Replication of the LEAD-2 Trial in Healthcare Claims

RCT DUPLICATE – LEAD-2

August 4, 2021

1. RCT Details

This section provides a high-level overview of a **published** 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

Efficacy and Safety Comparison of Liraglutide, Glimepiride, and Placebo, All in Combination With Metformin, in Type 2 Diabetes. The LEAD (Liraglutide Effect and Action in Diabetes)-2 study (NCT00318461).

1.2 Intended aim(s)

To assess whether the glycemic control achieved by adding liraglutide to metformin was non-inferior to glimepiride and metformin combination therapy after 26 weeks of treatment, in subjects with type 2 diabetes and previously treated with oral antidiabetic therapy.

1.3 Primary endpoint for replication

Long-term glycemic control defined as change in HbA1c from baseline to the end of follow-up.

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

The sample size calculation was based on both HbA1c and body weight endpoints. The assumed standard deviation for HbA1c and the coefficient of variance for body weight were 1.2% and 3%, respectively. The combined power (calculated as the product of the marginal powers for HbA1c and body weight) was at least 85%. Noninferiority of glycemic control with liraglutide versus glimepiride was concluded if the upper limit of the two-sided 95% CI for the treatment difference was < 0.4%.

With a standard deviation of 1.2% for HbA1c and a coefficient of variance of 3% for body weight, it was concluded that at least 168 subjects were required to complete the treatment in the liraglutide and in the glimepiride, respectively. Assuming a dropout rate of 25% after 26 weeks of treatment, the number of subjects to be randomized was calculated to be 228 in each of the liraglutide and glimepiride treatment groups.

1.5 Secondary endpoint for replication (assay sensitivity) and RCT finding

n/a

1.6 Trial estimate

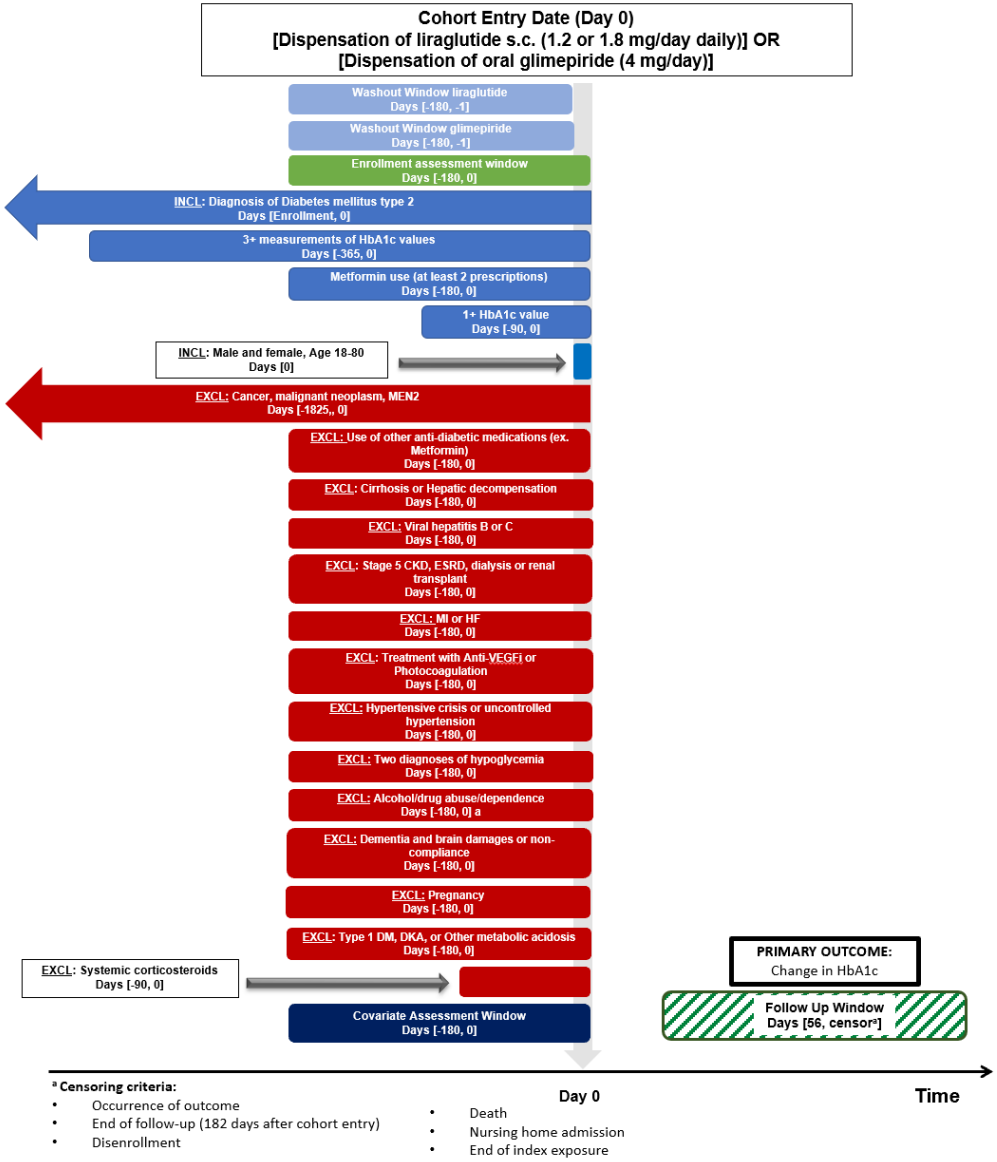
The HbA1c mean decreases of 1.0% (± 0.1) for both the 1.2 and 1.8 mg/day liraglutide groups and 1.0% (± 0.1) for glimepiride group. Treatment difference in HbA1c was 0.0% [95% CI: -0.2 to 0.2] for both comparisons liraglutide 1.2 mg/day versus glimepiride and liraglutide 1.8 mg/day versus glimepiride (Nauck M et al. 2009).

2. **Person responsible for implementation of replication in Aetion**
   Elvira D'Andrea, MD, MPH, implemented the study design in the Aetion Evidence Platform and SAS 9.4. She 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)**
   Optum CDM

4. **Study Design Diagram**
   The study design diagram visualizes key aspects of the longitudinal study design for expedited review.

Figure 1. Design Diagram – LEAD-2 TRIAL REPLICATION



5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, propensity score-matched, retrospective cohort design comparing injectable subcutaneous liraglutide (1.2 or 1.8 mg/day) to oral glimepiride (4 mg once daily). Treatments in both arms are administered in combination with metformin (up to 2,000 mg/day). Patients will be required to have continuous enrollment during a baseline period of 180 days before initiation of liraglutide or glimepiride. The analyses will be restricted to individuals with type 2 diabetes mellitus who have been previously treated with antidiabetic drugs. In the replication, previous anti-diabetic treatment was defined as the presence of at least 2 prescriptions for metformin within 6 months before and including cohort entry.

5.2 Important steps for cohort formation

New use of liraglutide (exposure) is defined as no use of the exposure drug within 180 days prior to index date. New use of glimepiride (comparator) is defined as no use of the comparator drug within 180 days prior to index date. Eligible patients are required to be new users with respect to both exposure and comparator groups (i.e., no use of both exposure and comparator drugs) within 180 days prior to index date.

5.2.1 Eligible cohort entry dates

Liraglutide indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus was approved by FDA on Jan 25, 2010 (the approval of glimepiride for the same indication was antecedent to 2010). Thus, the initial eligible cohort entry date is the first date after the FDA approval available in the data.

The last eligible date is June 30, 2020, three months before the end of all available data in Optum CDM. Since the effects of liraglutide and glimepiride on the outcome (i.e., change in HbA1c) will be estimated between 56 and 212 days after cohort entry (see Section 6.3), this will allow all eligible patients to contribute to the outcome.

The database used is Optum CDM because lab results/values are available in this database for a subset of laboratory tests, including the A1C tests. The following eligible cohort entry dates were included:

- Optum CDM: Jan 26, 2010 – Jun 30, 2020

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.

Note. Patients who are censored between cohort entry and the beginning of the outcome assessment window (i.e., 0.x-56 days after cohort entry) for the reasons reported in the Section 6.3.2 will not contribute to the unmatched or matched cohorts. Further details on the number of patients who are excluded from the study cohort are reported in the Section 7.

5.3 Flowchart of the study cohort assembly

For liraglutide vs. glimepiride: Aetion link: https://bwh-dope.aetion.com/cohorts/details/23482/1688/71700

	Optum	
	Excluded Patients	**Remaining Patients**
All patients		79,335,559
Did not meet cohort entry criteria	-78,554,666 (99%)	780,893
Excluded due to insufficient enrollment	-119,528 (15%)	661,365
Excluded due to prior use of referent	-424,186 (64%)	237,179
Excluded due to prior use of exposure	-138,679 (58%)	98,500
Excluded because patient qualified in >1 exposure category	-85 (<1%)	98,415
Excluded based on nursing home admission in the prior 180 days	-3,784 (4%)	94,631
Excluded based on gender missing or unknown	-10 (<1%)	94,621
Excluded based on Inclusion #1.1 - Type 2 diabetes mellitus	-6,027 (6%)	88,594
Excluded based on Inclusion #1.2 - Metformin use (2 prescriptions within 183 days)	-55,832 (63%)	32,762
Excluded based on Inclusion #1.3 - Concomitant initiation or concurrent use of metformin	-3,670 (11%)	29,092
Excluded based on Inclusion #1.4 - No use of other anti-diabetic meds	-9,861 (34%)	19,231
Excluded based on Inclusion #2.1 - 3 records of HbA1c 2-20% values/results within 365 days	-13,962 (73%)	5,269
Excluded based on Inclusion #2.2 - At least 1 lab value HbA1c 7-11% recorded within 90 days	-808 (15%)	4,461
Excluded based on Inclusion #3.1 - Age > 18	-0 (<1%)	4,461
Excluded based on Inclusion #3.2 - Age < 80	-87 (2%)	4,374
Excluded based on Exclusion #1 - Morbid Obesity BMI > 40	-147 (3%)	4,227
Excluded based on Exclusion #2 - Any insulin use	-234 (6%)	3,993
Excluded based on Exclusion #3 - End-stage liver disease	-9 (<1%)	3,984
Excluded based on Exclusion #4 - Viral Hepatitis B and C	-7 (<1%)	3,977
Excluded based on Exclusion #5 - CKD stage 5, End-stage renal disease, dialysis, or renal transplant	-0 (<1%)	3,977

Excluded based on Exclusion #6.1 - Myocardial Infarction	-1 (<1%)	3,976
Excluded based on Exclusion #6.2 - Heart Failure	-1 (<1%)	3,975
Excluded based on Exclusion #7 - Anti-VEGFi OR Photocoagulation	-5 (<1%)	3,970
Excluded based on Exclusion #8 - Uncontrolled hypertension	-34 (<1%)	3,936
Excluded based on Exclusion #9 - Malignant neoplasm (except non-melanoma skin cancer)	-79 (2%)	3,857
Excluded based on Exclusion #10 - Recurrent Hypoglycemia	-8 (<1%)	3,849
Excluded based on Exclusion #11 - Systemic glucocorticoids use	-48 (1%)	3,801
Excluded based on Exclusion #12 - Drug addiction or alcohol abuse and dependence	-11 (<1%)	3,790
Excluded based on Exclusion #13 - Mental incapacity, unwillingness to comply	-13 (<1%)	3,777
Excluded based on Exclusion #14 - Pregnancy	-0 (<1%)	3,777
Excluded based on Exclusion #15.1 - Type 1 diabetes mellitus (contraindication glimepiride)	-10 (<1%)	3,767
Excluded based on Exclusion #15.2 - Diabetic ketoacidosis (contraindication glimepiride)	-2 (<1%)	3,765
Excluded based on Exclusion #15.3 - Other metabolic acidosis (contraindication glimepiride)	-1 (<1%)	3,764
Excluded based on Exclusion #16 - Multiple endocrine neoplasia type 2 (MEN2)	-0 (<1%)	3,764
Final cohort		3,764

6. Variables

6.1 Exposure-related variables:

Study drug:

New initiation of injectable subcutaneous liraglutide (1.2 or 1.8 mg/day), a glucagon-like peptide-1 receptor agonist. New initiation is defined as no use of liraglutide within 180 days before treatment initiation (washout period). New users of liraglutide are not allowed to receive glimepiride within 180 days prior to treatment initiation. Concurrent use of metformin is required (2,000 mg/day).

Comparator agent:

New initiation of oral glimepiride (4 mg once daily). New initiation is defined as no use of glimepiride within 180 days before treatment initiation (washout period). New users of glimepiride are not allowed to receive liraglutide within 180 days prior to treatment initiation. Concurrent use of metformin is required (2,000 mg/day).

6.2 Preliminary Covariates:

- Age
- Gender
- 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**).

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

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

- **Primary outcome:** Changes in HbA1c from baseline to 26 weeks of treatment (end of follow-up).

  Note**.** In the trial, HbA1c was also measured at 8, 12, 18 weeks (± 3 days) after randomization. Missing values of HbA1c at 26 weeks were replaced using last observation carried forward (LOCF) in the intention-to-treat (ITT) analysis set.
  In the replication, *HbA1c at baseline* will be defined as the last recorded HbA1c value measured within 90 days before and including cohort entry date in both groups. *HbA1c at the end of follow-up* will be defined as a recorded HbA1c value closest to the end of the 26^{th} week and measured between 56 and 212 days (8-30 weeks) after cohort entry.

- **Secondary outcome**: --

6.3.2 Primary analysis and study follow-up

As-treated (AT) analysis will be performed as main analysis. The treatment drug will be defined as the index drug assigned on the day of cohort entry. Patients will be followed for about 30 weeks (212 days). Compared to the trial (Nauck M et al. 2009), we will

extend the follow-up and the outcome assessment periods of 4 weeks. The follow-up and outcome assessment window will start 56 days after cohort entry date and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest (measured between 56 and 212 days after cohort entry),
- The date of end of continuous registration in the database (disenrollment or end of available data),
- End of the study period,
- Measured death event occurs,
- Index drugs discontinuation (liraglutide, glimepiride or metformin),
- Crossover or addition of drug from the other treatment group,
- Addition of any other anti-diabetic medications,
- 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.

Note. To decrease the incidence of missing values of the outcome (specifically, missing of HbA1c values measured between 56-212 days after cohort entry), we required that the eligible patients had at least 3 HbA1c measurements recorded within 365 days before and including cohort entry. This will increase the probability of including in the final cohort patients who are adherent to a routinely HbA1c testing and, consequently, will decrease the frequency of missing values of the outcome. Multiple imputation will be used to handle missing values in the primary analysis, while complete case analysis will be applied in a sensitivity analysis.

7. Initial Feasibility Analysis

Aetion report name:

For liraglutide vs. glimepiride
Optum CDM (continuous HbA1c outcome) https://bwh-dope.aetion.com/projects/details/1688/rwrs/71723
Optum CDM (binary HbA1c outcome [flag: presence or absence of an HbA1c result within 56-212 days after cohort entry]) – calculated merging the databases from https://bwh-dope.aetion.com/projects/details/1688/rwrs/71715 and https://bwh-dope.aetion.com/projects/details/1688/rwrs/71716 – see file LEAD-2_programming_steps and output of "STEP 1 - Initial FEASIBILITY Analysis (with study outcome) - Paragraph 7 of the protocol"

Date conducted: 06/17/2021

Complete Aetion feasibility analysis using age 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 mean and standard deviation of the HbA1c outcome stratified by treatment group.

- Report patient characteristics by treatment group
  For liraglutide vs. glimepiride

	Optum CDM		
	Glimepiride - Comparator	**Liraglutide - Exposure**	**Difference**
Number of patients *	3,096	378	- (-, -)
Age			
...mean (sd)	64.24 (10.37)	59.22 (10.94)	5.02 (3.90, 6.13)
...median [IQR]	67.00 [58.00, 72.00]	60.00 [51.00, 68.00]	- (-, -)
Gender			
...M = MALE; n (%)	1,726 (55.7%)	179 (47.4%)	8.39% (3.08%, 13.7%)
...F = FEMALE; n (%)	1,370 (44.3%)	199 (52.6%)	-8.39% (-13.7%, -3.08%)
Combined Comorbidity Score - CCI (180 days)			
...mean (sd)	2.06 (1.56)	1.86 (1.36)	0.19 (0.03, 0.36)
...median [IQR]	2.00 [1.00, 3.00]	2.00 [1.00, 2.00]	- (-, -)

* The overall n. of patients in the unmatched cohort is 3,470. Patients who were censored between cohort entry and the beginning of the outcome assessment window (n. 290 patients) are excluded from the Table reporting patient characteristics by groups because they will not contribute to the unmatched or matched cohorts.

- Report summary parameters of study population **FEASIBILITY- FOR STUDY OUTCOME**
  For liraglutide vs. glimepiride

	Optum CDM
Number of patients in full cohort	3,764
Number of patients that did not begin follow-up *	290
Number of patients	3,474
Number of person-years of patients that did begin the follow-up	1,118.53
Number of patients in group: Glimepiride	3,096
Number of patients in group: Liraglutide	378
Outcome - Lab value HbA1c	
...mean (sd)	7.24 (1.01)
...median [IQR]	7.00 [6.60, 7.70]
...minimum	4.1
...maximum	13.4
Number of patients with zero value	0
Non-zero mean value (SD)	7.24 (1.01)
Non-zero median value [IQR]	7.00 [6.60, 7.70]

* patients who were censored between cohort entry and the beginning of the outcome assessment window/follow-up (i.e., 0.5-56 days after cohort entry) will not contribute to the unmatched and matched cohorts.

- Report median follow-up time by treatment group

  For liraglutide vs. glimepiride

Median Follow-Up Time (Days) [IQR] – AT analysis	
Patient Group	**Optum CDM**
Overall Patient Population	99 [84, 148]
Referent	101 [84, 148]
Exposure	88 [79, 130]

- Report reasons for censoring in the overall study population

- **For** liraglutide vs. glimepiride

	Overall (n. 3,470)	Liraglutide (n. 378)	Glimepiride (n. 3,092)
Outcome *	2,262 (65.2%)	233 (61.6%)	2,029 (65.6%)
Death	2 (0.1%)	0 (0%)	2 (0.1%)
Start of an additional exposure	8 (0.2%)	3 (0.8%)	5 (0.2%)
End of index exposure	368 (10.6%)	74 (19.6%)	294 (9.5%)
Maximum follow-up time	336 (9.7%)	22 (5.8%)	314 (10.2%)
End of patient data	37 (1.0%)	3 (0.8%)	34 (1.1%)
End of patient enrollment	108 (3.1%)	12 (3.2%)	96 (3.1%)
Start of additional antidiabetic drugs + Nursing home + Metformin discontinuation with allowed 60 days gap	349 (10.1%)	22 (5.82%)	314 (10.2%)

* patients with outcome recorded between 56-212 days after cohort entry.

- Report overall mean (sd) of the primary outcome.

	Optum CDM
Outcome – Lab value HbA1c ...mean (sd)	7.24 (1.01)

8. Initial Power Assessment

Analysis report name:

For liraglutide vs. glimepiride

Optum CDM – see file LEAD-2_programming_steps and output of "STEP 2 - INITIAL POWER Assessment - PS matching on age, gender, CCI (with dummy outcome) - Paragraphs 8 of the protocol"

Date conducted: 06/16/2021

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, gender and combined comorbidity index. Power calculations are based on the formulas from Julios 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.

    - Optum CDM

Non-inferiority Analysis	
Standard deviation of outcome	1.01
Non-inferiority limit	0.4
Alpha (2-sided)	0.05
Power (1-beta)	90%
Sample size required per group	110
Total sample size required	220
Number of patients matched	752
Reference	376
Exposed	376

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

Reviewed by PI:	Shirley Wang	Date reviewed:	07/16/2021
Reviewed by FDA:	Ken Quinto	Date reviewed:	08/2/2021
Reasons for stopping analysis (if required):			

9. Balance Assessment

For liraglutide vs. glimepiride

Optum CDM: see file LEAD-2_programming_steps and output of "STEP 3 - BALANCE Assessment (with dummy outcome) - Paragraphs 9-10 of the protocol"

Date conducted: 06/16/2021

After review of initial feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. 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.

- 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 (n. 746)	**Liraglutide – exposure (n. 373)**	**Glimepiride – comparator (n. 373)**
Outcome (dummy)	0 (0%)	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)	0 (0%)
Start of an additional exposure	9 (1.2%)	6 (0.8%)	3 (0.4%)
End of index exposure	194 (26.0%)	137 (18.4%)	57 (7.6%)
Maximum follow-up time	340 (45.6%)	137 (18.4%)	203 (27.2 %)
End of patient data	5 (0.7%)	3 (0.4%)	2 (0.3%)
End of patient enrollment	61 (6.3%)	25 (3.4%)	36 (4.8%)
Start of additional antidiabetic drugs + Nursing home + Metformin discontinuation with allowed 60 days gap	137 (18.4%)	65 (8.7%)	72 (9.7%)

- Report follow-up time by treatment group.

Median Follow-Up Time (Days) [IQR]			
Patient Group	**Overall (n. 746)**	**Liraglutide (n. 373)**	**Glimepiride (n. 373)**
Overall Patient Population	188 [97 - 212]	150 [89 - 212]	212 [119 -212]

- Report overall mean (sd) of the primary outcome (from initial feasibility analysis).

	Optum CDM
Outcome – Lab value HbA1c ...mean (sd)	7.24 (1.01)

10. Final Power Assessment

Date conducted:

- 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.

Non-inferiority Analysis	
Standard deviation of outcome	1.01
Non-inferiority limit	0.4
Alpha (2-sided)	0.05
Power (1-beta)	90%
Sample size required per group	110
Total sample size required	220
Number of patients matched	746
Reference	373
Exposed	373

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

Reviewed by PI:	Shirley Wang	Date reviewed:	07/16/2021
Reviewed by FDA:	Ken Quinto	Date reviewed:	08/2/2021
Reasons for stopping analysis (if required):			

11. Study Confidence and Concerns

Deadline for voting on study confidence and listing concerns:
Date votes and concerns are summarized:

- 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.

- After the deadline for voting has passed, provide the distribution of responses and summarize all concerns here.

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:

13.2 For sensitivity analyses:

14. Requested Results

14.1 Table 1: Baseline characteristics before and after adjustment

Variable	Before adjustment			After adjustment		
	Referent	Exposure	Std. diff.	Referent	Exposure	Std. diff.
Number of patients			-			-
Age categories						
…						

14.2 Table 2: Follow-up time

Patient Group	**Median Follow-Up Time (Days) [IQR]**
Overall Patient Population	
Referent	
Exposure	

14.3 Table 3: Censoring events

	Overall	**Referent**	**Exposure**
Outcome			
Death			
Start of an additional exposure			
End of index exposure			
Specified date reached			
End of patient data			
End of patient enrollment			
…			

14.4 Table 4: Results from primary analyses;

Analysis	**No. exposed events**	**No. referent events**	**Exposed rate**	**Referent rate**	**HR (95% CI)**
Crude					
Analysis 1					
Analysis 2					
...					

HR, Hazard Ratio; CI, Confidence Interval.

14.5 Table 5: Results from secondary analyses.

15. References

Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, Düring M, Matthews DR; LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care. 2009 Jan;32(1):84-90. doi: 10.2337/dc08-1355.

Julious SA. Sample sizes for clinical trials with Normal data. Statist. Med. 2004; 23:1921-1986. Sealed Envelope Ltd. 2012. Power calculator for continuous outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/continuous-noninferior/ [Accessed Fri May 07, 2021].

Appendix A

#	LEAD-2 trial definitions	Implementation in routine care	Please see the following Google Drive for further details or any missing information: https://drive.google.com/drive/folders/1WD618wrvwYjEaXzfLTcuK-VCcnb6b-gV?usp=sharing	
Trial details - clinicaltrial.gov NCT00318461			**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**	
EXPOSURE vs. COMPARISON			References/Rationale	Color coding
	Exposure: Liraglutide s.c. 0.6 mg/day, 1.2 mg/day and 1.8 mg/day in combination with metformin (1500-2000 mg/day) for 26 weeks Reference for non-inferiority: Glimepiride (4 mg/day) in combination with metformin (1500-2000 mg/day) Reference for superiority: Metformin monotherapy (1500-2000 mg/day) Aim: To evaluate whether the effect on glycaemic control (as measured by change in HbA1c) of treatment with 0.6 mg/day, 1.2 mg/day and 1.8 mg/day of liraglutide in combination with metformin was superior to metformin monotherapy and non-inferior to metformin and glimepiride combination therapy after 26 weeks of treatment.	Exposure: new-use of Liraglutide (washout **180 days**) in combination with metformin **NDC Generic Name:** LIRAGLUTIDE **NDC Brand name:** Viktoza (FlexPen) Reference: new use of Glimepiride (washout **180 days**) in combination with metformin **NDC Generic Name:** GLIMEPIRIDE **NDC Brand name:** GLIMEPIRIDE AMARYL		Criteria
PRIMARY OUTCOME				Adequate mapping in claims
	Change in HbA1c from baseline to week 26 Note: in the trial missing values are replaced with last value carried forward [LVCF]	**Measured as change in HbA1c from baseline to the last recorded HbA1c value between 56 and 212 days after drug initiation:** Loinc codes: 17855-8, 17856-6, 41995-2, 43150-2, 4548-4, 4549-2, 55454-3, 71875-9, 74246-0		Intermediate mapping in claims
INCLUSION CRITERIA				Poor mapping or cannot be measured in claims
0	Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the subject).	N/A		Can't be measured in claims but not important for the analysis
1	**(1.1)** Subjects diagnosed with type 2 diabetes and **(1.2)** treated with OAD(s) for at least three months.	**1.1 Selecting patients with a diagnosis of type 2 diabetes measured from the time of enrollment to the day of drug initiation inpatient (any position), outpatient (any position):** Type 2 diabetes: ICD 9 diagnosis: 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92 ICD 10 diagnosis: E11.x **1.2 Selecting patients with at least two prescriptions of metformin within 183 days before cohort entry (OADs treatment ≥ 3 months), and** **1.3 Concomitant or current use of metformin at cohort entry date in both treatment groups:** Generic name: Metformin Hcl **1.4 Selecting patients with no other anti-diabetic treatments within the 180 days before cohort entry:** Please refer to ***Anti-diabetic treatments (other than insulin)*** in "Anti-diabetic treatment"		
2	HbA1c: − 7.0-10.0% (both incl.) in subjects on OAD combination therapy − 7.0-11.0% (both incl.) in subjects on OAD monotherapy.	**2.1 Selecting patients with 3 measurements of HbA1c values (between 2-20%) recorded within 365 days prior to and including cohort entry:** Loinc codes: 17855-8, 17856-6, 41995-2, 43150-2, 4548-4, 4549-2, 55454-3, 71875-9, 74246-0 AND Result value 2-20% **2.2 Selecting patients with at least one measurement of HbA1c value (between and included 7-11%) recorded within the last 91 days prior to and including cohort entry:** Loinc codes: 17855-8, 17856-6, 41995-2, 43150-2, 4548-4, 4549-2, 55454-3, 71875-9, 74246-0 AND Result value 7-11%		
3	Age 18-80 years, both inclusive (as allowed according to local guidelines for metformin and glimepiride treatment). This inclusion criterion has been modified for Site 344 in Australia according to Substantial Protocol Amendment No. 1-AU, see Section 9.8.1.	Female and male, 18-80 years at the time of drug initiation		
EXCLUSION CRITERIA				

Appendix A

1	Body mass index (BMI) >= 40.0 kg/m2.	**Measured 180 days prior to and including the day of drug initiation inpatient (any position), outpatient (any position):** Morbid obesity diagnosis or BMI >= 40 kg/m2: ICD 9 diagnosis:: 278.01, 278.03, V85.4x ICD 10 diagnosis: E66.01, E66.2, Z68.4x NB. Codes for bariatric surgey, complications of bariatric surgery and prescriptions of drugs for weight loss were not included in the measure since this exclusion criterion aims to exclude specifically patients with morbid obesity. Codes for obesity during pregnancy were not included because of the exclusion criterion #17.	
2	Treatment with insulin within the last three months prior to trial (except for short-term treatment due to intercurrent illness at the discretion of the investigator).	**Measured 180 days prior to and including the day of drug initiation:** NDC Generic Name: Please refer to ***Insulin*** in "Anti-diabetic treatments" NB. Although the trial excluded patients in treatment with insulin within the 90 days before drug initiation, with real-world data we are required to be more conservative and to extend the washout period to 180 days. In fact, a 90-day washout applied in real world does not guarantee the exclusion of prevalent users (i.e. patients on active insulin therapy) from the cohort.	
3	Impaired liver function, defined as alanine aminotransferase (ALAT) >= 2.5 times upper limit of normal (one retest analysed at the central laboratory within a week is permitted with the result of the last sample being conclusive).	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Cirrhosis: ICD-9 Diagnosis: 571.2, 571.5, 571.6 ICD-10 Diagnosis: K70.11, K70.2, K70.3x, K70.4x, K74.x Hepatic decompensation: ICD-9 Diagnosis: 456.0, 456.20, 456.1, 456.21, 789.5, 789.59, 572.2, 567.0, 567.2, 567.21, 567.22, 567.29, 567.8, 567.89, 567.9, 572.4 ICD-10 Diagnosis: R18.x, I85.x, K72.x, K65.x, K66.x, K67 HCC is already excluded with exclusion criterion 9	
4	Subjects known to be Hepatitis B antigen or Hepatitis C antibody positive.	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Viral hepatitis B or C: ICD-9 diagnosis: 070.2x, 070.3x, 070.4x, 070.51, 070.54, 070.71, 070.74, V02.61, V02.62 ICD-10 diagnosis: B16.x, B17.0, B17.1x, B18.0-B18.2, B19.1x, B19.2x, Z22.51, Z22.52	
5	Impaired renal function defined as serum creatinine >= 135 µmol/L (>= 1.5 mg/dL) for males and >= 110 µmol/L (>= 1.3 mg/dL) for females (one retest analysed at the central laboratory within a week is permitted with the result of the last sample being conclusive)	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** CKD stage 5, End-stage renal disease, dialysis or renal transplant: ICD-9 diagnosis: 585.5, 585.6, 996.81, V42.0, V45.1x, V56.xx ICD-9 procedure: 39.95, 54.98, 55.6x ICD-10 diagnosis: N18.5, N18.6, R88.0, T82.41, T82.42, T82.49, T85.611, T85.621, T85.631, T86.1x, Y84.1, Z48.22, Z49.xx, Z91.15, Z94.0, Z99.2 ICD-10 procedure: 0TY00Zx, 0TY10Zx, 3E1M39Z, 5A1Dx0Z CPT: 50360, 50365, 90920, 90921, 90924, 90925, 90935, 90937, 90939, 90940, 90945, 90947, 90957, 90958, 90959, 90960, 90961, 90962, 90965, 90966, 90969, 90970, 90989, 90993, 90999, 90997, 99512, 99559, 99512, G0257, G0314, G0315, G0316, G0317, G0318, G0319, G0322, G0323, G0326, G0327, S9335, S9339	
6	Clinically significant active cardiovascular disease including history of myocardial infarction within the past 6 months and/or heart failure (New York Heart Association class III and IV) at the discretion of the investigator.	**Measured 180 days prior to and including the day of drug initiation in inpatient care setting, any position:** Myocardial Infarction: ICD-9 DX: 410.xx ICD-10 DX: I21.xx, I22.xx **Measured 180 days prior to and including the day of drug initiation in inpatient care setting, primary position:** Heart Failure: ICD-9 DX: 428.xx, 398.91, 402.x1, 404.x1, 404.x3 ICD-10 DX: I09.81, I11.0, I13.0, I13.2, I50.xxx, I97.13x NB. HF is included only if inpatient / primary position to detect the most severe cases as specified in the exclusion criterion of the trial	

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7	Proliferative retinopathy or maculopathy requiring acute treatment as judged by the investigator.	**Measured 180 days prior to and including the day of drug initiation:** Anti-VEGFi CPT: 67028 (Intravitreal injection for pharmacologic agent) AND HCPCS: J9035 OR C9257 OR Q5107 (Bevacizumab 10 mg injection) OR HCPCS: J2778 (Ranibizumab 0.1 mg) OR HCPCS: C9291 OR Q2046 OR J0178 OR C9296 OR J9400 (Aflibercept 2 mg injection) Photocoagulation: CPT: 67228 (Panretinal photocoagulation) OR CPT: 67220 (Focal/Grid photocoagulation) OR CPT: 67028 (Intravitreal injection for pharmacologic agent)	
8	Uncontrolled treated/untreated hypertension (systolic blood pressure >= 180 mmHg and/or diastolic blood pressure >= 100 mmHg).	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position in the inpatient and outpatient and emergency care setting:** Hypertensive crisis ICD-10 diagnosis: I16.x (includes hypertensive urgency, emergency, crisis, unspecified) OR **Measured 180 days prior to and including the day of drug initiation in primary diagnosis position for inpatient or any position for emergency care setting:** Uncontrolled hypertension: ICD-9 diagnosis: 401.9 (unspecified essential hypertension) 401.0 (malignant essential hypertension) 402.0x (malignant hypertensive heart disease) 403.0x (malignant hypertensive kidney disease) 404.0x (malignant hypertensive heart and kidney disease) 405.0x (malignant secondary hypertension) 403.9x (unspecified hypertensive kidney disease) 796.2 (elevated BP reading without Dx of HTN)	
9	Cancer (except basal cell skin cancer or squamous cell skin cancer) or any clinically significant disease or disorder, except for conditions associated to type 2 diabetes, which in the investigator's opinion could interfere with the results of the trial.	**Measured 1825 prior to and including the day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Cancer: ICD 9 diagnosis: 140.x-209.x (except 173.x, non-melanoma skin cancer and 209.4x, 209.5x, 209.6x) ICD 10 diagnosis: C00.x-C96, D45 (except C44.x, non-melanoma skin cancer)	
10	Recurrent major hypoglycaemia as judged by the investigator.	**At least two measurements in the 180 days prior to and including the day of drug initiation inpatient or emergency department settings:** Hypoglycemia: ICD-9 diagnosis: 251.0, 251.1, 251.2, 962.3, or 270.3 (primary position) or 250.8 without co-existence of 259.8, 272.7, 681.x,682.x, 686.9, 707.1–707.9, 730.0–730.2, or 731.8 (any position) ICD-10 diagnosis: E10.641, E11.641, E13.641, E10.649, E11.649, E13.649, E16.0, E16.1, E16.2 (primary position) or E11.69, E13.69, E10.69 without coexistence of E34.1, E34.8, E35, E75.2, E75.3, E77, L01, L02, L03, L97, M86, M90	
N/A	Known or suspected allergy to trial product(s) or related products.	N/A	
11	Use of any drug (except for OADs), which in the investigator's opinion could interfere with glucose levels (e.g. systemic corticosteroids).	**Measured 90 days prior to and including the day of drug initiation:** ***Injectable (IV) or (IM):*** NDC Generic Name: methylprednisolone, hydrocortisone, dexamethasone CPT/HCPCS Procedure Code: J1020, J1030, J1040, J1720, J2920, J2930 ***Oral:*** NDC Generic Name: Cortisone, hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone	
N/A	Receipt of any investigational drug within the four weeks prior to this trial.	N/A	
N/A	Previous participation in the randomised phase of this trial. Re-screening is allowed once within the recruitment period.	N/A	

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12	Known or suspected abuse of alcohol or narcotics.	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position in inpatient or outpatient care setting:** Alcohol Abuse or Dependence ICD-9 diagnosis: 291.x, 303.xx, 305.9x, 357.5, 425.5, 535.30, 535.31, 571.0 - 571.3, 760.71, 790.3, 980.0, E860.0, E860.1, E860.8, E860.9, V11.3, V79.1 ICD-10 diagnosis: E24.4, F10.1xx (excluding F10.13x), F10.2xx, F10.9xx (excluding F10.93x), G31.2, G62.1, G72.1, I42.6, K29.2x, K70.xx, K85.2x, K86.0, O35.4, P04.3, Q86.0, R78.0, T51.0X1x, Z50.2, Z71.4, Z72.1 OR Drug Abuse or Dependence ICD-9 diagnosis: 292.xx, 304.xx, 305.xx (excluding 305.0x and 305.1), 648.3x, 779.5, 965.0x, 967.x, 969.xx, 970.xx, V65.42 ICD-10 diagnosis: F11.xxx, F12.xxx, F13.xxx, F14.xxx, F15.xxx, F16.xxx, F18.xxx, F19.xxx, O99.32x, P96.1,	
13	Mental incapacity, unwillingness or language barrier precluding adequate understanding or cooperation.	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position in inpatient or outpatient care setting:** Dementia and brain damages: ICD-9 diagnosis: 290.x, 294.x, 330.x, 331.x ICD-10 diagnosis: F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, F04, F05, F06.x, F84.2, G13.2, G13.8, G30.x, G31.x, G91.x, G93.x, G94, E750, E751, E752, E754 NDC generic names: RIVASTIGMINE, DONEPEZIL HCL, ERGOLOID MESYLATES, GALANTAMINE HBR, MEMANTINE HCL, MEMANTINE HCL/DONEPEZIL HCL, RIVASTIGMINE TARTRATE, TACRINE HCL OR Non-compliance: ICD-9 diagnosis: V45.12, V15.81	
14	Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice). This exclusion criterion has been modified in Germany according to Substantial Protocol Amendment No. 2-DE, see Section 9.8.1.	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Please refer to "Pregnancy definition"	
15	Any contraindications to metformin or glimepiride (according to local requirements).	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** **Contraindications to Glimepiride:** Type 1 diabetes: ICD 9 diagnosis: 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 ICD 10 diagnosis: E10.x Diabetic ketoacidosis (DKA): ICD9 diagnosis: 250.1x ICD10 diagnosis: E10.1x, E11.1x, E13.1x, E08.1x, E09.1x Other metabolic acidosis: ICD9 diagnosis: 276.2 ICD10 diagnosis: E87.2 NB. All patients no treated with metformin at cohort entry have been excluded from the eligible cohort, assuming that all	
16	Subjects with medical history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC) if total thyroidectomy has not been performed or cannot be ensured (i.e. posterior capsule of the thyroid gland not removed). This exclusion criterion has been added only in Germany according to Substantial Protocol Amendment No. 2-DE, see Section 9.8.1.	**Measured 1825 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** ICD-9 diagnosis: 258.02, 258.03 ICD-10 diagnosis: E31.22, E31.23 NB. Thyroid carcinoma is already excluded with exclusion criterion 9	

Appendix A

PREGNANCY DEFINITION	
1. Delivery Codes	
Procedure Codes	**Description**
CPT-4 codes	
1960	Anesthesia for vaginal delivery only
1961	Anesthesia for cesarean delivery only
1962	Anesthesia for urgent hysterectomy following delivery
1963	Anesthesia for cesarean hysterectomy w/o any labor analgesia/anesthesia care
1967	Neuraxial labor analgesia/anesthesia, planned vaginal delivery
1968	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia
1969	Anes for cesarean hysterectomy following neuraxial labor analgesia/anesthesia
59050	Fetal monitoring in labor, physician w/written report; s & i
59051	Fetal monitoring in labor, physician w/written report; intrepretation only
59400	ROUTINE TOTAL OBSTETRIC CARE including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care.
59409	Vaginal delivery only (w/wo episiotomy &/or forceps)
59410	Vaginal delivery only (w/wo episiotomy &/or forceps); w/postpartum care
59412	Ext cephalic version, w/wo tocolysis
59414	Delivery of placenta (separate proc)
59430	Postpartum care only
59510	Routine obstetric care w/antepartum care, cesarean delivery, & postpartum care
59514	Cesarean delivery only
59515	Cesarean delivery only; w/postpartum care
59525	Subtotal/total hysterectomy after cesarean delivery
59610	Routine obstetric care including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care, after previous cesarean delivery
59612	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy and/or forceps)
59614	Vaginal delivery only, previous cesarean delivery w/postpartum care
59618	Routine obstetric care including antepartum care, cesarean delivery, and postpartum care, following attempted vaginal delivery after previous cesarean delivery
59620	Cesarean delivery after failed vaginal delivery, previous cesarean delivery
59622	Cesarean delivery after failed vaginal delivery, previous cesarean delivery; w/postpartum care
99436	Attendance at delivery, at request of delivering physician, & stabilization of newborn
99440	Newborn resuscitation
ICD-9 procedure codes	
72.xx	Forceps, vacuum, & breech
73.xx	Other including manual delivery
74xx	Cesarean section
75.4x	Manual removal of placenta
ICD-10 procedure codes	
Normal Delivery	
10E0XZZ	Delivery of Products of Conception, External Approach
C-Section	
10D00Z0	Extraction of Products of Conception, High, Open Approach
10D00Z1	Extraction of Products of Conception, Low, Open Approach
10D00Z2	Extraction of Products of Conception, Extraperitoneal, Open Approach
Other assisted delivery (forceps, vacuum, internal version, other)	
10D07Z3	Extraction of Products of Conception, Low Forceps, Via Natural or Artificial Opening
10D07Z4	Extraction of Products of Conception, Mid Forceps, Via Natural or Artificial Opening
10D07Z5	Extraction of Products of Conception, High Forceps, Via Natural or Artificial Opening
10D07Z6	Extraction of Products of Conception, Vacuum, Via Natural or Artificial Opening
10D07Z7	Extraction of Products of Conception, Internal Version, Via Natural or Artificial Opening
10D07Z8	Extraction of Products of Conception, Other, Via Natural or Artificial Opening

Appendix A

2. Identify preterm births	
a. Codes that have a specific gestational age mentioned	
ICD-9 code	Definition
765.21	Less than 24 completed weeks of gestation
765.22	24 completed weeks of gestation
765.23	25-26 completed weeks of gestation
765.24	27-28 completed weeks of gestation
765.25	29-30 completed weeks of gestation
765.26	31-32 completed weeks of gestation
765.27	33-34 completed weeks of gestation
765.28	35-36 completed weeks of gestation
ICD-10 code	Definition
P07.21	Extreme immaturity of newborn, gestational age less than 23 completed weeks
P07.22	Extreme immaturity of newborn, gestational age 23 completed weeks
P07.23	Extreme immaturity of newborn, gestational age 24 completed weeks
P07.24	Extreme immaturity of newborn, gestational age 25 completed weeks
P07.25	Extreme immaturity of newborn, gestational age 26 completed weeks
P07.26	Extreme immaturity of newborn, gestational age 27 completed weeks
P07.31	Preterm newborn, gestational age 28 completed weeks
P07.32	Preterm newborn, gestational age 29 completed weeks
P07.33	Preterm newborn, gestational age 30 completed weeks
P07.34	Preterm newborn, gestational age 31 completed weeks
P07.35	Preterm newborn, gestational age 32 completed weeks
P07.36	Preterm newborn, gestational age 33 completed weeks
P07.37	Preterm newborn, gestational age 34 completed weeks
P07.38	Preterm newborn, gestational age 35 completed weeks
P07.39	Preterm newborn, gestational age 36 completed weeks
b. Codes indicating extreme prematurity	
ICD-9 code	Definition
765	Disorders relating to extreme immaturity of infant
765.00	Extreme immaturity, unspecified [weight]
765.01	Extreme immaturity, less than 500 grams
765.02	Extreme immaturity, 500-749 grams
765.03	Extreme immaturity, 750-999 grams
765.04	Extreme immaturity, 1,000-1,249 grams
765.05	Extreme immaturity, 1,250-1,499 grams
765.06	Extreme immaturity, 1,500-1,749 grams
765.07	Extreme immaturity, 1,750-1,999 grams
765.08	Extreme immaturity, 2,000-2,499 grams
ICD-10 code	Definition
P07.2	Extreme immaturity of newborn
P07.20	Extreme immaturity of newborn, unspecified weeks of gestation
O42.012	Preterm premature rupture of membranes, onset of labor within 24 hours of rupture, second trimester
c. Other preterm codes	
ICD-9 code	Definition
765.1	Disorders relating to other preterm infants
765.10	Other preterm infants, unspecified [weight]
765.11	Other preterm infants, less than 500 grams
765.12	Other preterm infants, 500-749 grams
765.13	Other preterm infants, 750-999 grams

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765.14	Other preterm infants, 1,000-1,249 grams
765.15	Other preterm infants, 1,250-1,499 grams
765.16	Other preterm infants, 1,500-1,749 grams
765.17	Other preterm infants, 1,750-1,999 grams
765.18	Other preterm infants, 2,000-2,499 grams
644.21	Onset of delivery before 37 completed weeks of gestation
ICD-10 code	Definition
P05.01	Disorders of newborn related to slow fetal growth and fetal malnutrition less than 500 grams
P05.02	Disorders of newborn related to slow fetal growth and fetal malnutrition, 500-749 grams
P05.03	Disorders of newborn related to slow fetal growth and fetal malnutrition, 750-999 grams
P05.04	Disorders of newborn related to slow fetal growth and fetal malnutrition, 1000-1249 grams
P05.05	Disorders of newborn related to slow fetal growth and fetal malnutrition, 1250-1499 grams
P05.06	Disorders of newborn related to slow fetal growth and fetal malnutrition, 1500-1749 grams
P05.11	Newborn small for gestational age, less than 500 grams
P05.12	Newborn small for gestational age, 500-749 grams
P05.13	Newborn small for gestational age, 750-999 grams
P05.14	Newborn small for gestational age, 1000-1249 grams
P05.15	Newborn small for gestational age, 1250-1499 grams
P05.16	Newborn small for gestational age, 1500-1749 grams
P07.01	Extremely low birth weight newborn, less than 500 grams
P07.02	Extremely low birth weight newborn, 500-749 grams
P07.03	Extremely low birth weight newborn, 750-999 grams
P07.14	Other low birth weight newborn,1000-1249 grams
P07.15	Other low birth weight newborn,1250-1499 grams
P07.16	Other low birth weight newborn,1500-1749 grams
P07.3	Preterm [premature] newborn [other]
P07.30	Preterm newborn, unspecified weeks of gestation
O60.1	Preterm labor with preterm delivery
O42.01	Preterm premature rupture of membranes, onset of labor within 24 hours of rupture
O42.019	Preterm premature rupture of membranes, onset of labor within 24 hours of rupture, unspecified trimester
O42.013	Preterm premature rupture of membranes, onset of labor within 24 hours of rupture, third trimester
Other Codes	Description
ICD-9	
644.2	early onset of delivery
644.2	Early onset of delivery, unspecified as to episode of care or not applicable
644.21	Early onset of delivery, delivered, with or without mention of antepartum condition
776.6	anemia of prematurity
362.2	retinopathy of prematurity, unspecified
362.22	retinopathy of prematurity, stage 0
362.23	retinopathy of prematurity, stage 1
362.24	retinopathy of prematurity, stage 2
362.25	retinopathy of prematurity, stage 3
362.26	retinopathy of prematurity, stage 4
362.27	retinopathy of prematurity, stage 5
CPT	
49491	repair, initial inguinal hernia, preterm infant (younger than 37 weeks gestation at birth), performed from birth up to 50 weeks postconception
49492	repair, initial inguinal hernia, preterm infant (younger than 37 weeks gestation at birth), performed from birth up to 50 weeks postconception
67229	treatment of extensive or progressive retinopathy, 1 or more sessions; preterm infant (less than 37 weeks gestation at birth), performed from
836	anesthesia for hernia repairs in the lower abdomen not otherwise specified, infants younger than 37 weeks gestational age at birth
ICD-10 code	Definition

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H35.1	Retinopathy of prematurity
P61.2	Anemia of prematurity
2. Multiple Gestation (V for ICD-9 and Z for ICD-10 codes excluded)	
ICD9 Code	Description
V27.2	Twins both liveborn
V27.3	Mother with twins one liveborn and one stillborn
V27.4	Mother with twins both stillborn
V27.5	Other multiple birth, all liveborn
V27.6	Other multiple birth, some liveborn
V31	Twin, mate liveborn
V32	Twin birth mate stillborn
V33	Twin, unspecified
V34	Other multiple, mates all liveborn
V35	Other multiple birth (three or more) mates all stillborn
V36	Other multiple, mates live- and stillborn
V37	Other multiple, unspecified
651	Multiple gestation
651.0x	Twin Pregnancy
651.1x	Triplet pregnancy
651.2x	Quadruplet pregnancy
651.3x	Twin pregnancy with fetal loss and retention of one fetus
651.4x	Triplet pregnancy with fetal loss and retention of one or more fetus(es)
651.5x	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es)
651.6x	Other multiple pregnancy with fetal loss and retention of one or more fetus(es)
651.7x	Multiple gestation following (elective) fetal reduction
651.8x	Other specified multiple gestation
651.9x	Unspecified multiple gestation
652.6x	Multiple gestation with malpresentation of one fetus or more
660.5x	Locked Twins
662.3x	Delayed delivery of second twin, triplet, etc.
761.5x	Multiple pregnancy
ICD10 Code	Description
O30xxxx	Multiple gestation
O31xxxx	Complications specific to multiple gestation
O43.02	Fetus-to-fetus placental transfusion syndrome
O63.2	Delayed delivery of second twin, triplet, etc.
Z37.2	Twins, both liveborn
Z37.3	Twins, one liveborn and one stillborn
Z37.5	Other multiple births, all liveborn
Z37.50	Multiple births, unspecified, all liveborn
Z37.51	Triplets, all liveborn
Z37.52	Quadruplets, all liveborn
Z37.53	Quintuplets, all liveborn
Z37.54	Sextuplets, all liveborn
Z37.59	Other multiple births, all liveborn
Z37.6	Other multiple births, some liveborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.61	Triplets, some liveborn
Z37.62	Quadruplets, some liveborn
Z37.63	Quintuplets, some liveborn

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Z37.64	Sextuplets, some liveborn
Z37.69	Other multiple births, some liveborn
Z38.3	Twin liveborn infant, born in hospital
Z38.30	Twin liveborn infant, delivered vaginally
Z38.31	Twin liveborn infant, delivered by cesarean
Z38.4	Twin liveborn infant, born outside hospital
Z38.5	Twin liveborn infant, unspecified as to place of birth
Z38.6	Other multiple liveborn infant, born in hospital
Z38.61	Triplet liveborn infant, delivered vaginally
Z38.62	Triplet liveborn infant, delivered by cesarean
Z38.63	Quadruplet liveborn infant, delivered vaginally
Z38.64	Quadruplet liveborn infant, delivered by cesarean
Z38.65	Quintuplet liveborn infant, delivered vaginally
Z38.66	Quintuplet liveborn infant, delivered by cesarean
Z38.68	Other multiple liveborn infant, delivered vaginally
Z38.69	Other multiple liveborn infant, delivered by cesarean
Z38.7	Other multiple liveborn infant, born outside hospital
Z38.8	Other multiple liveborn infant, unspecified as to place of birth
P01.5	Newborn affected by multiple pregnancy
3. Post-Term Codes	
ICD-9 code	Definition
645	Late Pregnancy
645.1	Post term pregnancy
645.1	Post term pregnancy, unspecified as to episode of care or not applicable
645.11	Post term pregnancy, delivered, with or without mention of antepartum condition
645.13	Post term pregnancy, antepartum condition or complication
645.2	Prolonged pregnancy
645.2	Prolonged pregnancy, unspecified as to episode of care or not applicable
645.21	Prolonged pregnancy, delivered, with or without mention of antepartum condition
645.23	Prolonged pregnancy, antepartum condition or complication
766.2	Late infant, not 'heavy-for-dates'
766.21	Post-term infant
766.22	Prolonged gestation of infant
ICD-10 code	Definition
O48	Late pregnancy
O48.0	Post-term pregnancy
O48.1	Prolonged pregnancy
P08.2	Late newborn, not heavy for gestational age
P08.21	Post-term newborn
P08.22	Prolonged gestation of newborn
Z3A.41	41 weeks gestation of pregnancy
Z3A.42	42 weeks gestation of pregnancy
Z3A.49	Greater than 42 weeks gestation of pregnancy
4. Codes indicating a prenatal care visit:	
ICD-9: V220x, V221x, V23xx	
ICD-10: O0900, O0901, O0902, O0903, O0910, O0911, O0912, O0913, O09211, O09212, O09213, O09219, O09291, O09292, O09293, O09299, O0930, O0931, O0932, O0933, O0940, O0941, O0942, O0943, O09511, O09512, O09513, O09519, O09521, O09522, O09523, O09529, O09611, O09612, O09613, O09619, O09621, O09622, O09623, O09629, O0970, O0971, O0972, O0973, O09811, O09812, O09813, O09819, O09821, O09822, O09823, O09829, O09891, O09892, O09893, O09899, O0990, O0991, O0992, O0993, O09A0, O09A1, O09A2, O09A3, O3680X0, O3680X1, O3680X2, O3680X3, O3680X4, O3680X5, O3680X9, Z3400, Z3401, Z3402, Z3403, Z3480, Z3481, Z3482, Z3483, Z3490, Z3491, Z3492, Z3493, Z362	

Appendix A

Anti-diabetic treatments (other than insulin)
1st and 2nd Generation Sus (excluding glimepiride)
GLIPIZIDE/METFORMIN HCL
ACETOHEXAMIDE
GLYBURIDE,MICRONIZED
TOLBUTAMIDE
GLYBURIDE/METFORMIN HCL
TOLAZAMIDE
CHLORPROPAMIDE
GLYBURIDE
GLIPIZIDE
AGIs
ACARBOSE
MIGLITOL
DPP-4 Inhibitors
ALOGLIPTIN BENZOATE
DAPAGLIFLOZIN PROPANEDIOL/SAXAGLIPTIN HCL
ERTUGLIFLOZIN PIDOLATE/SITAGLIPTIN PHOSPHATE
SAXAGLIPTIN HCL/METFORMIN HCL
LINAGLIPTIN
ALOGLIPTIN BENZOATE/METFORMIN HCL
ALOGLIPTIN BENZOATE/PIOGLITAZONE HCL
EMPAGLIFLOZIN/LINAGLIPTIN
SAXAGLIPTIN HCL
SITAGLIPTIN PHOSPHATE/METFORMIN HCL
SITAGLIPTIN PHOSPHATE/SIMVASTATIN
SITAGLIPTIN PHOSPHATE
Glitazones
ALOGLIPTIN BENZOATE/PIOGLITAZONE HCL
PIOGLITAZONE HCL
PIOGLITAZONE HCL/GLIMEPIRIDE
PIOGLITAZONE HCL/METFORMIN HCL
ROSIGLITAZONE MALEATE
ROSIGLITAZONE MALEATE/GLIMEPIRIDE
ROSIGLITAZONE MALEATE/METFORMIN HCL

Appendix A

GLP-1 RA (excluding liraglutide monotherapy)
ALBIGLUTIDE
DULAGLUTIDE
EXENATIDE
EXENATIDE MICROSPHERES
INSULIN DEGLUDEC/LIRAGLUTIDE
INSULIN GLARGINE,HUMAN RECOMBINANT ANALOG/LIXISENATIDE
LIXISENATIDE
SEMAGLUTIDE
Meglitinides
NATEGLINIDE
REPAGLINIDE
REPAGLINIDE/METFORMIN HCL
SGLT-2 Inhibitors
CANAGLIFLOZIN
CANAGLIFLOZIN/METFORMIN HCL
DAPAGLIFLOZIN PROPANEDIOL/SAXAGLIPTIN HCL
ERTUGLIFLOZIN PIDOLATE
ERTUGLIFLOZIN PIDOLATE/SITAGLIPTIN PHOSPHATE
DAPAGLIFLOZIN PROPANEDIOL/METFORMIN HCL
EMPAGLIFLOZIN/LINAGLIPTIN
EMPAGLIFLOZIN
DAPAGLIFLOZIN PROPANEDIOL
ERTUGLIFLOZIN PIDOLATE/METFORMIN HCL
EMPAGLIFLOZIN/METFORMIN HCL

Insulin

Bolus insulins
INSULIN GLULISINE
INSULIN REGULAR,BEEF-PORK
INSULIN ASPART (NIACINAMIDE)
INSULIN REGULAR, HUMAN/INSULIN RELEASE UNIT
INSULIN REGULAR,HUMAN BUFFERED
INSULIN REGULAR, HUMAN/INSULIN RELEASE UNIT/CHAMBER/INHALER
INSULIN ASPART
INSULIN ASPART PROTAMINE HUMAN/INSULIN ASPART

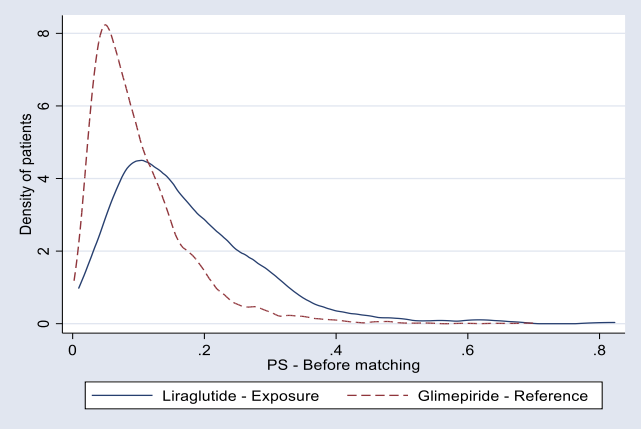
Appendix A

INSULIN LISPRO PROTAMINE AND INSULIN LISPRO
INSULIN LISPRO
INSULIN REGULAR, HUMAN
Intermediate and Long-acting Insulins
INSULIN DEGLUDEC
INSULIN DETEMIR
INSULIN DEGLUDEC/LIRAGLUTIDE
INSULIN NPH HUMAN AND INSULIN REGULAR HUMAN SEMI-SYNTHETIC
INSULIN NPH HUMAN SEMI-SYNTHETIC
INSULIN ISOPHANE NPH,BF-PK
INSULIN GLARGINE,HUMAN RECOMBINANT ANALOG/LIXISENATIDE
INSULIN GLARGINE,HUMAN RECOMBINANT ANALOG
INSULIN NPH HUMAN ISOPHANE
INSULIN NPH HUMAN ISOPHANE/INSULIN REGULAR, HUMAN

Appendix B

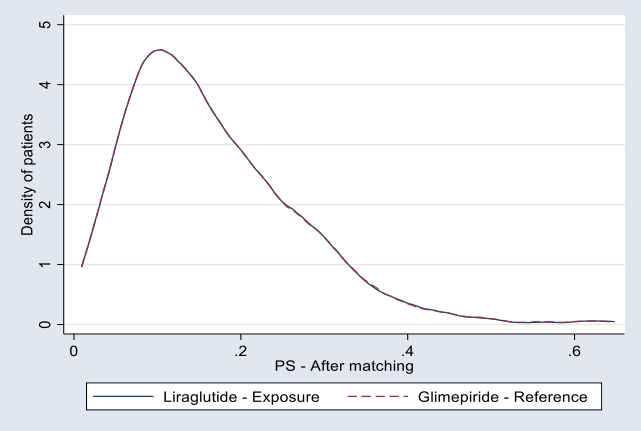
Optum

BEFORE PS MATCHING



The c-statistics for the propensity score model, pre-matching was 0.722

AFTER PS MATCHING



The c-statistics for the propensity score model, post-matching was 0.576

Appendix B

	UNMATCHED Optum			MATCHED Optum		
Variable	**Glimepiride**	**Liraglutide**	**St. Diff**	**Glimepiride**	**Liraglutide**	**St. Diff**
Number of patients	**3,096**	**378**		**373**	**373**	
Age squared						
...mean (sd)	761406 (223830.2)	651214 (225218.8)	0.491	631746.5 (235037.9)	653328.8 (225529.3)	-0.094
Age (continuous)						
...mean (sd)	64.24 (10.37)	59.22 (10.94)	0.471	58.19 (11.58)	59.31 (10.96)	-0.099
Age (categories)						
...18 - 40; n (%)	95 (3.1%)	20 (5.3%)	-0.110	32 (8.6%)	20 (5.4%)	0.126
...41 - 50; n (%)	266 (8.6%)	64 (16.9%)	-0.251	63 (16.9%)	62 (16.6%)	0.008
...51 - 60; n (%)	602 (19.4%)	106 (28.0%)	-0.203	104 (27.9%)	104 (27.9%)	0.000
...61 - 70; n (%)	1187 (38.3%)	133 (35.2%)	0.064	127 (34.0%)	132 (35.4%)	-0.029
...71 - 80; n (%)	946 (30.6%)	55 (14.6%)	0.390	47 (12.6%)	55 (14.7%)	-0.061
Gender						
...M = MALE; n (%)	1726 (55.7%)	179 (47.4%)	0.167	188 (50.4%)	194 (52.0%)	-0.032
...F = FEMALE; n (%)	1370 (44.3%)	199 (52.6%)	-0.167	185 (49.6%)	179 (48.0%)	0.032
Race						
...White; n (%)	1492 (48.2%)	220 (58.2%)	-0.201	202 (54.2%)	217 (58.2%)	-0.081
...Not white; n (%)	1604 (51.8%)	158 (41.8%)	0.201	171 (45.8%)	156 (41.8%)	0.081
Calendar time years (Jan 2010 - Jun 2020)						
...Jan 26, 2010 - Dec 31, 2017; n (%)	1850 (59.8%)	255 (67.5%)	-0.161	254 (68.1%)	251 (67.3%)	0.017
...Jan 1, 2018 - Jun 30, 2020; n (%)	1246 (40.2%)	123 (32.5%)	0.161	119 (31.9%)	122 (32.7%)	-0.017
General Health						
Smoking; n (%)	296 (9.6%)	30 (7.9%)	0.060	22 (5.9%)	30 (8.0%)	-0.083
Obesity or Overweight; n (%)	760 (24.5%)	93 (24.6%)	-0.002	89 (23.9%)	91 (24.4%)	-0.012
Obesity; n (%)	554 (17.9%)	79 (20.9%)	-0.076	72 (19.3%)	77 (20.6%)	-0.033
Overweight; n (%)	247 (8.0%)	16 (4.2%)	0.159	21 (5.6%)	16 (4.3%)	0.060
Combined comorbidity score, 180 days						
...mean (sd)	2.06 (1.56)	1.86 (1.36)	0.137	1.92 (1.35)	1.86 (1.37)	0.044
Frailty Score: Empirical Version 180 days						
...mean (sd)	0.99 (0.77)	1.03 (0.73)	-0.053	1.05 (0.73)	1.02 (0.72)	0.041
Lab value HbA1c						
...mean (sd)	8.16 (0.96)	8.18 (0.99)	-0.021	8.16 (0.98)	8.18 (0.99)	-0.020
Cardiovascular Comorbidities				**Cardiovascular Disorders**		
Hypertension; n (%)	391 (12.6%)	66 (17.5%)	-0.137	Hypertension; n (%)*	69 (18.5%)	63 (16.9%)	0.042
Hyperlipidemia; n (%)	2296 (74.2%)	299 (79.1%)	-0.116	Hyperlipidemia; n (%)*	297 (79.6%)	296 (79.4%)	0.005
Atherosclerosis Disease (MI, angina, CAD and other forms of chronic ischemic heart disease, History of CABG or PTCA); n (%)	566 (18.3%)	43 (11.4%)	0.195	Atherosclerosis Disease (MI, angina, CAD and other forms of chronic ischemic heart disease, History of CABG or PTCA); n (%)*	43 (11.5%)	42 (11.3%)	0.006
Old MI; n (%)	64 (2.1%)	3 (0.8%)	0.109	Old MI; n (%)	6 (1.6%)	3 (0.8%)	0.074
Acute MI ; n (%)	10 (0.3%)	1 (0.3%)	0.000	Acute MI ; n (%)	0 (0.0%)	1 (0.3%)	-0.078
ACS/unstable angina; n (%)	18 (0.6%)	1 (0.3%)	0.045	ACS/unstable angina; n (%)	0 (0.0%)	1 (0.3%)	-0.078
Stable angina; n (%)	80 (2.6%)	6 (1.6%)	0.070	Stable angina; n (%)	3 (0.8%)	6 (1.6%)	-0.074
CAD and other forms of chronic ischemic heart disease; n (%)	415 (13.4%)	30 (7.9%)	0.179	CAD and other forms of chronic ischemic heart disease; n (%)	33 (8.8%)	29 (7.8%)	0.036
History of CABG or PTCA ; n (%)	107 (3.5%)	9 (2.4%)	0.065	History of CABG or PTCA ; n (%)	5 (1.3%)	9 (2.4%)	-0.082
PAD or PAD surgery; n (%)	166 (5.4%)	11 (2.9%)	0.126	PAD or PAD surgery; n (%)	9 (2.4%)	11 (2.9%)	-0.031
Cerebrovascular disease (Stroke, TIA, Late effects); n (%)	77 (2.5%)	2 (0.5%)	0.165	Cerebrovascular disease (Stroke, TIA, Late effects); n (%)*	1 (0.3%)	2 (0.5%)	-0.032
Stroke (Ischemic or hemorrhagic); n (%)	40 (1.3%)	1 (0.3%)	0.112	Stroke (Ischemic or hemorrhagic); n (%)	1 (0.3%)	1 (0.3%)	0.000
TIA; n (%)	27 (0.9%)	1 (0.3%)	0.078	TIA; n (%)	1 (0.3%)	1 (0.3%)	0.000
Late effects of cerebrovascular disease; n (%)	28 (0.9%)	0 (0.0%)	0.135	Late effects of cerebrovascular disease; n (%)	1 (0.3%)	0 (0.0%)	0.078
Heart Failure; n (%)	103 (3.3%)	10 (2.6%)	0.041	Heart Failure; n (%)*	10 (2.7%)	10 (2.7%)	0.000
Atrial fibrillation; n (%)	121 (3.9%)	14 (3.7%)	0.010	Atrial fibrillation; n (%)*	13 (3.5%)	14 (3.8%)	-0.016
Other cardiac dysrhythmia; n (%)	190 (6.1%)	18 (4.8%)	0.057	Other cardiac dysrhythmia; n (%)	25 (6.7%)	17 (4.6%)	0.091
Diabetes Mellitus Comorbidities				**Diabetes Mellitus Complications**		
Hypoglycemia; n (%)	20 (0.6%)	4 (1.1%)	-0.054	Hypoglycemia; n (%)*	6 (1.6%)	4 (1.1%)	0.043
Diabetic nephropathy; n (%)	434 (14.0%)	48 (12.7%)	0.038	Diabetic Nephropathy; n (%)*	39 (10.5%)	46 (12.3%)	-0.057
Diabetic Neuropathy; n (%)	495 (16.0%)	60 (15.9%)	0.003	Diabetic Neuropathy; n (%)*	61 (16.4%)	59 (15.8%)	0.016
Diabetic Retinopathy ; n (%)	134 (4.3%)	20 (5.3%)	-0.047	Diabetic Retinopathy ; n (%)*	15 (4.0%)	20 (5.4%)	-0.066
Diabetes with unspecified complications; n (%)	122 (3.9%)	14 (3.7%)	0.010	Diabetes with unspecified complications; n (%)	14 (3.8%)	13 (3.5%)	0.016
Diabetes with peripheral circulatory disorders and amputations, DF; n (%)*	70 (2.3%)	9 (2.4%)	-0.007	Diabetes with peripheral circulatory disorders and amputations, DF; n (%)*	7 (1.9%)	9 (2.4%)	-0.034
Diabetes with peripheral circulatory disorders; n (%)	38 (1.2%)	5 (1.3%)	-0.009	Diabetes with peripheral circulatory disorders; n (%)	3 (0.8%)	5 (1.3%)	-0.049
Lower-limb amputations; n (%)	4 (0.1%)	1 (0.3%)	-0.045	Lower-limb amputations; n (%)	0 (0.0%)	1 (0.3%)	-0.078
Diabetic Foot; n (%)	32 (1.0%)	3 (0.8%)	0.021	Diabetic Foot; n (%)	5 (1.3%)	3 (0.8%)	0.049
Renal Comorbidities				**Renal Disorders**		
Chronic kidney disease stages I-IV and NOS; n (%)	381 (12.3%)	40 (10.6%)	0.053	Chronic kidney disease stages I-IV and NOS; n (%)*	36 (9.7%)	40 (10.7%)	-0.033
Miscellaneous renal disease; n (%)	109 (3.5%)	10 (2.6%)	0.052	Miscellaneous renal disease; n (%)	10 (2.7%)	10 (2.7%)	0.000
Mood disorders (Anxiety and Depression); n (%)	332 (10.7%)	47 (12.4%)	-0.053	**Mood disorders (Anxiety and Depression); n (%)***	47 (12.6%)	47 (12.6%)	0.000
Anxiety; n (%)	211 (6.8%)	27 (7.1%)	-0.012	Anxiety; n (%)	28 (7.5%)	27 (7.2%)	0.011
Depression; n (%)	162 (5.2%)	28 (7.4%)	-0.091	Depression; n (%)	26 (7.0%)	28 (7.5%)	-0.019
Other Comorbidities				**Other Disorders**		
Obstructive sleep apnea; n (%)	259 (8.4%)	41 (10.8%)	-0.082	Obstructive sleep apnea; n (%)*	38 (10.2%)	39 (10.5%)	-0.010
COPD; n (%)	207 (6.7%)	9 (2.4%)	0.207	COPD; n (%)*	15 (4.0%)	9 (2.4%)	0.091
Asthma; n (%)	96 (3.1%)	14 (3.7%)	-0.033	Asthma; n (%)	19 (5.1%)	13 (3.5%)	0.079
Osteoarthrosis; n (%)	363 (11.7%)	49 (13.0%)	-0.040	Osteoarthrosis; n (%)	50 (13.4%)	48 (12.9%)	0.015
NASH/NAFLD; n (%)	98 (3.2%)	16 (4.2%)	-0.053	NASH/NAFLD; n (%)	14 (3.8%)	15 (4.0%)	-0.010
Medications				**Medications**		
Antihypertensive medications; n (%)	2585 (83.5%)	324 (85.7%)	-0.061	Antihypertensive medications; n (%)*	318 (85.3%)	320 (85.8%)	-0.014
ACEI/ARBs; n (%)	2257 (72.9%)	285 (75.4%)	-0.057	ACEI/ARBs; n (%)	282 (75.6%)	281 (75.3%)	0.007
Beta blockers; n (%)	971 (31.4%)	94 (24.9%)	0.145	Beta blockers; n (%)	98 (26.3%)	94 (25.2%)	0.025
Calcium channel blockers; n (%)	795 (25.7%)	83 (22.0%)	0.087	Calcium channel blockers; n (%)	91 (24.4%)	81 (21.7%)	0.064
Thiazide; n (%)	369 (11.9%)	52 (13.8%)	-0.057	Thiazide; n (%)	54 (14.5%)	51 (13.7%)	0.023
Diuretics; n (%)	1108 (35.8%)	133 (35.2%)	0.013	Diuretics; n (%)	137 (36.7%)	129 (34.6%)	0.044
Statins Other lipid-lowering drugs; n (%)	2402 (77.6%)	291 (77.0%)	0.014	Statins Other lipid-lowering drugs; n (%)*	299 (80.2%)	287 (76.9%)	0.080
Statins; n (%)	2285 (73.8%)	273 (72.2%)	0.036	Statins; n (%)	281 (75.3%)	269 (72.1%)	0.025
Other lipid-lowering drugs; n (%)	370 (12.0%)	49 (13.0%)	-0.030	Other lipid-lowering drugs; n (%)	50 (13.4%)	48 (12.9%)	0.015
Opioids; n (%)	507 (16.4%)	72 (19.0%)	-0.068	Opioids; n (%)*	74 (19.8%)	69 (18.5%)	0.033
Mood Stabilizing Medications; n (%)	719 (23.2%)	129 (34.1%)	-0.243	Mood Stabilizing Medications; n (%)*	127 (34.0%)	125 (33.5%)	-0.041
Antidepressants; n (%)	540 (17.4%)	105 (27.8%)	-0.251	Antidepressants; n (%)	98 (26.3%)	101 (27.1%)	-0.018
Anxiolytics/hypnotics; n (%)	114 (3.7%)	25 (6.6%)	-0.131	Anxiolytics/hypnotics; n (%)	23 (6.2%)	24 (6.4%)	-0.008
Benzodiazepine; n (%)	256 (8.3%)	42 (11.1%)	-0.095	Benzodiazepine; n (%)	47 (12.6%)	40 (10.7%)	0.059
Gabapentinoids; n (%)	319 (10.3%)	49 (13.0%)	-0.084	Gabapentinoids; n (%)*	47 (12.6%)	47 (12.6%)	0.000
Healthcare Utlization				**Healthcare Utlization**		
Number of medication claims				Number of medication claims*		
...mean (sd)	11.47 (6.60)	12.82 (6.94)	-0.199	...mean (sd)	12.76 (7.08)	12.73 (6.89)	0.004
Number of office visits				Number of office visits*		
...mean (sd)	4.76 (3.58)	5.24 (3.72)	-0.131	...mean (sd)	4.91 (3.59)	5.19 (3.66)	-0.071
Number of hospitalizations or ED visits				Number of hospitalizations or ED visits*		
...mean (sd)	0.24 (0.87)	0.20 (0.66)	0.052	...mean (sd)	0.25 (0.91)	0.20 (0.67)	0.025
Number of Endocrinologist visits				Number of Endocrinologist visits*		
...mean (sd)	0.13 (0.55)	0.27 (0.85)	-0.196	...mean (sd)	0.25 (0.75)	0.24 (0.73)	0.013
Number of HbA1c test orders				Number of HbA1c test orders		
...mean (sd)	1.77 (0.68)	1.79 (0.78)	-0.012	...mean (sd)	1.84 (0.64)	1.78 (0.78)	0.083
Number of lexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy (CRC screening); n (%)	149 (4.8%)	17 (4.5%)	0.014	Number of flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy (CRC screening); n (%)	57 (15.3%)	54 (14.5%)	0.022
Number of Mammograms (Breast cancer screening); n (%)	400 (12.9%)	59 (15.6%)	-0.077	Number of Mammograms (Breast cancer screening); n (%)	15 (4.0%)	16 (4.3%)	-0.015
Number of Pap smear (Cervical cancer screening); n (%)	120 (3.9%)	16 (4.2%)	-0.015	Number of Pap smear (Cervical cancer screening); n (%)	48 (12.9%)	59 (15.8%)	-0.083
Flu vaccine; n (%)	659 (21.3%)	93 (24.6%)	-0.079	Flu vaccine; n (%)	20 (5.4%)	15 (4.0%)	0.066
Pneumococcal vaccine; n (%)	671 (21.7%)	82 (21.7%)	0.000	Pneumococcal vaccine; n (%)	87 (23.3%)	93 (24.9%)	-0.037
Number of DXA tests				Number of DXA tests	76 (20.4%)	82 (22.0%)	-0.039
...mean (sd)	0.04 (0.19)	0.03 (0.18)	0.002	...mean (sd)	0.03 (0.18)	0.03 (0.18)	0.000
Copay for pharmacy cost (charges in U.S. $)				Copay for pharmacy cost (charges in U.S. $)*#			
...mean (sd)	180.68 (259.85)	280.36 (336.80)	-0.331	...mean (sd)	268.00 (356.42)	269.85 (316.10)	-0.005
Business type				Business type*			
...Commercial; n (%)	1016 (32.8%)	201 (53.2%)	-0.421	...Commercial; n (%)	201 (53.9%)	196 (52.5%)	0.028
...Medicare; n (%)	2080 (67.2%)	177 (46.8%)	0.421	...Medicare; n (%)	172 (46.1%)	177 (47.5%)	-0.028
Generic/Brand unique prescriptions				Generic/Brand unique prescriptions			
...mean (sd)	0.99 (0.04)	0.99 (0.04)	0.000	...mean (sd)	0.99 (0.04)	0.99 (0.04)	0.000
Brand name prescription - unique value				Brand name prescription - unique value*			
...mean (sd)	8.55 (3.69)	9.35 (3.85)	-0.212	...mean (sd)	9.32 (4.11)	9.25 (3.70)	0.018
Generic name prescription - unique value				Generic name prescription - unique value*			
...mean (sd)	8.47 (3.64)	9.23 (3.76)	-0.205	...mean (sd)	9.20 (4.05)	9.13 (3.62)	0.018

*** variables included in the PS model**
 # copay of index drugs is not included