Combination Therapies with Thiazolidinediones are Associated with a Lower Risk of Acute Exacerbations in New-Onset COPD Patients with Advanced Diabetic Mellitus: A Nested Case-Control Study

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Abstract

BACKGROUND: The effects of oral antihyperglycemic drugs (OADs) for T2DM on outcomes of co-existing COPD patients have been less concerned. We examined the association of combinational OADs and risk of AECOPD in T2DM patients with co-existing COPD

METHODS: A nested case-control study was conducted using data from the National Health Insurance Research Database of Taiwan. Among new-onset COPD-T2DM patients, 65,370 were prescribed with metformin and 2nd line OADs before the date of COPD onset. Each AECOPD case was matched to 4 randomly selected controls according to the propensity score estimated by patient's baseline characteristics. Conditional logistic regression analysis was performed to estimate the association between AECOPD risk and OADs use.

RESULTS: Among COPD-T2DM patients, 3,355 AECOPD cases and 13,420 matched controls were selected. All COPD-T2DM patients with a double combination of oral OADs (n=12,916), AECOPD patients were less likely to be exposed to SU and thiazolidinediones (TZD) compared to the patients received metformin (MET) and sulfonylurea (SU), with an adjusted odds ratio (OR) of 0.69 (95% confidence interval [CI]: 0.51–0.94, *P*=0.02). Of the patients with a triple combination of oral OADs (n=3,859), we found that MET, SU and TZD had a lower risk of AECOPD (adjusted OR=0.81 (0.68-0.96, *P*=0.01) compared to a combination of MET, SU and a-glucosidase inhibitors (AGI) regardless the level of COPD complexity.

CONCLUSION: Combination therapies with TZD were associated with reducing risk of AECOPD in advanced T2DM patients with co-existing COPD.

Background

Multiple comorbidities in type 2 diabetes mellitus (T2DM) are common, and there might be only 14% patients without other comorbidities (1). This would add complexity in choosing therapeutic drugs for glycemic control when considering impact of different classes of medication on comorbidities. Chronic obstructive pulmonary disease (COPD) is a common comorbidity in patients with T2DM; about 10% of T2DM patients coexisting with COPD (2, 3). Recent studies have demonstrated that either pre-existing or incident diabetes can worsen risk of mortality in COPD or acute examinations of COPD (AECOPD) patients (4, 5). Therefore, it is imperative to optimize DM care of the COPD population.

The recently updated guideline from American Diabetes Association (ADA) recommends metformin, if not contraindicated and if tolerated, is the preferred initial oral antihyperglycemic drug (OAD) for the treatment of T2DM (6). As the progressive natural course of T2DM, when metformin monotherapy is no longer effective, the majority of advanced T2DM patients require combination of different 2nd OADs or insulin therapy to achieve and maintain optimal glycemic control. ADA dose not prioritize specific 2nd drugs based on their efficacy, side effects and impact on comorbidities except for cardiovascular and renal effect (6).

In COPD-T2DM patients, it is uncertain whether tighter glucose control can improve COPD outcome, but poor sugar control worsen the severity and clinical course of COPD was reported in on year prospective study (7, 8). Though there were studies explored the influence of OADs on clinical outcomes of COPD such as metformin (MET) and thiozolidinediones (TZDs) (9–11), comparative little research focus on effect of glucose-lowing agents on COPD outcomes with T2DM patients, particularly in those with poorly glycemic control requiring add-on therapy to metformin. There is still a knowledge gap for selecting optimal drugs both beneficial to glycemic control and better clinical outcomes of new-onset COPD patients with advanced T2DM currently. Therefore, the aim of this study was to examine the effect of add-on OADs on AECOPD risk in new-onset COPD patients with advanced T2DM required combinational therapy. We conducted a nested case-control study by using data from the National Health Insurance Research Database (NHIRD) of Taiwan.

Methods

Data Source

The NHIRD, provided by the National Health Insurance Administration (NHIA) of Taiwan, is a nationwide claims-based database of the National Health Insurance (NHI) program. The NHI program, launched in 1995, is a compulsory insurance program that provides reimbursement for most medical services and over 30 000 prescription drugs. The data used in the study were collected between 2000 and 2015 and were maintained by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Executive Yuan, Taiwan. The NHIRD files include inpatient, outpatient and drug prescription claims and use the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and the Anatomical Therapeutic Chemical (ATC) system to define the patients had a specific disease diagnosis or drug prescription. To verify the accuracy of the diagnoses and the rationale for treatments, the NHIA also routinely samples and reviews a proportion of NHI claims. In addition, hospitals and clinics are penalized if they provide any unnecessary medical treatment to patients. Besides, each patient has a unique encrypted identifier which can be linked to National Death Registry under the regulation of HWDC. This study was approved by the Joint Institutional Review Board of Taipei Medical University (approval no. N201808075).

Study Cohort

The initial cohort consisted of new-onset COPD patients with diabetes between 2003 and 2014. COPD patients were defined if the patients had at least three disease diagnostic claims within a year of follow-up and at least a three-year washout period was adopted to ensure the patients were newly diagnosed with COPD. We then excluded the patients had unknown sex, were not a citizen in Taiwan, or were aged less than 40-year old (1); had no COPD prescription claim within a year after the first date of COPD diagnosis (2); had a disease history of asthma, malignant tumor, chronic kidney disease, and renal dialysis (3); had a diagnosis of type 1 diabetes or had no antidiabetic drug prescription claim or had metformin monotherapy and had insulin therapy before the first COPD diagnosis (4). The later exclusion was made to increase the homogeneity of the study cohort.

Case and Control Patient Selection

There is no general agreement on definition of AECOPD. Mostly, the definition of AECOPD was based on increasing symptoms and/or increased health care utilization. Thus, in this claim-based study, we used the following approach to identify the patients with AECOPD modified according to previous study (12, 13) if they 1) had a hospital admission or an emergency visit due to COPD and also requiring oral or injection corticosteroid (CS), or 2) added on oral or injection CS therapy in a new visit. To increase the comparability, matched controls were selected based on incidence density sampling which involved in matching each AECOPD case to a sample of those potential controls who were at risk at the time of case occurrence, resulting obtaining unbiased estimates of relative risk. Before matching, we additionally excluded the patients had monotherapy and then included subjects with double or triple combination therapy of OADs which regimen were validated by clinical trials and meta-analyses (14). Finally, each case was matched to 4 randomly selected controls according to the propensity score estimation by sex, age, the year of COPD diagnosis, the initial year of DM status, previous and coexisting disease conditions, Charlson comorbidity index (CCI), level complexity of COPD and the COPD medication use three month prior to the date of AECOPD. The initial year of DM status was defined based on the first claim year of the patients initially received 2nd line OADs continuously for at least three month. Since control patients did not occurred AECOPD, they were assigned a date for pseudo-AECOPD which corresponded to the index date of their matched cases.

Exposure to oral antihyperglycemic drugs (OADs)

We examined all OAD prescription records within three month before the index date of AECOPD of cases and pseudo-AECOPD date of controls, respectively. We investigated the type of OADs, including metformin (MET), sulfonyurea (SU), α-glucosidase inhibitors (AGI), thiazolidinediones (TZD) and dipeptidyl peptidase-4 inhibitor (DPP-4i). The aim of our study is to answer what is the best drug as add-on OADs to monotherapy for progressive T2DM in the context of considering effect on COPD outcomes. Then, we further categorized T2DM-COPD patients by using a double or triple combination of OADs.

Potential Confounding Variables

Previous or coexisting medical conditions were recorded if patients were diagnosed with chronic artery disease (CAD), hypertension (HTN), congestive heart failure (CHF), pneumonia, chronic liver disease (CLD), dementia/Parkinson and osteoporosis. Additionally, CCI which is represented the severity of comorbid conditions of patients was also considered a major risk and the CCI in this current study has been modified since all patients had diagnosed with both diabetes and COPD but did not have a history of malignant neoplasm. To adjust the severity of COPD itself, we categorized patients into low, moderate and high complexity according to the previous study (15) and further grouped the patients into low and moderate/high complexity group due to a small sample size of high complexity. Besides, we also considered the history of COPD medication use of AECOPD cases and non-AECOPD controls, respectively (15), including short acting beta agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs) and inhaled corticosteroids (ICS).

Statistical Analysis

The baseline differences between case and control patients were measured by standardized mean difference (SMD). Conditional logistic regression was used to estimate the odd ratios (OR), adjusted odds ratios (aOR), and 95% confidence intervals (CI) for the association of AECOPD risk and OADs use. The statistical analyses were performed using SAS/STAT, Version 9.4, (SAS Institute, Cary, NC, USA) and STATA 13 (Stata Corp, College Station, TX, USA). A P value < 0.05 and SMD > 0.1 was set as the level of statistical significance.

Results

Baseline Characteristics

Of new-onset COPD patients with advanced T2DM, 3,355 AECOPD cases and 13,420 non-AECOPD matched controls were selected by using an incidence density sampling method (Fig. 1). The baseline characteristics of the case and control patients are shown in Table 1. In COPD-T2DM cohort, two-third of AECOPD cases were male and the mean age was 72 years old (SD: 10.5). The 3 most common previous or coexisting disease conditions were hypertension (65.0%), CAD (20.8%) and pneumonia (12.9%) and 42.1% had a modified CCI between 1 and 2. In terms of the level of COPD complexity at initial diagnosis, around half and half patients were classified into a low-level and moderate/high-level, respectively. For COPD medication three months before the index date of AECOPD, majority of patients had received ICS or steroid and only 3% of the patients received either SABA, SAMA, LABA or LAMA. Since we used the propensity score approach to adjust the baseline characteristics of AECOPD cases and non-AECOPD controls, the groups were not different in the variables listed in Table 1.

Table 1
Baseline difference between AECOPD case patients and non-AECOPD control T2DM patients

Variables	Non-AECOPD controls		AECOPD cases		SMD
	n	(%)	n	(%)	
Sample size	13,420		3,355		
Male, yes	8,956	(66.7)	2,239	(66.7)	0.000
Age, [mean, SD]	[72.2, 10.4]		[72.1, 10.5]		
40–49	350	(2.6)	92	(2.7)	0.008
50–59	1,437	(10.7)	357	(10.6)	0.002
60–69	2,902	(21.6)	759	(22.6)	0.024
70–79	5,318	(39.6)	1,266	(37.7)	0.039
>=80	3,413	(25.4)	881	(26.3)	0.019
Year of the first DM claim					
2000 ~ 2002	8,059	(60.1)	2,035	(60.7)	0.012
2003 ~ 2006	3,114	(23.2)	769	(22.9)	0.007
2007 ~ 2010	1,681	(12.5)	418	(12.5)	0.002
2011 ~ 2014	566	(4.2)	133	(4.0)	0.013
Year of COPD diagnosis					
2003 ~ 2006	4,411	(32.9)	1,121	(33.4)	0.012
2007 ~ 2010	4,906	(36.6)	1,228	(36.6)	0.001
2011 ~ 2014	4,103	(30.6)	1,006	(30.0)	0.013
Previous or coexisting disease conditions, yes					
HTN	8,671	(64.6)	2,182	(65.0)	0.009
CAD	2,867	(21.4)	698	(20.8)	0.014
CHF	1,109	(8.3)	282	(8.4)	0.005
AF	581	(4.3)	154	(4.6)	0.013
Pneumonia	1,761	(13.1)	433	(12.9)	0.006
CLD	849	(6.3)	216	(6.4)	0.005
Dementia/Parkinson	1,425	(10.6)	364	(10.8)	0.007
Osteoporosis	447	(3.3)	114	(3.4)	0.004
CCI, [mean, SD]	[1.5, 1.5]		[1.6, 1.5]		
0	4,294	(32.0)	1,078	(32.1)	0.003

*SMD = difference in means or proportions divided by standard error; imbalance defined as absolute value greater than 0.1

Abbreviation: AECOPD, acute exacerbations chronic obstructive pulmonary disease; CAD, coronary artery disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; SMD, standardized mean difference; SABA, short-acting beta agonists; SAMA, short-acting muscarinic antagonist; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonist; ICS, Inhaled corticosteroids

Variables	Non-AECOPD controls		AECOPD cases		SMD
	n	(%)	n	(%)	
1 ~ 2	5,893	(43.9)	1,412	(42.1)	0.037
>=3	3,233	(24.1)	865	(25.8)	0.039
Level of COPD complexity at initial diagnosis					
Low	6,689	(49.8)	1,722	(51.3)	0.030
Moderate/high	6,731	(50.2)	1,633	(48.7)	0.030
COPD medication use 3 month prior to index date, yes					
SABA or SAMA	169	(1.3)	39	(1.2)	0.009
LABA or LAMA	417	(3.1)	60	(1.8)	0.085
ICS or Steroid	12,682	(94.5)	3,210	(95.7)	0.054
Others	152	(1.1)	46	(1.4)	0.021
*SMD = difference in means or proportions divided by standard error; imbalance defined as absolute value greater than 0.1					
Abbreviation: AECOPD, acute exacerbations chronic obstructive pulmonary disease; CAD, coronary artery disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; SMD, standardized mean difference; SABA, short-acting beta agonists; SAMA, short-acting muscarinic antagonist; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonist; ICS, Inhaled corticosteroids					

Table 2
The association between double oral OADs use and risk of AECOPD in T2DM patients with COPD (n = 12,916)

Level of COPD complexity	Combination of OADs	Non-AECOPD controls		AECOPD cases		Odds Ratio					
Overall		n	(%)	n	(%)	Crude	(95% CI)	*P*	Adjusted*	(95% CI)	*P*
	SU + AGI	526	(5.1)	111	(4.4)	0.87	(0.72–1.05)	0.15	0.87	(0.72–1.05)	0.14
	SU + DPP-4i	394	(3.8)	89	(3.5)	0.92	(0.74–1.14)	0.43	0.93	(0.75–1.15)	0.50
	SU + TZD	247	(2.4)	41	(1.6)	0.71	(0.52–0.97)	0.03	0.69	(0.51–0.94)	0.02
	MET + AGI	348	(3.4)	79	(3.1)	0.92	(0.74–1.16)	0.48	0.92	(0.73–1.15)	0.45
	MET + DPP-4i	816	(7.9)	190	(7.5)	0.94	(0.81–1.09)	0.43	0.95	(0.82–1.11)	0.51
	MET + TZD	238	(2.3)	60	(2.4)	1.00	(0.78–1.30)	0.98	1.01	(0.78–1.30)	0.96
	MET + SU	7,816	(75.3)	1,961	(77.5)	1.00	(Ref.)		1.00	(Ref.)	
Moderate/high											
	SU + AGI	290	(5.5)	49	(4.0)	0.75	(0.56-1.00)	0.05	0.77	(0.58–1.03)	0.08
	SU + DPP-4i	232	(4.4)	40	(3.3)	0.76	(0.55–1.04)	0.09	0.78	(0.57–1.07)	0.13
	SU + TZD	95	(1.8)	23	(1.9)	1.01	(0.67–1.53)	0.97	0.99	(0.66–1.51)	0.98
	MET + AGI	172	(3.3)	47	(3.8)	1.11	(0.83–1.49)	0.48	1.16	(0.86–1.56)	0.32
	MET + DPP-4i	375	(7.1)	78	(6.4)	0.89	(0.71–1.12)	0.33	0.89	(0.70–1.13)	0.34
	MET + TZD	92	(1.7)	26	(2.1)	1.14	(0.77–1.68)	0.51	1.15	(0.78–1.70)	0.48
	MET + SU	4,004	(76.1)	959	(78.5)	1.00	(Ref.)		1.00	(Ref.)	
Low											

*Adjusted for age, sex, DM status, previous and coexisting disease conditions, modified CCI, complexity of COPD and COPD medications listed in Table 1

Abbreviation: AECOPD, acute exacerbations chronic obstructive pulmonary disease; AGI: α-glucosidase inhibitors; CCI, Charlson comorbidity index; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; DM, diabetes; MET, metformin; OADs, oral antihyperglycemic drugs; OR, odd ratio; Ref., reference group; SU, sulfonylurea; TZD, thiazolidinediones

Level of COPD complexity	Combination of OADs	Non-AECOPD controls		AECOPD cases		Odds Ratio					
	SU + AGI	236	(4.6)	62	(4.7)	1.00	(0.77–1.29)	1.00	0.96	(0.74–1.24)	0.76
	SU + DPP-4i	162	(3.2)	49	(3.7)	1.12	(0.84–1.49)	0.45	1.11	(0.83–1.47)	0.49
	SU + TZD	152	(3.0)	18	(1.4)	0.51	(0.32–0.81)	< 0.01	0.50	(0.32–0.80)	< 0.01
	MET + AGI	176	(3.4)	32	(2.4)	0.74	(0.52–1.05)	0.09	0.74	(0.52–1.05)	0.10
	MET + DPP-4i	441	(8.6)	112	(8.6)	0.97	(0.80–1.18)	0.78	0.99	(0.81–1.21)	0.90
	MET + TZD	146	(2.8)	34	(2.6)	0.91	(0.64–1.28)	0.58	0.93	(0.66–1.32)	0.70
	MET + SU	3,812	(74.4)	1,002	(76.5)	1.00	(Ref.)		1.00	(Ref.)	

*Adjusted for age, sex, DM status, previous and coexisting disease conditions, modified CCI, complexity of COPD and COPD medications listed in Table 1

Abbreviation: AECOPD, acute exacerbations chronic obstructive pulmonary disease; AGI: α-glucosidase inhibitors; CCI, Charlson comorbidity index; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; DM, diabetes; MET, metformin; OADs, oral antihyperglycemic drugs; OR, odd ratio; Ref., reference group; SU, sulfonylurea; TZD, thiazolidinediones

Table 3
The association between triple oral OADs use and risk of AECOPD in T2DM patients with COPD (n = 3,859)

Level of COPD complexity	Combination of OADs	Non-AECOPD controls		AECOPD cases		Odds Ratio					
Overall		n	(%)	n	(%)	Crude	(95% CI)	*P*	Adjusted*	(95% CI)	*P*
	MET + SU + TZD	1,074	(35.4)	243	(29.5)	0.81	(0.68–0.95)	0.01	0.81	(0.68–0.96)	0.01
	MET + SU + DPP-4i	933	(30.7)	276	(33.5)	1.00	(0.85–1.17)	0.98	1.02	(0.87–1.21)	0.78
	MET + SU + AGI	1,028	(33.9)	305	(37.0)	1.00	(Ref.)		1.00	(Ref.)	
Moderate/high											
	MET + SU + TZD	479	(32.6)	104	(25.3)	0.76	(0.60–0.97)	0.03	0.75	(0.58–0.96)	0.02
	MET + SU + DPP-4i	440	(29.9)	138	(33.6)	1.02	(0.81–1.28)	0.87	1.06	(0.84–1.34)	0.63
	MET + SU + AGI	552	(37.5)	169	(41.1)	1.00	(Ref.)		1.00	(Ref.)	
Low											
	MET + SU + TZD	595	(38.0)	139	(33.7)	0.85	(0.67–1.08)	0.18	0.88	(0.79–1.28)	0.28
	MET + SU + DPP-4i	493	(31.5)	138	(33.4)	0.98	(0.78–1.25)	0.89	1.00	(0.69–1.11)	0.97
	MET + SU + AGI	476	(30.4)	136	(32.9)	1.00	(Ref.)		1.00	(Ref.)	

*Adjusted for age, sex, DM status, previous and coexisting disease conditions, modified CCI, complexity of COPD and COPD medications listed in Table 1

Abbreviation: AECOPD, acute exacerbations chronic obstructive pulmonary disease; AGI: α-glucosidase inhibitors; CCI, Charlson comorbidity index; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; DM, diabetes; MET, metformin; OADs, oral antihyperglycemic drugs; OR, odd ratio; Ref., reference group; SU, sulfonylurea; TZD, thiazolidinediones

OADs Use and the Risk of AECOPD

Among COPD-T2DM with double combination of oral OADs (n = 12,916), compared to patients who had received both MET and SU, AECOPD case patients were less likely to be exposed to a combination of SU and TZD within three months before the date of AECOPD compared to matched controls, with an adjusted odds ratio (OR) of 0.69 (95% confidence interval [CI]: 0.51–0.94, *P* = 0.02). When further divided the patients into low and moderate/high level of COPD complexity at the initial COPD diagnosis, we still found that the OADs use of a combination of SU and TZD was associated with a reduced risk of AECOPD of the patients with lower COPD complexity (adjusted OR = 0.20, 95% CI of 0.32–0.80).

For the patients with a combination of triple OADs (n = 3,859), compared to the patients had MET, SU and AI, we found that AECOPD patients were less likely to have MET, SU and TZD, with an adjusted OR of 0.81 (95% CI: 0.68–0.96, *P* = 0.01). Similar results were found in different level of COPD complexity; however, the finding was significant of the patients with a moderate/high level.

Discussion

Our study presented that COPD-T2DM patients use OADs only for sugar control, a double combination of SU and TZDs and a triple combination of MET, SU, and TZDs were associated with an decreased risk of AECOPD. The results were fairly consistent in patients with moderate or high complexity of COPD.

We found add-on TZDs could reduce risk of AECOPD in the double as well as the triple combination of OADs in COPD-T2DM cohorts. The result was in parallel with previous study which demonstrated TZDs are associated with a reduced risk of AECOPD after adjusting severity of DM per se with possible impact on AECOPD (11). In our study, we further considered the effect of COPD severity itself on AECOPD by using COPD complexity classification. We also took into account for the impact of medications use for COPD on AECOPD and founded the similar effect of TZD on decreasing frequency of AECOPD after adjusting these confounders.

COPD-T2DM are considered syndromes that can share risk factors (such as smoking) (16), genes (such as β2-adrenergic receptor gene, ADRB2) (17), proteins (such as Nod-like receptor containing a pyrin domain 3, NLRP3) (18, 19) and pathways (such as systemic inflammation and oxidative stress) (20–22). Although the underlying mechanistic links between these shared components are complex and not fully clarified, targeting systemic inflammation, an important common pathway to treat COPD and T2DM concurrently would be a rationale therapeutic approach (23).

Some OADs might have anti-inflammatory activity due to their pleiotropic effects in addition to reduce blood glucose (24, 25). TZDs, a class of OADs, have been studied with anti-inflammatory activity and introduced in the treatment of T2DM, mostly use in combination with metformin since the late 1990s (26). The cellular mechanisms of anti-inflammatory effects of TZD are through activating the nuclear transcription factor of peroxisome proliferator-activated receptor gamma (PPAR-γ) and at least in part, of glucocorticoid nuclear translocation (27, 28). Frequent AECOPD patients have more inflamed existing airway and systemic inflammation during exacerbations and even in the recovery period due to poor response of inflammation resolution from each episode (29–33). Therefore, TZDs may exert anti-inflammatory effect and downregulating the pro-inflammatory status for preventing from AECOPD. Besides, major comorbidities of COPD-T2DM such as cardiovascular diseases (CVDs) may induce or worsen AECOPD (34). Activating PPAR-γ by TZDs also exert important function in regulating vascular inflammation and inhibiting vascular smooth muscle proliferation with effect against atherosclerosis (35–37). The protective role of TZDs on cardiovascular outcomes, particular in cumulative evidence from pioglitazone, may contribute to reduce CVDs-related AECOPD (38, 39).

There were two studies reported that metformin use had lower health care utilization and mitigated the adverse prognostic effect in COPD-T2DM patients (9, 10). However, no significant benefit effect of combination therapy with metformin use in our research. The major causes of the different results were attributed to the enrolled and analyzed patients. The favorable effect of metformin on reducing COPD-specific health care utilization only presented in lower complexity of COPD patients but not moderate to high complexities and the study did not showed the effect from mono- or combinational therapy with metformin. In our study, we clearly defined the combinational therapy with metformin and the data demonstrated no effect on reducing the risk of AECOPD in all COPD complexities. Furthermore, the other study presented COPD-T2DM patients get survival benefits of metformin but the effect may be confounded with the severity of COPD and the medications regimen for COPD. So the strength of our study is providing treatment suggestion that TZDs are better choice for combinational therapy whenever deterioration of glycemic control from initial control in COPD-T2DM patients. This recommendation was based on more strictly defined patient population, controlled of important clinical confounders and considered the impact of OADs on AECOPD. However, there were some limitations in the study. First, the data on drug exposure were acquired from prescription records, which might not reflect actual use. Second, the NHIRD lacks patient's other important information such as tobacco use, some vaccination administrated, medication compliance, which might contribute to AECOPD occurrence. Third, the administrative claims database from which the NHIRD sample was derived did not consider certain clinical characteristics, such as the severity of COPD. Although we applied the cross-sectional analysis developed by Mapel et al. (15) to adjust the potential effect of level of COPD severity on AECOPD risk, there was still some uncontrolled effects which might affect the finding in the study. Finally, this study included a cohort of Taiwanese patients, therefore, may not be generalizable to other populations due to variations of genetic and treatment guidelines for both diseases in other areas. Future prospective studies on the effects of TZDs are warranted to confirm our findings.

Conclusion

These results showed combination therapy with TZDs are associated with reducing risk of AECOPD regardless of double or triple combinational regimens in COPD-T2DM patients, particular in moderate to severe complexity COPD populations. It is believed the T2DM patients with co-existing COPD increase in the future, TZDs play different protection role for both diseases and suggested use in these patients but prospective randomized controlled trial are need to proof the results.

Abbreviations

COPD, Chronic obstructive pulmonary disease; OADs, oral antihyperglycemic drugs; TZDs, thiazolidinediones; CCI, Charlson comorbidity index; DPP-4i, dipeptidyl peptidase-4 inhibitor; T2DM, type 2 diabetes mellitus; AECOPD, acute exacerbation chronic obstructive pulmonary disease; MET, metformin; SU, sulfonylurea; OR, odds ratio; aOR, adjusted odds ratios; CI, confidence interval; AGI, α-glucosidase inhibitors; CAD, chronic artery disease; HTN, hypertension; CHF, congestive heart failure; CLD, chronic liver disease; SABA, short-acting beta-agonists; SAMA, short-acting muscarinic antagonists; LABAs, long-acting beta-agonists; LAMAs, long-acting muscarinic antagonists; ICS, inhaled corticosteroids; NLRP3, Nod-like receptor containing a pyrin domain; PPAR-γ, peroxisome proliferator-activated receptor gamma.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Taipei Medical University-Joint Institutional Review Board (TMU-JIRB N201808075). All analyzes were performed in accordance with the relevant guidelines and regulations. Since all data were anonymously used, the TMU-IRB ethics committee approved a waiver of the requirement for informed consent. Individual patients consent was not obtained since all data used in this study were acquired retrospectively from the National Health Insurance Research Database of Taiwan.

Consent for publication

Not Applicable.

Availability of data and materials

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest or competing financial interests

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Author contributions

K.Y.C. designed the research and wrote the manuscript. S.M.W. and C.H.T. supervised the analyses of statistics and patient information and reviewed the manuscript. Y.H.L and H.Y.L performed the analysis of statistics and patient information. K.Y.L. and L.N.C. supervised and reviewed the entire project and the manuscript. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Figures

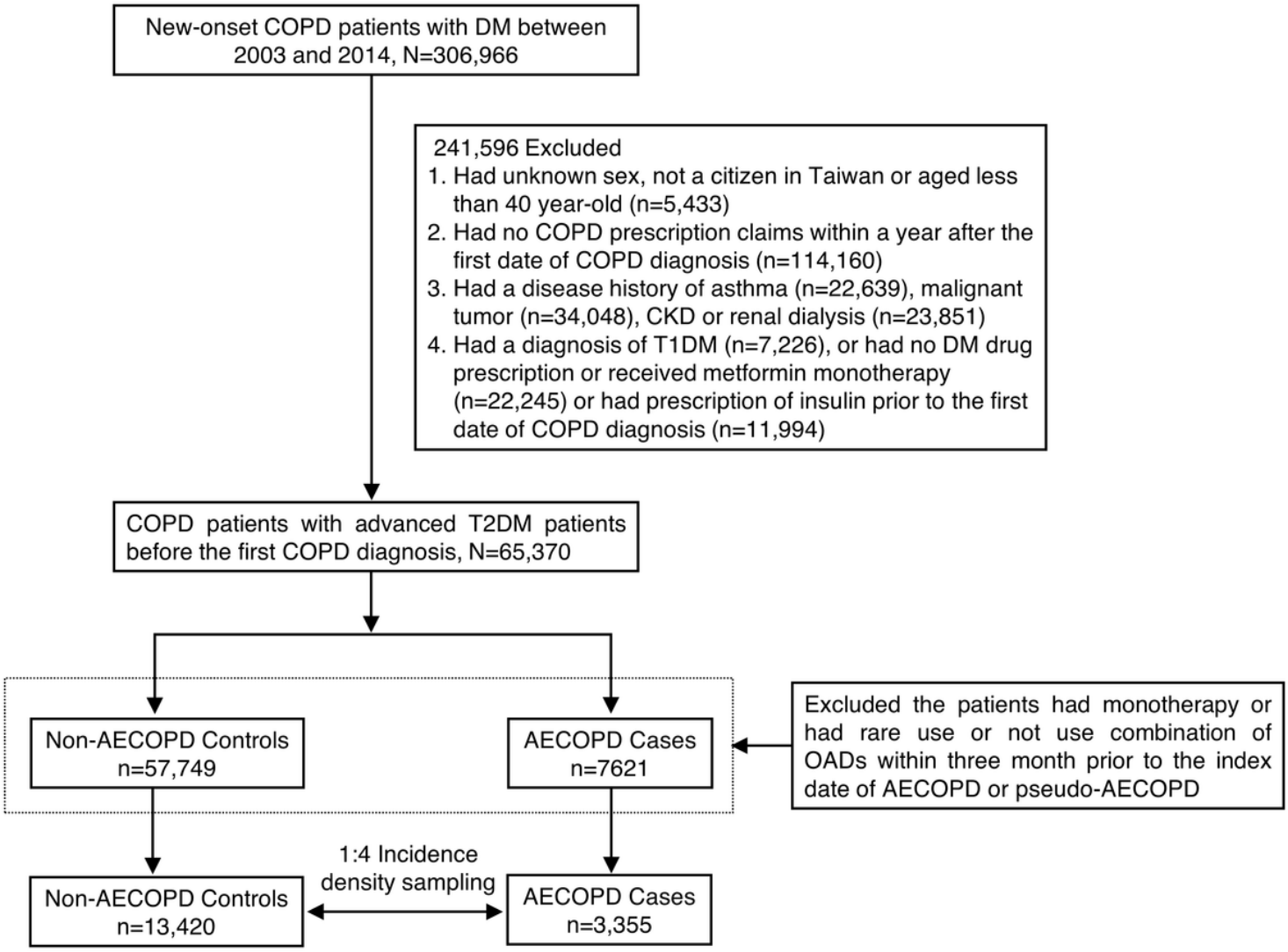

Figure 1

Figure 1

Patient selection process Abbreviation: AECOPD, acute exacerbations chronic obstructive pulmonary disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; OADs, oral antihyperglycemic drugs; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus