Association of novel antihyperglycaemic drugs *versus* metformin with COPD exacerbations

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Shareable abstract (@ERSpublications)
In this nationwide retrospective cohort study, GLP-1 RAs and SGLT-2 Is offered COPD control comparable to that of metformin, while DPP-4 Is were associated with poorer control of COPD compared with metformin https://bit.ly/3UdaBd2

Cite this article as: Kimura Y, Jo T, Inoue N, *et al*. Association of novel antihyperglycaemic drugs *versus* metformin with COPD exacerbations. *ERJ Open Res* 2025; 11: 00757-2024 [DOI: 10.1183/23120541.00757-2024].

Received: 28 July 2024
Accepted: 9 Oct 2024

Abstract

Background Dipeptidyl peptidase-4 inhibitors (DPP-4 Is), glucagon-like peptidase 1 receptor agonists (GLP-1 RAs) and sodium glucose co-transporter-2 inhibitors (SGLT-2 Is) may contribute to better control of COPD due to their anti-inflammatory effects, like those observed with metformin. We aimed to investigate the association of these novel antihyperglycaemic drugs *versus* metformin with fewer COPD exacerbations in patients with type 2 diabetes (T2DM) comorbid with COPD.

Methods Using the national administrative database covering 99% of the medical facilities in Japan, we constructed three active comparators new-user cohorts comprising 36 317 patients with T2DM and COPD who initiated treatment with the novel antihyperglycaemic drugs and metformin between 2014 and 2022. Patients' backgrounds were balanced using overlap propensity score weighting. We calculated the hazard ratios (HRs) and their 95% confidence intervals (CIs) for the initial occurrence of COPD exacerbation requiring systemic corticosteroids using a weighted Cox proportional hazards model.

Results DPP-4 Is were associated with a higher incidence of exacerbations requiring systemic corticosteroids (22.4 *versus* 20.4 per 100 person-years; HR 1.16, 95% CI 1.07–1.25) compared with metformin. In contrast, the incidence of such exacerbations in the GLP-1 RAs (30.1 *versus* 24.4 per 100 person-years; HR 1.07, 95% CI 0.87–1.32) and SGLT-2 Is (20.7 *versus* 21.8 per 100 person-years; HR 1.00, 95% CI 0.94–1.06) groups were comparable with that in the metformin group.

Conclusions While DPP-4 Is were associated with poorer control of COPD compared with metformin, GLP-1 RAs and SGLT-2 Is offered COPD control comparable with that of metformin.

Introduction

Diabetes mellitus is a major comorbidity among patients with COPD [1, 2]. The disease burden associated with type 2 diabetes mellitus (T2DM) and COPD is substantial, due to the increased risk of poor COPD-related outcomes and high healthcare utilisation [3]. The burden is projected to become more substantial, as the prevalence of T2DM is estimated to increase by 54% by 2030 [4]. Metformin may be an additional treatment option for patients with T2DM comorbid with COPD. This medication showed protective effects against cigarette smoke-induced pulmonary inflammation, airspace enlargement and small airway remodelling in mice; furthermore, the use of metformin was associated with reduced emphysema progression in humans [5]. Metformin has long been the sole first-line treatment for T2DM in Western countries owing to its therapeutic efficacy and cost-effectiveness [6]. However, new evidence

accumulated over recent decades regarding novel antihyperglycaemic drugs has led to their inclusion in first-line treatments for T2DM comorbid with specific conditions. Glucagon-like peptidase 1 receptor agonists (GLP-1 RAs) and sodium glucose co-transporter-2 inhibitors (SGLT-2 Is) are now recommended for patients with T2DM comorbid with atherosclerotic cardiovascular disease, heart failure and chronic kidney disease [7]. In contrast, Japanese diabetes guidelines have not specified particular drugs as first-line treatments for T2DM. Instead, they permit the selection of initial treatment drugs from all available classes, considering several factors, such as metabolic abnormalities, age, obesity and insulin secretion [8]. In a real-world study, dipeptidyl peptidase-4 inhibitors (DPP-4 Is) were the most favoured among patients newly initiating T2DM treatments, accounting for 65.1%, followed by biguanides (15.9%, including metformin) and SGLT-2 Is (7.6%) [9].

Similar to metformin, novel antihyperglycaemic drugs (DPP-4 Is, GLP-1 RAs and SGLT-2 Is) also demonstrate anti-inflammatory effects, potentially leading to better control of COPD [10, 11]. Thus, several population-based studies have investigated the potential effectiveness of these novel antihyperglycaemic drugs in reducing COPD exacerbations [12–14]. All these studies examined the relationship between the use of these novel antihyperglycaemic drugs and COPD exacerbations in patients with T2DM, utilising active comparators and new user designs. The first study, based on a large UK primary care database, was the largest among them [12]. It found that GLP-1 RAs were associated with a lower incidence of COPD exacerbations requiring systemic corticosteroids compared with sulfonylureas (weighted hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.43–0.94), while the incidence in the DPP-4 Is (HR 0.93, 0.82–1.07) and SGLT-2 Is (HR 1.02, 0.83–1.27) groups was comparable with that in the sulfonylureas group. For COPD exacerbations requiring hospitalisation, both GLP-1 RAs (weighted HR 0.70, 95% CI 0.49–0.99) and SGLT-2 Is (HR 0.62, 0.48–0.81) were associated with a lower incidence, whereas the incidence in the DPP-4 Is group was similar to that in the sulfonylureas group (HR 0.91, 0.82–1.02). The second study, utilising electronic health records from an integrated healthcare system in the United States, found that GLP-1 RAs were associated with lower COPD exacerbations (including both exacerbations requiring systemic corticosteroids and those requiring hospitalisations) compared with DPP-4 Is (adjusted risk ratio (RR) 0.68, 95% CI 0.49–0.93) and sulfonylureas (RR 0.48, 0.37–0.62) [13]. The incidence of exacerbations in the GLP-1 RAs group was comparable with that in the SGLT-2 Is group (RR 1.06, 0.79–1.45). Subgroup analyses suggested that the body mass index (BMI) may modify the effects observed. The third study focused on patients with chronic lower respiratory disease (COPD and asthma) using a US commercial claims database [14]. GLP-1 RAs, compared with DPP-4 Is, were associated with a lower incidence of exacerbations requiring hospitalisation (adjusted HR 0.52, 95% CI 0.32–0.85) and fewer exacerbations requiring systemic corticosteroids (adjusted RR 0.70, 95% CI 0.57–0.87). The association persisted even when the analysis was limited to patients with comorbid COPD. These findings suggest that the risk of COPD exacerbations may be the lowest with GLP-1 RAs and SGLT-2 Is, followed by DPP-4 Is and sulfonylureas.

The abovementioned population-based studies provide valuable insights into treatment strategies for patients with T2DM and comorbid COPD and are informative for designing prospective studies. However, as all the studies originated from Western countries, the applicability of the findings to other ethnic groups or patients with lower BMIs remains uncertain. Therefore, this study aimed to investigate the association of the novel antihyperglycaemic drugs *versus* metformin with COPD exacerbations in Asian populations, who generally have lower BMIs compared with Western populations, using a Japanese national administrative database. This study is unique as we adopted metformin as an active comparator because metformin has not been designated as the sole first-line treatment for T2DM in Japan [8]. We present the data consistently with our previous study involving patients with T2DM and comorbid asthma to ensure comparability of findings [15].

Methods

Data source

We utilised data from the National Database of Health Insurance Claims and Specific Health Checkups (NDB) spanning between 1 January 2014 and 31 December 2022. This national administrative database covers data from 99% of the medical facilities (including both hospitals and clinics) in Japan [16]. The database includes a wide range of variables, including unique identifiers and demographic characteristics for each patient, diagnoses based on diagnostic codes [17], and details of examinations and treatments (*e.g.* prescription dates, drug contents and drug amounts), all extracted from both inpatient and outpatient settings. Additionally, for individuals aged ⩾40 years, the database also includes health checkup data, including data not typically found in standard administrative databases, such as BMI, smoking status and blood test results. Further details are provided elsewhere [16].

Study design and study population

We constructed three separate active comparator new-user cohorts to compare patients initiating treatment with DPP-4 Is, GLP-1 RAs and SGLT-2 Is against those initiating metformin (for drugs in each class, see the online supplement). Sulfonylureas and thiazolidinediones were not included in the study drugs because the number of patients initiating these drugs as an initial treatment for T2DM was very small in Japan [9]. The study periods for each cohort extended from 1 January 2014, to 31 December 2022. The process for identifying the study population in each cohort is illustrated in figure 1. Patients with COPD were identified by combining the corresponding diagnostic codes and COPD-related drugs. Further details are provided in the online supplement.

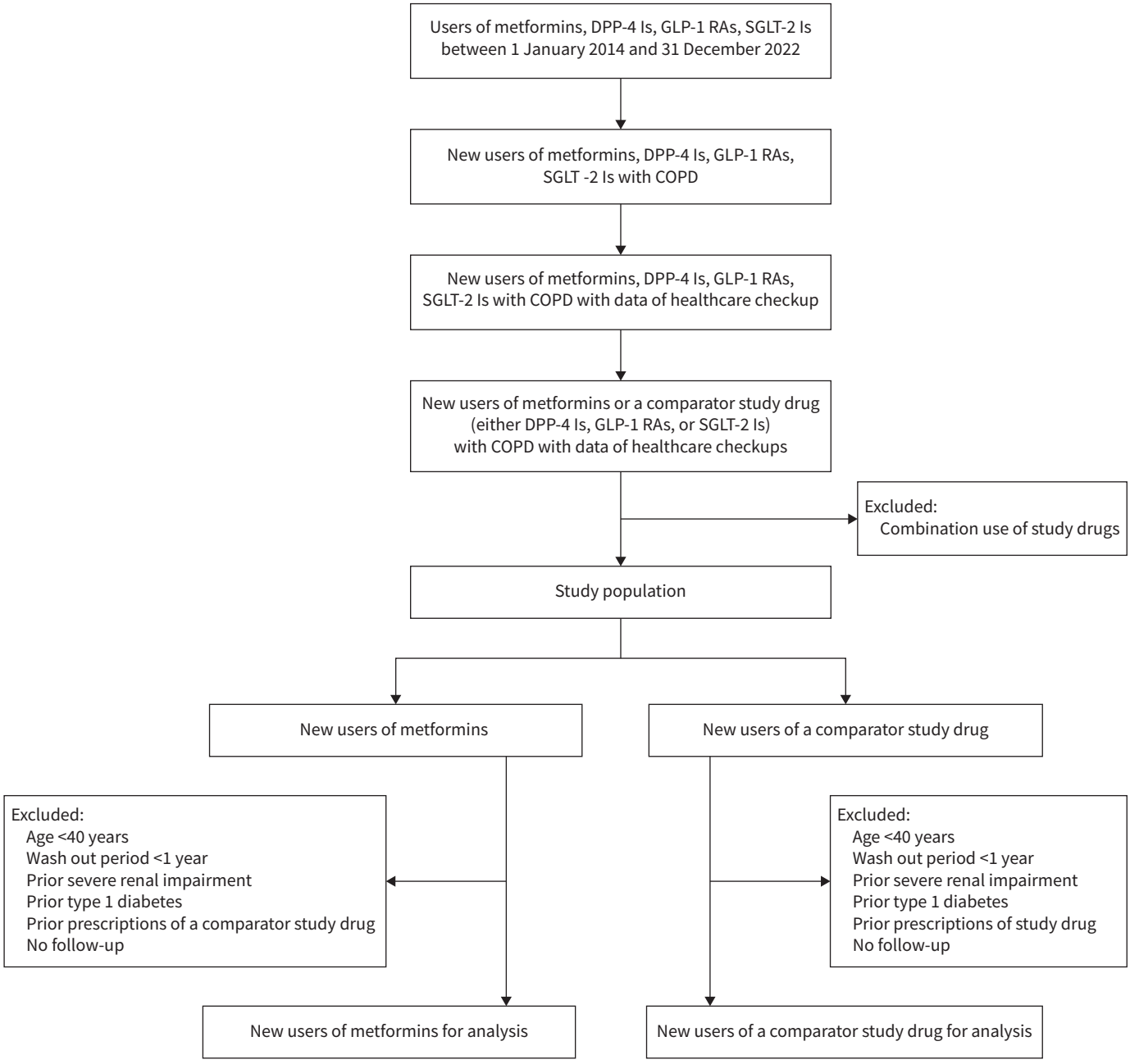


FIGURE 1 Patient flow schema. DPP-4 Is: dipeptidyl peptidase-4 inhibitors; GLP-1 RAs: glucagon-like peptidase 1 receptor agonists; SGLT-2: sodium glucose co-transporter-2 inhibitors.

Primary and secondary outcomes

The primary outcome was the initial occurrence of a COPD exacerbation requiring systemic corticosteroids [13, 14]. A COPD exacerbation requiring systemic corticosteroids was defined as a prescription of oral corticosteroids (equivalent to ⩾15 mg·day^{-1} of prednisolone) or intravenous corticosteroids for ⩾3 days. Such exacerbations within 14 days were treated as one exacerbation. Additionally, we explored three secondary outcomes during the follow-up periods: (1) the number of COPD exacerbations requiring systemic corticosteroids; (2) initial occurrence of a COPD exacerbation requiring hospitalisation; and (3) number of COPD exacerbations requiring hospitalisation. A COPD exacerbation requiring hospitalisation was defined as a hospital admission with a primary diagnostic code for COPD or an overlap of asthma and COPD, or if not identifiable in the primary position, the use of systemic corticosteroids within 2 days of admission with a diagnostic code for COPD or an overlap of asthma and COPD listed in any position. We did not designate a COPD exacerbation requiring hospitalisation as the primary outcome because such exacerbations were expected to be low [18]. We could not identify COPD exacerbations requiring emergency department visits because such visits cannot be distinguished in the NDB.

Exposure definition

We defined drug exposures as the period from the day when a prescription was filled until 60 days after the dispensed supply was exhausted, allowing for exposure gaps of <60 days. Switching between drugs within the same group was permitted (DPP-4 Is and GLP-1 RAs were not treated as the same group at this stage) [12, 15]. Due to varying outcome definitions, the end of the exposure periods differed according to the type of outcomes. For outcomes related to the initial occurrence of exacerbations, patients were followed from cohort entry until the first exacerbation, treatment discontinuation, addition or switching to one of the study drugs, all-cause death or final registration with the NDB within the study period, whichever came first. For outcomes measuring the number of exacerbations, the initial occurrence of exacerbations was not considered as the end of follow-up.

Potential confounders

Based on a literature review and clinical experience, we selected various potential confounders, all of which were measured using data collected before or at cohort entry. The potential confounders included demographic characteristics, comorbidities, treatments, healthcare resource use, health-related behaviours and blood test results. We treated missing data as an unknown category. Details about these potential confounders are described in the online supplement.

Statistical analysis

We employed overlap propensity score weighting to adjust for potential confounders. In each cohort, we calculated the propensity score (the probability of being assigned to the new antihyperglycaemic drugs) using a multivariate logistic regression model that included the potential confounders. Overlap weighting was conducted by weighting patients with a predicted probability of receiving the opposing treatment. That is, patients who received new antihyperglycaemic drugs were weighted by the probability of receiving metformin (1 − propensity score), and patients who received metformin were weighted by the probability of receiving antihyperglycaemic drugs (propensity score). Overlap propensity score weighting allows for a precise balance in measured variables and yields a more accurate estimation of the association between the treatment of interest and outcomes, compared with traditional propensity score methods [19]. We assessed the balance of potential confounders before and after weighting between the two groups, using the absolute standardised mean difference, with a value ⩽0.1 typically indicating well-balanced confounders [20].

We calculated an incidence rate of COPD exacerbation for each study drug using a negative binomial distribution, incorporating an offset term for the logarithm of observational periods. We also plotted the weighted Kaplan–Meier curves to illustrate the cumulative incidence of initial exacerbations during the follow-up periods. The HRs and their 95% CIs for the initial occurrence of exacerbations in patients using novel antihyperglycaemic drugs *versus* metformin were estimated using a weighted Cox proportional hazards model. Additionally, we calculated the weighted RRs and their 95% CIs for the number of exacerbations using a weighted negative binomial regression model, again with an offset term of logarithm of observational periods. Robust variance estimators, accounting for within-year clustering, were employed in these models [21]. Because of the potential for type 1 error due to multiple comparisons, findings from analyses other than those for the primary outcome in the main analysis should be interpreted as exploratory.

Secondary analysis

We conducted subgroup analyses according to the following subgroups: (1) age (<65 and ⩾65 years); (2) BMI (<18.5, 18.5–24.9, 25.0–29.9 and ⩾30.0 kg·m^{-2}); (3) asthma (with and without asthma); (4) haemoglobin A1c (HbA1c) (⩽7.0%, 7.1–8.0% and >8.0%); (5) triglyceride (TG) (<150, 151–200 and

>200 mg·dL^{-1}); (6) low-density lipoprotein cholesterol (LDL-C) (⩽130, 131–160 and >160 mg·dL^{-1}); (7) individual drug within each study drug group; (8) no prior use of drugs for T2DM (including metformin, DPP-4 Is, GLP-1 RAs, SGLT-2 Is, sulfonylureas, thiazolidinediones, glinide, α-glucosidase inhibitors and insulin) before cohort entry; and (9) no prior use of the study drugs (either metformin, DPP-4 Is, GLP-1 RAs or SGLT-2 Is) before cohort entry.

Sensitivity analysis

We conducted three sensitivity analyses to evaluate the robustness of our primary findings. First, we changed the exposure gap from <60 days to either <30 days or <90 days. Second, we imputed missing data using multiple imputations to address the effects of missing data [22]. Ten imputed datasets were prepared, and the results from each imputed dataset were aggregated using Rubin's rule [23]. Third, we examined the occurrence of herpes zoster, identified by the combination of corresponding diagnostic codes and prescriptions for antiviral drugs specific to this condition, as a negative outcome [24, 25]. A negative outcome analysis examines outcomes that are not expected to be associated with the exposure of interest. If a null or negligible effect is observed for these negative outcomes, it strengthens confidence in the validity of the observed associations for the primary outcomes, suggesting that the primary findings are less likely to be influenced by bias or confounding factors.

Exploratory analysis

As an exploratory analysis, we set the outcome as all-cause death. We calculated the unweighted and weighted HRs and their 95% CIs for this outcome, following the same approach as in the main analysis. Furthermore, we plotted weighted Kaplan–Meier curves to illustrate the cumulative incidence of all-cause death during the follow-up periods. However, we could not clarify this information in the GLP-1 RAs cohort because the number of deceased patients in the GLP-1 RAs group was less than 10. Disclosing such values and relevant information was prohibited owing to the governmental privacy protection policy.

Ethics

The study was approved by the institutional review board of The University of Tokyo (approval number 11187-(8), approval date 22 February 2023) and was performed in accordance with the tenets of the Declaration of Helsinki. The requirement for written informed consent was waived owing to the anonymous nature of the data.

Results

DPP-4 inhibitors versus metformin for COPD

The cohort included 13 183 and 3773 patients initiating treatment with DPP-4 Is and metformin, respectively (supplementary figure 1). Patients were followed for a median of 0.8 (interquartile range (IQR), 0.2–2.1) years, and the most common reason for the end of follow-up was first exacerbation and final registration in the DPP-4 Is and metformin groups, respectively (supplementary table 1). During the follow-up periods of 24 308 patient-years, 5775 initial exacerbations requiring systemic corticosteroids occurred, resulting in a crude incidence rate of 23.8 per 100 person-years. Before propensity score overlap weighting, DPP-4 I users were more likely to be older and underweight than metformin users (table 1 and supplementary table 2). After weighing, the two groups were balanced.

Supplementary table 3 presents the outcomes before and after weighting. After weighting, DPP-4 Is (*versus* metformin) were associated with a higher incidence of exacerbations requiring systemic corticosteroids (22.4 *versus* 20.4 per 100 person-years; HR 1.16, 1.07–1.25) and hospitalisation (1.29 *versus* 0.94 per 100 person-years; HR 1.41, 1.06–1.88). The cumulative incidence curves for both initial exacerbations requiring systemic corticosteroids and hospitalisation consistently showed differences between the two groups from the beginning to the end (figure 2). However, the curve for exacerbations requiring hospitalisation in the metformin group exhibited abrupt fluctuations. Additionally, DPP-4 Is (*versus* metformin) were associated with higher counts of exacerbations requiring systemic corticosteroids (85.2 *versus* 73.6 per 100 person-years; RR 1.16, 1.05–1.27) and hospitalisation (2.22 *versus* 1.48 per 100 person-years; RR 1.50, 1.08–2.08).

Supplementary figure 2 shows the results of the secondary analyses. In patients with BMIs of 18.5–24.9 (HR 1.14, 1.03–1.26) and 25.0–29.9 (HR 1.24, 1.09–1.41), DPP-4 Is (*versus* metformin) were associated with a higher incidence of exacerbations requiring systemic corticosteroids. However, such an association was not confirmed in patients with BMIs <18.5 and ⩾30. DPP-4 Is did not show a tendency to be associated with a higher incidence of exacerbations in patients with lower BMIs. Sensitivity analyses provided consistent results (supplementary figure 3).

TABLE 1 Baseline patient characteristics before and after overlap weighting for each cohort of patients with COPD

Characteristic	DPP-4 Is cohort					
	Before weighting			After weighting		
	DPP-4 Is	Metformin	ASD	DPP-4 Is	Metformin	ASD
Total	13 183	3773		13 183	3773	
Age, years	66.3±7.7	63.0±9.0	0.39	64.0±8.8	64.0±8.5	0.00
Female	3355 (25.4)	1101 (29.2)	0.09	3695 (28.0)	1057 (28.0)	0.00
Smoking status						
Current	3352 (25.4)	941 (24.9)	0.01	3331 (25.3)	953 (25.3)	0.00
Past/never	9828 (74.6)	2832 (75.1)	0.01	9852 (74.7)	2820 (74.7)	0.00
Unknown	3 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
Body mass index, kg·m^{-2}						
<18.5	562 (4.3)	63 (1.7)	0.15	265 (2.0)	76 (2.0)	0.00
18.5–24.9	6352 (48.2)	1362 (36.1)	0.25	5175 (39.3)	1481 (39.3)	0.00
25.0–29.9	4511 (34.2)	1495 (39.6)	0.11	5137 (39.0)	1470 (39.0)	0.00
⩾30.0	1756 (13.3)	853 (22.6)	0.24	2606 (19.8)	746 (19.8)	0.00
Unknown	2 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
HbA1c, %						
⩽7.0	7847 (59.5)	2012 (53.3)	0.13	7209 (54.7)	2063 (54.7)	0.00
7.1–8.0	2408 (18.3)	750 (19.9)	0.04	2592 (19.7)	742 (19.7)	0.00
>8.0	1011 (7.7)	368 (9.8)	0.07	1211 (9.2)	347 (9.2)	0.00
Unknown	1917 (14.5)	643 (17.0)	0.07	2171 (16.5)	621 (16.5)	0.00
Characteristic	**GLP-1 RAs cohort**					
	Before weighting			After weighting		
	GLP-1 RAs	Metformin	ASD	GLP-1 RAs	Metformin	ASD
Total	449	4315		449	4315	
Age, years	60.7±10.1	63.1±9.0	0.25	61.3±9.9	61.3±9.7	0.00
Female	197 (43.9)	1233 (28.6)	0.32	184 (40.9)	1767 (40.9)	0.00
Smoking status						
Current	121 (26.9)	1095 (25.4)	0.03	116 (25.9)	1118 (25.9)	0.00
Past/never	328 (73.1)	3220 (74.6)	0.03	333 (74.1)	3197 (74.1)	0.00
Unknown	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
Body mass index, kg·m^{-2}						
<18.5	<10	73 (1.7)	(-)	<10	30 (0.7)	0.00
18.5–24.9	100–108	1580 (36.6)	(-)	111–119	1122 (26.0)	0.00
25.0–29.9	150 (33.4)	1699 (39.4)	0.07	161 (35.8)	1545 (35.8)	0.00
⩾30.0	190 (42.3)	963 (22.3)	0.44	168 (37.5)	1618 (37.5)	0.00
Unknown	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
HbA1c, %						
⩽7.0	242 (53.9)	2240 (51.9)	0.04	244 (54.4)	2345 (54.4)	0.00
7.1–8.0	54 (12.0)	853 (19.8)	0.21	57 (12.7)	547 (12.7)	0.00
>8.0	57 (12.7)	479 (11.1)	0.05	52 (11.7)	504 (11.7)	0.00
Unknown	96 (21.4)	743 (17.2)	0.11	96 (21.3)	919 (21.3)	0.00
Characteristic	**SGLT-2 Is cohort**					
	Before weighting			After weighting		
	SGLT-2 Is	Metformin	ASD	SGLT-2 Is	Metformin	ASD
Total	9518	8641		9518	8641	
Age, years	64.7±8.7	65.0±8.4	0.03	64.7±8.7	64.7±8.6	0.00
Female	2477 (26.0)	2282 (26.4)	0.01	2574 (27.0)	2337 (27.0)	0.00
Smoking status						
Current	2375 (25.0)	2277 (26.4)	0.03	2440 (25.6)	2215 (25.6)	0.00
Past/never	7140 (75.0)	6364 (73.6)	0.03	7078 (74.4)	6426 (74.4)	0.00
Unknown	3 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
Body mass index, kg·m^{-2}						
<18.5	209 (2.2)	236 (2.7)	0.03	213 (2.2)	193 (2.2)	0.00
18.5–24.9	3455 (36.3)	3815 (44.1)	0.16	3743 (39.3)	3398 (39.3)	0.00

Continued

TABLE 1 Continued

Characteristic	SGLT-2 Is cohort					
	Before weighting			After weighting		
	SGLT-2 Is	Metformin	ASD	SGLT-2 Is	Metformin	ASD
25.0–29.9	3736 (39.3)	3135 (36.3)	0.06	3663 (38.5)	3325 (38.5)	0.00
⩾30.0	2118 (22.3)	1455 (16.8)	0.14	1900 (20.0)	1725 (20.0)	0.00
Unknown	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
HbA1c, %						
⩽7.0	5181 (54.4)	4126 (47.7)	0.13	4748 (49.9)	4311 (49.9)	0.00
7.1–8.0	1789 (18.8)	2012 (23.3)	0.11	2070 (21.7)	1879 (21.7)	0.00
>8.0	914 (9.6)	1125 (13.0)	0.11	1111 (11.7)	1008 (11.7)	0.00
Unknown	1634 (17.2)	1378 (15.9)	0.03	1589 (16.7)	1443 (16.7)	0.00

Data are presented as mean±SD and n (%). ASD: absolute standard difference; DPP-4 Is: dipeptidyl peptidase-4 inhibitors; GLP-1 RAs: glucagon-like peptidase 1 receptor agonists; HbA1c: haemoglobin A1c; SGLT-2 Is: sodium glucose co-transporter-2 inhibitors.

During the follow-up periods, 0.4% (14 of 3773) and 1.7% (220 of 13 183) of patients died in the metformin and DPP-4 Is groups, respectively (supplementary table 1). DPP-4 Is were associated with a higher incidence of all-cause death than metformin (unweighted HR 3.99, 2.44–6.54; weighted HR 2.28, 1.38–3.78) (supplementary figure 10).

GLP-1 receptor agonists versus *metformin for COPD*

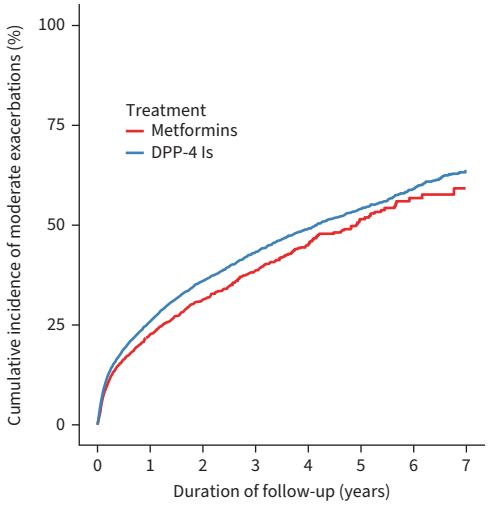
The cohort included 449 and 4315 patients initiating treatment with GLP-1 RAs and metformin, respectively (supplementary figure 4). Patients were followed for a median of 0.8 (IQR 0.3–2.0) years, and the most common reason for the end of follow-up was final registration and treatment discontinuation in the GLP-1 RAs and metformin groups, respectively (supplementary table 4). During the follow-up period of 6676 patient-years, 1393 exacerbations requiring systemic corticosteroids occurred, resulting in a crude incidence rate of 20.9 per 100 person-years. Before weighting, GLP-1 RAs users were more likely to be younger, female, obese and previous users of SGLT-2 Is or insulin than metformin users (table 1 and supplementary table 5). After weighing, the two groups were balanced.

Supplementary table 6 presents the outcomes before and after weighting. After weighting, the incidence rates of exacerbations requiring systemic corticosteroids were similar in the GLP-1 RAs and metformin groups (30.1 *versus* 24.4 per 100 person-years; HR 1.07, 0.87–1.32). The cumulative incidence curve for exacerbations requiring systemic corticosteroids did not show any apparent differences between the two groups (figure 2). Additionally, the incidence rates of exacerbations requiring hospitalisation were also similar in the two groups (105.8 *versus* 83.6 per 100 person-years; RR 1.26, 0.96–1.66). We could not elucidate exacerbations requiring hospitalisation because the number of severe exacerbations in the GLP-1 RAs group was less than 10, and disclosing such values was prohibited owing to the governmental privacy protection policy.

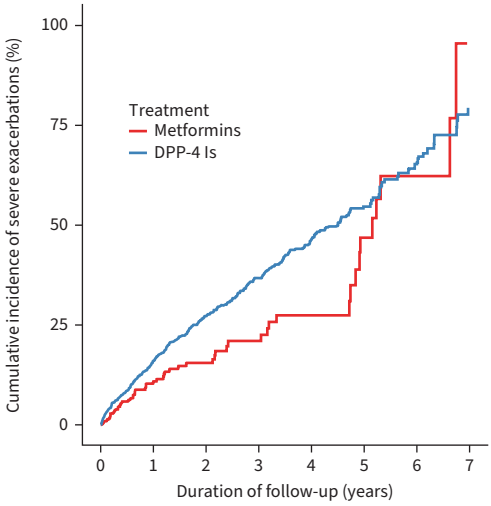
Supplementary figure 5 shows the results of the secondary analyses. In patients with BMIs <18.5, GLP-1 RAs (*versus* metformin) were associated with a higher incidence of exacerbations requiring systemic corticosteroids (HR 2.23, 1.08–4.60), although the sample size in the GLP-1 RAs group was small. GLP-1 RAs tended to be associated with a higher incidence of exacerbations in patients with lower BMIs. Sensitivity analyses provided consistent results (supplementary figure 6). However, we could not obtain valid results in the negative outcome analysis because no outcomes occurred in the GLP-1 RAs group.

SGLT-2 inhibitors versus *metformin for COPD*

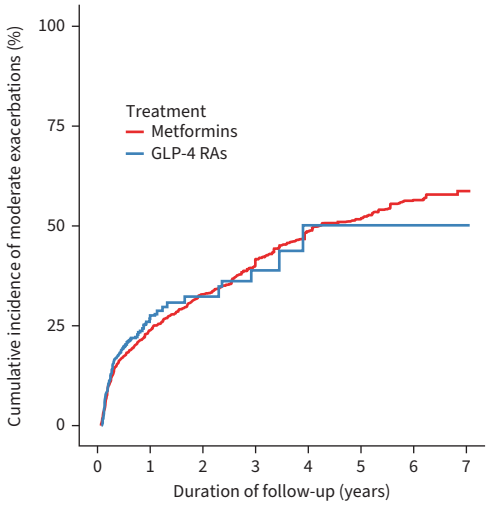
The cohort included 9518 and 8641 patients initiating treatment with SGLT-2 Is and metformin, respectively (supplementary figure 7). Patients were followed for a median of 0.7 (IQR 0.3–1.8) years, and the most common reason for the end of follow-up was final registration and treatment discontinuation in the SGLT-2 Is and metformin groups, respectively (supplementary table 7). During the follow-up periods of 23 244 patient-years, a total of 4988 exacerbations requiring systemic corticosteroids occurred, resulting in a crude incidence rate of 21.5 per 100 person-years. Before weighting, SGLT-2 I users were more likely to have comorbid chronic heart failure and lower HbA1c levels than metformin users (table 1 and supplementary table 8). After weighing, the two groups were balanced.



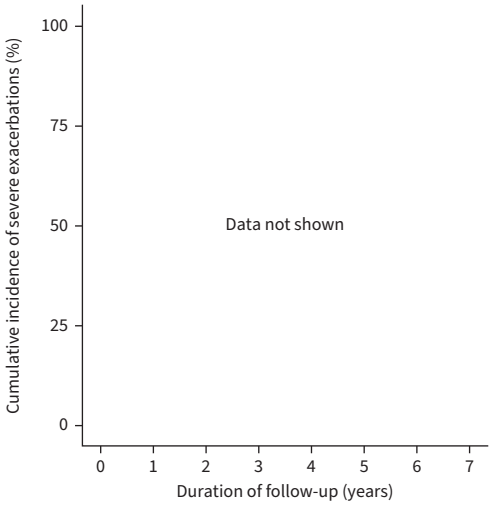
Number at risk								
Metformins	3773	1531	856	450	241	118	57	21
DPP-4 Is	13 183	5934	3545	2209	1330	751	349	130



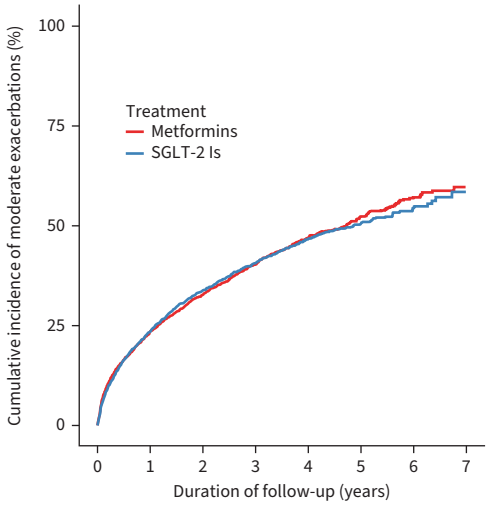
Number at risk								
Metformins	3773	1921	1167	705	418	230	115	43
DPP-4 Is	13 183	7896	5336	3665	2467	1556	792	292



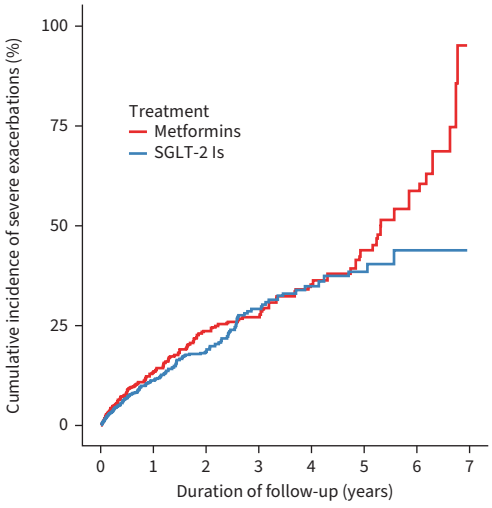
Number at risk								
Metformins	4315	1993	1167	668	378	199	102	38
GLP-1 RAs	449	99	37	20	<10	<10	<10	0



Number at risk								
Metformins								
GLP-1 RAs								



Number at risk								
Metformins	8641	3538	1897	1086	587	298	138	48
SGLT-2 Is	9518	4039	2042	1123	547	256	97	24



Number at risk								
Metformins	8641	4502	2718	1727	1040	601	297	96
SGLT-2 Is	9518	5053	2882	1766	982	511	198	56

FIGURE 2 Weighted cumulative incidence of first COPD exacerbations requiring systemic corticosteroids (left) and hospitalisation (right) in each cohort. The cumulative incidence curve for exacerbations requiring hospitalisation could not be shown because the number of severe exacerbations in the glucagon-like peptidase 1 receptor agonists (GLP-1 Ras) group was <10, and disclosing such values was prohibited owing to the governmental privacy protection policy. DPP-4 Is: dipeptidyl peptidase-4 inhibitors.

Supplementary table 9 shows the outcomes before and after weighting. After weighting, the incidence rates of exacerbations requiring systemic corticosteroids were similar in the SGLT-2 Is and metformin groups (20.7 *versus* 21.8 per 100 person-years; HR 1.00, 0.94–1.06). The incidence rates of exacerbations requiring hospitalisation were also similar between the groups (0.94 *versus* 1.13 per 100 person-years; HR 0.86, 0.67–1.11). The cumulative incidence curve for moderate exacerbations yielded comparable results between the two groups, whereas the curve for exacerbations requiring hospitalisation initially showed a slight divergence between the two groups, then converged and finally diverged again, with a more apparent gap (figure 2). The numbers of exacerbations requiring systemic corticosteroids and hospitalisation were similar between the groups.

Supplementary figure 8 shows the results of the secondary analyses. In patients with BMIs of 18.5–24.9, SGLT-2 Is (*versus* metformin) were associated with a lower incidence of exacerbations requiring systemic corticosteroids (HR 0.88, 0.80–0.97). In contrast, in patients with BMIs of 25.0–29.9, SGLT-2 Is were associated with a higher incidence of exacerbations (HR 1.10, 1.00–1.22). A subtle tendency for SGLT-2 Is to be associated with a lower incidence of exacerbations was observed in patients with lower BMIs. Sensitivity analyses provided consistent results (supplementary figure 9).

During the follow-up periods, 0.9% (81 of 8641) and 1.0% (92 of 9518) of patients died in the metformin and SGLT-2 Is groups, respectively (supplementary table 7). The number of deceased patients was similar between the metformin and SGLT-2 Is groups (unweighted HR 1.03, 0.76–1.40; weighted HR 0.92, 0.67–1.28) (supplementary figure 10).

Discussion

This population-based study demonstrated that, compared with metformin, DPP-4 Is were associated with an increased risk of COPD exacerbations requiring systemic corticosteroids and hospitalisation. Conversely, the risks of such exacerbations with GLP-1 RAs and SGLT-2 Is were comparable with those observed with metformin. These findings suggest that the risk of COPD exacerbations may be lowest with SGLT-2 Is, metformin and GLP-1 RAs, followed by DPP-4 Is. This hierarchy aligns with the findings of previous studies [12–14]. Such a hierarchy can guide physicians in selecting treatments for patients with T2DM comorbid with COPD. Although data are sparse regarding the mechanisms underlying the differential effects of novel antihyperglycemic drugs on COPD control, the difference between DPP-4 Is and GLP-1 RAs, which share pharmacological mechanisms, can be explained as follows: DPP-4 Is increase endogenous GLP-1, which can exert both local and systemic anti-inflammatory effects; however, GLP-1 RAs are more potent than endogenous GLP-1 [26, 27].

Our secondary analyses suggest that GLP-1 RAs may be more effective in patients with higher BMIs compared with metformin, while SGLT-2 Is may perform better in those with lower BMIs. Consistent with these findings, a previous study reported a lower incidence of COPD exacerbations with GLP-1 RAs in patients with BMIs ⩾30 compared with sulfonylureas, with no such association in those with BMIs <30. Similarly, SGLT-2 Is were associated with a lower incidence of COPD exacerbations in patients with BMIs of 25–29.9 compared with GLP-1 RAs, with no such association in other BMI categories [13]. However, the effectiveness of GLP-1 RAs and SGLT-2 Is across BMI categories may vary among ethnic groups, as shown by their differential cardiovascular effects in Asian *versus* white patients [28]. Further research is needed to investigate this variation to advance personalised treatment strategies for patients with T2DM comorbid with COPD.

Compared with the results from our research on asthma [15], the findings from this study on COPD show both similarities and differences. The association of DPP-4 Is with an increased risk of COPD exacerbations requiring systemic corticosteroids and hospitalisation was confirmed in both studies. Similarly, the comparable risk in the SGLT-2 Is and metformin groups was confirmed in both studies. Although GLP-1 RAs were associated with an increased risk of asthma exacerbations requiring systemic corticosteroids in the asthma study [15], this association was not confirmed in this study on COPD. Given the smaller sample size in the GLP-1 RAs group than in the asthma study, this association may be

confirmed with a larger sample size, even in patients with COPD. Given the similarities and differences between COPD and asthma [29, 30], further confirmatory research is necessary for both conditions.

The incidence of all-cause death was significantly higher with DPP-4 Is than with metformin, which was consistent with the findings related to COPD exacerbations requiring systemic corticosteroids or hospitalisation. The risk of all-cause death with SGLT-2 Is was comparable with that with metformin, also aligning with the results for COPD exacerbations. However, as these analyses were exploratory, further research is needed to explore this relationship.

Our study has some limitations. First, the diagnostic codes for COPD have not been validated. Therefore, to ensure accurate identification of patients with COPD, we combined treatment drugs and diagnostic codes to identify patients with COPD. Second, we did not define COPD exacerbations based on antibiotic use. This was because antibiotic use is variable and only indicated when specific patient criteria are met, whereas systemic corticosteroids are recommended for COPD exacerbations [13, 31]. Third, the healthcare checkup data might not accurately reflect the status at cohort entry, as we utilised the most recent data from the 2 years prior to cohort entry to ensure adequate sample sizes. Fourth, individuals included in the NDB are predominantly of Asian ethnicity. Fifth, due to the retrospective nature of this study, residual confounding could exist (*i.e.* therapies may not have been selected randomly). While the findings from negative outcome analyses indicated an absence of residual confounding in the DPP-4 Is and SGLT-2 Is cohorts, this could not be ascertained for the GLP-1 RAs cohort owing to the infrequency of negative outcomes and the limited sample size of GLP-1 RAs users. Finally, because this was an observational study, we could not definitively establish a causal relationship.

Conclusions

In this population-based study, the risks of COPD exacerbations requiring systemic corticosteroids and hospitalisation in the GLP-1 RAs and SGLT-2 Is groups were comparable with those in the metformin group. Conversely, DPP-4 Is were associated with a higher incidence of both types of exacerbations. GLP-1 RAs may be more effective in patients with higher BMIs, whereas SGLT-1 Is may perform better in those with lower BMIs. Further research is necessary to confirm the reproducibility of these findings for advanced personalised treatment strategies for patients with T2DM comorbid with COPD.

Provenance: Submitted article, peer reviewed.

Ethics statement: The study was approved by the institutional review board of The University of Tokyo (approval number 11187-(8), approval date 22 February 2023) and was performed in accordance with the tenets of the Declaration of Helsinki. The requirement for written informed consent was waived owing to the anonymous nature of the data.

Author contributions: Conceptualisation: Y. Kimura, T. Jo, N. Inoue and M. Suzukawa; methodology: Y. Kimura, T. Jo, N. Inoue and M. Suzukawa; software: Y. Kimura; formal analysis: Y. Kimura; original draft preparation: Y. Kimura; review and editing: Y. Kimura, T. Jo, N. Inoue, M. Suzukawa, H. Matsui, Y. Sasabuchi and H. Yasunaga; supervision: H. Yasunaga. All authors have read and agreed to the published version of this manuscript.

Conflict of interest: Y. Kimura, T. Jo, N. Inoue, H. Matsui, Y. Sasabuchi and H. Yasunaga declare no conflict of interest. M. Suzukawa received research funding from Shionogi, MSD, Sanofi, Kyorin, AstraZeneca and GlaxoSmithKline.

Support statement: This work was supported by grants from the Ministry of Health, Labour, and Welfare, Japan (23AA2003), and a Grant-in-Aid for Scientific Research (20FC1027, 23FC1031) from the Ministry of Health, Labour, and Welfare of Japan. Funding information for this article has been deposited with the Crossref Funder Registry.

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