilar artery                                |
| G606.00    | Subarachnoid haemorrhage from vertebral artery                              |
| G60X.00    | Subarachnoid haemorrh from intracranial artery, unspec                      |
| G60z.00    | Subarachnoid haemorrhage NOS                                                |
| G680.00    | Sequelae of subarachnoid haemorrhage                                       |
| Gyu6000    | [X]Subarachnoid haemorrhage from other intracranial arteries                |
| Gyu6100    | [X]Other subarachnoid haemorrhage                                          |
| Gyu6E00    | [X]Subarachnoid haemorrh from intracranial artery, unspec                   |
| S62..12    | Subarachnoid haemorrhage following injury                                    |
| S620.00    | Closed traumatic subarachnoid haemorrhage                                  |
| S620000    | Subarachnoid h'ge inj no open intracran wound + unspec consc                |
| S620100    | Subarachnoid h'ge inj no open intracranal wnd+no loss consc                 |
| S620200    | Subarachnoid h'ge inj no open intracranal wnd<<1hr loss consc               |
| S620300    | Subarachnoid h'ge inj no open intracranal wound + 1-24hr LOC                |
| Code     | Description                                                                 |
|----------|-----------------------------------------------------------------------------|
| S620400 | Subarachnoid h'ge inj no open intracran wnd+>24 LOC+recovery                |
| S620500 | Subarach h'ge inj no open intracran wnd+>24hrs LOC-restored                 |
| S620600 | Subarach h'ge inj no open intracran wnd+LOC unspec duration                  |
| S620z00 | Subarach h'ge inj no open intracran wnd + concussion unspec                  |
| S621.00 | Open traumatic subarachnoid haemorrhage                                      |
| S621000 | Subarachnoid h'ge inj + open intracran wound + unspec consc                  |
| S621100 | Subarachnoid h'ge inj + open intracranial wound + no LOC                     |
| S621200 | Subarachnoid h'ge inj + open intracran wound+<1hr loss consc                |
| S621300 | Subarachnoid h'ge inj + open intracran wnd+1-24hr loss consc                 |
| S621400 | Subarachnoid h'ge inj + open intracran wnd+>24hr LOC + recovery             |
| S621500 | Subarach h'ge inj + open intracran wnd+>24hr LOC -restored                  |
| S621600 | Subarach h'ge inj + open intracran wnd+LOC unspec duration                   |
| S621700 | Subarachnoid h'ge inj + open intracran wnd+concussion unspec                |
| S627.00 | Traumatic subarachnoid haemorrhage                                          |
| 7032000 | Evacuation of extradural haematoma                                          |
| G600.00 | Ruptured berry aneurysm                                                     |
| G62..00 | Other and unspecified intracranial haemorrhage                              |
| G620.00 | Extradural haemorrhage - nontraumatic                                       |
| G62z.00 | Intracranial haemorrhage NOS                                                |
| G682.00 | Sequelae of other nontraumatic intracranial haemorrhage                     |
| Gyu6B00 | [X]Sequelae of other nontraumatic intracranial haemorrhage                  |
| S62..00 | Cerebral haemorrhage following injury                                       |
| S62..11 | Extradural haemorrhage following injury                                     |
| S62..14 | Traumatic cerebral haemorrhage                                             |
| S620.11 | Middle meningeal haemorrhage following injury                               |
| S624.00 | Closed traumatic extradural haemorrhage                                     |
| S624.11 | Epidural haematoma following injury                                         |
| S624000 | Extradural h'ge inj no open intracranial wnd + unspec consc                 |
| S624100 | Extradural h'ge inj no open intracranial wnd + no loss consc                |
| S624200 | Extradural h'ge inj no open intracranial wnd+<1hr loss consc                |
| S624300 | Extradural h'ge inj no open intracran wnd+1-24hr loss consc                 |
| S624400 | Extradural h'ge inj no open intracran wnd+>24hr LOC+recovery                |
| S624500 | Extradural h'ge inj no open intracran wnd+>24hr LOC-restored                |
| Code   | Description                                                                 |
|--------|------------------------------------------------------------------------------|
| S624600 | Extradural h'ge inj no open intracran wnd+LOC unspec duration                |
| S624200 | Extradural h'ge inj no open intracran wnd+concussion unspec                  |
| S625.00 | Open traumatic extradural haemorrhage                                        |
| S625000 | Extradural h'ge inj + open intracranial wnd + unspec consc                   |
| S625100 | Extradural h'ge inj + open intracranial wound+no loss consc                 |
| S625200 | Extradural h'ge inj + open intracranial wound+<1hr loss consc               |
| S625300 | Extradural h'ge inj + open intracranial wound+1-24hr loss consc             |
| S625400 | Extradural h'ge inj + open intracranial wound+>24hr LOC+recovery            |
| S625500 | Extradural h'ge inj + open intracranial wound+>24hr LOC -restored           |
| S625600 | Extradural h'ge inj + open intracranial wnd+LOC unspec duration             |
| S625200 | Extradural h'ge inj + open intracranal wound+conclusion unspec              |
| S626.00 | Epidural haemorrhage                                                         |
| S62A.00 | Traumatic extradural haematoma                                               |
| S62A000 | Traumatic extradural haemat without open intracranial wound                  |
| S62A100 | Traumatic extradural haematoma with open intracranial wound                  |
| S62z.00 | Cerebral haemorrhage following injury NOS                                    |
| S63..00 | Other cerebral haemorrhage following injury                                 |
| S630.00 | Other cerebral h'ge after injury no open intracranial wound                  |
| S630.11 | Cerebral compression due to injury                                           |
| S630.12 | Intracranial haematoma following injury                                     |
| S630000 | Oth cerebral h'ge inj no open intracran wnd+unspec consc                    |
| S630100 | Oth cerebral h'ge inj no open intracranal wnd+no loss consc                 |
| S630200 | Oth cerebral h'ge inj no open intracranial wnd+<1hr loss consc               |
| S630300 | Oth cerebral h'ge inj no open intracran wn+>1-24hr LOC                       |
| S630400 | Oth cereb h'ge inj no open intracran wnd+>24hr LOC +recovery                |
| S630500 | Oth cereb h'ge inj no open intracran wnd+>24hr LOC +restored                |
| S630600 | Oth cereb h'ge inj no open intracran wnd+LOC unspec duration                |
| S630200 | Oth cereb h'ge inj no open intracran wnd+concussion unspec                  |
| S631.00 | Other cerebral h'ge after injury + open intracranial wound                   |
| S631000 | Oth cerebral h'ge inj + open intracranal wnd + unspec consc                 |
| S631100 | Oth cerebral h'ge inj + open intracranial wnd+no loss consc                 |
| S631200 | Oth cerebral h'ge inj + open intracranal wnd+<1hr loss consc                |
| S631300 | Oth cerebral h'ge inj + open intracranal wnd+1-24hr loss consc              |
| Code   | Description                                                                 |
|--------|-----------------------------------------------------------------------------|
| S631400 | Oth cereb h'ge inj + open intracr wnd+>24hr LOC + recovery                  |
| S631500 | Oth cereb h'ge inj + open intracr wnd+>24hr LOC -restored                  |
| S631600 | Oth cereb h'ge inj + open intracr wnd+LOC unspec duration                   |
| S631z00 | Oth cereb h'ge inj + open intracr wnd+concussion unspec                     |
| S63z.00 | Other cerebral haemorrhage following injury NOS                              |
|        | **Heart Failure**                                                           |
| 14A6.00 | H/O: heart failure                                                          |
| 14AM.00 | H/O: Heart failure in last year                                             |
| 1O1..00 | Heart failure confirmed                                                     |
| 388D.00 | New York Heart Assoc classification heart failure symptoms                   |
| 662f.00 | New York Heart Association classification - class I                         |
| 662g.00 | New York Heart Association classification - class II                        |
| 662h.00 | New York Heart Association classification - class III                       |
| 662i.00 | New York Heart Association classification - class IV                        |
| 662p.00 | Heart failure 6 month review                                                |
| 662T.00 | Congestive heart failure monitoring                                         |
| 662W.00 | Heart failure annual review                                                 |
| 679X.00 | Heart failure education                                                     |
| 67D4.00 | Heart failure information given to patient                                  |
| 8B29.00 | Cardiac failure therapy                                                     |
| 8CL3.00 | Heart failure care plan discussed with patient                              |
| 8H2S.00 | Admit heart failure emergency                                                |
| 8HBE.00 | Heart failure follow-up                                                     |
| 8Hg8.00 | Discharge from practice nurse heart failure clinic                          |
| 8HHb.00 | Referral to heart failure nurse                                             |
| 8HHz.00 | Referral to heart failure exercise programme                                |
| 8Hk0.00 | Referred to heart failure education group                                   |
| 8HTL.00 | Referral to heart failure clinic                                            |
| 9N0k.00 | Seen in heart failure clinic                                                |
| 9N2p.00 | Seen by community heart failure nurse                                      |
| 9N4s.00 | Did not attend practice nurse heart failure clinic                          |
| 9N6T.00 | Referred by heart failure nurse specialist                                  |
| 9Or..00 | Heart failure monitoring administration                                     |
| Code  | Description                              |
|-------|------------------------------------------|
| 9Or0.00 | Heart failure review completed          |
| 9Or1.00 | Heart failure monitoring telephone invite |
| 9Or2.00 | Heart failure monitoring verbal invite   |
| 9Or3.00 | Heart failure monitoring first letter    |
| 9Or4.00 | Heart failure monitoring second letter   |
| 9Or5.00 | Heart failure monitoring third letter    |
| G232.00 | Hypertensive heart & renal dis wth (congestive) heart failure |
| G234.00 | Hyperten heart & renal dis + both (congestive) heart renal fail |
| G1yz100 | Rheumatic left ventricular failure       |
| G5y4z00 | Post cardiac operation heart failure NOS |
| G5yy900 | Left ventricular systolic dysfunction   |
| G5yyA00 | Left ventricular diastolic dysfunction  |
| L09y200 | Cardiac failure following abortive pregnancy |
| Q48y100 | Congenital cardiac failure              |
| Q490.00 | Neonatal cardiac failure                |
| SP08400 | Heart transplant failure and rejection  |
| SP08500 | Heart-lung transplant failure and rejection |
| SP11100 | Cardiac insufficiency as a complication of care |
| SP11111 | Heart failure as a complication of care  |
| G58..00 | Heart failure                           |
| G58..11 | Cardiac failure                         |
| G580.00 | Congestive heart failure                |
| G580.11 | Congestive cardiac failure              |
| G580.12 | Right heart failure                     |
| G580.13 | Right ventricular failure               |
| G580.14 | Biventricular failure                   |
| G580000 | Acute congestive heart failure          |
| G580100 | Chronic congestive heart failure        |
| G580200 | Decompensated cardiac failure           |
| G580300 | Compensated cardiac failure             |
| G580400 | Congestive heart failure due to valvular disease |
| G581.00 | Left ventricular failure                |
| G581.11 | Asthma - cardiac                        |
| Code    | Description                                      |
|---------|--------------------------------------------------|
| G581.12 | Pulmonary oedema - acute                         |
| G581.13 | Impaired left ventricular function               |
| G581000 | Acute left ventricular failure                   |
| G582.00 | Acute heart failure                              |
| G583.00 | Heart failure with normal ejection fraction      |
| G583.11 | HFNEF - heart failure with normal ejection fraction |
| G583.12 | Heart failure with preserved ejection fraction   |
| G584.00 | Right ventricular failure                        |
| G58z.00 | Heart failure NOS                                |
| G58z.11 | Weak heart                                       |
| G58z.12 | Cardiac failure NOS                              |

**Transient ischemic attack**

| Code    | Description                                      |
|---------|--------------------------------------------------|
| G65..00 | Stroke / transient ischaemic attack referral     |
| G65..11 | Drop attack                                      |
| G65..12 | Transient ischaemic attack                       |
| G65..13 | Vertebro-basilar insufficiency                   |
| G650.00 | Basilar artery syndrome                          |
| G650.11 | Insufficiency - basilar artery                   |
| G651.00 | Vertebral artery syndrome                        |
| G651000 | Vertebro-basilar artery syndrome                 |
| G652.00 | Subclavian steal syndrome                        |
| G653.00 | Carotid artery syndrome hemispheric              |
| G654.00 | Multiple and bilateral precerebral artery syndromes |
| G655.00 | Transient global amnesia                         |
| G656.00 | Vertebrobasilar insufficiency                    |
| G65y.00 | Other transient cerebral ischaemia               |
| G65z.00 | Transient cerebral ischaemia NOS                 |
| G65z000 | Impending cerebral ischaemia                     |
| G65z100 | Intermittent cerebral ischaemia                  |
| G65zz00 | Transient cerebral ischaemia NOS                 |

**Coronary artery bypass graft**
| Code       | Description                                         |
|------------|-----------------------------------------------------|
| 7922z00    | Allograft replacement of coronary artery NOS        |
| 7922300    | Allograft replacement of four or more coronary arteries |
| 7922000    | Allograft replacement of one coronary artery        |
| 7922200    | Allograft replacement of three coronary arteries    |
| 7922100    | Allograft replacement of two coronary arteries      |
| 7921300    | Autograft replacement of four or more coronary arteries NEC |
| 7921000    | Autograft replacement of one coronary artery NEC    |
| 7921200    | Autograft replacement of three coronary arteries NEC |
| 7921100    | Autograft replacement of two coronary arteries NEC  |
| 7925z00    | Connection of mammary artery to coronary artery NOS |
| 7925y00    | Connection of mammary artery to coronary artery OS  |
| 7926z00    | Connection of other thoracic artery to coronary artery NOS |
| 7926y00    | Connection of other thoracic artery to coronary artery OS |
| 792�11     | Coronary artery bypass graft operations             |
| 7926000    | Double anastom thoracic arteries to coronary arteries NEC |
| 7925000    | Double anastomosis of mammary arteries to coronary arteries |
| 7925100    | Double implant of mammary arteries into coronary arteries |
| 7926100    | Double implant thoracic arteries into coronary arteries NEC |
| SP00300    | Mechanical complication of coronary bypass         |
| 7921z00    | Other autograft replacement of coronary artery NOS  |
| 7921y00    | Other autograft replacement of coronary artery OS   |
| 792D.00    | Other bypass of coronary artery                     |
| 792Dz00    | Other bypass of coronary artery NOS                 |
| 792C.00    | Other replacement of coronary artery                |
| 7922y00    | Other specified allograft replacement of coronary artery |
| 792Dy00    | Other specified other bypass of coronary artery     |
| 7923y00    | Other specified prosthetic replacement of coronary artery |
| 792Cy00    | Other specified replacement of coronary artery      |
| 7924y00    | Other specified revision of bypass for coronary artery |
| 7928200    | Percut translum balloon angioplasty bypass graft coronary artery |
| 7923z00    | Prosthetic replacement of coronary artery NOS       |
| 7923300    | Prosthetic replacement of four or more coronary arteries |
| 7923000    | Prosthetic replacement of one coronary artery       |
| Code       | Description                                           |
|------------|-------------------------------------------------------|
| 7923200    | Prosthetic replacement of three coronary arteries      |
| 7923100    | Prosthetic replacement of two coronary arteries        |
| 792C000    | Replacement of coronary arteries using multiple methods|
| 792C200    | Replacement of coronary artery NOS                    |
| 7924z00    | Revision of bypass for coronary artery NOS             |
| 7924000    | Revision of bypass for one coronary artery             |
| 7924200    | Revision of bypass for three coronary arteries         |
| 7924100    | Revision of bypass for two coronary arteries           |
| 7924400    | Revision of connection of thoracic artery to coronary artery |
| 7920z00    | Saphenous vein graft replacement coronary artery NOS   |
| 7920y00    | Saphenous vein graft replacement of coronary artery OS |
| 7920300    | Saphenous vein graft replacement of four+ coronary arteries |
| 7920000    | Saphenous vein graft replacement of one coronary artery|
| 7920200    | Saphenous vein graft replacement of three coronary arteries |
| 7920100    | Saphenous vein graft replacement of two coronary arteries |
| 7925200    | Single anastomosis of mammmary art to left ant descend coronary art |
| 7925300    | Single anastomosis of mammmary artery to coronary artery NEC |
| 7926200    | Single anastomosis of thoracic artery to coronary artery NEC |
| 7925400    | Single implantation of mammmary artery into coronary artery |
| 7926300    | Single implantation thoracic artery into coronary artery NEC |
| 7927200    | Transection of muscle bridge of coronary artery        |
| 7927300    | Transposition of coronary artery NEC                   |
| ZV45700    | [V]Presence of aortocoronary bypass graft              |
| ZV45K00    | [V]Presence of coronary artery bypass graft            |
| ZV45K00    | [V]Presence of coronary artery bypass graft            |
| ZV45K11    | [V]Presence of coronary artery bypass graft - CABG     |
| ZV45K11    | [V]Presence of coronary artery bypass graft - CABG     |
| 7925011    | LIMA sequential anastomosis                           |
| 7925012    | RIMA sequential anastomosis                           |
| 7925311    | LIMA single anastomosis                               |
| 7925312    | RIMA single anastomosis                               |
| 7935600    | Perc trans three dimen electroanat mapping conduct sys heart |
| Code     | Description                                                      |
|----------|------------------------------------------------------------------|
| 7927000  | Repair of arteriovenous fistula of coronary artery                |
| 7927100  | Repair of aneurysm of coronary artery                             |
| 7927y00  | Other specified other open operation on coronary artery           |
| 7927z00  | Other open operation on coronary artery NOS                       |
| 792B000  | Endarterectomy of coronary artery NEC                             |
| 792B.00  | Repair of coronary artery NEC                                     |
| 792By00  | Other specified repair of coronary artery                         |
| 792Bz00  | Repair of coronary artery NOS                                     |
| 792y.00  | Other specified operations on coronary artery                     |
| 792z.00  | Coronary artery operations NOS                                   |
| 7927.00  | Other open operations on coronary artery                          |
| 7927.00  | Other open operations on coronary artery                          |
| 7924.00  | Revision of bypass for coronary artery                            |
| 7923.00  | Prosthetic replacement of coronary artery                         |
| 7923.11  | Prosthetic bypass of coronary artery                              |
| 7921.00  | Other autograft replacement of coronary artery                    |
| 7925.11  | Creation of bypass from mammary artery to coronary artery         |
| 7925.00  | Connection of mammary artery to coronary artery                   |
| 7926.00  | Connection of other thoracic artery to coronary artery            |
| 7922.00  | Allograft replacement of coronary artery                          |
| **Percutaneous coronary intervention** |                                                 |
| 7927500  | Open angioplasty of coronary artery                               |
| 7928000  | Percut transluminal balloon angioplasty one coronary artery       |
| 7928.00  | Transluminal balloon angioplasty of coronary artery               |
| 7928100  | Percut transm balloon angioplasty mult coronary arteries         |
| 7928.11  | Percutaneous balloon coronary angioplasty                        |
| 7928y00  | Transluminal balloon angioplasty of coronary artery OS            |
| 7928z00  | Transluminal balloon angioplasty of coronary artery NOS           |
| 7929000  | Percutaneous transluminal laser coronary angioplasty              |
| 7929.00  | Other therapeutic transluminal operations on coronary artery      |
| 7929100  | Percut transluminal coronary thrombolysis with streptokinase     |
| 7929111  | Percut translum coronary thrombolytic therapy- streptokinase     |
| 7929200  | Percut translum inject therap subst to coronary artery NEC        |
| Code   | Description                                                                 |
|--------|-----------------------------------------------------------------------------|
| 7929300 | Rotary blade coronary angioplasty                                           |
| 7929400 | Insertion of coronary artery stent                                          |
| 7929y00 | Other therapeutic transluminal op on coronary artery OS                      |
| 7929z00 | Other therapeutic transluminal op on coronary artery NOS                     |
| ZV45800 | [V]Presence of coronary angioplasty implant and graft                       |
| ZV45L00 | [V]Status following coronary angioplasty NOS                                |
| 793G.00 | Perc translum balloon angioplasty stenting coronary artery                   |
| 793K.00 | Transluminal operations internal mammary artery side branch                 |
| 7933.00 | Transluminal heart assist operations                                        |
| 7934.00 | Other therapeutic transluminal operations on heart                           |
| 7935.00 | Diagnostic transluminal operations on heart                                 |
| 793Gy00 | OS perc translumina balloon angioplast stenting coronary art                 |
| 793Gz00 | Perc translum balloon angioplasty stenting coronary art NOS                  |
| 793Ky00 | OS transluminal operations internal mammary art side branch                 |
| 793Kz00 | Transluminal operations internal mammary art side branch NOS                |
| 793G00 | Perc translum ball angio insert 1-2 drug elut stents cor art                |
| 793H00 | Percutaneous transluminal balloon dilation cardiac conduit                   |
| 793GK00 | Translum occlusion left internal mammary artery side branch                 |
| 793G100 | Perc tran ball angio ins 3 or more drug elut stents cor art                 |
| 793G200 | Perc translum balloon angioplasty insert 1-2 stents cor art                 |
| 793G300 | Percutaneous cor balloon angiop 3 more stents cor art NEC                   |
| 793y00 | Other therapeutic transluminal operation on heart OS                         |
| 793z00 | Other therapeutic transluminal operation on heart NOS                        |
| 7935y00 | Other specified diagnostic transluminal operation on heart                  |
| 7935z00 | Diagnostic transluminal operation on heart NOS                               |
| 792B300 | Percut translum cutting balloon angioplasty coronary artery                 |
| 7929500 | Insertion of drug-eluting coronary artery stent                             |
| 7929600 | Percutaneous transluminal atherectomy of coronary artery                     |
| 7933000 | Transluminal insertion of pulsation balloon into aorta                      |
| 792B200 | Percut translum balloon angioplasty bypass graft coronary a                 |

**Peripheral artery disease**

| Code   | Description                           |
|--------|---------------------------------------|
| 700.11 | Aorto-iliac disease                   |
| G702.00 | Extremity artery atheroma             |
| Code    | Description                                      |
|---------|--------------------------------------------------|
| G702z00 | Extremity artery atheroma NOS                    |
| 35.11   | Peripheral ischaemic vascular disease            |
| 35.12   | Ischaemia of legs                                |
| 35.13   | Peripheral ischaemia                             |
| G730100 | Raynaud's phenomenon                             |
| G731000 | Buerger's disease                                |
| G731100 | Presenile gangrene                               |
| G732.00 | Peripheral gangrene                              |
| G732100 | Gangrene of toe                                  |
| G733.00 | Gangrene of foot                                 |
| G733.00 | Ischaemic foot                                   |
| G734.00 | Peripheral arterial disease                      |
| 73y.00  | Other specified peripheral vascular disease       |
| G73y000 | Diabetic peripheral angiopathy                   |
| G73y100 | Peripheral angiopathic disease EC NOS             |
| G73yz00 | Other specified peripheral vascular disease NOS   |
| G73z.00 | Peripheral vascular disease NOS                  |
| G73z000 | Intermittent claudication                        |
| G73z011 | Claudication                                     |
| G73z012 | Vascular claudication                            |
| G73z100 | Spasm of peripheral artery                       |
| G73zz00 | Peripheral vascular disease NOS                  |
| G74.00  | Arterial embolism and thrombosis                 |
| G74.11  | Arterial embolus and thrombosis                  |
| G74.12  | Thrombosis - arterial                            |
| G74.13  | Arterial embolic and thrombotic occlusion         |
| G740.12 | Aortoiliac obstruction                           |
| G740.13 | Lerche's syndrome                                |
| G742400 | Embolism and thrombosis of the femoral artery    |
| G742500 | Embolism and thrombosis of the popliteal artery  |
| G742600 | Embolism and thrombosis of the anterior tibial artery |
| G742700 | Embolism and thrombosis of the dorsalis pedis artery |
| G742800 | Embolism and thrombosis of the posterior tibial artery |
| Code   | Description                                                |
|--------|------------------------------------------------------------|
| G742900 | Embolism and thrombosis of a leg artery NOS                |
| G742B00 | Post radiological embolism of lower limb artery            |
| G742Z00 | Peripheral arterial embolism and thrombosis NOS            |
| G74Y000 | Embolism and/or thrombosis of the common iliac artery      |
| G74Y100 | Embolism and/or thrombosis of the internal iliac artery    |
| G74Y200 | Embolism and/or thrombosis of the external iliac artery    |
| G74Y300 | Embolism and thrombosis of the iliac artery unspecified    |
| G74Z00  | Arterial embolism and thrombosis NOS                       |
| G76100  | Stricture of artery                                        |
| G76500  | Necrosis of artery                                         |
| G76A00  | Arterial insufficiency                                     |
| G76Z00  | Disorders of arteries and arterioles NOS                   |
| G76Z100 | Iliac artery occlusion                                    |
| G76Z200 | Femoral artery occlusion                                  |
| G76Z300 | Popliteal artery occlusion                                |
| G7Y00   | Other specified arterial, arteriole or capillary disease   |
| G7Z00   | Arterial, arteriole and capillary diseases NOS             |
| Rango 14NB.00 | H/O: Peripheral vascular disease procedure     |
| 2116.00 | O/E - gangrene                                             |
| R054.00 | [D]Gangrene                                               |
| R054200 | [D]Gangrene of toe in diabetic                            |
| R054300 | [D]Widespread diabetic foot gangrene                       |
| 8HIP.00 | Referred for peripheral artery disease assessment         |
| 7A12100 | Bypass bifurc aorta by anastom aorta to femoral artery NEC |
| 7A12300 | Bypass bifurcation aorta by anastom aorta to iliac artery |
| 7A4..00 | Iliac and femoral artery operations                       |
| 7A41.00 | Other bypass of iliac artery                              |
| 7A41.11 | Other bypass of iliac artery by anastomosis               |
| 7A41100 | Bypass iliac artery by iliac/femoral artery anastomosis NEC |
| 7A41200 | Emerg bypass iliac artery by femoral/femoral art anast NEC |
| 7A41300 | Bypass iliac artery by femoral/femoral art anastomosis NEC |
| 7A41500 | Emerg bypass iliac artery by aorta/ext iliac art anast NEC |
| Code   | Description                                                      |
|--------|------------------------------------------------------------------|
| 7A41600 | Emerg bypass leg artery by aorta/com fem art anastomosis NEC     |
| 7A41700 | Emerg bypass leg artery by aorta/deep fem anastomosis NEC        |
| 7A41800 | Emerg bypass iliac artery by iliac/iliac art anastomosis NEC     |
| 7A41900 | Bypass common iliac artery by aorta/com iliac art anast NEC      |
| 7A41A00 | Bypass iliac artery by aorta/ext iliac art anastomosis NEC       |
| 7A41B00 | Bypass leg artery by aorta/com femoral art anastomosis NEC       |
| 7A41C00 | Bypass leg artery by aorta/deep femoral art anastomosis NEC      |
| 7A41D00 | Bypass iliac artery by iliac/iliac artery anastomosis NEC        |
| 7A41E00 | Emergency bypass of iliac artery by unspecified anastomosis      |
| 7A41y00 | Other specified other bypass of iliac artery                     |
| 7A41z00 | Other bypass of iliac artery NOS                                  |
| 7A42.00 | Reconstruction of iliac artery                                  |
| 7A42.11 | Reconstruction of common iliac artery                            |
| 7A42000 | Endarterectomy and patch repair of iliac artery                  |
| 7A42011 | Endarterectomy and patch repair of common iliac artery           |
| 7A42100 | Endarterectomy of iliac artery NEC                               |
| 7A42111 | Endarterectomy of common iliac artery NEC                        |
| 7A42y00 | Other specified reconstruction of iliac artery                   |
| 7A42z00 | Reconstruction of iliac artery NOS                               |
| 7A43.00 | Other open operations on iliac artery                            |
| 7A43.11 | Other open operations on common iliac artery                     |
| 7A43000 | Repair of iliac artery NEC                                      |
| 7A43011 | Repair of common iliac artery NEC                                |
| 7A43100 | Open embolectomy of iliac artery                                 |
| 7A43111 | Open embolectomy of common iliac artery                          |
| 7A43300 | Open insertion of iliac artery stent                              |
| 7A43y00 | Other specified other open operation on iliac artery             |
| 7A43z00 | Other open operation on iliac artery NOS                         |
| 7A44.00 | Transluminal operations on iliac artery                          |
| 7A44.11 | Transluminal operations on common iliac artery                   |
| 7A44000 | Percutaneous transluminal angioplasty of iliac artery             |
| 7A44100 | Percutaneous transluminal embolectomy of iliac artery            |
| 7A44200 | Arteriography of iliac artery                                   |
| Code     | Description                                                  |
|----------|--------------------------------------------------------------|
| 7A44211  | Arteriography of common iliac artery                         |
| 7A44300  | Insertion of iliac artery stent                              |
| 7A44400  | Percutaneous transluminal insertion of iliac artery stent     |
| 7A44y00  | Other specified transluminal operation on iliac artery        |
| 7A44z00  | Transluminal operation on iliac artery NOS                   |
| 7A47.00  | Other emergency bypass of femoral or popliteal artery        |
| 7A47.11  | Other emerg bypass femoral or popliteal art by anastomosis    |
| 7A47.12  | Other emergency bypass of common femoral artery              |
| 7A47.13  | Other emergency bypass of deep femoral artery                |
| 7A47.14  | Other emergency bypass of popliteal artery                   |
| 7A47.15  | Other emergency bypass of superficial femoral artery         |
| 7A47.16  | Other emergency bypass of femoral artery                     |
| 7A47100  | Emerg bypass popliteal art by pop/pop art anast c prosth NEC |
| 7A47500  | Emerg bypass popliteal art by pop/tib art anast c prosth NEC |
| 7A47700  | Emerg bypass pop art by pop/tib art anast c vein graft NEC   |
| 7A47900  | Emerg bypass popliteal art by pop/peron a anast c prosth NEC |
| 7A47C00  | Emerg bypass femoral artery by fem/fem art anastomosis NEC   |
| 7A47D00  | Emerg bypass popliteal artery by pop/fem art anastomosis NEC |
| 7A47y00  | Other emergency bypass of femoral or popliteal artery OS     |
| 7A47z00  | Other emergency bypass of femoral or popliteal artery NOS    |
| 7A48.00  | Other bypass of femoral artery or popliteal artery           |
| 7A48.11  | Other bypass of femoral or popliteal artery by anastomosis    |
| 7A48.12  | Other bypass of common femoral artery                        |
| 7A48.13  | Other bypass of deep femoral artery                          |
| 7A48.14  | Other bypass of femoral artery                               |
| 7A48.15  | Other bypass of popliteal artery                             |
| 7A48000  | Bypass femoral artery by fem/pop art anast c prosthosis NEC  |
| 7A48100  | Bypass popliteal artery by pop/pop a anast c prosthesis NEC  |
| 7A48200  | Bypass femoral artery by fem/pop art anast c vein graft NEC  |
| 7A48300  | Bypass popliteal artery by pop/pop a anast c vein graft NEC  |
| 7A48400  | Bypass femoral artery by fem/tib art anast c prosthesis NEC  |
| 7A48500  | Bypass popliteal artery by fem/tib a anast c prosthesis NEC  |
| 7A48600  | Bypass femoral artery by fem/tib art anast c vein graft NEC  |
| Code | Description |
|------|-------------|
| 7A48700 | Bypass popliteal artery by pop/tib a anast c vein graft NEC |
| 7A48800 | Bypass femoral artery by fem/peron a anast c prosthesis NEC |
| 7A48900 | Bypass popliteal artery by pop/peron art anast c prosth NEC |
| 7A48A00 | Bypass femoral artery by fem/peron a anast c vein graft NEC |
| 7A48B00 | Bypass popliteal art by pop/peron art anast c vein graft NEC |
| 7A48C00 | Bypass femoral artery by femoral/femoral art anastomosis NEC |
| 7A48D00 | Bypass popliteal artery by pop/fem artery anastomosis NEC |
| 7A48Y00 | Other bypass of femoral artery or popliteal artery OS |
| 7A48Z00 | Other bypass of femoral artery or popliteal artery NOS |
| 7A49.00 | Reconstruction of femoral artery or popliteal artery |
| 7A49.11 | Reconstruction of common femoral artery |
| 7A49.12 | Reconstruction of deep femoral artery |
| 7A49.13 | Reconstruction of femoral artery |
| 7A49.14 | Reconstruction of popliteal artery |
| 7A49.15 | Reconstruction of superficial femoral artery |
| 7A49000 | Endarterectomy and patch repair of femoral artery |
| 7A49100 | Endarterectomy and patch repair of popliteal artery |
| 7A49200 | Endarterectomy of femoral artery NEC |
| 7A49300 | Endarterectomy of popliteal artery NEC |
| 7A49400 | Profundoplasty femoral artery & patch repair deep fem artery |
| 7A49500 | Profundoplasty and patch repair of popliteal artery |
| 7A49600 | Profundoplasty of femoral artery NEC |
| 7A49700 | Profundoplasty of popliteal artery NEC |
| 7A49800 | Reconstruction of femoral artery with vein graft |
| 7A49900 | Reconstruction of popliteal artery with vein graft |
| 7A4Y00 | Reconstruction of femoral or popliteal artery OS |
| 7A49Z00 | Reconstruction of femoral or popliteal artery NOS |
| 7A4A.00 | Other open operations on femoral artery or popliteal artery |
| 7A4A.11 | Other open operations on common femoral artery |
| 7A4A.12 | Other open operations on deep femoral artery |
| 7A4A.13 | Other open operations on popliteal artery |
| 7A4A.14 | Other open operations on superficial femoral artery |
| 7A4A000 | Repair of femoral artery NEC |
| Code      | Description                                          |
|-----------|------------------------------------------------------|
| 7A4A100   | Repair of popliteal artery NEC                       |
| 7A4A200   | Open embolectomy of femoral artery                   |
| 7A4A211   | Open thrombectomy of femoral artery                  |
| 7A4A300   | Open embolectomy popliteal artery                    |
| 7A4A311   | Open thrombectomy of popliteal artery                |
| 7A4A600   | Operation on popliteal artery NEC                    |
| 7A4A700   | Repair of femoral artery with temporary silastic shunt |
| 7A4A800   | Repair of popliteal artery with temporary silastic shunt |
| 7A4A900   | Other open operation on femoral or popliteal artery OS |
| 7A4A9200  | Other open operation on femoral or popliteal artery NOS |
| 7A4B.00   | Transluminal operations on femoral or popliteal artery |
| 7A4B.11   | Transluminal procedure on common femoral artery      |
| 7A4B.12   | Transluminal procedure on deep femoral artery        |
| 7A4B.13   | Transluminal procedure on femoral artery             |
| 7A4B.14   | Transluminal procedure on popliteal artery           |
| 7A4B.15   | Transluminal procedure on superficial femoral artery |
| 7A4B000   | Percutaneous transluminal angioplasty of femoral artery |
| 7A4B100   | Percutaneous transluminal angioplasty of popliteal artery |
| 7A4B200   | Percutaneous transluminal embolectomy of femoral artery |
| 7A4B300   | Percutaneous transluminal embolectomy of popliteal artery |
| 7A4B400   | Percutaneous transluminal embolisation of femoral artery |
| 7A4B500   | Percutaneous transluminal embolisation of popliteal artery |
| 7A4B900   | Percutaneous transluminal insertion of stent femoral artery |
| 7A4B900   | Transluminal operation on femoral or popliteal artery OS |
| 7A4B9200  | Transluminal operation on femoral or popliteal artery NOS |
| 7A4y.00   | Other specified operations on iliac and femoral artery |
| 7A4z.00   | Iliac and femoral artery operations NOS              |
| 7A50100   | Revision of reconstruction involving iliac artery    |
| 7A50200   | Revision of reconstruction involving femoral artery  |
| 7A50300   | Revision of reconstruction of popliteal artery       |
| 7A53400   | Operation on aneurysm of artery NEC                  |
| 7A56.00   | Other therapeutic transluminal operations on artery   |
| 7A56000   | Percutaneous transluminal arterial thrombolysis reconstruct |
| Code     | Description                                                      |
|----------|------------------------------------------------------------------|
| 7A56100  | Percutaneous transluminal stent reconstruction of artery         |
| 7A56400  | Percutaneous transluminal balloon angioplasty of artery           |
| 7A56600  | Percutaneous transluminal placement peripheral stent artery       |
| 7A56y00  | Other specified other therapeutic transluminal operat artery      |
| 7A56z00  | Other therapeutic transluminal operations on artery NOS           |
| 7M1D300  | Transluminal approach to organ through femoral artery             |
| 7M25M00  | Deep circumflex iliac artery flap                                 |
| 7N46000  | [SO]Common iliac artery                                          |
| 7N46100  | [SO]Internal iliac artery                                        |
| 7N46200  | [SO]Common femoral artery                                        |
| 7N46300  | [SO]Deep femoral artery                                          |
| 7N46311  | [SO]Profunda femoris artery                                      |
| 7N46400  | [SO]Superficial femoral artery                                   |
| 7N46500  | [SO]Popliteal artery                                             |
| 7N46600  | [SO]Tibial artery                                                |
| 7N46700  | [SO]External iliac artery                                        |
| 7N46800  | [SO]Deep circumflex iliac artery                                 |
| 7N46800  | [SO]Other artery of thigh                                        |
| 7N46C00  | [SO]Anterior tibial artery                                       |
| 7N46D00  | [SO]Posterior tibial artery                                      |
| 7N46F00  | [SO]Medial plantar artery                                        |
| 7N46G00  | [SO]Lateral plantar artery                                       |
| 7N46H00  | [SO]Dorsalis pedis artery                                        |
| 7N46J00  | [SO]Digital artery of toe                                        |
| 7NB8000  | [SO]Anterior tibial artery                                       |
| 7NB8100  | [SO]Posterior tibial artery                                      |
| 7NB8300  | [SO]Dorsalis pedis artery                                        |
| 7NB8400  | [SO]External iliac artery                                        |
| 7NB8500  | [SO]Iliac artery NEC                                             |
| 7NB8600  | [SO]Tibial artery NEC                                             |
| F336.00  | Phantom limb syndrome                                            |
| F336000  | Phantom limb syndrome with pain                                  |
| F336100  | Phantom limb syndrome without pain                               |
|                      | US Truven MarketScan Mortality subset | US Truven MarketScan Total data | Difference Mortality vs Total |
|----------------------|-------------------------------------|---------------------------------|-----------------------------|
|                      | SGLT-2i (N=71,632) | oGLD (N=71,632) | SGLT-2i (N=116,899) | oGLD (N=116,899) | SGLT-2i | oGLD |
| Age in years, mean (SD) | 55.8 (9.5) | 56.0 (10.2) | 55.76 (9.68) | 55.79 (10.24) | -1.3 | -1.1 |
| Women                | 31,715 | 44.3 | 32,151 | 44.9 | 53,293 | 45.6 | 53,806 | 46.0 | -1.3 | -1.1 |
| Frailty (yes)        | 2,869 | 4.0 | 3,295 | 4.6 | 5,340 | 4.6 | 5,382 | 4.6 | -0.6 | 0.0 |
| Established CVD*     | 6,452 | 9.0 | 6,918 | 9.7 | 11,218 | 9.6 | 11,292 | 9.7 | -0.6 | 0.0 |
| Acute MI             | 576 | 0.8 | 630 | 0.9 | 1,052 | 0.9 | 1,036 | 0.9 | -0.1 | 0.0 |
| Unstable angina      | 711 | 1.0 | 756 | 1.1 | 1,222 | 1.0 | 1,227 | 1.0 | 0.0 | 0.1 |
| Heart failure        | 1,638 | 2.3 | 1,845 | 2.6 | 3,025 | 2.6 | 3,039 | 2.6 | -0.3 | 0.0 |
| Atrial fibrillation  | 1,892 | 2.6 | 2,085 | 2.9 | 3,308 | 2.8 | 3,330 | 2.8 | -0.2 | 0.1 |
| Stroke               | 2,413 | 3.4 | 2,615 | 3.7 | 4,165 | 3.6 | 4,219 | 3.6 | -0.2 | 0.1 |
| PAD                  | 1,835 | 2.6 | 1,884 | 2.6 | 3,119 | 2.7 | 3,128 | 2.7 | -0.1 | -0.1 |
| Microvascular disease| 18,673 | 26.1 | 18,896 | 26.4 | 31,454 | 26.9 | 31,548 | 27.0 | -0.8 | -0.6 |
| CKD                  | 1,742 | 2.4 | 2,112 | 2.9 | 3,305 | 2.8 | 3,501 | 3.0 | -0.4 | -0.1 |
| Statin therapy       | 48,567 | 67.8 | 48,120 | 67.2 | 78,061 | 66.8 | 77,992 | 66.7 | 1.0 | 0.5 |
| Antihypertensive therapy | 59,172 | 82.6 | 58,711 | 82.0 | 95,336 | 81.6 | 95,247 | 81.5 | 1.0 | 0.5 |
| Loop diuretics       | 5,581 | 7.8 | 5,768 | 8.1 | 9,504 | 8.1 | 9,452 | 8.1 | -0.3 | 0.0 |
| Metformin            | 59,007 | 82.4 | 57,210 | 79.9 | 92,569 | 79.2 | 93,369 | 79.9 | 3.2 | 0.0 |
| SU                   | 29,943 | 41.8 | 28,973 | 40.4 | 47,582 | 40.7 | 47,771 | 40.9 | 1.1 | -0.5 |
| DPP-4 inhibitor      | 26,876 | 37.5 | 24,681 | 34.5 | 41,970 | 35.9 | 40,683 | 34.8 | 1.6 | -0.3 |
| TZD                  | 7,890 | 11.0 | 7,282 | 10.2 | 12,497 | 10.7 | 11,872 | 10.2 | 0.3 | 0.0 |
| GLP-1RA              | 14,880 | 20.8 | 11,916 | 16.6 | 23,513 | 20.1 | 19,843 | 17.0 | 0.7 | -0.4 |
| Insulin              | 21,548 | 30.1 | 20,411 | 28.5 | 34,844 | 29.8 | 34,251 | 29.3 | 0.3 | -0.8 |
| Index year:          |                                               |                                               |                                               |                                               |
| 2013                 | 9,266 | 12.9 | 12,811 | 17.9 | 16,426 | 14.1 | 21,068 | 18.0 | -1.2 | -0.1 |
| 2014                 | 34,832 | 48.6 | 27,152 | 37.9 | 58,305 | 49.9 | 46,303 | 39.6 | -1.3 | -1.7 |
| 2015                 | 27,534 | 38.4 | 31,669 | 44.2 | 42,168 | 36.1 | 49,528 | 42.4 | 2.3 | 1.8 |
| Index medication:    |                                               |                                               |                                               |                                               |
| Amylin analog        | NA | NA | 78 | 0.10 | NA | NA | 132 | 0.10 | 0.0 |
| Metformin            | NA | NA | 8,335 | 11.6 | NA | NA | 13,624 | 11.7 | -0.1 |
| SU                   | NA | NA | 12,781 | 17.8 | NA | NA | 20,725 | 17.7 | 0.1 |
| Drug Type | NA | NA | 11,525 | 16.1 | NA | NA | 18,350 | 15.7 | 0.4 |
|-----------|----|----|---------|------|----|----|---------|------|-----|
| TZD       | NA | NA | 4,200   | 5.9  | NA | NA | 6,954   | 5.9  | 0.0 |
| GLP-1RA   | NA | NA | 9,940   | 13.9 | NA | NA | 16,337  | 14.0 | -0.1|
| Insulin   | NA | NA | 23,438  | 32.7 | NA | NA | 38,529  | 33.0 | -0.3|
| Meglitinides | NA | NA | 986     | 1.4  | NA | NA | 1,623   | 1.4  | 0.0 |
| Acarbose, | NA | NA | 349     | 0.5  | NA | NA | 625     | 0.5  | 0.0 |
| Dapagliflozin | 16,091 | 22.5 | NA | NA | 25,940 | 0.222 | NA | NA | 0.3 |
| Empagliflozin | 5,783 | 8.1 | NA | NA | 9,097 | 0.078 | NA | NA | 0.3 |
| Canagliflozin | 49,758 | 69.5 | NA | NA | 81,862 | 0.7 | NA | NA | -0.5 |

*Defined as myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention) or occlusive peripheral artery disease on or ever prior to start; CKD=chronic kidney disease; CVD=cardiovascular disease; DPP-4=dipeptidyl peptidase-4; oGLD=other glucose-lowering drug; GLP-1RA= Glucagon-like peptide-1 receptor agonists; MI=myocardial infarction; NA=not applicable; PAD=peripheral arterial disease; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; SU=sulfonylurea; TZD=thiazolidinedione; US=United States
| Table S4. List of variables used to develop propensity score |
|----------------------------------------------------------|
| Gender                                                   |
| Age                                                      |
| Race (Caucasian, Black, Asian, Other)                     |
| Migrant                                                  |
| Frailty (yes)                                            |
| Index year                                               |
| Duration of Type 2 diabetes (years)                       |
| Cardiovascular history                                   |
| Smoker                                                   |
| HbA1c >7% (UK only)                                      |
| Body mass index ≥30 kg/m² (UK only)                       |
| Duration of Type 2 diabetes                              |
| Estimated Glomerular Filtration Rate <60 mL/min/1.73 m² (UK only) |
| Acute myocardial infarction                              |
| Stroke                                                   |
| Heart failure                                            |
| Unstable angina                                          |
| Atrial fibrillation                                      |
| Peripheral artery disease                                |
| Hypertension                                             |
| Coronary revascularization                               |
| Coronary artery bypass grafting                          |
| Percutaneous coronary intervention                       |
| Carotid intervention                                     |
| Chronic kidney disease                                   |
| Microvascular disease                                    |
| Nephropathy                                              |
| Peripheral neuropathy                                    |
Retinopathy
Bariatric surgery
Metformin
Sulfonylurea
DPP-4 inhibitor
thiazolidinedione
GLP-1 receptor agonist
Insulin
Statin therapy
Antihypertensive therapy
P2Y12 inhibitors
Antithrombotics
Warfarin
Anticoagulants
Low dose acetylsalicylic acid
Beta-blocker
Loop diuretics
Thiazides
Aldosterone antagonists
Weight loss drugs

DPP-4 = dipeptidyl peptidase-4; GLP-1 = Glucagon-like peptide-1.

The full list of variables for each individual country is dependent on the variables available in each database.
Table S5. Baseline characteristics for all countries/databases pre-match

|                        | US Truven MarketScan | Norway national registers | Denmark national registers | Sweden national registers | UK CPRD/THIN | Germany DPV |
|------------------------|-----------------------|---------------------------|---------------------------|---------------------------|--------------|-------------|
|                        | SGLT-2i               | oGLD                      | SGLT-2i                   | oGLD                      | SGLT-2i      | oGLD        | SGLT-2i     | oGLD        | SGLT-2i     | oGLD        | SGLT-2i     | oGLD        |
| Age, years, mean       |                       |                           |                           |                           |              |              |             |              |             |              |             |              |              |
|                        | 55.7                  | 58.1                      | 59.7                      | 61.2                      | 60.3         | 62.3         | 61.4        | 65.4         | 58.5        | 63.6         | 61.5        | 69.5         |
| Women                  | 45.5                  | 46.7                      | 39.4                      | 43.6                      | 39.5         | 44.6         | 37.7        | 42.5         | 41.2        | 42.8         | 42.0        | 47.6         |
| Established CVD*       | 9.5                   | 15.3                      | 19.3                      | 22.4                      | 29.6         | 32.0         | 24.5        | 30.3         | 15.2        | 22.1         | 35.1        | 48.2         |
| Acute MI               | 0.9                   | 1.9                       | 5.9                       | 6.6                       | 7.6          | 8.4          | 9.4         | 10.4         | 5.9         | 8.2          | 10.0        | 11.1         |
| Unstable angina        | 1.0                   | 1.5                       | 3.4                       | 3.0                       | 3.5          | 3.5          | 4.8         | 4.7          | 1.5         | 1.7          | 3.4         | 5.3          |
| HF                     | 2.5                   | 6.1                       | 4.1                       | 6.9                       | 3.9          | 5.3          | 6.2         | 9.8          | 2.3         | 5.1          | 5.3         | 9.4          |
| AF                     | 2.8                   | 5.5                       | 6.1                       | 9.3                       | 5.6          | 7.7          | 7.5         | 11.6         | 3.7         | 7.7          | 5.2         | 8.2          |
| Stroke                 | 3.5                   | 6.1                       | 2.9                       | 4.4                       | 7.2          | 9.5          | 5.3         | 8.7          | 3.1         | 5.5          | 5.3         | 9.3          |
| PAD                    | 2.6                   | 3.9                       | 5.6                       | 6.5                       | 5.0          | 6.4          | 4.7         | 5.8          | 3.0         | 4.3          | 21.5        | 31.5         |
| Microvascular disease  | 27.2                  | 23.6                      | 31.2                      | 22.6                      | 34.9         | 19.0         | 13.7        | 12.0         | 34.4        | 23.4         | 50.8        | 49.5         |
| CKD                    | 2.7†                  | 5.9†                      | 1.5                       | 5.5                       | 0.5          | 2.5          | 0.9         | 3.5          | 0.7†        | 2.3†         | 19.6        | 46.5         |
| Frailty(yes)           | 4.4                   | 11.5                      | 11.3                      | 21.7                      | 30.9         | 31.3         | 11.5        | 22.2         | 17.2†       | 22.7‡         | 19.8        | 47.7         |
| Glucose-lowering therapies |                  |                            |                           |                           |              |              |             |              |             |              |             |              |
| MET                    | 80.2                  | 41.5                      | 70.6                      | 35.3                      | 78.9         | 36.2         | 80.2        | 37.4         | 90.5        | 51.1         | 71.3        | 45.3         |
| SU                     | 41.2                  | 22.9                      | 36.8                      | 15.0                      | 28.4         | 12.6         | 23.2        | 11.9         | 51.6        | 27.0         | 10.1        | 14.5         |
| DPP-4i                 | 36.9                  | 13.1                      | 22.4                      | 6.1                       | 20.8         | 4.6          | 25.4        | 5.1          | 44.1        | 10.9         | 31.2        | 20.4         |
| TZD                    | 11.1                  | 4.9                       | 2.3                       | 0.6                       | 0.5          | 0.1          | 3.2         | 0.6          | 10.7        | 5.7          | 4.8         | 0.9          |
| GLP-1RA                | 22.4                  | 4.6                       | 15.8                      | 2.5                       | 35.3         | 5.0          | 21.6        | 2.2          | 22.9        | 3.2          | 17.5        | 4.0          |
| Insulin                | 30.8                  | 17.2                      | 19.0                      | 18.4                      | 28.7         | 16.5         | 44.4        | 25.1         | 21.6        | 5.1          | 48.4        | 61.6         |
| Cardiovascular therapies |                  |                            |                           |                           |              |              |             |              |             |              |             |              |
| Antihypertensive       | 81.8                  | 77.3                      | 69.9                      | 62.2                      | 79.1         | 64.5         | 79.4        | 72.2         | 75.7        | 73.6         | 65.3        | 56.7         |
| therapies | 2012 | 2013 | 2014 | 2015 | 2016 |
|-----------|------|------|------|------|------|
| Loop diuretics | 8.1  | 11.5 | 10.1 | 15.0 | 13.5 |
| Thiazide diuretics | –    | –    | 1.9  | 2.4  | 16.3 |
| Statin therapy | 67.2 | 58.7 | 62.4 | 49.4 | 75.6 |

Index year

| Index year | 2012 | 2013 | 2014 | 2015 | 2016 |
|------------|------|------|------|------|------|
| 2012       | –    | –    | –    | 0.2  | 2.8  |
| 2013       | 13.5 | 38.2 | 9.0  | 24.8 | 20.1 |
| 2014       | 49.1 | 39.5 | 32.7 | 28.4 | 31.4 |
| 2015       | 37.4 | 22.4 | 35.6 | 30.1 | 48.2 |
| 2016       | –    | –    | 22.7 | 16.7 | –    |

Data are % unless otherwise stated; *Defined as myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention) or occlusive peripheral artery disease on or ever prior to start; †CKD in the indicated database does not include end stage renal disease; ‡Frailty in the indicated database is defined as ≥1 hospitalization within 1 year prior to or on index date; §Includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, Ca^2+ channel blockers β-blockers, thiazides; AF=atrial fibrillation; CKD=chronic kidney disease; CPRD, Clinical Practice Research Datalink; CVD=cardiovascular disease; DPP-4i=dipeptidyl peptidase-4 inhibitor; DPV, Diabetes Patientenverlaufsdocumentation; eGFR=estimated Glomerular Filtration Rate; HF=heart failure; oGLD=other glucose-lowering drug; GLP-1RA=Glucagon-like peptide-1 receptor agonists; MET=metformin; MI=myocardial infarction; PAD=peripheral arterial disease; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; SU=sulfonylurea; THIN, The Health Improvement Network; TZD, thiazolidinedione
Table S6. Baseline characteristics for all countries/databases post-match

|                              | US Truven MarketScan | Norway national registers | Denmark national registers | Sweden national registers | UK CPRD/THIN | Germany DPV |
|------------------------------|-----------------------|---------------------------|---------------------------|---------------------------|--------------|-------------|
|                              | SGLT-2i N=116,899     | oGLD N=116,899            | SGLT-2i N=12,525          | oGLD N=12,525             | SGLT-2i N=9189 | oGLD N=9189 | SGLT-2i N=5231 | oGLD N=5231 | SGLT-2i N=1450 | oGLD N=1450 |
| Age, years, mean (SD)        | 55.8 (9.7)            | 60.4 (11.3)               | 60.4 (12.7)               | 60.4 (12.4)               | 61.5 (10.2)  | 61.4 (11.5) | 58.8 (10.5)  | 58.8 (10.8) | 61.7 (11.2) | 61.7 (11.7) |
| Women                        | 45.6                  | 41.4                      | 39.8                      | 39.7                      | 39.8         | 39.8         | 41.9          | 42.4         | 42.7          | 42.3          |
| Established CVD*             | 9.6                   | 20.0                      | 29.6                      | 24.5                      | 24.6         | 15.7         | 16.2          | 35.5         | 37.1          |
| Acute MI                     | 0.9                   | 5.9                       | 7.7                       | 9.3                       | 9.3          | 5.6          | 6.4           | 9.8          | 10.3          |
| Unstable angina              | 1.0                   | 3.4                       | 3.4                       | 4.7                       | 4.7          | 1.4          | 1.6           | 3.6          | 3.8           |
| HF                           | 2.6                   | 4.4                       | 3.9                       | 6.2                       | 6.2          | 2.4          | 2.5           | 5.5          | 5.7           |
| AF                           | 2.8                   | 6.6                       | 5.7                       | 7.5                       | 7.7          | 4.1          | 3.6           | 5.2          | 5.5           |
| Stroke                       | 3.6                   | 4.6                       | 7.3                       | 7.3                       | 7.2          | 3.3          | 3.7           | 5.6          | 5.9           |
| PAD                          | 2.7                   | 5.9                       | 5.1                       | 4.8                       | 4.6          | 3.0          | 2.8           | 21.7         | 21.3          |
| Microvascular disease        | 26.9                  | 31.4                      | 34.3                      | 33.0                      | 32.5         | 32.4         | 49.7          | 51.6         |
| CKD                          | 2.8†                  | 1.8                       | 0.5                       | 0.9                       | 0.8†         | 0.8†         | 19.5          | 28.4         |
| Frailty(yes)                 | 4.6                   | 12.2                      | 30.7                      | 11.6                      | 17.5†        | 20.5†        | 20.0          | 51.7         |
| Glucose-lowering therapies   |                       |                           |                           |                           |              |              |               |              |
| MET                          | 79.2                  | 69.2                      | 73.4                      | 78.3                      | 81.4         | 80.0         | 82.8          | 88.9         | 71.2          | 72.1          |
| SU                           | 40.7                  | 34.4                      | 34.2                      | 28.0                      | 29.2         | 23.0         | 24.1          | 50.9         | 51.4          | 10.3          |
| DPP-4i                       | 35.9                  | 21.0                      | 21.5                      | 20.1                      | 19.3         | 25.0         | 24.9          | 41.8         | 31.6          | 33.2          |
| TZD                          | 10.7                  | 2.1                       | 2.0                       | 3.0                       | 2.6          | 10.8         | 10.8          | 3.4          | 3.1           |
| GLP-1RA                      | 20.1                  | 13.6                      | 12.7                      | 33.6                      | 31.0         | 20.6         | 18.3          | 17.4         | 16.0          | 15.2          |
| Insulin                      | 29.8                  | 20.0                      | 21.6                      | 27.8                      | 28.6         | 43.8         | 42.7          | 17.5         | 49.3          | 48.6          |
| Cardiovascular therapies     |                       |                           |                           |                           |              |              |               |              |
| Antihypertensive therapy§    | 81.6                  | 70.9                      | 70.8                      | 78.9                      | 78.5         | 79.6         | 79.7          | 75.4         | 64.5          | 65.0          |
| Loop diuretics               | 8.1                   | 11.0                      | 11.3                      | 13.6                      | 14.1         | 15.2         | 14.9          | 12.8         | 5.2           | 5.5           |
| Thiazide diuretics           | 33.1                  | 33.1                      | 2.0                       | 16.3                      | 16.3         | 7.4          | 7.6           | 16.9         | 27.9          | 28.5          |
| Index year | 2012 | 2013 | 2014 | 2015 | 2016 |
|-----------|------|------|------|------|------|
| ACE inhibitors | 46.6 | 46.6 | 18.9 | 19.8 | 39.7 |
| ARBs      | 30.0 | 29.8 | 45.3 | 44.6 | 34.8 |
| Statin therapy | 66.6 | 66.7 | 62.4 | 62.6 | 75.3 |
| Aspirin   | NA   | NA   | 38.1 | 37.9 | 37.4 |

Data are % unless otherwise stated; *Defined as myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention) or occlusive peripheral artery disease on or ever prior to start †CKD in the indicated database does not include end stage renal disease; ‡Frailty in the indicated database is defined as ≥1 hospitalization within 1 year prior to or on index date; §Includes ACE inhibitors, ARBs, Ca^2+ channel blockers β-blockers, thiazides; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; AF=atrial fibrillation; CKD=chronic kidney disease; CPRD, Clinical Practice Research Datalink; CV=cardiovascular; CVD=cardiovascular disease; DPP-4i=dipeptidyl peptidase-4 inhibitor; DPV, Diabetes Patientenverlaufsdocumentation; eGFR=estimated Glomerular Filtration Rate; HF=heart failure; oGLD=other glucose-lowering drug; GLP-1RA= Glucagon-like peptide-1 receptor agonists; MET=metformin; MI=myocardial infarction; PAD=peripheral arterial disease; SGLT-2i=sodium-glucose cotransporter-2 inhibitor; SU=sulfonylurea; THIN, The Health Improvement Network; TZD, thiazolidinedione
Table S7. Standardized differences in baseline characteristics between SGLT-2i and oGLD treatment groups pre- and post-propensity match by country

|                      | Standardized Difference (%) |
|----------------------|----------------------------|
|                      | US Truven MarketScan (N=233,798) | Norway national registers (N=25,050) | Denmark national registers (N=18,468) | Sweden national registers (N=18,378) | UK CPRD/THIN (N=10,462) | Germany DPV (N=2900) |
|                      | Pre-match | Post-match | Pre-match | Post-match | Pre-match | Post-match | Pre-match | Post-match | Pre-match | Post-match | Pre-match | Post-match |
| Age                  | 21.1      | 0.3       | 11.3      | 0.8       | 15.3      | 4.3       | 33.2      | 0.6       | 43.1      | 0         | 27.2      | 0.1       |
| Women                | 2.4       | 0.9       | 6.8       | 2.6       | 8.5       | 0.2       | 7.9       | 0         | 3.4       | 1.0       | 4.3       | 0.2       |
| Established CVD*     | NA        | NA        | 6.0       | 0.8       | 4.3       | 1.4       | 10.4      | 0.1       | 17.7      | 1.5       | 10.4      | 0.9       |
| Acute MI             | 8.7       | 0.1       | 2.4       | 0.7       | 2.4       | 0.9       | 2.9       | 0.1       | 8.9       | 3.6       | 1.3       | 0.4       |
| Unstable angina      | 4.5       | 0         | 2.0       | 0.1       | 0         | 1.3       | 0.2       | 0         | 2.0       | 1.7       | 4.0       | 0.3       |
| Heart failure        | 17.5      | 0.1       | 9.8       | 0.3       | 5.6       | 1.3       | 10.5      | 0.2       | 14.9      | 0.1       | 6.8       | 0.2       |
| Stroke               | 11.9      | 0.2       | 6.3       | 0.9       | 6.9       | 0.6       | 10.7      | 0.9       | 12.0      | 2.0       | 6.7       | 0.3       |
| PAD                  | 6.8       | 0         | 3.1       | 0.4       | 5.0       | 0.7       | 3.8       | 0.5       | 6.6       | 1.0       | 9.2       | 0.3       |
| Coronary revascularization | NA | NA | 2.0       | 0.7       | NA | NA | NA | NA | 6.6 | 2.2 | 2.6 | 0.1 |
| CABG                 | 5.8       | 0.1       | 0.7       | 0.9       | NA | NA | 0.9 | 0.4 | 5.6 | 0.1 | NA | NA |
| PCI                  | 3.1       | 0.2       | 2.0       | 1.3       | NA | NA | 2.9 | 0.3 | 3.3 | 1.9 | NA | NA |
| Carotid intervention | 2.3       | 0.1       | NA | NA | NA | NA | NA | NA | 4.3 | NA | 0.4 | 0.4 |
| Atrial fibrillation  | 13.5      | 0.1       | 9.6       | 0.6       | 7.1       | 0.7       | 11.0      | 0.6       | 17.3      | 2.3       | 4.9       | 0.2       |
| Microvascular disease | NA | NA | 16.2 | 0.9 | 28.8 | 2.2 | 4.1 | 1.8 | 24.3 | 0 | 1.0 | 1.0 |
|                         | 15.5 | 1.0  | 16.3 | 0.4  | 15.3 | 1.2  | 13.2 | 1.4  | 12.7 | 0   | NA  | NA  |
|-------------------------|------|------|------|------|------|------|------|------|------|-----|-----|-----|
| CKD†                    |      |      |      |      |      |      |      |      |      |     |     |     |
| Frailty(yes)‡           | 26.4 | 0.2  | 22.2 | 1.6  | 0.7  | 0    | 22.7 | 0.3  | 13.8 | 7.7 | 26.2 | 18.9|
| Migrant                 | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA  | 8.0 | 0.6 |
| Smoker (yes)            | 6.5  | 0.6  | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 3.6 | 0.1 | 4.3 | 2.0 |
| HbA1c (mean)            | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 19.1| 11.0| 7.3 | 3.1 |
| HbA1c >7%               | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 39.1| 1.5 | 10.15| 1.8 |
| BMI (mean)              | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 42.4| 10.9| 14.55| 2.35|
| BMI≥30                  | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 44.6| 1.3 | 14.8 | 4.6 |
| Total cholesterol       | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 14.8| 0   | 5.3 | 2.1 |
| eGFR (mean)             | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 24.2| 10.9| 27.1 | 5.0 |
| eGFR <60                | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 46.8| 0.1 | 25.2 | 5.7 |
| Nephropathy             | 3.6  | 0.5  | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 0.1 | 0.3 | NA  | NA  |
| Peripheral neuropathy   | 6.1  | 0.1  | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 6.4 | 0.8 | 5.1 | 0.5 |
| Retinopathy             | 7.4  | 0.1  | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 23.8| 0.1 | 0.2 | 0.5 |
| Hypertension            | 9.4  | 0    | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 1.0 | 2.1 | NA  | NA  |
| Microalbuminuria        | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA  | 0.4 | NA  | 0.4 |
| Weight-loss drugs       | 8.2  | 0.8  | 3.2  | 0.4  | 2.1  | 0    | 6.3  | 0.4  | 7.1  | 0.9 | 1.2 | 0   |     |
| Bariatric surgery       | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 1.7 | 0.2 | 4.5 | 2.9 |
| Time from start         | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | NA   | 90.9| 0   | 55.2| 0.6 |
| T2D duration            | NA   | NA   | 67.4 | 1.7  | 9.4  | 15.5 | 77.9 | 1.6  | 43.8 | 1.7 | 8.9 | 0   |     |
| Glucose-lowering therapies |

52
|                |       |       |      |      |      |      |      |      |      |      |
|----------------|-------|-------|------|------|------|------|------|------|------|------|
|               | 61.3  | 7.7   | 80.4 | 6.3  | 76.5 | 6.0  | 96.0 | 2.7  | 21.7 | 0.5  |
| Metformin      | 86.2  | 1.7   |      |      |      |      |      |      |      |      |
| Sulfonylurea   | 44.2  | 0.5   | 31.1 | 2.2  | 76.5 | 2.0  | 52.1 | 1.1  | 5.5  | 0.6  |
| DPP-4 inhibitor| 43.1  | 1.0   | 37.5 | 1.6  | 25.6 | 0.1  | 79.9 | 1.4  | 8.9  | 0.9  |
| TZD            | 13.0  | 0.7   | NA   | NA   | 17.9 | 2.1  | 18.0 | 0.1  | NA   | NA   |
| GLP-1 RA       | 44.3  | 2.3   | 60.3 | 4.5  | 59.8 | 4.8  | 61.3 | 0.6  | 13.8 | 0.6  |
| Insulin        | 32.3  | 1.1   | 1.1  | 3.2  | 23.3 | 1.5  | 34.6 | 1.8  | 49.8 | 2.3  |

**Cardiovascular therapies**

|                        |       |       |      |      |      |      |      |      |      |      |
|------------------------|-------|-------|------|------|------|------|------|------|------|------|
| Antihypertensive therapy§| 11.0  | 0.2   | 13.2 | 0.3  | 27.6 | 0.8  | 14.2 | 0.1  | 5.0  | 0.9  |
| Loop diuretics         | 11.8  | 0.2   | 11.8 | 0.9  | 10.7 | 1.2  | 7.1  | 0.7  | 7.5  | 1.1  |
| Thiazide diuretics     | 5.1   | 0     | 2.7  | 0.5  | 2.9  | 0    | 1.7  | 0.8  | 1.7  | 0.1  |
| β-blocker              | 6.7   | 0.3   | 0.5  | 1.3  | 0.9  | 1.6  | 2.8  | 0.5  | 9.4  | 0.2  |
| Statin therapy         | 17.8  | 0.1   | 21.4 | 0.3  | 42.3 | 4.8  | 25.2 | 0.2  | 21.1 | 2.2  |
| Aspirin                | NA    | NA    | 7.2  | 0.4  | 13.6 | 1.7  | 5.6  | 0.4  | 2.1  | 2.5  |
| PY12 inhibitors        | NA    | NA    | 0.6  | 0.4  | 3.5  | 0.7  | 1.0  | 0.8  | 1.9  | 0.5  |
| Antiplatelets          | 6.0   | 0.2   | NA   | NA   | NA   | NA   | NA   | 0.2  | 2.1  | NA   |
| Warfarin               | NA    | NA    | 10.1 | 0.8  | 8.3  | 1.2  | 8.1  | 0.7  | 13.4 | 2.5  |
| Anticoagulants         | 10.6  | 0.3   | NA   | NA   | NA   | NA   | NA   | NA   | 14.2 | 1.8  |
| Aldosterone antagonists| 3.2   | 0     | 2.0  | 0.4  | 2.2  | 1.1  | 0.8  | 0.5  | 8.2  | 1.0  |

*Defined as myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention) or occlusive peripheral artery disease on or ever prior to start; †CKD in UK CPRD/THIN and US Truven MarketScan does not include end stage renal disease; ‡Frailty in UK CPRD/THIN is defined as ≥1 hospitalization within 1 year prior to index date; §Includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, Ca²⁺ channel blockers β-blockers, thiazides; BMI=body mass index; CABG=Coronary artery bypass
grafting; CKD=chronic kidney disease; CPRD, Clinical Practice Research Datalink; CV=cardiovascular; DPP-4=dipeptidyl peptidase-4; DPV=Diabetes Patientenverlaufsdatenbank; eGFR=estimated Glomerular Filtration Rate; GLP-1RA=Glucagon-like peptide-1 receptor agonist; MI=myocardial infarction; OAD=oral antidiabetic drugs; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; T2D=Type 2 diabetes; THIN=The Health Improvement Network; TZD=thiazolidinedione; UK=United Kingdom; US=United States; NA=not applicable (some characteristics were not available in every country)
Table S8. Composition of SGLT-2 inhibitor class in propensity matched cohorts

| SGLT-2 inhibitor patients, N | Canagliflozin, % | Dapagliflozin, % | Empagliflozin, % |
|-----------------------------|------------------|-----------------|-----------------|
| Hospitalization for heart failure analysis |                  |                 |                 |
| US Truven MarketScan        | 116,899          | 70              | 22              | 8               |
| Norway national registers   | 12,525           | 0               | 83              | 17              |
| Denmark national registers  | 9234             | 4               | 79              | 17              |
| Sweden national registers   | 9189             | 0               | 83              | 17              |
| UK CPRD/THIN                | 5231             | 2               | 86              | 12              |
| Germany DPV                 | 1450             | 2               | 64              | 33              |
| Total                       | 154,528          | 53              | 37              | 10              |
| All-cause death analysis, and composite (HHF or all-cause death) analysis |                  |                 |                 |
| US Truven MarketScan        | 71,632           | 69              | 22              | 8               |
| Norway national registers   | 12,525           | 0               | 83              | 17              |
| Denmark national registers  | 9234             | 4               | 79              | 17              |
| Sweden national registers   | 9189             | 0               | 83              | 17              |
| UK CPRD/THIN                | 5231             | 2               | 86              | 12              |
| Total                       | 107,811          | 47              | 43              | 11              |
Table S9. Index glucose-lowering medication classes for patients in the other GLD group: all countries combined (HHF analysis)

| Variable                        | Other GLD (N=154,528) |
|---------------------------------|-----------------------|
| Index medication*, n (%)        |                       |
| MET                             | 17,899 (11.6)         |
| SU                              | 26,203 (17.0)         |
| DPP-4 inhibitor                 | 26,957 (17.4)         |
| TZD                             | 7496 (4.9)            |
| GLP-1 receptor agonist          | 21,199 (13.7)         |
| Insulin                         | 51,838 (33.5)         |
| Acarbose                        | 708 (0.5)             |
| Amylin analog                   | 132 (0.1)             |
| Meglitinides                    | 2096 (1.4)            |

*In cases of ≥2 medications, one was randomly selected; DPP-4=dipeptidyl peptidase-4; GLD=glucose-lowering drug; GLP-1=Glucagon-like peptide-1; HHF=hospitalization for heart failure; MET=metformin; SU=sulfonylurea; TZD=thiazolidinedione
Table S10. Index glucose-lowering medication classes for patients in the other GLD group: all countries combined (all-cause death analysis and HHF or all-cause death analysis)

| Variable                          | Other GLD (N=107,811) |
|-----------------------------------|-----------------------|
| Index medication*, n (%)          |                       |
| MET                               | 12,134 (11.3)         |
| SU                                | 18,203 (16.9)         |
| DPP-4 inhibitor                   | 19,665 (18.2)         |
| TZD                               | 4731 (4.4)            |
| GLP-1 receptor agonist            | 14,743 (13.7)         |
| Insulin                           | 36,432 (33.8)         |
| Acarbose                          | 424 (0.4)             |
| Amylin analog                     | 78 (0.1)              |
| Meglitinides                      | 1401 (1.3)            |

*In cases of ≥2 medications, one was randomly selected; DPP-4=dipeptidyl peptidase-4; GLD=glucose-lowering drug; GLP-1= Glucagon-like peptide-1; HHF=hospitalization for heart failure; MET=metformin; SU=sulfonylurea; TZD= thiazolidinedione
Table S11: Number of patients, person-years at risk (on treatment), events and events/100 person-years (incidence rates) for each of the endpoints

| Country/database          | Patients, N | Person-years | Events, n | Events / 100 person-years |
|--------------------------|-------------|--------------|-----------|---------------------------|
| **Hospitalization for heart failure** |             |              |           |                           |
| US Truven MarketScan     | 233,798     | 125,904      | 298       | 0.24                      |
| Norway national registers| 25,050      | 25,166       | 278       | 1.10                      |
| Denmark national registers| 18,468     | 17,159       | 167       | 0.97                      |
| Sweden national registers| 18,378      | 13,688       | 191       | 1.40                      |
| UK CPRD/THIN             | 10,462      | 6833         | 16        | 0.23                      |
| Germany DPV              | 2900        | 1414         | 11        | 0.78                      |
| **Total**                | 309,056     | 190,164      | 961       | 0.51                      |
| **All-cause death**      |             |              |           |                           |
| US Truven MarketScan     | 143,264     | 80,556       | 250       | 0.31                      |
| Norway national registers| 25,050      | 25,368       | 364       | 1.43                      |
| Denmark national registers| 18,468     | 17,267       | 323       | 1.87                      |
| Sweden national registers| 18,378      | 23,946       | 317       | 1.32                      |
| UK CPRD/THIN             | 10,462      | 6853         | 80        | 1.17                      |
| **Total**                | 215,622     | 153,990      | 1334      | 0.87                      |
| **Composite of hospitalization for heart failure or all-cause death** |             |              |           |                           |
| US Truven MarketScan     | 143,264     | 80,496       | 424       | 0.53                      |
| Norway national registers| 25,050      | 25,166       | 622       | 2.47                      |
| Denmark national registers| 18,468     | 17,159       | 477       | 2.78                      |
| Sweden national registers| 18,378      | 13,688       | 364       | 2.66                      |
| UK CPRD/THIN             | 10,462      | 6833         | 96        | 1.40                      |
| **Total**                | 215,622     | 143,342      | 1983      | 1.38                      |

CPRD= Clinical Practice Research Datalink; DPV= Diabetes Patientenverlaufsdocumentation; SGLT-2=sodium-glucose cotransporter-2; THIN=The Health Improvement Network; UK=United Kingdom; US=United States
|                                | SGLT-2i | oGLD |                  |                  |                  |                  |
|--------------------------------|---------|------|------------------|------------------|------------------|------------------|
|                                | Events  | Person-years | Events/100 person-years | Events | Person-years | Events/100 person-years |
| Hospitalization for heart failure | 367     | 100,952 | 0.36             | 594     | 89,212 | 0.67             |
| All-cause death                 | 412     | 79,888 | 0.52             | 922     | 74,102 | 1.24             |
| Hospitalization for heart failure and all-cause death | 667     | 74,665 | 0.89             | 1316    | 68,677 | 1.92             |
Table S13. Mean on treatment follow-up time (in days) by country and endpoint

|                  | HHF  | ACD  | HHF/ACD |
|------------------|------|------|---------|
|                  | SGLT-2i | oGLD | SGLT-2i | oGLD | SGLT-2i | oGLD |
| US MarketScan/Truven | 217  | 176  | 225     | 186  | 225     | 186  |
| UK-CPRD/THIN      | 225  | 252  | 226     | 253  | 225     | 252  |
| Sweden            | 261  | 283  | 463     | 489  | 261     | 283  |
| Norway            | 364  | 370  | 366     | 374  | 364     | 370  |
| Denmark           | 328  | 351  | 330     | 353  | 328     | 351  |
| Germany           | 236  | 124  |         |      |         |      |
| Total             | 239  | 211  | 271     | 251  | 253     | 233  |

ACD=all-cause death; HHF=hospitalization for heart failure; oGLD=other glucose-lowering drug; SGLT-2i=sodium-glucose cotransporter-2
Table S14. Sensitivity analyses examining association between treatment with SGLT-2i vs. oGLD and outcomes of HHF in Sweden, among patients with both in- and outpatient hospital visits with primary diagnosis of heart failure, and those with only inpatient hospital visits with the primary diagnosis of heart failure.

|                                      | oGLD Events, n (events/100PY) | SGLT-2i Events, n (events/100PY) | Hazard ratio | 95% CI        | P-value |
|--------------------------------------|-------------------------------|---------------------------------|--------------|---------------|---------|
| On treatment, both in- and outpatient| 122 (17.1)                   | 69 (10.5)                       | 0.61         | 0.45-0.82     | 0.001   |
| On treatment, only inpatient         | 70 (9.8)                     | 30 (4.6)                       | 0.46         | 0.30-0.71     | <0.001  |
| ITT, both in- and outpatient         | 150 (17.1)                   | 101 (12.3)                     | 0.72         | 0.56-0.93     | 0.012   |
| ITT, only inpatient                  | 89 (10.1)                    | 49 (5.9)                       | 0.59         | 0.42-0.84     | 0.003   |

CI=confidence interval; HHF=hospitalization for heart failure; oGLD=other glucose-lowering drug; PY=person-years; SGLT-2i=sodium-glucose cotransporter-2.
SUPPLEMENTARY FIGURES

Figure S1: Patient selection flow-charts for each country

A. US Truven MarketScan

| Step                                                                 | SGLT2i Patients | Other GLD Patients |
|----------------------------------------------------------------------|-----------------|-------------------|
| New users of glucose-lowering drugs*                                 | 179,581         | 5,492,777         |
| Excluded for not meeting the study eligibility criteria              | 55,933          | 4,780,351         |
| Patients used in propensity score 1:1 matching                       | 123,648         | 712,426           |
| Excluded because match was not available                             | 6749            | 595,527           |
| Final cohort (after 1:1 match)                                       | 116,899         | 116,899           |
| For HHF analysis                                                      | 116,899         | 116,899           |
| For all-cause death analysis;                                        |                 |                   |
| For HHF or all-cause death analysis                                  | 71,632          | 71,632            |

*Any users of glucose-lowering drugs

B. Norway National Registers

| Step                                                                 | SGLT2i Patients | Other GLD Patients |
|----------------------------------------------------------------------|-----------------|-------------------|
| New users of glucose-lowering drugs                                  | 14,438          | 96,947            |
| Excluded for not meeting the study eligibility criteria*             | N/A             | N/A               |
| Patients used in propensity score 1:1 matching                       | 14,438          | 96,947            |
| Excluded because match was not available                             | 1913            | 84,422            |
| Final cohort (after 1:1 match)                                       | 12,525          | 12,525            |
| For HHF analysis                                                      | 12,525          | 12,525            |
| For all-cause death analysis;                                        |                 |                   |
| For HHF or all-cause death analysis                                  | 12,525          | 12,525            |

*Inclusion/exclusion criteria were already applied prior to the first step
### C. Denmark National Registers

| Step                                          | SGLT2i Patients | Other GLD Patients |
|-----------------------------------------------|-----------------|--------------------|
| New users of glucose-lowering drugs           | 9522            | 119,137            |
| Excluded for not meeting the study eligibility criteria* | N/A             | N/A                |
| Patients used in propensity score 1:1 matching | 9522            | 119,137            |
| Excluded because match was not available      | 288             | 109,903            |
| Final cohort (after 1:1 match)                | 9234            | 9234               |
| For HHF analysis                              | 9234            | 9234               |
| For all-cause death analysis;                 |                 |                    |
| For HHF or all-cause death analysis           |                 |                    |

*Inclusion/exclusion criteria were already applied prior to the first step

### D. Sweden National Registers

| Step                                          | SGLT2i Patients | Other GLD Patients |
|-----------------------------------------------|-----------------|--------------------|
| New users of glucose-lowering drugs           | 9337            | 200,284            |
| Excluded for not meeting the study eligibility criteria* | N/A             | N/A                |
| Patients used in propensity score 1:1 matching | 9337            | 200,284            |
| Excluded because match was not available      | 148             | 191,095            |
| Final cohort (after 1:1 match)                | 9189            | 9189               |
| For HHF analysis                              | 9189            | 9189               |
| For all-cause death analysis;                 |                 |                    |
| For HHF or all-cause death analysis           |                 |                    |

*Inclusion/exclusion criteria were already applied prior to the first step
E. UK CPRD/THIN

| Step | SGLT2i Patients | Other GLD Patients |
|------|-----------------|-------------------|
| New users of glucose-lowering drugs | 7556 | 73,436 |
| Excluded for not meeting the study eligibility criteria* | N/A | N/A |
| Patients used in the propensity score model | 7556 | 73,436 |
| Patients used in propensity score 1:1 matching** | 6298 | 65007 |
| Excluded because match was not available | 1067 | 59776 |
| Final cohort (after 1:1 match) | 5231 | 5231 |
| For HHF analysis | 5231 | 5231 |
| For all-cause death analysis; For HHF or all-cause death analysis | 5231 | 5231 |

*Inclusion/exclusion criteria were already applied prior to the first step; **Matching between cohorts was conducted within THIN patients and within CPRD patients with Hospital Episode Statistics (HES) and mortality data linkage (not overlapping with THIN)

F. Germany DPV

| Step | SGLT2i Patients | Other GLD Patients |
|------|-----------------|-------------------|
| New users of glucose-lowering drugs | 1532 | 23,991 |
| Excluded for not meeting the study eligibility criteria* | N/A | N/A |
| Patients used in propensity score 1:1 matching | 1532 | 23,991 |
| Excluded because match was not available | 87 | 22,546 |
| Final cohort (after 1:1 match) | 1450 | 1450 |
| For HHF analysis | 1450 | 1450 |

*Inclusion/exclusion criteria were already applied prior to the first step

CPRD=Clinical Practice Research Datalink; DPV= Diabetes Patientenverlaufsdocumentation; GLD=glucose-lowering drugs; HHF=hospitalization for heart failure; SGLT-2=sodium-glucose cotransporter-2 inhibitors; THIN=The Health Improvement Network; UK=United Kingdom; US=United States
Figure S2: Propensity score distribution by country pre-match

A

US Truven Marketscan
- Other GLD
- SGLT-2i

B

Norway national registers
- Other GLD
- SGLT-2i

C

Denmark national registers
- Other GLD
- SGLT-2i

D

Sweden national registers
- Other GLD
- SGLT-2i

E

UK CPRD/THIN
- Other GLD
- SGLT-2i

F

Germany DPV
- Other GLD
- SGLT-2i

CPRD=Clinical Practice Research Datalink; DPV=Diabetes Patientenverlaufsdocumentation; SGLT-2=sodium-glucose cotransporter-2; THIN=The Health Improvement Network; UK=United Kingdom; US=United States
Figure S3: Propensity score distribution by country post-match

CPRD=Clinical Practice Research Datalink; DPV=Diabetes Patientenverlaufsdokumentation; SGLT-2=sodium-glucose cotransporter-2; THIN=The Health Improvement Network; UK=United Kingdom; US=United States
Figure S4: Standardized difference between SGLT-2 inhibitor and other GLD treatment groups by country

A. US Truven MarketScan

Pre-match • Post-match

Standardized Difference

- Metformin
- DPP-4 inhibitor
- GLP-1 receptor agonist
- Sulfonylurea
- Insulin
- Frailty (yes)
- Thiazolidinedione
- Age (years)
- Statin therapy
- Heart failure
- Chronic kidney disease
- Atrial fibrillation
- Stroke
- Loop diuretics
- Anti-hypertensives
- Anticoagulants
- Hypertension
- Acute myocardial infarction
- Weight loss drugs
- Retinopathy
- Peripheral artery disease
- Beta-blocker
- Smoker
- Peripheral neuropathy
- Anti-platelets
- Carotid artery bypass grafting
- Thiazides
- Unstable angina
- Nephropathy
- Aldosterone antagonists
- Percutaneous coronary intervention
- Women
- Carotid intervention
B. Norway National Registers
C. Denmark National Registers

- Metformin
- GLP-1 receptor agonist
- Statin therapy
- DPP-4 inhibitor
- Sulfonylurea
- Microvascular disease
- Antihypertensives
- Insulin
- Age (years)
- Chronic kidney disease
- Low dose aspirin
- Loop diuretics
- T2D duration (days)
- Women
- Warfarin
- Atrial fibrillation
- Stroke
- Heart failure
- Peripheral artery disease
- Cardiovascular history
- P2Y12 inhibitors
- Thiazides
- Acute myocardial infarction
- Aldosterone antagonists
- Weight loss drugs
- Beta-blocker
- Frailty (yes)
- Unstable angina

Standardized Difference
D. Sweden National Registers

- T2D duration (days)
- Metformin
- Sulfonylurea
- GLP-1 receptor agonist
- Insulin
- Age (years)
- DPP-4 inhibitor
- Statin therapy
- Frailty (yes)
- Thiazolidinedione
- Antihypertensives
- Chronic kidney disease
- Atrial fibrillation
- Stroke
- Heart failure
- Cardiovascular history
- Warfarin
- Women
- Loop diuretics
- Weight loss drugs
- Low dose aspirin
- Microvascular disease
- Peripheral artery disease
- Acute myocardial infarction
- Percutaneous coronary intervention
- Beta-blocker
- Thiazides
- Bariatric surgery
- P2Y12 inhibitors
- Carotid artery bypass grafting
- Aldosterone antagonists
- Unstable angina

![Graph showing standardized differences in matched and unmatched data.](image)
E.  UK CPRD/THIN
DPP-4=dipeptidyl peptidase-4; eGFR=estimated Glomerular Filtration Rate; GLP-1=Glucagon-like peptide-1; oGLD=other glucose-lowering drug; SGLT-2i=sodium-glucose cotransporter -2 inhibitor; T2D=Type 2 diabetes
Figure S5: Stepwise sensitivity analysis (sequentially removing comparators): Outcome of hospitalization for heart failure

A. On treatment, adjusted* – TZD removed

*Adjusted for history of heart failure, age, gender, frailty, history of myocardial infarction, history of atrial fibrillation, hypertension, obesity / body mass index, duration of diabetes, ACE inhibitor or ARB use; β-blocker or α-blocker use, Ca²⁺-channel blocker use, loop diuretic use, thiazide diuretic use; TZD=thiazolidinedione
B. On treatment, adjusted* – TZD and insulin removed

P-value for SGLT-2i vs. oGLD comparison: <0.001
P-value for Heterogeneity: 0.879

| Dataset                          | Hazard Ratio (95% CI) |
|----------------------------------|-----------------------|
| US Truven MarketScan             | 0.62 [0.47, 0.83]     |
| Norway National Registers        | 0.64 [0.47, 0.86]     |
| Denmark National Registers       | 0.54 [0.34, 0.86]     |
| Sweden National Registers        | 0.70 [0.46, 1.08]     |
| **Total**                        | **0.63 [0.53, 0.75]** |

*Adjusted for history of heart failure, age, gender, frailty, history of myocardial infarction, history of atrial fibrillation, hypertension, obesity / body mass index, duration of diabetes, ACE inhibitor or ARB use; β-blocker or α-blocker use, Ca⁺-channel blocker use, loop diuretic use, thiazide diuretic use; TZD= thiazolidinedione
C. On treatment, adjusted* – TZD, insulin and SU removed

*Adjusted for history of heart failure, age, gender, frailty, history of myocardial infarction, history of atrial fibrillation, hypertension, obesity / body mass index, duration of diabetes, ACE inhibitor or ARB use; β-blocker or α-blocker use, Ca²⁺-channel blocker use, loop diuretic use, thiazide diuretic use; SU=sulfonylurea; TZD=thiazolidinedione
Figure S6: Outcome of hospitalization for heart failure excluding patients with baseline GLP-1 RAs, on treatment, adjusted*

P-value for SGLT-2i vs. oGLD comparison: <0.001
P-value for Heterogeneity: 0.229

| Dataset                          | Hazard Ratio (95% CI) |
|----------------------------------|-----------------------|
| US Truven MarketScan             | 0.54 [0.42, 0.69]     |
| Norway National Registers        | 0.60 [0.46, 0.79]     |
| Denmark National Registers       | 0.88 [0.59, 1.32]     |
| Sweden National Registers        | 0.56 [0.40, 0.79]     |
| Total                            | 0.61 [0.51, 0.73]     |

*Adjusted for history of heart failure, age, gender, frailty, history of myocardial infarction, history of atrial fibrillation, hypertension, obesity / body mass index, duration of diabetes, ACE inhibitor or ARB use; β-blocker or α-blocker use, Ca⁺-channel blocker use, loop diuretic use, thiazide diuretic use; SU=sulfonylurea; TZD=thiazolidinedione

Data from Germany and UK not included as they contributed too few HHF events after removal of GLP1-RA class
Figure S7: Outcomes for hospitalization for heart failure, all-cause death, and hospitalization for heart failure or all-cause death for the SGLT-2 inhibitor versus other GLD treatment groups

A. US only

| Outcome                                           | Hazard Ratio | 95% CI       |
|---------------------------------------------------|--------------|--------------|
| Hospitalization for heart failure                 | 0.55         | [0.44, 0.69] |
| All-cause death                                   | 0.38         | [0.29, 0.50] |
| Hospitalization for heart failure or all-cause death | 0.44       | [0.36, 0.54] |

B. European countries combined

| Outcome                                           | Hazard Ratio | 95% CI       |
|---------------------------------------------------|--------------|--------------|
| Hospitalization for heart failure                 | 0.63         | [0.51, 0.79] |
| All-cause death                                   | 0.51         | [0.44, 0.60] |
| Hospitalization for heart failure or all-cause death | 0.57       | [0.51, 0.62] |

P-value for SGLT-2i versus oGLD comparison <0.001 for all endpoints; oGLD=other glucose-lowering drug;
SGLT-2i=sodium-glucose cotransporter-2; US=United States
References for the supplementary appendices

1. Hansen LG, Chang S. Health research data for the real world: The marketscan databases. White Paper. Truven Health Analytics, Ann Arbor, USA, July 2011. http://truvenhealth.com/portals/0/assets/PH_11238_0612_TEMP_MarketScan_WP_FINAL.pdf. Last Accessed: May 12, 2017.

2. Truven Health Analytics. Comparative Effectiveness Research. Truven Health Analytics, Ann Arbor, USA, 2012. https://truvenhealth.com/portals/0/assets/ACRS_11228_0912_CompEffectResearch_SS_Web.pdf. Last Accessed: May 12, 2017.

3. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data resource profile: Clinical practice research datalink (cprd). Int J Epidemiol. 2015;44:827-836. doi:10.1093/ije/dyv098

4. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the general practice research database: A systematic review. Br J Clin Pharmacol. 2010;69:4-14. doi:10.1111/j.1365-2125.2009.03537.x

5. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the general practice research database as an example of a uk primary care data resource. Ther Adv Drug Saf. 2012;3:89-99. doi:10.1177/2042098611435911

6. Carbonari DM, Saine ME, Newcomb CW, Blak B, Roy JA, Haynes K, Wood J, Gallagher AM, Bhullar H, Cardillo S, Hennessy S, Strom BL, Lo Re V, 3rd. Use of demographic and pharmacy data to identify patients included within both the clinical practice research datalink (cprd) and the health improvement network (thin). Pharmacoepidemiol Drug Saf. 2015;24:999-1003. doi:10.1002/pds.3844

7. IMS Health. Statistics. IMS Health, UK, 2015. http://www.epic-uk.org/our-data/statistics.shtml. Last Accessed: May 12, 2017.

8. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of the health improvement network (thin) database: Demographics, chronic disease prevalence and mortality rates. Inform Prim Care. 2011;19:251-255.

9. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. Inform Prim Care. 2004;12:171-177.

10. Lewis JD, Schinnar R, Bilkner WB, Wang X, Strom BL. Validation studies of the health improvement network (thin) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf. 2007;16:393-401. doi:10.1002/pds.1335

11. Ruigomez A, Martin-Merino E, Rodriguez LA. Validation of ischemic cerebrovascular diagnoses in the health improvement network (thin) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf. 2010;19:579-585. doi:10.1002/pds.1919

12. Cea Soriano L, Soriano-Gabarro M, Garcia Rodriguez LA. Validity and completeness of colorectal cancer diagnoses in a primary care database in the united kingdom. Pharmacoepidemiol Drug Saf. 2016;25:385-391. doi:10.1002/pds.3877

13. Martin-Merino E, Ruigomez A, Johansson S, Garcia-Rodriguez LA. Hospitalised ischaemic cerebrovascular accident and risk factors in a primary care database. Pharmacoepidemiol Drug Saf. 2011;20:1050-1056. doi:10.1002/pds.2201

14. Vassilev ZP, Ruigomez A, Soriano-Gabarro M, Garcia Rodriguez LA. Diabetes, cardiovascular morbidity, and risk of age-related macular degeneration in a primary care population. Invest Ophthalmol Visual Sci. 2015;56:1585-1592. doi:10.1167/iovs.14-16271

15. Rodriguez LA, Ruigomez A, Wallander MA, Johansson S. Acid-suppressive drugs and community-acquired pneumonia. Epidemiology. 2009;20:800-806. doi:10.1097/EDE.0b013e3181b5f27d
16. Martin-Merino E, Ruigomez A, Johansson S, Wallander MA, Garcia-Rodriguez LA. Study of a cohort of patients newly diagnosed with depression in general practice: Prevalence, incidence, comorbidity, and treatment patterns. *Prim Care Companion J Clin Psychiatry*. 2010;12:PCC.08m00764. doi:10.4088/PCC.08m00764blu

17. Martin-Merino E, Ruigomez A, Wallander MA, Johansson S, Garcia-Rodriguez LA. Prevalence, incidence, morbidity and treatment patterns in a cohort of patients diagnosed with anxiety in uk primary care. *Fam Pract*. 2010;27:9-16. doi:10.1093/fampra cmp071

18. Requena G, Abbing-Karahagopian V, Huerta C, De Bruin ML, Alvarez Y, Miret M, Hesse U, Gardarsdottir H, Souverein PC, Slattery J, Schneider C, Rottenkolber M, Schmiedl S, Gil M, De Groot MC, Bate A, Ruigomez A, Garcia Rodriguez LA, Johansson S, de Vries F, Montero D, Schlienger R, Reynolds R, Klungel OH, de Abajo FJ. Incidence rates and trends of hip/femur fractures in five european countries: Comparison using e-healthcare records databases. *Calcif Tissue Int*. 2014;94:580-589. doi:10.1007/s00223-014-9850-y

19. Garcia Rodriguez LA, Johansson S, Nagy P, Cea Soriano L. Use of proton pump inhibitors and the risk of coronary events in new users of low-dose acetylsalicylic acid in uk primary care. *Thromb Haemost*. 2014;111:131-139. doi:10.1160/TH13-07-0542

20. Diabetes-Patienten-Verlaufsdocumentation (DPV). Ulm University-DPV. Ed. Esther Bollow. *Ulm University, Ulm, Germany*. [http://buster.zibmt.uni-ulm.de/dpv/index.php/en/](http://buster.zibmt.uni-ulm.de/dpv/index.php/en/). Last Accessed: May 12, 2017.

21. Heidemann C, Du Y, Paprott R, Haftenberger M, Rathmann W, Scheidt-Nave C. Temporal changes in the prevalence of diagnosed diabetes, undiagnosed diabetes and prediabetes: Findings from the german health interview and examination surveys in 1997-1999 and 2008-2011. *Diabet Med*. 2016;33:1406-1414. doi:10.1111/dme.13008

22. Norhammar A, Bodegard J, Nystrom T, Thresson M, Eriksson JW, Nathanson D. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: A nationwide study in sweden, 2006-2013. *Diabetologia*. 2016;59:1692-1701. doi:10.1007/s00125-016-3971-y

23. Norwegian Institute of Public Health. Norwegian Cause of Death Registry (DAPYNE database). [Norwegian Institute of Public Health, Oslo, Norway](https://www.fhi.no/en/hn/health-registries/cause-of-death-registry/). Last Accessed: May 12, 2017.

24. Statistics Denmark. (DAFFODIL database). [Statistics Denmark, Copenhagen, Denmark](http://www.dst.dk/en). Last Accessed: May 12, 2017.

25. The R Foundation. The R Project for Statistical Computing. [https://www.R-project.org/](https://www.R-project.org/). Last Accessed: May 12, 2017.

26. Viechtbauer W. Conducting meta-analyses in r with the metafor package. *J Stat Soft*. 2010;36:1-48.