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ORIGINAL RESEARCH

# Dipeptidyl Peptidase-4 Inhibitor Use and Risk of Major Adverse Cardiovascular Events in Patients with COPD and Diabetes: A Nationwide Retrospective Cohort Study

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**Background:** Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory disorder frequently followed by cardiovascular disease and diabetes mellitus (DM) that may increase the risk of major adverse cardiovascular events (MACE). Dipeptidyl peptidase-4 inhibitors (DPP-4i) are widely used antidiabetic agents with potential anti-inflammatory and cardiovascular protective effects beyond glycemic control. This study investigated the association between DPP-4i use and the risk of MACE in patients with COPD and comorbid DM.

**Methods:** This nationwide retrospective cohort study used data from Taiwan's National Health Insurance Research Database between 2016 and 2021. Patients aged ≥40 years with at least one hospitalization for COPD and a diagnosis of DM were included. DPP-4i users were identified by prescription records (ATC code A10BH*), and non-users were defined as patients receiving other antidiabetic agents without DPP-4i. The primary outcome was MACE, defined as a composite of cardiovascular death, myocardial infarction, and stroke. Cox proportional hazards analysis was used to estimate hazard ratios (HRs) of MACE with 95% confidence intervals (CIs), adjusting for demographic characteristics, comorbidities, and overall disease burden.

**Results:** A total of 24,215 patients with COPD and DM were included, of whom 5737 (23.7%) were DPP-4i users and 18,478 (76.3%) were non-users. During follow-up, DPP-4i users had a significantly lower incidence of MACE compared with non-users (17.88% vs 26.34%, $p < 0.0001$). Non-DPP-4i use was associated with a higher risk of MACE (adjusted HR: 1.56; 95% CI: 1.46–1.67; $p < 0.0001$) compared with DPP-4i use. The association of DPP-4i was consistent across sex, age groups, and patients with prior myocardial infarction, stroke, or hypertension.

**Conclusion:** In this nationwide retrospective cohort study, DPP-4i use was associated with a lower risk of MACE among patients with COPD and comorbid DM. These findings suggest that DPP-4i may provide cardiovascular benefits beyond glycemic control in this high-risk population. However, given the observational design, causal relationships cannot be established, and the findings should be interpreted with caution due to potential residual confounding and selection bias. Further randomized controlled trials are warranted to confirm findings.

**Keywords:** chronic obstructive pulmonary disease, diabetes mellitus, dipeptidyl peptidase-4 inhibitor, major adverse cardiovascular events

## Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation and a chronic systemic inflammatory state. COPD severity is an important determinant of clinical outcomes, with more advanced disease associated with increased systemic inflammation and a higher risk of cardiovascular events.[1,2] Beyond

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its pulmonary manifestations, COPD is increasingly recognized as a multisystem disease with substantial extrapulmonary consequences. Cardiovascular disease is one of the most important comorbidities in this population. Patients with COPD have a significantly higher prevalence of atrial fibrillation, heart failure, and ischemic heart disease compared with the general population.[3] Moreover, acute exacerbations of COPD are associated with a markedly increased risk of subsequent cardiovascular events, particularly among patients requiring hospitalization and within the first 30 days after an exacerbation.[4] The coexistence of cardiovascular disease portends a worse prognosis in COPD, and it is estimated that approximately 12% to 60% of COPD-related deaths are attributable to cardiovascular causes.[5–7]

Diabetes mellitus (DM) is another highly prevalent comorbidity in individuals with COPD, with reported prevalence rates ranging from 12.2% to 40%.[8–11] The frequent coexistence of COPD and DM is likely driven by shared pathophysiological mechanisms, including chronic systemic inflammation, oxidative stress, insulin resistance, and common risk factors such as cigarette smoking and physical inactivity. Importantly, the presence of DM in patients with COPD is associated with an increased risk of acute exacerbations, accelerated decline in lung function, higher hospitalization rates, and increased mortality.[12] In addition, DM is a well-established risk factor for major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke, thereby further compounding the already elevated cardiovascular risk observed in COPD.

A variety of pharmacologic agents are available for the management of DM, and emerging therapeutic strategies suggest potential benefits beyond glycemic control. Among these, dipeptidyl peptidase-4 (DPP-4) inhibitors have attracted attention because of their pleiotropic effects.[13] DPP-4 inhibitors not only improve glucose homeostasis but also exhibit anti-inflammatory effects.[14] DPP-4 is expressed in respiratory tissues, including the distal airways and alveolar structures, and its expression may be upregulated in chronic lung diseases, potentially enhancing inflammatory responses.[15,16] Beyond glycemic control, DPP-4 inhibitors may also provide cardiovascular benefits, with evidence suggesting improvements in endothelial function and reductions in atherosclerosis and myocardial injury, possibly through incretin-mediated pathways.[17]

Given the shared inflammatory pathways linking COPD, diabetes, and cardiovascular disease, DPP-4 inhibitors may therefore offer both cardiovascular and pulmonary protective effects in this high-risk population. A previous meta-analysis of randomized trials among 52,520 patients with type 2 DM reported that DPP-4 inhibitors had overall neutral effects on major cardiovascular outcomes compared with placebo, without significant reductions in myocardial infarction, hospitalization for heart failure, cardiovascular death, or unstable angina.[18]

Although the overlap among COPD, diabetes mellitus, and cardiovascular disease is well recognized, real-world evidence about the association between DPP-4 inhibitor use and the risk of MACE in patients with concomitant COPD and DM remains limited.

We therefore hypothesized that the use of DPP-4 inhibitors in patients with COPD and comorbid diabetes may reduce the risk of MACE in addition to achieving glycemic control. To test this hypothesis, we conducted a nationwide cohort study to evaluate the association between DPP-4 inhibitor use and the incidence of MACE in patients with COPD and diabetes.

# Materials and Methods

## Data Source

Taiwan's National Health Insurance Research Database (NHIRD) was used to identify patients with chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM), as well as their associated comorbidities. The National Health Insurance (NHI) program is a single-payer healthcare system that has covered more than 99.6% of Taiwan's population since 1995.

The healthcare information in NHIRD included demographic characteristics, dates of clinical visits and hospitalizations, diagnostic codes, procedures, and prescription records. Diagnoses and procedures were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) before 2016, and the Tenth Revision (ICD-10-CM) after 2016.

## Ethics Statement

This study was approved by the Institutional Review Board of Chi Mei Medical Center (IRB No. 11502-021). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013 revision). Because the NHIRD consists of anonymized secondary data, the requirement for informed consent was waived by the Institutional Review Board of Chi Mei Medical Center.

## Study Population and Exposure Definition

Patients with COPD were identified from the NHIRD between January 1, 2016, and December 31, 2021, using ICD-10-CM codes J41–J44. To increase diagnostic validity, only patients aged ≥40 years who had at least one hospitalization with a primary or secondary diagnosis of COPD were included.

Among patients with COPD, those with a diagnosis of DM between 2017 and 2021 were further identified as study population, with 2016 serving as a washout period to confirm incident cases. The date of DM diagnosis was defined as the index date for all participants. Those patients who used DPP-4 inhibitor were defined from prescription records, using Anatomical Therapeutic Chemical (ATC) code: A10BH*. Patients were classified into two groups: DPP-4 inhibitor users and non–DPP-4 inhibitor users. Non–DPP-4 inhibitor users were defined as patients without any record of DPP-4 inhibitor prescriptions but received other antidiabetic agents. The flowchart of patients' selection presented in Figure 1.

## Outcome and Covariates

The primary outcome was MACE, defined as a mixed endpoint including cardiovascular death (ICD-10-CM: I00–I82), myocardial infarction (ICD-10-CM: I21, I22, and I25.2), and stroke (ICD-10-CM: I60–I69). All participants were followed from the index date until the incidence of the first MACE event, loss to follow-up, death, or the end of the study period (December 31, 2021), whichever occurred first.

Additionally, potential confounding factors were age, sex, Charlson Comorbidity Index (CCI) score, and baseline comorbidities, including prior myocardial infarction (ICD-10-CM: I21, I22, and I25.2), prior stroke (ICD-10-CM: I60–I69), hyperlipidemia (ICD-10-CM: E78), and hypertension (ICD-10-CM: I10–I15). These variables were assessed before the index date and adjusted for in multivariable analyses.

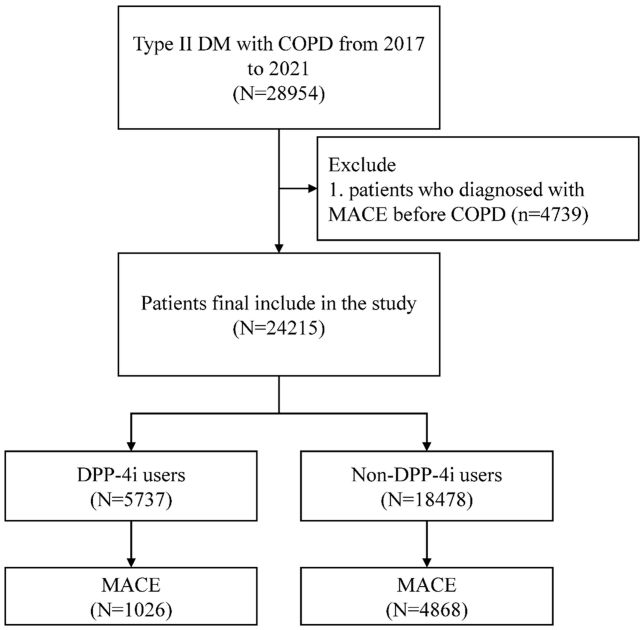


**Figure 1** Flowchart of study subjects' selection.

## Statistical Analysis

Baseline characteristics were summarized as means with standard deviations for continuous variables and frequencies with percentages for categorical variables. Differences between DPP-4 inhibitor users and non-users were assessed using Student's *t* test for continuous variables and Pearson's chi-square test for categorical variables.

Cox proportional hazards regression models were applied to estimate crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between DPP-4 inhibitor use and the risk of MACE. The proportional hazards assumption was assessed and found to be satisfied. Stratified analyses were used to evaluate the consistency of associations across predefined subgroups. Additionally, as the variables in this study were derived from structured claims data within the NHIRD, no missing data were identified. Therefore, no imputation procedures were required. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided p value <0.05 was considered statistically significant.

# Results

A total of 24,215 COPD patients with DM were included in the study, of whom 5737 (23.7%) were DPP-4 inhibitor users and 18,478 (76.3%) were non–DPP-4 inhibitor users. The baseline characteristics of the study population are summarized in Table 1. The overall cohort was predominantly male (73.65%), and more than one-third of patients were aged ≥80

**Table 1** The Characteristics of DM Patients

| | Overall (N=24,215) | DPP-4 Users (N=5737) | Non DPP-4 Users (N=18,478) | p-value |
|---|---|---|---|---|
| Gender | | | | |
| Male | 17,835 (73.65) | 4174 (72.76) | 13,661 (73.93) | 0.0775 |
| Female | 6380 (26.35) | 1563 (27.24) | 4817 (26.07) | |
| Age group | | | | |
| 40–59 | 3163 (13.06) | 774 (13.49) | 2389 (12.93) | 0.0593 |
| 60–69 | 5378 (22.21) | 1209 (21.07) | 4169 (22.56) | |
| 70–79 | 6653 (27.47) | 1562 (27.23) | 5091 (27.55) | |
| ≥80 | 9021 (37.25) | 2192 (38.21) | 6829 (36.96) | |
| Comorbidity | | | | |
| MI | 803 (3.32) | 151 (2.63) | 652 (3.53) | 0.0009 |
| Stroke | 4344 (17.94) | 618 (10.77) | 3726 (20.16) | <0.0001 |
| Hypertension | 13,964 (57.67) | 3173 (55.31) | 10,791 (58.4) | <0.0001 |
| CCI score, mean±SD | 1.96±1.86 | 1.86±1.91 | 2.00±1.84 | <0.0001 |
| CCI group | | | | |
| 0 | 4943 (20.41) | 1396 (24.33) | 3547 (19.2) | <0.0001 |
| 1–2 | 12,033 (49.69) | 2756 (48.04) | 9277 (50.21) | |
| ≥3 | 7239 (29.89) | 1585 (27.63) | 5654 (30.6) | |
| Outcome | | | | |
| Death | 9044 (37.35) | 2192 (38.21) | 6852 (37.08) | 0.1235 |
| MACE | 5894 (24.34) | 1026 (17.88) | 4868 (26.34) | <0.0001 |
| Death in CVD | 1727 (7.13) | 356 (6.21) | 1371 (7.42) | 0.0018 |
| MI | 881 (3.64) | 174 (3.03) | 707 (3.83) | 0.0051 |
| Stroke | 4113 (16.99) | 641 (11.17) | 3472 (18.79) | <0.0001 |
| Time to follow up, year | | | | |
| Mean±SD | 1.87±1.54 | 2.31±1.51 | 1.74±1.52 | <0.0001 |
| Time to MACE, year | | | | |
| Mean±SD | 0.75±1.06 | 1.27±1.26 | 0.64±0.97 | <0.0001 |

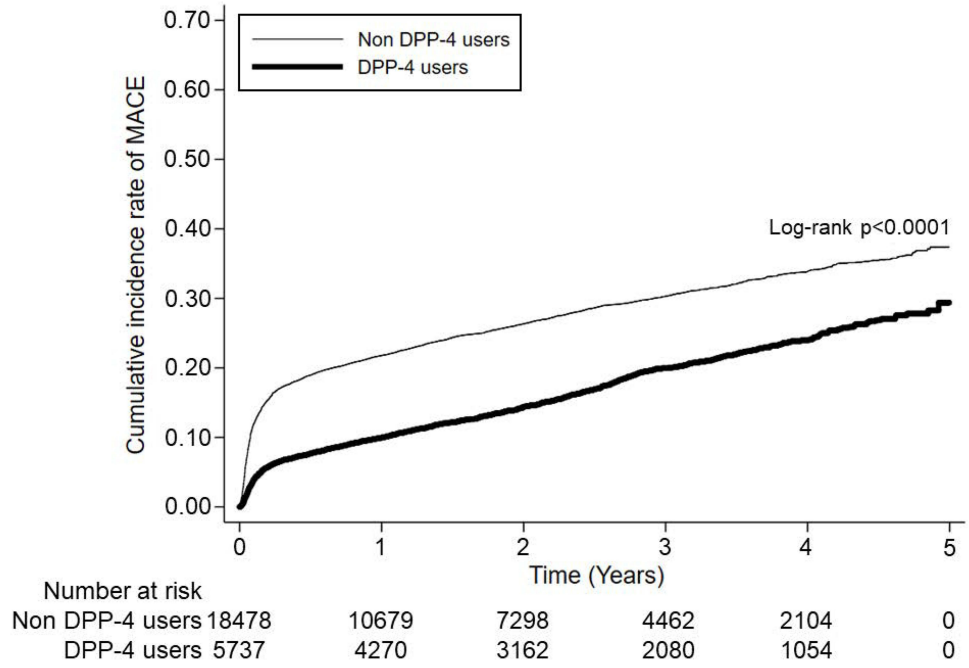


**Figure 2** Cumulative incidence trend of MACE risk between DDP-4 users and non-DPP-4 users.

years. There were no significant differences in sex distribution or age group between DPP-4 inhibitor users and non–DPP-4 inhibitor users. However, patients receiving DPP-4 inhibitor had a lower prevalence of major cardiovascular comorbidities, including myocardial infarction (2.63% vs 3.53%), stroke (10.77% vs 20.16%), and hypertension (55.31% vs 58.40%), compared with non–DPP-4 inhibitor users (all $p < 0.01$). Additionally, DPP-4 inhibitor users had a lower comorbidity burden from CCI score (1.86±1.91 vs 2.00±1.84, $p < 0.0001$). During follow-up, the incidence of MACE was significantly lower among DPP-4 inhibitor users than among non–DPP-4i users (17.88% vs 26.34%, $p < 0.0001$). DPP-4 inhibitor users also had longer time to first MACE event occurrence.

Figure 2 demonstrated Kaplan–Meier survival curves of cumulative incidence of MACE between DPP-4 inhibitor users and non–DPP-4 inhibitor users throughout the follow-up period. DPP-4 inhibitor users had a significantly lower cumulative incidence of MACE compared with non–DPP-4 inhibitor users (Log rank test: $p < 0.0001$). Additionally, Table 2 presents

**Table 2** Risk of MACE Among DM Patients

| | Total (N=24,215) | MACE (N=5894) | Crude HR (95% CI) | p-value | aHR (95% CI) | p-value |
|---|---|---|---|---|---|---|
| DPP-4 | | | | | | |
| DPP-4 users | 5737 | 1026 (17.88) | Ref. | | Ref. | |
| Non DPP-4 users | 18,478 | 4868 (26.34) | 1.77 (1.65–1.89) | <0.0001 | 1.56 (1.46–1.67) | <0.0001 |
| Gender | | | | | | |
| Male | 17,835 | 4316 (24.2) | Ref. | | Ref. | |
| Female | 6380 | 1578 (24.73) | 1.02 (0.97–1.08) | 0.4415 | 0.95 (0.89–1) | 0.0685 |
| Age group | | | | | | |
| 40–59 | 3163 | 444 (14.04) | Ref. | | Ref. | |
| 60–69 | 5378 | 978 (18.19) | 1.37 (1.23–1.53) | <0.0001 | 1.11 (0.99–1.24) | 0.0681 |
| 70–79 | 6653 | 1689 (25.39) | 2.07 (1.87–2.30) | <0.0001 | 1.42 (1.28–1.58) | <0.0001 |
| ≥80 | 9021 | 2783 (30.85) | 2.94 (2.66–3.25) | <0.0001 | 1.67 (1.51–1.86) | <0.0001 |

(*Continued*)


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**Table 2** (Continued).

| | Total (N=24,215) | MACE (N=5894) | Crude HR (95% CI) | p-value | aHR (95% CI) | p-value |
|---|---|---|---|---|---|---|
| Comorbidity | | | | | | |
| MI | 803 | 481 (59.9) | 4.18 (3.81–4.59) | <0.0001 | 3.54 (3.22–3.89) | <0.0001 |
| Stroke | 4344 | 3017 (69.45) | 12.13 (11.50–12.80) | <0.0001 | 10.04 (9.48–10.63) | <0.0001 |
| Hypertension | 13,964 | 3897 (27.91) | 1.54 (1.46–1.63) | <0.0001 | 1.08 (1.03–1.15) | 0.0047 |
| CCI group | | | | | | |
| 0 | 4943 | 686 (13.88) | Ref. | | Ref. | |
| 1–2 | 12,033 | 2687 (22.33) | 1.84 (1.70–2.01) | <0.0001 | 1.18 (1.08–1.28) | 0.0002 |
| ≥3 | 7239 | 2521 (34.83) | 3.65 (3.36–3.97) | <0.0001 | 1.33 (1.21–1.46) | <0.0001 |

the crude and adjusted hazard ratios for MACE among COPD patients with diabetes mellitus. In the multivariable Cox proportional hazards model, non–DPP-4 inhibitor users were associated with a higher risk of MACE compared with DPP-4 inhibitor users (adjusted hazard ratio [aHR]: 1.56; 95% confidence interval [CI]: 1.46–1.67; $p < 0.0001$).

The association between DPP-4 inhibitor use and the risk of MACE across all subgroups presented in Table 3. Compared with DPP-4 inhibitor users, non–DPP-4 inhibitor users exhibited a significantly higher risk of MACE in both males (aHR: 1.47; 95% CI: 1.36–1.59) and females (aHR: 1.84; 95% CI: 1.61–2.11). In different age groups, non–DPP-4 inhibitor users were associated with an increased risk of MACE, with AHR from 1.44 (95% CI: 1.13–1.85) in patients aged 40–59 years to 1.64 (95% CI: 1.49–1.81) in those aged ≥80 years. Similarly, the elevated MACE risk among non–DPP-4 inhibitor users still had higher risks in patients with history of MI (aHR: 2.00; 95% CI: 1.54–2.59; p<0.0001), stroke (aHR: 1.74; 95% CI: 1.56–1.94; p<0.0001), and hypertension (aHR: 1.63; 95% CI: 1.49–1.77; p<0.0001).

**Table 3** Difference in Risk of MACE Between DPP-4 Users and Non-DPP-4 Users

| Non DPP-4 Users vs DPP-4 Users | DPP-4 Users | | Non DPP-4 Users | | Crude HR (95% CI) | p-value | aHR (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| | Patients | MACE | Patients | MACE | | | | |
| Overall | 5737 | 1026 (17.88) | 18,478 | 4868 (26.34) | 1.77 (1.65–1.89) | <0.0001 | 1.56 (1.46–1.67) | <0.0001 |
| Stratified | | | | | | | | |
| Gender | | | | | | | | |
| Male | 4174 | 763 (18.28) | 13,661 | 3553 (26.01) | 1.71 (1.58–1.85) | <0.0001 | 1.47 (1.36–1.59) | <0.0001 |
| Female | 1563 | 263 (16.83) | 4817 | 1315 (27.3) | 1.94 (1.70–2.21) | <0.0001 | 1.84 (1.61–2.11) | <0.0001 |
| Age group | | | | | | | | |
| 40–59 | 774 | 81 (10.47) | 2389 | 363 (15.19) | 1.70 (1.33–2.16) | <0.0001 | 1.44 (1.13–1.85) | 0.0035 |
| 60–69 | 1209 | 161 (13.32) | 4169 | 817 (19.6) | 1.71 (1.45–2.03) | <0.0001 | 1.52 (1.28–1.80) | <0.0001 |
| 70–79 | 1562 | 281 (17.99) | 5091 | 1408 (27.66) | 1.86 (1.63–2.11) | <0.0001 | 1.51 (1.32–1.71) | <0.0001 |
| ≥80 | 2192 | 503 (22.95) | 6829 | 2280 (33.39) | 1.83 (1.66–2.02) | <0.0001 | 1.64 (1.49–1.81) | <0.0001 |
| Comorbidity | | | | | | | | |
| MI | 151 | 67 (44.37) | 652 | 414 (63.5) | 2.01 (1.55–2.60) | <0.0001 | 2.00 (1.54–2.59) | <0.0001 |
| Stroke | 618 | 361 (58.41) | 3726 | 2656 (71.28) | 1.75 (1.57–1.95) | <0.0001 | 1.74 (1.56–1.94) | <0.0001 |
| Hypertension | 3173 | 628 (19.79) | 10,791 | 3269 (30.29) | 1.87 (1.71–2.03) | <0.0001 | 1.63 (1.49–1.77) | <0.0001 |
| CCI group | | | | | | | | |
| 0 | 1396 | 183 (13.11) | 3547 | 503 (14.18) | 1.25 (1.06–1.48) | 0.0095 | 1.34 (1.13–1.59) | 0.0007 |
| 1–2 | 2756 | 452 (16.4) | 9277 | 2235 (24.09) | 1.74 (1.58–1.93) | <0.0001 | 1.61 (1.46–1.78) | <0.0001 |
| ≥3 | 1585 | 391 (24.67) | 5654 | 2130 (37.67) | 1.94 (1.74–2.16) | <0.0001 | 1.63 (1.46–1.81) | <0.0001 |

## Discussion

Our study demonstrated that DPP-4 inhibitors reduce the incidence of MACE in patients with COPD and DM. Our findings are consistent with recently published results showing that the adjusted hazard ratios (aHRs) (95% confidence interval [CI]) for DPP-4 inhibitor use were 0.47 (0.45–0.49) for all-cause mortality, 0.92 (0.88–0.95) for MACEs, and 0.73 (0.62–0.85), respectively.[19]

Analysis of data from the Japanese Registry of Acute Decompensated Heart Failure (JROADHF) further supports the potential phenotypic benefits of DPP-4 inhibitors. In a cohort of 2999 patients with type 2 DM and heart failure, DPP-4 inhibitor use was associated with a significant 31% reduction in the composite outcome of cardiovascular death or heart failure hospitalization (HR: 0.69; 95% CI: 0.55–0.87).[20] Similar to our study, this analysis was retrospective and observational in nature, and therefore carries a different level of evidence compared with randomized, placebo-controlled trials.

The potential mechanisms underlying the protective effects of DPP-4 inhibition may include reductions in proinflammatory cytokine levels.[21] Previous studies have shown that DPP-4 inhibitors exert direct anti-inflammatory effects beyond glycemic control by targeting immune and metabolic cells, including T cells, macrophages, and adipocytes. They inhibit T-cell activation and proliferation, promote polarization toward an anti-inflammatory M2 macrophage phenotype rather than the pro-inflammatory M1 phenotype, and reduce proinflammatory cytokine expression in visceral adipose tissue.[22]

In addition, DPP-4 inhibitors modulate traditional atherosclerotic risk factors through favorable metabolic and hemodynamic effects. Beyond improving glycemic control, they have been shown to improve lipid profiles, potentially slowing the progression of atherosclerosis in patients with cardiometabolic disease.[23,24] Moreover, DPP-4 inhibitors exert direct anti-atherosclerotic actions. They ameliorate endothelial dysfunction by increasing nitric oxide production and reducing oxidative stress, enhance circulating endothelial progenitor cell levels to promote vascular repair, and modulate monocyte/macrophage and vascular smooth muscle cell activity. Furthermore, they suppress inflammatory cytokine release and decrease oxidative stress. Collectively, these mechanisms inhibit plaque progression and enhance plaque stability, supporting potential cardiovascular protective effects independent of glucose lowering.[25]

DPP-4 is an enzyme that cleaves and inactivates stromal cell–derived factor-1α, a key chemokine involved in stem cell homing, tissue repair, and angiogenesis. Inhibition of DPP-4 increases circulating levels of active stromal cell–derived factor-1α, thereby promoting tissue repair following injury, such as myocardial infarction, and potentially improving cardiovascular outcomes.[26–28] Furthermore, DPP-4 inhibitors suppress the upregulation of Nox4 expression induced by angiotensin II stimulation in cardiac tissue. They significantly reduce reactive oxygen species production and inhibit HDAC4 phosphorylation in the myocardium. These molecular effects translate into attenuation of cardiac hypertrophy. Importantly, this cardioprotective effect occurs without significant changes in systemic blood pressure, indicating that the benefits are independent of hemodynamic alterations.[29]

Previous studies indicate that MACE and cardiovascular-related deaths occurred with similar frequency in both early-stage COPD (GOLD 1–2) and advanced-stage COPD (GOLD 3–4). Therefore, COPD is an independent cardiovascular risk factor, regardless of its severity.[30–32] The cardiovascular outcomes did not have significantly difference between these groups, so even mild COPD had an elevated cardiovascular risk that warrants clinical attention. The absence of detailed information on COPD severity in the NHIRD limits our ability to evaluate its impact. Nevertheless, our results indicate that cardiovascular risk is consistently significant in patients with both diabetes and COPD, regardless of COPD stage.

Additionally, cardiovascular disease and chronic kidney disease are among the most prevalent comorbidities in patients with COPD, and their coexistence has been associated with a 6.32-fold increased risk of MACE compared to those without these conditions.[33] Furthermore, COPD has been linked to a 29–41% increase in MACE among patients with multiple comorbid conditions, including diabetes, chronic kidney disease, and asthma.[34,35]

Several limitations of our study should be acknowledged. First, as with other studies based on administrative databases, our dataset lacked detailed information on important lifestyle factors, such as family history, physical activity, and nutritional status, which may influence outcomes in both diabetes and COPD. Second, although the database captured prescribed medications, it did not provide information on actual medication adherence, limiting our ability to assess patient compliance. In addition, exposure to DPP-4 inhibitors was defined by prescription records without

consideration of treatment duration, dosage, or adherence. It may have potential misclassification of exposure. Third, although we adjusted for multiple related clinical covariates and performed stratified analyses, the effect of confounding could not be completely excluded. The advanced methods, such as propensity score matching or weighting, should be considered in the future research. Therefore, the observed protective effect of DPP-4 inhibitors should be interpreted with caution, as it may be affected by selection and confounding bias. Moreover, the magnitude of the observed effect appears stronger than that reported in randomized controlled trials, and this difference should be carefully interpreted. In addition, variability in follow-up duration and relatively short follow-up in some patients may limit the evaluation of long-term outcomes. Furthermore, we were unable to fully adjust for variations in socioeconomic status and HbA1c data, which may affect access to care and clinical outcomes. In addition, information on disease severity and patient functional status was not available in the database, which may affect both treatment selection and clinical outcomes and may result in residual confounding. Further interdisciplinary research is warranted to address these challenges and to advance the integrated management of patients with chronic respiratory and metabolic diseases.

Despite these limitations, our study provides real-world evidence from a large nationwide population. However, the findings should be interpreted with caution, and randomized controlled trials are needed to confirm these associations and establish causality. Concurrently, additional mechanistic studies on DPP-4 may yield novel insights into the shared pathophysiology of COPD and DM.

## Conclusion

In patients with COPD concomitant with DM, DPP-4 inhibitors use was associated with a lower risk of MACE in this real-word database research. These findings from real-world evidence suggest that DPP-4 inhibitors may provide a potential cardiovascular benefit in this high-risk population. However, these findings should be interpreted with caution due to the study's observational design and potential confounding and selection bias. In addition, the magnitude of the observed association appears stronger than that reported in randomized controlled trials, which have shown neutral cardiovascular outcomes for DPP-4 inhibitors. Future prospective and randomized trials are warranted to confirm these results and further define the role of DPP-4 inhibitors in this high-risk population.

## Abbreviations

COPD, Chronic obstructive pulmonary disease; DM, diabetes mellitus; MACE, major adverse cardiovascular events; HRs, hazard ratios; CIs, confidence intervals; NHIRD, National Health Insurance Research Database; NHI, National Health Insurance; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; CCI, Charlson Comorbidity Index; aHR, adjusted hazard ratio; JROADHF, Japanese Registry of Acute Decompensated Heart Failure.

## Data Sharing Statement

The data have been sourced from the Taiwan Nation Health Insurance Database and Taiwan Cancer Registry. The data are available with permission from the Taiwan Health and Welfare Data Science Centre: https://dep.mohw.gov.tw/DOS/np-2497-113.html (accessed 2 March 2026). Restrictions apply to the availability of these data, which were used under license for this study.

## Ethics Approval and Consent to Participate

This study was conducted in compliance with the ethical standards and guidelines of the 2013 revision of the Declaration of Helsinki and approved by the Institutional Review Board of Chi Mei Medical Centre (IRB: 11502-021). Informed consent was also waived by the Institutional Review Board of Chi Mei Medical Centre owing to the use of secondary data and the absence of personal information in the study.

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## Author Contributions

C-H Ho: Conceptualization, Data curation, Methodology, Formal analysis, Writing – original draft and Writing – review and editing; Y-C Shao: Conceptualization, Methodology, and Writing – original draft; Y-C Wu: Formal analysis and Visualization; K-M Liao: Conceptualization, Methodology, Validation, and Writing–review and editing; All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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