Replication of CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA trial)

NCT03936036

December 27, 2019

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

CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA trial)

1.2 Intended aim(s)

The primary hypothesis was that treatment with linagliptin would be non-inferior with a hazard ratio of < 1.3 compared with placebo as assessed by the time to first occurrence of any of the 3P-MACE (primary endpoint) events.

1.3 Primary endpoint for replication and RCT finding

First occurrence of CV death, non-fatal myocardial infarction, or non-fatal stroke.

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

Power- 0.90. Assuming a HR of 1.0, to demonstrate non-inferiority of linagliptin versus placebo within the pre-specified non-inferiority margin of 1.3 at a one-sided α-level of 2.5%.

1.5 Primary trial estimate targeted for replication

HR = 1.02 (95% CI 0.89-1.17) comparing linagliptin to placebo (Rosenstock et al.)

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.

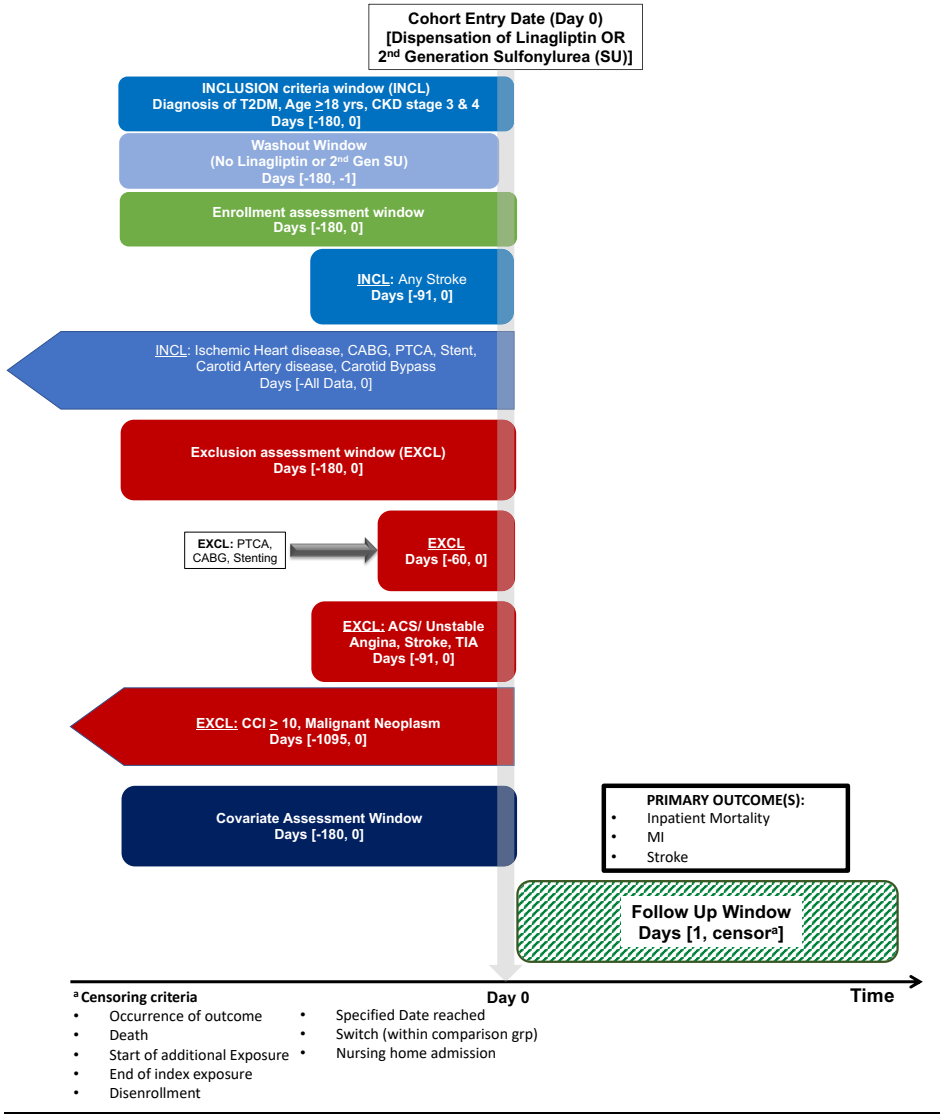
3. Data Source(s)

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 – CARMELINA TRIAL REPLICATION



5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, cohort study design comparing linagliptin to the 2nd generation sulfonylurea (SU) antidiabetic class as a proxy for placebo. 2nd generation SUs are not known to have an impact on the outcome of interest. In addition, SUs were the most frequent background treatment in CARMELINA (after metformin), and DPP4i and SUs are preferentially prescribed to similarly older patients in real world (Patorno et al., 2019). The patients will be required to have continuous enrollment during the baseline period of 180 days before initiation of linagliptin 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 study follow-up.

5.2 Important steps for cohort formation

5.2.1 Eligible cohort entry dates

Market availability of linagliptin in the U.S. started on May 2, 2011.

- For Marketscan: May 2, 2011-Dec 31, 2017 (end of data availability).
- For Medicare: Jan 1, 2012-Dec 31, 2017 (start- end of data availability).
- For Optum: May 2, 2011-March 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 in the database		74,864,884		191,990,035		23,466,175
Patients who used exposure or a reference between **02 May 2011** to Dec 2017 (for Marketscan)/March 2019 (for Optum) and 01 January 2012-December 2017 for Medicare	-73,493,670	1,371,214	-190,287,730	1,702,305	-19,944,169	3,522,006
Patients who have continuous 6 months registration in the database	-185,581	1,185,633	-171,524	1,530,781	-972,275	2,549,731
Patients without prior use of reference	-877,495	308,138	-1,180,188	350,593	-1,838,491	711,240
Patients without prior use of exposure	-68,637	239,501	-59,423	291,170	-133,733	577,507
Excluded because patient qualified in >1 exposure category	-275	239,226	-211	290,959	-370	577,137
Patients who did not have missing age information	-12	239,214	0	290,959	0	577,137
Patients who did not have missing gender information	-19	239,195	0	290,959	0	577,137
Excluded based on Inclusion 1- DM Type 2	-18,341	220,854	-37,618	253,341	-10,507	566,630
Excluded based on Inclusion 5- Age >= 18	-19	220,835	-76	253,265	0	566,630
Excluded based on Inclusion 6- Body Mass Index (BMI) =< 45 kg/m2 at visit 1 (as a proxy, excluding patients with morbid obesity)	-9,096	211,739	-8,032	245,233	-13,155	553,475
Excluded based on Inclusion 8 - High risk of CV events	-64,122	147,617	-98,434	146,799	-67,114	486,361
Excluded based on Exclusion 1- Type 1 DM with ICD10 CODES	-2,983	144,634	-3,481	143,318	-12,175	474,186
Excluded based on Exclusion 2- Treatment (≥ 7 days) with GLP-1 RA, other DPP-4i or SGLT-2i	-7,712	136,922	-9,388	133,930	-23,347	450,839
Excluded based on Exclusion 3- Liver disease	-2,648	134,274	-1,931	131,999	-8,953	441,886
Excluded based on Exclusion 4- CKD Stage 5 (proxy for eGFR <15 ml/min/1.73 m2)/Dialysis	-707	133,567	-470	131,529	-3,368	438,518
Excluded based on Exclusion 5- Any history of or planned bariatric surgery	0	133,567	0	131,529	0	438,518
Excluded based on Exclusion 6- Previous cardiac procedure (CABG or PTCA or Stent) ≤ 2 months	-436	133,131	-569	130,960	-1101	437,417
Excluded based on Exclusion 8- Alcohol abuse/Drug abuse	-1036	132,095	-493	130,467	-2,259	435,158
Excluded based on Exclusion 10- Pregnancy	-14	132,081	-8	130,459	-9	435,149
Excluded based on Exclusion 11 part 1- life expectancy less than 5 years [using combined comorbidity index as a proxy (365 days)	-2,263	129,818	-1,125	129,334	-12,200	422,949
Excluded based on Exclusion 11 part 2- History of Malignant Neoplasm (within last 3 years)	-4,153	125,665	-4,128	125,206	-14,241	408,708
Excluded based on Exclusion 12- ACS/unstable angina (≤ 2 months prior)	-374	125,291	-332	124,874	-788	407,920
Excluded based on Exclusion 13- Stroke or TIA (≤ 3 months prior)	-2,292	122,999	-1,981	122,893	-7,081	400,839

Final cohort		**122,999**		**122,893**		**400,839**

* Medicare database includes only patients ≥65 years of age with at least one diagnosis for diabetes, heart failure, or stroke.

6. Variables

6.1 Exposure-related variables:

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

Comparator agents:

- Initiators of linagliptin will be compared to initiators of-
    - 2nd generation sulfonylureas

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

6.2 Preliminary 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 MACE 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. End Stage Renal Disease (we expect to see no association; Rosenstock et al., 2019)

Control outcome definitions

Outcome	Definition	Comments
Control Outcomes		
End Stage Renal Disease (ESRD)	**ESRD with dialysis, defined as:** An ICD9 diagnosis (inpatient or outpatient) for ESRD: o 585.5x, Chronic kidney disease, Stage V (for ESRD with no mention of dialysis) o 585.6x, End stage renal disease (for ESRD with dialysis) AND an ICD9 procedural codes for dialysis (=index date): o 39.95, Hemodialysis o 54.98, Peritoneal dialysis AND an additional procedural code for dialysis or physician provider code indicating dialysis procedure or ESRD-related activity within two time windows 31-60 and 61-90 days from index date. For patients who die prior to 61 days (31 days), the second (second and first) confirmation requirement(s) can be dropped. *This*	Note- The corresponding ICD-10 codes will be used also

	ensures the inclusion of patients with true ESRD outcomes who die early (high early mortality) as well as early withdrawals from dialysis (which lead to high fatality within days or weeks). Additional procedural codes for dialysis or physician provider codes indicating dialysis procedure or ESRD-related activity include: - ICD9 procedural codes: o 39.95, Hemodialysis o 54.98, Peritoneal dialysis - ICD9 diagnostic codes: o 585.6x, End stage renal disease (for ESRD with dialysis) o V56.0x, encounter for dialysis NOS o V56.8x, encounter for peritoneal dialysis - CPT4 codes: o 90957, 90960, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 4 or more face-to-face physician visits per month o 90958, 90961, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 2-3 face-to-face physician visits per month o 90959, 90962, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 1 face-to-face physician visit per month o 90920, 90921, ESRD related services per full month; for patients 12-19 and twenty years of age and over o 90924, 90925, ESRD related services (less than full month), per day; for patients 12-19 and twenty years of age and over o 90935, Hemodialysis procedure with single physician evaluation o 90937, Hemodialysis procedure requiring repeated evaluation(s) with or without substantial revision of dialysis prescription o 90945, Dialysis procedure other than hemodialysis (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies), with single physician evaluation o 90947, Dialysis procedure other than hemodialysis (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies) requiring repeated physician evaluations, with or without substantial revision of dialysis prescription o 90965, 90966, ESRD related services for home dialysis per full month, for patients 12-19 and 20 years of age and older o 90969, 90970, ESRD related services for dialysis less than a full month of service, per day; for patients 12-19 and 20 years of age and older o 90989, Dialysis training, patient, including helper where applicable, any mode, completed course o 90993, Dialysis training, patient, including helper where applicable, any mode, course not completed, per training session o 90999, Unlisted dialysis procedure, inpatient or outpatient o 99512, Home visit for hemodialysis - HCPCS codes: o G0257, Unscheduled or emergency dialysis treatment for ESRD patient in a hospital outpatient dept. that is not certified as an ESRD facility o G0314, G0317, ESRD related services during the course of treatment, for patients 12-19 and 20 yrs of age an over to include monitoring for the adequacy of nutrition, etc. w/4 or more physician visit per month	

	o G0315, G0318, ESRD related services during the course of treatment, for patients 12-19 and 20yrs of age and over to include monitoring for the adequacy of nutrition, etc. w/2 or 3 physician visit per month o G0316, G0319, ESRD related services during the course of treatment, for patients 12-19 and 20 yrs of age and over to include monitoring for the adequacy of nutrition, etc. w/1 physician visit per month o G0322, G0323, ESRD related services for home dialysis patients per full month: for patients 12-19 and 20 yrs of age and over to include monitoring for adequacy of nutrition and etc. o G0326, G0327, ESRD related services for home dialysis (less than full month), per day; for patients 12-19 and 20 yrs of age and over o S9335, Home therapy, hemodialysis; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing services coded separately), per diem o S9339, Home therapy, peritoneal dialysis, administrative services, care coordination and all necessary supplies and equipment, per diem OR Kidney transplant, defined as either 1 inpatient or 1 outpatient code Codes include: - ICD9 prox codes: o 55.6x, Transplant of kidney (Exclude 55.61) - CPT4 codes: o 50360, Renal allotransplantation, implantation, graft, w/o donor & recipient nephrectomy o 50365, Renal allotransplantation, implantation, graft, w/ donor & recipient nephrectomy	

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 linagliptin 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 (linagliptin 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 glimepiride to glipizide 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 linagliptin 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 links:
Optum: https://bwh-dope.aetion.com/#/projects/details/702/results/30636/result/0
Marketscan: https://bwh-dope.aetion.com/#/projects/details/701/results/30634/result/0
Medicare: https://bwh-dope.aetion.com/#/projects/details/703/results/30635/result/0

Date conducted: rerun on January 28, 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 links:
Optum: https://bwh-dope.aetion.com/#/projects/details/702/results/30639/result/1
Marketscan: https://bwh-dope.aetion.com/#/projects/details/701/results/30637/result/1
Medicare: https://bwh-dope.aetion.com/#/projects/details/703/results/30638/result/1

Date conducted: rerun on January 28, 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 and FDA. Reviewers evaluate the results of the analyses described above in Sections 7 and 8, including numbers of patients, patient characteristics, follow-up time, and reasons for censoring by treatment group, as well as overall rates of outcomes and study power. These parameters are re-evaluated and reported in the subsequent sections, after incorporating feedback and refining the protocol.

Reviewed by PI:	Jessica M. Franklin	Date reviewed:	10/26/18
Reviewed by FDA:	Ken Quinto	Date reviewed:	12/19/18
Reasons for stopping analysis (if required):			

9. Balance Assessment after PS matching

Aetion report name:
Optum: https://bwh-dope.aetion.com/projects/details/702/results/44872/result/0
Marketscan: https://bwh-dope.aetion.com/projects/details/701/results/44873/result/0
Medicare: https://bwh-dope.aetion.com/projects/details/703/results/45415/result/0

Date conducted: 11/18/2019 (Medicare 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	1,704 (1.67%)	929 (1.82%)	775 (1.52%)
Start of an additional exposure	4,752 (4.67%)	746 (1.47%)	4,006 (7.87%)
End of index exposure	58,792 (57.74%)	29,602 (58.14%)	29,190 (57.33%)
Specified date reached	18,168 (17.84%)	9,825 (19.30%)	8,343 (16.39%)
End of patient enrollment	9,190 (9.02%)	4,583 (9.00%)	4,607 (9.05%)
Switch to other SUs (for censoring) + nursing home admission	9,224 (9.06%)	5,230 (10.27%)	3,994 (7.84%)

- Report follow-up time by treatment group.

	Median Follow-Up Time (Days) [IQR]		
Patient Group	**Optum**	**Marketscan**	**Medicare**
Overall Patient Population	118 [58-286]	128 [63-304]	137 [65-323]
Referent	122 [65-304]	148 [86-344]	148 [86-344]
Exposure	118 [58-269]	127 [58-303]	127 [58-303]

- Report overall risk of the primary outcome.

	Optum	Marketscan	Medicare
Risk per 1,000 patients	16.55	18.7	42.47

10. Final Power Assessment

Date conducted: 12/01/2019

- 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

Non-inferiority Analysis	
Number of patients matched	
Reference	50,915
Exposed	50,915
Risk per 1,000 patients	25.91
Assumed HR from RCT	1
Alpha (2-sided)	0.05
Non-inferiority margin	1.3
Number of events expected	2638.4153
Power	0.999999116

    - Optum

Non-inferiority Analysis	
Number of patients matched	
Reference	8,880
Exposed	8,880
Risk per 1,000 patients	16.55
Assumed HR from RCT	1
Alpha (2-sided)	0.05
Non-inferiority margin	1.3
Number of events expected	293.928
Power	0.613734405

- Marketscan

Non-inferiority Analysis	
Number of patients matched	
Reference	8,716
Exposed	8,716
Risk per 1,000 patients	18.7
Assumed HR from RCT	1
Alpha (2-sided)	0.05
Non-inferiority margin	1.3
Number of events expected	325.9784
Power	0.658551313

- Medicare

Non-inferiority Analysis	
Number of patients matched	
Reference	33,319
Exposed	33,319
Risk per 1,000 patients	42.47
Assumed HR from RCT	1
Alpha (2-sided)	0.05
Non-inferiority margin	1.3
Number of events expected	2830.11586
Power	0.99999974

- 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:	12/9/19
Reviewed by FDA:	Ken Quinto	Date reviewed:	12/20/19
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 linagliptin 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 canagliflozin 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

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; in press. (https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.118.039177)

Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, Zinman B, Woerle HJ, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, McGuire DK, CARMELINA Investigators. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA*. 2019; 321(1):69-79.

Appendix A

#	CARMELINA trial definitions	Implementation in routine care	References/Rationale	Color coding
	5a- Successful NI with label change		**Please see the following Google Drive for further details or any missing information:** https://drive.google.com/open?id=1WD618wrywYjEaXzfLTcuK-VCcnb6b-gV	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
	Linagliptin 5mg/day vs. placebo	linagliptin vs. 2nd generation sulfonylureas		Intermediate mapping in claims
	PRIMARY OUTCOME			Poor mapping or cannot be measured in claims
	The primary outcome is the time to the first occurrence of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke—the so-called 3-point major adverse CV events (3P-MACE) composite outcome.	**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 Dx 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) Documented diagnosis of T2DM before visit 1 (screening).	**Measured 180 days prior to drug initiation any diagnosis position in inpatient or outpatient care settings:** Patients with a diagnosis of T2DM (ICD-9 Dx code of 250.x0 or 250.x2; ICD-10 Dx code of E11.x) in the 6 months prior to drug initiation	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	
	2) Male or female patients who are drug-naïve or pre-treated with any antidiabetic background therapy, excluding treatment with GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors if ≥ 7 consecutive days.	This is basically everyone except for those with treatment with GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors if ≥ 7 consecutive days. One of the exclusion criteria below is exclusion based on ≥ 7 consecutive days use of GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors, so ignoring this inclusion criteria.		
	3) Ssheetle antidiabetic background medication (unchanged daily dose) for at least 8 weeks prior to randomization. If insulin is part of the background therapy, the average daily insulin dose should not have been changed by more than 10% within the 8 weeks prior to randomization compared with the daily insulin dose at randomization.	N/A	-	
	4) HbA1c of ≥ 6.5% and ≤ 10.0% at visit 1 (screening).	N/A	-	
	5) Age ≥ 18 years at visit 1 (screening). *For Japan only: Age ≥ 20 years at Visit 1.*	**Measured 180 days prior to drug initiation** Age ≥18 years		

Appendix A

	6) Body Mass Index (BMI) £ 45 kg/m2 at visit 1 (screening).	**Measured 180 days prior to drug initiation any diagnosis position in inpatient or outpatient care setting:** Excluding patients with ICD-9 Diagnosis Code (any position) is any of: { "278.01" } 278.01 - MORBID OBESITY	
	7) Signed and dated written informed consent by date of visit 1 (screening) in accordance with GCP and local legislation prior to any study related procedure.	N/A	-
	8) High risk of CV events (**I and/or II**):		
I.	Albuminuria (UACR ≥ 30 mg/g creatinine or ≥ 30 µg/min [microgram albumin per minute] or ≥ 30 mg/24 h [milligram albumin per 24 hours] in two out of three unrelated spot urine or timed samples in the last 24 months prior to randomization)* AND previous macrovascular disease, defined as either one or more:	**Measured from the start of all available data to on the date of drug initiation with diagnosis/procedure position and care setting as noted below:**	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
Ia	Confirmed history of MI (> 2 months prior to Visit 1)		
Ib	Advanced coronary artery disease, defined by any one of the following: • ≥ 50% narrowing of the luminal diameter in 2 or more major coronary arteries by coronary angiography, MRI angiography or CT angiography; Definition of major coronary arteries: LAD (Left Anterior Descending). CX (Circumflex) or RCA (right coronary artery) • Left main stem coronary artery with ≥ 50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography; • Prior percutaneous or surgical revascularization of ≥ 2 major coronary arteries at least 2 months prior to Visit 1 (screening); • The combination of prior percutaneous or surgical revascularization of 1 major coronary artery at least 2 months prior to visit 1 (screening), and ≥ 50% narrowing of the luminal diameter by coronary angiography, MRI angiography or CT angiography of at least 1 additional major coronary artery.	**Ischemic heart disease in any diagnosis position and inpatient or outpatient care setting:** ICD-9 410.xx-414.xx OR **Previous cardiac procedure (CABG or PTCA or Stent) in any procedure position and care setting defined below:** PTCA: Inpatient CPT-4: 92973, 92982, 92984, 92995, 92996, 92920 – 92921, 92924 – 92925, 92937, 92938, 92941, 92943, 92944 OR – Inpatient or outpatient ICD-9 procedure: 00.66, 36.01, 36.02, 36.03, 36.05, 36.09 Stenting: Inpatient CPT-4: 92980, 92981, 92928 – 92929, 92933 - 92934 OR – Inpatient or outpatient ICD-9 procedure: 36.06, 36.07 CABG: Inpatient CPT-4: 33510 – 33536, 33545, 33572. OR – Inpatient or outpatient ICD-9 procedure: 36.1x, 36.2x Transmyocardial revascularization: Inpatient or Outpatient CPT-4: 33140, 33141 OR - Inpatient or outpatient ICD-9 procedure: 36.31-36.34	
Ic	High-risk single-vessel coronary artery disease, defined as the presence of ≥ 50% narrowing of the luminal diameter of one major coronary artery by coronary angiography, MRI angiography or CT angiography in patients not revascularized: AND at least one of the following: • A positive non invasive stress test, confirmed by either: o a positive ECG exercise tolerance test in patients without left bundle branch block, Wolff-Parkinson-White syndrome, left ventricular hypertrophy with repolarization abnormality, or paced ventricular rhythm, atrial fibrillation in case of abnormal ST-T segments; o a positive stress echocardiogram showing induced regional systolic wall motion abnormalities; o a positive nuclear myocardial perfusion imaging stress test showing stress- induced reversible perfusion abnormality; o a positive cardiac stress perfusion MRI showing a stress induced perfusion defect; • Patient discharged from hospital with a documented diagnosis of unstable angina pectoris between 2 and 12 months prior to visit 1 (screening).		
Id	History of ischemic or haemorrhagic stroke (>3 months prior to visit 1)	**Measured from the start of all available data to on the date of drug initiation in any diagnosis position and procedure position in inpatient or outpatient care setting:** Any stroke ICD-9 Dx: 430.xx, 431.xx, 433.xx, 434.xx, 436.xx	We including anytime prior to drug initiation here, but then any patients with any stroke within last 3 months are excluded due to the last exclusion criteria.
Ie	Presence of carotid artery disease (symptomatic or not) documented by either: o imaging techniques with at least one lesion estimated to be ≥50% narrowing of the luminal diameter; o prior percutaneous or surgical carotid revascularization.	**Measured from the start of all available data to on the date of drug initiation in any diagnosis position and procedure position in inpatient or outpatient care setting:** Carotid artery disease ICD-9 433.10 : Occlusion and stenosis of carotid artery without mention of cerebral infarction. ICD-10-CM I65.29 Occlusion and stenosis of unspecified carotid artery	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

If	Presence of peripheral artery disease documented by either: o previous limb angioplasty, stenting or bypass surgery; o previous limb or foot amputation due to macrocirculatory insufficiency; o angiographic evidence of peripheral artery stenosis ≥ 50% narrowing of the luminal diameter in at least one limb (definition of peripheral artery: common iliac artery, internal iliac artery, external iliac artery, femoral artery, popliteal artery).	**Measured from the start of all available data to on the date of drug initiation in any diagnosis position and procedure position in inpatient or outpatient care setting** **Carotid bypass:** ICD9 procedure: 39.28 ICD 10 procedure: 031H09G Bypass Right Common Carotid Artery to Intracranial Artery with Autologous Venous Tissue, Open Approach 031H0AG Bypass Right Common Carotid Artery to Intracranial Artery with Autologous Arterial Tissue, Open Approach 031H0JG Bypass Right Common Carotid Artery to Intracranial Artery with Synthetic Substitute, Open Approach 031H0KG Bypass Right Common Carotid Artery to Intracranial Artery with Nonautologous Tissue Substitute, Open Approach 031H0ZG Bypass Right Common Carotid Artery to Intracranial Artery, Open Approach 031J09G Bypass Left Common Carotid Artery to Intracranial Artery with Autologous Venous Tissue, Open Approach 031J0AG Bypass Left Common Carotid Artery to Intracranial Artery with Autologous Arterial Tissue, Open Approach 031J0JG Bypass Left Common Carotid Artery to Intracranial Artery with Synthetic Substitute, Open Approach 031J0KG Bypass Left Common Carotid Artery to Intracranial Artery with Nonautologous Tissue Substitute, Open Approach 031J0ZG Bypass Left Common Carotid Artery to Intracranial Artery, Open Approach	
II.	**Evidence of impaired renal function with predefined UACR, with or without CV co- morbidities, defined as follows (and/or criteria):**		CKD stage 1: GFR >90 CKD stage 2: GFR 60 to 89 CKD stage 3a: GFR 45 to 59 CKD stage 3b: GFR 30 to 44 CKD stage 4: GFR 15 to 29 CKD stage 5: GFR <15
	· Impaired renal function (as defined by MDRD formula) with an eGFR: 15- <45 mL/min/1.73 m2 at visit 1 (screening) with any UACR.	**Measured 180 days prior to drug initiation in any diagnosis position in inpatient or outpatient filters:** **CKD stage 3 and stage 4** 585.3x-585.4x	
	· Impaired renal function (as defined by MDRD formula) with an eGFR ≥ 45-75 mL/min/1.73 m2 at visit 1 (screening) with an UACR > 200 mg/g creatinine or		
	> 200 µg/min (microgram albumin per minute) or > 200 mg/24 h [milligram albumin per 24 hours] demonstrated in two out of three unrelated spot urine or timed samples in the last 24 months prior to randomization.	N/A	
	EXCLUSION CRITERIA		
	1) Type 1 diabetes mellitus.	**Measured 180 days prior to drug initiation in any diagnosis position in inpatient or outpatient care setting:** **DM type 1-** At least 1 inpatient or outpatient ICD-9 Dx code of 250.x1 or 250.x3 or ICD-10 Dx code of E10.x in the 12 months prior to drug initiation. 6-months prior	
	2) Treatment (≥ 7 consecutive days) with GLP-1 receptor agonists, other DPP-4 inhibitors or SGLT-2 inhibitors prior to informed consent. Note: This also includes clinical trials where these antidiabetic drugs have been provided to the patient.	**Measured 180 days prior to drug initiation as a dispensing for one of the following:** Treatment (≥ 7 days) with GLP-1 receptor agonists (lixisenatide, dulaglutide, albiglutide, liraglutide, exenatide), other DPP-4 inhibitors (alogliptin, sitagliptin, saxagliptin) or SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) prior to CED	
	3) Active liver disease or impaired hepatic function, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase (AP) ≥3 x upper limit of normal (ULN) as determined at Visit 1.	**Measured 180 days prior to drug initiation in any diagnosis/procedure position in 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 codes: 39.1x, 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
	4) eGFR <15 ml/min/1.73 m2 (severe renal impairment or ESRD, MDRD formula), as determined during screening at Visit 1 and/or the need for maintenance dialysis.	**Measured 180 days prior to drug initiation :** **CKD stage 5 in any diagnosis/procedure position in inpatient or outpatient care setting-** 585.5x OR **Dialysis in any diagnosis/procedure position and inpatient care setting:** Codes are in the sheet **'Dialysis'** Sheet	

Appendix A

	5) Any previous (or planned within next 12 months) bariatric surgery (open or laparoscopic) or intervention (gastric sleeve).	**Measured 180 days prior to drug initiation in any procedure position in inpatient or outpatient care setting:** Any history CPT -Code- Abbreviation Procedure 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	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
	6) Pre-planned coronary artery re-vascularization (PCI, CABG) or any previous PCI and/or CABG ≤ 2 months prior informed consent	**Measured 60 days prior to drug initiation in any diagnosis position and procedure position in care settings indicated below:** **(≤ 2 months)** PTCA: Inpatient CPT-4: 92973, 92982, 92984, 92995, 92996, 92920 – 92921, 92924 – 92925, 92937, 92938, 92941, 92943, 92944 OR – Inpatient or outpatient: ICD-9 procedure: 00.66, 36.01, 36.02, 36.03, 36.05, 36.09 Stenting: Inpatient CPT-4: 92980, 92981, 92928 – 92929, 92933 -92934 OR – Inpatient or outpatient ICD-9 procedure: 36.06, 36.07 CABG: Inpatient CPT-4: 33510 – 33536, 33545, 33572. OR – Inpatient or outpatient ICD-9 procedure: 36.1x, 36.2x	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
	7) Known hypersensitivity or allergy to the investigational products or its excipients.	N/A	-
	8) Any previous or current alcohol or drug abuse that would interfere with trial participation in the opinion of the investigator.	**Measured 180 days prior to drug initiation in any diagnosis position in inpatient or outpatient care setting:** Alcohol abuse or dependence 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 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
	9) Participation in another trial with an investigational drug ongoing or within 2 months prior to visit 1 (screening)*.	N/A	-
	9) Participation in another trial with an investigational drug ongoing or within 2 months prior to visit 1 (screening)*.	**Measured 180 days prior to drug initiation in any diagnosis/procedure position in inpatient or outpatient care setting:** Please see **Pregnancy codes** sheet.	
	11) Patients considered unreliable by the investigator concerning the requirements for follow- up during the study and/or compliance with study drug administration, have a life expectancy less than 5 years for non-CV causes, or have cancer other than non-melanoma skin cancer within last 3 years, or has any other condition than mentioned which in the opinion of the investigator, would not allow safe participation in the study.	**Measured over 365 days prior to drug initiation:** **CCI >=10** **OR** **Measured 1095 days prior to drug initiation in any diagnosis position in inpatient and outpatient care setting:** **History of malignant neoplasm** ICD-9: 140.xx-208.xx (except 173.xx, non-melanoma skin cancer)- in prior 3 years	"Gagne, Josh J et. al. ""A combined comorbidity score predicted mortality in elderly patients better than existing scores."" J Clin Epidemiol. 2011 Jul;64(7):749-59. doi: 10.1016/j.jclinepi.2010.10.004. Sun, Jenny W et. al. ""Validation of the Combined Comorbidity Index of Charlson and Elixhauser to Predict 30-Day Mortality Across ICD-9 and ICD-10."" Med Care. 2018 Sep;56(9):812. doi: 10.1097/MLR.0000000000000954."
	12) Acute coronary syndrome (ACS), diagnosed ≤ 2 months prior to visit 1 (screening).	**Measured 60 days prior to drug initiation in any diagnosis position in inpatient and outpatient care setting:** ACS/unstable angina 411.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

Appendix A

	13) Stroke or TIA ≤ 3 months prior to visit 1 (screening).	**Measured 90 days prior to drug initiation in any diagnosis position in inpatient and outpatient care setting:** **Any stroke** ICD-9 Dx: 430.xx, 431.xx, 433.xx, 434.xx, 436.xx **TIA** 435.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

Appendix A

Trial ID	
Trial Name (with web links)	CARMELINA
NCT	NCT01897532
Trial category	5a- Successful NI with label change
Therapeutic Area	Endocrinology
RCT Category	Secondary indication
Brand Name	
Generic Name	Linagliptin
Sponsor	Boehringer Ingelheim
Year	2019
Measurable endpoint	Composite of Cardiovascular Death, Non-fatal Myocardial Infarction, or Non-fatal Stroke
Exposure	Linagliptin
Comparator	Placebo
Population	
Trial finding	1.02 (95% CI 0.89-1.17)
No. of Patients	6979
Non-inferiority margin	1.3
Assay Sens. Endpoint	
Assay Sens. Finding	
Power	Power- 0.90. Assuming a HR of 1.0, to demonstrate non-inferiority of linagliptin versus placebo within the pre-specified non-inferiority margin of 1.3 at a one-sided α-level of 2.5%.
Blinding	
Statistical Method	

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)
- 41 - Other died status or Expired in medical facility (Hospice claims only) (depends on year)

Appendix A

- 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	

Appendix A

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

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

Appendix A

72.31 HIGH FORCEPS OPERATION WITH EPISIOTOMY
72.39 OTHER HIGH FORCEPS OPERATION
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

Appendix A

74.1 LOW CERVICAL CESAREAN SECTION
74.2 EXTRAPERITONEAL CESAREAN SECTION
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 A

Dialysis
Dialysis Codes include: - ICD9 prox codes: 39.95, Hemodialysis 54.98, Peritoneal dialysis - ICD9 dx codes: V56.0x, encounter for dialysis NOS V56.8x, encounter for peritoneal dialysis V45.1x, renal dialysis status - CPT4 codes: 90957, 90960, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 4 or more face-to-face physician visits per month 90958, 90961, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 2-3 face-to-face physician visits per month 90959, 90962, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 1 face-to-face physician visit per month 90920, 90921, ESRD related services per full month; for patients 12-19 and twenty years of age and over 90924, 90925, ESRD related services (less than full month), per day; for patients 12-19 and twenty years of age and over 90935, Hemodialysis procedure with single physician evaluation 90937, Hemodialysis procedure requiring repeated evaluation(s) with or without substantial revision of dialysis prescription 90945, Dialysis procedure other than hemodialysis (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies), with single physician evaluation 90947, Dialysis procedure other than hemodialysis (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies) requiring repeated physician evaluations, with or without substantial revision of dialysis prescription 90965, 90966, ESRD related services for home dialysis per full month, for patients 12-19 and 20 years of age and older 90969, 90970, ESRD related services for dialysis less than a full month of service, per day; for patients 12-19 and 20 years of age and older 90989, Dialysis training, patient, including helper where applicable, any mode, completed course 90993, Dialysis training, patient, including helper where applicable, any mode, course not completed, per training session 90999, Unlisted dialysis procedure, inpatient or outpatient 99512, Home visit for hemodialysis - HCPCS codes: G0257, Unscheduled or emergency dialysis treatment for ESRD patient in a hospital outpatient dept. that is not certified as an ESRD facility G0314, G0317, ESRD related services during the course of treatment, for patients 12-19 and 20 yrs of age an over to include monitoring for the adequacy of nutrition, etc. w/4 or more physician visit per month G0315, G0318, ESRD related services during the course of treatment, for patients 12-19 and 20yrs of age and over to include monitoring for the adequacy of nutrition, etc. w/2 or 3 physician visit per month G0316, G0319, ESRD related services during the course of treatment, for patients 12-19 and 20 yrs of age and over to include

Appendix A

monitoring for the adequacy of nutrition, etc. w/1 physician visit per month
G0322, G0323, ESRD related services for home dialysis patients per full month: for patients 12-19 and 20 yrs of age and over to include monitoring for adequacy of nutrition and etc.
G0326, G0327, ESRD related services for home dialysis (less than full month), per day; for patients 12-19 and 20 yrs of age and over
S9335, Home therapy, hemodialysis; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing services coded separately), per diem
S9339, Home therapy, peritoneal dialysis, administrative services, care coordination and all necessary supplies and equipment, per diem

Appendix B

Optum	MarketScan	Medicare

BEFORE PS MATCHING

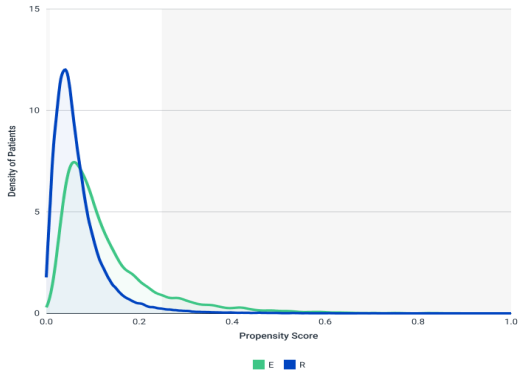


Figure 49: Pre-matching propensity score overlap

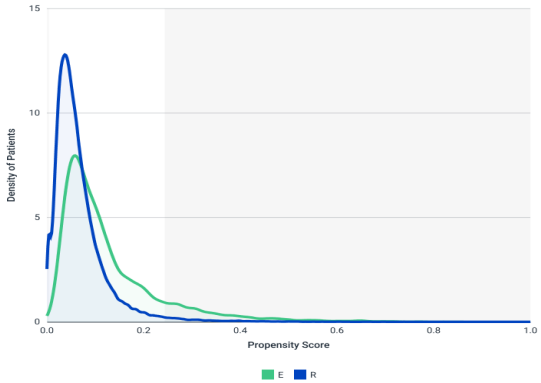
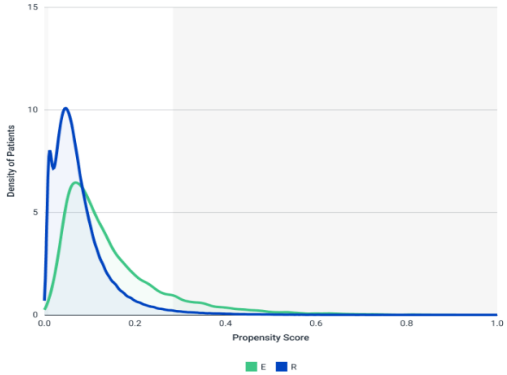


Figure 49: Pre-matching propensity score overlap



igure 24: Pre-matching propensity score overlap

The c-statistics for the propensity score model, pre-matching was 0.728. The post-matching c-statistic was 0.535.	The c-statistics for the propensity score model, pre-matching was 0.724. The post-matching c-statistic was 0.531.	The c-statistics for the propensity score model, pre-matching was 0.732. The post-matching c-statistic was 0.519.

AFTER PS MATCHING

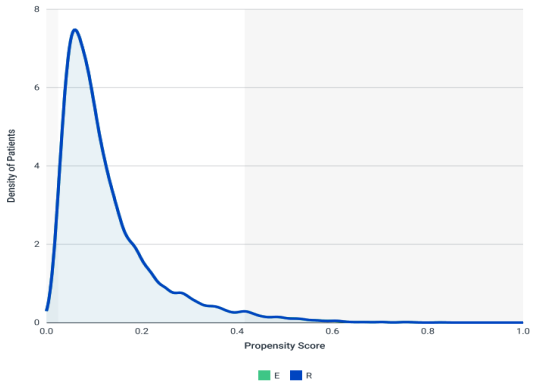


Figure 50: Post-matching propensity score overlap

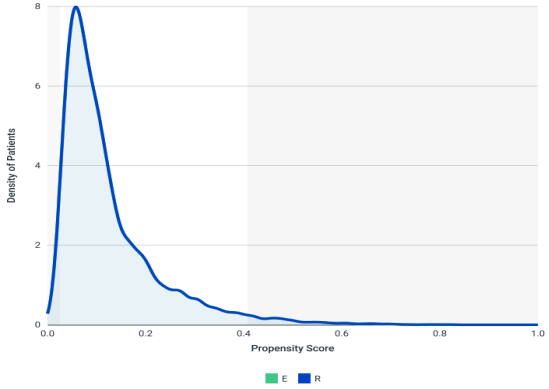


Figure 50: Post-matching propensity score overlap

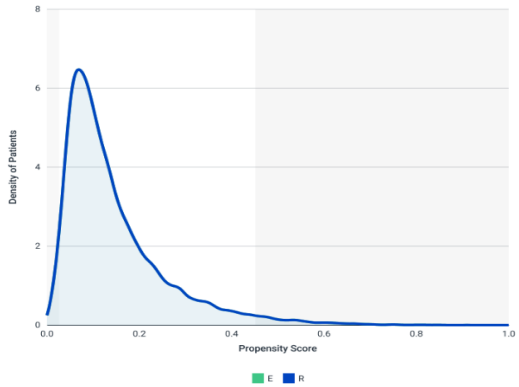


Figure 25: Post-matching propensity score overlap

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

	Unmatched								
	Optum		MarketScan		Medicare		POOLED		
Variable	Reference- 2nd Generation SUs	Exposure- Linagliptin	Reference- 2nd Generation SUs	Exposure- Linagliptin	Reference- 2nd Generation SUs	Exposure- Linagliptin	Reference- 2nd Generation SUs	Exposure- Linagliptin	St. Diff.
Number of patients	**113,991**	**8,904**	**114,025**	**8,736**	**366,136**	**33,401**	**594,152**	**51,041**	
Age									
...mean (sd)	69.66 (10.39)	66.94 (11.64)	65.35 (11.87)	63.75 (11.53)	75.67 (7.35)	75.97 (7.44)	72.54 (9.00)	72.30 (9.09)	0.03
...median [IQR]	70.00 [64.00, 77.00]	67.00 [59.00, 76.00]	64.00 [57.00, 74.00]	62.00 [56.00, 71.00]	75.00 [70.00, 81.00]	5.00 [70.00, 81.00]	71.93 (9.00)	71.38 (9.09)	0.06
Age categories									
...18 - 54; n (%)	10,233 (9.0%)	1,320 (14.8%)	19,802 (17.4%)	1,718 (19.7%)	0 (0.0%)	0 (0.0%)	30,035 (5.1%)	3,038 (6.0%)	-0.04
...55 - 64; n (%)	20,561 (18.0%)	2,441 (27.4%)	40,305 (35.3%)	3,535 (40.5%)	4,429 (1.2%)	340 (1.0%)	65,295 (11.0%)	6,316 (12.4%)	-0.04
...65 - 74; n (%)	44,396 (38.9%)	2,639 (29.6%)	26,643 (23.4%)	1,785 (20.4%)	177,715 (48.5%)	15,653 (46.9%)	248,754 (41.9%)	20,077 (39.3%)	0.05
...>= 75; n (%)	38,801 (34.0%)	2,504 (28.1%)	27,275 (23.9%)	1,698 (19.4%)	183,992 (50.3%)	17,408 (52.1%)	250,068 (42.1%)	21,610 (42.3%)	0.00
Gender									
...Males; n (%)	63,640 (55.8%)	4,680 (52.6%)	68,352 (59.9%)	5,051 (57.8%)	175,512 (47.9%)	14,152 (42.4%)	307,504 (51.8%)	23,883 (46.8%)	0.10
...Females; n (%)	50,351 (44.2%)	4,224 (47.4%)	45,673 (40.1%)	3,685 (42.2%)	190,624 (52.1%)	19,249 (57.6%)	286,648 (48.2%)	27,158 (53.2%)	-0.10
Race									
...White; n (%)	N/A	N/A	N/A	N/A	288,259 (78.7%)	23,448 (70.2%)	288,259 (78.7%)	23,448 (70.2%)	0.20
...Black; n (%)	N/A	N/A	N/A	N/A	40,279 (11.0%)	4,263 (12.8%)	40,279 (11.0%)	4,263 (12.8%)	-0.06
...Asian; n (%)	N/A	N/A	N/A	N/A	11,760 (3.2%)	2,180 (6.5%)	11,760 (3.2%)	2,180 (6.5%)	-0.15
...Hispanic; n (%)	N/A	N/A	N/A	N/A	13,446 (3.7%)	1,876 (5.6%)	13,446 (3.7%)	1,876 (5.6%)	-0.09
...North American Native; n (%)	N/A	N/A	N/A	N/A	2,376 (0.6%)	270 (0.8%)	2,376 (0.6%)	270 (0.8%)	-0.02
...Other/Unknown; n (%)	N/A	N/A	N/A	N/A	10,016 (2.7%)	1,364 (4.1%)	10,016 (2.7%)	1,364 (4.1%)	-0.08
Region (lumping missing&other category with West)									
...Northeast; n (%)	11,593 (10.2%)	1,146 (12.9%)	18,556 (16.3%)	1,945 (22.3%)	59,526 (16.3%)	6,826 (20.4%)	89,675 (15.1%)	9,917 (19.4%)	-0.11
...South; n (%)	54,025 (47.4%)	4,626 (52.0%)	33,925 (29.8%)	1,644 (18.8%)	159,156 (43.5%)	14,335 (42.9%)	247,106 (41.6%)	20,605 (40.4%)	0.02
...Midwest; n (%)	22,555 (19.8%)	1,593 (17.9%)	45,492 (39.9%)	4,155 (47.6%)	89,214 (24.4%)	5,801 (17.4%)	157,261 (26.5%)	11,549 (22.6%)	0.09
...West; n (%)	25,818 (22.6%)	1,539 (17.3%)	15,054 (13.2%)	897 (10.3%)	58,240 (15.9%)	6,439 (19.3%)	99,112 (16.7%)	8,875 (17.4%)	-0.02
...Unknown+missing; n (%)	N/A	N/A	998 (0.9%)	95 (1.1%)	N/A	N/A	998 (0.9%)	95 (1.1%)	-0.02
CV Covariates									
Ischemic heart disease; n (%)	45,790 (40.2%)	3,476 (39.0%)	41,586 (36.5%)	3,037 (34.8%)	159,800 (43.6%)	13,793 (41.3%)	247,176 (41.6%)	20,306 (39.8%)	0.04
Acute MI; n (%)	2,328 (2.0%)	211 (2.4%)	2,429 (2.1%)	164 (1.9%)	7,206 (2.0%)	572 (1.7%)	11,963 (2.0%)	947 (1.9%)	0.01
ACS/unstable angina; n (%)	1,604 (1.4%)	117 (1.3%)	1,705 (1.5%)	125 (1.4%)	4,863 (1.3%)	443 (1.3%)	8,172 (1.4%)	685 (1.3%)	0.01
Old MI; n (%)	6,271 (5.5%)	428 (4.8%)	3,486 (3.1%)	243 (2.8%)	19,590 (5.4%)	1,572 (4.7%)	29,347 (4.9%)	2,243 (4.4%)	0.02
Stable angina; n (%)	6,380 (5.6%)	540 (6.1%)	4,778 (4.2%)	382 (4.4%)	17,135 (4.7%)	1,710 (5.1%)	28,293 (4.8%)	2,632 (5.2%)	-0.02
Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	42,037 (36.9%)	3,219 (36.2%)	38,319 (33.6%)	2,842 (32.5%)	151,932 (41.5%)	13,061 (39.1%)	232,288 (39.1%)	19,122 (37.5%)	0.03
Other atherosclerosis with ICD10 ; n (%)	1,534 (1.3%)	114 (1.3%)	1,423 (1.2%)	107 (1.2%)	7,853 (2.1%)	681 (2.0%)	10,810 (1.8%)	902 (1.8%)	0.00
Previous cardiac procedure (CABG or PTCA or Stent) ; n (%)	720 (0.6%)	56 (0.6%)	919 (0.8%)	80 (0.9%)	2,049 (0.6%)	170 (0.5%)	3,688 (0.6%)	306 (0.6%)	0.00
History of CABG or PTCA; n (%)	9,769 (8.6%)	778 (8.7%)	4,953 (4.3%)	382 (4.4%)	40,597 (11.1%)	3,417 (10.2%)	55,319 (9.3%)	4,577 (9.0%)	0.01
Any stroke; n (%)	5,024 (4.4%)	347 (3.9%)	4,490 (3.9%)	355 (4.1%)	20,639 (5.6%)	1,835 (5.5%)	30,153 (5.1%)	2,537 (5.0%)	0.00
Ischemic stroke (w and w/o mention of cerebral infarction); n (%)	4,945 (4.3%)	339 (3.8%)	4,425 (3.9%)	349 (4.0%)	20,378 (5.6%)	1,815 (5.4%)	29,748 (5.0%)	2,503 (4.9%)	0.00
Hemorrhagic stroke; n (%)	114 (0.1%)	13 (0.1%)	100 (0.1%)	10 (0.1%)	431 (0.1%)	32 (0.1%)	645 (0.1%)	55 (0.1%)	0.00
TIA; n (%)	847 (0.7%)	56 (0.6%)	801 (0.7%)	63 (0.7%)	3,716 (1.0%)	337 (1.0%)	5,364 (0.9%)	456 (0.9%)	0.00
Other cerebrovascular disease; n (%)	2,079 (1.8%)	179 (2.0%)	1,489 (1.3%)	112 (1.3%)	9,408 (2.6%)	949 (2.8%)	12,976 (2.2%)	1,240 (2.4%)	-0.01
Late effects of cerebrovascular disease; n (%)	2,041 (1.8%)	172 (1.9%)	1,238 (1.1%)	71 (0.8%)	8,670 (2.4%)	846 (2.5%)	11,949 (2.0%)	1,089 (2.1%)	-0.01
Cerebrovascular procedure; n (%)	63 (0.1%)	3 (0.0%)	63 (0.1%)	3 (0.0%)	192 (0.1%)	11 (0.0%)	318 (0.1%)	17 (0.0%)	0.04
Heart failure (CHF); n (%)	13,795 (12.1%)	1,146 (12.9%)	10,022 (8.8%)	822 (9.4%)	54,617 (14.9%)	5,354 (16.0%)	78,434 (13.2%)	7,322 (14.3%)	-0.03
Peripheral Vascular Disease (PVD) or PVD Surgery ; n (%)	10,030 (8.8%)	875 (9.8%)	6,941 (6.1%)	559 (6.4%)	45,805 (12.5%)	4,977 (14.9%)	62,776 (10.6%)	6,411 (12.6%)	-0.06
Atrial fibrillation; n (%)	12,216 (10.7%)	849 (9.5%)	9,816 (8.6%)	734 (8.4%)	55,664 (15.2%)	4,895 (14.7%)	77,696 (13.1%)	6,478 (12.7%)	0.01
Other cardiac dysrhythmia; n (%)	13,746 (12.1%)	1,109 (12.5%)	9,751 (8.6%)	803 (9.2%)	55,599 (15.2%)	5,545 (16.6%)	79,096 (13.3%)	7,457 (14.6%)	-0.04
Cardiac conduction disorders; n (%)	4,173 (3.7%)	329 (3.7%)	2,960 (2.6%)	238 (2.7%)	18,071 (4.9%)	1,582 (4.7%)	25,204 (4.2%)	2,149 (4.2%)	0.00
Other CVD; n (%)	16,453 (14.4%)	1,283 (14.4%)	13,648 (12.0%)	1,135 (13.0%)	65,860 (18.0%)	6,376 (19.1%)	95,961 (16.2%)	8,794 (17.2%)	-0.03
Diabetes-related complications									
Diabetic retinopathy; n (%)	6,853 (6.0%)	677 (7.6%)	4,623 (4.1%)	398 (4.6%)	22,873 (6.2%)	2,677 (8.0%)	34,349 (5.8%)	3,752 (7.4%)	-0.06
Diabetes with other ophthalmic manifestations; n (%)	793 (0.7%)	58 (0.7%)	3,389 (3.0%)	255 (2.9%)	8,854 (2.4%)	943 (2.8%)	13,036 (2.2%)	1,256 (2.5%)	-0.02
Retinal detachment, vitreous hemorrhage, vitrectomy; n (%)	459 (0.4%)	62 (0.7%)	356 (0.3%)	52 (0.6%)	1,303 (0.4%)	165 (0.5%)	2,118 (0.4%)	279 (0.5%)	-0.01
Retinal laser coagulation therapy; n (%)	578 (0.5%)	70 (0.8%)	602 (0.5%)	67 (0.8%)	1,792 (0.5%)	253 (0.8%)	2,972 (0.5%)	390 (0.8%)	-0.04
Occurrence of Diabetic Neuropathy ; n (%)	21,622 (19.0%)	1,842 (20.7%)	12,232 (10.7%)	1,115 (12.8%)	65,212 (17.8%)	7,325 (21.9%)	99,066 (16.7%)	10,282 (20.1%)	-0.09

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

Occurrence of diabetic nephropathy with ICD10 ; n (%)	23,814 (20.9%)	2,283 (25.6%)	8,997 (7.9%)	1,121 (12.8%)	40,660 (11.1%)	6,463 (19.3%)	73,471 (12.4%)	9,867 (19.3%)	-0.19
Hypoglycemia ; n (%)	2,895 (2.5%)	227 (2.5%)	3,373 (3.0%)	207 (2.4%)	10,042 (2.7%)	1,090 (3.3%)	16,310 (2.7%)	1,524 (3.0%)	-0.02
Hyperglycemia; n (%)	5,084 (4.5%)	547 (6.1%)	3,784 (3.3%)	344 (3.9%)	17,473 (4.8%)	2,169 (6.5%)	26,341 (4.4%)	3,060 (6.0%)	-0.07
Disorders of fluid electrolyte and acid-base balance; n (%)	10,275 (9.0%)	1,058 (11.9%)	7,196 (6.3%)	620 (7.1%)	38,971 (10.6%)	4,031 (12.1%)	56,442 (9.5%)	5,709 (11.2%)	-0.06
Diabetic ketoacidosis; n (%)	356 (0.3%)	35 (0.4%)	391 (0.3%)	24 (0.3%)	1,273 (0.3%)	126 (0.4%)	2,020 (0.3%)	185 (0.4%)	-0.02
Hyperosmolar hyperglycemic nonketotic syndrome (HONK); n (%)	590 (0.5%)	55 (0.6%)	452 (0.4%)	41 (0.5%)	1,806 (0.5%)	217 (0.6%)	2,848 (0.5%)	313 (0.6%)	-0.01
Diabetes with peripheral circulatory disorders with ICD-10 ; n (%)	9,520 (8.4%)	811 (9.1%)	4,372 (3.8%)	400 (4.6%)	29,150 (8.0%)	3,138 (9.4%)	43,042 (7.2%)	4,349 (8.5%)	-0.05
Diabetic Foot; n (%)	2,764 (2.4%)	269 (3.0%)	2,556 (2.2%)	199 (2.3%)	11,287 (3.1%)	1,082 (3.2%)	16,607 (2.8%)	1,550 (3.0%)	-0.01
Gangrene ; n (%)	361 (0.3%)	31 (0.3%)	272 (0.2%)	16 (0.2%)	1,087 (0.3%)	101 (0.3%)	1,720 (0.3%)	148 (0.3%)	0.00
Lower extremity amputation; n (%)	894 (0.8%)	96 (1.1%)	413 (0.4%)	38 (0.4%)	2,771 (0.8%)	277 (0.8%)	4,078 (0.7%)	411 (0.8%)	-0.01
Osteomyelitis; n (%)	772 (0.7%)	78 (0.9%)	681 (0.6%)	46 (0.5%)	2,477 (0.7%)	211 (0.6%)	3,930 (0.7%)	335 (0.7%)	0.00
Skin infections ; n (%)	6,727 (5.9%)	540 (6.1%)	6,925 (6.1%)	522 (6.0%)	26,721 (7.3%)	2,539 (7.6%)	40,373 (6.8%)	3,601 (7.1%)	-0.01
Erectile dysfunction; n (%)	2,715 (2.4%)	241 (2.7%)	2,209 (1.9%)	216 (2.5%)	6,905 (1.9%)	647 (1.9%)	11,829 (2.0%)	1,104 (2.2%)	-0.01
Diabetes with unspecified complication; n (%)	5,499 (4.8%)	613 (6.9%)	3,886 (3.4%)	389 (4.5%)	16,369 (4.5%)	2,081 (6.2%)	25,754 (4.3%)	3,083 (6.0%)	-0.08
Diabetes mellitus without mention of complications; n (%)	98,647 (86.5%)	7,625 (85.6%)	105,362 (92.4%)	7,961 (91.1%)	342,350 (93.5%)	30,829 (92.3%)	546,359 (92.0%)	46,415 (90.9%)	0.04
Hypertension: 1 inpatient or 2 outpatient claims within 365 days; n (%)	98,566 (86.5%)	7,879 (88.5%)	82,028 (71.9%)	6,834 (78.2%)	336,292 (91.8%)	31,533 (94.4%)	516,886 (87.0%)	46,246 (90.6%)	-0.11
Hyperlipidemia ; n (%)	81,202 (71.2%)	6,711 (75.4%)	64,841 (56.9%)	5,646 (64.6%)	275,172 (75.2%)	26,459 (79.2%)	421,215 (70.9%)	38,816 (76.0%)	-0.12
Edema; n (%)	8,887 (7.8%)	811 (9.1%)	5,991 (5.3%)	557 (6.4%)	39,092 (10.7%)	4,456 (13.3%)	53,970 (9.1%)	5,824 (11.4%)	-0.08
Renal Dysfunction (non-diabetic) ; n (%)	37,562 (33.0%)	3,755 (42.2%)	20,954 (18.4%)	2,525 (28.9%)	104,923 (28.7%)	14,337 (42.9%)	163,439 (27.5%)	20,617 (40.4%)	-0.27
Occurrence of acute renal disease ; n (%)	5,514 (4.8%)	609 (6.8%)	3,904 (3.4%)	423 (4.8%)	18,677 (5.1%)	2,393 (7.2%)	28,095 (4.7%)	3,425 (6.7%)	-0.09
Occurrence of chronic renal insufficiency; n (%)	33,235 (29.2%)	3,393 (38.1%)	16,471 (14.4%)	2,164 (24.8%)	89,032 (24.3%)	12,832 (38.4%)	138,738 (23.4%)	18,389 (36.0%)	-0.28
Chronic kidney disease ; n (%)	32,418 (28.4%)	3,336 (37.5%)	16,038 (14.1%)	2,116 (24.2%)	85,680 (23.4%)	12,415 (37.2%)	134,136 (22.6%)	17,867 (35.0%)	-0.28
CKD Stage 3-4; n (%)	25,804 (22.6%)	2,799 (31.4%)	12,085 (10.6%)	1,713 (19.6%)	64,688 (17.7%)	9,828 (29.4%)	102,577 (17.3%)	14,340 (28.1%)	-0.26
Occurrence of hypertensive nephropathy; n (%)	14,013 (12.3%)	1,488 (16.7%)	6,307 (5.5%)	758 (8.7%)	38,737 (10.6%)	5,386 (16.1%)	59,057 (9.9%)	7,632 (15.0%)	-0.15
Occurrence of miscellaneous renal insufficiency ; n (%)	7,420 (6.5%)	794 (8.9%)	5,159 (4.5%)	589 (6.7%)	29,680 (8.1%)	3,744 (11.2%)	42,259 (7.1%)	5,127 (10.0%)	-0.10
Glaucoma or cataracts ; n (%)	22,333 (19.6%)	1,771 (19.9%)	17,722 (15.5%)	1,514 (17.3%)	91,357 (25.0%)	9,149 (27.4%)	131,412 (22.1%)	12,434 (24.4%)	-0.05
Cellulitis or abscess of toe; n (%)	1,682 (1.5%)	138 (1.5%)	1,126 (1.0%)	101 (1.2%)	5,368 (1.5%)	594 (1.8%)	8,176 (1.4%)	833 (1.6%)	-0.02
Foot ulcer; n (%)	2,718 (2.4%)	257 (2.9%)	2,566 (2.3%)	194 (2.2%)	11,316 (3.1%)	1,073 (3.2%)	16,600 (2.8%)	1,524 (3.0%)	-0.01
Bladder stones; n (%)	159 (0.1%)	16 (0.2%)	126 (0.1%)	17 (0.2%)	657 (0.2%)	66 (0.2%)	942 (0.2%)	99 (0.2%)	0.00
Kidney stones; n (%)	2,539 (2.2%)	272 (3.1%)	2,472 (2.2%)	260 (3.0%)	9,310 (2.5%)	1,017 (3.0%)	14,321 (2.4%)	1,549 (3.0%)	-0.04
Urinary tract infections (UTIs); n (%)	11,118 (9.8%)	1,016 (11.4%)	7,802 (6.8%)	641 (7.3%)	53,506 (14.6%)	6,142 (18.4%)	72,426 (12.2%)	7,799 (15.3%)	-0.09
Dipstick urinalysis; n (%)	39,810 (34.9%)	3,686 (41.4%)	33,397 (29.3%)	3,102 (35.5%)	145,826 (39.8%)	16,212 (48.5%)	219,033 (36.9%)	23,000 (45.1%)	-0.17
Non-dipstick urinalysis; n (%)	44,276 (38.8%)	3,916 (44.0%)	29,777 (26.1%)	2,820 (32.3%)	130,875 (35.7%)	14,659 (43.9%)	204,928 (34.5%)	21,395 (41.9%)	-0.15
Urine function test; n (%)	2,905 (2.5%)	212 (2.4%)	2,885 (2.5%)	281 (3.2%)	12,778 (3.5%)	1,377 (4.1%)	18,568 (3.1%)	1,870 (3.7%)	-0.03
Cytology; n (%)	888 (0.8%)	90 (1.0%)	1,110 (1.0%)	120 (1.4%)	3,902 (1.1%)	439 (1.3%)	5,900 (1.0%)	649 (1.3%)	-0.03
Cystos; n (%)	1,367 (1.2%)	111 (1.2%)	1,490 (1.3%)	151 (1.7%)	5,876 (1.6%)	563 (1.7%)	8,733 (1.5%)	825 (1.6%)	-0.01
Other Covariates									
Liver disease; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!	000 (0.0%)	#VALUE!
Osteoarthritis; n (%)	18,149 (15.9%)	1,516 (17.0%)	13,857 (12.2%)	1,082 (12.4%)	85,234 (23.3%)	8,776 (26.3%)	117,240 (19.7%)	11,374 (22.3%)	-0.06
Other arthritis, arthropathies and musculoskeletal pain; n (%)	40,678 (35.7%)	3,528 (39.6%)	36,555 (32.1%)	2,991 (34.2%)	165,558 (45.2%)	16,538 (49.5%)	242,791 (40.9%)	23,057 (45.2%)	-0.09
Dorsopathies; n (%)	24,710 (21.7%)	2,038 (22.9%)	21,713 (19.0%)	1,834 (21.0%)	96,989 (26.5%)	9,505 (28.5%)	143,412 (24.1%)	13,377 (26.2%)	-0.05
Fractures; n (%)	3,692 (3.2%)	305 (3.4%)	3,370 (3.0%)	223 (2.6%)	16,248 (4.4%)	1,513 (4.5%)	23,310 (3.9%)	2,041 (4.0%)	-0.01
Falls ; n (%)	4,478 (3.9%)	392 (4.4%)	1,629 (1.4%)	107 (1.2%)	18,341 (5.0%)	1,807 (5.4%)	24,448 (4.1%)	2,306 (4.5%)	-0.02
Osteoporosis; n (%)	5,505 (4.8%)	541 (6.1%)	3,204 (2.8%)	263 (3.0%)	28,297 (7.7%)	3,994 (12.0%)	37,006 (6.2%)	4,798 (9.4%)	-0.12
Hyperthyroidism; n (%)	699 (0.6%)	97 (1.1%)	500 (0.4%)	55 (0.6%)	3,221 (0.9%)	427 (1.3%)	4,420 (0.7%)	579 (1.1%)	-0.04
Hypothyroidism ; n (%)	17,357 (15.2%)	1,673 (18.8%)	11,200 (9.8%)	1,124 (12.9%)	54,516 (14.9%)	5,258 (15.7%)	83,073 (14.0%)	8,055 (15.8%)	-0.05
Other disorders of thyroid gland ; n (%)	3,224 (2.8%)	422 (4.7%)	2,773 (2.4%)	387 (4.4%)	12,515 (3.4%)	1,791 (5.4%)	18,512 (3.1%)	2,600 (5.1%)	-0.10
Depression; n (%)	9,096 (8.0%)	805 (9.0%)	7,304 (6.4%)	557 (6.4%)	38,741 (10.6%)	3,845 (11.5%)	55,141 (9.3%)	5,207 (10.2%)	-0.03
Anxiety; n (%)	7,943 (7.0%)	784 (8.8%)	5,215 (4.6%)	448 (5.1%)	30,541 (8.3%)	3,196 (9.6%)	43,699 (7.4%)	4,428 (8.7%)	-0.05
Sleep_Disorder; n (%)	8,147 (7.1%)	590 (6.6%)	11,134 (9.8%)	870 (10.0%)	29,743 (8.1%)	2,723 (8.2%)	49,024 (8.3%)	4,183 (8.2%)	0.00
Dementia; n (%)	5,612 (4.9%)	540 (6.1%)	3,565 (3.1%)	223 (2.6%)	32,684 (8.9%)	3,540 (10.6%)	41,861 (7.0%)	4,303 (8.4%)	-0.05
Delirium; n (%)	1,424 (1.2%)	149 (1.7%)	1,104 (1.0%)	72 (0.8%)	7,315 (2.0%)	849 (2.5%)	9,843 (1.7%)	1,070 (2.1%)	-0.03
Psychosis; n (%)	1,263 (1.1%)	129 (1.4%)	968 (0.8%)	55 (0.6%)	7,939 (2.2%)	793 (2.4%)	10,170 (1.7%)	977 (1.9%)	-0.02
Obesity; n (%)	16,061 (14.1%)	1,661 (18.7%)	10,204 (8.9%)	989 (11.3%)	37,005 (10.1%)	3,919 (11.7%)	63,270 (10.6%)	6,569 (12.9%)	-0.07
Overweight; n (%)	5,405 (4.7%)	591 (6.6%)	1,779 (1.6%)	164 (1.9%)	11,533 (3.1%)	1,342 (4.0%)	18,717 (3.2%)	2,097 (4.1%)	-0.05
Smoking; n (%)	12,866 (11.3%)	1,123 (12.6%)	6,558 (5.8%)	472 (5.4%)	48,039 (13.1%)	4,237 (12.7%)	67,463 (11.4%)	5,832 (11.4%)	0.00
Alcohol abuse or dependence; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!	00 (0.0%)	#VALUE!
Drug abuse or dependence; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!	00 (0.0%)	#VALUE!
COPD; n (%)	12,993 (11.4%)	882 (9.9%)	9,142 (8.0%)	618 (7.1%)	50,518 (13.8%)	4,685 (14.0%)	72,653 (12.2%)	6,185 (12.1%)	0.00

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

Asthma; n (%)	5,959 (5.2%)	569 (6.4%)	5,213 (4.6%)	426 (4.9%)	22,404 (6.1%)	2,223 (6.7%)	33,576 (5.7%)	3,218 (6.3%)	-0.03
Obstructive sleep apnea; n (%)	9,320 (8.2%)	876 (9.8%)	10,424 (9.1%)	939 (10.7%)	22,520 (6.2%)	2,217 (6.6%)	42,264 (7.1%)	4,032 (7.9%)	-0.03
Pneumonia; n (%)	3,866 (3.4%)	318 (3.6%)	3,558 (3.1%)	241 (2.8%)	16,296 (4.5%)	1,507 (4.5%)	23,720 (4.0%)	2,066 (4.0%)	0.00
Imaging; n (%)	155 (0.1%)	17 (0.2%)	131 (0.1%)	7 (0.1%)	712 (0.2%)	54 (0.2%)	998 (0.2%)	78 (0.2%)	0.00
Diabetes Medications									
DM Medications - AGIs; n (%)	359 (0.3%)	32 (0.4%)	308 (0.3%)	32 (0.4%)	1,322 (0.4%)	202 (0.6%)	1,989 (0.3%)	266 (0.5%)	-0.03
DM Medications - Glitazones; n (%)	7,693 (6.7%)	617 (6.9%)	9,595 (8.4%)	839 (9.6%)	22,794 (6.2%)	2,478 (7.4%)	40,082 (6.7%)	3,934 (7.7%)	-0.04
DM Medications - Insulin; n (%)	15,753 (13.8%)	2,424 (27.2%)	15,075 (13.2%)	1,908 (21.8%)	55,854 (15.3%)	9,388 (28.1%)	86,682 (14.6%)	13,720 (26.9%)	-0.31
DM Medications - Meglitinides; n (%)	719 (0.6%)	184 (2.1%)	1,020 (0.9%)	248 (2.8%)	3,957 (1.1%)	1,190 (3.6%)	5,696 (1.0%)	1,622 (3.2%)	-0.15
DM Medications - Metformin; n (%)	67,785 (59.5%)	4,911 (55.2%)	68,989 (60.5%)	4,989 (57.1%)	211,273 (57.7%)	17,663 (52.9%)	348,047 (58.6%)	27,563 (54.0%)	0.09
Concomitant initiation or current use of SGLT2i; n (%)	222 (0.2%)	268 (3.0%)	167 (0.1%)	566 (6.5%)	259 (0.1%)	412 (1.2%)	#VALUE!	1,246 (2.4%)	#VALUE!
Concomitant initiation or current use of AGIs; n (%)	260 (0.2%)	26 (0.3%)	230 (0.2%)	23 (0.3%)	938 (0.3%)	134 (0.4%)	1,428 (0.2%)	183 (0.4%)	-0.04
Concomitant initiation or current use of Glitazones; n (%)	5,876 (5.2%)	424 (4.8%)	7,225 (6.3%)	527 (6.0%)	17,490 (4.8%)	1,741 (5.2%)	30,591 (5.1%)	2,692 (5.3%)	-0.01
Concomitant initiation or current use of Insulin; n (%)	10,884 (9.5%)	1,862 (20.9%)	10,876 (9.5%)	1,443 (16.5%)	39,560 (10.8%)	7,259 (21.7%)	61,320 (10.3%)	10,564 (20.7%)	-0.29
Concomitant initiation or current use of Meglitinides; n (%)	453 (0.4%)	134 (1.5%)	655 (0.6%)	195 (2.2%)	2,488 (0.7%)	892 (2.7%)	3,596 (0.6%)	1,221 (2.4%)	-0.15
Concomitant initiation or current use of Metformin; n (%)	56,752 (49.8%)	3,913 (43.9%)	58,199 (51.0%)	3,978 (45.5%)	177,256 (48.4%)	13,934 (41.7%)	292,207 (49.2%)	21,825 (42.8%)	0.13
Past use of SGLT2i; n (%)	1 (0.0%)	0 (0.0%)	19 (0.0%)	1 (0.0%)	4 (0.0%)	0 (0.0%)	#VALUE!	001 (0.0%)	#VALUE!
Past use of AGIs ; n (%)	99 (0.1%)	6 (0.1%)	78 (0.1%)	9 (0.1%)	384 (0.1%)	68 (0.2%)	561 (0.1%)	83 (0.2%)	-0.03
Past use of Glitazones ; n (%)	1,817 (1.6%)	193 (2.2%)	2,371 (2.1%)	312 (3.6%)	5,304 (1.4%)	737 (2.2%)	9,492 (1.6%)	1,242 (2.4%)	-0.06
Past use of Insulin ; n (%)	4,869 (4.3%)	562 (6.3%)	4,199 (3.7%)	465 (5.3%)	16,297 (4.5%)	2,129 (6.4%)	25,365 (4.3%)	3,156 (6.2%)	-0.09
Past use of Meglitinides ; n (%)	266 (0.2%)	50 (0.6%)	365 (0.3%)	53 (0.6%)	1,469 (0.4%)	298 (0.9%)	2,100 (0.4%)	401 (0.8%)	-0.05
Past use of metformin ; n (%)	11,033 (9.7%)	998 (11.2%)	10,790 (9.5%)	1,011 (11.6%)	34,017 (9.3%)	3,729 (11.2%)	55,840 (9.4%)	5,738 (11.2%)	-0.06
Other Medications									
Use of ACE inhibitors; n (%)	52,181 (45.8%)	3,676 (41.3%)	50,776 (44.5%)	3,495 (40.0%)	163,750 (44.7%)	12,790 (38.3%)	266,707 (44.9%)	19,961 (39.1%)	0.12
Use of ARBs; n (%)	28,284 (24.8%)	2,777 (31.2%)	28,769 (25.2%)	2,858 (32.7%)	97,329 (26.6%)	11,969 (35.8%)	154,382 (26.0%)	17,604 (34.5%)	-0.19
Use of Loop Diuretics ; n (%)	20,910 (18.3%)	1,833 (20.6%)	19,444 (17.1%)	1,688 (19.3%)	88,445 (24.2%)	9,010 (27.0%)	128,799 (21.7%)	12,531 (24.6%)	-0.07
Use of other diuretics; n (%)	4,374 (3.8%)	435 (4.9%)	4,519 (4.0%)	441 (5.0%)	16,078 (4.4%)	1,632 (4.9%)	24,971 (4.2%)	2,508 (4.9%)	-0.03
Use of nitrates-United; n (%)	10,414 (9.1%)	772 (8.7%)	11,043 (9.7%)	747 (8.6%)	42,214 (11.5%)	3,874 (11.6%)	63,671 (10.7%)	5,393 (10.6%)	0.00
Use of other hypertension drugs; n (%)	10,825 (9.5%)	920 (10.3%)	9,771 (8.6%)	794 (9.1%)	37,611 (10.3%)	3,867 (11.6%)	58,207 (9.8%)	5,581 (10.9%)	-0.04
Use of digoxin; n (%)	3,374 (3.0%)	219 (2.5%)	3,676 (3.2%)	272 (3.1%)	16,616 (4.5%)	1,350 (4.0%)	23,666 (4.0%)	1,841 (3.6%)	0.02
Use of Anti-arrhythmics; n (%)	2,343 (2.1%)	176 (2.0%)	2,629 (2.3%)	216 (2.5%)	10,532 (2.9%)	1,055 (3.2%)	15,504 (2.6%)	1,447 (2.8%)	-0.01
Use of COPD/asthma meds; n (%)	16,005 (14.0%)	1,608 (18.1%)	16,846 (14.8%)	1,465 (16.8%)	61,145 (16.7%)	7,008 (21.0%)	93,996 (15.8%)	10,081 (19.8%)	-0.10
Use of statins; n (%)	77,398 (67.9%)	6,449 (72.4%)	74,851 (65.6%)	6,099 (69.8%)	249,773 (68.2%)	24,666 (73.8%)	402,022 (67.7%)	37,214 (72.9%)	-0.11
Use of other lipid-lowering drugs; n (%)	12,848 (11.3%)	1,223 (13.7%)	16,602 (14.6%)	1,528 (17.5%)	42,913 (11.7%)	4,879 (14.6%)	72,363 (12.2%)	7,630 (14.9%)	-0.08
Use of antiplatelet agents; n (%)	19,863 (17.4%)	1,752 (19.7%)	23,347 (20.5%)	1,865 (21.3%)	70,313 (19.2%)	7,213 (21.6%)	113,523 (19.1%)	10,830 (21.2%)	-0.05
Use of oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban, Warfarin); n (%)	10,082 (8.8%)	749 (8.4%)	9,718 (8.5%)	793 (9.1%)	44,487 (12.2%)	4,020 (12.0%)	64,287 (10.8%)	5,562 (10.9%)	0.00
Use of heparin and other low-molecular weight heparins; n (%)	469 (0.4%)	50 (0.6%)	23 (0.0%)	1 (0.0%)	1,950 (0.5%)	157 (0.5%)	2,442 (0.4%)	208 (0.4%)	0.00
Use of NSAIDs; n (%)	15,070 (13.2%)	1,274 (14.3%)	15,571 (13.7%)	1,294 (14.8%)	52,701 (14.4%)	5,618 (16.8%)	83,342 (14.0%)	8,186 (16.0%)	-0.06
Use of oral corticosteroids; n (%)	18,755 (16.5%)	1,600 (18.0%)	18,563 (16.3%)	1,501 (17.2%)	70,096 (19.1%)	6,887 (20.6%)	107,414 (18.1%)	9,988 (19.6%)	-0.04
Use of bisphosphonate (United); n (%)	2,806 (2.5%)	227 (2.5%)	1,930 (1.7%)	137 (1.6%)	11,978 (3.3%)	1,663 (5.0%)	16,714 (2.8%)	2,027 (4.0%)	-0.07
Use of opioids; n (%)	28,735 (25.2%)	2,259 (25.4%)	30,829 (27.0%)	2,294 (26.3%)	100,433 (27.4%)	9,027 (27.0%)	159,997 (26.9%)	13,580 (26.6%)	0.01
Use of antidepressants; n (%)	25,596 (22.5%)	2,240 (25.2%)	25,079 (22.0%)	2,142 (24.5%)	92,511 (25.3%)	9,505 (28.5%)	143,186 (24.1%)	13,887 (27.2%)	-0.07
Use of antipsychotics; n (%)	2,655 (2.3%)	305 (3.4%)	2,436 (2.1%)	213 (2.4%)	12,838 (3.5%)	1,506 (4.5%)	17,929 (3.0%)	2,024 (4.0%)	-0.05
Use of anticonvulsants; n (%)	17,961 (15.8%)	1,682 (18.9%)	14,538 (12.7%)	1,316 (15.1%)	63,740 (17.4%)	7,030 (21.0%)	96,239 (16.2%)	10,028 (19.6%)	-0.09
Use of lithium; n (%)	160 (0.1%)	9 (0.1%)	188 (0.2%)	15 (0.2%)	453 (0.1%)	40 (0.1%)	801 (0.1%)	064 (0.1%)	0.00
Use of Benzos; n (%)	10,450 (9.2%)	1,032 (11.6%)	13,201 (11.6%)	1,036 (11.9%)	38,343 (10.5%)	4,251 (12.7%)	61,994 (10.4%)	6,319 (12.4%)	-0.06
Use of anxiolytics/hypnotics; n (%)	6,200 (5.4%)	596 (6.7%)	7,418 (6.5%)	642 (7.3%)	23,082 (6.3%)	2,419 (7.2%)	36,700 (6.2%)	3,657 (7.2%)	-0.04
Use of dementia meds; n (%)	3,527 (3.1%)	323 (3.6%)	2,889 (2.5%)	206 (2.4%)	21,174 (5.8%)	2,631 (7.9%)	27,590 (4.6%)	3,160 (6.2%)	-0.07
Use of antiparkinsonian meds; n (%)	2,831 (2.5%)	261 (2.9%)	2,799 (2.5%)	207 (2.4%)	13,280 (3.6%)	1,369 (4.1%)	18,910 (3.2%)	1,837 (3.6%)	-0.02
Any use of pramlintide; n (%)	8 (0.0%)	5 (0.1%)	29 (0.0%)	5 (0.1%)	26 (0.0%)	3 (0.0%)	063 (0.0%)	013 (0.0%)	#DIV/0!
Any use of 1st generation sulfonylureas; n (%)	34 (0.0%)	1 (0.0%)	92 (0.1%)	1 (0.0%)	249 (0.1%)	8 (0.0%)	375 (0.1%)	010 (0.0%)	0.00
Entresto (sacubitril/valsartan); n (%)	153 (0.1%)	25 (0.3%)	46 (0.0%)	6 (0.1%)	212 (0.1%)	40 (0.1%)	411 (0.1%)	071 (0.1%)	0.00
Labs							228,016	17,640	
Lab values- HbA1c (%) ; n (%)	38,300 (33.6%)	3,628 (40.7%)	7,256 (6.4%)	411 (4.7%)	N/A	N/A	45,556 (20.0%)	4,039 (22.9%)	-0.07
Lab values- HbA1c (%) (within 3 months) ; n (%)	29,271 (25.7%)	2,900 (32.6%)	5,567 (4.9%)	334 (3.8%)	N/A	N/A	34,838 (15.3%)	3,234 (18.3%)	-0.08
Lab values- HbA1c (%) (within 6 months) ; n (%)	38,300 (33.6%)	3,628 (40.7%)	7,256 (6.4%)	411 (4.7%)	N/A	N/A	45,556 (20.0%)	4,039 (22.9%)	-0.07
Lab values- BNP; n (%)	940 (0.8%)	116 (1.3%)	159 (0.1%)	11 (0.1%)	N/A	N/A	1,099 (0.5%)	127 (0.7%)	-0.03
Lab values- BNP (within 3 months); n (%)	586 (0.5%)	66 (0.7%)	96 (0.1%)	8 (0.1%)	N/A	N/A	682 (0.3%)	074 (0.4%)	-0.02
Lab values- BNP (within 6 months); n (%)	940 (0.8%)	116 (1.3%)	159 (0.1%)	11 (0.1%)	N/A	N/A	1,099 (0.5%)	127 (0.7%)	-0.03
Lab values- BUN (mg/dl); n (%)	39,671 (34.8%)	3,848 (43.2%)	5,599 (4.9%)	460 (5.3%)	N/A	N/A	45,270 (19.9%)	4,308 (24.4%)	-0.11

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

Lab values- BUN (mg/dl) (within 3 months); n (%)	30,338 (26.6%)	3,054 (34.3%)	4,205 (3.7%)	362 (4.1%)	N/A	N/A	34,543 (15.1%)	3,416 (19.4%)	-0.11
Lab values- BUN (mg/dl) (within 6 months); n (%)	39,671 (34.8%)	3,848 (43.2%)	5,599 (4.9%)	460 (5.3%)	N/A	N/A	45,270 (19.9%)	4,308 (24.4%)	-0.11
Lab values- Creatinine (mg/dl) ; n (%)	40,504 (35.5%)	3,967 (44.6%)	5,824 (5.1%)	501 (5.7%)	N/A	N/A	46,328 (20.3%)	4,468 (25.3%)	-0.12
Lab values- Creatinine (mg/dl) (within 3 months) ; n (%)	30,955 (27.2%)	3,154 (35.4%)	4,374 (3.8%)	392 (4.5%)	N/A	N/A	35,329 (15.5%)	3,546 (20.1%)	-0.12
Lab values- Creatinine (mg/dl) (within 6 months) ; n (%)	40,504 (35.5%)	3,967 (44.6%)	5,824 (5.1%)	501 (5.7%)	N/A	N/A	46,328 (20.3%)	4,468 (25.3%)	-0.12
Lab values- HDL level (mg/dl); n (%)	31,938 (28.0%)	3,092 (34.7%)	6,175 (5.4%)	398 (4.6%)	N/A	N/A	38,113 (16.7%)	3,490 (19.8%)	-0.08
Lab values- HDL level (mg/dl) (within 3 months); n (%)	23,022 (20.2%)	2,313 (26.0%)	4,413 (3.9%)	307 (3.5%)	N/A	N/A	27,435 (12.0%)	2,620 (14.9%)	-0.09
Lab values- HDL level (mg/dl) (within 6 months); n (%)	31,938 (28.0%)	3,092 (34.7%)	6,175 (5.4%)	398 (4.6%)	N/A	N/A	38,113 (16.7%)	3,490 (19.8%)	-0.08
Lab values- LDL level (mg/dl) ; n (%)	32,964 (28.9%)	3,182 (35.7%)	6,625 (5.8%)	403 (4.6%)	N/A	N/A	39,589 (17.4%)	3,585 (20.3%)	-0.07
Lab values- LDL level (mg/dl) (within 3 months) ; n (%)	23,766 (20.8%)	2,384 (26.8%)	4,732 (4.1%)	310 (3.5%)	N/A	N/A	28,498 (12.5%)	2,694 (15.3%)	-0.08
Lab values- LDL level (mg/dl) (within 6 months) ; n (%)	32,964 (28.9%)	3,182 (35.7%)	6,625 (5.8%)	403 (4.6%)	N/A	N/A	39,589 (17.4%)	3,585 (20.3%)	-0.07
Lab values- NT-proBNP; n (%)	131 (0.1%)	12 (0.1%)	12 (0.0%)	2 (0.0%)	N/A	N/A	143 (0.1%)	14 (0.1%)	0.00
Lab values- NT-proBNP (within 3 months); n (%)	84 (0.1%)	6 (0.1%)	6 (0.0%)	1 (0.0%)	N/A	N/A	90 (0.0%)	7 (0.0%)	-
Lab values- NT-proBNP (within 6 months); n (%)	131 (0.1%)	12 (0.1%)	12 (0.0%)	2 (0.0%)	N/A	N/A	143 (0.1%)	14 (0.1%)	-
Lab values- Total cholesterol (mg/dl) ; n (%)	32,336 (28.4%)	3,154 (35.4%)	6,131 (5.4%)	405 (4.6%)	N/A	N/A	38,467 (16.9%)	3,559 (20.2%)	-0.08
Lab values- Total cholesterol (mg/dl) (within 3 months) ; n (%)	23,343 (20.5%)	2,357 (26.5%)	4,361 (3.8%)	312 (3.6%)	N/A	N/A	27,704 (12.2%)	2,669 (15.1%)	-0.08
Lab values- Total cholesterol (mg/dl) (within 6 months) ; n (%)	32,336 (28.4%)	3,154 (35.4%)	6,131 (5.4%)	405 (4.6%)	N/A	N/A	38,467 (16.9%)	3,559 (20.2%)	-0.08
Lab values- Triglyceride level (mg/dl); n (%)	32,012 (28.1%)	3,140 (35.3%)	6,014 (5.3%)	400 (4.6%)	N/A	N/A	38,026 (16.7%)	3,540 (20.1%)	-0.09
Lab values- Triglyceride level (mg/dl) (within 3 months); n (%)	23,144 (20.3%)	2,346 (26.3%)	4,302 (3.8%)	307 (3.5%)	N/A	N/A	27,446 (12.0%)	2,653 (15.0%)	-0.09
Lab values- Triglyceride level (mg/dl) (within 6 months); n (%)	32,012 (28.1%)	3,140 (35.3%)	6,014 (5.3%)	400 (4.6%)	N/A	N/A	38,026 (16.7%)	3,540 (20.1%)	-0.09
Lab result number- HbA1c (%) mean (only 2 to 20 included)	38,074	3,615	5,890	390	N/A	N/A	43,964	4,005	
...mean (sd)	7.99 (1.81)	8.01 (1.81)	8.11 (1.90)	7.88 (1.83)	N/A	N/A	8.01 (1.82)	8.00 (1.81)	0.01
...median [IQR]	7.55 [6.80, 8.73]	7.60 [6.70, 8.80]	7.60 [6.80, 8.95]	7.42 [6.60, 8.60]	N/A	N/A	7.56 (1.82)	7.58 (1.81)	-0.01
...Missing; n (%)	75,917 (66.6%)	5,289 (59.4%)	108,135 (94.8%)	8,346 (95.5%)	N/A	N/A	184,052 (80.7%)	13,635 (77.3%)	0.08
Lab result number- BNP mean	940	116	159	11	N/A	N/A	1,099	127	
...mean (sd)	227.35 (358.83)	199.85 (371.31)	2,946.36 (33,054.02)	607.19 (1,393.52)	N/A	N/A	620.73 (12554.50)	235.13 (533.36)	0.04
...median [IQR]	97.30 [38.75, 251.23]	82.60 [32.35, 208.35]	109.00 [40.00, 327.00]	49.00 [15.10, 188.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	113,051 (99.2%)	8,788 (98.7%)	113,866 (99.9%)	8,725 (99.9%)	N/A	N/A	226,917 (99.5%)	17,513 (99.3%)	0.03
Lab result number- BUN (mg/dl) mean	39,671	3,848	5,599	460	N/A	N/A	45,270	4,308	
...mean (sd)	20.56 (9.20)	22.06 (10.35)	782.69 (11,615.02)	306.16 (6,060.48)	N/A	N/A	114.82 (4084.57)	52.40 (1978.94)	0.02
...median [IQR]	18.50 [14.50, 24.00]	19.67 [15.00, 27.00]	17.00 [13.50, 22.00]	18.25 [14.00, 25.88]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	74,320 (65.2%)	5,056 (56.8%)	108,426 (95.1%)	8,276 (94.7%)	N/A	N/A	182,746 (80.1%)	13,332 (75.6%)	0.11
Lab result number- Creatinine (mg/dl) mean (only 0.1 to 15 included)	40,229	3,945	5,443	469	N/A	N/A	45,672	4,414	
...mean (sd)	1.14 (0.45)	1.24 (0.52)	1.09 (0.46)	1.18 (0.61)	N/A	N/A	1.13 (0.45)	1.23 (0.53)	-0.20
...median [IQR]	1.04 [0.85, 1.32]	1.14 [0.88, 1.48]	1.00 [0.82, 1.21]	1.02 [0.84, 1.35]	N/A	N/A	1.04 (0.45)	1.13 (0.53)	-0.18
...Missing; n (%)	73,762 (64.7%)	4,959 (55.7%)	108,582 (95.2%)	8,267 (94.6%)	N/A	N/A	182,344 (80.0%)	13,226 (75.0%)	0.12
Lab result number- HDL level (mg/dl) mean (only =<5000 included)	31,938	3,092	6,157	397	N/A	N/A	38,095	3,489	
...mean (sd)	46.04 (13.96)	46.52 (14.16)	43.97 (14.10)	51.75 (174.25)	N/A	N/A	45.71 (13.98)	47.12 (60.22)	-0.03
...median [IQR]	44.00 [37.00, 53.00]	44.50 [37.00, 54.00]	43.00 [36.00, 51.00]	41.00 [34.00, 52.00]	N/A	N/A	43.84 (13.98)	44.10 (60.22)	-0.01
...Missing; n (%)	82,053 (72.0%)	5,812 (65.3%)	107,868 (94.6%)	8,339 (95.5%)	N/A	N/A	189,921 (83.3%)	14,151 (80.2%)	0.08
Lab result number- LDL level (mg/dl) mean (only =<5000 included)	32,245	3,111	5,964	377	N/A	N/A	38,209	3,488	
...mean (sd)	85.89 (40.32)	85.56 (40.40)	87.23 (42.41)	85.12 (45.45)	N/A	N/A	86.10 (40.65)	85.51 (40.98)	0.01
...median [IQR]	82.00 [61.00, 108.00]	82.50 [61.00, 109.00]	84.50 [63.00, 111.00]	85.00 [59.00, 111.25]	N/A	N/A	82.39 (40.65)	82.77 (40.98)	-0.01
...Missing; n (%)	81,746 (71.7%)	5,793 (65.1%)	108,061 (94.8%)	8,359 (95.7%)	N/A	N/A	189,807 (83.2%)	14,152 (80.2%)	0.08
Lab result number- Total cholesterol (mg/dl) mean (only =<5000 included)	32,317	3,153	6,112	403	N/A	N/A	38,429	3,556	
...mean (sd)	172.24 (48.74)	173.80 (47.85)	173.02 (52.38)	174.06 (57.08)	N/A	N/A	172.36 (49.34)	173.83 (48.99)	-0.03
...median [IQR]	165.50 [140.00, 197.00]	166.00 [142.00, 197.50]	168.00 [142.00, 200.00]	170.00 [141.00, 205.00]	N/A	N/A	165.90 (49.34)	166.45 (48.99)	-0.01
...Missing; n (%)	81,674 (71.6%)	5,751 (64.6%)	107,913 (94.6%)	8,333 (95.4%)	N/A	N/A	189,587 (83.1%)	14,084 (79.8%)	0.08
Lab result number- Triglyceride level (mg/dl) mean (only =<5000 included)	32,008	3,140	5,996	398	N/A	N/A	38,004	3,538	
...mean (sd)	185.40 (155.50)	189.62 (172.91)	193.09 (188.17)	212.32 (232.65)	N/A	N/A	186.61 (161.10)	192.17 (180.63)	-0.03
...median [IQR]	151.00 [108.00, 217.00]	152.00 [107.00, 222.00]	151.00 [107.00, 221.00]	159.00 [107.25, 235.00]	N/A	N/A	151.00 (161.10)	152.79 (180.63)	-0.01
...Missing; n (%)	81,983 (71.9%)	5,764 (64.7%)	108,029 (94.7%)	8,338 (95.4%)	N/A	N/A	190,012 (83.3%)	14,102 (79.9%)	0.09

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

Lab result number- Hemoglobin mean (only >0 included)	28,631	2,909	3,766	353	N/A	N/A	32,397	3,262	
...mean (sd)	13.29 (1.75)	13.17 (1.73)	6,103.13 (230,642.43)	443.69 (8,089.45)	N/A	N/A	721.21 (78630.20)	59.76 (2658.57)	0.01
...median [IQR]	13.30 [12.10, 14.50]	13.20 [11.95, 14.40]	13.60 [12.30, 14.75]	13.30 [12.00, 14.53]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	85,360 (74.9%)	5,995 (67.3%)	110,259 (96.7%)	8,383 (96.0%)	N/A	N/A	195,619 (85.8%)	14,378 (81.5%)	0.12
Lab result number- Serum sodium mean (only > 90 and < 190 included)	39,251	3,841	5,097	458	N/A	N/A	44,348	4,299	
...mean (sd)	139.42 (2.88)	139.59 (2.83)	138.84 (2.83)	139.10 (2.65)	N/A	N/A	139.35 (2.87)	139.54 (2.81)	-0.07
...median [IQR]	139.75 [138.00, 141.00]	140.00 [138.00, 141.50]	139.00 [137.00, 141.00]	139.37 [137.00, 141.00]	N/A	N/A	139.66 (2.87)	139.93 (2.81)	-0.10
...Missing; n (%)	74,740 (65.6%)	5,063 (56.9%)	108,928 (95.5%)	8,278 (94.8%)	N/A	N/A	183,668 (80.6%)	13,341 (75.6%)	0.12
Lab result number- Albumin mean (only >0 and <=10 included)	36,154	3,614	4,374	398	N/A	N/A	40,528	4,012	
...mean (sd)	4.21 (0.33)	4.21 (0.36)	4.12 (0.64)	4.09 (0.71)	N/A	N/A	4.20 (0.38)	4.20 (0.41)	0.00
...median [IQR]	4.20 [4.00, 4.40]	4.20 [4.00, 4.45]	4.20 [4.00, 4.40]	4.20 [4.00, 4.40]	N/A	N/A	4.20 (0.38)	4.20 (0.41)	0.00
...Missing; n (%)	77,837 (68.3%)	5,290 (59.4%)	109,651 (96.2%)	8,338 (95.4%)	N/A	N/A	187,488 (82.2%)	13,628 (77.3%)	0.12
Lab result number- Glucose (fasting or random) mean (only 10-1000 included)	39,051	3,838	4,988	457	N/A	N/A	44,039	4,295	
...mean (sd)	168.55 (73.40)	164.67 (71.92)	177.16 (79.94)	166.24 (76.35)	N/A	N/A	169.53 (74.17)	164.84 (72.41)	0.06
...median [IQR]	150.00 [121.00, 195.00]	146.00 [118.50, 187.00]	156.00 [124.00, 208.00]	145.00 [120.92, 188.00]	N/A	N/A	150.68 (74.17)	145.89 (72.41)	0.07
...Missing; n (%)	74,940 (65.7%)	5,066 (56.9%)	109,037 (95.6%)	8,279 (94.8%)	N/A	N/A	183,977 (80.7%)	13,345 (75.7%)	0.12
Lab result number- Potassium mean (only 1-7 included)	40,186	3,936	5,475	450	N/A	N/A	45,661	4,386	
...mean (sd)	4.47 (0.45)	4.49 (0.46)	4.35 (0.46)	4.36 (0.50)	N/A	N/A	4.46 (0.45)	4.48 (0.46)	-0.04
...median [IQR]	4.45 [4.20, 4.75]	4.50 [4.20, 4.80]	4.32 [4.00, 4.60]	4.38 [4.07, 4.70]	N/A	N/A	4.43 (0.45)	4.49 (0.46)	-0.13
...Missing; n (%)	73,805 (64.7%)	4,968 (55.8%)	108,550 (95.2%)	8,286 (94.8%)	N/A	N/A	182,355 (80.0%)	13,254 (75.1%)	0.12
Comorbidity Scores									
CCI (180 days)- ICD9 and ICD10									
...mean (sd)	2.99 (2.02)	3.36 (2.10)	2.08 (1.78)	2.46 (1.86)	3.19 (2.08)	3.77 (2.11)	2.94 (2.01)	3.47 (2.07)	-0.26
...median [IQR]	3.00 [1.00, 4.00]	3.00 [2.00, 5.00]	2.00 [1.00, 3.00]	2.00 [1.00, 4.00]	3.00 [2.00, 4.00]	4.00 [2.00, 5.00]	2.81 (2.01)	3.48 (2.07)	-0.33
Frailty Score: Qualitative Version 365 days as Categories, v1									
...0; n (%)	44,743 (39.3%)	4,273 (48.0%)	28,949 (25.4%)	2,610 (29.9%)	87,576 (23.9%)	9,710 (29.1%)	161,268 (27.1%)	16,593 (32.5%)	-0.12
...1 to 2; n (%)	39,522 (34.7%)	2,883 (32.4%)	50,470 (44.3%)	3,722 (42.6%)	119,132 (32.5%)	10,236 (30.6%)	209,124 (35.2%)	16,841 (33.0%)	0.05
...3 or more; n (%)	29,726 (26.1%)	1,748 (19.6%)	34,606 (30.3%)	2,404 (27.5%)	159,428 (43.5%)	13,455 (40.3%)	223,760 (37.7%)	17,607 (34.5%)	0.07
Frailty Score: Empirical Version 365 days as Categories,									
...< 0.12908; n (%)	14,662 (12.9%)	1,228 (13.8%)	16,898 (14.8%)	1,340 (15.3%)	20,704 (5.7%)	1,564 (4.7%)	52,264 (8.8%)	4,132 (8.1%)	0.03
...0.12908 - 0.1631167; n (%)	33,703 (29.6%)	2,522 (28.3%)	33,908 (29.7%)	2,586 (29.6%)	67,558 (18.5%)	5,402 (16.2%)	135,169 (22.7%)	10,510 (20.6%)	0.05
...>= 0.1631167; n (%)	65,626 (57.6%)	5,154 (57.9%)	63,219 (55.4%)	4,810 (55.1%)	277,874 (75.9%)	26,435 (79.1%)	406,719 (68.5%)	36,399 (71.3%)	-0.06
Non-Frailty; n (%)	63,097 (55.4%)	5,173 (58.1%)	55,924 (49.0%)	4,718 (54.0%)	15,747 (4.3%)	1,403 (4.2%)	134,768 (22.7%)	11,294 (22.1%)	0.01
Frailty Score (mean): Qualitative Version 365 days, v1									
...mean (sd)	1.68 (2.08)	1.33 (1.90)	1.97 (1.98)	1.79 (1.89)	2.57 (2.41)	2.36 (2.39)	2.28 (2.27)	2.08 (2.23)	0.09
...median [IQR]	1.00 [0.00, 3.00]	1.00 [0.00, 2.00]	2.00 [0.00, 3.00]	1.00 [0.00, 3.00]	2.00 [1.00, 4.00]	2.00 [0.00, 4.00]	1.81 (2.27)	1.65 (2.23)	0.07
Frailty Score (mean): Empirical Version 365 days,									
...mean (sd)	0.18 (0.06)	0.18 (0.06)	0.17 (0.05)	0.17 (0.05)	0.21 (0.07)	0.21 (0.07)	0.20 (0.06)	0.20 (0.07)	0.00
...median [IQR]	0.17 [0.14, 0.21]	0.17 [0.14, 0.21]	0.16 [0.14, 0.20]	0.16 [0.14, 0.19]	0.20 [0.16, 0.24]	0.20 [0.17, 0.25]	0.19 (0.06)	0.19 (0.07)	0.00
Healthcare Utilization									
Any hospitalization; n (%)	11,956 (10.5%)	920 (10.3%)	13,485 (11.8%)	899 (10.3%)	50,583 (13.8%)	4,291 (12.8%)	76,024 (12.8%)	6,110 (12.0%)	0.02
Any hospitalization within prior 30 days; n (%)	4,508 (4.0%)	319 (3.6%)	4,953 (4.3%)	263 (3.0%)	18,266 (5.0%)	1,389 (4.2%)	27,727 (4.7%)	1,971 (3.9%)	0.04
Any hospitalization during prior 31-180 days; n (%)	8,158 (7.2%)	653 (7.3%)	9,220 (8.1%)	679 (7.8%)	35,844 (9.8%)	3,185 (9.5%)	53,222 (9.0%)	4,517 (8.8%)	0.01
Endocrinologist Visit; n (%)	6,826 (6.0%)	1,500 (16.8%)	7,000 (6.1%)	1,485 (17.0%)	27,770 (7.6%)	5,512 (16.5%)	41,596 (7.0%)	8,497 (16.6%)	-0.30
Endocrinologist Visit (30 days prior); n (%)	3,954 (3.5%)	1,079 (12.1%)	4,239 (3.7%)	1,088 (12.5%)	15,203 (4.2%)	3,902 (11.7%)	23,396 (3.9%)	6,069 (11.9%)	-0.30
Endocrinologist Visit (31 to 180 days prior); n (%)	4,733 (4.2%)	966 (10.8%)	4,701 (4.1%)	963 (11.0%)	20,849 (5.7%)	3,759 (11.3%)	30,283 (5.1%)	5,688 (11.1%)	-0.22
Internal medicine/family medicine visits; n (%)	98,689 (86.6%)	7,064 (79.3%)	94,269 (82.7%)	7,569 (86.6%)	306,858 (83.8%)	27,861 (83.4%)	499,816 (84.1%)	42,494 (83.3%)	0.02
Internal medicine/family medicine visits (30 days prior) ; n (%)	72,530 (63.6%)	5,239 (58.8%)	68,880 (60.4%)	5,670 (64.9%)	214,056 (58.5%)	20,278 (60.7%)	355,466 (59.8%)	31,187 (61.1%)	-0.03
Internal medicine/family medicine visits (31 to 180 days prior) ; n (%)	85,493 (75.0%)	6,235 (70.0%)	79,062 (69.3%)	6,601 (75.6%)	268,278 (73.3%)	25,080 (75.1%)	432,833 (72.8%)	37,916 (74.3%)	-0.03
Cardiologist visit; n (%)	40,644 (35.7%)	3,396 (38.1%)	33,564 (29.4%)	2,878 (32.9%)	153,453 (41.9%)	14,288 (42.8%)	227,661 (38.3%)	20,562 (40.3%)	-0.04
Number of Cardiologist visits (30 days prior); n (%)	14,207 (12.5%)	1,245 (14.0%)	11,295 (9.9%)	980 (11.2%)	52,867 (14.4%)	4,868 (14.6%)	78,369 (13.2%)	7,093 (13.9%)	-0.02
Number of Cardiologist visits (31 to 180 days prior); n (%)	34,459 (30.2%)	2,890 (32.5%)	28,626 (25.1%)	2,486 (28.5%)	132,578 (36.2%)	12,584 (37.7%)	195,663 (32.9%)	17,960 (35.2%)	-0.05
Electrocardiogram ; n (%)	39,835 (34.9%)	3,371 (37.9%)	39,798 (34.9%)	3,239 (37.1%)	142,743 (39.0%)	13,763 (41.2%)	222,376 (37.4%)	20,373 (39.9%)	-0.05
Use of glucose test strips; n (%)	3,782 (3.3%)	428 (4.8%)	3,883 (3.4%)	401 (4.6%)	12,324 (3.4%)	1,343 (4.0%)	19,989 (3.4%)	2,172 (4.3%)	-0.05
Dialysis; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	000 (0.0%)	000 (0.0%)	#DIV/0!
Naive new user ; n (%)	34,575 (30.3%)	2,522 (28.3%)	35,230 (30.9%)	2,410 (27.6%)	97,997 (26.8%)	8,357 (25.0%)	167,802 (28.2%)	13,289 (26.0%)	0.05

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

N antidiabetic drugs at index date									
...mean (sd)	1.67 (0.64)	1.75 (0.68)	1.70 (0.65)	1.77 (0.71)	1.66 (0.63)	1.73 (0.67)	1.67 (0.64)	1.74 (0.68)	-0.11
...median [IQR]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 (0.64)	2.00 (0.68)	0.00
number of different/distinct medication prescriptions									
...mean (sd)	9.76 (4.67)	11.09 (5.37)	9.57 (4.62)	10.67 (5.07)	10.00 (4.50)	11.47 (5.03)	9.87 (4.56)	11.27 (5.10)	-0.29
...median [IQR]	9.00 [6.00, 12.00]	10.00 [7.00, 14.00]	9.00 [6.00, 12.00]	10.00 [7.00, 14.00]	9.00 [7.00, 12.00]	11.00 [8.00, 14.00]	9.00 (4.56)	10.65 (5.10)	-0.34
Number of Hospitalizations									
...mean (sd)	0.13 (0.41)	0.13 (0.41)	0.14 (0.41)	0.12 (0.39)	0.18 (0.50)	0.16 (0.48)	0.16 (0.47)	0.15 (0.45)	0.02
...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 (0.47)	0.00 (0.45)	0.00
Number of hospital days									
...mean (sd)	0.69 (3.15)	0.67 (2.66)	0.77 (3.34)	0.66 (2.86)	1.09 (4.32)	1.02 (3.97)	0.95 (3.94)	0.90 (3.60)	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, 0.00]	0.00 (3.94)	0.00 (3.60)	0.00
Number of Emergency Department (ED) visits									
...mean (sd)	0.47 (1.25)	0.49 (1.40)	0.22 (1.51)	0.19 (1.26)	0.64 (1.48)	0.63 (1.44)	0.53 (1.44)	0.53 (1.40)	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 (1.44)	0.00 (1.40)	0.00
Number of Office visits									
...mean (sd)	4.81 (3.84)	5.54 (4.37)	4.90 (4.19)	5.87 (4.32)	5.48 (4.37)	6.38 (4.77)	5.24 (4.24)	6.15 (4.63)	-0.20
...median [IQR]	4.00 [2.00, 6.00]	5.00 [3.00, 7.00]	4.00 [2.00, 6.00]	5.00 [3.00, 8.00]	4.00 [2.00, 7.00]	5.00 [3.00, 9.00]	4.00 (4.24)	5.00 (4.63)	-0.23
Number of Endocrinologist visits									
...mean (sd)	0.26 (1.68)	0.81 (2.91)	0.26 (1.60)	0.84 (3.11)	0.41 (2.46)	0.95 (3.72)	0.35 (2.18)	0.91 (3.49)	-0.19
...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 (2.18)	0.00 (3.49)	0.00
Number of internal medicine/family medicine visits									
...mean (sd)	10.22 (13.48)	9.35 (14.19)	6.96 (10.00)	7.84 (9.99)	8.22 (10.66)	8.99 (11.61)	8.36 (11.14)	8.86 (11.85)	-0.04
...median [IQR]	6.00 [2.00, 13.00]	5.00 [1.00, 12.00]	4.00 [1.00, 9.00]	5.00 [2.00, 10.00]	5.00 [2.00, 11.00]	6.00 [2.00, 12.00]	5.00 (11.14)	5.65 (11.85)	-0.06
Number of Cardiologist visits									
...mean (sd)	1.70 (3.99)	1.95 (4.52)	1.27 (3.33)	1.48 (3.46)	2.19 (4.88)	2.34 (5.18)	1.92 (4.46)	2.12 (4.81)	-0.04
...median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 (4.46)	0.00 (4.81)	0.00
Number electrocardiograms received									
...mean (sd)	0.71 (1.48)	0.76 (1.50)	0.66 (1.30)	0.67 (1.23)	0.82 (1.50)	0.86 (1.50)	0.77 (1.46)	0.81 (1.46)	-0.03
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (1.46)	0.00 (1.46)	0.00
Number of HbA1c tests ordered									
...mean (sd)	1.14 (0.90)	1.30 (0.95)	0.81 (0.87)	0.98 (0.94)	1.26 (0.88)	1.47 (0.91)	1.15 (0.88)	1.36 (0.92)	-0.23
...median [IQR]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [0.00, 1.00]	1.00 [0.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 (0.88)	1.00 (0.92)	0.00
Number of glucose tests ordered									
...mean (sd)	0.47 (2.91)	1.00 (8.11)	0.38 (1.34)	0.49 (1.26)	0.39 (1.05)	0.58 (1.32)	0.40 (1.63)	0.64 (3.59)	-0.09
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 (1.63)	0.00 (3.59)	0.00
Number of lipid tests ordered									
...mean (sd)	0.91 (0.94)	1.03 (1.00)	0.69 (1.15)	0.86 (1.33)	0.92 (0.83)	1.08 (0.90)	0.87 (0.92)	1.03 (1.00)	-0.17
...median [IQR]	1.00 [0.00, 1.00]	1.00 [0.00, 2.00]	0.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 2.00]	0.81 (0.92)	1.00 (1.00)	-0.20
Number of creatinine tests ordered									
...mean (sd)	0.06 (0.35)	0.07 (0.47)	0.10 (0.49)	0.07 (0.58)	0.10 (0.43)	0.09 (0.40)	0.09 (0.43)	0.08 (0.45)	0.02
...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 (0.43)	0.00 (0.45)	0.00
Number of BUN tests ordered									
...mean (sd)	0.04 (0.29)	0.04 (0.38)	0.06 (0.40)	0.05 (0.58)	0.06 (0.34)	0.06 (0.32)	0.06 (0.34)	0.05 (0.39)	0.03
...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 (0.34)	0.00 (0.39)	0.00
Number of tests for microalbuminuria									
...mean (sd)	0.73 (1.16)	0.87 (1.32)	0.44 (0.92)	0.58 (1.05)	0.42 (0.70)	0.57 (0.84)	0.48 (0.85)	0.62 (0.98)	-0.15
...median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (0.85)	0.00 (0.98)	0.00
Total N distinct ICD9/ICD10 diagnoses at the 3rd digit level									
...mean (sd)	5.56 (7.61)	7.38 (8.79)	2.27 (5.00)	2.87 (5.40)	6.02 (8.58)	7.70 (9.44)	5.21 (7.83)	6.82 (8.76)	-0.19
...median [IQR]	3.00 [0.00, 9.00]	5.00 [0.00, 11.00]	0.00 [0.00, 3.00]	0.00 [0.00, 4.00]	3.00 [0.00, 9.00]	5.00 [0.00, 12.00]	2.42 (7.83)	4.14 (8.76)	-0.21
Use of thiazide; n (%)	14,325 (12.6%)	1,077 (12.1%)	13,611 (11.9%)	1,008 (11.5%)	50,169 (13.7%)	4,605 (13.8%)	78,105 (13.1%)	6,690 (13.1%)	0.00
Use of beta blockers; n (%)	57,310 (50.3%)	4,545 (51.0%)	57,096 (50.1%)	4,427 (50.7%)	202,981 (55.4%)	19,093 (57.2%)	317,387 (53.4%)	28,065 (55.0%)	-0.03
Use of calcium channel blockers; n (%)	35,824 (31.4%)	3,051 (34.3%)	33,870 (29.7%)	2,789 (31.9%)	128,069 (35.0%)	13,043 (39.0%)	197,763 (33.3%)	18,883 (37.0%)	-0.08

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

PS-matched									
	Optum		MarketScan		Medicare		POOLED		
Variable	Reference- 2nd Generation SUs	Exposure- Linagliptin	Reference- 2nd Generation SUs	Exposure- Linagliptin	Reference- 2nd Generation SUs	Exposure- Linagliptin	Reference- 2nd Generation SUs	Exposure- Linagliptin	St. Diff.
Number of patients	**8880**	**8880**	**8716**	**8716**	**33319**	**33319**	**50,915**	**50,915**	
Age									
...mean (sd)	66.96 (10.94)	66.96 (11.63)	63.85 (11.51)	63.76 (11.53)	75.92 (7.38)	75.97 (7.44)	72.29 (8.90)	72.31 (9.09)	0.00
...median [IQR]	68.00 [60.00, 75.00]	67.00 [59.00, 76.00]	63.00 [56.00, 72.00]	62.00 [56.00, 71.00]	75.00 [70.00, 81.00]	75.00 [70.00, 81.00]	71.72 (8.90)	71.38 (9.09)	0.04
Age categories									
...18 - 54; n (%)	1,227 (13.8%)	1,313 (14.8%)	1,726 (19.8%)	1,715 (19.7%)	0 (0.0%)	0 (0.0%)	2,953 (5.8%)	3,028 (5.9%)	0.00
...55 - 64; n (%)	1,986 (22.4%)	2,434 (27.4%)	3,404 (39.1%)	3,524 (40.4%)	307 (0.9%)	339 (1.0%)	5,697 (11.2%)	6,297 (12.4%)	-0.04
...65 - 74; n (%)	3,436 (38.7%)	2,634 (29.7%)	1,870 (21.5%)	1,781 (20.4%)	15,789 (47.4%)	15,632 (46.9%)	21,095 (41.4%)	20,047 (39.4%)	0.04
...>= 75; n (%)	2,231 (25.1%)	2,499 (28.1%)	1,716 (19.7%)	1,696 (19.5%)	17,223 (51.7%)	17,348 (52.1%)	21,170 (41.6%)	21,543 (42.3%)	-0.01
Gender									
...Males; n (%)	4,699 (52.9%)	4,669 (52.6%)	4,973 (57.1%)	5,039 (57.8%)	14,083 (42.3%)	14,131 (42.4%)	23,755 (46.7%)	23,839 (46.8%)	0.00
...Females; n (%)	4,181 (47.1%)	4,211 (47.4%)	3,743 (42.9%)	3,677 (42.2%)	19,236 (57.7%)	19,188 (57.6%)	27,160 (53.3%)	27,076 (53.2%)	0.00
Race									
...White; n (%)	N/A	N/A	N/A	N/A	23,508 (70.6%)	23,421 (70.3%)	23,508 (70.6%)	23,421 (70.3%)	0.01
...Black; n (%)	N/A	N/A	N/A	N/A	4,254 (12.8%)	4,256 (12.8%)	4,254 (12.8%)	4,256 (12.8%)	0.00
...Asian; n (%)	N/A	N/A	N/A	N/A	2,120 (6.4%)	2,151 (6.5%)	2,120 (6.4%)	2,151 (6.5%)	0.00
...Hispanic; n (%)	N/A	N/A	N/A	N/A	1,819 (5.5%)	1,861 (5.6%)	1,819 (5.5%)	1,861 (5.6%)	0.00
...North American Native; n (%)	N/A	N/A	N/A	N/A	273 (0.8%)	270 (0.8%)	273 (0.8%)	270 (0.8%)	0.00
...Other/Unknown; n (%)	N/A	N/A	N/A	N/A	1,345 (4.0%)	1,360 (4.1%)	1,345 (4.0%)	1,360 (4.1%)	-0.01
Region (lumping missing&other category with West)									
...Northeast; n (%)	1,134 (12.8%)	1,141 (12.8%)	1,872 (21.5%)	1,936 (22.2%)	6,759 (20.3%)	6,789 (20.4%)	9,765 (19.2%)	9,866 (19.4%)	-0.01
...South; n (%)	4,622 (52.0%)	4,611 (51.9%)	1,654 (19.0%)	1,644 (18.9%)	14,504 (43.5%)	14,319 (43.0%)	20,780 (40.8%)	20,574 (40.4%)	0.01
...Midwest; n (%)	1,575 (17.7%)	1,590 (17.9%)	4,154 (47.7%)	4,147 (47.6%)	5,737 (17.2%)	5,801 (17.4%)	11,466 (22.5%)	11,538 (22.7%)	0.00
...West; n (%)	1,549 (17.4%)	1,538 (17.3%)	934 (10.7%)	895 (10.3%)	6,319 (19.0%)	6,410 (19.2%)	8,802 (17.3%)	8,843 (17.4%)	0.00
...Unknown+missing; n (%)	N/A	N/A	102 (1.2%)	94 (1.1%)	N/A	N/A	102 (1.2%)	94 (1.1%)	0.01
CV Covariates									
Ischemic heart disease; n (%)	3,488 (39.3%)	3,469 (39.1%)	3,098 (35.5%)	3,028 (34.7%)	13,743 (41.2%)	13,751 (41.3%)	20,329 (39.9%)	20,248 (39.8%)	0.00
Acute MI; n (%)	203 (2.3%)	211 (2.4%)	156 (1.8%)	164 (1.9%)	583 (1.7%)	570 (1.7%)	942 (1.9%)	945 (1.9%)	0.00
ACS/unstable angina; n (%)	133 (1.5%)	117 (1.3%)	120 (1.4%)	125 (1.4%)	459 (1.4%)	440 (1.3%)	712 (1.4%)	682 (1.3%)	0.01
Old MI; n (%)	416 (4.7%)	428 (4.8%)	242 (2.8%)	241 (2.8%)	1,583 (4.8%)	1,570 (4.7%)	2,241 (4.4%)	2,239 (4.4%)	0.00
Stable angina; n (%)	547 (6.2%)	539 (6.1%)	387 (4.4%)	381 (4.4%)	1,727 (5.2%)	1,702 (5.1%)	2,661 (5.2%)	2,622 (5.1%)	0.00
Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	3,205 (36.1%)	3,212 (36.2%)	2,873 (33.0%)	2,834 (32.5%)	13,040 (39.1%)	13,022 (39.1%)	19,118 (37.5%)	19,068 (37.5%)	0.00
Other atherosclerosis with ICD10 ; n (%)	94 (1.1%)	114 (1.3%)	92 (1.1%)	107 (1.2%)	657 (2.0%)	680 (2.0%)	843 (1.7%)	901 (1.8%)	-0.01
Previous cardiac procedure (CABG or PTCA or Stent) ; n (%)	55 (0.6%)	56 (0.6%)	66 (0.8%)	80 (0.9%)	168 (0.5%)	170 (0.5%)	289 (0.6%)	306 (0.6%)	0.00
History of CABG or PTCA; n (%)	755 (8.5%)	776 (8.7%)	363 (4.2%)	380 (4.4%)	3,490 (10.5%)	3,405 (10.2%)	4,608 (9.1%)	4,561 (9.0%)	0.00
Any stroke; n (%)	337 (3.8%)	343 (3.9%)	345 (4.0%)	353 (4.1%)	1,782 (5.3%)	1,830 (5.5%)	2,464 (4.8%)	2,526 (5.0%)	-0.01
Ischemic stroke (w and w/o mention of cerebral infarction); n (%)	333 (3.8%)	335 (3.8%)	341 (3.9%)	347 (4.0%)	1,754 (5.3%)	1,810 (5.4%)	2,428 (4.8%)	2,492 (4.9%)	0.00
Hemorrhagic stroke; n (%)	6 (0.1%)	13 (0.1%)	7 (0.1%)	10 (0.1%)	33 (0.1%)	32 (0.1%)	046 (0.1%)	055 (0.1%)	0.00
TIA; n (%)	57 (0.6%)	56 (0.6%)	52 (0.6%)	62 (0.7%)	329 (1.0%)	336 (1.0%)	438 (0.9%)	454 (0.9%)	0.00
Other cerebrovascular disease; n (%)	198 (2.2%)	177 (2.0%)	98 (1.1%)	111 (1.3%)	957 (2.9%)	948 (2.8%)	1,253 (2.5%)	1,236 (2.4%)	0.01
Late effects of cerebrovascular disease; n (%)	172 (1.9%)	170 (1.9%)	73 (0.8%)	70 (0.8%)	822 (2.5%)	842 (2.5%)	1,067 (2.1%)	1,082 (2.1%)	0.00
Cerebrovascular procedure; n (%)	4 (0.0%)	3 (0.0%)	4 (0.0%)	3 (0.0%)	13 (0.0%)	11 (0.0%)	021 (0.0%)	017 (0.0%)	#DIV/0!
Heart failure (CHF); n (%)	1,118 (12.6%)	1,140 (12.8%)	839 (9.6%)	820 (9.4%)	5,351 (16.1%)	5,337 (16.0%)	7,308 (14.4%)	7,297 (14.3%)	0.00
Peripheral Vascular Disease (PVD) or PVD Surgery ; n (%)	878 (9.9%)	872 (9.8%)	593 (6.8%)	558 (6.4%)	4,957 (14.9%)	4,955 (14.9%)	6,428 (12.6%)	6,385 (12.5%)	0.00
Atrial fibrillation; n (%)	835 (9.4%)	845 (9.5%)	738 (8.5%)	733 (8.4%)	4,861 (14.6%)	4,884 (14.7%)	6,434 (12.6%)	6,462 (12.7%)	0.00
Other cardiac dysrhythmia; n (%)	1,125 (12.7%)	1,103 (12.4%)	799 (9.2%)	800 (9.2%)	5,521 (16.6%)	5,531 (16.6%)	7,445 (14.6%)	7,434 (14.6%)	0.00
Cardiac conduction disorders; n (%)	336 (3.8%)	329 (3.7%)	248 (2.8%)	238 (2.7%)	1,680 (5.0%)	1,576 (4.7%)	2,264 (4.4%)	2,143 (4.2%)	0.01
Other CVD; n (%)	1,272 (14.3%)	1,278 (14.4%)	1,147 (13.2%)	1,134 (13.0%)	6,324 (19.0%)	6,350 (19.1%)	8,743 (17.2%)	8,762 (17.2%)	0.00
Diabetes-related complications									
Diabetic retinopathy; n (%)	630 (7.1%)	670 (7.5%)	375 (4.3%)	397 (4.6%)	2,635 (7.9%)	2,651 (8.0%)	3,640 (7.1%)	3,718 (7.3%)	-0.01
Diabetes with other ophthalmic manifestations; n (%)	74 (0.8%)	58 (0.7%)	258 (3.0%)	254 (2.9%)	953 (2.9%)	937 (2.8%)	1,285 (2.5%)	1,249 (2.5%)	0.00
Retinal detachment, vitreous hemorrhage, vitrectomy; n (%)	44 (0.5%)	61 (0.7%)	36 (0.4%)	52 (0.6%)	137 (0.4%)	163 (0.5%)	217 (0.4%)	276 (0.5%)	-0.01
Retinal laser coagulation therapy; n (%)	41 (0.5%)	70 (0.8%)	51 (0.6%)	67 (0.8%)	205 (0.6%)	253 (0.8%)	297 (0.6%)	390 (0.8%)	-0.02
Occurrence of Diabetic Neuropathy ; n (%)	1,816 (20.5%)	1,833 (20.6%)	1,090 (12.5%)	1,109 (12.7%)	7,317 (22.0%)	7,280 (21.8%)	10,223 (20.1%)	10,222 (20.1%)	0.00

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

Occurrence of diabetic nephropathy with ICD10 ; n (%)	2,215 (24.9%)	2,268 (25.5%)	1,124 (12.9%)	1,114 (12.8%)	6,355 (19.1%)	6,416 (19.3%)	9,694 (19.0%)	9,798 (19.2%)	-0.01
Hypoglycemia ; n (%)	216 (2.4%)	226 (2.5%)	195 (2.2%)	207 (2.4%)	1,053 (3.2%)	1,079 (3.2%)	1,464 (2.9%)	1,512 (3.0%)	-0.01
Hyperglycemia; n (%)	568 (6.4%)	544 (6.1%)	348 (4.0%)	342 (3.9%)	2,120 (6.4%)	2,159 (6.5%)	3,036 (6.0%)	3,045 (6.0%)	0.00
Disorders of fluid electrolyte and acid-base balance; n (%)	1,091 (12.3%)	1,051 (11.8%)	568 (6.5%)	617 (7.1%)	4,041 (12.1%)	4,017 (12.1%)	5,700 (11.2%)	5,685 (11.2%)	0.00
Diabetic ketoacidosis; n (%)	37 (0.4%)	35 (0.4%)	41 (0.5%)	24 (0.3%)	171 (0.5%)	126 (0.4%)	249 (0.5%)	185 (0.4%)	0.01
Hyperosmolar hyperglycemic nonketotic syndrome (HONK); n (%)	49 (0.6%)	55 (0.6%)	37 (0.4%)	41 (0.5%)	205 (0.6%)	216 (0.6%)	291 (0.6%)	312 (0.6%)	0.00
Diabetes with peripheral circulatory disorders with ICD-10 ; n (%)	808 (9.1%)	808 (9.1%)	373 (4.3%)	400 (4.6%)	3,068 (9.2%)	3,123 (9.4%)	4,249 (8.3%)	4,331 (8.5%)	-0.01
Diabetic Foot; n (%)	268 (3.0%)	269 (3.0%)	184 (2.1%)	199 (2.3%)	1,098 (3.3%)	1,078 (3.2%)	1,550 (3.0%)	1,546 (3.0%)	0.00
Gangrene ; n (%)	31 (0.3%)	31 (0.3%)	14 (0.2%)	16 (0.2%)	107 (0.3%)	101 (0.3%)	152 (0.3%)	148 (0.3%)	0.00
Lower extremity amputation; n (%)	80 (0.9%)	96 (1.1%)	31 (0.4%)	38 (0.4%)	277 (0.8%)	276 (0.8%)	388 (0.8%)	410 (0.8%)	0.00
Osteomyelitis; n (%)	66 (0.7%)	78 (0.9%)	54 (0.6%)	46 (0.5%)	240 (0.7%)	210 (0.6%)	360 (0.7%)	334 (0.7%)	0.00
Skin infections ; n (%)	569 (6.4%)	539 (6.1%)	501 (5.7%)	522 (6.0%)	2,480 (7.4%)	2,528 (7.6%)	3,550 (7.0%)	3,589 (7.0%)	0.00
Erectile dysfunction; n (%)	246 (2.8%)	241 (2.7%)	220 (2.5%)	216 (2.5%)	644 (1.9%)	644 (1.9%)	1,110 (2.2%)	1,101 (2.2%)	0.00
Diabetes with unspecified complication; n (%)	627 (7.1%)	606 (6.8%)	370 (4.2%)	388 (4.5%)	2,097 (6.3%)	2,070 (6.2%)	3,094 (6.1%)	3,064 (6.0%)	0.00
Diabetes mellitus without mention of complications; n (%)	7,608 (85.7%)	7,607 (85.7%)	7,937 (91.1%)	7,943 (91.1%)	30,740 (92.3%)	30,751 (92.3%)	46,285 (90.9%)	46,301 (90.9%)	0.00
Hypertension: 1 inpatient or 2 outpatient claims within 365 days; n (%)	7,873 (88.7%)	7,855 (88.5%)	6,785 (77.8%)	6,815 (78.2%)	31,536 (94.6%)	31,451 (94.4%)	46,194 (90.7%)	46,121 (90.6%)	0.00
Hyperlipidemia ; n (%)	6,695 (75.4%)	6,689 (75.3%)	5,614 (64.4%)	5,628 (64.6%)	26,315 (79.0%)	26,388 (79.2%)	38,624 (75.9%)	38,705 (76.0%)	0.00
Edema; n (%)	818 (9.2%)	809 (9.1%)	556 (6.4%)	553 (6.3%)	4,504 (13.5%)	4,434 (13.3%)	5,878 (11.5%)	5,796 (11.4%)	0.00
Renal Dysfunction (non-diabetic) ; n (%)	3,697 (41.6%)	3,732 (42.0%)	2,456 (28.2%)	2,511 (28.8%)	13,956 (41.9%)	14,275 (42.8%)	20,109 (39.5%)	20,518 (40.3%)	-0.02
Occurrence of acute renal disease ; n (%)	643 (7.2%)	603 (6.8%)	422 (4.8%)	419 (4.8%)	2,452 (7.4%)	2,378 (7.1%)	3,517 (6.9%)	3,400 (6.7%)	0.01
Occurrence of chronic renal insufficiency; n (%)	3,381 (38.1%)	3,371 (38.0%)	2,101 (24.1%)	2,150 (24.7%)	12,524 (37.6%)	12,774 (38.3%)	18,006 (35.4%)	18,295 (35.9%)	-0.01
Chronic kidney disease ; n (%)	3,319 (37.4%)	3,314 (37.3%)	2,065 (23.7%)	2,102 (24.1%)	12,176 (36.5%)	12,358 (37.1%)	17,560 (34.5%)	17,774 (34.9%)	-0.01
CKD Stage 3-4; n (%)	2,764 (31.1%)	2,781 (31.3%)	1,669 (19.1%)	1,702 (19.5%)	9,803 (29.4%)	9,776 (29.3%)	14,236 (28.0%)	14,259 (28.0%)	0.00
Occurrence of hypertensive nephropathy; n (%)	1,472 (16.6%)	1,471 (16.6%)	723 (8.3%)	751 (8.6%)	5,364 (16.1%)	5,361 (16.1%)	7,559 (14.8%)	7,583 (14.9%)	0.00
Occurrence of miscellaneous renal insufficiency ; n (%)	800 (9.0%)	790 (8.9%)	601 (6.9%)	586 (6.7%)	3,837 (11.5%)	3,718 (11.2%)	5,238 (10.3%)	5,094 (10.0%)	0.01
Glaucoma or cataracts ; n (%)	1,689 (19.0%)	1,764 (19.9%)	1,481 (17.0%)	1,507 (17.3%)	9,097 (27.3%)	9,110 (27.3%)	12,267 (24.1%)	12,381 (24.3%)	0.00
Cellulitis or abscess of toe; n (%)	166 (1.9%)	138 (1.6%)	82 (0.9%)	101 (1.2%)	570 (1.7%)	591 (1.8%)	818 (1.6%)	830 (1.6%)	0.00
Foot ulcer; n (%)	250 (2.8%)	257 (2.9%)	185 (2.1%)	194 (2.2%)	1,091 (3.3%)	1,069 (3.2%)	1,526 (3.0%)	1,520 (3.0%)	0.00
Bladder stones; n (%)	17 (0.2%)	16 (0.2%)	17 (0.2%)	17 (0.2%)	70 (0.2%)	66 (0.2%)	104 (0.2%)	099 (0.2%)	0.00
Kidney stones; n (%)	290 (3.3%)	272 (3.1%)	270 (3.1%)	260 (3.0%)	1,031 (3.1%)	1,010 (3.0%)	1,591 (3.1%)	1,542 (3.0%)	0.01
Urinary tract infections (UTIs); n (%)	1,036 (11.7%)	1,013 (11.4%)	622 (7.1%)	641 (7.4%)	6,198 (18.6%)	6,107 (18.3%)	7,856 (15.4%)	7,761 (15.2%)	0.01
Dipstick urinalysis; n (%)	3,574 (40.2%)	3,671 (41.3%)	2,997 (34.4%)	3,094 (35.5%)	15,526 (46.6%)	16,153 (48.5%)	22,097 (43.4%)	22,918 (45.0%)	-0.03
Non-dipstick urinalysis; n (%)	4,002 (45.1%)	3,900 (43.9%)	2,841 (32.6%)	2,809 (32.2%)	14,418 (43.3%)	14,601 (43.8%)	21,261 (41.8%)	21,310 (41.9%)	0.00
Urine function test; n (%)	264 (3.0%)	209 (2.4%)	267 (3.1%)	280 (3.2%)	1,361 (4.1%)	1,370 (4.1%)	1,892 (3.7%)	1,859 (3.7%)	0.00
Cytology; n (%)	81 (0.9%)	88 (1.0%)	105 (1.2%)	120 (1.4%)	438 (1.3%)	437 (1.3%)	624 (1.2%)	645 (1.3%)	-0.01
Cystos; n (%)	114 (1.3%)	111 (1.2%)	154 (1.8%)	150 (1.7%)	666 (2.0%)	561 (1.7%)	934 (1.8%)	822 (1.6%)	0.02
Other Covariates									
Liver disease; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	000 (0.0%)	000 (0.0%)	#DIV/0!
Osteoarthritis; n (%)	1,546 (17.4%)	1,513 (17.0%)	1,091 (12.5%)	1,080 (12.4%)	8,803 (26.4%)	8,745 (26.2%)	11,440 (22.5%)	11,338 (22.3%)	0.00
Other arthritis, arthropathies and musculoskeletal pain; n (%)	3,601 (40.6%)	3,513 (39.6%)	2,985 (34.2%)	2,986 (34.3%)	16,525 (49.6%)	16,480 (49.5%)	23,111 (45.4%)	22,979 (45.1%)	0.01
Dorsopathies; n (%)	2,069 (23.3%)	2,033 (22.9%)	1,824 (20.9%)	1,828 (21.0%)	9,548 (28.7%)	9,466 (28.4%)	13,441 (26.4%)	13,327 (26.2%)	0.00
Fractures; n (%)	297 (3.3%)	304 (3.4%)	232 (2.7%)	222 (2.5%)	1,576 (4.7%)	1,511 (4.5%)	2,105 (4.1%)	2,037 (4.0%)	0.01
Falls ; n (%)	385 (4.3%)	392 (4.4%)	97 (1.1%)	107 (1.2%)	1,769 (5.3%)	1,804 (5.4%)	2,251 (4.4%)	2,303 (4.5%)	0.00
Osteoporosis; n (%)	547 (6.2%)	538 (6.1%)	266 (3.1%)	262 (3.0%)	3,873 (11.6%)	3,962 (11.9%)	4,686 (9.2%)	4,762 (9.4%)	-0.01
Hyperthyroidism; n (%)	76 (0.9%)	97 (1.1%)	52 (0.6%)	55 (0.6%)	415 (1.2%)	425 (1.3%)	543 (1.1%)	577 (1.1%)	0.00
Hypothyroidism ; n (%)	1,610 (18.1%)	1,667 (18.8%)	1,178 (13.5%)	1,119 (12.8%)	5,372 (16.1%)	5,234 (15.7%)	8,160 (16.0%)	8,020 (15.8%)	0.01
Other disorders of thyroid gland ; n (%)	377 (4.2%)	415 (4.7%)	349 (4.0%)	382 (4.4%)	1,687 (5.1%)	1,772 (5.3%)	2,413 (4.7%)	2,569 (5.0%)	-0.01
Depression; n (%)	817 (9.2%)	801 (9.0%)	567 (6.5%)	557 (6.4%)	3,892 (11.7%)	3,839 (11.5%)	5,276 (10.4%)	5,197 (10.2%)	0.01
Anxiety; n (%)	788 (8.9%)	781 (8.8%)	438 (5.0%)	448 (5.1%)	3,208 (9.6%)	3,189 (9.6%)	4,434 (8.7%)	4,418 (8.7%)	0.00
Sleep_Disorder; n (%)	602 (6.8%)	590 (6.6%)	882 (10.1%)	870 (10.0%)	2,750 (8.3%)	2,717 (8.2%)	4,234 (8.3%)	4,177 (8.2%)	0.00
Dementia; n (%)	534 (6.0%)	533 (6.0%)	247 (2.8%)	223 (2.6%)	3,583 (10.8%)	3,529 (10.6%)	4,364 (8.6%)	4,285 (8.4%)	0.01
Delirium; n (%)	143 (1.6%)	147 (1.7%)	72 (0.8%)	72 (0.8%)	837 (2.5%)	848 (2.5%)	1,052 (2.1%)	1,067 (2.1%)	0.00
Psychosis; n (%)	112 (1.3%)	129 (1.5%)	57 (0.7%)	55 (0.6%)	795 (2.4%)	792 (2.4%)	964 (1.9%)	976 (1.9%)	0.00
Obesity; n (%)	1,752 (19.7%)	1,655 (18.6%)	1,002 (11.5%)	983 (11.3%)	3,985 (12.0%)	3,909 (11.7%)	6,739 (13.2%)	6,547 (12.9%)	0.01
Overweight; n (%)	576 (6.5%)	587 (6.6%)	146 (1.7%)	164 (1.9%)	1,351 (4.1%)	1,340 (4.0%)	2,073 (4.1%)	2,091 (4.1%)	0.00
Smoking; n (%)	1,147 (12.9%)	1,120 (12.6%)	445 (5.1%)	472 (5.4%)	4,307 (12.9%)	4,230 (12.7%)	5,899 (11.6%)	5,822 (11.4%)	0.01
Alcohol abuse or dependence; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	000 (0.0%)	000 (0.0%)	#DIV/0!
Drug abuse or dependence; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	000 (0.0%)	000 (0.0%)	#DIV/0!
COPD; n (%)	947 (10.7%)	878 (9.9%)	636 (7.3%)	617 (7.1%)	4,686 (14.1%)	4,669 (14.0%)	6,269 (12.3%)	6,164 (12.1%)	0.01

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

Asthma; n (%)	572 (6.4%)	566 (6.4%)	453 (5.2%)	423 (4.9%)	2,227 (6.7%)	2,213 (6.6%)	3,252 (6.4%)	3,202 (6.3%)	0.00
Obstructive sleep apnea; n (%)	916 (10.3%)	873 (9.8%)	947 (10.9%)	934 (10.7%)	2,238 (6.7%)	2,212 (6.6%)	4,101 (8.1%)	4,019 (7.9%)	0.01
Pneumonia; n (%)	325 (3.7%)	313 (3.5%)	229 (2.6%)	240 (2.8%)	1,503 (4.5%)	1,501 (4.5%)	2,057 (4.0%)	2,054 (4.0%)	0.00
Imaging; n (%)	9 (0.1%)	17 (0.2%)	11 (0.1%)	7 (0.1%)	74 (0.2%)	54 (0.2%)	94 (0.2%)	78 (0.2%)	0.00
Diabetes Medications									
DM Medications - AGIs; n (%)	40 (0.5%)	32 (0.4%)	33 (0.4%)	32 (0.4%)	210 (0.6%)	194 (0.6%)	283 (0.6%)	258 (0.5%)	0.01
DM Medications - Glitazones; n (%)	625 (7.0%)	616 (6.9%)	856 (9.8%)	836 (9.6%)	2,492 (7.5%)	2,468 (7.4%)	3,973 (7.8%)	3,920 (7.7%)	0.00
DM Medications - Insulin; n (%)	2,377 (26.8%)	2,402 (27.0%)	1,870 (21.5%)	1,896 (21.8%)	9,270 (27.8%)	9,320 (28.0%)	13,517 (26.5%)	13,618 (26.7%)	0.00
DM Medications - Meglitinides; n (%)	171 (1.9%)	179 (2.0%)	249 (2.9%)	240 (2.8%)	1,105 (3.3%)	1,154 (3.5%)	1,525 (3.0%)	1,573 (3.1%)	-0.01
DM Medications - Metformin; n (%)	5,016 (56.5%)	4,907 (55.3%)	5,021 (57.6%)	4,978 (57.1%)	17,725 (53.2%)	17,642 (52.9%)	27,762 (54.5%)	27,527 (54.1%)	0.01
Concomitant initiation or current use of SGLT2i; n (%)	51 (0.6%)	267 (3.0%)	62 (0.7%)	559 (6.4%)	22 (0.1%)	412 (1.2%)	#VALUE!	1,238 (2.4%)	#VALUE!
Concomitant initiation or current use of AGIs; n (%)	31 (0.3%)	26 (0.3%)	26 (0.3%)	23 (0.3%)	138 (0.4%)	128 (0.4%)	195 (0.4%)	177 (0.3%)	0.02
Concomitant initiation or current use of Glitazones; n (%)	427 (4.8%)	423 (4.8%)	539 (6.2%)	525 (6.0%)	1,750 (5.3%)	1,734 (5.2%)	2,716 (5.3%)	2,682 (5.3%)	0.00
Concomitant initiation or current use of Insulin; n (%)	1,806 (20.3%)	1,841 (20.7%)	1,393 (16.0%)	1,435 (16.5%)	7,081 (21.3%)	7,195 (21.6%)	10,280 (20.2%)	10,471 (20.6%)	-0.01
Concomitant initiation or current use of Meglitinides; n (%)	118 (1.3%)	129 (1.5%)	191 (2.2%)	187 (2.1%)	821 (2.5%)	860 (2.6%)	1,130 (2.2%)	1,176 (2.3%)	-0.01
Concomitant initiation or current use of Metformin; n (%)	4,016 (45.2%)	3,909 (44.0%)	4,013 (46.0%)	3,970 (45.5%)	13,978 (42.0%)	13,920 (41.8%)	22,007 (43.2%)	21,799 (42.8%)	0.01
Past use of SGLT2i; n (%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	001 (0.0%)	001 (0.0%)	#DIV/0!
Past use of AGIs ; n (%)	9 (0.1%)	6 (0.1%)	7 (0.1%)	9 (0.1%)	72 (0.2%)	66 (0.2%)	088 (0.2%)	081 (0.2%)	0.00
Past use of Glitazones ; n (%)	198 (2.2%)	193 (2.2%)	317 (3.6%)	311 (3.6%)	742 (2.2%)	734 (2.2%)	1,257 (2.5%)	1,238 (2.4%)	0.01
Past use of Insulin ; n (%)	571 (6.4%)	561 (6.3%)	477 (5.5%)	461 (5.3%)	2,189 (6.6%)	2,125 (6.4%)	3,237 (6.4%)	3,147 (6.2%)	0.01
Past use of Meglitinides ; n (%)	53 (0.6%)	50 (0.6%)	58 (0.7%)	53 (0.6%)	284 (0.9%)	294 (0.9%)	395 (0.8%)	397 (0.8%)	0.00
Past use of metformin ; n (%)	1,000 (11.3%)	998 (11.2%)	1,008 (11.6%)	1,008 (11.6%)	3,747 (11.2%)	3,722 (11.2%)	5,755 (11.3%)	5,728 (11.3%)	0.00
Other Medications									
Use of ACE inhibitors; n (%)	3,677 (41.4%)	3,668 (41.3%)	3,499 (40.1%)	3,486 (40.0%)	12,931 (38.8%)	12,775 (38.3%)	20,107 (39.5%)	19,929 (39.1%)	0.01
Use of ARBs; n (%)	2,818 (31.7%)	2,768 (31.2%)	2,906 (33.3%)	2,848 (32.7%)	11,910 (35.7%)	11,911 (35.7%)	17,634 (34.6%)	17,527 (34.4%)	0.00
Use of Loop Diuretics ; n (%)	1,851 (20.8%)	1,824 (20.5%)	1,700 (19.5%)	1,683 (19.3%)	8,927 (26.8%)	8,978 (26.9%)	12,478 (24.5%)	12,485 (24.5%)	0.00
Use of other diuretics; n (%)	441 (5.0%)	433 (4.9%)	413 (4.7%)	439 (5.0%)	1,637 (4.9%)	1,626 (4.9%)	2,491 (4.9%)	2,498 (4.9%)	0.00
Use of nitrates-United; n (%)	753 (8.5%)	769 (8.7%)	730 (8.4%)	744 (8.5%)	3,871 (11.6%)	3,853 (11.6%)	5,354 (10.5%)	5,366 (10.5%)	0.00
Use of other hypertension drugs; n (%)	886 (10.0%)	915 (10.3%)	768 (8.8%)	793 (9.1%)	3,857 (11.6%)	3,850 (11.6%)	5,511 (10.8%)	5,558 (10.9%)	0.00
Use of digoxin; n (%)	202 (2.3%)	219 (2.5%)	280 (3.2%)	272 (3.1%)	1,335 (4.0%)	1,344 (4.0%)	1,817 (3.6%)	1,835 (3.6%)	0.00
Use of Anti-arrhythmics; n (%)	160 (1.8%)	176 (2.0%)	211 (2.4%)	216 (2.5%)	1,078 (3.2%)	1,054 (3.2%)	1,449 (2.8%)	1,446 (2.8%)	0.00
Use of COPD/asthma meds; n (%)	1,624 (18.3%)	1,602 (18.0%)	1,488 (17.1%)	1,459 (16.7%)	6,907 (20.7%)	6,986 (21.0%)	10,019 (19.7%)	10,047 (19.7%)	0.00
Use of statins; n (%)	6,456 (72.7%)	6,428 (72.4%)	6,090 (69.9%)	6,081 (69.8%)	24,525 (73.6%)	24,594 (73.8%)	37,071 (72.8%)	37,103 (72.9%)	0.00
Use of other lipid-lowering drugs; n (%)	1,261 (14.2%)	1,221 (13.8%)	1,542 (17.7%)	1,522 (17.5%)	4,758 (14.3%)	4,860 (14.6%)	7,561 (14.9%)	7,603 (14.9%)	0.00
Use of antiplatelet agents; n (%)	1,797 (20.2%)	1,745 (19.7%)	1,849 (21.2%)	1,859 (21.3%)	7,227 (21.7%)	7,176 (21.5%)	10,873 (21.4%)	10,780 (21.2%)	0.00
Use of oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban, Warfarin); n (%)	738 (8.3%)	745 (8.4%)	777 (8.9%)	791 (9.1%)	3,971 (11.9%)	4,016 (12.1%)	5,486 (10.8%)	5,552 (10.9%)	0.00
Use of heparin and other low-molecular weight heparins; n (%)	48 (0.5%)	50 (0.6%)	0 (0.0%)	1 (0.0%)	153 (0.5%)	157 (0.5%)	201 (0.4%)	208 (0.4%)	0.00
Use of NSAIDs; n (%)	1,244 (14.0%)	1,269 (14.3%)	1,257 (14.4%)	1,290 (14.8%)	5,605 (16.8%)	5,590 (16.8%)	8,106 (15.9%)	8,149 (16.0%)	0.00
Use of oral corticosteroids; n (%)	1,594 (18.0%)	1,591 (17.9%)	1,506 (17.3%)	1,498 (17.2%)	6,811 (20.4%)	6,858 (20.6%)	9,911 (19.5%)	9,947 (19.5%)	0.00
Use of bisphosphonate (United); n (%)	251 (2.8%)	227 (2.6%)	145 (1.7%)	137 (1.6%)	1,662 (5.0%)	1,654 (5.0%)	2,058 (4.0%)	2,018 (4.0%)	0.00
Use of opioids; n (%)	2,261 (25.5%)	2,252 (25.4%)	2,322 (26.6%)	2,292 (26.3%)	9,179 (27.5%)	9,004 (27.0%)	13,762 (27.0%)	13,548 (26.6%)	0.01
Use of antidepressants; n (%)	2,221 (25.0%)	2,233 (25.1%)	2,105 (24.2%)	2,136 (24.5%)	9,564 (28.7%)	9,481 (28.5%)	13,890 (27.3%)	13,850 (27.2%)	0.00
Use of antipsychotics; n (%)	299 (3.4%)	303 (3.4%)	225 (2.6%)	213 (2.4%)	1,538 (4.6%)	1,500 (4.5%)	2,062 (4.0%)	2,016 (4.0%)	0.00
Use of anticonvulsants; n (%)	1,634 (18.4%)	1,672 (18.8%)	1,336 (15.3%)	1,314 (15.1%)	6,898 (20.7%)	7,000 (21.0%)	9,868 (19.4%)	9,986 (19.6%)	-0.01
Use of lithium; n (%)	16 (0.2%)	9 (0.1%)	20 (0.2%)	15 (0.2%)	55 (0.2%)	40 (0.1%)	091 (0.2%)	064 (0.1%)	0.03
Use of Benzos; n (%)	1,041 (11.7%)	1,028 (11.6%)	1,030 (11.8%)	1,033 (11.9%)	4,194 (12.6%)	4,237 (12.7%)	6,265 (12.3%)	6,298 (12.4%)	0.00
Use of anxiolytics/hypnotics; n (%)	592 (6.7%)	594 (6.7%)	633 (7.3%)	641 (7.4%)	2,449 (7.4%)	2,406 (7.2%)	3,674 (7.2%)	3,641 (7.2%)	0.00
Use of dementia meds; n (%)	333 (3.8%)	319 (3.6%)	234 (2.7%)	206 (2.4%)	2,601 (7.8%)	2,618 (7.9%)	3,168 (6.2%)	3,143 (6.2%)	0.00
Use of antiparkinsonian meds; n (%)	283 (3.2%)	259 (2.9%)	222 (2.5%)	207 (2.4%)	1,350 (4.1%)	1,365 (4.1%)	1,855 (3.6%)	1,831 (3.6%)	0.00
Any use of pramlintide; n (%)	0 (0.0%)	5 (0.1%)	10 (0.1%)	5 (0.1%)	1 (0.0%)	3 (0.0%)	011 (0.0%)	013 (0.0%)	#DIV/0!
Any use of 1st generation sulfonylureas; n (%)	4 (0.0%)	1 (0.0%)	2 (0.0%)	1 (0.0%)	17 (0.1%)	8 (0.0%)	023 (0.0%)	010 (0.0%)	0.00
Entresto (sacubitril/valsartan); n (%)	12 (0.1%)	25 (0.3%)	8 (0.1%)	6 (0.1%)	29 (0.1%)	40 (0.1%)	049 (0.1%)	071 (0.1%)	0.00
Labs							17,596	17,596	
Lab values- HbA1c (%) ; n (%)	3,567 (40.2%)	3,619 (40.8%)	591 (6.8%)	410 (4.7%)	N/A	N/A	4,158 (23.6%)	4,029 (22.9%)	0.02
Lab values- HbA1c (%) (within 3 months) ; n (%)	2,757 (31.0%)	2,895 (32.6%)	460 (5.3%)	333 (3.8%)	N/A	N/A	3,217 (18.3%)	3,228 (18.3%)	0.00
Lab values- HbA1c (%) (within 6 months) ; n (%)	3,567 (40.2%)	3,619 (40.8%)	591 (6.8%)	410 (4.7%)	N/A	N/A	4,158 (23.6%)	4,029 (22.9%)	0.02
Lab values- BNP; n (%)	75 (0.8%)	116 (1.3%)	9 (0.1%)	11 (0.1%)	N/A	N/A	084 (0.5%)	127 (0.7%)	-0.03
Lab values- BNP (within 3 months); n (%)	54 (0.6%)	66 (0.7%)	5 (0.1%)	8 (0.1%)	N/A	N/A	059 (0.3%)	074 (0.4%)	-0.02
Lab values- BNP (within 6 months); n (%)	75 (0.8%)	116 (1.3%)	9 (0.1%)	11 (0.1%)	N/A	N/A	084 (0.5%)	127 (0.7%)	-0.03
Lab values- BUN (mg/dl); n (%)	3,723 (41.9%)	3,839 (43.2%)	534 (6.1%)	459 (5.3%)	N/A	N/A	4,257 (24.2%)	4,298 (24.4%)	0.00

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

Lab values- BUN (mg/dl) (within 3 months); n (%)	2,904 (32.7%)	3,046 (34.3%)	411 (4.7%)	361 (4.1%)	N/A	N/A	3,315 (18.8%)	3,407 (19.4%)	-0.02
Lab values- BUN (mg/dl) (within 6 months); n (%)	3,723 (41.9%)	3,839 (43.2%)	534 (6.1%)	459 (5.3%)	N/A	N/A	4,257 (24.2%)	4,298 (24.4%)	0.00
Lab values- Creatinine (mg/dl) ; n (%)	3,814 (43.0%)	3,958 (44.6%)	567 (6.5%)	500 (5.7%)	N/A	N/A	4,381 (24.9%)	4,458 (25.3%)	-0.01
Lab values- Creatinine (mg/dl) (within 3 months) ; n (%)	2,972 (33.5%)	3,146 (35.4%)	436 (5.0%)	391 (4.5%)	N/A	N/A	3,408 (19.4%)	3,537 (20.1%)	-0.02
Lab values- Creatinine (mg/dl) (within 6 months) ; n (%)	3,814 (43.0%)	3,958 (44.6%)	567 (6.5%)	500 (5.7%)	N/A	N/A	4,381 (24.9%)	4,458 (25.3%)	-0.01
Lab values- HDL level (mg/dl); n (%)	2,999 (33.8%)	3,087 (34.8%)	502 (5.8%)	397 (4.6%)	N/A	N/A	3,501 (19.9%)	3,484 (19.8%)	0.00
Lab values- HDL level (mg/dl) (within 3 months); n (%)	2,179 (24.5%)	2,308 (26.0%)	362 (4.2%)	306 (3.5%)	N/A	N/A	2,541 (14.4%)	2,614 (14.9%)	-0.01
Lab values- HDL level (mg/dl) (within 6 months); n (%)	2,999 (33.8%)	3,087 (34.8%)	502 (5.8%)	397 (4.6%)	N/A	N/A	3,501 (19.9%)	3,484 (19.8%)	0.00
Lab values- LDL level (mg/dl) ; n (%)	3,088 (34.8%)	3,177 (35.8%)	528 (6.1%)	402 (4.6%)	N/A	N/A	3,616 (20.6%)	3,579 (20.3%)	0.01
Lab values- LDL level (mg/dl) (within 3 months) ; n (%)	2,230 (25.1%)	2,379 (26.8%)	374 (4.3%)	309 (3.5%)	N/A	N/A	2,604 (14.8%)	2,688 (15.3%)	-0.01
Lab values- LDL level (mg/dl) (within 6 months) ; n (%)	3,088 (34.8%)	3,177 (35.8%)	528 (6.1%)	402 (4.6%)	N/A	N/A	3,616 (20.6%)	3,579 (20.3%)	0.01
Lab values- NT-proBNP; n (%)	15 (0.2%)	12 (0.1%)	0 (0.0%)	2 (0.0%)	N/A	N/A	15 (0.1%)	0 (0.1%)	-
Lab values- NT-proBNP (within 3 months); n (%)	10 (0.1%)	6 (0.1%)	0 (0.0%)	1 (0.0%)	N/A	N/A	10 (0.1%)	0 (0.0%)	-
Lab values- NT-proBNP (within 6 months); n (%)	15 (0.2%)	12 (0.1%)	0 (0.0%)	2 (0.0%)	N/A	N/A	15 (0.1%)	14 (0.1%)	-
Lab values- Total cholesterol (mg/dl) ; n (%)	3,051 (34.4%)	3,149 (35.5%)	505 (5.8%)	404 (4.6%)	N/A	N/A	3,556 (20.2%)	3,553 (20.2%)	0.00
Lab values- Total cholesterol (mg/dl) (within 3 months) ; n (%)	2,212 (24.9%)	2,352 (26.5%)	361 (4.1%)	311 (3.6%)	N/A	N/A	2,573 (14.6%)	2,663 (15.1%)	-0.01
Lab values- Total cholesterol (mg/dl) (within 6 months) ; n (%)	3,051 (34.4%)	3,149 (35.5%)	505 (5.8%)	404 (4.6%)	N/A	N/A	3,556 (20.2%)	3,553 (20.2%)	0.00
Lab values- Triglyceride level (mg/dl); n (%)	3,015 (34.0%)	3,135 (35.3%)	500 (5.7%)	399 (4.6%)	N/A	N/A	3,515 (20.0%)	3,534 (20.1%)	0.00
Lab values- Triglyceride level (mg/dl) (within 3 months); n (%)	2,190 (24.7%)	2,341 (26.4%)	355 (4.1%)	306 (3.5%)	N/A	N/A	2,545 (14.5%)	2,647 (15.0%)	-0.01
Lab values- Triglyceride level (mg/dl) (within 6 months); n (%)	3,015 (34.0%)	3,135 (35.3%)	500 (5.7%)	399 (4.6%)	N/A	N/A	3,515 (20.0%)	3,534 (20.1%)	0.00
Lab result number- HbA1c (%) mean (only 2 to 20 included)	3,541	3,606	529	389	N/A	N/A	4,070	3,995	
...mean (sd)	8.14 (1.86)	8.00 (1.81)	8.11 (1.85)	7.88 (1.83)	N/A	N/A	8.14 (1.86)	7.99 (1.81)	0.08
...median [IQR]	7.70 [6.85, 9.04]	7.60 [6.70, 8.80]	7.60 [6.80, 9.00]	7.45 [6.60, 8.60]	N/A	N/A	7.69 (1.86)	7.59 (1.81)	0.05
...Missing; n (%)	5,339 (60.1%)	5,274 (59.4%)	8,187 (93.9%)	8,327 (95.5%)	N/A	N/A	13,526 (76.9%)	13,601 (77.3%)	-0.01
Lab result number- BNP mean	75	116	9	11	N/A	N/A	84	127	
...mean (sd)	182.81 (288.14)	199.85 (371.31)	209.22 (333.71)	607.19 (1,393.52)	N/A	N/A	185.64 (294.70)	235.13 (533.36)	-0.11
...median [IQR]	65.50 [32.60, 167.50]	82.60 [32.35, 208.35]	80.00 [47.00, 204.50]	49.00 [15.10, 188.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	8,805 (99.2%)	8,764 (98.7%)	8,707 (99.9%)	8,705 (99.9%)	N/A	N/A	17,512 (99.5%)	17,469 (99.3%)	0.03
Lab result number- BUN (mg/dl) mean	3,723	3,839	534	459	N/A	N/A	4,257	4,298	
...mean (sd)	21.39 (9.92)	22.02 (10.30)	550.42 (9,028.78)	306.80 (6,067.08)	N/A	N/A	87.75 (3195.92)	52.43 (1981.24)	0.01
...median [IQR]	19.00 [15.00, 25.50]	19.50 [15.00, 27.00]	18.00 [13.50, 24.00]	18.50 [14.00, 26.00]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	5,157 (58.1%)	5,041 (56.8%)	8,182 (93.9%)	8,257 (94.7%)	N/A	N/A	13,339 (75.8%)	13,298 (75.6%)	0.00
Lab result number- Creatinine (mg/dl) mean (only 0.1 to 15 included)	3,791	3,936	520	468	N/A	N/A	4,311	4,404	
...mean (sd)	1.20 (0.50)	1.24 (0.51)	1.15 (0.52)	1.18 (0.61)	N/A	N/A	1.19 (0.50)	1.23 (0.52)	-0.08
...median [IQR]	1.08 [0.87, 1.41]	1.14 [0.88, 1.48]	1.00 [0.84, 1.36]	1.01 [0.84, 1.35]	N/A	N/A	1.07 (0.50)	1.13 (0.52)	-0.12
...Missing; n (%)	5,089 (57.3%)	4,944 (55.7%)	8,196 (94.0%)	8,248 (94.6%)	N/A	N/A	13,285 (75.5%)	13,192 (75.0%)	0.01
Lab result number- HDL level (mg/dl) mean (only =<5000 included)	2,999	3,087	501	396	N/A	N/A	3,500	3,483	
...mean (sd)	45.64 (13.89)	46.51 (14.12)	43.93 (15.31)	51.64 (174.45)	N/A	N/A	45.40 (14.10)	47.09 (60.26)	-0.04
...median [IQR]	44.00 [36.00, 53.00]	44.50 [37.00, 54.00]	42.50 [35.00, 52.00]	41.00 [34.00, 52.00]	N/A	N/A	43.79 (14.10)	44.10 (60.26)	-0.01
...Missing; n (%)	5,881 (66.2%)	5,793 (65.2%)	8,215 (94.3%)	8,320 (95.5%)	N/A	N/A	14,096 (80.1%)	14,113 (80.2%)	0.00
Lab result number- LDL level (mg/dl) mean (only =<5000 included)	3,014	3,106	481	376	N/A	N/A	3,495	3,482	
...mean (sd)	85.21 (41.48)	85.59 (40.41)	86.93 (43.78)	85.05 (45.50)	N/A	N/A	85.45 (41.81)	85.53 (40.99)	0.00
...median [IQR]	81.75 [60.00, 108.00]	82.75 [61.00, 109.00]	85.00 [62.00, 109.58]	84.50 [59.00, 111.38]	N/A	N/A	82.20 (41.81)	82.94 (40.99)	-0.02
...Missing; n (%)	5,866 (66.1%)	5,774 (65.0%)	8,235 (94.5%)	8,340 (95.7%)	N/A	N/A	14,101 (80.1%)	14,114 (80.2%)	0.00
Lab result number- Total cholesterol (mg/dl) mean (only =<5000 included)	3,048	3,148	504	402	N/A	N/A	3,552	3,550	
...mean (sd)	172.69 (47.81)	173.80 (47.86)	173.39 (53.59)	173.95 (57.11)	N/A	N/A	172.79 (48.68)	173.82 (49.00)	-0.02
...median [IQR]	166.00 [141.00, 199.00]	166.00 [142.00, 197.50]	168.00 [143.00, 202.88]	170.00 [141.00, 205.00]	N/A	N/A	166.28 (48.68)	166.45 (49.00)	0.00
...Missing; n (%)	5,832 (65.7%)	5,732 (64.5%)	8,212 (94.2%)	8,314 (95.4%)	N/A	N/A	14,044 (79.8%)	14,046 (79.8%)	0.00
Lab result number- Triglyceride level (mg/dl) mean (only =<5000 included)	3,015	3,135	499	397	N/A	N/A	3,514	3,532	
...mean (sd)	193.31 (156.70)	189.61 (172.97)	195.78 (174.50)	212.71 (232.81)	N/A	N/A	193.66 (159.37)	192.21 (180.70)	0.01
...median [IQR]	156.00 [112.00, 225.00]	152.00 [107.00, 222.00]	151.00 [105.00, 224.00]	159.00 [107.67, 235.00]	N/A	N/A	155.29 (159.37)	152.79 (180.70)	0.01
...Missing; n (%)	5,865 (66.0%)	5,745 (64.7%)	8,217 (94.3%)	8,319 (95.4%)	N/A	N/A	14,082 (80.0%)	14,064 (79.9%)	0.00

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

Lab result number- Hemoglobin mean (only >0 included)	2,720	2,902	370	352	N/A	N/A	3,090	3,254	
...mean (sd)	13.16 (1.75)	13.17 (1.73)	377.00 (7,000.31)	444.91 (8,100.93)	N/A	N/A	56.73 (2420.26)	59.87 (2661.83)	0.00
...median [IQR]	13.20 [11.90, 14.40]	13.20 [11.95, 14.40]	13.30 [12.00, 14.70]	13.30 [12.00, 14.54]	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
...Missing; n (%)	6,160 (69.4%)	5,978 (67.3%)	8,346 (95.8%)	8,364 (96.0%)	N/A	N/A	14,506 (82.4%)	14,342 (81.5%)	0.02
Lab result number- Serum sodium mean (only > 90 and < 190 included)	3,702	3,832	514	457	N/A	N/A	4,216	4,289	
...mean (sd)	139.51 (2.85)	139.59 (2.84)	139.02 (3.31)	139.09 (2.65)	N/A	N/A	139.45 (2.91)	139.54 (2.82)	-0.03
...median [IQR]	140.00 [138.00, 141.33]	140.00 [138.00, 141.50]	139.00 [137.50, 141.00]	139.33 [137.00, 141.00]	N/A	N/A	139.88 (2.91)	139.93 (2.82)	-0.02
...Missing; n (%)	5,178 (58.3%)	5,048 (56.8%)	8,202 (94.1%)	8,259 (94.8%)	N/A	N/A	13,380 (76.0%)	13,307 (75.6%)	0.01
Lab result number- Albumin mean (only >0 and <=10 included)	3,422	3,605	447	397	N/A	N/A	3,869	4,002	
...mean (sd)	4.20 (0.35)	4.21 (0.36)	4.04 (0.76)	4.09 (0.71)	N/A	N/A	4.18 (0.42)	4.20 (0.41)	-0.05
...median [IQR]	4.20 [4.00, 4.40]	4.20 [4.00, 4.45]	4.15 [4.00, 4.40]	4.20 [4.00, 4.40]	N/A	N/A	4.19 (0.42)	4.20 (0.41)	-0.02
...Missing; n (%)	5,458 (61.5%)	5,275 (59.4%)	8,269 (94.9%)	8,319 (95.4%)	N/A	N/A	13,727 (78.0%)	13,594 (77.3%)	0.02
Lab result number- Glucose (fasting or random) mean (only 10-1000 included)	3,684	3,829	509	456	N/A	N/A	4,193	4,285	
...mean (sd)	171.75 (75.07)	164.58 (71.69)	171.74 (71.84)	166.42 (76.33)	N/A	N/A	171.75 (74.69)	164.78 (72.21)	0.09
...median [IQR]	153.00 [122.28, 201.33]	146.00 [118.50, 187.00]	152.50 [124.25, 198.50]	145.00 [121.12, 188.00]	N/A	N/A	152.94 (74.69)	145.89 (72.21)	0.10
...Missing; n (%)	5,196 (58.5%)	5,051 (56.9%)	8,207 (94.2%)	8,260 (94.8%)	N/A	N/A	13,403 (76.2%)	13,311 (75.6%)	0.01
Lab result number- Potassium mean (only 1-7 included)	3,791	3,927	523	449	N/A	N/A	4,314	4,376	
...mean (sd)	4.49 (0.46)	4.49 (0.46)	4.34 (0.47)	4.37 (0.50)	N/A	N/A	4.47 (0.46)	4.48 (0.46)	-0.02
...median [IQR]	4.50 [4.20, 4.80]	4.50 [4.20, 4.80]	4.30 [4.00, 4.70]	4.40 [4.07, 4.70]	N/A	N/A	4.48 (0.46)	4.49 (0.46)	-0.02
...Missing; n (%)	5,089 (57.3%)	4,953 (55.8%)	8,193 (94.0%)	8,267 (94.8%)	N/A	N/A	13,282 (75.5%)	13,220 (75.1%)	0.01
Comorbidity Scores									
CCI (180 days)- ICD9 and ICD10									
...mean (sd)	3.36 (2.08)	3.35 (2.10)	2.46 (1.88)	2.45 (1.86)	3.77 (2.14)	3.77 (2.11)	3.47 (2.09)	3.47 (2.07)	0.00
...median [IQR]	3.00 [2.00, 5.00]	3.00 [2.00, 5.00]	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	4.00 [2.00, 5.00]	4.00 [2.00, 5.00]	3.48 (2.09)	3.48 (2.07)	0.00
Frailty Score: Qualitative Version 365 days as Categories, v1									
...0; n (%)	4,324 (48.7%)	4,263 (48.0%)	2,619 (30.0%)	2,596 (29.8%)	9,977 (29.9%)	9,686 (29.1%)	16,920 (33.2%)	16,545 (32.5%)	0.01
...1 to 2; n (%)	2,752 (31.0%)	2,873 (32.4%)	3,661 (42.0%)	3,717 (42.6%)	10,036 (30.1%)	10,218 (30.7%)	16,449 (32.3%)	16,808 (33.0%)	-0.01
...3 or more; n (%)	1,804 (20.3%)	1,744 (19.6%)	2,436 (27.9%)	2,403 (27.6%)	13,306 (39.9%)	13,415 (40.3%)	17,546 (34.5%)	17,562 (34.5%)	0.00
Frailty Score: Empirical Version 365 days as Categories,									
...< 0.12908; n (%)	1,119 (12.6%)	1,228 (13.8%)	1,240 (14.2%)	1,338 (15.4%)	1,500 (4.5%)	1,563 (4.7%)	3,859 (7.6%)	4,129 (8.1%)	-0.02
...0.12908 - 0.1631167; n (%)	2,577 (29.0%)	2,521 (28.4%)	2,640 (30.3%)	2,578 (29.6%)	5,589 (16.8%)	5,398 (16.2%)	10,806 (21.2%)	10,497 (20.6%)	0.01
...>= 0.1631167; n (%)	5,184 (58.4%)	5,131 (57.8%)	4,836 (55.5%)	4,800 (55.1%)	26,230 (78.7%)	26,358 (79.1%)	36,250 (71.2%)	36,289 (71.3%)	0.00
Non-Frailty; n (%)	4,985 (56.1%)	5,157 (58.1%)	4,680 (53.7%)	4,703 (54.0%)	1,469 (4.4%)	1,398 (4.2%)	11,134 (21.9%)	11,258 (22.1%)	0.00
Frailty Score (mean): Qualitative Version 365 days, v1									
...mean (sd)	1.34 (1.92)	1.33 (1.90)	1.80 (1.89)	1.79 (1.89)	2.36 (2.43)	2.36 (2.39)	2.09 (2.26)	2.08 (2.23)	0.00
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]	2.00 [0.00, 4.00]	2.00 [0.00, 4.00]	1.65 (2.26)	1.65 (2.23)	0.00
Frailty Score (mean): Empirical Version 365 days,									
...mean (sd)	0.19 (0.06)	0.18 (0.06)	0.17 (0.05)	0.17 (0.05)	0.21 (0.07)	0.21 (0.07)	0.20 (0.07)	0.20 (0.07)	0.00
...median [IQR]	0.17 [0.14, 0.21]	0.17 [0.14, 0.21]	0.16 [0.14, 0.20]	0.16 [0.14, 0.19]	0.20 [0.17, 0.25]	0.20 [0.17, 0.25]	0.19 (0.07)	0.19 (0.07)	0.00
Healthcare Utilization									
Any hospitalization; n (%)	951 (10.7%)	916 (10.3%)	906 (10.4%)	897 (10.3%)	4,351 (13.1%)	4,278 (12.8%)	6,208 (12.2%)	6,091 (12.0%)	0.01
Any hospitalization within prior 30 days; n (%)	309 (3.5%)	317 (3.6%)	272 (3.1%)	263 (3.0%)	1,445 (4.3%)	1,387 (4.2%)	2,026 (4.0%)	1,967 (3.9%)	0.01
Any hospitalization during prior 31-180 days; n (%)	693 (7.8%)	651 (7.3%)	677 (7.8%)	677 (7.8%)	3,166 (9.5%)	3,174 (9.5%)	4,536 (8.9%)	4,502 (8.8%)	0.00
Endocrinologist Visit; n (%)	1,343 (15.1%)	1,478 (16.6%)	1,393 (16.0%)	1,466 (16.8%)	5,278 (15.8%)	5,440 (16.3%)	8,014 (15.7%)	8,384 (16.5%)	-0.02
Endocrinologist Visit (30 days prior); n (%)	991 (11.2%)	1,058 (11.9%)	1,024 (11.7%)	1,071 (12.3%)	3,820 (11.5%)	3,835 (11.5%)	5,835 (11.5%)	5,964 (11.7%)	-0.01
Endocrinologist Visit (31 to 180 days prior); n (%)	887 (10.0%)	950 (10.7%)	917 (10.5%)	947 (10.9%)	3,673 (11.0%)	3,706 (11.1%)	5,477 (10.8%)	5,603 (11.0%)	-0.01
Internal medicine/family medicine visits; n (%)	7,278 (82.0%)	7,050 (79.4%)	7,636 (87.6%)	7,551 (86.6%)	28,049 (84.2%)	27,792 (83.4%)	42,963 (84.4%)	42,393 (83.3%)	0.03
Internal medicine/family medicine visits (30 days prior) ; n (%)	5,304 (59.7%)	5,228 (58.9%)	5,717 (65.6%)	5,661 (64.9%)	20,249 (60.8%)	20,237 (60.7%)	31,270 (61.4%)	31,126 (61.1%)	0.01
Internal medicine/family medicine visits (31 to 180 days prior) ; n (%)	6,220 (70.0%)	6,222 (70.1%)	6,651 (76.3%)	6,585 (75.6%)	24,952 (74.9%)	25,013 (75.1%)	37,823 (74.3%)	37,820 (74.3%)	0.00
Cardiologist visit; n (%)	3,365 (37.9%)	3,383 (38.1%)	2,819 (32.3%)	2,869 (32.9%)	14,336 (43.0%)	14,230 (42.7%)	20,520 (40.3%)	20,482 (40.2%)	0.00
Number of Cardiologist visits (30 days prior); n (%)	1,244 (14.0%)	1,238 (13.9%)	963 (11.0%)	974 (11.2%)	4,841 (14.5%)	4,850 (14.6%)	7,048 (13.8%)	7,062 (13.9%)	0.00
Number of Cardiologist visits (31 to 180 days prior); n (%)	2,851 (32.1%)	2,880 (32.4%)	2,408 (27.6%)	2,477 (28.4%)	12,553 (37.7%)	12,531 (37.6%)	17,812 (35.0%)	17,888 (35.1%)	0.00
Electrocardiogram ; n (%)	3,280 (36.9%)	3,359 (37.8%)	3,176 (36.4%)	3,230 (37.1%)	13,574 (40.7%)	13,706 (41.1%)	20,030 (39.3%)	20,295 (39.9%)	-0.01
Use of glucose test strips; n (%)	423 (4.8%)	427 (4.8%)	410 (4.7%)	399 (4.6%)	1,375 (4.1%)	1,338 (4.0%)	2,208 (4.3%)	2,164 (4.3%)	0.00
Dialysis; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	000 (0.0%)	000 (0.0%)	#DIV/0!
Naive new user ; n (%)	2,349 (26.5%)	2,521 (28.4%)	2,348 (26.9%)	2,409 (27.6%)	7,673 (23.0%)	8,355 (25.1%)	12,370 (24.3%)	13,285 (26.1%)	-0.04

Table 1: Linagliptin vs 2nd Generation Sulfonylureas

N antidiabetic drugs at index date									
...mean (sd)	1.76 (0.70)	1.75 (0.68)	1.77 (0.72)	1.77 (0.70)	1.73 (0.70)	1.73 (0.67)	1.74 (0.70)	1.74 (0.68)	0.00
...median [IQR]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 (0.70)	2.00 (0.68)	0.00
number of different/distinct medication prescriptions									
...mean (sd)	11.06 (5.30)	11.07 (5.36)	10.74 (5.13)	10.66 (5.07)	11.45 (5.09)	11.45 (5.01)	11.26 (5.13)	11.25 (5.08)	0.00
...median [IQR]	10.00 [7.00, 14.00]	10.00 [7.00, 14.00]	10.00 [7.00, 13.00]	10.00 [7.00, 14.00]	11.00 [8.00, 14.00]	11.00 [8.00, 14.00]	10.65 (5.13)	10.65 (5.08)	0.00
Number of Hospitalizations									
...mean (sd)	0.13 (0.41)	0.13 (0.41)	0.12 (0.38)	0.12 (0.39)	0.17 (0.48)	0.16 (0.48)	0.15 (0.45)	0.15 (0.45)	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 (0.45)	0.00 (0.45)	0.00
Number of hospital days									
...mean (sd)	0.65 (2.51)	0.67 (2.66)	0.63 (2.74)	0.66 (2.86)	1.03 (3.87)	1.02 (3.97)	0.90 (3.49)	0.90 (3.60)	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 (3.49)	0.00 (3.60)	0.00
Number of Emergency Department (ED) visits									
...mean (sd)	0.50 (1.18)	0.49 (1.40)	0.19 (1.07)	0.19 (1.26)	0.63 (1.43)	0.63 (1.44)	0.53 (1.33)	0.53 (1.40)	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 (1.33)	0.00 (1.40)	0.00
Number of Office visits									
...mean (sd)	5.54 (4.50)	5.53 (4.36)	5.93 (5.53)	5.86 (4.31)	6.33 (4.88)	6.36 (4.75)	6.12 (4.93)	6.13 (4.61)	0.00
...median [IQR]	4.00 [2.00, 7.00]	5.00 [3.00, 7.00]	5.00 [3.00, 8.00]	5.00 [3.00, 8.00]	5.00 [3.00, 9.00]	5.00 [3.00, 9.00]	4.83 (4.93)	5.00 (4.61)	-0.04
Number of Endocrinologist visits									
...mean (sd)	0.69 (2.65)	0.80 (2.89)	0.72 (2.77)	0.83 (3.11)	0.94 (3.83)	0.94 (3.69)	0.86 (3.48)	0.90 (3.47)	-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, 0.00]	0.00 (3.48)	0.00 (3.47)	0.00
Number of internal medicine/family medicine visits									
...mean (sd)	10.20 (14.44)	9.35 (14.18)	7.99 (10.52)	7.84 (10.00)	8.97 (12.50)	8.98 (11.60)	9.02 (12.55)	8.85 (11.84)	0.01
...median [IQR]	6.00 [2.00, 13.00]	5.00 [1.00, 12.00]	5.00 [2.00, 10.00]	5.00 [2.00, 10.00]	5.00 [2.00, 12.00]	6.00 [2.00, 12.00]	5.17 (12.55)	5.65 (11.84)	-0.04
Number of Cardiologist visits									
...mean (sd)	1.85 (4.06)	1.95 (4.53)	1.46 (3.59)	1.47 (3.43)	2.25 (5.02)	2.33 (5.16)	2.04 (4.64)	2.12 (4.80)	-0.02
...median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 (4.64)	0.00 (4.80)	0.00
Number electrocardiograms received									
...mean (sd)	0.76 (1.49)	0.76 (1.50)	0.68 (1.29)	0.67 (1.22)	0.86 (1.52)	0.86 (1.50)	0.81 (1.48)	0.81 (1.46)	0.00
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (1.48)	0.00 (1.46)	0.00
Number of HbA1c tests ordered									
...mean (sd)	1.31 (0.95)	1.30 (0.94)	0.99 (0.95)	0.98 (0.93)	1.47 (1.03)	1.47 (0.91)	1.36 (1.00)	1.36 (0.92)	0.00
...median [IQR]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	1.00 (1.00)	1.00 (0.92)	0.00
Number of glucose tests ordered									
...mean (sd)	0.80 (6.63)	0.93 (7.31)	0.49 (2.13)	0.49 (1.26)	0.55 (1.52)	0.57 (1.31)	0.58 (3.16)	0.62 (3.27)	-0.01
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (3.16)	0.00 (3.27)	0.00
Number of lipid tests ordered									
...mean (sd)	1.04 (1.03)	1.03 (1.00)	0.85 (1.36)	0.86 (1.33)	1.08 (0.95)	1.08 (0.89)	1.03 (1.05)	1.03 (1.00)	0.00
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	1.00 [0.00, 1.00]	1.00 [0.00, 1.00]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	1.00 (1.05)	1.00 (1.00)	0.00
Number of creatinine tests ordered									
...mean (sd)	0.06 (0.33)	0.07 (0.47)	0.07 (0.44)	0.07 (0.58)	0.10 (0.47)	0.09 (0.40)	0.09 (0.44)	0.08 (0.45)	0.02
...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 (0.44)	0.00 (0.45)	0.00
Number of BUN tests ordered									
...mean (sd)	0.04 (0.27)	0.04 (0.38)	0.04 (0.38)	0.05 (0.58)	0.06 (0.39)	0.06 (0.32)	0.05 (0.37)	0.05 (0.39)	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 (0.37)	0.00 (0.39)	0.00
Number of tests for microalbuminuria									
...mean (sd)	0.89 (1.29)	0.87 (1.32)	0.58 (1.12)	0.57 (1.04)	0.56 (0.85)	0.56 (0.84)	0.62 (0.99)	0.62 (0.98)	0.00
...median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 (0.99)	0.00 (0.98)	0.00
Total N distinct ICD9/ICD10 diagnoses at the 3rd digit level									
...mean (sd)	7.43 (8.69)	7.35 (8.77)	2.83 (5.33)	2.85 (5.39)	7.78 (9.41)	7.69 (9.43)	6.87 (8.72)	6.80 (8.75)	0.01
...median [IQR]	5.00 [0.00, 11.00]	5.00 [0.00, 11.00]	0.00 [0.00, 4.00]	0.00 [0.00, 4.00]	5.00 [0.00, 12.00]	5.00 [0.00, 12.00]	4.14 (8.72)	4.14 (8.75)	0.00
Use of thiazide; n (%)	1,042 (11.7%)	1,075 (12.1%)	1,002 (11.5%)	1,005 (11.5%)	4,626 (13.9%)	4,591 (13.8%)	6,670 (13.1%)	6,671 (13.1%)	0.00
Use of beta blockers; n (%)	4,537 (51.1%)	4,527 (51.0%)	4,436 (50.9%)	4,413 (50.6%)	19,108 (57.3%)	19,031 (57.1%)	28,081 (55.2%)	27,971 (54.9%)	0.01
Use of calcium channel blockers; n (%)	2,943 (33.1%)	3,037 (34.2%)	2,769 (31.8%)	2,780 (31.9%)	13,117 (39.4%)	12,995 (39.0%)	18,829 (37.0%)	18,812 (36.9%)	0.00