Replication of Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME Trial)

May 27, 2021

1. RCT Details

This section provides a high-level overview of the RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

1.1 Title

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME trial)

1.2 Intended aim(s)

To determine the long-term cardiovascular (CV) safety of empagliflozin, as well as investigating potential benefits on macro-/microvascular outcomes.

1.3 Primary endpoint for replication and RCT finding

Major Adverse Cardiovascular Events, Including CV Death, Nonfatal Myocardial Infarction (MI), and Nonfatal Stroke

1.4 Required power for primary endpoint and noninferiority margin (if applicable)

For the test of noninferiority for the primary outcome with a margin of 1.3 at a one-sided level of 0.0249, at least 691 events were required to provide a power of at least 90% on the assumption of a true hazard ratio of 1.0.

1.5 Primary trial estimate targeted for replication

HR = 0.86 (95% CI 0.74–0.99) comparing empagliflozin to placebo (Zinman et al., 2015)

2. Person responsible for implementation of replication in Aetion

Ajinkya Pawar, Ph.D. implemented the study design in the Aetion Evidence Platform. S/he is not responsible for the validity of the design and analytic choices. All implementation steps are recorded and the implementation history is archived in the platform.

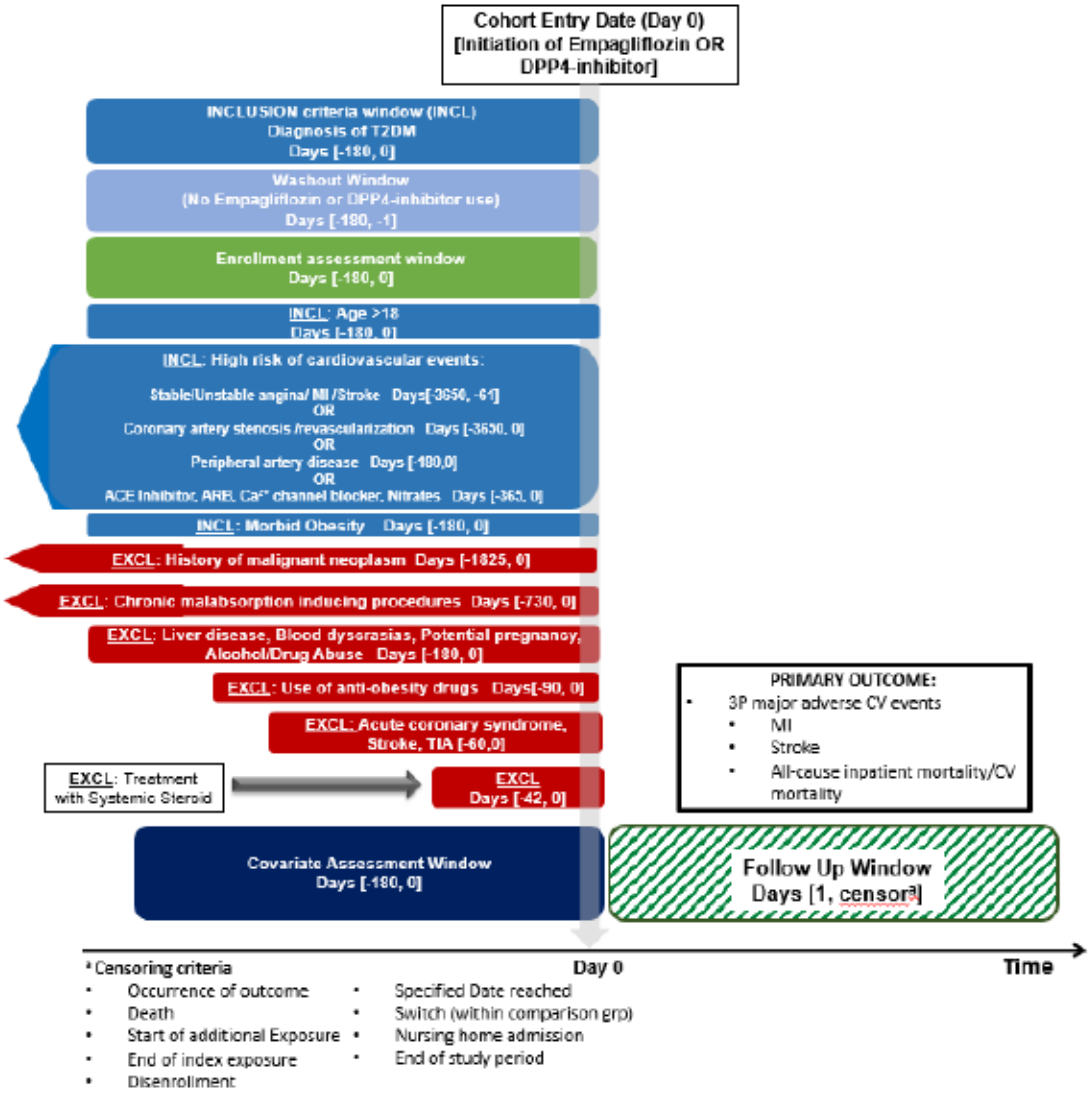
3. Data Source(s)

United/Optum, MarketScan, Medicare

4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expedited review.

Design Diagram – EMPA-REG TRIAL REPLICATION



5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, cohort study design comparing empagliflozin to the DPP-4 inhibitor (DPP4i) antidiabetic class. DPP4is serve as a proxy for placebo, since this class of antidiabetic drugs is not known to have an impact on the outcome of interest. The comparison against DPP4 inhibitors is the **primary comparison**. The patients will be required to have continuous enrollment during the baseline period of 180 days before initiation of empagliflozin or a comparator drug (cohort entry date). Follow-up for the outcome (3P-MACE), begins the day after drug initiation. As in the trial, patients are allowed to take other antidiabetic medications during the study.

5.2 Important steps for cohort formation

5.2.1 Eligible cohort entry dates

Market availability of empagliflozin in the U.S. started on August 1, 2014.

- For Marketscan and Medicare: Aug 1, 2014-Dec 31, 2017 (end of data availability).
- For Optum: Aug 1, 2014-Mar 31, 2019 (end of data availability).

5.2.2 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix A** and are summarized in the flowcharts below.

5.3 Flowchart of the study cohort assembly

	Optum		Marketscan		Medicare*	
	Less Excluded Patients	Remaining Patients	Less Excluded Patients	Remaining Patients	Less Excluded Patients	Remaining Patients
All patients		74,864,884		191,990,035		23,466,175

Patients who used exposure or a reference between Aug 1, 2014 to Dec 2017 (for Marketscan/Medicare)/March 2019 (for Optum)	-74,294,229	570,655	-191,387,941	602,094	-22,015,231	1,450,944
Patients who have continuous 6 months registration in the database	-77,109	493,546	-41,856	560,238	-387,934	1,063,010
Excluded due to prior use of referent	-281,236	212,310	-365,720	194,518	-738,467	324,543
Excluded due to prior use of exposure	-45,709	166,601	-35,973	158,545	-25,468	299,075
Excluded because patient qualified in >1 exposure category	-716	165,885	-1,192	157,353	-546	298,529
Excluded based on missing Age	-6	165,879	0	157,353	0	298,529
Excluded based on missing Gender	-8	165,871	0	157,353	0	298,529
Excluded based on Inclusion 1- Age >=18	-5	165,866	-44	157,309	0	298,529
Excluded based on Inclusion 2- DM Type 2 with ICD-10 codes	-4,270	161,596	-6,031	151,278	-3,158	295,371
Excluded based on Inclusion 5- High risk of cardiovascular events	-13,525	148,071	-15,359	135,919	-12,190	283,181
Excluded based on Inclusion 6- BMI ≤45 kg/m2 (excluded morbid obese patients)	-4,602	143,469	-3,000	132,919	-6,924	276,257
Excluded based on Exclusion 2- Liver disease with ICD-10 and Exclusion 5- Bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption	-458	143,011	-2,049	130,870	-7,325	268,932
Excluded based on Exclusion 6- Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells	-9,118	133,893	-5,029	125,841	-29,542	239,390
Excluded based on Exclusion 7- History of Malignant Neoplasm past 5 years	-3,550	130,343	-2,870	122,971	-11,850	227,540
Excluded based on Exclusion 9- Obesity claim or drug 3 months prior	-466	129,877	-2,810	120,161	-4,053	223,487
Excluded based on Exclusion 10- Use of corticosteroids	-1504	128,373	-1147	119,014	-2,798	220,689
Excluded based on Exclusion 12- Pregnancy OR Contraceptive	-398	127,975	-627	118,387	-425	220,264
Excluded based on Exclusion 13- Alcohol or drug abuse	-67	127,908	-258	118,129	-568	219,696
Excluded based on Exclusion 16- Acute coronary syndrome, stroke, or transient ischemic attack within 2 months	-390	127,518	-677	117,452	-2,625	217,071
Final cohort		**127,518**		**117,452**		**217,071**

* Medicare database includes only patients with at least one diagnosis for diabetes, heart failure, or cerebrovascular disease.

**Exclusion 2 and 5 collapsed to adhere to CMS cell suppression guidelines.

6. Variables

6.1 Exposure-related variables:

Study drug:
The study exposure of interest is initiation of empagliflozin. Initiation will be defined by no use of empagliflozin or a comparator in the prior 6 months before treatment initiation (washout period).

Comparator agents-

- Initiators of empagliflozin will be compared to initiators of-
    - DPP4i

Because empagliflozin and comparators are frequently used as second or third line treatments of T2DM, we expect it to be unlikely that empagliflozin and comparators are initiated in patients with substantially different baseline risk for proposed outcomes.

6.2 Covariates:

- Age
- Sex
- Combined Comorbidity Index (CCI), measured over the baseline covariate assessment period, defined as 180 days prior to and including index date

Covariates listed above represent only a small subset of covariates that will ultimately be controlled for in the design and analysis. We use the covariates above only for initial feasibility analyses to judge whether there is likely to be sufficient overlap between treatment groups to proceed with the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and the initial power assessment and are listed in Table 1 (**Appendix B**). These covariates are based on those used by Patorno et al. (2019).

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

Effectiveness outcomes of interest (definitions provided in **Appendix A**):

- **Primary outcome**: 3-point major adverse cardiovascular events (MACE), i.e., non-fatal myocardial infarction, non-fatal stroke, or CV mortality
- Secondary outcomes: Individual components:
    - Hospital admission for MI (for purposes of this individual component, fatal MI is included)
    - Hospital admission for stroke (for purposes of this individual component, fatal stroke is included)
    - All-cause mortality/CV mortality:
        - All-cause inpatient mortality identified using discharge status codes will be used as a proxy for "CV mortality" in commercial databases

Information on CV mortality through data linkage with the National Death Index (NDI) will only become available at a later date for Medicare and will be used in secondary analyses.

Control outcomes of interest (control outcomes only serve to assess aspects of study validity but are not further interpreted):

1. Diabetes Ketoacidosis (we expect to see a positive association; Neal et al., 2017)
2. Heart failure (we expect to see a protective effect; Neal et al., 2017)

Control outcome definitions

Outcome	Definition	Comments
Control Outcomes		
Diabetic Ketoacidosis	Inpatient ICD-9 diagnosis: 250.1x	Note- The corresponding ICD-10 codes will also be used
Heart Failure	Inpatient ICD-9 diagnosis (primary diagnosis): 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93	Note- The corresponding ICD-10 codes will also be used

6.3.2 Study follow-up

Both as-treated (AT) and intention-to-treat (ITT) analyses will be conducted with treatment defined as the index drug on the day of cohort entry. Because adherence in the real world databases is expected to be much worse than in the trial, the AT analysis is the **primary** analysis, as it targets the relative hazard of outcomes on treatment.

For the AT analyses, the follow-up will start the day after initiation of empagliflozin and comparator and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest, unless otherwise specified for selected outcomes,
- The date of end of continuous registration in the database,
- End of the study period,
- Measured death event occurs,
- Nursing home admission
    - Nursing home admissions are considered a censoring event because the data sources utilized typically provide little to no data on a patient, particularly on drug utilization, after admission. We will utilize this as an exclusion reason for cohorts for the same reason.
- The date of drug discontinuation, defined as the date of the last continuous treatment episode of the index drug (empagliflozin and comparator) plus a defined grace period (i.e., 30 days after the end of the last prescription's days' supply in main analyses).
- The date of augmentation or switching from an exposure to a comparator or any other agent in the comparator class and vice versa (e.g. switching from saxagliptin to linagliptin would be a censoring event);
    - A dosage change on the index treatment does not fulfill this criterion
    - An added treatment that is not part of the exposure or comparator group does not fulfill this criterion (e.g. if a empagliflozin user adds insulin, he or she does not get censored at the time of insulin augmentation)

For the ITT analyses, the censoring based on the augmentation/switching and treatment discontinuation will be replaced with a maximum allowed follow-up time of 365 days.

7. Initial Feasibility Analysis

Aetion report name:

For empagliflozin vs. DPP4i

Optum-https://bwh-dope.aetion.com/projects/details/654/results/43641/result/0

Marketscan- https://bwh-dope.aetion.com/projects/details/655/results/43642/result/0

Medicare- https://bwh-dope.aetion.com/projects/details/653/results/43643/result/0

Date conducted: 10/29/2019

Complete Aetion feasibility analysis using age, sex, and CCI as the only covariates and the primary endpoint (Section 6.3.1) as the

outcome. No measures of association will be computed nor will incidence rates stratified by treatment group.

- Report patient characteristics by treatment group
- Report summary parameters of the overall study population
- Report median follow-up time by treatment group
- Report reasons for censoring in the overall study population

8. Initial Power Assessment

Aetion report name:

For empagliflozin vs. DPP4i

Optum- https://bwh-dope.aetion.com/projects/details/654/results/43644/result/0

Marketscan- https://bwh-dope.aetion.com/projects/details/655/results/43645/result/0

Medicare- https://bwh-dope.aetion.com/projects/details/653/results/43646/result/0

Date conducted: 10/29/2019

In order to complete the initial power analysis, the dummy outcome of a 90-day gap in database enrollment will be used. This outcome is used to ensure that no information on the comparative risks of the outcomes of interest are available at this stage. Complete a 1:1 PS-matched comparative analysis using this outcome. PS should include only 3 covariates: age, sex, and combined comorbidity index. Power calculations are based on the formulas from Chow et al. (2008).

- Stop analyses until feasibility and power are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Jessica Franklin	Date reviewed:	11/4/2019
Reviewed by FDA:		Date reviewed:	
Reasons for stopping analysis (if required):			

9. Balance Assessment after PS matching

Aetion report name:
Optum- https://bwh-dope.aetion.com/projects/details/654/results/45417/result/0
Marketscan- https://bwh-dope.aetion.com/projects/details/655/results/45418/result/0
Medicare- https://bwh-dope.aetion.com/projects/details/653/results/45419/result/0

Date conducted: 11/30/2019

After review of initial feasibility and power analyses, complete creation of the remaining covariates (see Table 1 below for list of covariates). Again, using the dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates (excluding laboratory values, which are missing in some patients).

- Provide plot of PS distributions stratified by treatment group.

  Note- Please refer to **Appendix B**.

- Report covariate balance after matching.

  Note- For Table 1, please refer to **Appendix B**.

- Report reasons for censoring by treatment group.

	Overall	**Referent**	**Exposure**
Dummy Outcome	0 (0.00%)	0 (0.00%)	0 (0.00%)
Death	228 (0.22%)	142 (0.27%)	86 (0.17%)
Start of an additional exposure	3,474 (3.35%)	1,357 (2.62%)	2,117 (4.08%)
End of index exposure	50,368 (48.55%)	26,107 (50.33%)	24,261 (46.77%)
Specified date reached (Dec 16/Sep 17)	35,687 (34.40%)	17,006 (32.78%)	18,681 (36.01%)
End of patient enrollment	11,469 (11.05%)	5,415 (10.44%)	6,054 (11.67%)
Switch to other DPP4i (for censoring) + nursing home admission	2,526 (2.43%)	1,849 (3.56%)	677 (1.31%)

- Report follow-up time by treatment group.

	Median Follow-Up Time (Days) [IQR]		
Patient Group	**Optum**	**Marketscan**	**Medicare**
Overall Patient Population	118 [58-243]	118 [58-268]	118 [58-215]
Referent	118 [58-228]	118 [58-218]	118 [58-218]
Exposure	118 [58-262]	118 [58-211]	118 [58-211]

- Report overall risk of the primary outcome.

	Optum	Marketscan	Medicare
Risk per 1,000 patients	12.51	7.31	23.78

10. Final Power Assessment

Date conducted: 12/1/2019

- Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in Section 9. All other parameters in the table should be the same as in Section 8. If the study is to be implemented in more than one database, copy and paste excel sheet to report power for each database separately and for the pooled analysis that uses data from all databases together. Power calculations are based on the formulas from Chow et al. (2008).
    - Pooled

Superiority Analysis		**Non-inferiority Analysis**	
Number of patients matched		Number of patients matched	
Reference	51,876	Reference	51,876
Exposed	51,876	Exposed	51,876
Risk per 1,000 patients	14.53	Risk per 1,000 patients	14.53
Desired HR from RCT	0.86	Assumed HR from RCT	1
Alpha (2-sided)	0.05	Alpha (2-sided)	0.05
		Non-inferiority margin	1.3
Number of events expected	1507.51656	Number of events expected	1507.51656
Power	0.833482663	Power	0.999136066

- Optum

Superiority Analysis		**Non-inferiority Analysis**	
Number of patients matched		Number of patients matched	
Reference	23,348	Reference	23,348
Exposed	23,348	Exposed	23,348
Risk per 1,000 patients	12.51	Risk per 1,000 patients	12.51
Desired HR from RCT	0.86	Assumed HR from RCT	1
Alpha (2-sided)	0.05	Alpha (2-sided)	0.05
		Non-inferiority margin	1.3
Number of events expected	584.16696	Number of events expected	584.16696
Power	0.445473008	Power	0.886984947

- Marketscan

Superiority Analysis		**Non-inferiority Analysis**	
Number of patients matched		Number of patients matched	
Reference	16,256	Reference	16,256
Exposed	16,256	Exposed	16,256
Risk per 1,000 patients	7.31	Risk per 1,000 patients	7.31
Desired HR from RCT	0.86	Assumed HR from RCT	1
Alpha (2-sided)	0.05	Alpha (2-sided)	0.05
		Non-inferiority margin	1.3
Number of events expected	237.66272	Number of events expected	237.66272
Power	0.213506619	Power	0.524870241

- Medicare

Superiority Analysis		**Non-inferiority Analysis**	
Number of patients matched		Number of patients matched	
Reference	12,272	Reference	12,272
Exposed	12,272	Exposed	12,272
Risk per 1,000 patients	23.78	Risk per 1,000 patients	23.78
Desired HR from RCT	0.86	Assumed HR from RCT	1
Alpha (2-sided)	0.05	Alpha (2-sided)	0.05
		Non-inferiority margin	1.3
Number of events expected	583.65632	Number of events expected	583.65632
Power	0.44515838	Power	0.886719001

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board. Reviewers evaluate the results of the analyses described above in Sections 9 and 10, including numbers of patients, balance in patient characteristics, follow-up time, and reasons for censoring by treatment group, as well as overall rates of outcomes and study power.

Reviewed by PI:	Jessica Franklin	Date reviewed:	12/5/19
Reviewed by FDA:	David Martin	Date reviewed:	12/20/2019
Reasons for stopping analysis (if required):			

11. Study Confidence and Concerns

Deadline for voting on study confidence and listing concerns: 12/20/19

- If final feasibility and power analyses are reviewed and approved, proceed to the remaining protocol steps.
- All study team and advisory board members that review this protocol should at this stage provide their level of confidence for the success of the RWD study in the Google Form. This form also provides space for reviewers to list any concerns that they feel may contribute to a failure to replicate the findings of the RCT, including differences in study populations, poor measurement of study variables, or residual confounding. All responses will be kept confidential and individual-level results will only be shared with the individual respondent.

12. Register study protocol on clinicalTrials.gov

Date conducted:

- Register the study on clinicalTrials.gov and upload this document.

13. Comparative Analyses

Aetion report name:
Date conducted:

13.1 For **primary analysis:**

- In the PS-matched cohort from Section 9, calculate the HR for each outcome for empagliflozin versus referent patients using a Cox proportional hazards model.

13.2 For secondary analyses:

- In the pre-matched cohort, perform asymmetrical trimming to remove patients with PS values below the 2.5th percentile of treated patients and above the 97.5th percentile of untreated patients. In the trimmed cohort, calculate the HR for empagliflozin versus referent patients using a Cox proportional hazards model, adjusting for deciles of the PS.

14. Requested Results

14.1 Results from primary and secondary analyses:

Separately for each endpoint:

Analysis	No. exposed events	No. referent events	Exposed rate	Referent rate	HR (95% CI)
Crude					
Primary analysis					
Analysis 2					
…					

HR, Hazard Ratio; CI, Confidence Interval.

15. References

American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85. doi:10.2337/dc18-S008.

Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. **page 177**

Patorno E, Pawar A, Franklin JM, et al. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study. Circulation. 2019;139:2822-30.

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015;373(22):2117-28.

Appendix A

#	Empa-Reg trial definitions	Implementation in routine care	References/Rationale	Color coding
	Trial details- Secondary Indication; 4a- Unintended 5 with label change		**Please see the following Google Drive for further details or any missing information:** https://drive.google.com/open?id=[illegible]	Criteria
	EXPOSURE vs. COMPARISON		**ICD-10 codes are not listed in this document because of excel cell size limitations and excessive number of ICD-10 codes. Full ICD-10 code lists will be available in the above Google Drive Folder (link above). ICD-9 to ICD-10 code conversions were completed using a SAS macro that implements forward/ backward mapping based on the CMS ICD-9 to ICD-10 mapping:** https://www.nber.org/data/icd9-icd-10-cm-and-pcs-crosswalk-general-equivalence-mapping.html	Adequate mapping in claims
	empagliflozin 10 mg, empagliflozin 25 mg, or placebo	**Empagliflozin vs. individual non-gliflozin antidiabetic class (ie, a DPP-4i, a GLP-1RA, and a sulfonylurea)**	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119	Intermediate mapping in claims
	PRIMARY OUTCOME			Poor mapping or cannot be measured in claims
	Primary composite endpoint of time to occurrence of CV death, non-fatal MI, non-fatal stroke. HR = 0.86 (95% CI 0.74–0.99)	**Measured 1 days after drug initiation in diagnosis position specified below and inpatient care setting:** **Inpatient mortality/MI/Stroke –** **For MI** **Any diagnosis position in inpatient care setting** **ICD-9 diagnosis:** 410.X (acute myocardial infarction) excluding 410.x2 (subsequent episode of care) **For stroke** **Primary diagnosis position in inpatient care setting** **ICD-9 discharge diagnosis:** 430.xx Subarachnoid hemorrhage (SAH) 431.xx Intracerebral hemorrhage (ICH) 433.x1 Occlusion and stenosis of precerebral arteries with cerebral infarction 434.xx (excluding 434.x0) Occlusion and stenosis of cerebral arteries with cerebral infarction 436.x Acute, but ill-defined cerebrovascular events **Mortality- See Mortality Sheet.**	For MI: →PPV 94% in Medicare claims data [Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. American heart journal 2004;148:99-104.] →PPV 88.4% in commercially-insured population [Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiology and Drug Safety 2010;19:596-603.] For stroke: PPV of 85% or higher for ischemic stroke PPV ranging from 80% to 98% for hemorrhagic stroke →[Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiology and Drug Safety 2012;21 Suppl 1:100-28.] →[Tirschwell DL, Longstreth WT, Jr. Validating administrative data in stroke research. Stroke; a journal of cerebral circulation 2002;33:2465-70.] →[Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. Pharmacoepidemiology and drug safety 2008;17:20-6.]	Can't be measured in claims but not important for the analysis
	INCLUSION CRITERIA			
1	Age ≥18 years (For Japan: Age ≥20 years); (For India: Age ≥18 years and ≤65 years)	Age ≥18 years at drug initiation		
2	Diagnosis of type 2 diabetes mellitus prior to informed consent	**Measured 180 days prior to drug initiation in any diagnosis position and the inpatient or outpatient care setting** Type 2 Diabetes ICD-9 diagnosis: 250.x0, 250.x2	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177	
3	On a diet and exercise regimen	N/A		
4	Insufficient glycemic control, defined as either:	-		
4a	• Drug-naïve (no anti-diabetes agents for >=12 weeks prior to randomization) + HbA1c ≥7.0% (≥53 mmol/mol) and ≤9.0% (≤75 mmol/mol) at screening	(Covered below in 4b)	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177	
4b	• Taking any background anti-diabetes therapy (except pioglitazone in Japan) + HbA1c ≥7.0% (≥53 mmol/mol) and ≤10.0% (≤86 mmol/mol) at screening	During the cohort creation, depending on the comparison group, we will require new-use (defined as no use 180 days prior to index date) of empagliflozin and a comparator drug		
	– Background anti-diabetes therapy had to be unchanged for ≥12 weeks prior to randomization	-		
	– If background anti-diabetes therapy included insulin, insulin dose had to be unchanged by >10% from the dose at randomization in the previous 12 weeks			
5	High risk of cardiovascular events, defined by >=1 of the following:	**Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any diagnosis position and the inpatient or outpatient care setting** Stable angina ICD-9 diagnosis: 413.xx **OR** **Measured 365 days prior to drug initiation as a dispensing of one of the following medications** **ACE inhibitor** Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril **ARB** Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan **Calcium channel blocker** Diltiazem, mibefradil, verapamil, amlodipine, clevidipine, bepridil, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine **Nitrates** Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, ranolazine		

Appendix A

5a	• History of myocardial infarction >2 months prior to informed consent	**Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any diagnosis position and the inpatient or outpatient care setting -** Acute MI ICD-9 diagnosis: 410.xx, Old MI ICD-9 diagnosis: 412.xx	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
5b	• Evidence of multi-vessel CAD i.e. in ≥ 2 major coronary arteries or the left main coronary artery, documented by any of the following:	-	
	– Presence of significant stenosis: ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography)	**Measured 1 days prior to drug initiation to 3650 days prior to drug initiation in any diagnosis position and the inpatient or outpatient care setting** Coronary atherosclerosis and other forms of chronic ischemic heart disease ICD9 diagnosis: 414.xx	
	– Previous revascularization (percutaneous transluminal coronary angioplasty ± stent or coronary artery bypass graft >2 months prior to consent	Coronary revascularization: CABG: **Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any procedure position and inpatient care setting** -CPT-4: 33510 – 33536, 33545, 33572. OR – **Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any procedure position and inpatient or outpatient care setting** -ICD-9 procedure: 36.1x, 36.2x PTCA: **Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any procedure position and inpatient care setting** -CPT-4: 92973, 92982, 92984, 92995, 92996, 92920 – 92921, 92924 – 92925, 92937, 92938, 92941, 92943, 92944 OR – **Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any procedure position and inpatient or outpatient care setting** -ICD-9 procedure: 00.66, 36.01, 36.02, 36.03, 36.05, 36.09 Stenting: **Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any procedure position and inpatient care setting**-CPT-4: 92980, 92981, 92928 – 92929, 92933 -92934 OR – **Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any procedure position and inpatient or outpatient care setting**-ICD-9 procedure: 36.06, 36.07 Transmyocardial revascularization: **Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any procedure position and inpatient care setting**-CPT-4: 33140, 33141 OR – **Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any procedure position and inpatient or outpatient care setting**-ICD-9 procedure: 36.31-36.34	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
	• Evidence of single-vessel CAD, ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography) not subsequently successfully revascularized, with at least 1 of the following:	-	
	– A positive non-invasive stress test for ischemia	-	
	– Hospital discharge for unstable angina ≤12 months prior to consent	**Measured 365 days prior to drug initiation in any diagnosis position and the inpatient care setting** ACS/unstable angina ICD-9 diagnosis: 411.xx	
5c	• Unstable angina >2 months prior to consent with evidence of single- or multi-vessel CAD	**Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any diagnosis position and the outpatient care setting** ACS/unstable angina ICD-9 diagnosis: 411.xx	
5d	• History of stroke (ischemic or hemorrhagic) >2 months prior to consent	**Measured 61 days prior to drug initiation to 3650 days prior to drug initiation in any diagnosis position and the inpatient or outpatient care setting** Any stroke ICD-9 diagnosis: 430.xx, 431.xx, 433.xx, 434.xx, 436.xx	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
5e	• Occlusive peripheral artery disease documented by any of the following:	**Measured 180 days prior to drug initiation in any procedure position and the inpatient or outpatient care setting** Peripheral arterial stenting or surgical revascularition ICD-9 procedure: 39.25, 39.50, 39.99	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
	– Limb angioplasty, stenting, or bypass surgery	**Measured 180 days prior to drug initiation in any procedure position and the inpatient or outpatient care setting** Lower extremity bypass: ICD-9 procedure: 39.25, 39.29 (Outpatient only) CPT-4: 35351, 35355, 35361, 35363, 35371, 35372, 35521, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35621, 35623, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35666, 35671, 35570, 35582, 35583, 35585, 35587, 35637, 35638, 35681, 35682, 35683 Lower extremity endarterectomy, stenting, angioplasty, or atherectomy: ICD-9 procedure: 38.18, 38.19 (Outpatient only) CPT-4: 35454, 35456, 35459, 35470, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 37207, 37208, 37220-37235 Other peripheral vascular surgery: ICD-9 procedure: 38.08, 38.09, 38.38, 38.39,38.48, 38.49, 39.5x, 39.9x (Outpatient only) CPT-4: 35256, 35286, 35381, 35879	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
	– Limb or foot amputation due to circulatory insufficiency	**Measured 180 days prior to drug initiation in any diagnosis/procedure position and the inpatient or outpatient care setting** Lower extremity amputation ICD-9 diagnosis: V49.7x ICD-9 procedure: 84.10-84.18 (Outpatient only) CPT-4: 27590, 27591, 27592, 27880, 27881, 27882, 27884, 27886, 27888, 27889, 28800, 28805, 28810, 28820, 28825	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177

Appendix A

	– Evidence of significant peripheral artery stenosis (>50% on angiography, or >50% or hemodynamically significant via non-invasive methods) in 1 limb	**Measured 180 days prior to drug initiation in any diagnosis position and the inpatient or outpatient care setting** Peripheral vascular disease ICD-9 diagnosis: 440.20 –440.24, 440.29 –440.32, 440.3, 440.4, 443.9	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
	– Ankle brachial index <0.9 in ≥1 ankle	**Measured 180 days prior to drug initiation in any diagnosis position and the inpatient or outpatient care setting** Ankle brachial index <0.9 ICD-9 diagnosis: 440.21	
6	BMI ≥45 kg/m2 at baseline	**Measured 180 days prior to drug initiation in any diagnosis position and the inpatient or outpatient care setting** Morbid Obesity ICD-9 diagnosis: 278.01	
7	An estimated glomerular filtration rate [eGFR] of at least 30 ml per minute per 1.73 m2 of body-surface area	N/A	
8	Signed and dated written informed consent prior to screening in accordance with Good Clinical Practice and local legislation	N/A	
	EXCLUSION CRITERIA		
1	Uncontrolled hyperglycemia with glucose >240 mg/dl. (>13.3 mmol/L) after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day)	N/A	we decided not to apply this criteria because we can captured hyperglycemia but can't capture severity of it and we may end up losing many patients at this step. In case we decide to apply it, the codes would be ICD-9 790.21 and ICD-10 R73.01
2	Indication of liver disease, defined by serum levels of alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase above 3 x upper limit of normal (ULN) during screening or run-in phase	**Measured 180 days prior to and including day of drug initiation in any diagnosis/procedure position and the inpatient or outpatient care setting** Liver disease ICD-9 diagnosis: 070.xx, 570.xx-573.xx, 456.0x-456.2x, 576.8x, 782.4x, 789.5x ICD-9 procedure: 38.1x, 42.91	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
3	Planned cardiac surgery or angioplasty within 3 months	N/A	
4	Estimated glomerular filtration rate <30 ml/min/1.73m2 (according to the Modification of Diet in Renal Disease equation) at screening or during run-in phase	N/A	N/A
5	Bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption	**Measured 730 days prior to drug initiation in any procedure position and inpatient or outpatient care setting** CPT-4: 43644 -LRYBG -Laparoscopic Roux-en-Y gastric bypass (Roux limb 150 cm or less) 43645 -LRYGBX- Laparoscopic gastric bypass with small intestine reconstruction to limit absorption 43770 -LAGB- Laparoscopic adjustable gastric band 43846 -ORYGB-Open Roux-en-Y gastric bypass (Roux limb 150 cm or less) 43847 -ORYGBX-Open gastric bypass with small intestine reconstruction to limit absorption	Hatoum, Ida J, et al. "Clinical Factors Associated With Remission of Obesity-Related Comorbidities After Bariatric Surgery." JAMA Surg. 2016;151(3):130-137. doi:10.1001/jamasurg.2015.3231
6	Blood dyscrasias or any disorders causing hemolysis or unstabilened blood cells e.g. malaria, babesiosis, hemolytic anemia)	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting** Diseases of the blood and blood-forming organs ICD-9 diagnosis: 280.xx-289.xx, ICD-10 diagnosis: D50.xx-D77.xx Malignant neoplasms of lymphoid, hematopoietic and related tissue ICD-9 diagnosis: 200.xx-208.xx, ICD-10 diagnosis: C81.xx-C96.xx Hemochromatosis ICD-9 diagnosis: 275.0x, ICD-10 diagnosis: E83.11x	
7	Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years	**Measured 1825 days prior to drug initiation in any diagnosis position and inpatient or outpatient care setting** History of malignant neoplasm ICD-9 diagnosis: 140.xx-208.xx (except 173.xx, non-melanoma skin cancer)	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
8	Contraindications to background therapy according to the local label	N/A	
9	Treatment with anti-obesity drugs 3 months prior to informed consent or any other treatment at time of screening leading to unstable body weight (e.g. surgery, aggressive diet regimen, etc.)	**Measured 90 days prior to drug initiation as a dispensing of one of the following medications** Use of orlistat, lorcaserin, phentermine/topiramate (fixed combo), bupropion/naltrexone (fixed combo), phentermine, diethylpropion, phendimetrazine, benzphetamine, sibutramine, dexfenfluramine, fenfluramine OR **Measured 90 days prior to drug initiation in any diagnosis/procedure position and inpatient or outpatient care setting** ICD-9 diagnosis: 278.0, 278.00, 278.01, 278.03, 539.xx, 649.1x, 649.2x, V85.3x, V85.4x ICD-9 procedure: 43.82, 43.89, 44.31, 44.38, 44.39, 44.68, 44.69, 44.95, 45.51, 45.91 CPT-4: 43644, 43645, 43659, 43770, 43842, 43843, 43844, 43845, 43846, 43847, 43999, S2082	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
10	Treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent	**Measured 42 days prior to drug initiation as a dispensing of one of the following medications** Corticosteroids: Cortisone, hydrocortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
11	Any uncontrolled endocrine disorder except T2DM	-	We are unable to capture "uncontrolled" endocrine disorders.

Appendix A

12	Pre-menopausal women (last menstruation ≤1 year prior to informed consent) who were nursing, pregnant, or of child-bearing potential and were not practicing an acceptable method of birth control, or did not plan to continue using this method throughout the study, or did not agree to submit to periodic pregnancy testing during the trial	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting-** Encounter for contraceptive management ICD-9 diagnosis: V25 **OR** Pregnancy - See "Pregnancy" for ICD-9 diagnosis and procedure codes. **OR** **Measured 180 days prior to and including day of drug initiation as a dispensing of one of the following medications** Non-oral contraceptives (brand names)- Depo-subQ Provera 104 Depo-Provera, generic Mirena Ortho Evra Nuvaring Implanon Oral contraceptives (generic names)- See "oral contraceptives - generic" sheet. Oral contraceptives (brand names)-See "oral contraceptives - brand" sheet.	Krumme, Alexis A, et. al. "Study protocol for the dabigatran, apixaban, rivaroxaban, edoxaban, warfarin comparative effectiveness research study." J. Comp. Eff. Res. (2018);7(1). 57-66. doi: 10.2217/cer-2017-0053. We excluded patients using contraceptives because this trial includes non-pregnant women, patients without childbearing potential, and patients who have childbearing potential but are taking precautions such as oral contraceptives (among many other ways) to avoid pregnancy during the trial period. It is impossible to implement such inclusion in real-world data, as childbearing potential is not recorded in claims. In this trials setting, this limitation to implement as an inclusion criteria is due to the following: i) lack of recording of contraceptives and other precautions to avoid pregnancy and ii) patients with diabetes and baseline CV tend to be older and are not likely to be at childbearing age. Therefore, we assumed that patients taking oral contraceptives have childbearing potential, so if they were to stop contraceptive use during follow-up, they could then become pregnant. Also, just to note, this exclusion of contraceptives use excludes very few patients (typically less than 0.1% of patients).
	–Acceptable methods of birth control include tubal ligation, transdermal patch, intrauterine devices/systems, oral, implantable or injectable contraceptives, sexual abstinence, double barrier method, vasectomy of partner		
13	Alcohol or drug abuse within 3 months of informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting-** Alcohol abuse or dependence ICD-9 diagnosis: 291.xx, 303.xx, 305.0x, 571.0x, 571.1x, 571.2x, 571.3x, 357.5x, 425.5x, E860.0x, V11.3x Drug abuse or dependence ICD-9 diagnosis: 292.xx, 304.xx, 305.2x-305.9x, 648.3x	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
14	Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial or participating in another trial involving an investigational drug and/or follow-up	N/A	
15	Any clinical condition that would jeopardize patient safety while participating in this clinical trial (in Canada, this included current genito-urinal infection or genito-urinal infection within 2 weeks prior to informed consent)	N/A	
16	Acute coronary syndrome, stroke, or transient ischemic attack within 2 months prior to informed consent	**Measured 60 days prior to day of drug initiation in any diagnosis position and inpatient or outpatient care setting-** ACS/unstable angina ICD-9 diagnosis: 411.xx Stroke ICD-9 diagnosis : 430.xx Subarachnoid hemorrhage (SAH) 431.xx Intracerebral hemorrhage (ICH) 433.x1 Occlusion and stenosis of precerebral arteries with cerebral infarction 434.x1 Occlusion and stenosis of cerebral arteries with cerebral infarction 436.x Acute, but ill-defined cerebrovascular events. TIA ICD-9 diagnosis: 435.xx Acute MI ICD-9 diagnosis: 410.X (acute myocardial infarction) excluding 410.x2 (subsequent episode of care)	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119 Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
17	In South Africa: blood pressure >160/100 mmHg at screening	N/A	

Appendix A

Trial ID	sNDA21
Trial Name (with web links)	EMPA-REG OUTCOME
Trial Name (with pdf links)	EMPA-REG OUTCOME
NCT	NCT01131676
Trial category	Secondary indication
Therapeutic Area	Endocrinology
RCT Category	4a- Unintended S with label change
Brand Name	Synjardy
Generic Name	Empagliflozin; metformin hydrochloride
Sponsor	Boehringer Ingelheim
Year	2016
Measurable endpoint	Primary composite endpoint of CV death, non-fatal MI, non-fatal stroke
Exposure	Empagliflozin
Comparator	Placebo
Population	95% on Anti-hypertensive therapy, 80% on Lipid-lowering therapy & 89% on Anti-coagulants
Trial finding	HR = 0.86 (95% CI 0.74–0.99)
No. of Patients	7,064
Non-inferiority margin	HR = 1.3
Assay Sens. Endpoint	
Assay Sens. Finding	
Power	0.90. For the test of noninferiority for the primary outcome with a margin of 1.3 at a one-sided level of 0.0249, at least 691 events were required to provide a power of at least 90% on the assumption of a true hazard ratio of 1.0.
Blinding	Double-blinded
Statistical Method	Accidental superiority, the non-inferiority margin was chosen as 1.3 based on Food and Drug Administration (FDA) Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes
Approval indication	Proposes a new indication for Synjardy based on results of the cardiovascular safety study 1245.25, the EMPA-REG OUTCOME trial.

Appendix A

Mortality- Dependent on data source.

1. All-cause mortality / inpatient mortality
Identified using the vital status file-

Medicare
Identified using the discharge status codes-

Optum-
- 20 = EXPIRED
- 21 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 22 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 23 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 24 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 25 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 26 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 27 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 28 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 29 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 40 = EXPIRED AT HOME (HOSPICE)
- 41 = EXPIRED IN A MEDICAL FACILITY (HOSPICE)
- 42 = EXPIRED - PLACE UNKNOWN (HOSPICE)

Truven-
- 20 - Died
- 22 - Died
- 23 - Died
- 24 - Died
- 25 - Died
- 26 - Died
- 27 - Died
- 28 - Died
- 29 - Died
- 40 - Other died status or Expired at home (Hospice claims only) (depends on year)

Appendix A

- 41 - Other died status or Expired in medical facility (Hospice claims only) (depends on year)
- 42 - Other died status or Expired - place unknown (Hospice claims only) (depends on year)
- 21 - Died or Disch./Transf. to court/law enforcement (depends on year)

2. CV mortality

Information on CV mortality through data linkage with the National Death Index (NDI) will be available for Medicare at a later date. We will conduct secondary analyses using CV mortality at that time.

Appendix A

Antidiabetic class	Specific agent	Notes
SGLT2-inhibitors	Canagliflozin	Approved 3/29/2013
	Dapagliflozin	
	Empagliflozin	
	Ertugliflozin	Approved Dec 21, 2017
2nd generation sulfonylureas	Glimepiride	
	Glipizide	
	Glyburide	
DPP-4 inhibitors	Alogliptin	
	Linagliptin	
	Saxagliptin	
	Sitagliptin	
GLP-1 receptor agonist (GLP1-RA)	Exenatide	
	Liraglutide	
	Albiglutide	Approved April 15, 2014 and discontinued July 26, 2017
	Dulaglutide	Approved Sep 18, 2014
	Lixisenatide	Approved July 28, 2016
	Semaglutide	Approved Dec 5, 2017
Insulin	Insulin Aspart	
	Insulin Aspart/Insulin Aspart Protamine	
	Insulin Degludec	
	Insulin Detemir	
	Insulin Glargine	
	Insulin Glulisine	
	Insulin human isophane (NPH)	
	Insulin human regular *(search with NPH, don't want bf-pk)*	
	Insulin human regular/ Insulin human isophane (NPH)	
	Insulin Lispro	
	Insulin Lispro/Insulin Lispro Protamine	
Glitazones	Pioglitazone	

Appendix A

Glitazones	Rosiglitazone	
Meglitinides	Nateglinide	
	Repaglinide	
Alpha-glucosidase inhibitors	Acarbose	
	Miglitol	
Pramlintide	Pramlintide	
1st generation sulfonylureas	Acetohexamide	
	Chlorpropamide	
	Tolazamide	
	Tolbutamide	

Appendix A

drug_class	Brand Name
oral contraceptive	Apri;
oral contraceptive	Desogen;
oral contraceptive	Ortho-Cept;
oral contraceptive	Reclipsen
oral contraceptive	Kariva;
oral contraceptive	Mircette
oral contraceptive	Cyclessa;
oral contraceptive	Velivet
oral contraceptive	Yasmin
oral contraceptive	Yaz
oral contraceptive	Demulen 1/35;
oral contraceptive	Kelnor;
oral contraceptive	Zovia 1/25
oral contraceptive	Demulen 1/50;
oral contraceptive	Zovia 1/50
oral contraceptive	Alesse;
oral contraceptive	Aviane;
oral contraceptive	Lessina;
oral contraceptive	Lutera
oral contraceptive	Nordette;
oral contraceptive	Portia;
oral contraceptive	Levora
oral contraceptive	Lybrel
oral contraceptive	Seasonale;
oral contraceptive	Quasense;
oral contraceptive	Jolessa
oral contraceptive	Seasonique
oral contraceptive	Empresse;
oral contraceptive	Triphasil;
oral contraceptive	Trivora
oral contraceptive	Ovcon 35
oral contraceptive	Balziva;

Appendix A

oral contraceptive	Femcon Fe
oral contraceptive	Brevicon;
oral contraceptive	Nortrel 0.5/35;
oral contraceptive	Modicon;
oral contraceptive	Necon 0.5/35
oral contraceptive	Norinyl 1/35;
oral contraceptive	Nortrel 1/35;
oral contraceptive	Ortho-Novum 1/35;
oral contraceptive	Necon 1/35
oral contraceptive	Ovcon 50;
oral contraceptive	Necon 1/50
oral contraceptive	Ortho-Novum 10/11
oral contraceptive	Aranelle;
oral contraceptive	Tri-Norinyl
oral contraceptive	Ortho-Novum 7/7/7;
oral contraceptive	Necon
oral contraceptive	Micronor;
oral contraceptive	Nor-QD;
oral contraceptive	Camila;
oral contraceptive	Errin;
oral contraceptive	Jolivette
oral contraceptive	Junel 21 1/20;
oral contraceptive	Junel 21 Fe 1/20;
oral contraceptive	Loestrin 21 1/20;
oral contraceptive	Loestrin 21 Fe 1/20;
oral contraceptive	Loestrin 24 Fe;
oral contraceptive	Microgestin 1/20
oral contraceptive	Microgestin Fe 1/20
oral contraceptive	Junel 21 1.5/30;
oral contraceptive	Junel 21 Fe 1.5/30;
oral contraceptive	Loestrin 1.5/30;
oral contraceptive	Loestrin Fe 1.5/30
oral contraceptive	Microgestin 1.5/30

Appendix A

oral contraceptive	Microgestin Fe 1.5/30
oral contraceptive	Estrostep Fe;
oral contraceptive	Tilia Fe;
oral contraceptive	TriLegest Fe
oral contraceptive	Ortho-Cyclen;
oral contraceptive	Sprintec;
oral contraceptive	MonoNessa;
oral contraceptive	Previfem
oral contraceptive	Ortho Tri-Cyclen Lo;
oral contraceptive	Tri-Previfem;
oral contraceptive	TriNessa
oral contraceptive	Ortho Tri-Cyclen;
oral contraceptive	Tri-Sprintec
oral contraceptive	Cryselle;
oral contraceptive	Lo/Ovral;
oral contraceptive	Low-Ogestrel
oral contraceptive	Ovral;
oral contraceptive	Ogestrel
oral contraceptive	Zovia 1/50
oral contraceptive	Alesse;
oral contraceptive	Aviane;
oral contraceptive	Lessina;
oral contraceptive	Lutera
oral contraceptive	Nordette;
oral contraceptive	Portia;
oral contraceptive	Levora
oral contraceptive	Lybrel
oral contraceptive	Seasonale;
oral contraceptive	Quasense;
oral contraceptive	Jolessa
oral contraceptive	Seasonique
oral contraceptive	Empresse;
oral contraceptive	Triphasil;

Appendix A

oral contraceptive	Trivora
oral contraceptive	Ovcon 35
oral contraceptive	Balziva;
oral contraceptive	Femcon Fe
oral contraceptive	Brevicon;
oral contraceptive	Nortrel 0.5/35;
oral contraceptive	Modicon;
oral contraceptive	Necon 0.5/35
oral contraceptive	Norinyl 1/35;
oral contraceptive	Nortrel 1/35;
oral contraceptive	Ortho-Novum 1/35;
oral contraceptive	Necon 1/35
oral contraceptive	Ovcon 50;
oral contraceptive	Necon 1/50
oral contraceptive	Ortho-Novum 10/11
oral contraceptive	Aranelle;
oral contraceptive	Tri-Norinyl
oral contraceptive	Ortho-Novum 7/7/7;
oral contraceptive	Necon
oral contraceptive	Micronor;
oral contraceptive	Nor-QD;
oral contraceptive	Camila;
oral contraceptive	Errin;
oral contraceptive	Jolivette
oral contraceptive	Junel 21 1/20;
oral contraceptive	Junel 21 Fe 1/20;
oral contraceptive	Loestrin 21 1/20;
oral contraceptive	Loestrin 21 Fe 1/20;
oral contraceptive	Loestrin 24 Fe;
oral contraceptive	Microgestin 1/20
oral contraceptive	Microgestin Fe 1/20
oral contraceptive	Junel 21 1.5/30;
oral contraceptive	Junel 21 Fe 1.5/30;

Appendix A

oral contraceptive	Loestrin 1.5/30;
oral contraceptive	Loestrin Fe 1.5/30
oral contraceptive	Microgestin 1.5/30
oral contraceptive	Microgestin Fe 1.5/30
oral contraceptive	Estrostep Fe;
oral contraceptive	Tilia Fe;
oral contraceptive	TriLegest Fe
oral contraceptive	Ortho-Cyclen;
oral contraceptive	Sprintec;
oral contraceptive	MonoNessa;
oral contraceptive	Previfem
oral contraceptive	Ortho Tri-Cyclen Lo;
oral contraceptive	Tri-Previfem;
oral contraceptive	TriNessa
oral contraceptive	Ortho Tri-Cyclen;
oral contraceptive	Tri-Sprintec
oral contraceptive	Cryselle;
oral contraceptive	Lo/Ovral;
oral contraceptive	Low-Ogestrel
oral contraceptive	Ovral;
oral contraceptive	Ogestrel

Appendix A

drug_class	generic	generic_ndc
oral contraceptive	estradiol	desogestrel-ethinyl estradiol
oral contraceptive	estradiol	desogestrel-ethinyl estradiol/ethinyl estradiol
oral contraceptive	estradiol	drospirenone/estradiol
oral contraceptive	estradiol	drospirenone/ethinyl estradiol/levomefolate calcium
oral contraceptive	estradiol	estradiol
oral contraceptive	estradiol	estradiol acetate
oral contraceptive	estradiol	estradiol benzoate
oral contraceptive	estradiol	estradiol cypionate
oral contraceptive	estradiol	estradiol cypionate/medroxyprogesterone acet
oral contraceptive	estradiol	estradiol hemihydrate, micronized
oral contraceptive	estradiol	estradiol micronized
oral contraceptive	estradiol	estradiol valerate
oral contraceptive	estradiol	estradiol valerate/dienogest
oral contraceptive	estradiol	estradiol valerate/sesame oil
oral contraceptive	estradiol	estradiol/estrone
oral contraceptive	estradiol	estradiol/estrone/vit b12
oral contraceptive	estradiol	estradiol/levonorgestrel
oral contraceptive	estradiol	estradiol/norethindrone acetate
oral contraceptive	estradiol	estradiol/norgestimate
oral contraceptive	estradiol	estradiol/progesterone
oral contraceptive	estradiol	ethinyl estradiol
oral contraceptive	estradiol	ethinyl estradiol/drospirenone
oral contraceptive	estradiol	ethinyl estradiol/norethindrone acetate
oral contraceptive	estradiol	ethynodiol d-ethinyl estradiol
oral contraceptive	estradiol	ethynodiol diacetate-ethinyl estradiol
oral contraceptive	estradiol	etonogestrel/ethinyl estradiol
oral contraceptive	estradiol	levonorgestrel-ethinyl estradiol
oral contraceptive	estradiol	levonorgestrel/ethinyl estradiol and ethinyl estradiol
oral contraceptive	estradiol	me-testosterone/eth estradiol
oral contraceptive	estradiol	metttm/estradiol/multivits
oral contraceptive	estradiol	norelgestromin/ethinyl estradiol
oral contraceptive	estradiol	norethindrone a-e estradiol

Appendix A

oral contraceptive	estradiol	norethindrone a-e estradiol/fe
oral contraceptive	estradiol	norethindrone a-e estradiol/ferrous fumarate
oral contraceptive	estradiol	norethindrone acetate-ethinyl estradiol
oral contraceptive	estradiol	norethindrone acetate-ethinyl estradiol/ferrous fumarate
oral contraceptive	estradiol	norethindrone-ethin estradiol
oral contraceptive	estradiol	norethindrone-ethinyl estradiol
oral contraceptive	estradiol	norethindrone-ethinyl estradiol/ferrous fumarate
oral contraceptive	estradiol	norgestimate-ethinyl estradiol
oral contraceptive	estradiol	norgestrel-ethinyl estradiol
oral contraceptive	estradiol	testosterone cypionate/estradiol cypionate
oral contraceptive	estradiol	testosterone enanthate/estradiol valerate
oral contraceptive	estradiol	testosterone/estradiol
oral contraceptive	levonorgestrel	estradiol/levonorgestrel
oral contraceptive	levonorgestrel	levonorgestrel
oral contraceptive	levonorgestrel	levonorgestrel-eth estra
oral contraceptive	levonorgestrel	levonorgestrel-eth estra/pregnancy test kit
oral contraceptive	levonorgestrel	levonorgestrel-ethinyl estradiol
oral contraceptive	levonorgestrel	levonorgestrel/ethinyl estradiol and ethinyl estradiol
oral contraceptive	norethindrone	estradiol/norethindrone acetate
oral contraceptive	norethindrone	ethinyl estradiol/norethindrone acetate
oral contraceptive	norethindrone	leuprolide acetate/norethindrone acetate
oral contraceptive	norethindrone	norethindrone
oral contraceptive	norethindrone	norethindrone a-e estradiol
oral contraceptive	norethindrone	norethindrone a-e estradiol/fe
oral contraceptive	norethindrone	norethindrone a-e estradiol/ferrous fumarate
oral contraceptive	norethindrone	norethindrone acetate
oral contraceptive	norethindrone	norethindrone acetate-ethinyl estradiol
oral contraceptive	norethindrone	norethindrone acetate-ethinyl estradiol/ferrous fumarate
oral contraceptive	norethindrone	norethindrone-ethin estradiol
oral contraceptive	norethindrone	norethindrone-ethinyl estrad
oral contraceptive	norethindrone	norethindrone-ethinyl estradiol
oral contraceptive	norethindrone	norethindrone-ethinyl estradiol/ferrous fumarate

Appendix A

oral contraceptive	norethindrone	norethindrone-mestranol
oral contraceptive	norgestrel	norgestrel
oral contraceptive	norgestrel	norgestrel-ethinyl estradiol
oral contraceptive	polyestradiol phosphate	polyestradiol phosphate

Appendix A

Pregnancy
Dx codes
650 NORMAL DELIVERY
660 OBSTRUCTED LABOR
661 ABNORMALITY OF FORCES OF LABOR
662 LONG LABOR
663 UMBILICAL CORD COMPLICATIONS DURING LABOR AND DELIVERY
664 TRAUMA TO PERINEUM AND VULVA DURING DELIVERY
665 OTHER OBSTETRICAL TRAUMA
667 RETAINED PLACENTA OR MEMBRANES WITHOUT HEMORRHAGE
668 COMPLICATIONS OF THE ADMINISTRATION OF ANESTHETIC OR OTHER SEDATION IN LABOR AND DELIVERY
669.94 UNSPECIFIED COMPLICATION OF LABOR AND DELIVERY POSTPARTUM CONDITION OR COMPLICATION
V24 POSTPARTUM CARE AND EXAMINATION
V24.0 POSTPARTUM CARE AND EXAMINATION IMMEDIATELY AFTER DELIVERY
V24.1 POSTPARTUM CARE AND EXAMINATION OF LACTATING MOTHER
V24.2 ROUTINE POSTPARTUM FOLLOW
V27 OUTCOME OF DELIVERY
V27.0 MOTHER WITH SINGLE LIVEBORN
V27.1 MOTHER WITH SINGLE STILLBORN
V27.2 MOTHER WITH TWINS BOTH LIVEBORN
V27.3 MOTHER WITH TWINS ONE LIVEBORN AND ONE STILLBORN
V27.4 MOTHER WITH TWINS BOTH STILLBORN
V27.5 MOTHER WITH OTHER MULTIPLE BIRTH ALL LIVEBORN
V27.6 MOTHER WITH OTHER MULTIPLE BIRTH SOME LIVEBORN
V27.7 MOTHER WITH OTHER MULTIPLE BIRTH ALL STILLBORN
V27.9 MOTHER WITH UNSPECIFIED OUTCOME OF DELIVERY
Procedure codes
72.0 LOW FORCEPS OPERATION
72.1 LOW FORCEPS OPERATION WITH EPISIOTOMY
72.2 MID FORCEPS OPERATION
72.21 MID FORCEPS OPERATION WITH EPISIOTOMY
72.29 OTHER MID FORCEPS OPERATION
72.3 HIGH FORCEPS OPERATION
72.31 HIGH FORCEPS OPERATION WITH EPISIOTOMY
72.39 OTHER HIGH FORCEPS OPERATION

Appendix A

72.4 FORCEPS ROTATION OF FETAL HEAD
72.5 BREECH EXTRACTION
72.51 PARTIAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD
72.52 OTHER PARTIAL BREECH EXTRACTION
72.53 TOTAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD
72.54 OTHER TOTAL BREECH EXTRACTION
72.6 FORCEPS APPLICATION TO AFTERCOMING HEAD
72.7 VACUUM EXTRACTION
72.71 VACUUM EXTRACTION WITH EPISIOTOMY
72.79 OTHER VACUUM EXTRACTION
72.8 OTHER SPECIFIED INSTRUMENTAL DELIVERY
72.9 UNSPECIFIED INSTRUMENTAL DELIVERY
73.0 ARTIFICIAL RUPTURE OF MEMBRANES
73.01 INDUCTION OF LABOR BY ARTIFICIAL RUPTURE OF MEMBRANES
73.09 OTHER ARTIFICIAL RUPTURE OF MEMBRANES
73.1 OTHER SURGICAL INDUCTION OF LABOR
73.2 INTERNAL AND COMBINED VERSION AND EXTRACTION
73.21 INTERNAL AND COMBINED VERSION WITHOUT EXTRACTION
73.22 INTERNAL AND COMBINED VERSION WITH EXTRACTION
73.3 FAILED FORCEPS
73.4 MEDICAL INDUCTION OF LABOR
73.5 MANUALLY ASSISTED DELIVERY
73.51 MANUAL ROTATION OF FETAL HEAD
73.59 OTHER MANUALLY ASSISTED DELIVERY
73.6 EPISIOTOMY
73.8 OPERATIONS ON FETUS TO FACILITATE DELIVERY
73.9 OTHER OPERATIONS ASSISTING DELIVERY
73.91 EXTERNAL VERSION ASSISTING DELIVERY
73.92 REPLACEMENT OF PROLAPSED UMBILICAL CORD
73.93 INCISION OF CERVIX TO ASSIST DELIVERY
73.94 PUBIOTOMY TO ASSIST DELIVERY
73.99 OTHER OPERATIONS ASSISTING DELIVERY
74.0 CLASSICAL CESAREAN SECTION
74.1 LOW CERVICAL CESAREAN SECTION
74.2 EXTRAPERITONEAL CESAREAN SECTION

Appendix A

74.3 REMOVAL OF EXTRATUBAL ECTOPIC PREGNANCY
74.4 CESAREAN SECTION OF OTHER SPECIFIED TYPE
74.9 CESAREAN SECTION OF UNSPECIFIED TYPE
74.91 HYSTEROTOMY TO TERMINATE PREGNANCY
74.99 OTHER CESAREAN SECTION OF UNSPECIFIED TYPE
75.4 MANUAL REMOVAL OF RETAINED PLACENTA
75.5 REPAIR OF CURRENT OBSTETRIC LACERATION OF UTERUS
75.6 REPAIR OF OTHER CURRENT OBSTETRIC LACERATION
75.7 MANUAL EXPLORATION OF UTERINE CAVITY, POSTPARTUM
75.9 OTHER OBSTETRIC OPERATIONS

Appendix B

Optum	MarketScan	Medicare
BEFORE PS MATCHING		

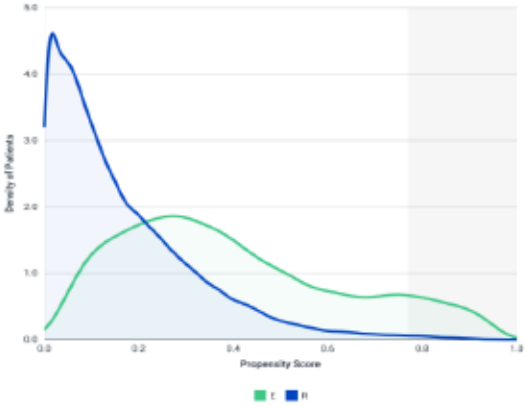
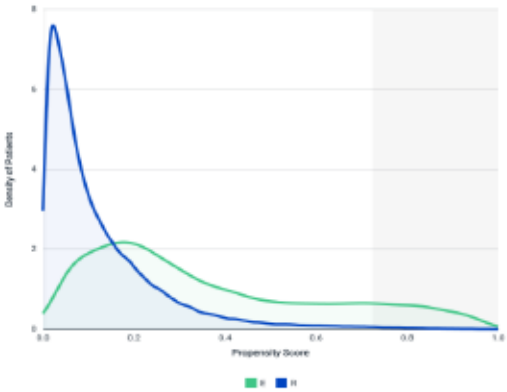
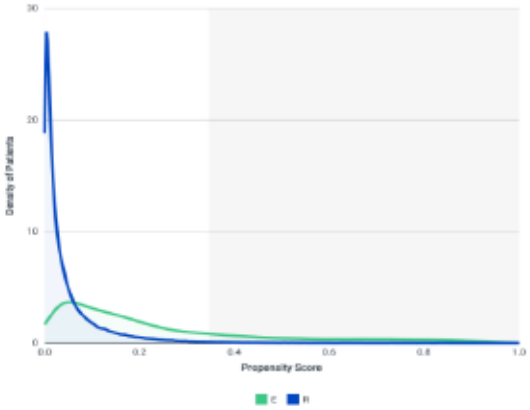

		

Figure 49: Pre-matching propensity score overlap	Figure 69: Pre-matching propensity score overlap	Figure 24: Pre-matching propensity score overlap
The c-statistics for the propensity score model, pre-matching was 0.809. The post-matching c-statistic was 0.524.	**The c-statistics for the propensity score model, pre-matching was 0.821. The post-matching c-statistic was 0.537.**	**The c-statistics for the propensity score model, pre-matching was 0.851. The post-matching c-statistic was 0.529.**
AFTER PS MATCHING		

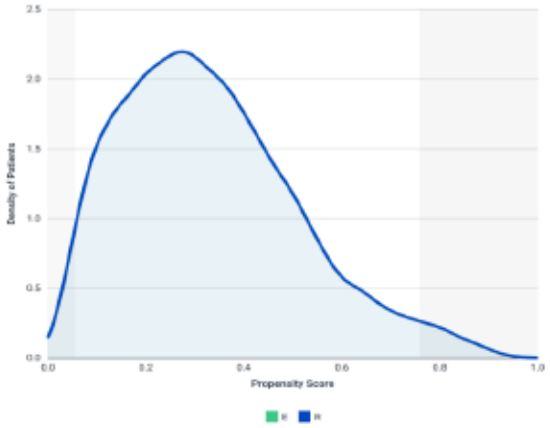
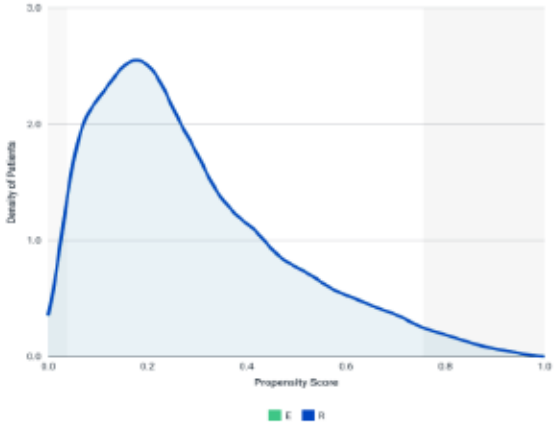
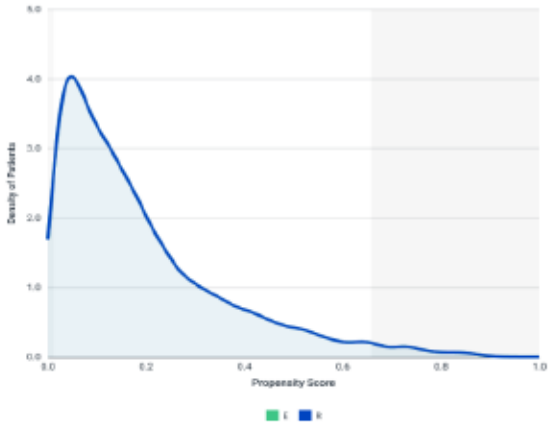

		

Figure 50: Post-matching propensity score overlap	Figure 50: Post-matching propensity score overlap	Figure 35: Post-matching propensity score overlap

Table 1

	Unmatched								
	Optum		MarketScan		Medicare		POOLED		
Variable	Reference- DPP4i v2	Exposure - Empagliflozin v3	Reference- DPP4i v2	Exposure - Empagliflozin v3	Reference- DPP4i v2	Exposure - Empagliflozin v3	Reference- DPP4i v2	Exposure - Empagliflozin v3	St. Diff.
Number of patients	99,903	27,394	98,345	18,912	203,294	13,156	401,542	59,462	
Age									
...mean (sd)	64.93 (11.69)	60.53 (10.62)	58.66 (11.12)	55.47 (8.77)	74.08 (6.94)	71.46 (5.19)	68.03 (9.42)	61.34 (9.08)	0.72
...median [IQR]	66.00 [57.00, 73.00]	61.00 [53.00, 68.00]	58.00 [52.00, 64.00]	56.00 [50.00, 61.00]	73.00 [68.00, 78.00]	0.00 [68.00, 74.00]	67.58 (9.42)	61.40 (9.08)	0.67
Age categories without zero category									
...18 - 34; n (%)	19,490 (19.5%)	7,748 (28.3%)	33,966 (34.5%)	7,944 (42.0%)	0 (0.0%)	0 (0.0%)	53,456 (13.3%)	15,692 (26.4%)	-0.33
...35 - 64; n (%)	23,551 (23.6%)	8,844 (32.3%)	41,612 (42.3%)	9,123 (48.2%)	1,132 (0.6%)	43 (0.3%)	66,295 (16.5%)	18,010 (30.3%)	-0.33
...65 - 74; n (%)	36,281 (36.3%)	8,539 (31.2%)	13,769 (14.0%)	1,483 (7.8%)	119,235 (58.7%)	9,986 (75.9%)	169,285 (42.2%)	20,008 (33.6%)	0.18
...>=75; n (%)	20,581 (20.6%)	2,263 (8.3%)	8,998 (9.1%)	362 (1.9%)	82,927 (40.8%)	3,127 (23.8%)	112,506 (28.0%)	5,752 (9.7%)	0.48
Gender without zero category- United									
...Males; n (%)	53,340 (53.4%)	16,618 (60.7%)	57,603 (58.6%)	11,785 (62.3%)	92,595 (45.5%)	7,494 (57.0%)	203,538 (50.7%)	35,897 (60.4%)	-0.20
...Females; n (%)	46,563 (46.6%)	10,776 (39.3%)	40,742 (41.4%)	7,127 (37.7%)	110,699 (54.5%)	5,662 (43.0%)	198,004 (49.3%)	23,565 (39.6%)	0.20
Race									
...White; n (%)	N/A	N/A	N/A	N/A	151,073 (74.3%)	10,799 (82.1%)	151,073 (74.3%)	10,799 (82.1%)	-0.19
...Black; n (%)	N/A	N/A	N/A	N/A	22,905 (11.3%)	916 (7.0%)	22,905 (11.3%)	916 (7.0%)	0.15
...Asian; n (%)	N/A	N/A	N/A	N/A	9,749 (4.8%)	387 (2.9%)	9,749 (4.8%)	387 (2.9%)	0.10
...Hispanic; n (%)	N/A	N/A	N/A	N/A	9,554 (4.7%)	333 (2.5%)	9,554 (4.7%)	333 (2.5%)	0.12
...North American Native; n (%)	N/A	N/A	N/A	N/A	1,385 (0.7%)	58 (0.4%)	1,385 (0.7%)	58 (0.4%)	0.04
...Other/Unknown; n (%)	N/A	N/A	N/A	N/A	8,628 (4.2%)	663 (5.0%)	8,628 (4.2%)	663 (5.0%)	-0.04
Region without zero category- United v3 (lumping missing&other category with West)									
...Northeast; n (%)	10,960 (11.0%)	2,334 (8.5%)	17,603 (17.9%)	2,575 (13.6%)	38,218 (18.8%)	2,505 (19.0%)	66,781 (16.6%)	7,414 (12.5%)	0.12
...South; n (%)	52,164 (52.2%)	15,303 (55.9%)	20,254 (20.6%)	3,296 (17.4%)	86,895 (42.7%)	5,524 (42.0%)	159,313 (39.7%)	24,123 (40.6%)	-0.02
...Midwest; n (%)	18,103 (18.1%)	5,373 (19.6%)	50,370 (51.2%)	11,006 (58.2%)	42,468 (20.9%)	2,506 (19.0%)	110,941 (27.6%)	18,885 (31.8%)	-0.09
...West; n (%)	18,676 (18.7%)	4,384 (16.0%)	9,489 (9.6%)	1,978 (10.5%)	35,713 (17.6%)	2,621 (19.9%)	63,878 (15.9%)	8,983 (15.1%)	0.02
...Unknown+missing; n (%)	N/A	N/A	629 (0.6%)	57 (0.3%)	N/A	N/A	629 (0.6%)	57 (0.3%)	0.04
CV Covariates									
Ischemic heart disease; n (%)	18,990 (19.0%)	5,885 (21.5%)	12,693 (12.9%)	2,535 (13.4%)	54,534 (26.8%)	4,200 (31.9%)	86,217 (21.5%)	12,620 (21.2%)	0.01
Acute MI; n (%)	931 (0.9%)	344 (1.3%)	372 (0.4%)	104 (0.5%)	1,288 (0.6%)	89 (0.7%)	2,591 (0.6%)	537 (0.9%)	-0.03
ACS/unstable angina; n (%)	702 (0.7%)	231 (0.8%)	500 (0.5%)	107 (0.6%)	1,499 (0.7%)	118 (0.9%)	2,701 (0.7%)	456 (0.8%)	-0.01
Old MI; n (%)	2,549 (2.6%)	819 (3.0%)	906 (0.9%)	191 (1.0%)	5,824 (2.9%)	466 (3.5%)	9,279 (2.3%)	1,476 (2.5%)	-0.01
Stable angina; n (%)	3,164 (3.2%)	1,100 (4.0%)	1,545 (1.6%)	382 (2.0%)	6,343 (3.1%)	626 (4.8%)	11,052 (2.8%)	2,108 (3.5%)	-0.04
Coronary atherosclerosis and other forms of chronic ischer	17,701 (17.7%)	5,558 (20.3%)	11,987 (12.2%)	2,406 (12.7%)	52,219 (25.7%)	4,074 (31.0%)	81,907 (20.4%)	12,038 (20.2%)	0.00
Other atherosclerosis with ICD10 v2 Copy; n (%)	501 (0.5%)	106 (0.4%)	451 (0.5%)	57 (0.3%)	2,443 (1.2%)	86 (0.7%)	3,395 (0.8%)	249 (0.4%)	0.05
Previous cardiac procedure (CABG or PTCA or Stent) v4; n (%	407 (0.4%)	189 (0.7%)	212 (0.2%)	52 (0.3%)	461 (0.2%)	55 (0.4%)	1,080 (0.3%)	296 (0.5%)	-0.03
History of CABG or PTCA; n (%)	4,493 (4.5%)	1,679 (6.1%)	1,629 (1.7%)	369 (2.0%)	13,342 (6.6%)	1,156 (8.8%)	19,464 (4.8%)	3,204 (5.4%)	-0.03
Any stroke; n (%)	4,963 (5.0%)	1,153 (4.2%)	2,035 (2.1%)	273 (1.4%)	10,123 (5.0%)	591 (4.5%)	17,121 (4.3%)	2,017 (3.4%)	0.05
Ischemic stroke (w and w/o mention of cerebral infarction)	4,899 (4.9%)	1,140 (4.2%)	2,000 (2.0%)	271 (1.4%)	9,999 (4.9%)	585 (4.4%)	16,898 (4.2%)	1,996 (3.4%)	0.04
Hemorrhagic stroke; n (%)	163 (0.2%)	23 (0.1%)	48 (0.0%)	4 (0.0%)	**	**	**	**	**
TIA; n (%)	1,176 (1.2%)	266 (1.0%)	465 (0.5%)	68 (0.4%)	1,913 (0.9%)	98 (0.7%)	3,554 (0.9%)	432 (0.7%)	0.02
Other cerebrovascular disease; n (%)	1,704 (1.7%)	322 (1.2%)	670 (0.7%)	86 (0.5%)	3,962 (1.9%)	236 (1.8%)	6,336 (1.6%)	644 (1.1%)	0.04
Late effects of cerebrovascular disease; n (%)	1,554 (1.6%)	233 (0.9%)	423 (0.4%)	34 (0.2%)	3,186 (1.6%)	107 (0.8%)	5,163 (1.3%)	374 (0.6%)	0.07
Cerebrovascular procedure; n (%)	70 (0.1%)	28 (0.1%)	15 (0.0%)	4 (0.0%)	**	**	**	**	**
Heart failure (CHF); n (%)	6,419 (6.4%)	1,435 (5.2%)	2,935 (3.0%)	399 (2.1%)	18,631 (9.2%)	951 (7.2%)	27,985 (7.0%)	2,785 (4.7%)	0.10
Peripheral Vascular Disease (PVD) or PVD Surgery v2; n (%)	6,638 (6.6%)	1,465 (5.3%)	3,369 (3.4%)	497 (2.6%)	20,972 (10.3%)	1,195 (9.1%)	30,979 (7.7%)	3,157 (5.3%)	0.10
Atrial fibrillation; n (%)	5,807 (5.8%)	1,313 (4.8%)	3,583 (3.6%)	474 (2.5%)	20,723 (10.2%)	1,268 (9.6%)	30,113 (7.5%)	3,055 (5.1%)	0.10
Other cardiac dysrhythmia; n (%)	8,278 (8.3%)	2,142 (7.8%)	4,579 (4.7%)	793 (4.2%)	24,622 (12.1%)	1,806 (13.7%)	37,479 (9.3%)	4,741 (8.0%)	0.05
Cardiac conduction disorders; n (%)	2,246 (2.2%)	580 (2.1%)	1,171 (1.2%)	192 (1.0%)	6,903 (3.4%)	459 (3.5%)	10,320 (2.6%)	1,231 (2.1%)	0.03
Other CVD; n (%)	8,797 (8.8%)	2,259 (8.2%)	5,483 (5.6%)	817 (4.3%)	25,637 (12.6%)	1,671 (12.7%)	39,917 (9.9%)	4,747 (8.0%)	0.07
Diabetes-related complications									
Diabetic retinopathy; n (%)	6,367 (6.4%)	2,196 (8.0%)	3,371 (3.4%)	764 (4.0%)	14,304 (7.0%)	1,298 (9.9%)	24,042 (6.0%)	4,258 (7.2%)	-0.05
Diabetes with other ophthalmic manifestations; n (%)	904 (0.9%)	230 (0.8%)	1,868 (1.9%)	305 (1.6%)	4,906 (2.4%)	267 (2.0%)	7,678 (1.9%)	802 (1.3%)	0.05
Retinal detachment, vitreous hemorrhage, vitrectomy; n (%	415 (0.4%)	135 (0.5%)	328 (0.3%)	76 (0.4%)	780 (0.4%)	80 (0.6%)	1,523 (0.4%)	291 (0.5%)	-0.01
Retinal laser coagulation therapy; n (%)	560 (0.6%)	158 (0.6%)	504 (0.5%)	115 (0.6%)	1,220 (0.6%)	74 (0.6%)	2,284 (0.6%)	347 (0.6%)	0.00
Occurrence of Diabetic Neuropathy v2 Copy; n (%)	19,198 (19.2%)	5,771 (21.1%)	10,496 (10.7%)	2,631 (13.9%)	39,771 (19.6%)	3,284 (25.0%)	69,465 (17.3%)	11,686 (19.7%)	-0.06

Table 1

Occurrence of diabetic nephropathy V3 with ICD10 Copy; r	15,429 (15.4%)	3,259 (11.9%)	6,218 (6.3%)	1,309 (6.9%)	22,695 (11.2%)	1,478 (11.2%)	44,342 (11.0%)	6,046 (10.2%)	0.03
Hypoglycemia v2; n (%)	1,757 (1.8%)	141 (0.5%)	1,705 (1.7%)	183 (1.0%)	4,423 (2.2%)	107 (0.8%)	7,885 (2.0%)	431 (0.7%)	0.11
Hyperglycemia; n (%)	4,186 (4.2%)	1,098 (4.0%)	3,136 (3.2%)	518 (2.7%)	8,064 (4.0%)	466 (3.5%)	15,386 (3.8%)	2,082 (3.5%)	0.02
Disorders of fluid electrolyte and acid-base balance; n (%)	6,080 (6.1%)	1,099 (4.0%)	3,203 (3.3%)	434 (2.3%)	12,731 (6.3%)	479 (3.6%)	22,014 (5.5%)	2,012 (3.4%)	0.10
Diabetic ketoacidosis; n (%)	385 (0.4%)	76 (0.3%)	309 (0.3%)	47 (0.2%)	668 (0.3%)	22 (0.2%)	1,362 (0.3%)	145 (0.2%)	0.02
Hyperosmolar hyperglycemic nonketotic syndrome (HONK	589 (0.6%)	166 (0.6%)	468 (0.5%)	92 (0.5%)	1,077 (0.5%)	80 (0.6%)	2,134 (0.5%)	338 (0.6%)	-0.01
Diabetes with peripheral circulatory disorders with ICD-10	7,150 (7.2%)	1,909 (7.0%)	2,798 (2.8%)	630 (3.3%)	15,464 (7.6%)	1,122 (8.5%)	25,412 (6.3%)	3,661 (6.2%)	0.00
Diabetic Foot; n (%)	1,967 (2.0%)	591 (2.2%)	1,422 (1.4%)	320 (1.7%)	4,932 (2.4%)	286 (2.2%)	8,321 (2.1%)	1,197 (2.0%)	0.01
Gangrene v2; n (%)	235 (0.2%)	63 (0.2%)	144 (0.1%)	28 (0.1%)	380 (0.2%)	33 (0.3%)	759 (0.2%)	124 (0.2%)	0.00
Lower extremity amputation; n (%)	644 (0.6%)	207 (0.8%)	256 (0.3%)	66 (0.3%)	1,155 (0.6%)	81 (0.6%)	2,055 (0.5%)	354 (0.6%)	-0.01
Osteomyelitis; n (%)	491 (0.5%)	155 (0.6%)	361 (0.4%)	78 (0.4%)	936 (0.5%)	54 (0.4%)	1,788 (0.4%)	287 (0.5%)	-0.01
Skin infections v2; n (%)	4,914 (4.9%)	1,384 (5.1%)	4,428 (4.5%)	886 (4.7%)	11,729 (5.8%)	781 (5.9%)	21,071 (5.2%)	3,051 (5.1%)	0.00
Erectile dysfunction; n (%)	2,938 (2.9%)	1,188 (4.3%)	2,680 (2.7%)	585 (3.1%)	4,367 (2.1%)	501 (3.8%)	9,985 (2.5%)	2,274 (3.8%)	-0.07
Diabetes with unspecified complication; n (%)	5,922 (5.9%)	1,946 (7.1%)	4,818 (4.9%)	1,306 (6.9%)	11,396 (5.6%)	953 (7.2%)	22,136 (5.5%)	4,205 (7.1%)	-0.07
Diabetes mellitus without mention of complications; n (%)	82,871 (83.0%)	21,178 (77.3%)	86,660 (88.1%)	15,269 (80.7%)	184,478 (90.7%)	11,109 (84.4%)	354,009 (88.2%)	47,556 (80.0%)	0.23
Hypertension: 1 inpatient or 2 outpatient claims within 36	84,740 (84.8%)	23,304 (85.1%)	75,314 (76.6%)	14,637 (77.4%)	185,875 (91.4%)	11,981 (91.1%)	345,929 (86.2%)	49,922 (84.0%)	0.06
Hyperlipidemia v2; n (%)	70,468 (70.5%)	19,569 (71.4%)	65,929 (67.0%)	13,478 (71.3%)	154,166 (75.8%)	10,169 (77.3%)	290,563 (72.4%)	43,216 (72.7%)	-0.01
Edema; n (%)	5,273 (5.3%)	1,202 (4.4%)	2,878 (2.9%)	467 (2.5%)	16,056 (7.9%)	876 (6.7%)	24,207 (6.0%)	2,545 (4.3%)	0.08
Renal Dysfunction (non-diabetic) v2; n (%)	19,582 (19.6%)	3,179 (11.6%)	8,494 (8.6%)	958 (5.1%)	42,497 (20.9%)	1,822 (13.8%)	70,573 (17.6%)	5,959 (10.0%)	0.22
Occurrence of acute renal disease v2; n (%)	2,581 (2.6%)	332 (1.2%)	1,243 (1.3%)	80 (0.4%)	5,423 (2.7%)	130 (1.0%)	9,247 (2.3%)	542 (0.9%)	0.11
Occurrence of chronic renal insufficiency; n (%)	16,369 (16.4%)	2,354 (8.6%)	6,265 (6.4%)	657 (3.5%)	36,061 (17.7%)	1,453 (11.0%)	58,695 (14.6%)	4,464 (7.5%)	0.23
Chronic kidney disease v2; n (%)	15,864 (15.9%)	2,270 (8.3%)	5,871 (6.0%)	615 (3.3%)	34,532 (17.0%)	1,391 (10.6%)	56,267 (14.0%)	4,276 (7.2%)	0.22
CKD Stage 3-4; n (%)	10,687 (10.7%)	1,245 (4.5%)	3,761 (3.8%)	303 (1.6%)	24,060 (11.8%)	839 (6.4%)	38,508 (9.6%)	2,387 (4.0%)	0.22
Occurrence of hypertensive nephropathy; n (%)	6,766 (6.8%)	968 (3.5%)	2,293 (2.3%)	229 (1.2%)	13,584 (6.7%)	526 (4.0%)	22,643 (5.6%)	1,723 (2.9%)	0.13
Occurrence of miscellaneous renal insufficiency v2; n (%)	4,400 (4.4%)	874 (3.2%)	2,417 (2.5%)	271 (1.4%)	11,162 (5.5%)	523 (4.0%)	17,979 (4.5%)	1,668 (2.8%)	0.09
Glaucoma or cataracts v2; n (%)	18,320 (18.3%)	4,419 (16.1%)	12,973 (13.2%)	2,270 (12.0%)	54,403 (26.8%)	3,639 (27.7%)	85,696 (21.3%)	10,328 (17.4%)	0.10
Cellulitis or abscess of toe; n (%)	1,284 (1.3%)	391 (1.4%)	849 (0.9%)	225 (1.2%)	2,592 (1.3%)	237 (1.8%)	4,725 (1.2%)	853 (1.4%)	-0.02
Foot ulcer; n (%)	1,877 (1.9%)	539 (2.0%)	1,377 (1.4%)	296 (1.6%)	4,802 (2.4%)	270 (2.1%)	8,056 (2.0%)	1,105 (1.9%)	0.01
Bladder stones; n (%)	125 (0.1%)	27 (0.1%)	71 (0.1%)	11 (0.1%)	307 (0.2%)	17 (0.1%)	503 (0.1%)	55 (0.1%)	0.00
Kidney stones; n (%)	1,974 (2.0%)	533 (1.9%)	1,775 (1.8%)	310 (1.6%)	4,340 (2.2%)	294 (2.2%)	8,289 (2.1%)	1,137 (1.9%)	0.01
Urinary tract infections (UTIs); n (%)	7,752 (7.8%)	1,339 (4.9%)	4,684 (4.8%)	565 (3.0%)	23,016 (11.3%)	885 (6.7%)	35,452 (8.8%)	2,789 (4.7%)	0.16
Dipstick urinalysis; n (%)	34,548 (34.6%)	8,269 (30.2%)	29,300 (29.8%)	5,259 (27.8%)	76,034 (37.4%)	4,496 (34.2%)	139,882 (34.8%)	18,024 (30.3%)	0.10
Non-dipstick urinalysis; n (%)	43,363 (43.4%)	12,648 (46.2%)	36,411 (37.0%)	8,432 (44.6%)	84,136 (41.4%)	6,319 (48.0%)	163,910 (40.8%)	27,399 (46.1%)	-0.11
Urine function test; n (%)	1,897 (1.9%)	418 (1.5%)	1,625 (1.7%)	200 (1.1%)	6,250 (3.1%)	434 (3.3%)	9,772 (2.4%)	1,052 (1.8%)	0.04
Cytology; n (%)	560 (0.6%)	117 (0.4%)	522 (0.5%)	60 (0.3%)	1,497 (0.7%)	67 (0.5%)	2,579 (0.6%)	244 (0.4%)	0.03
Cystoscopy; n (%)	843 (0.8%)	204 (0.7%)	726 (0.7%)	103 (0.5%)	2,199 (1.1%)	129 (1.0%)	3,768 (0.9%)	436 (0.7%)	0.02
Other Covariates									
Liver disease; n (%)	3,416 (3.4%)	1,355 (4.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3,416 (0.9%)	1,355 (2.3%)	-0.11
Osteoarthritis; n (%)	14,139 (14.2%)	3,503 (12.8%)	8,944 (9.1%)	1,439 (7.7%)	41,716 (20.5%)	2,523 (19.2%)	64,819 (16.1%)	7,485 (12.6%)	0.10
Other arthritis, arthropathies and musculoskeletal pain; n (	33,077 (33.1%)	8,620 (31.5%)	26,598 (27.0%)	4,912 (26.0%)	82,377 (40.5%)	4,956 (37.7%)	142,052 (35.4%)	18,488 (31.1%)	0.09
Dorsopathies; n (%)	20,631 (20.7%)	5,759 (21.0%)	15,907 (16.2%)	3,084 (16.3%)	48,687 (23.9%)	3,203 (24.3%)	85,225 (21.2%)	12,046 (20.3%)	0.02
Fractures; n (%)	2,412 (2.4%)	501 (1.8%)	1,716 (1.7%)	279 (1.5%)	6,339 (3.1%)	342 (2.6%)	10,467 (2.6%)	1,122 (1.9%)	0.05
Falls v2; n (%)	3,187 (3.2%)	522 (1.9%)	965 (1.0%)	123 (0.7%)	7,872 (3.9%)	346 (2.6%)	12,024 (3.0%)	991 (1.7%)	0.09
Osteoporosis; n (%)	4,316 (4.3%)	634 (2.3%)	1,543 (1.6%)	149 (0.8%)	15,070 (7.4%)	631 (4.8%)	20,929 (5.2%)	1,414 (2.4%)	0.15
Hyperthyroidism; n (%)	588 (0.6%)	179 (0.7%)	466 (0.5%)	85 (0.4%)	1,690 (0.8%)	99 (0.8%)	2,744 (0.7%)	363 (0.6%)	0.01
Hypothyroidism v2; n (%)	13,829 (13.8%)	3,532 (12.9%)	10,304 (10.5%)	2,178 (11.5%)	21,523 (10.6%)	946 (7.2%)	45,656 (11.4%)	6,656 (11.2%)	0.01
Other disorders of thyroid gland V2; n (%)	3,455 (3.5%)	1,215 (4.4%)	2,934 (3.0%)	902 (4.8%)	7,712 (3.8%)	667 (5.1%)	14,101 (3.5%)	2,784 (4.7%)	-0.06
Depression; n (%)	7,320 (7.3%)	1,821 (6.6%)	5,335 (5.4%)	914 (4.8%)	17,919 (8.8%)	902 (6.9%)	30,574 (7.6%)	3,637 (6.1%)	0.06
Anxiety; n (%)	7,953 (8.0%)	2,396 (8.7%)	5,309 (5.4%)	1,125 (5.9%)	15,687 (7.7%)	995 (7.6%)	28,949 (7.2%)	4,516 (7.6%)	-0.02
Sleep_Disorder; n (%)	3,987 (4.0%)	673 (2.5%)	5,785 (5.9%)	766 (4.1%)	11,002 (5.4%)	418 (3.2%)	20,774 (5.2%)	1,857 (3.1%)	0.11
Dementia; n (%)	3,796 (3.8%)	361 (1.3%)	1,343 (1.4%)	91 (0.5%)	14,445 (7.1%)	369 (2.8%)	19,584 (4.9%)	821 (1.4%)	0.20
Delirium; n (%)	1,038 (1.0%)	110 (0.4%)	410 (0.4%)	31 (0.2%)	2,997 (1.5%)	80 (0.6%)	4,445 (1.1%)	221 (0.4%)	0.08
Psychosis; n (%)	1,115 (1.1%)	171 (0.6%)	403 (0.4%)	36 (0.2%)	3,561 (1.8%)	67 (0.5%)	5,079 (1.3%)	274 (0.5%)	0.08
Obesity; n (%)	17,544 (17.6%)	7,711 (28.1%)	6,568 (6.7%)	1,684 (8.9%)	10,068 (5.0%)	806 (6.1%)	34,180 (8.5%)	10,201 (17.2%)	-0.26
Overweight; n (%)	7,117 (7.1%)	2,123 (7.7%)	3,068 (3.1%)	700 (3.7%)	8,443 (4.2%)	650 (4.9%)	18,628 (4.6%)	3,473 (5.8%)	-0.05
Smoking; n (%)	10,562 (10.6%)	3,243 (11.8%)	4,864 (4.9%)	882 (4.7%)	21,088 (10.4%)	1,434 (10.9%)	36,514 (9.1%)	5,559 (9.3%)	-0.01
Alcohol abuse or dependence; n (%)	685 (0.7%)	199 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!	199 (0.3%)	#VALUE!
Drug abuse or dependence; n (%)	1,133 (1.1%)	359 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,133 (0.3%)	359 (0.6%)	-0.04
COPD; n (%)	6,952 (7.0%)	1,485 (5.4%)	3,056 (3.1%)	386 (2.0%)	17,808 (8.8%)	895 (6.8%)	27,816 (6.9%)	2,766 (4.7%)	0.09

Table 1

Asthma; n (%)	4,622 (4.6%)	1,225 (4.5%)	3,363 (3.4%)	592 (3.1%)	9,980 (4.9%)	656 (5.0%)	17,963 (4.5%)	2,473 (4.2%)	0.01
Obstructive sleep apnea; n (%)	7,880 (7.9%)	3,326 (12.1%)	7,903 (8.0%)	2,046 (10.8%)	10,766 (5.3%)	1,274 (9.7%)	26,549 (6.6%)	6,646 (11.2%)	-0.16
Pneumonia; n (%)	1,745 (1.7%)	319 (1.2%)	1,136 (1.2%)	158 (0.8%)	4,422 (2.2%)	214 (1.6%)	7,303 (1.8%)	691 (1.2%)	0.05
Imaging; n (%)	73 (0.1%)	17 (0.1%)	17 (0.0%)	4 (0.0%)	**	**	**	**	**
Diabetes Medications									
DM Medications - AGIs; n (%)	499 (0.5%)	97 (0.4%)	310 (0.3%)	64 (0.3%)	1,243 (0.6%)	58 (0.4%)	2,052 (0.5%)	219 (0.4%)	0.01
DM Medications - Glitazones; n (%)	7,594 (7.6%)	2,318 (8.5%)	6,881 (7.0%)	1,520 (8.0%)	14,722 (7.2%)	1,253 (9.5%)	29,197 (7.3%)	5,091 (8.6%)	-0.05
DM Medications - GLP-1 RA; n (%)	4,184 (4.2%)	5,850 (21.4%)	4,354 (4.4%)	4,829 (25.5%)	5,290 (2.6%)	2,529 (19.2%)	13,828 (3.4%)	13,208 (22.2%)	-0.59
DM Medications - Insulin; n (%)	17,835 (17.9%)	7,838 (28.6%)	14,817 (15.1%)	5,867 (31.0%)	39,115 (19.2%)	4,548 (34.6%)	71,767 (17.9%)	18,253 (30.7%)	-0.30
DM Medications - Megitinides; n (%)	1,041 (1.0%)	212 (0.8%)	1,089 (1.1%)	171 (0.9%)	3,580 (1.8%)	247 (1.9%)	5,710 (1.4%)	630 (1.1%)	0.03
DM Medications - Metformin; n (%)	74,681 (74.8%)	20,362 (74.3%)	79,574 (80.9%)	14,355 (75.9%)	142,034 (69.9%)	9,591 (72.9%)	296,289 (73.8%)	44,308 (74.5%)	-0.02
Concomitant initiation or current use of 2nd Generation SI	33,222 (33.3%)	7,632 (27.9%)	29,037 (29.5%)	4,720 (25.0%)	73,210 (36.0%)	4,236 (32.2%)	135,469 (33.7%)	16,588 (27.9%)	0.13
Concomitant initiation or current use of AGIs; n (%)	359 (0.4%)	65 (0.2%)	216 (0.2%)	39 (0.2%)	888 (0.4%)	35 (0.3%)	1,463 (0.4%)	139 (0.2%)	0.04
Concomitant initiation or current use of Glitazones; n (%)	6,052 (6.1%)	1,790 (6.5%)	5,547 (5.6%)	1,221 (6.5%)	11,634 (5.7%)	990 (7.5%)	23,233 (5.8%)	4,001 (6.7%)	-0.04
Concomitant initiation or current use of GLP-1 RA; n (%)	2,392 (2.4%)	4,382 (16.0%)	2,527 (2.6%)	3,730 (19.7%)	2,849 (1.4%)	1,906 (14.5%)	7,768 (1.9%)	10,018 (16.8%)	-0.53
Concomitant initiation or current use of Insulin; n (%)	13,381 (13.4%)	5,986 (21.9%)	11,021 (11.2%)	4,466 (23.6%)	29,957 (14.7%)	3,603 (27.4%)	54,359 (13.5%)	14,055 (23.6%)	-0.26
Concomitant initiation or current use of Megitinides; n (%	773 (0.8%)	145 (0.5%)	768 (0.8%)	117 (0.6%)	2,607 (1.3%)	170 (1.3%)	4,148 (1.0%)	432 (0.7%)	0.03
Concomitant initiation or current use of Metformin; n (%)	64,669 (64.7%)	16,561 (60.5%)	70,407 (71.6%)	11,825 (62.5%)	122,594 (60.3%)	8,039 (61.1%)	257,670 (64.2%)	36,425 (61.3%)	0.06
Past use of 2nd Generation SUs Copy; n (%)	7,266 (7.3%)	2,028 (7.4%)	6,956 (7.1%)	1,253 (6.6%)	14,813 (7.3%)	902 (6.9%)	29,035 (7.2%)	4,183 (7.0%)	0.01
Past use of AGIs Copy; n (%)	140 (0.1%)	32 (0.1%)	94 (0.1%)	25 (0.1%)	355 (0.2%)	23 (0.2%)	589 (0.1%)	80 (0.1%)	0.00
Past use of Glitazones Copy; n (%)	1,542 (1.5%)	528 (1.9%)	1,334 (1.4%)	299 (1.6%)	3,088 (1.5%)	263 (2.0%)	5,964 (1.5%)	1,090 (1.8%)	-0.02
Past use of GLP-1 RA Copy; n (%)	1,977 (2.0%)	1,701 (6.2%)	2,007 (2.0%)	1,253 (6.6%)	2,441 (1.2%)	623 (4.7%)	6,425 (1.6%)	3,577 (6.0%)	-0.23
Past use of Insulin Copy; n (%)	4,454 (4.5%)	1,852 (6.8%)	3,797 (3.9%)	1,401 (7.4%)	9,160 (4.5%)	945 (7.2%)	17,411 (4.3%)	4,198 (7.1%)	-0.12
Past use of Megitinides Copy; n (%)	268 (0.3%)	67 (0.2%)	321 (0.3%)	54 (0.3%)	973 (0.5%)	77 (0.6%)	1,562 (0.4%)	198 (0.3%)	0.02
Past use of metformin (final) Copy; n (%)	10,012 (10.0%)	3,801 (13.9%)	9,167 (9.3%)	2,330 (13.4%)	19,440 (9.6%)	1,552 (11.8%)	38,619 (9.6%)	7,883 (13.3%)	-0.12
Other Medications									
Use of ACE inhibitors; n (%)	52,616 (52.7%)	14,800 (54.0%)	52,849 (53.7%)	10,492 (55.5%)	96,076 (47.3%)	6,205 (47.2%)	201,541 (50.2%)	31,497 (53.0%)	-0.06
Use of ARBs; n (%)	33,459 (33.5%)	9,268 (33.8%)	32,714 (33.3%)	6,489 (34.3%)	69,748 (34.3%)	4,833 (36.7%)	135,921 (33.8%)	20,590 (34.6%)	-0.02
Use of Loop Diuretics - United; n (%)	10,502 (10.5%)	2,316 (8.5%)	6,912 (7.0%)	1,075 (5.7%)	33,131 (16.3%)	1,744 (13.3%)	50,545 (12.6%)	5,135 (8.6%)	0.13
Use of other diuretics- United; n (%)	2,623 (2.6%)	833 (3.0%)	2,133 (2.2%)	433 (2.4%)	6,785 (3.3%)	483 (3.7%)	11,541 (2.9%)	1,769 (3.0%)	-0.01
Use of nitrates-United; n (%)	4,760 (4.8%)	1,425 (5.2%)	3,232 (3.3%)	624 (3.3%)	14,468 (7.1%)	976 (7.4%)	22,460 (5.6%)	3,025 (5.1%)	0.02
Use of other hypertension drugs; n (%)	6,251 (6.3%)	1,267 (4.6%)	4,450 (4.5%)	643 (3.4%)	15,746 (7.7%)	809 (6.1%)	26,447 (6.6%)	2,719 (4.6%)	0.09
Use of digoxin- United; n (%)	1,351 (1.4%)	278 (1.0%)	1,001 (1.0%)	112 (0.6%)	5,685 (2.8%)	306 (2.3%)	8,037 (2.0%)	696 (1.2%)	0.06
Use of Anti-arrhythmics; n (%)	1,058 (1.1%)	283 (1.0%)	807 (0.8%)	143 (0.8%)	3,770 (1.9%)	218 (1.7%)	5,635 (1.4%)	644 (1.1%)	0.03
Use of COPD/asthma meds- United; n (%)	14,067 (14.1%)	3,637 (13.3%)	12,756 (13.0%)	2,412 (12.8%)	32,384 (15.9%)	2,112 (16.1%)	59,207 (14.7%)	8,161 (13.7%)	0.03
Use of statins; n (%)	71,183 (71.3%)	20,272 (74.0%)	65,053 (66.1%)	13,377 (70.7%)	148,529 (73.1%)	10,331 (78.5%)	284,765 (70.9%)	43,980 (74.0%)	-0.07
Use of other lipid-lowering drugs; n (%)	11,144 (11.2%)	3,351 (12.2%)	12,301 (12.5%)	2,743 (14.5%)	24,891 (12.2%)	1,915 (14.6%)	48,336 (12.0%)	8,009 (13.5%)	-0.04
Use of antiplatelet agents; n (%)	12,026 (12.0%)	3,756 (13.7%)	10,435 (10.6%)	2,047 (10.8%)	30,403 (15.0%)	2,275 (17.3%)	52,864 (13.2%)	8,078 (13.6%)	-0.01
Use of oral anticoagulants (Dabigatran, Rivaroxaban, Apixa	5,155 (5.2%)	1,283 (4.7%)	3,619 (3.7%)	581 (3.1%)	17,505 (8.6%)	1,132 (8.6%)	26,279 (6.5%)	2,996 (5.0%)	0.06
Use of heparin and other low-molecular weight heparins; n	198 (0.2%)	43 (0.2%)	9 (0.0%)	1 (0.0%)	420 (0.2%)	21 (0.2%)	627 (0.2%)	065 (0.1%)	0.03
Use of NSAIDs; n (%)	16,220 (16.2%)	4,517 (16.5%)	16,087 (16.4%)	3,178 (16.8%)	32,311 (15.9%)	1,975 (15.0%)	64,618 (16.1%)	9,670 (16.3%)	-0.01
Use of oral corticosteroids; n (%)	10,445 (10.5%)	2,832 (10.3%)	9,420 (9.6%)	1,722 (9.1%)	23,684 (11.7%)	1,501 (11.4%)	43,549 (10.8%)	6,055 (10.2%)	0.02
Use of bisphosphonate (United); n (%)	2,212 (2.2%)	322 (1.2%)	803 (0.8%)	70 (0.4%)	6,829 (3.4%)	252 (1.9%)	9,844 (2.5%)	644 (1.1%)	0.11
Use of opioids- United; n (%)	20,346 (20.4%)	5,472 (20.0%)	18,620 (18.9%)	3,581 (18.9%)	42,529 (20.9%)	2,588 (19.7%)	81,495 (20.3%)	11,641 (19.6%)	0.02
Use of antidepressants; n (%)	22,602 (22.6%)	6,573 (24.0%)	19,480 (19.8%)	4,303 (22.8%)	48,867 (24.0%)	3,160 (24.0%)	90,949 (22.6%)	14,036 (23.6%)	-0.02
Use of antipsychotics; n (%)	2,584 (2.6%)	556 (2.0%)	1,381 (1.4%)	263 (1.4%)	6,338 (3.1%)	258 (2.0%)	10,303 (2.6%)	1,077 (1.8%)	0.05
Use of anticonvulsants; n (%)	16,330 (16.3%)	4,552 (16.6%)	10,690 (10.9%)	2,193 (11.6%)	34,272 (16.9%)	2,157 (16.4%)	61,292 (15.3%)	8,902 (15.0%)	0.01
Use of lithium- United; n (%)	147 (0.1%)	39 (0.1%)	115 (0.1%)	29 (0.2%)	**	**	**	**	**
Use of Benzos- United; n (%)	9,376 (9.4%)	2,472 (9.0%)	7,846 (8.0%)	1,587 (8.4%)	21,369 (10.5%)	1,277 (9.7%)	38,591 (9.6%)	5,336 (9.0%)	0.02
Use of anxiolytics/hypnotics- United; n (%)	4,899 (4.9%)	1,421 (5.2%)	5,117 (5.2%)	1,058 (5.6%)	10,049 (4.9%)	683 (5.2%)	20,065 (5.0%)	3,162 (5.3%)	-0.01
Use of dementia meds- United; n (%)	2,332 (2.3%)	208 (0.8%)	1,003 (1.0%)	51 (0.3%)	10,424 (5.1%)	272 (2.1%)	13,759 (3.4%)	531 (0.9%)	0.17
Use of antiparkinsonian meds- United; n (%)	2,112 (2.1%)	562 (2.1%)	1,514 (1.5%)	265 (1.4%)	6,081 (3.0%)	335 (2.5%)	9,707 (2.4%)	1,162 (2.0%)	0.03
Any use of pramlintide; n (%)	2 (0.0%)	9 (0.0%)	9 (0.0%)	23 (0.1%)	**	**	**	**	**
Any use of 1st generation sulfonylureas; n (%)	2 (0.0%)	1 (0.0%)	10 (0.0%)	1 (0.0%)	**	**	**	**	**
Entresto (sacubitril/valsartan); n (%)	158 (0.2%)	122 (0.4%)	52 (0.1%)	22 (0.1%)	158 (0.1%)	43 (0.3%)	368 (0.1%)	187 (0.3%)	0.00
Initiation as monotherapy v4 Copy; n (%)	85,916 (86.0%)	25,773 (94.1%)	84,176 (85.6%)	17,936 (94.8%)	184,924 (91.0%)	12,565 (95.5%)	355,016 (88.4%)	56,274 (94.6%)	-0.22
Labs							198,248	46,306	
Lab values- HbA1c (%) v3; n (%)	43,141 (43.2%)	11,298 (41.2%)	6,423 (6.5%)	1,049 (5.5%)	N/A	N/A	49,564 (25.0%)	12,347 (26.7%)	-0.04
Lab values- HbA1c (%) (within 3 months) v3; n (%)	34,616 (34.6%)	9,068 (33.1%)	5,174 (5.3%)	858 (4.5%)	N/A	N/A	39,790 (20.1%)	9,926 (21.4%)	-0.03

Table 1

Lab values- HbA1c (%) (within 6 months) v3; n (%)	43,141 (43.2%)	11,298 (41.2%)	6,423 (6.5%)	1,049 (5.5%)	N/A	N/A	49,564 (25.0%)	12,347 (26.7%)	-0.04
Lab values- BNP; n (%)	749 (0.7%)	156 (0.6%)	74 (0.1%)	5 (0.0%)	N/A	N/A	823 (0.4%)	161 (0.3%)	0.02
Lab values- BNP (within 3 months); n (%)	463 (0.5%)	98 (0.4%)	53 (0.1%)	1 (0.0%)	N/A	N/A	516 (0.3%)	099 (0.2%)	0.02
Lab values- BNP (within 6 months); n (%)	749 (0.7%)	156 (0.6%)	74 (0.1%)	5 (0.0%)	N/A	N/A	823 (0.4%)	161 (0.3%)	0.02
Lab values- BUN (mg/dl); n (%)	42,226 (42.3%)	10,947 (40.0%)	6,201 (6.3%)	967 (5.1%)	N/A	N/A	48,427 (24.4%)	11,914 (25.7%)	-0.03
Lab values- BUN (mg/dl) (within 3 months); n (%)	33,174 (33.2%)	8,603 (31.4%)	4,838 (4.9%)	783 (4.1%)	N/A	N/A	38,012 (19.2%)	9,386 (20.3%)	-0.03
Lab values- BUN (mg/dl) (within 6 months); n (%)	42,226 (42.3%)	10,947 (40.0%)	6,201 (6.3%)	967 (5.1%)	N/A	N/A	48,427 (24.4%)	11,914 (25.7%)	-0.03
Lab values- Creatinine (mg/dl) v2; n (%)	43,684 (43.7%)	11,561 (42.2%)	6,653 (6.8%)	1,095 (5.8%)	N/A	N/A	50,337 (25.4%)	12,656 (27.3%)	-0.04
Lab values- Creatinine (mg/dl) (within 3 months) v2; n (%)	34,353 (34.4%)	9,066 (33.1%)	5,215 (5.3%)	882 (4.7%)	N/A	N/A	39,568 (20.0%)	9,948 (21.5%)	-0.04
Lab values- Creatinine (mg/dl) (within 6 months) v2; n (%)	43,684 (43.7%)	11,561 (42.2%)	6,653 (6.8%)	1,095 (5.8%)	N/A	N/A	50,337 (25.4%)	12,656 (27.3%)	-0.04
Lab values- HDL level (mg/dl); n (%)	36,599 (36.6%)	9,688 (35.4%)	5,867 (6.0%)	1,004 (5.3%)	N/A	N/A	42,466 (21.4%)	10,692 (23.1%)	-0.04
Lab values- HDL level (mg/dl) (within 3 months); n (%)	27,311 (27.3%)	7,215 (26.3%)	4,458 (4.5%)	768 (4.1%)	N/A	N/A	31,769 (16.0%)	7,983 (17.2%)	-0.03
Lab values- HDL level (mg/dl) (within 6 months); n (%)	36,599 (36.6%)	9,688 (35.4%)	5,867 (6.0%)	1,004 (5.3%)	N/A	N/A	42,466 (21.4%)	10,692 (23.1%)	-0.04
Lab values- LDL level (mg/dl) v2; n (%)	37,864 (37.9%)	10,005 (36.5%)	6,037 (6.1%)	991 (5.2%)	N/A	N/A	43,901 (22.1%)	10,996 (23.7%)	-0.04
Lab values- LDL level (mg/dl) (within 3 months) v2; n (%)	28,216 (28.2%)	7,452 (27.2%)	4,563 (4.6%)	765 (4.0%)	N/A	N/A	32,779 (16.5%)	8,217 (17.7%)	-0.03
Lab values- LDL level (mg/dl) (within 6 months) v2; n (%)	37,864 (37.9%)	10,005 (36.5%)	6,037 (6.1%)	991 (5.2%)	N/A	N/A	43,901 (22.1%)	10,996 (23.7%)	-0.04
Lab values- NT-proBNP; n (%)	114 (0.1%)	43 (0.2%)	17 (0.0%)	2 (0.0%)	N/A	N/A	131 (0.1%)	45 (0.1%)	0.00
Lab values- NT-proBNP (within 3 months); n (%)	66 (0.1%)	27 (0.1%)	12 (0.0%)	2 (0.0%)	N/A	N/A	78 (0.0%)	29 (0.1%)	-
Lab values- NT-proBNP (within 6 months); n (%)	114 (0.1%)	43 (0.2%)	17 (0.0%)	2 (0.0%)	N/A	N/A	131 (0.1%)	45 (0.1%)	-
Lab values- Total cholesterol (mg/dl) v2; n (%)	37,177 (37.2%)	9,915 (36.2%)	5,903 (6.0%)	1,018 (5.4%)	N/A	N/A	43,080 (21.7%)	10,933 (23.6%)	-0.05
Lab values- Total cholesterol (mg/dl) (within 3 months) v2;	27,768 (27.8%)	7,384 (27.0%)	4,489 (4.6%)	783 (4.1%)	N/A	N/A	32,257 (16.3%)	8,167 (17.6%)	-0.03
Lab values- Total cholesterol (mg/dl) (within 6 months) v2;	37,177 (37.2%)	9,915 (36.2%)	5,903 (6.0%)	1,018 (5.4%)	N/A	N/A	43,080 (21.7%)	10,933 (23.6%)	-0.05
Lab values- Triglyceride level (mg/dl); n (%)	36,829 (36.9%)	9,848 (35.9%)	5,814 (5.9%)	1,000 (5.3%)	N/A	N/A	42,643 (21.5%)	10,848 (23.4%)	-0.05
Lab values- Triglyceride level (mg/dl) (within 3 months); n (%	27,527 (27.6%)	7,338 (26.8%)	4,418 (4.5%)	771 (4.1%)	N/A	N/A	31,945 (16.1%)	8,109 (17.5%)	-0.04
Lab values- Triglyceride level (mg/dl) (within 6 months); n (%	36,829 (36.9%)	9,848 (35.9%)	5,814 (5.9%)	1,000 (5.3%)	N/A	N/A	42,643 (21.5%)	10,848 (23.4%)	-0.05
Lab result number- HbA1c (%) mean (only 2 to 20 included	42,905	11,242	6,311	1,018	N/A	N/A	49,216	12,260	
...mean (sd)	8.36 (1.78)	8.55 (1.75)	8.53 (1.88)	8.32 (1.79)	N/A	N/A	8.38 (1.79)	8.53 (1.75)	-0.08
...median [IQR]	8.00 [7.15, 9.25]	8.20 [7.30, 9.55]	8.05 [7.15, 9.50]	8.00 [7.00, 9.00]	N/A	N/A	8.01 (1.79)	8.18 (1.75)	-0.10
...Missing; n (%)	56,998 (57.1%)	16,152 (59.0%)	92,034 (93.6%)	17,894 (94.6%)	N/A	N/A	149,032 (75.2%)	34,046 (73.5%)	0.04
Lab result number- BNP mean v2	749	156	74	5	N/A	N/A	823	161	
...mean (sd)	154.93 (290.29)	146.64 (314.40)	3,931.76 (32,532.43)	32.60 (34.74)	N/A	N/A	494.52 (9710.65)	143.10 (509.52)	0.05
...median [IQR]	63.20 [25.55, 167.50]	34.45 [14.55, 89.70]	76.50 [29.75, 193.00]	18.00 [13.50, 39.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	99,154 (99.3%)	27,238 (99.4%)	98,271 (99.9%)	18,907 (100.0%)	N/A	N/A	197,425 (99.6%)	46,145 (99.7%)	-0.02
Lab result number- BUN (mg/dl) mean v2	42,226	10,947	6,201	967	N/A	N/A	48,427	11,914	
...mean (sd)	17.98 (7.45)	16.64 (5.62)	1,795.05 (17,168.60)	2,184.17 (18,371.33)	N/A	N/A	245.53 (6143.29)	192.57 (5288.81)	0.01
...median [IQR]	16.50 [13.00, 21.00]	16.00 [13.00, 19.50]	16.00 [13.00, 20.00]	15.50 [13.00, 19.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	57,677 (57.7%)	16,447 (60.0%)	92,144 (93.7%)	17,945 (94.9%)	N/A	N/A	149,821 (75.6%)	34,392 (74.3%)	0.03
Lab result number- Creatinine (mg/dl) mean (only 0.1 to 15	43,333	11,484	6,645	711	N/A	N/A	48,978	12,195	
...mean (sd)	1.01 (0.39)	0.92 (0.24)	0.98 (0.33)	0.94 (0.20)	N/A	N/A	1.01 (0.38)	0.92 (0.24)	0.28
...median [IQR]	0.93 [0.78, 1.15]	0.89 [0.75, 1.05]	0.95 [0.79, 1.08]	0.95 [0.81, 1.00]	N/A	N/A	0.93 (0.38)	0.89 (0.24)	0.13
...Missing; n (%)	56,570 (56.6%)	15,910 (58.1%)	92,700 (94.3%)	18,201 (96.2%)	N/A	N/A	149,270 (75.3%)	34,111 (73.7%)	0.04
Lab result number- HDL level (mg/dl) mean (only =<1000 in	36,599	9,688	5,805	994	N/A	N/A	42,404	10,682	
...mean (sd)	45.86 (13.58)	44.26 (12.89)	44.94 (13.83)	47.81 (132.54)	N/A	N/A	45.73 (13.61)	44.59 (42.24)	0.04
...median [IQR]	44.00 [37.00, 53.00]	42.00 [36.00, 51.00]	43.00 [36.00, 52.00]	42.00 [35.00, 50.00]	N/A	N/A	43.86 (13.61)	42.00 (42.24)	0.06
...Missing; n (%)	63,304 (63.4%)	17,706 (64.6%)	92,540 (94.1%)	17,918 (94.7%)	N/A	N/A	155,844 (78.6%)	35,624 (76.9%)	0.04
Lab result number- LDL level (mg/dl) mean (only =<1000 in	36,994	9,836	5,343	919	N/A	N/A	42,337	10,775	
...mean (sd)	85.89 (39.91)	81.77 (40.57)	90.89 (42.17)	84.41 (40.86)	N/A	N/A	86.52 (40.20)	82.00 (40.60)	0.11
...median [IQR]	83.50 [52.00, 108.75]	80.50 [58.00, 105.00]	89.00 [67.00, 116.00]	84.00 [61.00, 109.00]	N/A	N/A	84.19 (40.20)	80.80 (40.60)	0.08
...Missing; n (%)	62,909 (63.0%)	17,538 (64.0%)	93,002 (94.6%)	17,993 (95.1%)	N/A	N/A	155,911 (78.6%)	35,531 (76.7%)	0.05
Lab result number- Total cholesterol (mg/dl) mean (only =<	37,141	9,912	5,841	1,005	N/A	N/A	42,982	10,917	
...mean (sd)	173.84 (47.32)	170.49 (47.05)	179.36 (49.26)	171.92 (49.48)	N/A	N/A	174.59 (47.59)	170.62 (47.28)	0.08
...median [IQR]	167.50 [143.00, 198.00]	165.00 [139.00, 195.00]	174.00 [148.00, 205.00]	165.50 [140.25, 196.00]	N/A	N/A	168.38 (47.59)	165.05 (47.28)	0.07
...Missing; n (%)	62,762 (62.8%)	17,482 (63.8%)	92,504 (94.1%)	17,907 (94.7%)	N/A	N/A	155,266 (78.3%)	35,389 (76.4%)	0.05

Table 1

Lab result number- Triglyceride level (mg/dl) mean (only =<	36,825	9,846	3,753	987	N/A	N/A	42,578	10,833	
...mean (sd)	193.49 (177.23)	207.63 (200.82)	197.08 (184.91)	210.43 (212.46)	N/A	N/A	193.98 (178.29)	207.89 (201.92)	-0.07
...median [IQR]	155.00 [110.00, 223.00]	160.00 [113.00, 236.00]	153.00 [106.50, 228.25]	157.50 [109.00, 233.00]	N/A	N/A	154.73 (178.29)	159.77 (201.92)	-0.03
...Missing; n (%)	63,078 (63.1%)	17,548 (64.1%)	92,592 (94.2%)	17,925 (94.8%)	N/A	N/A	155,670 (78.5%)	35,473 (76.6%)	0.05
Lab result number- Hemoglobin mean (only >0 included)	28,791	7,333	4,328	643	N/A	N/A	33,119	7,976	
...mean (sd)	13.72 (1.56)	14.15 (1.49)	6,342.54 (215,464.58)	1,919.68 (16,045.24)	N/A	N/A	840.77 (77884.39)	167.77 (4553.05)	0.01
...median [IQR]	13.70 [12.65, 14.80]	14.10 [13.10, 15.20]	13.90 [12.85, 15.00]	14.00 [13.00, 15.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	71,112 (71.2%)	20,061 (73.2%)	94,017 (95.6%)	18,269 (96.6%)	N/A	N/A	165,129 (83.3%)	38,330 (82.8%)	0.01
Lab result number- Serum sodium mean (only > 90 and < 15	42,353	11,249	6,243	1,027	N/A	N/A	48,396	12,276	
...mean (sd)	139.42 (2.77)	139.45 (2.68)	138.82 (2.61)	139.17 (2.53)	N/A	N/A	139.34 (2.75)	139.43 (2.67)	-0.03
...median [IQR]	139.50 [138.00, 141.00]	139.50 [138.00, 141.00]	139.00 [137.00, 140.50]	139.00 [137.50, 141.00]	N/A	N/A	139.44 (2.75)	139.46 (2.67)	-0.01
...Missing; n (%)	57,550 (57.6%)	16,145 (58.9%)	92,102 (93.7%)	17,885 (94.6%)	N/A	N/A	149,652 (75.5%)	34,030 (73.5%)	0.05
Lab result number- Albumin mean (only >0 and <=10 incluc	39,793	10,600	5,330	848	N/A	N/A	45,123	11,448	
...mean (sd)	4.29 (0.32)	4.32 (0.31)	4.20 (0.38)	4.10 (0.39)	N/A	N/A	4.28 (0.33)	4.30 (0.32)	-0.06
...median [IQR]	4.30 [4.10, 4.50]	4.30 [4.10, 4.50]	4.20 [4.00, 4.45]	4.00 [4.00, 4.30]	N/A	N/A	4.29 (0.33)	4.28 (0.32)	0.03
...Missing; n (%)	60,110 (60.2%)	16,794 (61.3%)	93,015 (94.6%)	18,064 (95.5%)	N/A	N/A	153,125 (77.2%)	34,858 (75.3%)	0.04
Lab result number- Glucose (fasting or random) mean (only	42,469	11,283	6,343	1,054	N/A	N/A	48,812	12,337	
...mean (sd)	178.34 (72.25)	182.55 (71.67)	181.56 (74.01)	177.65 (69.16)	N/A	N/A	178.76 (72.48)	182.13 (71.46)	-0.05
...median [IQR]	161.00 [129.00, 209.50]	167.00 [132.50, 217.00]	163.00 [130.50, 215.50]	161.75 [129.00, 209.00]	N/A	N/A	161.26 (72.48)	166.55 (71.46)	-0.07
...Missing; n (%)	57,434 (57.5%)	16,111 (58.8%)	92,002 (93.6%)	17,858 (94.4%)	N/A	N/A	149,436 (75.4%)	33,969 (73.4%)	0.05
Lab result number- Potassium mean (only 1-7 included)	43,384	11,485	6,118	973	N/A	N/A	49,502	12,458	
...mean (sd)	4.48 (0.43)	4.47 (0.40)	4.32 (0.46)	4.16 (0.50)	N/A	N/A	4.46 (0.43)	4.45 (0.41)	0.02
...median [IQR]	4.50 [4.20, 4.70]	4.45 [4.20, 4.70]	4.30 [4.00, 4.60]	4.00 [4.00, 4.50]	N/A	N/A	4.48 (0.43)	4.41 (0.41)	0.17
...Missing; n (%)	56,519 (56.6%)	15,909 (58.1%)	92,227 (93.8%)	17,939 (94.9%)	N/A	N/A	148,746 (75.0%)	33,848 (73.1%)	0.04
Comorbidity Scores									
CCI (180 days)- ICD9 and ICD10 v2									
...mean (sd)	2.43 (1.80)	2.23 (1.47)	1.64 (1.30)	1.67 (1.06)	2.63 (1.89)	2.46 (1.56)	2.34 (1.74)	2.11 (1.38)	0.15
...median [IQR]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	1.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 4.00]	2.00 [1.00, 3.00]	1.76 (1.74)	2.00 (1.38)	-0.15
Frailty Score: Qualitative Version 365 days as Categories, v1									
...0; n (%)	68,126 (68.2%)	23,602 (86.2%)	60,170 (61.2%)	14,653 (77.5%)	92,074 (45.3%)	10,006 (76.1%)	220,370 (54.9%)	48,261 (81.2%)	-0.59
...1 to 2; n (%)	24,208 (24.2%)	3,375 (12.3%)	29,743 (30.2%)	3,605 (19.1%)	66,971 (32.9%)	2,319 (17.6%)	120,922 (30.1%)	9,299 (15.6%)	0.35
...3 or more; n (%)	7,569 (7.6%)	417 (1.5%)	8,432 (8.6%)	634 (3.5%)	44,249 (21.8%)	831 (6.3%)	60,250 (15.0%)	1,902 (3.2%)	0.42
Frailty Score: Empirical Version 365 days as Categories, v3									
...<0.12908; n (%)	28,978 (29.0%)	9,111 (33.3%)	32,840 (33.4%)	6,951 (36.8%)	26,735 (13.2%)	2,162 (16.4%)	88,553 (22.1%)	18,224 (30.6%)	-0.19
...0.12908 - 0.1631167; n (%)	33,399 (33.4%)	9,641 (35.2%)	36,156 (36.8%)	7,300 (38.6%)	55,651 (27.4%)	4,179 (31.8%)	125,206 (31.2%)	21,120 (35.5%)	-0.09
...>=0.1631167; n (%)	37,526 (37.6%)	8,642 (31.5%)	29,349 (29.8%)	4,661 (24.6%)	120,908 (59.5%)	6,815 (51.8%)	187,783 (46.8%)	20,118 (33.8%)	0.27
Non-Frailty; n (%)	57,586 (57.6%)	16,315 (59.6%)	50,767 (51.6%)	10,157 (53.7%)	10,528 (5.2%)	611 (4.6%)	118,881 (29.6%)	27,083 (45.5%)	-0.33
Frailty Score (mean): Qualitative Version 365 days, v1									
...mean (sd)	0.64 (1.29)	0.21 (0.64)	0.75 (1.28)	0.37 (0.86)	1.43 (1.93)	0.48 (1.11)	1.07 (1.64)	0.32 (0.83)	0.58
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	1.00 [0.00, 2.00]	0.00 [0.00, 0.00]	0.51 (1.64)	0.00 (0.83)	0.39
Frailty Score (mean): Empirical Version 365 days, v2									
...mean (sd)	0.16 (0.05)	0.15 (0.04)	0.15 (0.04)	0.14 (0.03)	0.19 (0.06)	0.17 (0.05)	0.17 (0.05)	0.15 (0.04)	0.44
...median [IQR]	0.15 [0.13, 0.18]	0.14 [0.12, 0.17]	0.14 [0.12, 0.16]	0.13 [0.12, 0.16]	0.17 [0.14, 0.22]	0.17 [0.14, 0.20]	0.16 (0.05)	0.14 (0.04)	0.44
Healthcare Utilization									
Any hospitalization; n (%)	5,497 (5.5%)	1,088 (4.0%)	3,358 (3.4%)	417 (2.2%)	12,442 (6.1%)	482 (3.7%)	21,297 (5.3%)	1,987 (3.3%)	0.10
Any hospitalization within prior 30 days; n (%)	1,947 (1.9%)	275 (1.0%)	982 (1.0%)	61 (0.3%)	3,634 (1.8%)	65 (0.5%)	6,563 (1.6%)	401 (0.7%)	0.08
Any hospitalization during prior 31-180 days; n (%)	3,821 (3.8%)	845 (3.1%)	2,452 (2.5%)	362 (1.9%)	9,387 (4.6%)	424 (3.2%)	15,660 (3.9%)	1,631 (2.7%)	0.07
Endocrinologist Visit; n (%)	9,696 (9.7%)	6,083 (22.2%)	8,916 (9.1%)	4,696 (24.8%)	24,295 (12.0%)	3,503 (26.6%)	42,907 (10.7%)	14,282 (24.0%)	-0.36
Endocrinologist Visit (30 days prior); n (%)	6,358 (6.4%)	4,656 (17.0%)	5,990 (6.1%)	3,590 (19.0%)	15,500 (7.6%)	2,720 (20.7%)	27,848 (6.9%)	10,966 (18.4%)	-0.35
Endocrinologist Visit (31 to 180 days prior); n (%)	6,561 (6.6%)	4,086 (14.9%)	5,999 (6.1%)	3,222 (17.0%)	17,451 (8.6%)	2,594 (19.7%)	30,011 (7.5%)	9,902 (16.7%)	-0.28
Internal medicine/family medicine visits; n (%)	79,699 (79.8%)	19,568 (71.4%)	85,692 (87.1%)	15,991 (84.6%)	164,752 (81.0%)	10,436 (79.3%)	330,143 (82.2%)	45,995 (77.4%)	0.12
Internal medicine/family medicine visits (30 days prior) v2;	59,806 (59.9%)	14,110 (51.5%)	64,158 (65.2%)	11,352 (60.0%)	116,541 (57.3%)	7,146 (54.3%)	240,505 (59.9%)	32,608 (54.8%)	0.10
Internal medicine/family medicine visits (31 to 180 days pr	68,510 (68.6%)	16,887 (61.6%)	69,171 (70.3%)	13,393 (70.8%)	142,940 (70.3%)	9,188 (69.8%)	280,621 (69.9%)	39,468 (66.4%)	0.08
Cardiologist visit; n (%)	23,368 (23.4%)	6,777 (24.7%)	14,980 (15.2%)	3,006 (15.9%)	60,430 (29.7%)	4,227 (32.1%)	98,778 (24.6%)	14,010 (23.6%)	0.02
Number of Cardiologist visits (30 days prior); n (%)	8,018 (8.0%)	2,440 (8.9%)	4,841 (4.9%)	894 (4.7%)	19,046 (9.4%)	1,399 (10.6%)	31,905 (7.9%)	4,733 (8.0%)	0.00

Table 1

Number of Cardiologist visits (31 to 180 days prior); n (%)	19,586 (19.6%)	5,663 (20.7%)	12,542 (12.8%)	2,550 (13.5%)	52,580 (25.9%)	3,650 (27.7%)	84,708 (21.1%)	11,863 (20.0%)	0.03
Electrocardiogram v2; n (%)	26,602 (26.6%)	7,163 (26.1%)	22,603 (23.0%)	4,033 (21.3%)	61,061 (30.0%)	4,106 (31.2%)	110,266 (27.5%)	15,302 (25.7%)	0.04
Use of glucose test strips; n (%)	3,648 (3.7%)	852 (3.1%)	3,332 (3.4%)	754 (4.0%)	6,468 (3.2%)	414 (3.1%)	13,448 (3.3%)	2,020 (3.4%)	-0.01
Dialysis; n (%)	26 (0.0%)	1 (0.0%)	10 (0.0%)	0 (0.0%)	**	**	**	**	**
Naive new user v8 Copy; n (%)	13,650 (13.7%)	1,877 (6.9%)	13,152 (13.4%)	1,106 (5.8%)	24,032 (11.8%)	647 (4.9%)	50,834 (12.7%)	3,630 (6.1%)	0.23
N antidiabetic drugs at index date v3 Copy									
...mean (sd)	2.26 (0.83)	2.34 (0.93)	2.28 (0.82)	2.39 (0.96)	2.23 (0.83)	2.44 (0.93)	2.25 (0.83)	2.38 (0.94)	-0.15
...median [IQR]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 (0.83)	2.00 (0.94)	0.00
number of different/distinct medication prescriptions									
...mean (sd)	9.99 (4.61)	10.50 (4.73)	8.93 (4.09)	9.97 (4.24)	9.91 (4.25)	10.60 (4.22)	9.69 (4.30)	10.35 (4.47)	-0.15
...median [IQR]	9.00 [7.00, 12.00]	10.00 [7.00, 13.00]	8.00 [6.00, 11.00]	9.00 [7.00, 12.00]	9.00 [7.00, 12.00]	10.00 [8.00, 13.00]	8.76 (4.30)	9.68 (4.47)	-0.21
Number of Hospitalizations									
...mean (sd)	0.07 (0.30)	0.05 (0.24)	0.04 (0.21)	0.02 (0.16)	0.07 (0.32)	0.04 (0.23)	0.06 (0.29)	0.04 (0.22)	0.08
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (0.29)	0.00 (0.22)	0.00
Number of hospital days									
...mean (sd)	0.37 (2.52)	0.21 (1.44)	0.19 (1.31)	0.10 (0.90)	0.45 (2.78)	0.19 (1.28)	0.37 (2.46)	0.17 (1.26)	0.10
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (2.46)	0.00 (1.26)	0.00
Number of Emergency Department (ED) visits v3									
...mean (sd)	0.38 (1.19)	0.30 (1.09)	0.07 (0.75)	0.05 (0.57)	0.43 (1.21)	0.30 (0.93)	0.33 (1.11)	0.22 (0.92)	0.11
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (1.11)	0.00 (0.92)	0.00
Number of Office visits									
...mean (sd)	4.40 (3.47)	4.68 (3.48)	3.93 (3.12)	4.16 (3.11)	4.87 (3.70)	5.39 (3.66)	4.52 (3.51)	4.67 (3.41)	-0.04
...median [IQR]	4.00 [2.00, 6.00]	4.00 [2.00, 6.00]	3.00 [2.00, 5.00]	3.00 [2.00, 5.00]	4.00 [2.00, 7.00]	5.00 [3.00, 7.00]	3.76 (3.51)	3.90 (3.41)	-0.04
Number of Endocrinologist visits									
...mean (sd)	0.44 (2.07)	1.13 (3.39)	0.41 (2.05)	1.25 (3.46)	0.63 (2.84)	1.59 (4.88)	0.53 (2.49)	1.27 (3.79)	-0.23
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 (2.49)	0.00 (3.79)	0.00
Number of internal medicine/family medicine visits									
...mean (sd)	8.66 (12.52)	7.06 (10.58)	6.43 (7.97)	6.12 (7.44)	6.99 (9.20)	6.58 (8.74)	7.27 (9.87)	6.65 (9.28)	0.06
...median [IQR]	5.00 [1.00, 11.00]	4.00 [0.00, 9.00]	4.00 [2.00, 8.00]	4.00 [2.00, 8.00]	4.00 [1.00, 9.00]	4.00 [1.00, 9.00]	4.25 (9.87)	4.00 (9.28)	0.03
Number of Cardiologist visits									
...mean (sd)	1.05 (3.12)	1.18 (3.46)	0.59 (2.18)	0.60 (2.16)	1.39 (3.76)	1.50 (3.89)	1.11 (3.28)	1.07 (3.22)	0.01
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (3.28)	0.00 (3.22)	0.00
Number electrocardiograms received v2									
...mean (sd)	0.49 (1.20)	0.47 (1.16)	0.37 (0.88)	0.33 (0.83)	0.56 (1.18)	0.55 (1.12)	0.50 (1.12)	0.44 (1.06)	0.06
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (1.12)	0.00 (1.06)	0.00
Number of HbA1c tests ordered									
...mean (sd)	1.29 (0.88)	1.37 (0.88)	1.09 (0.85)	1.33 (0.82)	1.41 (0.85)	1.57 (0.81)	1.30 (0.86)	1.40 (0.85)	-0.12
...median [IQR]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [0.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	2.00 [1.00, 2.00]	1.00 (0.86)	1.22 (0.85)	-0.26
Number of glucose tests ordered									
...mean (sd)	0.55 (3.54)	0.46 (1.58)	0.34 (1.10)	0.43 (1.22)	0.42 (1.02)	0.48 (1.08)	0.43 (1.99)	0.45 (1.37)	-0.01
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 (1.99)	0.00 (1.37)	0.00
Number of lipid tests ordered									
...mean (sd)	0.97 (0.91)	1.01 (0.94)	0.89 (1.17)	1.05 (1.16)	0.98 (0.81)	1.07 (0.83)	0.96 (0.93)	1.04 (0.99)	-0.08
...median [IQR]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [1.00, 2.00]	1.00 (0.93)	1.00 (0.99)	0.00
Number of creatinine tests ordered									
...mean (sd)	0.04 (0.26)	0.04 (0.25)	0.03 (0.23)	0.04 (0.25)	0.06 (0.32)	0.07 (0.34)	0.05 (0.29)	0.05 (0.27)	0.00
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (0.29)	0.00 (0.27)	0.00
Number of BUN tests ordered									
...mean (sd)	0.02 (0.20)	0.02 (0.17)	0.02 (0.18)	0.02 (0.17)	0.04 (0.26)	0.04 (0.26)	0.03 (0.23)	0.02 (0.19)	0.05
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (0.23)	0.00 (0.19)	0.00
Number of tests for microalbuminuria									
...mean (sd)	0.81 (1.17)	0.87 (1.18)	0.64 (1.03)	0.81 (1.12)	0.48 (0.70)	0.56 (0.71)	0.60 (0.92)	0.78 (1.07)	-0.18
...median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (0.92)	0.00 (1.07)	0.00
Total N distinct ICD9/ICD10 diagnoses at the 3rd digit level Copy									
...mean (sd)	6.92 (7.38)	8.25 (6.87)	2.91 (3.94)	3.91 (3.75)	6.39 (7.39)	8.79 (7.04)	5.67 (6.71)	6.99 (6.10)	-0.21
...median [IQR]	5.00 [0.00, 10.00]	7.00 [4.00, 11.00]	2.00 [0.00, 5.00]	4.00 [0.00, 6.00]	5.00 [0.00, 10.00]	7.00 [4.00, 12.00]	4.27 (6.71)	6.05 (6.10)	-0.28
Use of thiazide; n (%)	11,963 (12.0%)	3,080 (11.2%)	10,371 (10.5%)	1,926 (10.2%)	27,843 (13.7%)	1,804 (13.7%)	50,177 (12.5%)	6,810 (11.5%)	0.03
Use of beta blockers; n (%)	36,576 (36.6%)	9,851 (36.0%)	30,224 (30.7%)	5,661 (29.9%)	96,233 (47.3%)	6,419 (48.8%)	163,033 (40.6%)	21,931 (36.9%)	0.08
Use of calcium channel blockers; n (%)	30,078 (30.1%)	7,288 (26.6%)	26,215 (26.7%)	4,370 (23.1%)	69,690 (34.3%)	4,001 (30.4%)	125,983 (31.4%)	15,639 (26.3%)	0.11

Table 1

	Unmatched								
	Optum		MarketScan		Medicare		POOLED		
Variable	Reference- DPP4i v2	Exposure - Empagliflozin v3	Reference- DPP4i v2	Exposure - Empagliflozin v3	Reference- DPP4i v2	Exposure - Empagliflozin v3	Reference- DPP4i v2	Exposure - Empagliflozin v3	St. Diff.
Number of patients	99,903	27,394	98,345	18,912	203,294	13,156	401,542	59,462	
Age									
...mean (sd)	64.93 (11.69)	60.53 (10.62)	58.66 (11.12)	55.47 (8.77)	74.08 (6.94)	71.46 (5.19)	68.03 (9.42)	61.34 (9.08)	0.72
...median [IQR]	66.00 [57.00, 73.00]	61.00 [53.00, 68.00]	58.00 [52.00, 64.00]	56.00 [50.00, 61.00]	73.00 [68.00, 78.00]	0.00 [68.00, 74.00]	67.58 (9.42)	61.40 (9.08)	0.67
Age categories without zero category									
...18 - 34; n (%)	19,490 (19.5%)	7,748 (28.3%)	33,966 (34.5%)	7,944 (42.0%)	0 (0.0%)	0 (0.0%)	53,456 (13.3%)	15,692 (26.4%)	-0.33
...35 - 64; n (%)	23,551 (23.6%)	8,844 (32.3%)	41,612 (42.3%)	9,123 (48.2%)	1,132 (0.6%)	43 (0.3%)	66,295 (16.5%)	18,010 (30.3%)	-0.33
...65 - 74; n (%)	36,281 (36.3%)	8,539 (31.2%)	13,769 (14.0%)	1,483 (7.8%)	119,235 (58.7%)	9,986 (75.9%)	169,285 (42.2%)	20,008 (33.6%)	0.18
...>=75; n (%)	20,581 (20.6%)	2,263 (8.3%)	8,998 (9.1%)	362 (1.9%)	82,927 (40.8%)	3,127 (23.8%)	112,506 (28.0%)	5,752 (9.7%)	0.48
Gender without zero category- United									
...Males; n (%)	53,340 (53.4%)	16,618 (60.7%)	57,603 (58.6%)	11,785 (62.3%)	92,595 (45.5%)	7,494 (57.0%)	203,538 (50.7%)	35,897 (60.4%)	-0.20
...Females; n (%)	46,563 (46.6%)	10,776 (39.3%)	40,742 (41.4%)	7,127 (37.7%)	110,699 (54.5%)	5,662 (43.0%)	198,004 (49.3%)	23,565 (39.6%)	0.20
Race									
...White; n (%)	N/A	N/A	N/A	N/A	151,073 (74.3%)	10,799 (82.1%)	151,073 (74.3%)	10,799 (82.1%)	-0.19
...Black; n (%)	N/A	N/A	N/A	N/A	22,905 (11.3%)	916 (7.0%)	22,905 (11.3%)	916 (7.0%)	0.15
...Asian; n (%)	N/A	N/A	N/A	N/A	9,749 (4.8%)	387 (2.9%)	9,749 (4.8%)	387 (2.9%)	0.10
...Hispanic; n (%)	N/A	N/A	N/A	N/A	9,554 (4.7%)	333 (2.5%)	9,554 (4.7%)	333 (2.5%)	0.12
...North American Native; n (%)	N/A	N/A	N/A	N/A	1,385 (0.7%)	58 (0.4%)	1,385 (0.7%)	58 (0.4%)	0.04
...Other/Unknown; n (%)	N/A	N/A	N/A	N/A	8,628 (4.2%)	663 (5.0%)	8,628 (4.2%)	663 (5.0%)	-0.04
Region without zero category- United v3 (lumping missing&other category with West)									
...Northeast; n (%)	10,960 (11.0%)	2,334 (8.5%)	17,603 (17.9%)	2,575 (13.6%)	38,218 (18.8%)	2,505 (19.0%)	66,781 (16.6%)	7,414 (12.5%)	0.12
...South; n (%)	52,164 (52.2%)	15,303 (55.9%)	20,254 (20.6%)	3,296 (17.4%)	86,895 (42.7%)	5,524 (42.0%)	159,313 (39.7%)	24,123 (40.6%)	-0.02
...Midwest; n (%)	18,103 (18.1%)	5,373 (19.6%)	50,370 (51.2%)	11,006 (58.2%)	42,468 (20.9%)	2,506 (19.0%)	110,941 (27.6%)	18,885 (31.8%)	-0.09
...West; n (%)	18,676 (18.7%)	4,384 (16.0%)	9,489 (9.6%)	1,978 (10.5%)	35,713 (17.6%)	2,621 (19.9%)	63,878 (15.9%)	8,983 (15.1%)	0.02
...Unknown+missing; n (%)	N/A	N/A	629 (0.6%)	57 (0.3%)	N/A	N/A	629 (0.6%)	57 (0.3%)	0.04
CV Covariates									
Ischemic heart disease; n (%)	18,990 (19.0%)	5,885 (21.5%)	12,693 (12.9%)	2,535 (13.4%)	54,534 (26.8%)	4,200 (31.9%)	86,217 (21.5%)	12,620 (21.2%)	0.01
Acute MI; n (%)	931 (0.9%)	344 (1.3%)	372 (0.4%)	104 (0.5%)	1,288 (0.6%)	89 (0.7%)	2,591 (0.6%)	537 (0.9%)	-0.03
ACS/unstable angina; n (%)	702 (0.7%)	231 (0.8%)	500 (0.5%)	107 (0.6%)	1,499 (0.7%)	118 (0.9%)	2,701 (0.7%)	456 (0.8%)	-0.01
Old MI; n (%)	2,549 (2.6%)	819 (3.0%)	906 (0.9%)	191 (1.0%)	5,824 (2.9%)	466 (3.5%)	9,279 (2.3%)	1,476 (2.5%)	-0.01
Stable angina; n (%)	3,164 (3.2%)	1,100 (4.0%)	1,545 (1.6%)	382 (2.0%)	6,343 (3.1%)	626 (4.8%)	11,052 (2.8%)	2,108 (3.5%)	-0.04
Coronary atherosclerosis and other forms of chronic ischer	17,701 (17.7%)	5,558 (20.3%)	11,987 (12.2%)	2,406 (12.7%)	52,219 (25.7%)	4,074 (31.0%)	81,907 (20.4%)	12,038 (20.2%)	0.00
Other atherosclerosis with ICD10 v2 Copy; n (%)	501 (0.5%)	106 (0.4%)	451 (0.5%)	57 (0.3%)	2,443 (1.2%)	86 (0.7%)	3,395 (0.8%)	249 (0.4%)	0.05
Previous cardiac procedure (CABG or PTCA or Stent) v4; n (%	407 (0.4%)	189 (0.7%)	212 (0.2%)	52 (0.3%)	461 (0.2%)	55 (0.4%)	1,080 (0.3%)	296 (0.5%)	-0.03
History of CABG or PTCA; n (%)	4,493 (4.5%)	1,679 (6.1%)	1,629 (1.7%)	369 (2.0%)	13,342 (6.6%)	1,156 (8.8%)	19,464 (4.8%)	3,204 (5.4%)	-0.03
Any stroke; n (%)	4,963 (5.0%)	1,153 (4.2%)	2,035 (2.1%)	273 (1.4%)	10,123 (5.0%)	591 (4.5%)	17,121 (4.3%)	2,017 (3.4%)	0.05
Ischemic stroke (w and w/o mention of cerebral infarction)	4,899 (4.9%)	1,140 (4.2%)	2,000 (2.0%)	271 (1.4%)	9,999 (4.9%)	585 (4.4%)	16,898 (4.2%)	1,996 (3.4%)	0.04
Hemorrhagic stroke; n (%)	163 (0.2%)	23 (0.1%)	48 (0.0%)	4 (0.0%)	**	**	**	**	**
TIA; n (%)	1,176 (1.2%)	266 (1.0%)	465 (0.5%)	68 (0.4%)	1,913 (0.9%)	98 (0.7%)	3,554 (0.9%)	432 (0.7%)	0.02
Other cerebrovascular disease; n (%)	1,704 (1.7%)	322 (1.2%)	670 (0.7%)	86 (0.5%)	3,962 (1.9%)	236 (1.8%)	6,336 (1.6%)	644 (1.1%)	0.04
Late effects of cerebrovascular disease; n (%)	1,554 (1.6%)	233 (0.9%)	423 (0.4%)	34 (0.2%)	3,186 (1.6%)	107 (0.8%)	5,163 (1.3%)	374 (0.6%)	0.07
Cerebrovascular procedure; n (%)	70 (0.1%)	28 (0.1%)	15 (0.0%)	4 (0.0%)	**	**	**	**	**
Heart failure (CHF); n (%)	6,419 (6.4%)	1,435 (5.2%)	2,935 (3.0%)	399 (2.1%)	18,631 (9.2%)	951 (7.2%)	27,985 (7.0%)	2,785 (4.7%)	0.10
Peripheral Vascular Disease (PVD) or PVD Surgery v2; n (%)	6,638 (6.6%)	1,465 (5.3%)	3,369 (3.4%)	497 (2.6%)	20,972 (10.3%)	1,195 (9.1%)	30,979 (7.7%)	3,157 (5.3%)	0.10
Atrial fibrillation; n (%)	5,807 (5.8%)	1,313 (4.8%)	3,583 (3.6%)	474 (2.5%)	20,723 (10.2%)	1,268 (9.6%)	30,113 (7.5%)	3,055 (5.1%)	0.10
Other cardiac dysrhythmia; n (%)	8,278 (8.3%)	2,142 (7.8%)	4,579 (4.7%)	793 (4.2%)	24,622 (12.1%)	1,806 (13.7%)	37,479 (9.3%)	4,741 (8.0%)	0.05
Cardiac conduction disorders; n (%)	2,246 (2.2%)	580 (2.1%)	1,171 (1.2%)	192 (1.0%)	6,903 (3.4%)	459 (3.5%)	10,320 (2.6%)	1,231 (2.1%)	0.03
Other CVD; n (%)	8,797 (8.8%)	2,259 (8.2%)	5,483 (5.6%)	817 (4.3%)	25,637 (12.6%)	1,671 (12.7%)	39,917 (9.9%)	4,747 (8.0%)	0.07
Diabetes-related complications									
Diabetic retinopathy; n (%)	6,367 (6.4%)	2,196 (8.0%)	3,371 (3.4%)	764 (4.0%)	14,304 (7.0%)	1,298 (9.9%)	24,042 (6.0%)	4,258 (7.2%)	-0.05
Diabetes with other ophthalmic manifestations; n (%)	904 (0.9%)	230 (0.8%)	1,868 (1.9%)	305 (1.6%)	4,906 (2.4%)	267 (2.0%)	7,678 (1.9%)	802 (1.3%)	0.05
Retinal detachment, vitreous hemorrhage, vitrectomy; n (%	415 (0.4%)	135 (0.5%)	328 (0.3%)	76 (0.4%)	780 (0.4%)	80 (0.6%)	1,523 (0.4%)	291 (0.5%)	-0.01
Retinal laser coagulation therapy; n (%)	560 (0.6%)	158 (0.6%)	504 (0.5%)	115 (0.6%)	1,220 (0.6%)	74 (0.6%)	2,284 (0.6%)	347 (0.6%)	0.00
Occurrence of Diabetic Neuropathy v2 Copy; n (%)	19,198 (19.2%)	5,771 (21.1%)	10,496 (10.7%)	2,631 (13.9%)	39,771 (19.6%)	3,284 (25.0%)	69,465 (17.3%)	11,686 (19.7%)	-0.06

Table 1

Occurrence of diabetic nephropathy V3 with ICD10 Copy; r	15,429 (15.4%)	3,259 (11.9%)	6,218 (6.3%)	1,309 (6.9%)	22,695 (11.2%)	1,478 (11.2%)	44,342 (11.0%)	6,046 (10.2%)	0.03
Hypoglycemia v2; n (%)	1,757 (1.8%)	141 (0.5%)	1,705 (1.7%)	183 (1.0%)	4,423 (2.2%)	107 (0.8%)	7,885 (2.0%)	431 (0.7%)	0.11
Hyperglycemia; n (%)	4,186 (4.2%)	1,098 (4.0%)	3,136 (3.2%)	518 (2.7%)	8,064 (4.0%)	466 (3.5%)	15,386 (3.8%)	2,082 (3.5%)	0.02
Disorders of fluid electrolyte and acid-base balance; n (%)	6,080 (6.1%)	1,099 (4.0%)	3,203 (3.3%)	434 (2.3%)	12,731 (6.3%)	479 (3.6%)	22,014 (5.5%)	2,012 (3.4%)	0.10
Diabetic ketoacidosis; n (%)	385 (0.4%)	76 (0.3%)	309 (0.3%)	47 (0.2%)	668 (0.3%)	22 (0.2%)	1,362 (0.3%)	145 (0.2%)	0.02
Hyperosmolar hyperglycemic nonketotic syndrome (HONK	589 (0.6%)	166 (0.6%)	468 (0.5%)	92 (0.5%)	1,077 (0.5%)	80 (0.6%)	2,134 (0.5%)	338 (0.6%)	-0.01
Diabetes with peripheral circulatory disorders with ICD-10	7,150 (7.2%)	1,909 (7.0%)	2,798 (2.8%)	630 (3.3%)	15,464 (7.6%)	1,122 (8.5%)	25,412 (6.3%)	3,661 (6.2%)	0.00
Diabetic Foot; n (%)	1,967 (2.0%)	591 (2.2%)	1,422 (1.4%)	320 (1.7%)	4,932 (2.4%)	286 (2.2%)	8,321 (2.1%)	1,197 (2.0%)	0.01
Gangrene v2; n (%)	235 (0.2%)	63 (0.2%)	144 (0.1%)	28 (0.1%)	380 (0.2%)	33 (0.3%)	759 (0.2%)	124 (0.2%)	0.00
Lower extremity amputation; n (%)	644 (0.6%)	207 (0.8%)	256 (0.3%)	66 (0.3%)	1,155 (0.6%)	81 (0.6%)	2,055 (0.5%)	354 (0.6%)	-0.01
Osteomyelitis; n (%)	491 (0.5%)	155 (0.6%)	361 (0.4%)	78 (0.4%)	936 (0.5%)	54 (0.4%)	1,788 (0.4%)	287 (0.5%)	-0.01
Skin infections v2; n (%)	4,914 (4.9%)	1,384 (5.1%)	4,428 (4.5%)	886 (4.7%)	11,729 (5.8%)	781 (5.9%)	21,071 (5.2%)	3,051 (5.1%)	0.00
Erectile dysfunction; n (%)	2,938 (2.9%)	1,188 (4.3%)	2,680 (2.7%)	585 (3.1%)	4,367 (2.1%)	501 (3.8%)	9,985 (2.5%)	2,274 (3.8%)	-0.07
Diabetes with unspecified complication; n (%)	5,922 (5.9%)	1,946 (7.1%)	4,818 (4.9%)	1,306 (6.9%)	11,396 (5.6%)	953 (7.2%)	22,136 (5.5%)	4,205 (7.1%)	-0.07
Diabetes mellitus without mention of complications; n (%)	82,871 (83.0%)	21,178 (77.3%)	86,660 (88.1%)	15,269 (80.7%)	184,478 (90.7%)	11,109 (84.4%)	354,009 (88.2%)	47,556 (80.0%)	0.23
Hypertension: 1 inpatient or 2 outpatient claims within 36	84,740 (84.8%)	23,304 (85.1%)	75,314 (76.6%)	14,637 (77.4%)	185,875 (91.4%)	11,981 (91.1%)	345,929 (86.2%)	49,922 (84.0%)	0.06
Hyperlipidemia v2; n (%)	70,468 (70.5%)	19,569 (71.4%)	65,929 (67.0%)	13,478 (71.3%)	154,166 (75.8%)	10,169 (77.3%)	290,563 (72.4%)	43,216 (72.7%)	-0.01
Edema; n (%)	5,273 (5.3%)	1,202 (4.4%)	2,878 (2.9%)	467 (2.5%)	16,056 (7.9%)	876 (6.7%)	24,207 (6.0%)	2,545 (4.3%)	0.08
Renal Dysfunction (non-diabetic) v2; n (%)	19,582 (19.6%)	3,179 (11.6%)	8,494 (8.6%)	958 (5.1%)	42,497 (20.9%)	1,822 (13.8%)	70,573 (17.6%)	5,959 (10.0%)	0.22
Occurrence of acute renal disease v2; n (%)	2,581 (2.6%)	332 (1.2%)	1,243 (1.3%)	80 (0.4%)	5,423 (2.7%)	130 (1.0%)	9,247 (2.3%)	542 (0.9%)	0.11
Occurrence of chronic renal insufficiency; n (%)	16,369 (16.4%)	2,354 (8.6%)	6,265 (6.4%)	657 (3.5%)	36,061 (17.7%)	1,453 (11.0%)	58,695 (14.6%)	4,464 (7.5%)	0.23
Chronic kidney disease v2; n (%)	15,864 (15.9%)	2,270 (8.3%)	5,871 (6.0%)	615 (3.3%)	34,532 (17.0%)	1,391 (10.6%)	56,267 (14.0%)	4,276 (7.2%)	0.22
CKD Stage 3-4; n (%)	10,687 (10.7%)	1,245 (4.5%)	3,761 (3.8%)	303 (1.6%)	24,060 (11.8%)	839 (6.4%)	38,508 (9.6%)	2,387 (4.0%)	0.22
Occurrence of hypertensive nephropathy; n (%)	6,766 (6.8%)	968 (3.5%)	2,293 (2.3%)	229 (1.2%)	13,584 (6.7%)	526 (4.0%)	22,643 (5.6%)	1,723 (2.9%)	0.13
Occurrence of miscellaneous renal insufficiency v2; n (%)	4,400 (4.4%)	874 (3.2%)	2,417 (2.5%)	271 (1.4%)	11,162 (5.5%)	523 (4.0%)	17,979 (4.5%)	1,668 (2.8%)	0.09
Glaucoma or cataracts v2; n (%)	18,320 (18.3%)	4,419 (16.1%)	12,973 (13.2%)	2,270 (12.0%)	54,403 (26.8%)	3,639 (27.7%)	85,696 (21.3%)	10,328 (17.4%)	0.10
Cellulitis or abscess of toe; n (%)	1,284 (1.3%)	391 (1.4%)	849 (0.9%)	225 (1.2%)	2,592 (1.3%)	237 (1.8%)	4,725 (1.2%)	853 (1.4%)	-0.02
Foot ulcer; n (%)	1,877 (1.9%)	539 (2.0%)	1,377 (1.4%)	296 (1.6%)	4,802 (2.4%)	270 (2.1%)	8,056 (2.0%)	1,105 (1.9%)	0.01
Bladder stones; n (%)	125 (0.1%)	27 (0.1%)	71 (0.1%)	11 (0.1%)	307 (0.2%)	17 (0.1%)	503 (0.1%)	55 (0.1%)	0.00
Kidney stones; n (%)	1,974 (2.0%)	533 (1.9%)	1,775 (1.8%)	310 (1.6%)	4,340 (2.2%)	294 (2.2%)	8,289 (2.1%)	1,137 (1.9%)	0.01
Urinary tract infections (UTIs); n (%)	7,752 (7.8%)	1,339 (4.9%)	4,684 (4.8%)	565 (3.0%)	23,016 (11.3%)	885 (6.7%)	35,452 (8.8%)	2,789 (4.7%)	0.16
Dipstick urinalysis; n (%)	34,548 (34.6%)	8,269 (30.2%)	29,300 (29.8%)	5,259 (27.8%)	76,034 (37.4%)	4,496 (34.2%)	139,882 (34.8%)	18,024 (30.3%)	0.10
Non-dipstick urinalysis; n (%)	43,363 (43.4%)	12,648 (46.2%)	36,411 (37.0%)	8,432 (44.6%)	84,136 (41.4%)	6,319 (48.0%)	163,910 (40.8%)	27,399 (46.1%)	-0.11
Urine function test; n (%)	1,897 (1.9%)	418 (1.5%)	1,625 (1.7%)	200 (1.1%)	6,250 (3.1%)	434 (3.3%)	9,772 (2.4%)	1,052 (1.8%)	0.04
Cytology; n (%)	560 (0.6%)	117 (0.4%)	522 (0.5%)	60 (0.3%)	1,497 (0.7%)	67 (0.5%)	2,579 (0.6%)	244 (0.4%)	0.03
Cystoscopy; n (%)	843 (0.8%)	204 (0.7%)	726 (0.7%)	103 (0.5%)	2,199 (1.1%)	129 (1.0%)	3,768 (0.9%)	436 (0.7%)	0.02
Other Covariates									
Liver disease; n (%)	3,416 (3.4%)	1,355 (4.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3,416 (0.9%)	1,355 (2.3%)	-0.11
Osteoarthritis; n (%)	14,139 (14.2%)	3,503 (12.8%)	8,944 (9.1%)	1,439 (7.7%)	41,716 (20.5%)	2,523 (19.2%)	64,819 (16.1%)	7,485 (12.6%)	0.10
Other arthritis, arthropathies and musculoskeletal pain; n (	33,077 (33.1%)	8,620 (31.5%)	26,598 (27.0%)	4,912 (26.0%)	82,377 (40.5%)	4,956 (37.7%)	142,052 (35.4%)	18,488 (31.1%)	0.09
Dorsopathies; n (%)	20,631 (20.7%)	5,759 (21.0%)	15,907 (16.2%)	3,084 (16.3%)	48,687 (23.9%)	3,203 (24.3%)	85,225 (21.2%)	12,046 (20.3%)	0.02
Fractures; n (%)	2,412 (2.4%)	501 (1.8%)	1,716 (1.7%)	279 (1.5%)	6,339 (3.1%)	342 (2.6%)	10,467 (2.6%)	1,122 (1.9%)	0.05
Falls v2; n (%)	3,187 (3.2%)	522 (1.9%)	965 (1.0%)	123 (0.7%)	7,872 (3.9%)	346 (2.6%)	12,024 (3.0%)	991 (1.7%)	0.09
Osteoporosis; n (%)	4,316 (4.3%)	634 (2.3%)	1,543 (1.6%)	149 (0.8%)	15,070 (7.4%)	631 (4.8%)	20,929 (5.2%)	1,414 (2.4%)	0.15
Hyperthyroidism; n (%)	588 (0.6%)	179 (0.7%)	466 (0.5%)	85 (0.4%)	1,690 (0.8%)	99 (0.8%)	2,744 (0.7%)	363 (0.6%)	0.01
Hypothyroidism v2; n (%)	13,829 (13.8%)	3,532 (12.9%)	10,304 (10.5%)	2,178 (11.5%)	21,523 (10.6%)	946 (7.2%)	45,656 (11.4%)	6,656 (11.2%)	0.01
Other disorders of thyroid gland V2; n (%)	3,455 (3.5%)	1,215 (4.4%)	2,934 (3.0%)	902 (4.8%)	7,712 (3.8%)	667 (5.1%)	14,101 (3.5%)	2,784 (4.7%)	-0.06
Depression; n (%)	7,320 (7.3%)	1,821 (6.6%)	5,335 (5.4%)	914 (4.8%)	17,919 (8.8%)	902 (6.9%)	30,574 (7.6%)	3,637 (6.1%)	0.06
Anxiety; n (%)	7,953 (8.0%)	2,396 (8.7%)	5,309 (5.4%)	1,125 (5.9%)	15,687 (7.7%)	995 (7.6%)	28,949 (7.2%)	4,516 (7.6%)	-0.02
Sleep_Disorder; n (%)	3,987 (4.0%)	673 (2.5%)	5,785 (5.9%)	766 (4.1%)	11,002 (5.4%)	418 (3.2%)	20,774 (5.2%)	1,857 (3.1%)	0.11
Dementia; n (%)	3,796 (3.8%)	361 (1.3%)	1,343 (1.4%)	91 (0.5%)	14,445 (7.1%)	369 (2.8%)	19,584 (4.9%)	821 (1.4%)	0.20
Delirium; n (%)	1,038 (1.0%)	110 (0.4%)	410 (0.4%)	31 (0.2%)	2,997 (1.5%)	80 (0.6%)	4,445 (1.1%)	221 (0.4%)	0.08
Psychosis; n (%)	1,115 (1.1%)	171 (0.6%)	403 (0.4%)	36 (0.2%)	3,561 (1.8%)	67 (0.5%)	5,079 (1.3%)	274 (0.5%)	0.08
Obesity; n (%)	17,544 (17.6%)	7,711 (28.1%)	6,568 (6.7%)	1,684 (8.9%)	10,068 (5.0%)	806 (6.1%)	34,180 (8.5%)	10,201 (17.2%)	-0.26
Overweight; n (%)	7,117 (7.1%)	2,123 (7.7%)	3,068 (3.1%)	700 (3.7%)	8,443 (4.2%)	650 (4.9%)	18,628 (4.6%)	3,473 (5.8%)	-0.05
Smoking; n (%)	10,562 (10.6%)	3,243 (11.8%)	4,864 (4.9%)	882 (4.7%)	21,088 (10.4%)	1,434 (10.9%)	36,514 (9.1%)	5,559 (9.3%)	-0.01
Alcohol abuse or dependence; n (%)	685 (0.7%)	199 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!	199 (0.3%)	#VALUE!
Drug abuse or dependence; n (%)	1,133 (1.1%)	359 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,133 (0.3%)	359 (0.6%)	-0.04
COPD; n (%)	6,952 (7.0%)	1,485 (5.4%)	3,056 (3.1%)	386 (2.0%)	17,808 (8.8%)	895 (6.8%)	27,816 (6.9%)	2,766 (4.7%)	0.09

Table 1

Asthma; n (%)	4,622 (4.6%)	1,225 (4.5%)	3,363 (3.4%)	592 (3.1%)	9,980 (4.9%)	656 (5.0%)	17,963 (4.5%)	2,473 (4.2%)	0.01
Obstructive sleep apnea; n (%)	7,880 (7.9%)	3,326 (12.1%)	7,903 (8.0%)	2,046 (10.8%)	10,766 (5.3%)	1,274 (9.7%)	26,549 (6.6%)	6,646 (11.2%)	-0.16
Pneumonia; n (%)	1,745 (1.7%)	319 (1.2%)	1,136 (1.2%)	158 (0.8%)	4,422 (2.2%)	214 (1.6%)	7,303 (1.8%)	691 (1.2%)	0.05
Imaging; n (%)	73 (0.1%)	17 (0.1%)	17 (0.0%)	4 (0.0%)	**	**	**	**	**
Diabetes Medications									
DM Medications - AGIs; n (%)	499 (0.5%)	97 (0.4%)	310 (0.3%)	64 (0.3%)	1,243 (0.6%)	58 (0.4%)	2,052 (0.5%)	219 (0.4%)	0.01
DM Medications - Glitazones; n (%)	7,594 (7.6%)	2,318 (8.5%)	6,881 (7.0%)	1,520 (8.0%)	14,722 (7.2%)	1,253 (9.5%)	29,197 (7.3%)	5,091 (8.6%)	-0.05
DM Medications - GLP-1 RA; n (%)	4,184 (4.2%)	5,850 (21.4%)	4,354 (4.4%)	4,829 (25.5%)	5,290 (2.6%)	2,529 (19.2%)	13,828 (3.4%)	13,208 (22.2%)	-0.59
DM Medications - Insulin; n (%)	17,835 (17.9%)	7,838 (28.6%)	14,817 (15.1%)	5,867 (31.0%)	39,115 (19.2%)	4,548 (34.6%)	71,767 (17.9%)	18,253 (30.7%)	-0.30
DM Medications - Megitinides; n (%)	1,041 (1.0%)	212 (0.8%)	1,089 (1.1%)	171 (0.9%)	3,580 (1.8%)	247 (1.9%)	5,710 (1.4%)	630 (1.1%)	0.03
DM Medications - Metformin; n (%)	74,681 (74.8%)	20,362 (74.3%)	79,574 (80.9%)	14,355 (75.9%)	142,034 (69.9%)	9,591 (72.9%)	296,289 (73.8%)	44,308 (74.5%)	-0.02
Concomitant initiation or current use of 2nd Generation SI	33,222 (33.3%)	7,632 (27.9%)	29,037 (29.5%)	4,720 (25.0%)	73,210 (36.0%)	4,236 (32.2%)	135,469 (33.7%)	16,588 (27.9%)	0.13
Concomitant initiation or current use of AGIs; n (%)	359 (0.4%)	65 (0.2%)	216 (0.2%)	39 (0.2%)	888 (0.4%)	35 (0.3%)	1,463 (0.4%)	139 (0.2%)	0.04
Concomitant initiation or current use of Glitazones; n (%)	6,052 (6.1%)	1,790 (6.5%)	5,547 (5.6%)	1,221 (6.5%)	11,634 (5.7%)	990 (7.5%)	23,233 (5.8%)	4,001 (6.7%)	-0.04
Concomitant initiation or current use of GLP-1 RA; n (%)	2,392 (2.4%)	4,382 (16.0%)	2,527 (2.6%)	3,730 (19.7%)	2,849 (1.4%)	1,906 (14.5%)	7,768 (1.9%)	10,018 (16.8%)	-0.53
Concomitant initiation or current use of Insulin; n (%)	13,381 (13.4%)	5,986 (21.9%)	11,021 (11.2%)	4,466 (23.6%)	29,957 (14.7%)	3,603 (27.4%)	54,359 (13.5%)	14,055 (23.6%)	-0.26
Concomitant initiation or current use of Megitinides; n (%	773 (0.8%)	145 (0.5%)	768 (0.8%)	117 (0.6%)	2,607 (1.3%)	170 (1.3%)	4,148 (1.0%)	432 (0.7%)	0.03
Concomitant initiation or current use of Metformin; n (%)	64,669 (64.7%)	16,561 (60.5%)	70,407 (71.6%)	11,825 (62.5%)	122,594 (60.3%)	8,039 (61.1%)	257,670 (64.2%)	36,425 (61.3%)	0.06
Past use of 2nd Generation SUs Copy; n (%)	7,266 (7.3%)	2,028 (7.4%)	6,956 (7.1%)	1,253 (6.6%)	14,813 (7.3%)	902 (6.9%)	29,035 (7.2%)	4,183 (7.0%)	0.01
Past use of AGIs Copy; n (%)	140 (0.1%)	32 (0.1%)	94 (0.1%)	25 (0.1%)	355 (0.2%)	23 (0.2%)	589 (0.1%)	80 (0.1%)	0.00
Past use of Glitazones Copy; n (%)	1,542 (1.5%)	528 (1.9%)	1,334 (1.4%)	299 (1.6%)	3,088 (1.5%)	263 (2.0%)	5,964 (1.5%)	1,090 (1.8%)	-0.02
Past use of GLP-1 RA Copy; n (%)	1,977 (2.0%)	1,701 (6.2%)	2,007 (2.0%)	1,253 (6.6%)	2,441 (1.2%)	623 (4.7%)	6,425 (1.6%)	3,577 (6.0%)	-0.23
Past use of Insulin Copy; n (%)	4,454 (4.5%)	1,852 (6.8%)	3,797 (3.9%)	1,401 (7.4%)	9,160 (4.5%)	945 (7.2%)	17,411 (4.3%)	4,198 (7.1%)	-0.12
Past use of Megitinides Copy; n (%)	268 (0.3%)	67 (0.2%)	321 (0.3%)	54 (0.3%)	973 (0.5%)	77 (0.6%)	1,562 (0.4%)	198 (0.3%)	0.02
Past use of metformin (final) Copy; n (%)	10,012 (10.0%)	3,801 (13.9%)	9,167 (9.3%)	2,330 (13.4%)	19,440 (9.6%)	1,552 (11.8%)	38,619 (9.6%)	7,883 (13.3%)	-0.12
Other Medications									
Use of ACE inhibitors; n (%)	52,616 (52.7%)	14,800 (54.0%)	52,849 (53.7%)	10,492 (55.5%)	96,076 (47.3%)	6,205 (47.2%)	201,541 (50.2%)	31,497 (53.0%)	-0.06
Use of ARBs; n (%)	33,459 (33.5%)	9,268 (33.8%)	32,714 (33.3%)	6,489 (34.3%)	69,748 (34.3%)	4,833 (36.7%)	135,921 (33.8%)	20,590 (34.6%)	-0.02
Use of Loop Diuretics - United; n (%)	10,502 (10.5%)	2,316 (8.5%)	6,912 (7.0%)	1,075 (5.7%)	33,131 (16.3%)	1,744 (13.3%)	50,545 (12.6%)	5,135 (8.6%)	0.13
Use of other diuretics- United; n (%)	2,623 (2.6%)	833 (3.0%)	2,133 (2.2%)	433 (2.4%)	6,785 (3.3%)	483 (3.7%)	11,541 (2.9%)	1,769 (3.0%)	-0.01
Use of nitrates-United; n (%)	4,760 (4.8%)	1,425 (5.2%)	3,232 (3.3%)	624 (3.3%)	14,468 (7.1%)	976 (7.4%)	22,460 (5.6%)	3,025 (5.1%)	0.02
Use of other hypertension drugs; n (%)	6,251 (6.3%)	1,267 (4.6%)	4,450 (4.5%)	643 (3.4%)	15,746 (7.7%)	809 (6.1%)	26,447 (6.6%)	2,719 (4.6%)	0.09
Use of digoxin- United; n (%)	1,351 (1.4%)	278 (1.0%)	1,001 (1.0%)	112 (0.6%)	5,685 (2.8%)	306 (2.3%)	8,037 (2.0%)	696 (1.2%)	0.06
Use of Anti-arrhythmics; n (%)	1,058 (1.1%)	283 (1.0%)	807 (0.8%)	143 (0.8%)	3,770 (1.9%)	218 (1.7%)	5,635 (1.4%)	644 (1.1%)	0.03
Use of COPD/asthma meds- United; n (%)	14,067 (14.1%)	3,637 (13.3%)	12,756 (13.0%)	2,412 (12.8%)	32,384 (15.9%)	2,112 (16.1%)	59,207 (14.7%)	8,161 (13.7%)	0.03
Use of statins; n (%)	71,183 (71.3%)	20,272 (74.0%)	65,053 (66.1%)	13,377 (70.7%)	148,529 (73.1%)	10,331 (78.5%)	284,765 (70.9%)	43,980 (74.0%)	-0.07
Use of other lipid-lowering drugs; n (%)	11,144 (11.2%)	3,351 (12.2%)	12,301 (12.5%)	2,743 (14.5%)	24,891 (12.2%)	1,915 (14.6%)	48,336 (12.0%)	8,009 (13.5%)	-0.04
Use of antiplatelet agents; n (%)	12,026 (12.0%)	3,756 (13.7%)	10,435 (10.6%)	2,047 (10.8%)	30,403 (15.0%)	2,275 (17.3%)	52,864 (13.2%)	8,078 (13.6%)	-0.01
Use of oral anticoagulants (Dabigatran, Rivaroxaban, Apixa	5,155 (5.2%)	1,283 (4.7%)	3,619 (3.7%)	581 (3.1%)	17,505 (8.6%)	1,132 (8.6%)	26,279 (6.5%)	2,996 (5.0%)	0.06
Use of heparin and other low-molecular weight heparins; n	198 (0.2%)	43 (0.2%)	9 (0.0%)	1 (0.0%)	420 (0.2%)	21 (0.2%)	627 (0.2%)	065 (0.1%)	0.03
Use of NSAIDs; n (%)	16,220 (16.2%)	4,517 (16.5%)	16,087 (16.4%)	3,178 (16.8%)	32,311 (15.9%)	1,975 (15.0%)	64,618 (16.1%)	9,670 (16.3%)	-0.01
Use of oral corticosteroids; n (%)	10,445 (10.5%)	2,832 (10.3%)	9,420 (9.6%)	1,722 (9.1%)	23,684 (11.7%)	1,501 (11.4%)	43,549 (10.8%)	6,055 (10.2%)	0.02
Use of bisphosphonate (United); n (%)	2,212 (2.2%)	322 (1.2%)	803 (0.8%)	70 (0.4%)	6,829 (3.4%)	252 (1.9%)	9,844 (2.5%)	644 (1.1%)	0.11
Use of opioids- United; n (%)	20,346 (20.4%)	5,472 (20.0%)	18,620 (18.9%)	3,581 (18.9%)	42,529 (20.9%)	2,588 (19.7%)	81,495 (20.3%)	11,641 (19.6%)	0.02
Use of antidepressants; n (%)	22,602 (22.6%)	6,573 (24.0%)	19,480 (19.8%)	4,303 (22.8%)	48,867 (24.0%)	3,160 (24.0%)	90,949 (22.6%)	14,036 (23.6%)	-0.02
Use of antipsychotics; n (%)	2,584 (2.6%)	556 (2.0%)	1,381 (1.4%)	263 (1.4%)	6,338 (3.1%)	258 (2.0%)	10,303 (2.6%)	1,077 (1.8%)	0.05
Use of anticonvulsants; n (%)	16,330 (16.3%)	4,552 (16.6%)	10,690 (10.9%)	2,193 (11.6%)	34,272 (16.9%)	2,157 (16.4%)	61,292 (15.3%)	8,902 (15.0%)	0.01
Use of lithium- United; n (%)	147 (0.1%)	39 (0.1%)	115 (0.1%)	29 (0.2%)	**	**	**	**	**
Use of Benzos- United; n (%)	9,376 (9.4%)	2,472 (9.0%)	7,846 (8.0%)	1,587 (8.4%)	21,369 (10.5%)	1,277 (9.7%)	38,591 (9.6%)	5,336 (9.0%)	0.02
Use of anxiolytics/hypnotics- United; n (%)	4,899 (4.9%)	1,421 (5.2%)	5,117 (5.2%)	1,058 (5.6%)	10,049 (4.9%)	683 (5.2%)	20,065 (5.0%)	3,162 (5.3%)	-0.01
Use of dementia meds- United; n (%)	2,332 (2.3%)	208 (0.8%)	1,003 (1.0%)	51 (0.3%)	10,424 (5.1%)	272 (2.1%)	13,759 (3.4%)	531 (0.9%)	0.17
Use of antiparkinsonian meds- United; n (%)	2,112 (2.1%)	562 (2.1%)	1,514 (1.5%)	265 (1.4%)	6,081 (3.0%)	335 (2.5%)	9,707 (2.4%)	1,162 (2.0%)	0.03
Any use of pramlintide; n (%)	2 (0.0%)	9 (0.0%)	9 (0.0%)	23 (0.1%)	**	**	**	**	**
Any use of 1st generation sulfonylureas; n (%)	2 (0.0%)	1 (0.0%)	10 (0.0%)	1 (0.0%)	**	**	**	**	**
Entresto (sacubitril/valsartan); n (%)	158 (0.2%)	122 (0.4%)	52 (0.1%)	22 (0.1%)	158 (0.1%)	43 (0.3%)	368 (0.1%)	187 (0.3%)	0.00
Initiation as monotherapy v4 Copy; n (%)	85,916 (86.0%)	25,773 (94.1%)	84,176 (85.6%)	17,936 (94.8%)	184,924 (91.0%)	12,565 (95.5%)	355,016 (88.4%)	56,274 (94.6%)	-0.22
Labs							198,248	46,306	
Lab values- HbA1c (%) v3; n (%)	43,141 (43.2%)	11,298 (41.2%)	6,423 (6.5%)	1,049 (5.5%)	N/A	N/A	49,564 (25.0%)	12,347 (26.7%)	-0.04
Lab values- HbA1c (%) (within 3 months) v3; n (%)	34,616 (34.6%)	9,068 (33.1%)	5,174 (5.3%)	858 (4.5%)	N/A	N/A	39,790 (20.1%)	9,926 (21.4%)	-0.03

Table 1

Lab values- HbA1c (%) (within 6 months) v3; n (%)	43,141 (43.2%)	11,298 (41.2%)	6,423 (6.5%)	1,049 (5.5%)	N/A	N/A	49,564 (25.0%)	12,347 (26.7%)	-0.04
Lab values- BNP; n (%)	749 (0.7%)	156 (0.6%)	74 (0.1%)	5 (0.0%)	N/A	N/A	823 (0.4%)	161 (0.3%)	0.02
Lab values- BNP (within 3 months); n (%)	463 (0.5%)	98 (0.4%)	53 (0.1%)	1 (0.0%)	N/A	N/A	516 (0.3%)	099 (0.2%)	0.02
Lab values- BNP (within 6 months); n (%)	749 (0.7%)	156 (0.6%)	74 (0.1%)	5 (0.0%)	N/A	N/A	823 (0.4%)	161 (0.3%)	0.02
Lab values- BUN (mg/dl); n (%)	42,226 (42.3%)	10,947 (40.0%)	6,201 (6.3%)	967 (5.1%)	N/A	N/A	48,427 (24.4%)	11,914 (25.7%)	-0.03
Lab values- BUN (mg/dl) (within 3 months); n (%)	33,174 (33.2%)	8,603 (31.4%)	4,838 (4.9%)	783 (4.1%)	N/A	N/A	38,012 (19.2%)	9,386 (20.3%)	-0.03
Lab values- BUN (mg/dl) (within 6 months); n (%)	42,226 (42.3%)	10,947 (40.0%)	6,201 (6.3%)	967 (5.1%)	N/A	N/A	48,427 (24.4%)	11,914 (25.7%)	-0.03
Lab values- Creatinine (mg/dl) v2; n (%)	43,684 (43.7%)	11,561 (42.2%)	6,653 (6.8%)	1,095 (5.8%)	N/A	N/A	50,337 (25.4%)	12,656 (27.3%)	-0.04
Lab values- Creatinine (mg/dl) (within 3 months) v2; n (%)	34,353 (34.4%)	9,066 (33.1%)	5,215 (5.3%)	882 (4.7%)	N/A	N/A	39,568 (20.0%)	9,948 (21.5%)	-0.04
Lab values- Creatinine (mg/dl) (within 6 months) v2; n (%)	43,684 (43.7%)	11,561 (42.2%)	6,653 (6.8%)	1,095 (5.8%)	N/A	N/A	50,337 (25.4%)	12,656 (27.3%)	-0.04
Lab values- HDL level (mg/dl); n (%)	36,599 (36.6%)	9,688 (35.4%)	5,867 (6.0%)	1,004 (5.3%)	N/A	N/A	42,466 (21.4%)	10,692 (23.1%)	-0.04
Lab values- HDL level (mg/dl) (within 3 months); n (%)	27,311 (27.3%)	7,215 (26.3%)	4,458 (4.5%)	768 (4.1%)	N/A	N/A	31,769 (16.0%)	7,983 (17.2%)	-0.03
Lab values- HDL level (mg/dl) (within 6 months); n (%)	36,599 (36.6%)	9,688 (35.4%)	5,867 (6.0%)	1,004 (5.3%)	N/A	N/A	42,466 (21.4%)	10,692 (23.1%)	-0.04
Lab values- LDL level (mg/dl) v2; n (%)	37,864 (37.9%)	10,005 (36.5%)	6,037 (6.1%)	991 (5.2%)	N/A	N/A	43,901 (22.1%)	10,996 (23.7%)	-0.04
Lab values- LDL level (mg/dl) (within 3 months) v2; n (%)	28,216 (28.2%)	7,452 (27.2%)	4,563 (4.6%)	765 (4.0%)	N/A	N/A	32,779 (16.5%)	8,217 (17.7%)	-0.03
Lab values- LDL level (mg/dl) (within 6 months) v2; n (%)	37,864 (37.9%)	10,005 (36.5%)	6,037 (6.1%)	991 (5.2%)	N/A	N/A	43,901 (22.1%)	10,996 (23.7%)	-0.04
Lab values- NT-proBNP; n (%)	114 (0.1%)	43 (0.2%)	17 (0.0%)	2 (0.0%)	N/A	N/A	131 (0.1%)	45 (0.1%)	0.00
Lab values- NT-proBNP (within 3 months); n (%)	66 (0.1%)	27 (0.1%)	12 (0.0%)	2 (0.0%)	N/A	N/A	78 (0.0%)	29 (0.1%)	-
Lab values- NT-proBNP (within 6 months); n (%)	114 (0.1%)	43 (0.2%)	17 (0.0%)	2 (0.0%)	N/A	N/A	131 (0.1%)	45 (0.1%)	-
Lab values- Total cholesterol (mg/dl) v2; n (%)	37,177 (37.2%)	9,915 (36.2%)	5,903 (6.0%)	1,018 (5.4%)	N/A	N/A	43,080 (21.7%)	10,933 (23.6%)	-0.05
Lab values- Total cholesterol (mg/dl) (within 3 months) v2;	27,768 (27.8%)	7,384 (27.0%)	4,489 (4.6%)	783 (4.1%)	N/A	N/A	32,257 (16.3%)	8,167 (17.6%)	-0.03
Lab values- Total cholesterol (mg/dl) (within 6 months) v2;	37,177 (37.2%)	9,915 (36.2%)	5,903 (6.0%)	1,018 (5.4%)	N/A	N/A	43,080 (21.7%)	10,933 (23.6%)	-0.05
Lab values- Triglyceride level (mg/dl); n (%)	36,829 (36.9%)	9,848 (35.9%)	5,814 (5.9%)	1,000 (5.3%)	N/A	N/A	42,643 (21.5%)	10,848 (23.4%)	-0.05
Lab values- Triglyceride level (mg/dl) (within 3 months); n (%	27,527 (27.6%)	7,338 (26.8%)	4,418 (4.5%)	771 (4.1%)	N/A	N/A	31,945 (16.1%)	8,109 (17.5%)	-0.04
Lab values- Triglyceride level (mg/dl) (within 6 months); n (%	36,829 (36.9%)	9,848 (35.9%)	5,814 (5.9%)	1,000 (5.3%)	N/A	N/A	42,643 (21.5%)	10,848 (23.4%)	-0.05
Lab result number- HbA1c (%) mean (only 2 to 20 included	42,905	11,242	6,311	1,018	N/A	N/A	49,216	12,260	
...mean (sd)	8.36 (1.78)	8.55 (1.75)	8.53 (1.88)	8.32 (1.79)	N/A	N/A	8.38 (1.79)	8.53 (1.75)	-0.08
...median [IQR]	8.00 [7.15, 9.25]	8.20 [7.30, 9.55]	8.05 [7.15, 9.50]	8.00 [7.00, 9.00]	N/A	N/A	8.01 (1.79)	8.18 (1.75)	-0.10
...Missing; n (%)	56,998 (57.1%)	16,152 (59.0%)	92,034 (93.6%)	17,894 (94.6%)	N/A	N/A	149,032 (75.2%)	34,046 (73.5%)	0.04
Lab result number- BNP mean v2	749	156	74	5	N/A	N/A	823	161	
...mean (sd)	154.93 (290.29)	146.64 (314.40)	3,931.76 (32,532.43)	32.60 (34.74)	N/A	N/A	494.52 (9710.65)	143.10 (509.52)	0.05
...median [IQR]	63.20 [25.55, 167.50]	34.45 [14.55, 89.70]	76.50 [29.75, 193.00]	18.00 [13.50, 39.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	99,154 (99.3%)	27,238 (99.4%)	98,271 (99.9%)	18,907 (100.0%)	N/A	N/A	197,425 (99.6%)	46,145 (99.7%)	-0.02
Lab result number- BUN (mg/dl) mean v2	42,226	10,947	6,201	967	N/A	N/A	48,427	11,914	
...mean (sd)	17.98 (7.45)	16.64 (5.62)	1,795.05 (17,168.60)	2,184.17 (18,371.33)	N/A	N/A	245.53 (6143.29)	192.57 (5288.81)	0.01
...median [IQR]	16.50 [13.00, 21.00]	16.00 [13.00, 19.50]	16.00 [13.00, 20.00]	15.50 [13.00, 19.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	57,677 (57.7%)	16,447 (60.0%)	92,144 (93.7%)	17,945 (94.9%)	N/A	N/A	149,821 (75.6%)	34,392 (74.3%)	0.03
Lab result number- Creatinine (mg/dl) mean (only 0.1 to 15	43,333	11,484	6,645	711	N/A	N/A	48,978	12,195	
...mean (sd)	1.01 (0.39)	0.92 (0.24)	0.98 (0.33)	0.94 (0.20)	N/A	N/A	1.01 (0.38)	0.92 (0.24)	0.28
...median [IQR]	0.93 [0.78, 1.15]	0.89 [0.75, 1.05]	0.95 [0.79, 1.08]	0.95 [0.81, 1.00]	N/A	N/A	0.93 (0.38)	0.89 (0.24)	0.13
...Missing; n (%)	56,570 (56.6%)	15,910 (58.1%)	92,700 (94.3%)	18,201 (96.2%)	N/A	N/A	149,270 (75.3%)	34,111 (73.7%)	0.04
Lab result number- HDL level (mg/dl) mean (only =<1000 in	36,599	9,688	5,805	994	N/A	N/A	42,404	10,682	
...mean (sd)	45.86 (13.58)	44.26 (12.89)	44.94 (13.83)	47.81 (132.54)	N/A	N/A	45.73 (13.61)	44.59 (42.24)	0.04
...median [IQR]	44.00 [37.00, 53.00]	42.00 [36.00, 51.00]	43.00 [36.00, 52.00]	42.00 [35.00, 50.00]	N/A	N/A	43.86 (13.61)	42.00 (42.24)	0.06
...Missing; n (%)	63,304 (63.4%)	17,706 (64.6%)	92,540 (94.1%)	17,918 (94.7%)	N/A	N/A	155,844 (78.6%)	35,624 (76.9%)	0.04
Lab result number- LDL level (mg/dl) mean (only =<1000 in	36,994	9,836	5,343	919	N/A	N/A	42,337	10,775	
...mean (sd)	85.89 (39.91)	81.77 (40.57)	90.89 (42.17)	84.41 (40.86)	N/A	N/A	86.52 (40.20)	82.00 (40.60)	0.11
...median [IQR]	83.50 [52.00, 108.75]	80.50 [58.00, 105.00]	89.00 [67.00, 116.00]	84.00 [61.00, 109.00]	N/A	N/A	84.19 (40.20)	80.80 (40.60)	0.08
...Missing; n (%)	62,909 (63.0%)	17,538 (64.0%)	93,002 (94.6%)	17,993 (95.1%)	N/A	N/A	155,911 (78.6%)	35,531 (76.7%)	0.05
Lab result number- Total cholesterol (mg/dl) mean (only =<	37,141	9,912	5,841	1,005	N/A	N/A	42,982	10,917	
...mean (sd)	173.84 (47.32)	170.49 (47.05)	179.36 (49.26)	171.92 (49.48)	N/A	N/A	174.59 (47.59)	170.62 (47.28)	0.08
...median [IQR]	167.50 [143.00, 198.00]	165.00 [139.00, 195.00]	174.00 [148.00, 205.00]	165.50 [140.25, 196.00]	N/A	N/A	168.38 (47.59)	165.05 (47.28)	0.07
...Missing; n (%)	62,762 (62.8%)	17,482 (63.8%)	92,504 (94.1%)	17,907 (94.7%)	N/A	N/A	155,266 (78.3%)	35,389 (76.4%)	0.05

Table 1

Lab result number- Triglyceride level (mg/dl) mean (only =<	36,825	9,846	3,753	987	N/A	N/A	42,578	10,833	
...mean (sd)	193.49 (177.23)	207.63 (200.82)	197.08 (184.91)	210.43 (212.46)	N/A	N/A	193.98 (178.29)	207.89 (201.92)	-0.07
...median [IQR]	155.00 [110.00, 223.00]	160.00 [113.00, 236.00]	153.00 [106.50, 228.25]	157.50 [109.00, 233.00]	N/A	N/A	154.73 (178.29)	159.77 (201.92)	-0.03
...Missing; n (%)	63,078 (63.1%)	17,548 (64.1%)	92,592 (94.2%)	17,925 (94.8%)	N/A	N/A	155,670 (78.5%)	35,473 (76.6%)	0.05
Lab result number- Hemoglobin mean (only >0 included)	28,791	7,333	4,328	643	N/A	N/A	33,119	7,976	
...mean (sd)	13.72 (1.56)	14.15 (1.49)	6,342.54 (215,464.58)	1,919.68 (16,045.24)	N/A	N/A	840.77 (77884.39)	167.77 (4553.05)	0.01
...median [IQR]	13.70 [12.65, 14.80]	14.10 [13.10, 15.20]	13.90 [12.85, 15.00]	14.00 [13.00, 15.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	71,112 (71.2%)	20,061 (73.2%)	94,017 (95.6%)	18,269 (96.6%)	N/A	N/A	165,129 (83.3%)	38,330 (82.8%)	0.01
Lab result number- Serum sodium mean (only > 90 and < 15	42,353	11,249	6,243	1,027	N/A	N/A	48,396	12,276	
...mean (sd)	139.42 (2.77)	139.45 (2.68)	138.82 (2.61)	139.17 (2.53)	N/A	N/A	139.34 (2.75)	139.43 (2.67)	-0.03
...median [IQR]	139.50 [138.00, 141.00]	139.50 [138.00, 141.00]	139.00 [137.00, 140.50]	139.00 [137.50, 141.00]	N/A	N/A	139.44 (2.75)	139.46 (2.67)	-0.01
...Missing; n (%)	57,550 (57.6%)	16,145 (58.9%)	92,102 (93.7%)	17,885 (94.6%)	N/A	N/A	149,652 (75.5%)	34,030 (73.5%)	0.05
Lab result number- Albumin mean (only >0 and <=10 incluc	39,793	10,600	5,330	848	N/A	N/A	45,123	11,448	
...mean (sd)	4.29 (0.32)	4.32 (0.31)	4.20 (0.38)	4.10 (0.39)	N/A	N/A	4.28 (0.33)	4.30 (0.32)	-0.06
...median [IQR]	4.30 [4.10, 4.50]	4.30 [4.10, 4.50]	4.20 [4.00, 4.45]	4.00 [4.00, 4.30]	N/A	N/A	4.29 (0.33)	4.28 (0.32)	0.03
...Missing; n (%)	60,110 (60.2%)	16,794 (61.3%)	93,015 (94.6%)	18,064 (95.5%)	N/A	N/A	153,125 (77.2%)	34,858 (75.3%)	0.04
Lab result number- Glucose (fasting or random) mean (only	42,469	11,283	6,343	1,054	N/A	N/A	48,812	12,337	
...mean (sd)	178.34 (72.25)	182.55 (71.67)	181.56 (74.01)	177.65 (69.16)	N/A	N/A	178.76 (72.48)	182.13 (71.46)	-0.05
...median [IQR]	161.00 [129.00, 209.50]	167.00 [132.50, 217.00]	163.00 [130.50, 215.50]	161.75 [129.00, 209.00]	N/A	N/A	161.26 (72.48)	166.55 (71.46)	-0.07
...Missing; n (%)	57,434 (57.5%)	16,111 (58.8%)	92,002 (93.6%)	17,858 (94.4%)	N/A	N/A	149,436 (75.4%)	33,969 (73.4%)	0.05
Lab result number- Potassium mean (only 1-7 included)	43,384	11,485	6,118	973	N/A	N/A	49,502	12,458	
...mean (sd)	4.48 (0.43)	4.47 (0.40)	4.32 (0.46)	4.16 (0.50)	N/A	N/A	4.46 (0.43)	4.45 (0.41)	0.02
...median [IQR]	4.50 [4.20, 4.70]	4.45 [4.20, 4.70]	4.30 [4.00, 4.60]	4.00 [4.00, 4.50]	N/A	N/A	4.48 (0.43)	4.41 (0.41)	0.17
...Missing; n (%)	56,519 (56.6%)	15,909 (58.1%)	92,227 (93.8%)	17,939 (94.9%)	N/A	N/A	148,746 (75.0%)	33,848 (73.1%)	0.04
Comorbidity Scores									
CCI (180 days)- ICD9 and ICD10 v2									
...mean (sd)	2.43 (1.80)	2.23 (1.47)	1.64 (1.30)	1.67 (1.06)	2.63 (1.89)	2.46 (1.56)	2.34 (1.74)	2.11 (1.38)	0.15
...median [IQR]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	1.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 4.00]	2.00 [1.00, 3.00]	1.76 (1.74)	2.00 (1.38)	-0.15
Frailty Score: Qualitative Version 365 days as Categories, v1									
...0; n (%)	68,126 (68.2%)	23,602 (86.2%)	60,170 (61.2%)	14,653 (77.5%)	92,074 (45.3%)	10,006 (76.1%)	220,370 (54.9%)	48,261 (81.2%)	-0.59
...1 to 2; n (%)	24,208 (24.2%)	3,375 (12.3%)	29,743 (30.2%)	3,605 (19.1%)	66,971 (32.9%)	2,319 (17.6%)	120,922 (30.1%)	9,299 (15.6%)	0.35
...3 or more; n (%)	7,569 (7.6%)	417 (1.5%)	8,432 (8.6%)	634 (3.5%)	44,249 (21.8%)	831 (6.3%)	60,250 (15.0%)	1,902 (3.2%)	0.42
Frailty Score: Empirical Version 365 days as Categories, v3									
...<0.12908; n (%)	28,978 (29.0%)	9,111 (33.3%)	32,840 (33.4%)	6,951 (36.8%)	26,735 (13.2%)	2,162 (16.4%)	88,553 (22.1%)	18,224 (30.6%)	-0.19
...0.12908 - 0.1631167; n (%)	33,399 (33.4%)	9,641 (35.2%)	36,156 (36.8%)	7,300 (38.6%)	55,651 (27.4%)	4,179 (31.8%)	125,206 (31.2%)	21,120 (35.5%)	-0.09
...>=0.1631167; n (%)	37,526 (37.6%)	8,642 (31.5%)	29,349 (29.8%)	4,661 (24.6%)	120,908 (59.5%)	6,815 (51.8%)	187,783 (46.8%)	20,118 (33.8%)	0.27
Non-Frailty; n (%)	57,586 (57.6%)	16,315 (59.6%)	50,767 (51.6%)	10,157 (53.7%)	10,528 (5.2%)	611 (4.6%)	118,881 (29.6%)	27,083 (45.5%)	-0.33
Frailty Score (mean): Qualitative Version 365 days, v1									
...mean (sd)	0.64 (1.29)	0.21 (0.64)	0.75 (1.28)	0.37 (0.86)	1.43 (1.93)	0.48 (1.11)	1.07 (1.64)	0.32 (0.83)	0.58
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	1.00 [0.00, 2.00]	0.00 [0.00, 0.00]	0.51 (1.64)	0.00 (0.83)	0.39
Frailty Score (mean): Empirical Version 365 days, v2									
...mean (sd)	0.16 (0.05)	0.15 (0.04)	0.15 (0.04)	0.14 (0.03)	0.19 (0.06)	0.17 (0.05)	0.17 (0.05)	0.15 (0.04)	0.44
...median [IQR]	0.15 [0.13, 0.18]	0.14 [0.12, 0.17]	0.14 [0.12, 0.16]	0.13 [0.12, 0.16]	0.17 [0.14, 0.22]	0.17 [0.14, 0.20]	0.16 (0.05)	0.14 (0.04)	0.44
Healthcare Utilization									
Any hospitalization; n (%)	5,497 (5.5%)	1,088 (4.0%)	3,358 (3.4%)	417 (2.2%)	12,442 (6.1%)	482 (3.7%)	21,297 (5.3%)	1,987 (3.3%)	0.10
Any hospitalization within prior 30 days; n (%)	1,947 (1.9%)	275 (1.0%)	982 (1.0%)	61 (0.3%)	3,634 (1.8%)	65 (0.5%)	6,563 (1.6%)	401 (0.7%)	0.08
Any hospitalization during prior 31-180 days; n (%)	3,821 (3.8%)	845 (3.1%)	2,452 (2.5%)	362 (1.9%)	9,387 (4.6%)	424 (3.2%)	15,660 (3.9%)	1,631 (2.7%)	0.07
Endocrinologist Visit; n (%)	9,696 (9.7%)	6,083 (22.2%)	8,916 (9.1%)	4,696 (24.8%)	24,295 (12.0%)	3,503 (26.6%)	42,907 (10.7%)	14,282 (24.0%)	-0.36
Endocrinologist Visit (30 days prior); n (%)	6,358 (6.4%)	4,656 (17.0%)	5,990 (6.1%)	3,590 (19.0%)	15,500 (7.6%)	2,720 (20.7%)	27,848 (6.9%)	10,966 (18.4%)	-0.35
Endocrinologist Visit (31 to 180 days prior); n (%)	6,561 (6.6%)	4,086 (14.9%)	5,999 (6.1%)	3,222 (17.0%)	17,451 (8.6%)	2,594 (19.7%)	30,011 (7.5%)	9,902 (16.7%)	-0.28
Internal medicine/family medicine visits; n (%)	79,699 (79.8%)	19,568 (71.4%)	85,692 (87.1%)	15,991 (84.6%)	164,752 (81.0%)	10,436 (79.3%)	330,143 (82.2%)	45,995 (77.4%)	0.12
Internal medicine/family medicine visits (30 days prior) v2;	59,806 (59.9%)	14,110 (51.5%)	64,158 (65.2%)	11,352 (60.0%)	116,541 (57.3%)	7,146 (54.3%)	240,505 (59.9%)	32,608 (54.8%)	0.10
Internal medicine/family medicine visits (31 to 180 days pr	68,510 (68.6%)	16,887 (61.6%)	69,171 (70.3%)	13,393 (70.8%)	142,940 (70.3%)	9,188 (69.8%)	280,621 (69.9%)	39,468 (66.4%)	0.08
Cardiologist visit; n (%)	23,368 (23.4%)	6,777 (24.7%)	14,980 (15.2%)	3,006 (15.9%)	60,430 (29.7%)	4,227 (32.1%)	98,778 (24.6%)	14,010 (23.6%)	0.02
Number of Cardiologist visits (30 days prior); n (%)	8,018 (8.0%)	2,440 (8.9%)	4,841 (4.9%)	894 (4.7%)	19,046 (9.4%)	1,399 (10.6%)	31,905 (7.9%)	4,733 (8.0%)	0.00

Table 1

Number of Cardiologist visits (31 to 180 days prior); n (%)	19,586 (19.6%)	5,663 (20.7%)	12,542 (12.8%)	2,550 (13.5%)	52,580 (25.9%)	3,650 (27.7%)	84,708 (21.1%)	11,863 (20.0%)	0.03
Electrocardiogram v2; n (%)	26,602 (26.6%)	7,163 (26.1%)	22,603 (23.0%)	4,033 (21.3%)	61,061 (30.0%)	4,106 (31.2%)	110,266 (27.5%)	15,302 (25.7%)	0.04
Use of glucose test strips; n (%)	3,648 (3.7%)	852 (3.1%)	3,332 (3.4%)	754 (4.0%)	6,468 (3.2%)	414 (3.1%)	13,448 (3.3%)	2,020 (3.4%)	-0.01
Dialysis; n (%)	26 (0.0%)	1 (0.0%)	10 (0.0%)	0 (0.0%)	**	**	**	**	**
Naive new user v8 Copy; n (%)	13,650 (13.7%)	1,877 (6.9%)	13,152 (13.4%)	1,106 (5.8%)	24,032 (11.8%)	647 (4.9%)	50,834 (12.7%)	3,630 (6.1%)	0.23
N antidiabetic drugs at index date v3 Copy									
...mean (sd)	2.26 (0.83)	2.34 (0.93)	2.28 (0.82)	2.39 (0.96)	2.23 (0.83)	2.44 (0.93)	2.25 (0.83)	2.38 (0.94)	-0.15
...median [IQR]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 (0.83)	2.00 (0.94)	0.00
number of different/distinct medication prescriptions									
...mean (sd)	9.99 (4.61)	10.50 (4.73)	8.93 (4.09)	9.97 (4.24)	9.91 (4.25)	10.60 (4.22)	9.69 (4.30)	10.35 (4.47)	-0.15
...median [IQR]	9.00 [7.00, 12.00]	10.00 [7.00, 13.00]	8.00 [6.00, 11.00]	9.00 [7.00, 12.00]	9.00 [7.00, 12.00]	10.00 [8.00, 13.00]	8.76 (4.30)	9.68 (4.47)	-0.21
Number of Hospitalizations									
...mean (sd)	0.07 (0.30)	0.05 (0.24)	0.04 (0.21)	0.02 (0.16)	0.07 (0.32)	0.04 (0.23)	0.06 (0.29)	0.04 (0.22)	0.08
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (0.29)	0.00 (0.22)	0.00
Number of hospital days									
...mean (sd)	0.37 (2.52)	0.21 (1.44)	0.19 (1.31)	0.10 (0.90)	0.45 (2.78)	0.19 (1.28)	0.37 (2.46)	0.17 (1.26)	0.10
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (2.46)	0.00 (1.26)	0.00
Number of Emergency Department (ED) visits v3									
...mean (sd)	0.38 (1.19)	0.30 (1.09)	0.07 (0.75)	0.05 (0.57)	0.43 (1.21)	0.30 (0.93)	0.33 (1.11)	0.22 (0.92)	0.11
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (1.11)	0.00 (0.92)	0.00
Number of Office visits									
...mean (sd)	4.40 (3.47)	4.68 (3.48)	3.93 (3.12)	4.16 (3.11)	4.87 (3.70)	5.39 (3.66)	4.52 (3.51)	4.67 (3.41)	-0.04
...median [IQR]	4.00 [2.00, 6.00]	4.00 [2.00, 6.00]	3.00 [2.00, 5.00]	3.00 [2.00, 5.00]	4.00 [2.00, 7.00]	5.00 [3.00, 7.00]	3.76 (3.51)	3.90 (3.41)	-0.04
Number of Endocrinologist visits									
...mean (sd)	0.44 (2.07)	1.13 (3.39)	0.41 (2.05)	1.25 (3.46)	0.63 (2.84)	1.59 (4.88)	0.53 (2.49)	1.27 (3.79)	-0.23
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 (2.49)	0.00 (3.79)	0.00
Number of internal medicine/family medicine visits									
...mean (sd)	8.66 (12.52)	7.06 (10.58)	6.43 (7.97)	6.12 (7.44)	6.99 (9.20)	6.58 (8.74)	7.27 (9.87)	6.65 (9.28)	0.06
...median [IQR]	5.00 [1.00, 11.00]	4.00 [0.00, 9.00]	4.00 [2.00, 8.00]	4.00 [2.00, 8.00]	4.00 [1.00, 9.00]	4.00 [1.00, 9.00]	4.25 (9.87)	4.00 (9.28)	0.03
Number of Cardiologist visits									
...mean (sd)	1.05 (3.12)	1.18 (3.46)	0.59 (2.18)	0.60 (2.16)	1.39 (3.76)	1.50 (3.89)	1.11 (3.28)	1.07 (3.22)	0.01
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (3.28)	0.00 (3.22)	0.00
Number electrocardiograms received v2									
...mean (sd)	0.49 (1.20)	0.47 (1.16)	0.37 (0.88)	0.33 (0.83)	0.56 (1.18)	0.55 (1.12)	0.50 (1.12)	0.44 (1.06)	0.06
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (1.12)	0.00 (1.06)	0.00
Number of HbA1c tests ordered									
...mean (sd)	1.29 (0.88)	1.37 (0.88)	1.09 (0.85)	1.33 (0.82)	1.41 (0.85)	1.57 (0.81)	1.30 (0.86)	1.40 (0.85)	-0.12
...median [IQR]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [0.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	2.00 [1.00, 2.00]	1.00 (0.86)	1.22 (0.85)	-0.26
Number of glucose tests ordered									
...mean (sd)	0.55 (3.54)	0.46 (1.58)	0.34 (1.10)	0.43 (1.22)	0.42 (1.02)	0.48 (1.08)	0.43 (1.99)	0.45 (1.37)	-0.01
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 (1.99)	0.00 (1.37)	0.00
Number of lipid tests ordered									
...mean (sd)	0.97 (0.91)	1.01 (0.94)	0.89 (1.17)	1.05 (1.16)	0.98 (0.81)	1.07 (0.83)	0.96 (0.93)	1.04 (0.99)	-0.08
...median [IQR]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [1.00, 2.00]	1.00 (0.93)	1.00 (0.99)	0.00
Number of creatinine tests ordered									
...mean (sd)	0.04 (0.26)	0.04 (0.25)	0.03 (0.23)	0.04 (0.25)	0.06 (0.32)	0.07 (0.34)	0.05 (0.29)	0.05 (0.27)	0.00
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (0.29)	0.00 (0.27)	0.00
Number of BUN tests ordered									
...mean (sd)	0.02 (0.20)	0.02 (0.17)	0.02 (0.18)	0.02 (0.17)	0.04 (0.26)	0.04 (0.26)	0.03 (0.23)	0.02 (0.19)	0.05
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 (0.23)	0.00 (0.19)	0.00
Number of tests for microalbuminuria									
...mean (sd)	0.81 (1.17)	0.87 (1.18)	0.64 (1.03)	0.81 (1.12)	0.48 (0.70)	0.56 (0.71)	0.60 (0.92)	0.78 (1.07)	-0.18
...median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (0.92)	0.00 (1.07)	0.00
Total N distinct ICD9/ICD10 diagnoses at the 3rd digit level Copy									
...mean (sd)	6.92 (7.38)	8.25 (6.87)	2.91 (3.94)	3.91 (3.75)	6.39 (7.39)	8.79 (7.04)	5.67 (6.71)	6.99 (6.10)	-0.21
...median [IQR]	5.00 [0.00, 10.00]	7.00 [4.00, 11.00]	2.00 [0.00, 5.00]	4.00 [0.00, 6.00]	5.00 [0.00, 10.00]	7.00 [4.00, 12.00]	4.27 (6.71)	6.05 (6.10)	-0.28
Use of thiazide; n (%)	11,963 (12.0%)	3,080 (11.2%)	10,371 (10.5%)	1,926 (10.2%)	27,843 (13.7%)	1,804 (13.7%)	50,177 (12.5%)	6,810 (11.5%)	0.03
Use of beta blockers; n (%)	36,576 (36.6%)	9,851 (36.0%)	30,224 (30.7%)	5,661 (29.9%)	96,233 (47.3%)	6,419 (48.8%)	163,033 (40.6%)	21,931 (36.9%)	0.08
Use of calcium channel blockers; n (%)	30,078 (30.1%)	7,288 (26.6%)	26,215 (26.7%)	4,370 (23.1%)	69,690 (34.3%)	4,001 (30.4%)	125,983 (31.4%)	15,639 (26.3%)	0.11