Online-Only Supplementary Contents

Glucagon-like Peptide-1 Receptor Agonists and Chronic Lower Respiratory Disease Exacerbations Among Patients with Type 2 Diabetes

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Table 1. Codes used to identify patients with type II diabetes

ICD.9	Definition	ICD-10	Definition
250.00	Diabetes mellitus without mention of complication, type ii or unspecified type, not stated as uncontrolled	E11	Type 2 diabetes mellitus
250.02	Diabetes mellitus without mention of complication, type ii or unspecified type, uncontrolled		
250.10	Diabetes with ketoacidosis, type ii or unspecified type, not stated as uncontrolled		
250.12	Diabetes mellitus with ketoacidosis type ii or unspecified type uncontrolled		
250.20	Diabetes with hyperosmolarity, type ii or unspecified type, not stated as uncontrolled		
250.22	Diabetes with hyperosmolarity, type ii or unspecified type, uncontrolled		
250.30	Diabetes with other coma, type ii or unspecified type, not stated as uncontrolled		
250.32	Diabetes with other coma, type ii or unspecified type, uncontrolled		
250.40	Diabetes with renal manifestations, type ii or unspecified type, not stated as uncontrolled		
250.42	Diabetes with renal manifestations, type ii or unspecified type, uncontrolled		
250.50	Diabetes with ophthalmic manifestations, type ii or unspecified type, not stated as uncontrolled		
250.52	Diabetes with ophthalmic manifestations, type ii or unspecified type, uncontrolled		
250.60	Diabetes with neurological manifestations, type ii or unspecified type, not stated as uncontrolled		
250.62	Diabetes with neurological manifestations, type ii or unspecified type, uncontrolled		
250.70	Diabetes with peripheral circulatory disorders, type ii or unspecified type, not stated as uncontrolled		
250.72	Diabetes with peripheral circulatory disorders, type ii or unspecified type, uncontrolled		
250.80	Diabetes with other specified manifestations, type ii or unspecified type, not stated as uncontrolled		
250.82	Diabetes with other specified manifestations, type ii or unspecified type, uncontrolled		
250.90	Diabetes with unspecified complication, type ii or unspecified type, not stated as uncontrolled		
250.92	Diabetes with unspecified complication, type ii or unspecified type, uncontrolled		

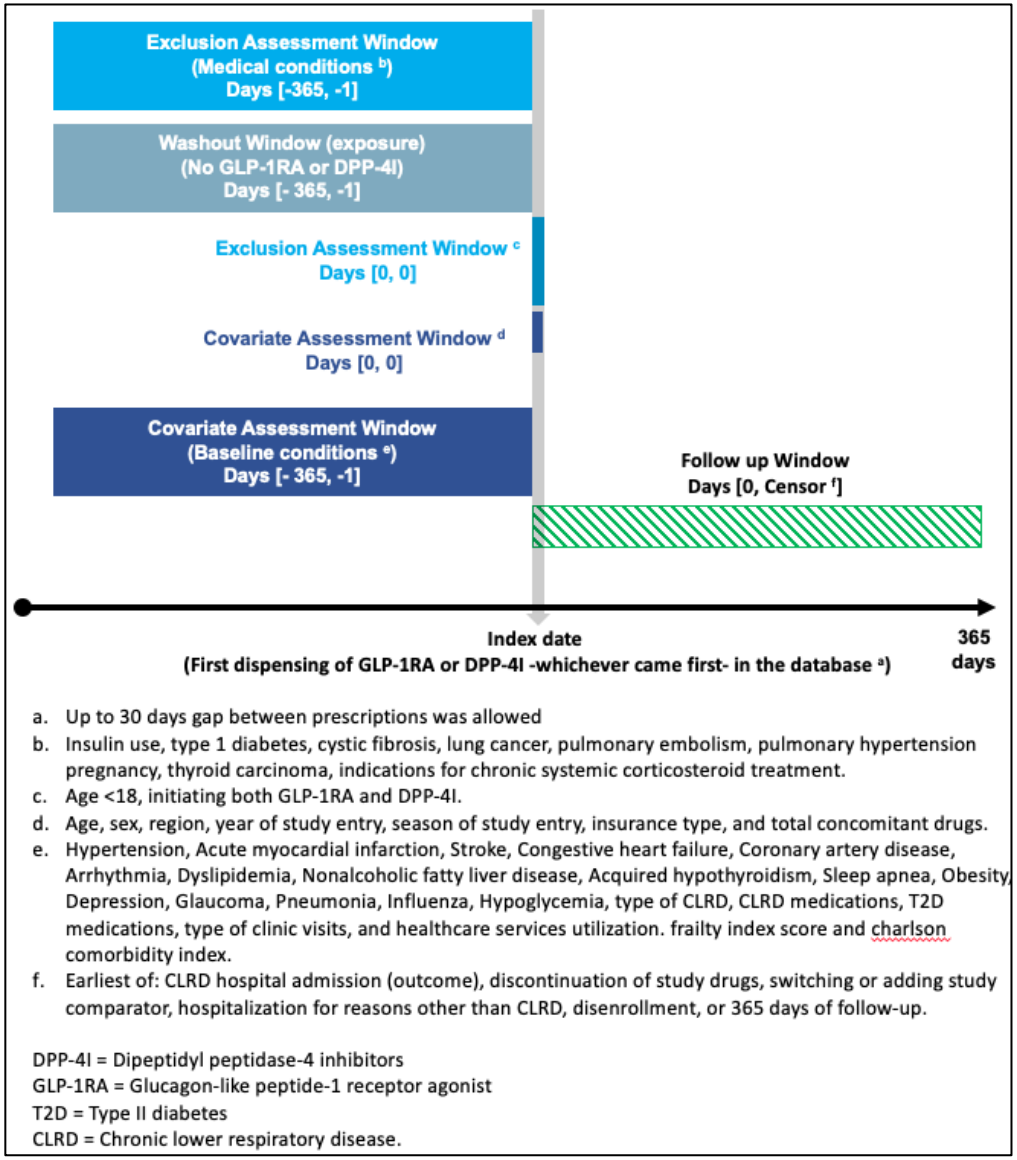
Table 2. Codes used to identify patients with chronic lower respiratory disease

ICD.9	Definition	ICD-10	Definition
493.0	Extrinsic asthma	J45	Asthma
493.00	Extrinsic asthma, unspecified	J45.2	Mild intermittent asthma
493.01	Extrinsic asthma with status asthmaticus	J45.3	Mild persistent asthma
493.02	Extrinsic asthma with (acute) exacerbation	J45.4	Moderate persistent asthma
493.1	Intrinsic asthma	J45.5	Severe persistent asthma
493.10	Intrinsic asthma, unspecified	J45.9	Other and unspecified asthma
493.11	Intrinsic asthma with status asthmaticus	J45.21	Mild intermittent asthma with (acute) exacerbation
493.12	Intrinsic asthma with (acute) exacerbation	J45.31	Mild persistent asthma with (acute) exacerbation
493.2	Chronic obstructive asthma	J45.41	Moderate persistent asthma with (acute) exacerbation
493.20	Chronic obstructive asthma, unspecified	J45.51	Severe persistent asthma with (acute) exacerbation
493.21	Chronic obstructive asthma with status asthmaticus	J45.901	Other and unspecified asthma with (acute) exacerbation
493.22	Chronic obstructive asthma with (acute) exacerbation	J45.990	Other asthma Exercise induced bronchospasm
493.8	Other forms of asthma	J40	Bronchitis, not specified as acute or chronic
493.81	Exercise induced bronchospasm	J41	Simple and mucopurulent chronic bronchitis
493.82	Cough variant asthma	J42	Unspecified chronic bronchitis
493.9	Asthma unspecified	J43	Emphysema
493.90	Asthma, unspecified type, unspecified	J44	Other chronic obstructive pulmonary disease
493.91	Asthma, unspecified type, with status asthmaticus		
493.92	Asthma, unspecified type, with (acute) exacerbation		
490	Bronchitis, not specified as acute or chronic		
491	Chronic bronchitis		
492	Emphysema		
496	Chronic airway obstruction, not elsewhere classified		
506.4	Chronic respiratory conditions due to fumes and vapors		

Table 3. Crude Number of users and events per study compounds

	GLP-1RA				DPP-4I			
	Liraglutide	**Exenatide**	**Albiglutide**	**Dulaglutide**	**Alogliptin**	**Linagliptin**	**Saxagliptin**	**Sitagliptin**
Users, No	**1784**	**1685**	**85**	**573**	**62**	**911**	**1764**	**9652**
Primary outcome, No	**16**	**5**	**1**	**1**	**1**	**13**	**23**	**114**
Proportion (per 100 users)	**0.89**	**0.30**	**1.1**	**0.17**	**1.6**	**1.4**	**1.3**	**1.2**

Figure 1. Study timeline, inclusion and exclusion criteria, exposure, outcome and confounders definition.



a. Up to 30 days gap between prescriptions was allowed
b. Insulin use, type 1 diabetes, cystic fibrosis, lung cancer, pulmonary embolism, pulmonary hypertension pregnancy, thyroid carcinoma, indications for chronic systemic corticosteroid treatment.
c. Age <18, initiating both GLP-1RA and DPP-4I.
d. Age, sex, region, year of study entry, season of study entry, insurance type, and total concomitant drugs.
e. Hypertension, Acute myocardial infarction, Stroke, Congestive heart failure, Coronary artery disease, Arrhythmia, Dyslipidemia, Nonalcoholic fatty liver disease, Acquired hypothyroidism, Sleep apnea, Obesity, Depression, Glaucoma, Pneumonia, Influenza, Hypoglycemia, type of CLRD, CLRD medications, T2D medications, type of clinic visits, and healthcare services utilization. frailty index score and charlson comorbidity index.
f. Earliest of: CLRD hospital admission (outcome), discontinuation of study drugs, switching or adding study comparator, hospitalization for reasons other than CLRD, disenrollment, or 365 days of follow-up.

DPP-4I = Dipeptidyl peptidase-4 inhibitors
GLP-1RA = Glucagon-like peptide-1 receptor agonist
T2D = Type II diabetes
CLRD = Chronic lower respiratory disease.

Figure 2. Sample selection flow chart

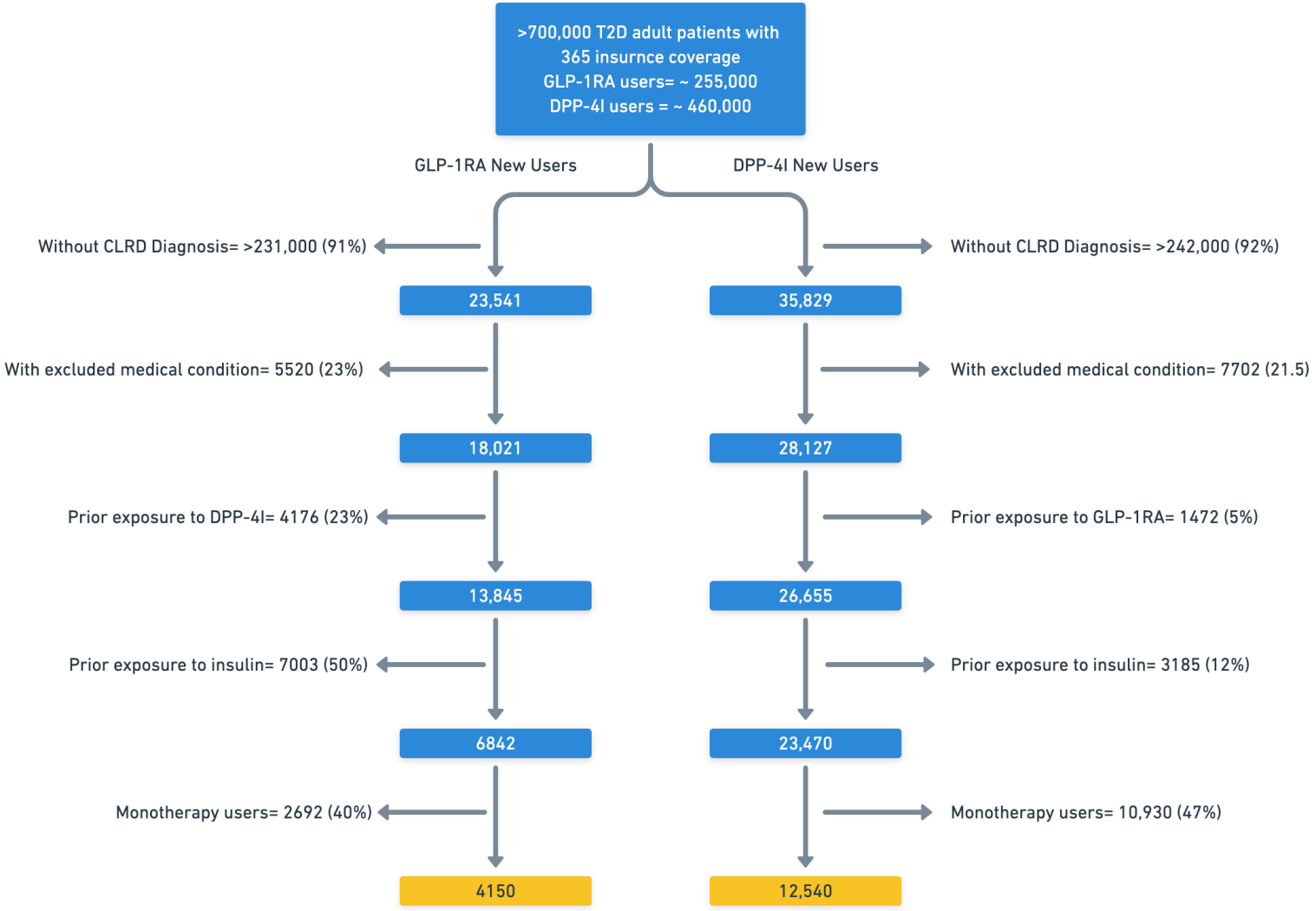
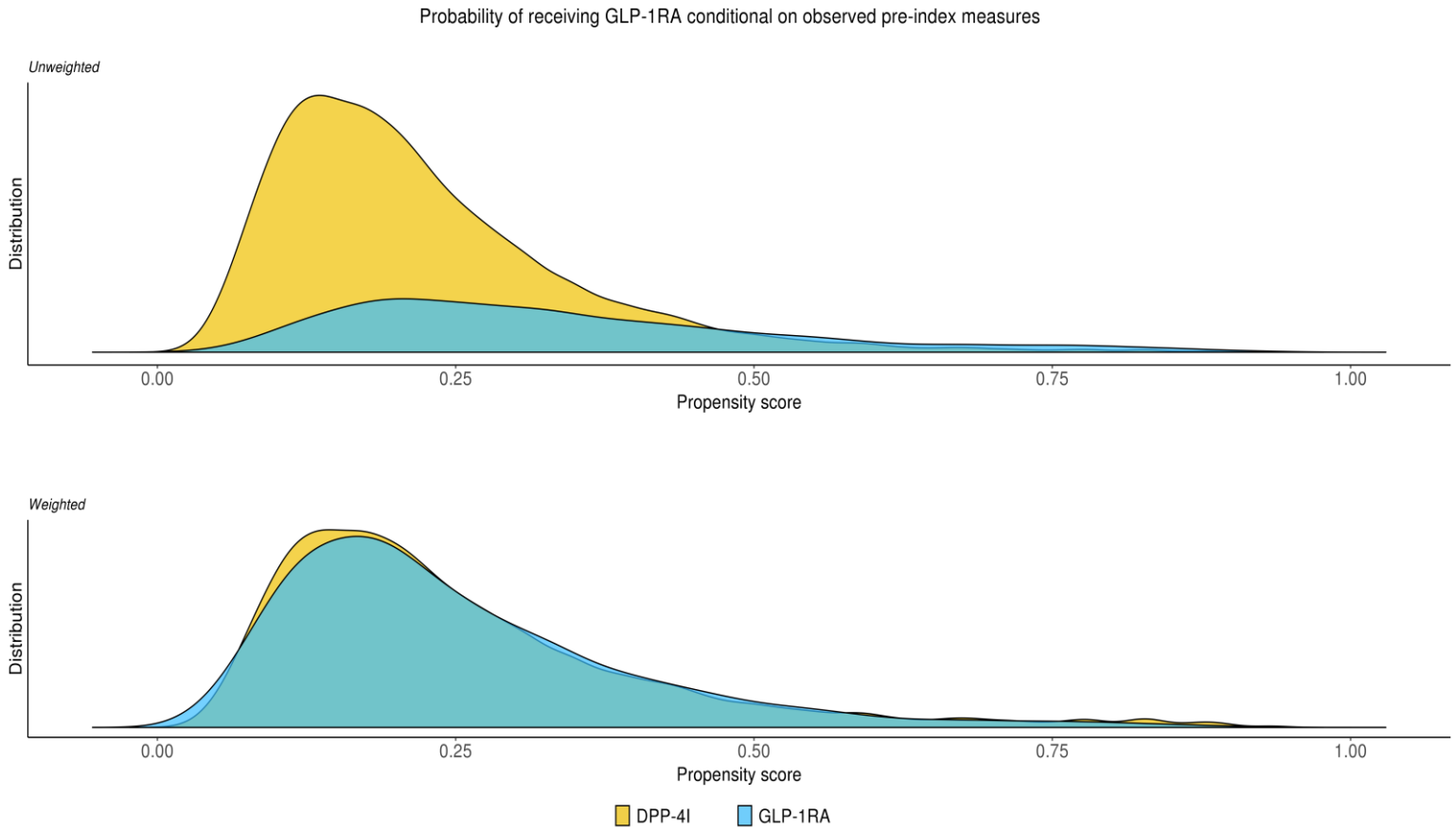
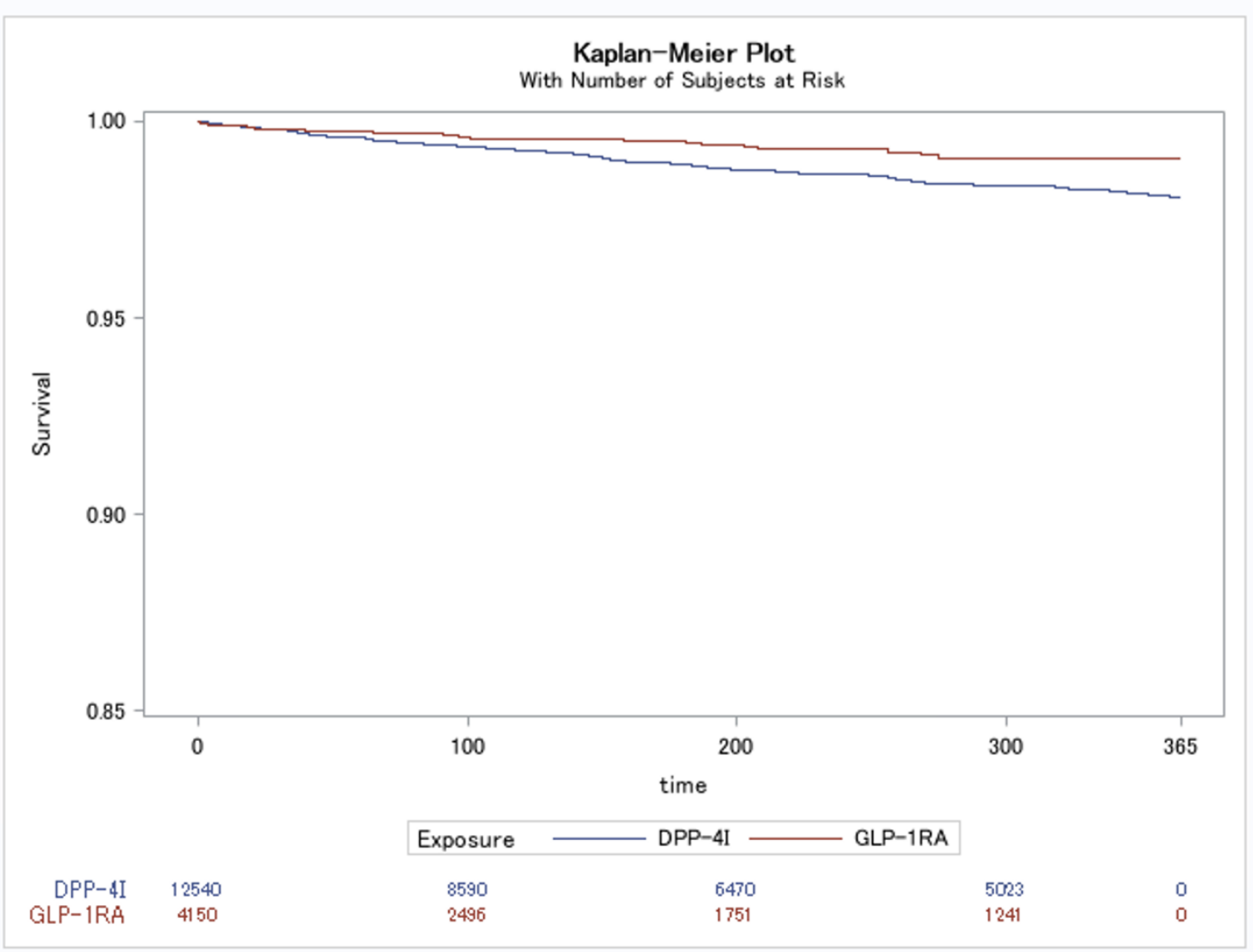


Figure 3. Propensity score distribution of GLP-1RA versus DPP-4I initiation before and after the application of stabilized inverse probability of treatment weighting



DPP-4I: Dipeptidyl peptidase-4 inhibitors
GLP-1RA: Glucagon-like peptide-1 receptor agonists

Figure 4. Kaplan–Meier Curve of CLRD hospitalization



Appendix 1. Potential confounders included in the study

Based on a literature search, in addition to clinical expert input, the following covariates were included as potential confounders: age, sex, comorbid conditions, geographic region, year of the index date, and health plan type. We also identified the physician specialty the patient visited, the number of outpatient visits, the number of hospitalizations, the number of emergency room visits, the number of unique prescriptions received during baseline and total unique prescriptions used at index date. Moreover, we identified measured the total number of oral corticosteroids having been dispensed, the total number of CLRD rescue medications having been dispensed, the total number of CLRD control medications having been dispensed, and type of CLRD (asthma, COPD, or both). We also identified patients who initiated the study drug as dual or triple therapy of diabetes regimen, the history of previous exposure to any hypoglycemic agents' class including sulfonylurea, SGLT-2I, metformin, and glitazones. We measured diabetes severity for the patients according to the validated Diabetes Complications Severity Index (DCSI) which translates the number of diabetes complications into a severity score ranging from 0 to 13. (1) Also, a frailty score for each patient was estimated using a validated claims-based index. (2) Finally, we measured the number of eye-exams, proteinuria analysis and blood glucose testing. All measured confounders were ascertained during the 1-year baseline period. The following table lists the measured confounders and corresponding measurements.

Variable	Type	Measurement
Demographics		
Sex	Categorical	1= Male, 2=Female
Age	Continuous	18 - 65 calendar year
Geographic region	Categorical	1=Northeast, 2=North Central, 3=South, 4=West, 5=Unknown
Health plan type	Categorical	1=Preferred Provider Organization Plan , 2=Non-Preferred Provider Organization Plan
Year of drug initiation	Categorical	2007 - 2017
Season of drug initiation	Categorical	Winter: December-February; Spring: March-May; Summer: June-August; Fall: September-November.
Visit to family medicine physicians	Categorical	Total number within a year of exposure initiation
Visit to endocrinologist	Categorical	Total number within a year of exposure initiation
Visit to pulmonologist	Categorical	Total number within a year of exposure initiation
Comorbidities		
Acquired hypothyroidism	Categorical	ICD-9:244.0, 244.1, 244.2, 244.3, 244.8, 244.9.
		ICD-10: E01.8, E02, E03.2, E03.3, E03.8, E03.9, E89.0
Acute myocardial infarction	Categorical	ICD-9: 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91.
		ICD-10: I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9
Glaucoma	Categorical	ICD-9: 362.85, 365.00, 365.01, 365.02, 365.03, 365.04, 365.10, 365.11, 365.12, 365.13, 365.15, 365.20, 365.21, 365.22, 365.23, 365.24, 365.31, 365.32, 365.41, 365.42, 365.43, 365.51, 365.52, 365.59, 365.60, 365.61, 365.62, 365.63, 365.64, 365.65, 365.81, 365.82, 365.83, 365.89, 365.9, 377.14
		ICD-10: H35.89, H40.001, H40.002, H40.003, H40.009, H40.011, H40.012, H40.013, H40.019, H40.031, H40.032, H40.033, H40.039, H40.041, H40.042, H40.043, H40.049,

		H40.051, H40.052, H40.053, H40.059, H40.10X0, H40.10X1, H40.10X2, H40.10X3, H40.10X4, H40.11X0, H40.11X1, H40.11X2, H40.11X3, H40.11X4, H40.1210, H40.1211, H40.1212, H40.1213, H40.1214, H40.1220, H40.1221, H40.1222, H40.1223, H40.1224, H40.1230, H40.1231, H40.1232, H40.1233, H40.1234, H40.1290, H40.1291, H40.1292, H40.1293, H40.1294, H40.1310, H40.1311, H40.1312, H40.1313, H40.1314, H40.1320, H40.1321, H40.1322, H40.1323, H40.1324, H40.1330, H40.1331, H40.1332, H40.1333, H40.1334, H40.1390, H40.1391, H40.1392, H40.1393, H40.1394, H40.1410, H40.1411, H40.1412, H40.1413, H40.1414, H40.1420, H40.1421, H40.1422, H40.1423, H40.1424, H40.1430, H40.1431, H40.1432, H40.1433, H40.1434, H40.1490, H40.1491, H40.1492, H40.1493, H40.1494, H40.151, H40.152, H40.153, H40.159, H40.20X0, H40.20X1, H40.20X2, H40.20X3, H40.20X4, H40.211, H40.212, H40.213, H40.219, H40.2210, H40.2211, H40.2212, H40.2213, H40.2214, H40.2220, H40.2221, H40.2222, H40.2223, H40.2224, H40.2230, H40.2231, H40.2232, H40.2233, H40.2234, H40.2290, H40.2291, H40.2292, H40.2293, H40.2294, H40.231, H40.232, H40.233, H40.239, H40.241, H40.242, H40.243, H40.249, H40.30X0, H40.30X1, H40.30X2, H40.30X3, H40.30X4, H40.31X0, H40.31X1, H40.31X2, H40.31X3, H40.31X4, H40.32X0, H40.32X1, H40.32X2, H40.32X3, H40.32.X4, H40.33X0, H40.33X1, H40.33X2, H40.33X3, H40.33X4, H40.40X0, H40.40X1, H40.40X2, H40.40X3, H40.40X4, H40.41X0, H40.41X1, H40.41X2, H40.41X3, H40.41X4, H40.42X0, H40.42X1, H40.42X2, H40.42X3, H40.42X4, H40.43X0, H40.43X1, H40.43X2, H40.43X3, H40.43X4, H40.50X0, H40.50X1, H40.50X2, H40.50X3, H40.50X4, H40.51X0, H40.51X1, H40.51X2, H40.51X3, H40.51X4, H40.52X0, H40.52X1, H40.52X2, H40.52X3, H40.52X4, H40.53X0, H40.53X1, H40.53X2, H40.53X3, H40.53X4, H40.60X0, H40.60X1, H40.60X2, H40.60X3, H40.60X4, H40.61X0, H40.61X1, H40.61X2, H40.61X3, H40.61X4, H40.62X0, H40.62X1, H40.62X2, H40.62X3, H40.62X4, H40.63X0, H40.63X1, H40.63X2, H40.63X3, H40.63X4, H40.811, H40.812, H40.813, H40.819, H40.821, H40.822, H40.823, H40.829, H40.831, H40.832, H40.833, H40.839, H40.89, H40.9, H47.231, H47.232, H47.233, H47.239
Congestive heart failure	Categorical	ICD-9: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
		ICD-10: I09.81, I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40. I50.41, I50.42, I50.43, I50.9
Nonalcoholic fatty liver disease	Categorical	ICD-9: 571.8
		ICD-10: K76.0
Hypertension	Categorical	ICD-9: 362.11, 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 437.2

		ICD-10: H35.031, H35.032, H35.033, H35.039, I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9, I67.4, N26.2
Stroke	Categorical	ICD-9: 430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
		ICD-10: G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2, G97.31, G97.32, I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.20, I60.21, I60.22, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.52, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63.00, I63.02, I63.011, I63.012, I63.019, I63.031, I63.032, I63.039, I63.09, I63.10, I63.111, I63.112, I63.119, I63.12, I63.131, I63.132, I63.139, I63.19, I63.20, I63.211, I63.212, I63.219, I63.22, I63.231, I63.232, I63.239, I63.29, I63.30, I63.311, I63.312, I63.319, I63.321, I63.322, I63.329, I63.331, I63.332, I63.339, I63.341, I63.342, I63.349, I63.39, I63.40, I63.411, I63.412, I63.419, I63.421, I63.422, I63.429, I63.431, I63.432, I63.439, I63.441, I63.442, I63.449, I63.49, I63.50, I63.511, I63.512, I63.519, I63.521, I63.522, I63.529, I63.531, I63.532, I63.539, I63.541, I63.542, I63.549, I63.59, I63.6, I63.8, I63.9, I66.01, I66.02, I66.03, I66.09, I66.11, I66.12, I66.13, I66.19, I66.21, I66.22, I66.23, I66.29, I66.3, I66.8, I66.9, I67.841, I67.848, I67.89, I97.810, I97.811, I97.820, I97.821
Coronary artery disease	Categorical	ICD-9: 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.4, 414.8, 414.9
		ICD-10: I20.0, I20.1, I20.8, I20.9, I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9, I24.0, I24.1, I24.8, I24.9, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.42, I25.5, I25.6, I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9
Arrhythmia	Categorical	ICD-9: 427.0, 427.1, 427.2, 427.4, 427.5, 427.6, 427.7, 427.8, 427.8
		ICD-10: I149
Dyslipidemia	Categorical	ICD-9: 272.0, 272.1, 272.2, 272.3, 272.4
		ICD-10: E78.0, E78.1, E78.2, E78.3, E78.4, E78.5
Sleep apnea	Categorical	ICD-9: 780.51, 780.57, G47.33, 327.23, 780.53
		ICD-10: G47.30, G47.33, G47.39
Obesity	Categorical	ICD-9: 278.00, 278.01, 278.03, V85.30, V85.31, V85.32, V85.33, V85.34, V85.35, V85.36, V85.37, V85.38, V85.39, V85.41, V85.42, V85.43, V85.44, V85.45, 278.01, V85.35, V85.36, V85.37, V85.38, V85.39, V85.41, V85.42, V85.43, V85.44, V85.45

		ICD-10: E66.09, E66.1, E66.2, E66.8, E66.9, Z68.30, Z68.31, Z68.32, Z68.33, Z68.34, Z68.35, Z68.36, Z68.37, Z68.38, Z68.39, Z68.41, Z68.42, Z68.43, Z68.44, Z68.45
Depression	Categorical	ICD-9: 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
		ICD-10: F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.75, F31.76, F31.77, F31.78, F31.81, F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.9, F33.0, F33.1, F33.2, F33.3, F33.40, F33.41, F33.42, F33.9, F34.1, F43.21
Pneumonia	Categorical	ICD-9: 480-486
		ICD-10: J18.9, J18.0, J18.1, J18.2, J18.8, J12.0 - J12.9, J13 - J17
Influenza	Categorical	ICD-9: 487-488
		ICD-10: J11.00, J11.1, J11.2, J11.83, J11.89
Hypoglycemia	Categorical	ICD-9: 2510, 2511, 2512
		ICD-10: E0864, E1164, E1364
Healthcare Services Utilization		
Total number of hospital visits	Continuous	Total number within a year of exposure initiation
Total number of total hospitalizations	Continuous	Total number within a year of exposure initiation
History of CLRD-related hospitalizations	Categorical	Exists of CLRD codes as primary diagnosis (1=Yes, 0=No)
Total number of total unique prescriptions dispensing	Continuous	Total number within a year of exposure initiation
Total number of total concomitant prescriptions	Continuous	Total number of unique prescriptions that the days of supply overlap with study index-date
Number of total emergency department visits	Continuous	Total number within a year of exposure initiation
Total number of oral corticosteroids dispensing	Continuous	Total number within a year of exposure initiation
Total number of CLRD rescue medications dispensing	Continuous	Total number within a year of exposure initiation (short-acting beta-agonist and short acting muscarinic antagonist)
Total number of CLRD controller medications dispensing	Continuous	Total number within a year of exposure initiation (inhaled corticosteroid, long-acting beta agonist, leukotrienes modifiers, long-acting muscarinic antagonist)
Oxygen supplement use	Categorical	HCPCS: E1352, E1354, E1356, E1357, E1358, E1390, E1391, E1392, E1405, E1406, E0424, E0430, E0431, E0433, E0434, E0435, E0439, E0440, E0441, E0442, E0443, E0444, E0445, E0446, E0447, E0455, E0467, E0550, E0560
Double or triple therapy	Categorical	1=double, 2=triple

Total number of metformin use	Continuous	Total number within a year of exposure initiation
Total number of sulfonylurea use	Continuous	Total number within a year of exposure initiation
Total number of glitazone use	Continuous	Total number within a year of exposure initiation
Total number of SGLT-2I use	Continuous	Total number within a year of exposure initiation
Eye-exams	Continuous	CPT: 92081, 92083, 2019F, 2020F, 2021F, 2022F, 5010F HCPCS: G2102
Proteinuria	Continuous	CPT: 82042, 82043, 82044
Blood glucose test	Continuous	CPT: 80047, 80048, 80050, 80053, 80069, 82947, 82950, 82951, 83036

Appendix 2. Sensitivity analyses

Bayesian additive regression trees (BART)

In the primary analysis, we fitted a logistic regression model to estimate the propensity score of initiating GLP-1RA. However, the model was likely to be mis-specified as no interaction terms or nonlinear effects were included. (3) Thus, we performed a sensitivity analysis by fitting the PS using BART. BART can identify interactions and nonlinearity and thus provide a more flexible model specification. The primary outcome analysis was repeated using propensity score estimated from BART model.

Propensity score matching

We also used matching instead of weighting to minimize the impact of extreme weights. We matched GLP-1RA users to at least two DPP-4I users based on the estimated propensity score. The matching method was nearest neighbor without replacement using a caliber of 0.2 We then repeated the primary outcome analysis.

Unmeasured confounders adjustment

Obesity and smoking are two well-known risk factors for diabetes and CLRD, but they are often considered unmeasured in claims data because of the very low sensitivity of measurement. To adjust for these measures, we used the IBM MarketScan® Health Risk Assessment (HRA) Database which contains self-reported data of enrollees in health plans that contribute to the IBM MarketScan® Commercial Claims data. The HRA data include body mass index (BMI) and the status of smoking which both can be linked to a sub-sample of the study participants. If the BMI is greater than 30, then the enrollee is deemed obese. Multiple imputations by chained equations (MICE) was used to fit classification and regression tree (CART) conditional on all measured confounders, exposure and outcome to create predictive models from which missing values were imputed. Finally, a pooled estimate was obtained from all imputed datasets with its corresponding 95% confidence interval for the primary outcome. Although the HRA data is available for only about 5% of the claims data populations, our analysis suggest that it is representative of the claims data, which allows for multiple imputation analysis. We have further evaluated this in a recent simulation study where even with extreme missingness multiple imputation approximated the true effect. (4)

High-dimensional propensity score (HdPS)

We performed HdPS which is a semi-automatic technique to identify potential confounders that were not prespecified or to capture proxies of unmeasured confounders if exist. (5) We included the top 100 potential confounders and proxies according to HdPS, in addition to the pre-specified ones, in the PS model. We then repeated the primary outcome analysis from which HR and 95% confidence intervals were estimated.

CLRD hospitalization definition

We restricted the definition of the CLRD hospitalization to appear only in the principal diagnosis of the admission to improve the specificity of the outcome measure.

Sulfonylurea as a comparison

A previous pharmacovigilance study has linked DPP-4I to lower respiratory tract infections. (6) If this is the case, the observed association may have been exaggerated. Even though this association was refuted by retrospective observational and RCTs data, (7–9) we conducted a sensitivity analysis with sulfonylurea drugs as a comparator instead of DPP-4I to validate the observed association.

Negative outcome

We conducted an analysis to replicate a known effect of GLP-1RA and DPP-4I. We assumed that the study drugs are not associated with skin infection hospitalization; otherwise, a healthy user bias may exist. Therefore, a negative outcome analysis using skin infection as the outcome was carried out.

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