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Glucose-Lowering Medications and Risk of Chronic Obstructive Pulmonary Disease Exacerbations in Patients With Type 2 Diabetes

Avik Ray, MD, MS; Julie M. Paik, MD, ScD, MPH; Deborah J. Wexler, MD, MSc; Sushama K. Sreedhara, MBBS, MSPH; Katsiaryna Bykov, PharmD, ScD; William B. Feldman, MD, DPhil, MPH; Elisabetta Patorno, MD, DrPH

IMPORTANCE Recent studies have suggested that sodium-glucose cotransporter-2 inhibitors (SGLT-2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and dipeptidyl peptidase 4 inhibitors (DPP-4is) may benefit patients with chronic obstructive pulmonary disease (COPD). However, clinical evidence is lacking on their comparative association with COPD exacerbations in US patients with type 2 diabetes (T2D).

OBJECTIVE To compare the risk of moderate or severe COPD exacerbations among SGLT-2is, GLP-1RAs, and DPP-4is.

DESIGN, SETTING, AND PARTICIPANTS This comparative effectiveness research study used data from three 1:1 propensity score–matched cohort studies that emulated 3 target trials comparing patients 40 years or older with T2D and active COPD who initiated treatment with SGLT-2is vs DPP-4is, GLP-1RAs vs DPP-4is, and SGLT-2is vs GLP-1RAs. Data were from 3 US insurance claims databases: the Optum deidentified Clinformatics Data Mart Database (2013-2023), IBM Health MarketScan (2013-2021), and Medicare fee for service (2013-2020). The data analysis was conducted from January to June 2024.

EXPOSURES Initiation of SGLT-2i or DPP-4i, GLP-1RA or DPP-4i, and SGLT-2i or GLP-1RA for the 3 target trials, respectively.

MAIN OUTCOMES AND MEASURES First occurrence of a moderate or severe COPD exacerbation, defined as a filled prescription for oral glucocorticoids in association with an outpatient COPD visit or hospitalization for COPD. Incidence rates, incidence rate differences (IRDs), and hazard ratios (HRs) with 95% CIs were calculated.

RESULTS There were 27 991, 32 107, and 36 218 pairs in the SGLT-2i vs DPP-4i, GLP-1RA vs DPP-4i, and SGLT-2i vs GLP-1RA propensity score–matched cohorts, respectively (mean [SD] age, 70.8 [8.6] and 70.7 [8.8], 70.4 [8.5] and 70.4 [8.2], and 69.8 [8.7] years, respectively; 13 767 [49.2%] and 13 847 [49.5%], 17 622 [54.9%] and 17 620 [54.9%], and 18 807 [51.9%] and 18 854 [52.1%] female individuals, respectively). During a median follow-up of 145 (IQR, 61-355) days of treatment, the risk of moderate or severe COPD exacerbation was lower among those treated with SGLT-2is vs DPP-4is (9.26 vs 11.4 per 100 person-years [PYs]; HR, 0.81; 95% CI, 0.76-0.86; IRD/100 PYs, −2.20; 95% CI, −2.83 to −1.58) and among those treated with GLP-1RAs vs DPP-4is (9.89 vs 11.49 per 100 PYs; HR, 0.86; 95% CI, 0.81-0.91; IRD/100 PYs, −1.60; 95% CI, −2.18 to −1.02), with minimal differences among those treated with SGLT-2is vs GLP-1RAs (9.47 vs 10.00 per 100 PYs; HR, 0.94; 95% CI, 0.89-1.00; IRD/100 PYs, −0.55; 95% CI, −1.09 to −0.01). Results were consistent across sensitivity and subgroup analyses.

CONCLUSIONS AND RELEVANCE The results of this comparative effectiveness research study suggest that SGLT-2is and GLP-1RAs were associated with a reduced risk of moderate or severe COPD exacerbations compared with DPP-4i in adults with T2D and active COPD. This may inform prescribing of glucose-lowering medications among patients with T2D and active COPD.

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Editor's Note
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Elisabetta Patorno, MD, DrPH, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont St, Ste 3030, Boston, MA 02120 (epatorno@bwh.harvard.edu).

Individuals with type 2 diabetes (T2D) and chronic obstructive pulmonary disease (COPD) face a heightened risk of adverse COPD-related outcomes, including longer hospital stays, severe complications (such as respiratory failure and sepsis), and increased medical expenses.[1] Sodium-glucose cotransporter-2 inhibitors (SGLT-2is), glucagon-like peptide 1 receptor agonists (GLP-1RAs), and dipeptidyl peptidase-4 inhibitors (DPP-4is) are commonly prescribed glucose-lowering medications for managing T2D. These medications have shown promise for potentially improving lung function, particularly for patients with COPD.[2] Recent meta-analyses and studies have shown an association of SGLT-2is with reduced COPD exacerbations,[3,4] GLP-1RAs with improved forced vital capacity,[5,6] and DPP-4is with reduced bronchial hyperresponsiveness by inhibiting the upregulated DPP-4 enzyme during COPD exacerbations.[7]

Previous observational studies on these medications and COPD exacerbations offered valuable insights but were limited by small populations, exclusion of moderate exacerbations, and unadjusted confounders, like body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and lung function.[8-10] A UK Clinical Practice Research Datalink study compared SGLT-2is, GLP-1RAs, and DPP-4is with sulfonylureas (SUs), but not with each other, which is more relevant given the declining use of SUs due to higher severe hypoglycemia risk[11] and lack of cardiovascular and kidney benefits compared with SGLT-2is and GLP-1RAs.[12]

Considering the elevated risk of COPD-related morbidity and mortality in individuals with T2D,[13,14] and the knowledge gap on the comparative association of glucose-lowering medications with COPD exacerbations for patients with T2D in the US, we conducted a comprehensive population-based cohort study using the target trial emulation framework[15] to assess the association of SGLT-2is, GLP-1RAs, and DPP-4is with COPD exacerbation risks.

Key Points

Question Is there a difference in chronic obstructive pulmonary disease (COPD) exacerbation risk among patients with type 2 diabetes (T2D) and active COPD who initiate treatment with sodium-glucose cotransporter-2 inhibitors (SGLT-2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), or dipeptidyl peptidase-4 inhibitors (DPP-4is)?

Findings In this comparative effectiveness research study of 393 847 patients with T2D and active COPD, in three 1:1 propensity score–matched studies using US insurance claims databases, the risk of moderate or severe COPD exacerbation was lower among those treated with SGLT-2is and GLP-1RAs vs DPP-4is (2.2 and 1.6 fewer events per 100 person-years, respectively), with no large differences between SGLT-2is and GLP-1RAs.

Meaning The study results suggest that SGLT-2is and GLP-1RAs may be preferable to DPP-4is for patients with T2D and active COPD; however, given the observational nature of the study, residual or unmeasured confounding cannot be ruled out.

Methods

Data Source

We used the Optum deidentified Clinformatics Data Mart database(April 2013 to November 2023), IBM Health MarketScan Research Database (April 2013 to December 2021), and Medicare fee-for-service claims data (April 2013 to December 2020), which contain longitudinal claims information on medical diagnoses, procedures, hospitalizations, physician visits, and pharmacy dispensing for commercially and federally insured adults across the US. The study protocol was approved by the institutional review board of Mass General Brigham, and data use agreements were in place. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[16]

Target Trial Specification and Emulation of Treatment Strategies

Specifications of the 3 target trials and their emulations are provided in eTables 1 to 3 in Supplement 1. We designed a target trial for each of the following pairwise comparisons: (1) SGLT-2is vs DPP-4is, (2) GLP-1RAs vs DPP-4is, and (3) SGLT-2is vs GLP-1RAs (see eTable 4 in Supplement 1 for the list of the individual medications included in each class). Cohort entry began on April 1, 2013, which corresponded with the approval of the first SGLT-2i (canagliflozin) by the US Food and Drug Administration,[17] extending to the latest available data for each data source. Patients were required to have at least 365 days of continuous enrollment in their health care plans before entry, with a permitted 30-day gap. The cohort entry date was a new prescription for a SGLT-2i, GLP-1RA, or DPP-4i without prior use of that medication class or the comparison class, depending on the specific target trial emulation, during the 365 days before cohort entry. All patients were required to have 1 or more diagnoses of T2D (defined by *International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* codes 250.xx and *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]* codes E11.xx)[18] along with an active COPD diagnosis, which was defined as 2 or more outpatient or 1 or more inpatient COPD diagnoses in any position. COPD was identified by *ICD-9-CM* codes 491.xx, 492.xx, or 496 and *ICD-10-CM* codes J41.x, J42, J43.x, J44.x during the 365 days before cohort entry.[19]

We excluded individuals who were younger than 40 years (to enhance the specificity of the COPD diagnosis) and those whose age or biological sex information were missing on the cohort entry date, along with pregnant individuals, patients with end-stage kidney disease or AIDS, or those who had undergone a bariatric surgery during the 365 days before cohort entry (eFigures 1-3 in Supplement 1).

Outcomes and Follow-Up

The primary study outcome was a severe or moderate COPD exacerbation. We defined severe exacerbation as a hospitalization for COPD, identified using the previously mentioned *ICD* codes in the primary discharge position (positive predictive value, 0.86).[20] A moderate COPD exacerbation was defined as an oral glucocorticoid (methylprednisolone, pred-

nisolone, or prednisone) prescription fill with a 5- to 14-day supply, accompanied by an outpatient visit within 3 days before or 7 days after the fill and COPD diagnosis in the primary position, and no hospitalization for COPD during the 14 days before or 14 days after the fill (positive predictive value, 0.73).[21] These definitions have been extensively used in treatment guidelines,[22] clinical trials,[23-25] and previous observational studies.[26-32] The secondary study outcome was severe COPD exacerbation only. We followed up patients from the day after cohort entry until the earliest day of discontinuation of the index treatment (with a grace period of 60 days between fills and an exposure risk extension period of 30 days after the end of the last fill's days supply), a switch to or addition of the comparator class, death, end of data, end of study period, or end of insurance coverage (eFigures 1-3 in Supplement 1).

Covariates

We measured potential confounders and their proxies during the 365-day baseline period before cohort entry (eFigures 1-3 in Supplement 1). We predefined covariates based on clinical expertise and prior evidence, including demographic characteristics (eg, age and sex), comorbidity burden (measured by a claims-based combined comorbidity score),[33] frailty (measured by a claims-based frailty score),[34] baseline COPD severity (eg, Global Initiative for Obstructive Lung Disease group E, defined as ≥1 severe exacerbations or ≥2 moderate exacerbations),[22] inhaler therapy use, active asthma diagnosis (defined as ≥2 outpatient or ≥1 inpatient asthma diagnosis at any position),[35] other comorbidities (eg, obesity, chronic kidney disease), diabetes medication use (eg, metformin and insulin), other medication classes (eg, diuretics and statins), and health care utilization (eg, hospitalizations and physician visits) (see eMethods in Supplement 1 for the complete list of covariates). Data on laboratory parameters, such as hemoglobin A_{1c} (HbA_{1c}) levels (approximately 50%, 90% and 100% missing data in Clinformatics Data Mart, MarketScan, and Medicare, respectively; to convert to the total proportion of hemoglobin, multiply by 0.01) were not available for all participants in any of the databases, and information on race and ethnicity was not available in MarketScan.

Statistical Analysis

We used 1:1 propensity score (PS) matching using logistic regression on 94 baseline covariates to balance characteristics across treatment arms within each database and achieve marginal exchangeability,[36] using a nearest neighbor approach with a 0.01 caliper on the PS scale.[37] Covariate balance was assessed using absolute standardized differences (ASDs), with values less than 0.10 indicating adequate balance.[38] Because information on race and ethnicity (in MarketScan) and HbA_{1c} levels were not available for all patients, these were not included in the PS model.

For each target trial emulation, we calculated the number of events, incidence rates, and incidence rate differences (IRDs) per 100 person-years [PYs], estimating hazard ratios (HRs) with 95% CIs using Cox proportional hazards models.[39] HRs and IRDs were pooled from each database via a random-effects meta-analysis (DerSimonian-Laird).[40] Finally, we produced cumulative incidence function plots with estimates calculated using the Kaplan-Meier method.

For the primary analysis, we assessed the on-treatment association (ie, the association of continued use of SGLT-2is, GLP-1RAs, or DPP-4is with the risk of COPD exacerbations). We performed several prespecified sensitivity and subgroup analyses that are described in the eMethods in Supplement 1. We redefined COPD exacerbations with greater specificity by including coprescriptions of respiratory antibiotics, oral glucocorticoids, and outpatient visits without recent COPD hospitalizations. We conducted intention-to-treat analyses to address potential informative censoring and shortened the exposure assessment window to 30 days to reduce potential exposure misclassification. We stratified analyses by baseline HbA_{1c} levels (<8.0% vs ≥8.0%) among the subset of patients with baseline HbA_{1c} values; and used PS fine stratification to include a larger study population for analysis.[41] All statistical analyses were conducted using the Aetion Evidence Platform, a software for clinical data analysis, version 4.73,[42] and RStudio, version 4.2 (Posit PBC). Statistical significance was set at .05.

Results

Study Population and Patient Characteristics

The overall study population included 143 696 patients, 146 795 patients, and 103 356 patients for the SGLT-2i vs DPP-4i, GLP-1RA vs DPP-4i, and SGLT-2i vs GLP-1RA target trial emulations, respectively. After 1:1 PS matching, 27 991 pairs for SGLT-2i vs DPP-4i, 32 107 pairs for GLP-1RA vs DPP-4i, and 36 218 pairs for SGLT-2i vs GLP-1RA were included in the analysis (eFigure 4 in Supplement 1).

Compared with SGLT-2i vs DPP-4i, the GLP-1RA vs DPP-4i cohort included more female individuals, individuals with active asthma, patients with frailty as measured by the frailty score, chronic kidney disease stage 3 to 4, and insulin and loop diuretic users. The SGLT-2i vs GLP-1RA cohort had more patients with sleep apnea or receiving continuous positive airway pressure/bilevel positive airway pressure and those with oxygen equipment use. The GLP-1RA vs DPP-4i and SGLT-2i vs GLP-1RA cohorts had higher proportion of patients with obesity compared with SGLT-2i vs DPP-4i (**Table 1**; eTables 5-7 in Supplement 1). The mean age was approximately 70 years, and approximately 11% were in Global Initiative for Obstructive Lung Disease group E for all cohorts. Covariates were well balanced postmatching.

Target Trial Emulation: SGLT-2i vs DPP-4i

The incidence rate of the primary COPD severe or moderate exacerbation outcome was lower for those treated with SGLT-2is (9.26/100 PYs) compared with those treated with DPP-4is (11.44/100 PYs) (HR, 0.81; 95% CI, 0.76-0.86; IRD/100 PYs, −2.20; 95% CI, −2.83 to −1.58) over a median follow-up time on treatment of 145 (IQR, 61-335) vs 147 (IQR, 62-336) days (**Table 2**). Discontinuation of the index treatment was the most common censoring reason (54.2% and 52.9%, respectively) for both arms (eTable 8 in Supplement 1). There were 6395 (11.4%)

Table 1. Selected Baseline Characteristics of Patients in the 1:1 PS-Matched Cohorts

Characteristic	1:1 PS-matched cohorts, No. (%)								
	SGLT-2i vs DPP-4i			GLP-1RA vs DPP-4i			SGLT-2i vs GLP-1RA		
	SGLT-2i (n = 27 991)	DPP-4i (n = 27 991)	Mean ASD	GLP-1RA (n = 32 107)	DPP-4i (n = 32 107)	Mean ASD	SGLT-2i (n = 36 218)	GLP-1RA (n = 36 218)	Mean ASD
Age, mean (SD), y	70.75 (8.62)	70.69 (8.79)	0.007	70.40 (8.49)	70.40 (8.18)	0.001	69.75 (8.72)	69.73 (8.68)	0.003
Sex									
Female	13 767 (49.2)	13 847 (49.5)	0.006	17 622 (54.9)	17 620 (54.9)	0.001	18 807 (51.9)	18 854 (52.1)	0.003
Race and ethnicity[a]									
Asian	280 (1.0)	300 (1.1)	0.061	225 (0.7)	321 (1.0)	0.089	398 (1.1)	326 (0.9)	0.045
Black	2687 (9.6)	3107 (11.1)		3082 (9.6)	3789 (11.8)		3875 (10.7)	3694 (10.2)	
Hispanic	868 (3.1)	1026 (3.7)		899 (2.8)	1060 (3.3)		1304 (3.6)	1195 (3.3)	
White	18 418 (65.8)	18 138 (64.8)		22 090 (68.8)	21 062 (65.6)		23 397 (64.6)	24 121 (66.6)	
Other/unknown/missing[b]	5738 (20.5)	5420 (19.4)		5811 (18.1)	5875 (18.3)		7244 (20.0)	6882 (19.1)	
Baseline HbA_{1c} level, mean (SD), %[a,c]	7.87 (1.78)	7.97 (1.76)	0.020	8.1 (1.8)	8.1 (1.8)	0.002	8.0 (1.8)	8.0 (1.8)	0.009
Baseline lung parameters									
GOLD group E[d]	3104 (11.1)	3098 (11.1)	0.001	3675 (11.4)	3660 (11.4)	0.001	3954 (10.9)	3906 (10.8)	0.004
Glucocorticoids (oral)	12 933 (46.2)	12 830 (45.8)	0.007	14 709 (45.8)	14 682 (45.7)	0.002	16 753 (46.3)	16 767 (46.3)	0.001
Pneumonia	7034 (25.1)	7015 (25.1)	0.002	8142 (25.4)	8141 (25.4)	0.001	8580 (23.7)	8633 (23.8)	0.003
Asthma (active)[e]	3547 (12.7)	3594 (12.8)	0.005	4534 (14.1)	4476 (13.9)	0.005	4725 (13.0)	4762 (13.1)	0.003
Pulmonary hypertension	2763 (9.9)	2821 (10.1)	0.007	2965 (9.2)	3025 (9.4)	0.006	3438 (9.5)	3547 (9.8)	0.010
Pulmonary embolism	1472 (5.3)	1437 (5.1)	0.006	1796 (5.6)	1830 (5.7)	0.005	1990 (5.5)	1989 (5.5)	0.001
Obstructive sleep apnea or CPAP/BiPAP	8103 (28.9)	8141 (29.1)	0.002	9835 (30.6)	9836 (30.6)	0.001	12537 (34.6)	12530 (34.6)	0.001
Dual therapy[f]	12700 (45.4)	12754 (45.6)	0.002	14702 (45.8)	14817 (46.1)	0.007	16767 (46.3)	16723 (46.2)	0.002
Triple therapy[g]	1607 (5.7)	1632 (5.8)	0.001	1715 (5.3)	1766 (5.5)	0.007	2704 (7.5)	2728 (7.5)	0.003
Respiratory events during the 60 d before cohort entry									
Moderate or severe COPD exacerbation	1223 (4.4)	1233 (4.4)	0.002	1330 (4.1)	1320 (4.1)	0.002	1445 (4.0)	1460 (4.0)	0.002
Respiratory antibiotics	8442 (30.2)	8460 (30.2)	0.001	10 035 (31.3)	10 078 (31.4)	0.003	10 816 (29.9)	10 878 (30.0)	0.004
COPD hospitalization	697 (2.5)	705 (2.5)	0.002	784 (2.4)	753 (2.3)	0.006	725 (2.0)	748 (2.1)	0.004
Oxygen equipment use	3473 (12.4)	3528 (12.6)	0.006	3603 (11.2)	3663 (11.4)	0.006	5473 (15.1)	5477 (15.1)	0.001
Comorbidities									
Obesity (BMI ≥30)	11 113 (39.7)	11 100 (39.7)	0.001	14 518 (45.2)	14 489 (45.1)	0.002	16 696 (46.1)	16 698 (46.1)	0.001
Combined comorbidity score, mean (SD)	5.31 (3.27)	5.27 (3.25)	0.012	5.46 (3.20)	5.46 (3.22)	0.002	5.19 (3.14)	5.21 (3.13)	0.005
Frailty score									
<0.15	1211 (4.3)	1218 (4.4)	0.005	1074 (3.3)	1072 (3.3)	0.003	1481 (4.1)	1489 (4.1)	0.002
0.15-0.25	12 826 (45.8)	12 885 (46.0)		13 245 (41.3)	13 285 (41.4)		16 953 (46.8)	16 967 (46.8)	
≥0.25	13 954 (49.9)	13 888 (49.6)		17 788 (55.4)	17 750 (55.3)		17 784 (49.1)	17 762 (49.0)	
Diabetic retinopathy	10 626 (38.0)	10 524 (37.6)	0.008	12 714 (39.6)	12 743 (39.7)	0.002	14 766 (40.8)	14 820 (40.9)	0.003
Diabetic neuropathy	9360 (33.4)	9301 (33.2)	0.004	11 541 (35.9)	11 547 (36.0)	0.001	13 218 (36.5)	13 181 (36.4)	0.002
Peripheral vascular disease/surgery	7352 (26.3)	7224 (25.8)	0.010	8729 (27.2)	8724 (27.2)	0.001	9146 (25.3)	9141 (25.2)	0.001
Congestive heart failure	12 352 (44.1)	12 237 (43.7)	0.008	14 239 (44.3)	14 127 (44.0)	0.007	15 671 (43.3)	15 725 (43.4)	0.003
CKD stage 1-2	1549 (5.5)	1532 (5.5)	0.003	1757 (5.5)	1701 (5.3)	0.008	2052 (5.7)	2038 (5.6)	0.002
CKD stage 3-4	6356 (22.7)	6194 (22.1)	0.014	8688 (27.1)	8705 (27.1)	0.001	8498 (23.5)	8539 (23.6)	0.003
MASH/MASLD	2029 (7.2)	2066 (7.4)	0.005	2347 (7.3)	2316 (7.2)	0.004	2962 (8.2)	2996 (8.3)	0.003

(continued)

Table 1. Selected Baseline Characteristics of Patients in the 1:1 PS-Matched Cohorts (continued)

Characteristic	1:1 PS-matched cohorts, No. (%)								
	SGLT-2i vs DPP-4i			GLP-1RA vs DPP-4i			SGLT-2i vs GLP-1RA		
	SGLT-2i (n = 27 991)	DPP-4i (n = 27 991)	Mean ASD	GLP-1RA (n = 32 107)	DPP-4i (n = 32 107)	Mean ASD	SGLT-2i (n = 36 218)	GLP-1RA (n = 36 218)	Mean ASD
Other medications									
Insulins (concurrent use)[h]	10 741 (38.4)	10 595 (37.9)	0.011	15 672 (48.8)	15 632 (48.7)	0.002	15 637 (43.2)	15 677 (43.3)	0.002
Sulfonylureas (second generation)	10 083 (36.0)	10 003 (35.7)	0.006	11 266 (35.1)	11 307 (35.2)	0.003	13 163 (36.3)	13 003 (35.9)	0.009
Metformin (concurrent use)[h]	13 860 (49.5)	13 873 (49.6)	0.001	14 321 (44.6)	14 357 (44.7)	0.002	16 545 (45.7)	16 593 (45.8)	0.003
GLP-1RA	3095 (11.1)	2894 (10.3)	0.023	NA	NA	NA	NA	NA	NA
SGLT-2i	NA	NA	NA	3052 (9.5)	3131 (9.8)	0.008	NA	NA	NA
DPP-4i	NA	NA	NA	NA	NA	NA	9107 (25.1)	9058 (25.0)	0.003
Thiazolidinediones	1853 (6.6)	1916 (6.8)	0.009	1957 (6.1)	1994 (6.2)	0.005	2464 (6.8)	2462 (6.8)	0.001
Health care utilization, mean (SD)									
No. of hospitalizations	1.21 (1.58)	1.20 (1.52)	0.009	1.24 (1.55)	1.24 (1.56)	0.001	1.09 (1.46)	1.09 (1.53)	0.001
No. of pulmonologist visits	1.93 (4.46)	1.94 (3.95)	0.001	1.96 (4.06)	1.93 (4.38)	0.006	1.83 (4.05)	1.83 (3.97)	0.001
Influenza vaccination	14 229 (50.8)	14 142 (50.5)	0.006	16 786 (52.3)	16 781 (52.3)	0.001	18 117 (50.0)	18 124 (50.0)	0.001
Socioeconomic status parameters, mean (SD)									
Ratio of unique brand to generic medicines	1.03 (0.04)	1.03 (0.04)	0.002	1.03 (0.04)	1.03 (0.04)	0.003	1.03 (0.04)	1.03 (0.04)	0.001

Abbreviations: ASD, absolute standardized difference; BiPAP, bilevel positive airway pressure; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HbA_{1c}, hemoglobin A_{1c}; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; MASH, nonalcoholic steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; NA, not applicable; PS, propensity score; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

SI conversion factor: to convert HbA_{1c} to the proportion of total hemoglobin, multiply by 0.01.

[a] Not used in the PS model.

[b] Missing: 100% in MarketScan; others/unknown/missing: approximately 5% in the Optum deidentified Clinformatics Data Mart Database and approximately 3% in Medicare.

[c] Available for approximately 50% in the Optum deidentified Clinformatics Data Mart Database, approximately 10% in MarketScan, and 0% in Medicare.

[d] GOLD group E refers to 2 or more moderate and/or 1 or more severe COPD exacerbations.

[e] Active asthma disease was defined as at least 2 outpatient or at least 1 inpatient asthma diagnoses at any position; asthma was identified by *International Classification of Diseases, Ninth Revision* codes 493.xx and *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* codes J45.xx.

[f] Use of SABA-SAMA, LABA-LAMA, or LABA-ICS in the 365 days prior to cohort entry.

[g] Use of LABA-LAMA-ICS during the 365 days before cohort entry.

[h] Measured during the 90 days before cohort entry up to the cohort entry date to indicate concurrent use.

and 6388 (11.4%) patients still undergoing follow-up at 1 year in the SGLT-2i and DPP-4i groups, respectively.

For the secondary outcome of severe COPD exacerbation, the initiation of treatment with SGLT-2is was also associated with a lower risk compared with DPP-4is (HR, 0.71; 95% CI, 0.65-0.78; IRD/100 PYs, −1.42; 95% CI, −1.81 to −1.03). The results showed consistency across subgroup analyses on relative and absolute scales, with indications of greater absolute benefit of SGLT-2is in patients with active asthma, heart failure, or a higher BMI (**Figure 1**).

Target Trial Emulation: GLP-1RA vs DPP-4i

The incidence rate of the primary COPD severe or moderate exacerbation outcome was lower for those treated with GLP-1RA (9.89/100 PYs) compared with those treated with DPP-4is (11.49/100 PYs) (HR, 0.86; 95% CI, 0.81-0.91; IRD/100 PYs, −1.60; 95% CI, −2.18 to −1.02) during a median follow-up time receiving treatment of 142 (IQR, 63-339) vs 156 (IQR, 66-355) days (Table 2). Discontinuation of index treatment was the most common censoring reason (57.5% and 56.1%) for both arms (eTable 8 in Supplement 1). There were 7432 (11.6%) and 7783 (12.1%) patients still undergoing follow-up at 1 year in the GLP-1RA and DPP-4i arms, respectively.

For the secondary outcome of severe COPD exacerbation, results remained consistent, with a lower risk among those treated with GLP-1RAs compared with DPP-4is (HR, 0.82; 95% CI, 0.76-0.89; IRD/100 PYs, −1.06; 95% CI, −2.18 to −1.02). Subgroup analyses showed largely consistent results overall on relative and absolute scales (**Figure 2**).

Table 2. First Chronic Obstructive Pulmonary Disease Exacerbation in the 1:1 Propensity Score–Matched Cohorts

Parameters	SGLT-2i vs DPP-4i		GLP-1RA vs DPP-4i		SGLT-2i vs GLP-1RA	
	SGLT-2i (n = 27 991)	DPP-4i (n = 27 991)	GLP-1RA (n = 32 107)	DPP-4i (n = 32 107)	SGLT-2i (n = 36 218)	GLP-1RA (n = 36 218)
Moderate or severe exacerbation						
No. of events	1886	2334	2365	2829	2363	2525
Follow-up time, median (IQR), d	145 (61 to 335)	147 (62 to 336)	142 (63 to 339)	156 (66 to 355)	141 (61 to 316)	139 (65 to 314)
IR/100 PYs	9.26	11.44	9.89	11.49	9.47	10.00
IRD/100 PYs (95% CI)	−2.20 (−2.83 to −1.58)		−1.60 (−2.18 to −1.02)		−0.55 (−1.09 to −0.01)	
HR (95% CI)	0.81 (0.76 to 0.86)		0.86 (0.81 to 0.91)		0.94 (0.89 to 1.00)	
Severe exacerbation						
No. of events	842	1201	1195	1510	1025	1121
Follow-up time, median (IQR), d	150 (67 to 354)	155 (69 to 356)	147 (69 to 356)	164 (73 to 377)	147 (67 to 329)	144 (70 to 331)
IR/100 PYs	3.95	5.61	4.79	5.84	3.94	4.24
IRD/100 PYs (95% CI)	−1.42 (−1.81 to −1.03)		−1.06 (−1.46 to −0.65)		−0.35 (−0.68 to −0.02)	
HR (95% CI)	0.71 (0.65 to 0.78)		0.82 (0.76 to 0.89)		0.93 (0.85 to 1.01)	

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; IR, incidence rate; IRD, incidence rate difference; PY, person-year; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

Target Trial Emulation: SGLT-2i vs GLP-1RA

The incidence rate of the primary COPD severe or moderate exacerbation outcome was slightly lower for those treated with SGLT-2is (9.47/100 PY) compared with GLP-1RAs (10.00/100 PY) (HR, 0.94; 95% CI, 0.89-1.00; IRD/100 PYs, −0.55; 95% CI, −1.09 to −0.01) during a median follow-up time on treatment of 141 (IQR, 61-316) vs 139 (IQR, 65-314) days (Table 2). Discontinuation of the index treatment was the most common censoring reason (51.2% and 55.2%) for both arms (eTable 8 in Supplement 1). There were 7688 (10.6%) and 7637 (10.5%) patients still undergoing follow-up at 1 year in the SGLT-2i and GLP-1RA arms, respectively.

For the secondary outcome of severe COPD exacerbation, results were also consistent, with a slightly lower risk associated with the initiation of SGLT-2is compared with GLP-1RA (HR, 0.93; 95% CI, 0.85-1.01; IRD/100 PYs, −0.35; 95% CI, −0.68 to −0.02). Results were largely consistent on relative and absolute scales across all subgroup analyses (**Figure 3**). Cumulative incidence plots of the primary outcome for all the emulated trials were consistent with these findings (eFigures 5-7 in Supplement 1).

Sensitivity and Subgroup Analyses

For SGLT-2i vs DPP-4i and GLP-1RA vs DPP-4i, results for primary and secondary outcomes remained largely consistent across sensitivity and subgroup analyses. Intention-to-treat analyses showed attenuated results, which was expected due to the underlying exposure misclassification (eFigure 8 in Supplement 1),[43] while smaller subgroups (eg, HbA_{1c} categories) yielded imprecise estimates with wide confidence intervals.

Discussion

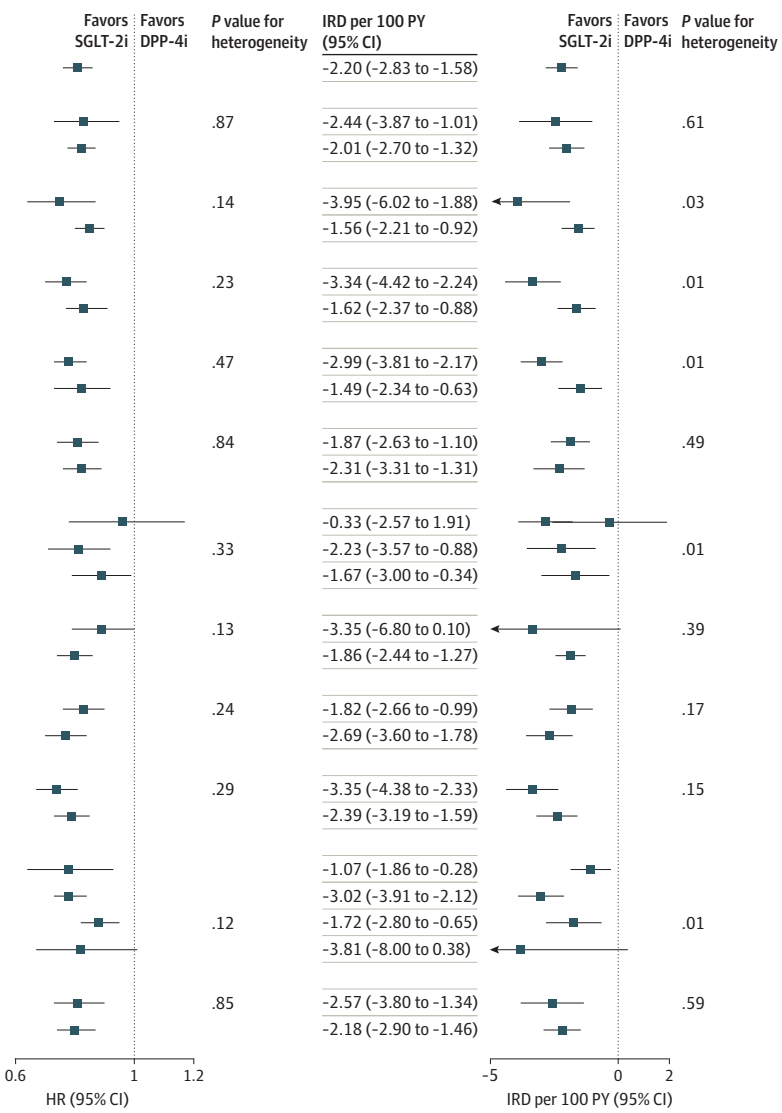
In these 3 large target trial emulations that included US commercially and federally insured adults with T2D and active COPD, we found that treatment initiations of SGLT-2is and GLP-1RAs were associated with a decreased likelihood of severe or moderate COPD exacerbations compared with DPP-4is. Additionally, a head-to-head comparison of SGLT-2is and GLP-1RAs did not show large differences between the 2 classes. These findings remained largely consistent across various sensitivity and subgroup analyses.

Our results indicate a 19% lower risk of moderate or severe COPD exacerbations (2.2 fewer events per 100 PYs) and a 29% reduction in severe exacerbations (1.4 fewer events per 100 PYs) with SGLT-2is compared with DPP-4is, which was consistent with UK primary care data showing a reduced risk of severe COPD exacerbations for patients with T2D and COPD who were using SGLT-2is (HR, 0.62; 95% CI, 0.48-0.81).[44] However, our study population was older and had more advanced diabetes and cardiovascular disease and lower prevalence of asthma. GLP-1RAs showed a 14% lower risk of moderate or severe exacerbations (1.6 fewer events per 100 PYs) and an 18% reduction in severe exacerbations (1.1 fewer events per 100 PYs) compared with DPP-4is, aligning with a study conducted using the US IBM MarketScan commercial claims database (HR, 0.52; 95% CI, 0.32-0.85), although it did not differentiate COPD from asthma, complicating clinical interpretation.[9]

SGLT-2is showed a 6% lower risk of moderate or severe COPD exacerbations (0.6 fewer events per 100 PYs) and a 7% reduction in severe exacerbations (0.4 fewer events per 100 PYs) compared with GLP-1RAs, consistent with a prior US electronic health record data-based study for combined severe or moderate exacerbations (HR, 0.94; 95% CI, 0.69-1.27), although that study had a smaller sample size (approximately 340 individuals per group), limited confounder adjustment, and a shorter follow-up (6 months).[10] Our study adjusted for more confounders. In addition, considering the potential confounding of the COPD exacerbation outcomes by underlying congestive heart failure, we used a primary (less sensitive) and an alternative (more sensitive) definition

Figure 1. Subgroup Analysis on the Incidence of First Moderate or Severe Chronic Obstructive Pulmonary Disease Exacerbation Among Patients Who Initiated Treatment With a Sodium-Glucose Cotransporter-2 Inhibitor (SGLT-2i) vs a Dipeptidyl Peptidase-4 Inhibitor (DPP-4i)

Subgroup	No./total No. SGLT-2i	No./total No. DPP-4i	HR (95% CI)	*P* value for heterogeneity	IRD per 100 PY (95% CI)	*P* value for heterogeneity
All patients	1886/327 991	2334/27 991	0.81 (0.76-0.86)		-2.20 (-2.83 to -1.58)	
Age, y						
<65	444/5282	489/5282	0.83 (0.73-0.95)	.87	-2.44 (-3.87 to -1.01)	.61
≥65	1470/22 710	1838/22 710	0.82 (0.77-0.87)		-2.01 (-2.70 to -1.32)	
Asthma[a]						
Yes	283/3389	386/3389	0.75 (0.64-0.87)	.14	-3.95 (-6.02 to -1.88)	.03
No	1615/24 417	1901/24 417	0.85 (0.80-0.90)		-1.56 (-2.21 to -0.92)	
CHF (primary definition)[b]						
Yes	837/11 599	1065/11 599	0.77 (0.70-0.84)	.23	-3.34 (-4.42 to -2.24)	.01
No	1020/16 106	1249/16 106	0.83 (0.77-0.91)		-1.62 (-2.37 to -0.88)	
CHF (alternative definition)[c]						
Yes	1355/18 808	1715/18 808	0.78 (0.73-0.84)	.47	-2.99 (-3.81 to -2.17)	.01
No	517/9064	648/9064	0.82 (0.73-0.92)		-1.49 (-2.34 to -0.63)	
Frailty score						
<0.25	830/14 017	1021/14 017	0.81 (0.74-0.88)	.84	-1.87 (-2.63 to -1.10)	.49
≥0.25	1046/13 754	1285/13 754	0.82 (0.76-0.89)		-2.31 (-3.31 to -1.31)	
BMI						
<30	190/2664	198/2664	0.96 (0.78-1.17)		-0.33 (-2.57 to 1.91)	
30-39.9	427/6268	508/6268	0.81 (0.71-0.92)	.33	-2.23 (-3.57 to -0.88)	.01
≥40	565/6947	614/6947	0.89 (0.79-0.99)		-1.67 (-3.00 to -0.34)	
Gold group E[d]						
Yes	509/2925	566/2925	0.89 (0.79-1.00)	.13	-3.35 (-6.80 to 0.10)	.39
No	1314/24 932	1679/24 932	0.80 (0.74-0.86)		-1.86 (-2.44 to -1.27)	
Metformin use[e]						
Yes	967/13 920	1185/13 920	0.83 (0.76-0.90)	.24	-1.82 (-2.66 to -0.99)	.17
No	885/13 931	1154/13 931	0.77 (0.70-0.84)		-2.69 (-3.60 to -1.78)	
Insulin use[e]						
Yes	709/10 494	923/10 494	0.74 (0.67-0.81)	.29	-3.35 (-4.38 to -2.33)	.15
No	1138/17 269	1454/17 269	0.79 (0.73-0.85)		-2.39 (-3.19 to -1.59)	
Therapeutic intensity						
None	196/7394	250/7394	0.78 (0.64-0.93)		-1.07 (-1.86 to -0.28)	
Monotherapy	1369/16 395	1744/16 395	0.78 (0.73-0.84)		-3.02 (-3.91 to -2.12)	
Dual therapy	1255/12 564	1442/12 564	0.88 (0.82-0.95)	.12	-1.72 (-2.80 to -0.65)	.01
Triple therapy	177/1442	199/1442	0.82 (0.67-1.01)		-3.81 (-8.00 to 0.38)	
Spirometry[f]						
Yes	666/8151	821/8151	0.81 (0.73-0.90)	.85	-2.57 (-3.80 to -1.34)	.59
No	1223/19 711	1522/19 711	0.80 (0.74-0.87)		-2.18 (-2.90 to -1.46)	



Monotherapy was defined as the use of short-acting β-agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting β-agonists (LABA), long-acting muscarinic antagonists (LAMA), or inhaled corticosteroids (ICS) during the 365 days before cohort entry; dual therapy as the use of SABA-SAMA, LABA-LAMA, or LABA-ICS during the 365 days before cohort entry; and triple therapy as the use of LABA-LAMA-ICS during the 365 days before cohort entry. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); CHF, congestive heart failure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; *ICD*, *International Classification of Diseases*; IRD, incidence risk difference; PY, person-years.

[a]Active asthma defined as 2 or more outpatient or 1 or more inpatient asthma diagnoses at any position as identified by *ICD-9*/*10-CM* codes.

[b]Defined as 1 or more outpatient or inpatient CHF diagnoses during the 365 days before cohort entry at any position using *ICD-9*/*10-CM* codes.

[c]Defined as 1 or more outpatient or inpatient CHF diagnoses at any position using *ICD-9*/*10-CM* codes, 1 or more prescription claims of loop diuretics, or 1 or more prescription claims of sacubitril/valsartan at any time before the cohort entry up to the cohort entry date.

[d]GOLD group E refers to 2 or more moderate and/or 1 or more severe chronic obstructive pulmonary disease exacerbations.

[e]Measured during the 90 days before cohort entry up to the cohort entry date to indicate concurrent use.

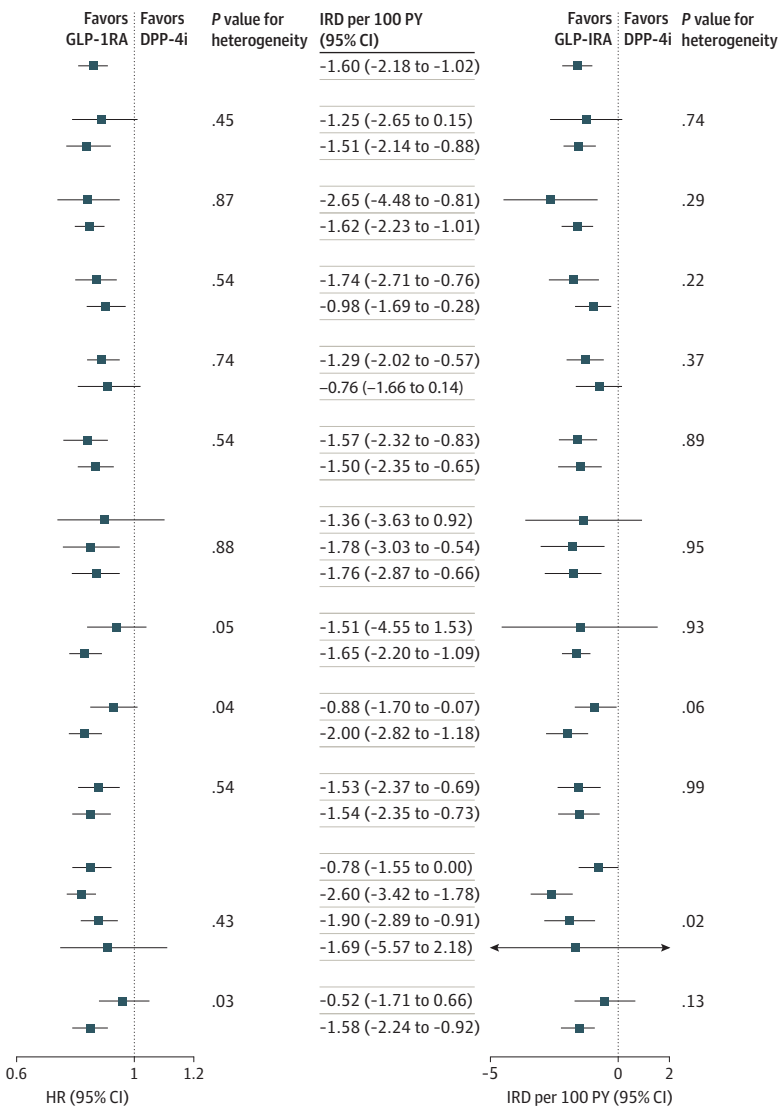
[f]Measured during the 365 days before cohort entry up to the cohort entry date.

of congestive heart failure (eMethods in Supplement 1) for the subgroup analysis that showed similar findings, thus alleviating chances of bias. Further, poor glycemic control has been shown to be associated with increased COPD exacerbation risk.[45] Our stratified analysis by baseline HbA_{1c} levels (<or ≥8.0%) did not reveal significant effect heterogeneity, although the small sample size led to imprecise estimates (eTable 9 in Supplement 1).

The biological mechanisms by which SGLT-2is and GLP-1RAs are associated with reduced COPD exacerbation risk for patients with T2D and COPD are unclear. Preclinical studies suggest that GLP-1RAs may be associated with

Figure 2. Subgroup Analysis on the Incidence of First Moderate or Severe Chronic Obstructive Pulmonary Disease Exacerbation Among Patients Who Initiated Treatment With a Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA) vs a Dipeptidyl Peptidase-4 Inhibitor (DPP-4i)

Subgroup	No./total No. GLP-1RA	No./total No. DPP-4i	HR (95% CI)	P value for heterogeneity	IRD per 100 PY (95% CI)	P value for heterogeneity
All patients	2525/32 107	2669/32 107	0.86 (0.81-0.91)		-1.60 (-2.18 to -1.02)	
Age, y						
<65	495/5740	539/5740	0.89 (0.79-1.01)	.45	-1.25 (-2.65 to 0.15)	.74
≥65	1896/26 720	2283/26 720	0.84 (0.77-0.92)		-1.51 (-2.14 to -0.88)	
Asthma[a]						
Yes	432/4334	521/4334	0.84 (0.74-0.95)	.87	-2.65 (-4.48 to -0.81)	.29
No	1909/27 604	2316/27 604	0.85 (0.80-0.90)		-1.62 (-2.23 to -1.01)	
CHF (primary definition)[b]						
Yes	1114/14 030	1309/14 030	0.87 (0.80 -0.94)	.54	-1.74 (-2.71 to -0.76)	.22
No	1239/17 936	1431/17 936	0.90 (0.84-0.97)		-0.98 (-1.69 to -0.28)	
CHF (alternative definition)[c]						
Yes	1871/23 010	2128/23 010	0.89 (0.84-0.95)	.74	-1.29 (-2.02 to -0.57)	.37
No	556/9351	648/9351	0.91 (0.81-1.02)		–0.76 (–1.66 to 0.14)	
Frailty score						
<0.25	837/14 103	1043/14 103	0.84 (0.76-0.91)	.54	-1.57 (-2.32 to -0.83)	.89
≥0.25	1475/17 838	1747/17 838	0.87 (0.81-0.93)		-1.50 (-2.35 to -0.65)	
BMI						
<30	177/2435	198/2435	0.90 (0.74-1.10)		-1.36 (-3.63 to 0.92)	
30-39.9	558/7445	655/7445	0.85 (0.76-0.95)	.88	-1.78 (-3.03 to -0.54)	.95
≥40	831/9428	915/9428	0.87 (0.79-0.95)		-1.76 (-2.87 to -0.66)	
Gold group E[d]						
Yes	641/3514	704/3514	0.94 (0.84-1.04)	.05	-1.51 (-4.55 to 1.53)	.93
No	1690/28 443	2112/28 443	0.83 (0.78-0.89)		-1.65 (-2.20 to -1.09)	
Metformin use[e]						
Yes	1109/14 350	1233/14 350	0.93 (0.85-1.01)	.04	-0.88 (-1.70 to -0.07)	.06
No	1275/17 735	1565/17 735	0.83 (0.78-0.89)		-2.00 (-2.82 to -1.18)	
Insulin use[e]						
Yes	1245/15 603	1393/15 603	0.88 (0.81-0.95)	.54	-1.53 (-2.37 to -0.69)	.99
No	1106/16 182	1396/16 182	0.85 (0.79-0.92)		-1.54 (-2.35 to -0.73)	
Therapeutic intensity						
None	237/8264	299/8264	0.85 (0.79-0.92)		-0.78 (-1.55 to 0.00)	
Monotherapy	1777/19 337	2182/19 337	0.82 (0.77-0.87)		-2.60 (-3.42 to -1.78)	
Dual therapy	1582/14 683	1791/14 683	0.88 (0.82-0.94)	.43	-1.90 (-2.89 to -0.91)	.02
Triple therapy	181/1538	201/1538	0.91 (0.75-1.11)		-1.69 (-5.57 to 2.18)	
Spirometry[f]						
Yes	910/9407	964/9407	0.96 (0.88-1.05)	.03	-0.52 (-1.71 to 0.66)	.13
No	1491/22 613	1820/22 613	0.85 (0.79-0.91)		-1.58 (-2.24 to -0.92)	



Monotherapy was defined as the use of short-acting β-agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting β-agonists (LABA), long-acting muscarinic antagonists (LAMA), or inhaled corticosteroids (ICS) during the 365 days before cohort entry; dual therapy as the use of SABA-SAMA, LABA-LAMA, or LABA-ICS during the 365 days before cohort entry; and triple therapy as the use of LABA-LAMA-ICS during the 365 days before cohort entry. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); CHF, congestive heart failure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; *ICD*, *International Classification of Diseases*; IRD, incidence risk difference; PY, person-years.

[a]Active asthma defined as 2 or more outpatient or 1 or more inpatient asthma diagnoses at any position as identified by *ICD-9*/*10-CM* codes.

[b]Defined as 1 or more outpatient or inpatient CHF diagnoses during the 365 days before cohort entry at any position using *ICD-9*/*10-CM* codes.

[c]Defined as 1 or more outpatient or inpatient CHF diagnoses at any position using *ICD-9*/*10-CM* codes, 1 or more prescription claims of loop diuretics, or 1 or more prescription claims of sacubitril/valsartan at any time before the cohort entry up to the cohort entry date.

[d]GOLD group E refers to 2 or more moderate and/or 1 or more severe chronic obstructive pulmonary disease exacerbations.

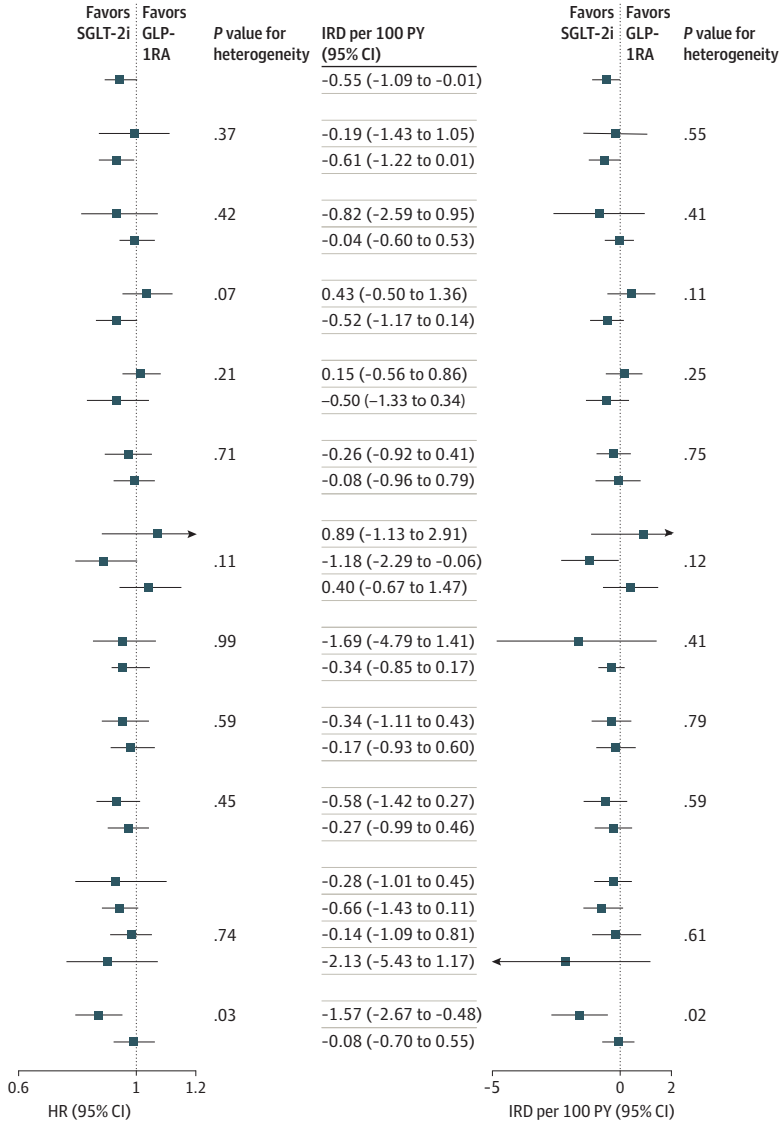
[e]Measured during the 90 days before cohort entry up to the cohort entry date to indicate concurrent use.

[f]Measured during the 365 days before cohort entry up to the cohort entry date.

reduced bronchial hyperresponsiveness via downregulation of interleukin 13[46] and interleukin 33.[47-51] To our knowledge, limited research exists on how SGLT-2is are associated with reduced COPD exacerbations. Their glucosuria effect may aid carbon dioxide expulsion, benefiting patients with COPD.[52] Additionally, their sustained association with fluid reduction[53] may help patients with COPD with coexisting congestive heart failure by alleviating fluid overload.[54] Finally, GLP-1RAs and SGLT-2is promote weight loss,[55] which might also be associated with reduced COPD exacerbation risk, although evidence on this association remains conflicting.[56,57]

Figure 3. Subgroup Analysis on the Incidence of First Moderate or Severe Chronic Obstructive Pulmonary Disease Exacerbation Among Patients Who Initiated Treatment With a Sodium-Glucose Cotransporter-2 Inhibitor (SGLT-2i) vs a Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA)

Subgroup	No./total No. SGLT-2i	No./total No. GLP-1RA	HR (95% CI)	*P* value for heterogeneity	IRD per 100 PY (95% CI)	*P* value for heterogeneity
All patients	2363/36218	2525/36218	0.94 (0.89-1.00)		-0.55 (-1.09 to -0.01)	
Age, y						
<65	612/7890	608/7890	0.99 (0.87-1.11)	.37	-0.19 (-1.43 to 1.05)	.55
≥65	1761/28126	1906/28126	0.93 (0.87-0.99)		-0.61 (-1.22 to 0.01)	
Asthma[a]						
Yes	362/4473	401/4473	0.93 (0.81-1.07)	.42	-0.82 (-2.59 to 0.95)	.41
No	1987/31516	2013/31516	0.99 (0.94-1.06)		-0.04 (-0.60 to 0.53)	
CHF (primary definition)[b]						
Yes	1123/15250	1081/15250	1.03 (0.95-1.12)	.07	0.43 (-0.50 to 1.36)	.11
No	1218/20406	1333/20406	0.93 (0.86-1.00)		-0.52 (-1.17 to 0.14)	
CHF (alternative definition)[c]						
Yes	1827/24908	1814/24908	1.01 (0.95-1.08)	.21	0.15 (-0.56 to 0.86)	.25
No	626/11287	672/11287	0.93 (0.83-1.04)		–0.50 (–1.33 to 0.34)	
Frailty score						
<0.25	1031/18245	1055/18245	0.97 (0.89-1.05)	.71	-0.26 (-0.92 to 0.41)	.75
≥0.25	1335/17628	1385/17628	0.99 (0.92-1.06)		-0.08 (-0.96 to 0.79)	
BMI						
<30	207/3045	191/3045	1.07 (0.88-1.31)		0.89 (-1.13 to 2.91)	
30-39.9	549/8959	615/8959	0.89 (0.79-1.00)	.11	-1.18 (-2.29 to -0.06)	.12
≥40	748/10587	760/10587	1.04 (0.94-1.15)		0.40 (-0.67 to 1.47)	
Gold group E[d]						
Yes	606/3632	640/3632	0.95 (0.85-1.06)	.99	-1.69 (-4.79 to 1.41)	.41
No	1704/32352	1799/32352	0.95 (0.89-1.02)		-0.34 (-0.85 to 0.17)	
Metformin use[e]						
Yes	1097/16498	1155/16498	0.95 (0.88-1.04)	.59	-0.34 (-1.11 to 0.43)	.79
No	1263/19387	1287/19387	0.98 (0.91-1.06)		-0.17 (-0.93 to 0.60)	
Insulin use[e]						
Yes	1010/15496	1111/15496	0.93 (0.86-1.01)	.45	-0.58 (-1.42 to 0.27)	.59
No	1327/20191	1354/20191	0.97 (0.90-1.04)		-0.27 (-0.99 to 0.46)	
Therapeutic intensity						
None	259/9272	265/9272	0.93 (0.79-1.10)		-0.28 (-1.01 to 0.45)	
Monotherapy	1673/21046	1820/21046	0.94 (0.88-1.00)		-0.66 (-1.43 to 0.11)	
Dual therapy	1548/16474	1633/16474	0.98 (0.91-1.05)	.74	-0.14 (-1.09 to 0.81)	.61
Triple therapy	257/2392	272/2392	0.90 (0.76-1.07)		-2.13 (-5.43 to 1.17)	
Spirometry[f]						
Yes	833/10681	956/10681	0.87 (0.79-0.95)	.03	-1.57 (-2.67 to -0.48)	.02
No	1528/25339	1555/25339	0.99 (0.92-1.06)		-0.08 (-0.70 to 0.55)	



Monotherapy was defined as the use of short-acting β-agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting β-agonists (LABA), long-acting muscarinic antagonists (LAMA), or inhaled corticosteroids (ICS) during the 365 days before cohort entry; dual therapy as the use of SABA-SAMA, LABA-LAMA, or LABA-ICS during the 365 days before cohort entry; and triple therapy as the use of LABA-LAMA-ICS during the 365 days before cohort entry. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); CHF, congestive heart failure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; *ICD*, *International Classification of Diseases*; IRD, incidence risk difference; PY, person-years.

[a]Active asthma defined as 2 or more outpatient or 1 or more inpatient asthma diagnoses at any position as identified by *ICD-9*/*10-CM* codes.

[b]Defined as 1 or more outpatient or inpatient CHF diagnoses during the 365 days before cohort entry at any position using *ICD-9*/*10-CM* codes.

[c]Defined as 1 or more outpatient or inpatient CHF diagnoses at any position using *ICD-9*/*10-CM* codes, 1 or more prescription claims of loop diuretics, or 1 or more prescription claims of sacubitril/valsartan at any time before the cohort entry up to the cohort entry date.

[d]GOLD group E refers to 2 or more moderate and/or 1 or more severe chronic obstructive pulmonary disease exacerbations.

[e]Measured during the 90 days before cohort entry up to the cohort entry date to indicate concurrent use.

[f]Measured during the 365 days before cohort entry up to the cohort entry date.

Strengths and Limitations

Our study's strengths included a large US adult population (approximately 35 000 per group) from 3 claims databases, enabling precise comparisons of glucose-lowering medications and their association with COPD exacerbation risk. This also allowed evaluation of potential treatment effect heterogeneity across multiple clinically relevant subgroups. Second, by emulating target trials with new users, we minimized biases from prevalent use and disease stage.[58] Third, validated COPD exacerbation definitions that

excluded asthma codes reduced potential outcome misclassification. Lastly, the diverse study population enhanced generalizability and external validity compared with previous research.[44]

Our study also had limitations. First, residual confounding cannot be ruled out in this observational study, particularly as pre PS matching showed that those who were treated with DPP-4is were older and more often male and had higher rates of severe COPD exacerbations or pneumonia than those treated with SGLT-2is and GLP-1RAs. However, emulating head-to-head randomized clinical trials of newer medications typically prescribed at a similar disease stage and clinical indications and with PS models addressing numerous confounders likely minimized this. Robust findings across sensitivity and subgroup analyses supported this, although smaller subgroup analyses, such as by HbA_{1c} levels, produced imprecise estimates with wide confidence intervals. Second, using claims data may have caused outcome misclassification,[59] which we mitigated by applying specific, validated definitions for COPD exacerbations. Third, while claims data lack information on actual medication adherence, our on-treatment primary analysis based on continuous use potentially helped to reduce exposure misclassification. Fourth, the absence of complete information on clinically relevant covariates, such as smoking status, forced expiratory volume, BMI, laboratory parameters (including HbA_{1c} levels and blood eosinophil cell counts), and demographic variables like ethnicity, prevented their inclusion in the PS models. However, we used proxy variables, like insulin use for HbA_{1c}, to account for disease severity and analyzed a subset of patients with baseline HbA_{1c} values that showed consistent findings (eTable 9 in Supplement 1). Further, prior studies have shown that balancing measured covariates in claims while using an active-comparator design leads to balance in clinical variables that are not available in claims, including laboratory measures.[60] Fifth, we lacked follow-up data on HbA_{1c} levels and BMI, preventing us from assessing how much the reduced COPD exacerbation risk with SGLT-2is and GLP-1RAs vs DPP-4is was mediated by changes in these measures. Ad hoc studies with fit-for-purpose data may clarify this. Lastly, the short study follow-up time (median of approximately 145 days), which was primarily driven by high medication discontinuation rates (approximately 55%), limited a longer-term assessment of the outcomes. Yet, the observed follow-up duration reflected clinical adherence patterns, making our findings clinically relevant. Although our study databases lacked reasons for medication discontinuation, factors like high costs, adverse reactions, and patient or physician preferences likely contribute to low persistence in practice.[61]

Conclusions

In this large, population-based, comparative effectiveness research study, the initiation of SGLT-2is and GLP-1RAs was associated with a reduced risk of severe or moderate COPD exacerbations for individuals with T2D compared with DPP-4is. Conversely, any risk reduction associated with the use of SGLT-2is vs GLP-1RAs, if present, was marginal. These findings suggest that SGLT-2is and GLP-1RAs may be preferable to DPP-4is when deciding among glucose-lowering medications for patients with T2D and active COPD. However, given the observational nature of the study, there is potential for residual or unmeasured confounding, and findings from similar clinical studies and clinical trials will help corroborate these results.

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Author Affiliations: Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Ray, Paik, Sreedhara, Bykov, Feldman, Patorno); Division of Renal (Kidney) Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Paik); New England Geriatric Research, Education and Clinical Center, VA Boston Healthcare System, Boston, Massachusetts (Paik); Diabetes Center, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (Wexler); Division of Pulmonary Critical Care, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Feldman).

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Concept and design: Ray, Paik, Bykov, Patorno.
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Drafting of the manuscript: Ray.
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REFERENCES

1. Belligund P, Attaway A, Lopez R, Damania D, Hatipoğlu U, Zein JG. Diabetes associated with higher health care utilization and poor outcomes after COPD-related hospitalizations. *Am J Manag*

Care. 2022;28(9):e325-e332. doi:10.37765/ajmc.2022.89225

2. ElSayed NA, Aleppo G, Aroda VR, et al; on behalf of the American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. *Diabetes Care*. 2023;46(suppl 1):S140-S157. doi:10.2337/dc23-S009

3. Qiu M, Ding LL, Zhan ZL, Liu SY. Use of SGLT2 inhibitors and occurrence of noninfectious respiratory disorders: a meta-analysis of large randomized trials of SGLT2 inhibitors. *Endocrine*. 2021;73(1):31-36. doi:10.1007/s12020-021-02644-x

4. Altintas Dogan AD, Hilberg O, Hess S, Jensen TT, Bladbjerg EM, Juhl CB. Respiratory effects of treatment with a glucagon-like peptide-1 receptor agonist in patients suffering from obesity and chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2022;17:405-414. doi:10.2147/COPD.S350133

5. Gupta S, Mohta A, Lauinger A, Thameem D. The role of sodium-glucose transporter-2 inhibitors (SGLT-2i) in preventing chronic obstructive disease exacerbation in patients with diabetes and COPD: an electronic health database analysis. *Heart Lung*. 2024;68:191-194. doi:10.1016/j.hrtlng.2024.07.003

6. López-Cano C, Ciudin A, Sánchez E, et al. Liraglutide improves forced vital capacity in individuals with type 2 diabetes: data from the randomized crossover LIRALUNG study. *Diabetes*. 2022;71(2):315-320. doi:10.2337/db21-0688

7. Kotnala S, Kim Y, Rajput C, et al. Contribution of dipeptidyl peptidase 4 to non-typeable haemophilus influenzae-induced lung inflammation in COPD. *Clin Sci (Lond)*. 2021;135(17):2067-2083. doi:10.1042/CS20210099

8. Wang MT, Lai JH, Huang YL, et al. Use of antidiabetic medications and risk of chronic obstructive pulmonary disease exacerbation requiring hospitalization: a disease risk score-matched nested case-control study. *Respir Res*. 2020;21(1):319. doi:10.1186/s12931-020-01547-1

9. Albogami Y, Cusi K, Daniels MJ, Wei YJ, Winterstein AG. Glucagon-like peptide 1 receptor agonists and chronic lower respiratory disease exacerbations among patients with type 2 diabetes. *Diabetes Care*. 2021;44(6):1344-1352. doi:10.2337/dc20-1794

10. Foer D, Strasser ZH, Cui J, et al. Association of GLP-1 receptor agonists with chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes. *Am J Respir Crit Care Med*. 2023;208(10):1088-1100. doi:10.1164/rccm.202303-0491OC

11. Sahin I, Bakiner O, Demir T, Sari R, Atmaca A. Current position of gliclazide and sulfonylureas in the contemporary treatment paradigm for type 2 diabetes: a scoping review. *Diabetes Ther*. 2024;15(8):1687-1716. doi:10.1007/s13300-024-01612-8

12. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2024. *Diabetes Care*. 2024;47(suppl 1):S158-S178. doi:10.2337/dc24-S009

13. Castañ-Abad MT, Montserrat-Capdevila J, Godoy P, et al. Diabetes as a risk factor for severe exacerbation and death in patients with COPD: a prospective cohort study. *Eur J Public Health*. 2020;30(4):822-827. doi:10.1093/eurpub/ckz219

14. Ho TW, Huang CT, Ruan SY, Tsai YJ, Lai F, Yu CJ. Diabetes mellitus in patients with chronic obstructive pulmonary disease—the impact on mortality. *PLoS One*. 2017;12(4):e0175794. doi:10.1371/journal.pone.0175794

15. Hernán MA, Wang W, Leaf DE. Target trial emulation: a framework for causal inference from observational data. *JAMA*. 2022;328(24):2446-2447. doi:10.1001/jama.2022.21383

16. Enhancing the Quality and Transparency Of Health Research. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Accessed November 15, 2024. https://www.equator-network.org/reporting-guidelines/strobe/

17. Johnson & Johnson. US FDA approves INVOKANA (canagliflozin) for the treatment of adults with type 2 diabetes. Accessed November 15, 2024. https://www.jnj.com/media-center/press-releases/us-fda-approves-invokana-canagliflozin-for-the-treatment-of-adults-with-type-2-diabetes

18. Teltsch DY, Fazeli Farsani S, Swain RS, et al. Development and validation of algorithms to identify newly diagnosed type 1 and type 2 diabetes in pediatric population using electronic medical records and claims data. *Pharmacoepidemiol Drug Saf*. 2019;28(2):234-243. doi:10.1002/pds.4728

19. Macaulay D, Sun SX, Sorg RA, et al. Development and validation of a claims-based prediction model for COPD severity. *Respir Med*. 2013;107(10):1568-1577. doi:10.1016/j.rmed.2013.05.012

20. Stein BD, Bautista A, Schumock GT, et al. The validity of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for identifying patients hospitalized for COPD exacerbations. *Chest*. 2012;141(1):87-93. doi:10.1378/chest.11-0024

21. Rothnie KJ, Müllerová H, Hurst JR, et al. Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records. *PLoS One*. 2016;11(3):e0151357. doi:10.1371/journal.pone.0151357

22. Global Initiative on Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2023 report. Accessed November 15, 2024. https://goldcopd.org/wp-content/uploads/2023/01/GOLD-2023-ver-1.2-7Jan2023_WMV.pdf

23. Wedzicha JA, Banerji D, Chapman KR, et al; FLAME Investigators. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med*. 2016;374(23):2222-2234. doi:10.1056/NEJMoa1516385

24. Lipson DA, Barnhart F, Brealey N, et al; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378(18):1671-1680. doi:10.1056/NEJMoa1713901

25. Rabe KF, Martinez FJ, Ferguson GT, et al; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35-48. doi:10.1056/NEJMoa1916046

26. Tavakoli H, Chen W, Sin DD, FitzGerald JM, Sadatsafavi M. Predicting severe chronic obstructive pulmonary disease exacerbations: developing a population surveillance approach with administrative data. *Ann Am Thorac Soc*. 2020;17(9):1069-1076. doi:10.1513/AnnalsATS.202001-070OC

27. Suissa S, Dell'Aniello S, Ernst P. Comparative effects of LAMA-LABA-ICS vs LAMA-LABA for COPD: cohort study in real-world clinical practice. *Chest*. 2020;157(4):846-855. doi:10.1016/j.chest.2019.11.007

28. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *Lancet Respir Med*. 2018;6(11):855-862. doi:10.1016/S2213-2600(18)30368-0

29. Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness and safety of LABA-LAMA vs LABA-ICS treatment of COPD in real-world clinical practice. *Chest*. 2019;155(6):1158-1165. doi:10.1016/j.chest.2019.03.005

30. Stanford RH, Nag A, Mapel DW, et al. Claims-based risk model for first severe COPD exacerbation. *Am J Manag Care*. 2018;24(2):e45-e53.

31. Samp JC, Joo MJ, Schumock GT, Calip GS, Pickard AS, Lee TA. Comparative effectiveness of long-acting beta2-agonist combined with a long-acting muscarinic antagonist or inhaled corticosteroid in chronic obstructive pulmonary disease. *Pharmacotherapy*. 2017;37(4):447-455. doi:10.1002/phar.1913

32. Rothnie KJ, Müllerová H, Thomas SL, et al. Recording of hospitalizations for acute exacerbations of COPD in UK electronic health care records. *Clin Epidemiol*. 2016;8:771-782. doi:10.2147/CLEP.S117867

33. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749-759. doi:10.1016/j.jclinepi.2010.10.004

34. Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring frailty in Medicare data: development and validation of a claims-based frailty index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-987. doi:10.1093/gerona/glx229

35. Jacob C, Haas JS, Bechtel B, Kardos P, Braun S. Assessing asthma severity based on claims data: a systematic review. *Eur J Health Econ*. 2017;18(2):227-241. doi:10.1007/s10198-016-0769-2

36. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758-764. doi:10.1093/aje/kwv254

37. Ripollone JE, Huybrechts KF, Rothman KJ, Ferguson RE, Franklin JM. Implications of the propensity score matching paradox in pharmacoepidemiology. *Am J Epidemiol*. 2018;187(9):1951-1961. doi:10.1093/aje/kwy078

38. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. doi:10.1002/sim.3697

39. Lash TL, Rothman KJ, VanderWeele TJ, Haneuse S. *Modern Epidemiology*. 4th edition. Wolters Kluwer;2020.

40. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

41. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A propensity-score–based Fine stratification approach for confounding adjustment when exposure is infrequent. *Epidemiology*. 2017;28(2):249-257. doi:10.1097/EDE.0000000000000595

42. Wang SV, Sreedhara SK, Schneeweiss S; REPEAT Initiative. Reproducibility of real-world evidence studies using clinical practice data to inform regulatory and coverage decisions. *Nat Commun*. 2022;13(1):5126. doi:10.1038/s41467-022-32310-3

43. Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. *Clin Trials*. 2012;9(1):48-55. doi:10.1177/1740774511420743

44. Pradhan R, Lu S, Yin H, et al. Novel antihyperglycaemic drugs and prevention of chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes: population based cohort study. *BMJ*. 2022;379:e071380. doi:10.1136/bmj-2022-071380

45. Chen G, Lin Q, Zhuo D, Cui J. Elevated Blood glucose is associated with severe exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2453-2459. doi:10.2147/COPD.S378259

46. Foer D, Beeler PE, Cui J, et al. Glucagon-like peptide-1 receptor agonist use is associated with lower serum periostin. *Clin Exp Allergy*. 2023;53(4):469-473. doi:10.1111/cea.14284

47. Toki S, Newcomb DC, Printz RL, et al. Glucagon-like peptide-1 receptor agonist inhibits aeroallergen-induced activation of ILC2 and neutrophilic airway inflammation in obese mice. *Allergy*. 2021;76(11):3433-3445. doi:10.1111/all.14879

48. Jiang M, Tao S, Zhang S, et al. Type 2 innate lymphoid cells participate in IL-33-stimulated Th2-associated immune response in chronic obstructive pulmonary disease. *Exp Ther Med*. 2019;18(4):3109-3116. doi:10.3892/etm.2019.7924

49. Gorska K, Nejman-Gryz P, Paplinska-Goryca M, Korczynski P, Prochorec-Sobieszek M, Krenke R. Comparative study of IL-33 and IL-6 levels in different respiratory samples in mild-to-moderate asthma and COPD. *COPD*. 2018;15(1):36-45. doi:10.1080/15412555.2017.1416074

50. Joo H, Park SJ, Min KH, Rhee CK. Association between plasma interleukin-33 level and acute exacerbation of chronic obstructive pulmonary disease. *BMC Pulm Med*. 2021;21(1):86. doi:10.1186/s12890-021-01423-8

51. Rabe KF, Celli BR, Wechsler ME, et al. Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial. *Lancet Respir Med*. 2021;9(11):1288-1298. doi:10.1016/S2213-2600(21)00167-3

52. Brikman S, Dori G. Sodium glucose cotransporter2 inhibitor-possible treatment for patients with diabetes, pulmonary disease and CO_2 retention. *Med Hypotheses*. 2020;139:109631. doi:10.1016/j.mehy.2020.109631

53. Mayne KJ, Staplin N, Keane DF, et al; EMPA-KIDNEY Collaborative Group. Effects of empagliflozin on fluid overload, weight, and blood pressure in CKD. *J Am Soc Nephrol*. 2024;35(2):202-215. doi:10.1681/ASN.0000000000000271

54. Castillo A, Edriss H, Selvan K, Nugent K. Characteristics of patients with congestive heart failure or chronic obstructive pulmonary disease readmissions within 30 days following an acute exacerbation. *Qual Manag Health Care*. 2017;26(3):152-159. doi:10.1097/QMH.0000000000000143

55. Frieling K, Monte SV, Jacobs D, Albanese NP. Weight loss differences seen between glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors for treatment of type 2 diabetes. *J Am Pharm Assoc (2003)*. 2021;61(6):772-777. doi:10.1016/j.japh.2021.06.015

56. Hallin R, Koivisto-Hursti UK, Lindberg E, Janson C. Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD). *Respir Med*. 2006;100(3):561-567. doi:10.1016/j.rmed.2005.05.020

57. Wang M, Ni X, Yu F. Impact of body mass index on risk of exacerbation in patients with COPD: a systematic review and meta-analysis. *Chronic Obstr Pulm Dis*. 2024;11(5):524-533. doi:10.15326/jcopdf.2024.0507

58. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol*. 2016;79:70-75. doi:10.1016/j.jclinepi.2016.04.014

59. Prada-Ramallal G, Takkouche B, Figueiras A. Bias in pharmacoepidemiologic studies using secondary health care databases: a scoping review. *BMC Med Res Methodol*. 2019;19(1):53. doi:10.1186/s12874-019-0695-y

60. Patorno E, Gopalakrishnan C, Franklin JM, et al. Claims-based studies of oral glucose-lowering medications can achieve balance in critical clinical variables only observed in electronic health records. *Diabetes Obes Metab*. 2018;20(4):974-984. doi:10.1111/dom.13184

61. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307. doi:10.2147/PPA.S106821