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ORIGINAL ARTICLE

Improving outcomes in chronic obstructive pulmonary disease by taking beta-blockers after acute myocardial infarction: a nationwide observational study

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Abstract

β-Blockers are a standard therapy for acute myocardial infarction (AMI) due to their better short-term and long-term outcomes. However, β-blockers are often under-prescribed in chronic obstructive pulmonary disease (COPD) patients with AMI, since they are thought be related to bronchospasm. The aim of this study was to investigate the association between the usage of β-blockers and the risk of mortality in COPD patients after first AMI via a nationwide, population-based cohort study. In this retrospective study, we identified 186,326 patients with AMI diagnosed between January 2000 and December 2012, 23,116 of whom had COPD, from the National Health Insurance Research Database. A total of 7609 patients (32.92%) were prescribed β-blockers, while 15,507 were not. The β-blocker patients were stratified into selective and non-selective β-blocker groups. Multivariate Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) with 95% confidence intervals (95% CI). Selective β-blocker use showed a reduced risk of mortality, as compared with patients without β-blockers (HR 0.93; 95% CI 0.89–0.98; $p<0.01$) while non-selective β-blocker groups did not increase the risk of mortality compared to the patients without β-blockers (HR 0.98; 95% CI 0.94–1.02; $p=0.38$). In addition, the use of β-blockers was found to be associated with a reduced risk of mortality in most stratified analyses which was seen particularly in males, patients aged 65 years and above, and in individuals with an array of comorbidities. These findings suggest that β-blockers improve overall survival among COPD patients after first AMI.

Keywords β-blockers · Chronic obstructive pulmonary disease · Acute myocardial infarction · Mortality

Abbreviations

AMI	Acute myocardial infarction
COPD	Chronic obstructive pulmonary disease
PCI	Percutaneous coronary intervention
ACEI	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blockers
SABA	Short-acting β-agonist
SAMA	Short-acting muscarinic antagonist
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database

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Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the US [1, 2]. COPD is a state of systemic inflammation characterized by high levels of inflammatory markers, which may lead to atherosclerosis, plaque rupture, and thrombosis [3]. Hence, in light of this, patients with COPD are at a significantly higher risk of coronary artery disease, angina, myocardial infarction (MI), and stroke [4]. Moreover, COPD patients suffer from poor outcomes (both short term and long term) after MI [5]. Since cardiovascular disease is a common cause of death in COPD patients, improving patient survival after MI is a key target for enhancing COPD survival outcomes [6]. β-blockers, which are one therapy option for MI, are capable of reducing hospital stay, presentation of malignant arrhythmias, mortality, and re-infarction of patients with acute MI (AMI) [7, 8] Despite this, however, β-blockers are thought to represent a relative pulmonary contraindication for COPD patients, since they may precipitate bronchospasm and cause acute deterioration of pulmonary function [8, 9]. Therefore, clinicians have predominantly been discouraged from prescribing β-blockers to AMI patients with COPD [10]. Some small-scale studies, though, have indicated more recently that β-blockers, especially cardio-selective β-blockers, do not increase the rate of COPD exacerbations, and may actually be tolerated in COPD patients [9, 11]. Other studies suggest that β-blocker use can improve short-term survival following AMI in COPD patients [10, 12]. However, the completion of large-scale studies is still lacking, and it is still questionable whether β-blockers can improve the overall long-term survival rate of COPD patients with AMI. With this in mind, the current study was designed to investigate the impact of β-blockers, both selective and non-selective, on overall survival in COPD patients after first AMI, using a nationwide database in Taiwan. We hypothesized that the use of β-blockers can improve the overall survival among COPD patients with AMI, regardless of selective or non-selective β-blockers.

Materials and methods

Data sources

This study involved searches conducted in the Taiwanese National Health Insurance (NHI) program. The NHI program has sponsored the health care system of Taiwanese residents since 1st March, 1995, and has enrolled more than 99% of the population in Taiwan to date. All medical records of patients during admission, including age, sex, diagnosis, medication, interventional procedures, and relevant survival data, are included in this National Health Insurance Research Database (NHIRD). This study was approved by the Human Research Committee of Kaohsiung Veterans General Hospital (VGHKS15-EM10-02).

Study population

To select the subject cohort for this study, we identified 186,326 patients discharged with a new diagnosis of AMI [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) from 410 to 410.92] from 23,000,000 patient records spanning from January 2000 to December 2012. To avoid double counting the patients, patients with a previous admission for AMI were excluded. This study also excluded those individuals who were younger than 18 years old and those patients whose sex was undetermined. Additionally, 23,116 patients with COPD (ICD-9-CM code: 491, 492 or 496) were identified from the group of 186,326. Those who had taken β-blockers anytime during admission were defined as β-blockers users, and were further stratified into selective and non-selective β-blockers groups, respectively. Data from 7609 patients with β-blocker use (2859 patients in the selective β-blockers group and 4750 patients in the non-selective β-blockers group), and 15,507 patients without β-blocker use, were included in the final analysis (Fig. 1).

This study considered a number of variables, such as sex, age, comorbidities (diabetes mellitus, heart failure, hypertension, peripheral vascular disease, end-stage renal disease, previous stroke, and atrial fibrillation), percutaneous coronary intervention (PCI), and related medication use (antiplatelet, ACEI/ or ARB, calcium channel blocker, xanthine, corticosteroid, SABA, and SAMA) in its analysis.

Definition of outcome

Mortality was defined as the duration of the date of hospital admission and the end date of NHI coverage. In Taiwan, NHI coverage is discontinued at the time of death, and can be traced only with a maximum error of one month, since the NHI premium is paid monthly. Using this information, we could thus define the endpoint date, since NHI coverage provides a valid proxy measure of mortality [13, 14].

Statistical analyses

The two-sample t test was used to compare continuous variables, while the Chi-squared test was used to test the differences between categorical variables. Multivariate

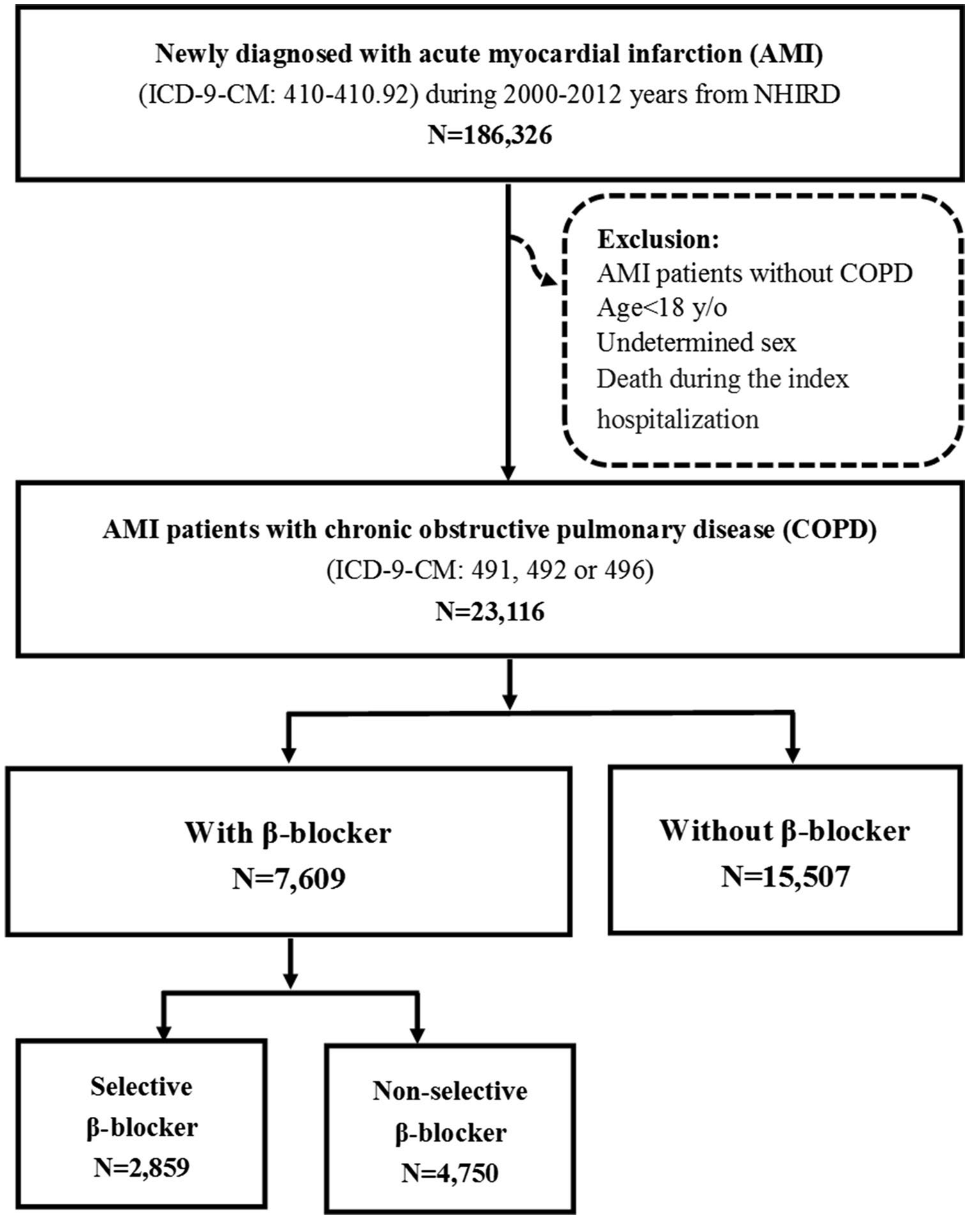

Fig. 1 Study flowchart. *NHIRD* : National Health Insurance Research Database, *AMI* acute myocardial infarction, *COPD* chronic obstructive pulmonary disease, *STEMI* ST elevation myocardial infarction, *NSTEMI* non-ST elevation myocardial infarction, *PCI* percutaneous coronary intervention, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *SABA* short-acting β-agonist, *SAMA* short-acting muscarinic antagonist, *SD* standard deviation

Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) with 95% confidence intervals (95% CI); adjusted survival curves were generated from the adjusted analysis. On stratified multivariable analyses, the association between β-blockers usage and the risk of mortality was reexamined in different subgroups. Covariates, including sex, age, comorbidities (diabetes mellitus, heart failure, hypertension, peripheral vascular disease, end-stage renal disease, previous stroke, and atrial fibrillation), percutaneous coronary intervention (PCI), and related medication use (antiplatelet, ACEI/ or ARB, calcium channel blocker, xanthine, corticosteroid, SABA, and SAMA) were used for multivariable analyses.

The statistical analyses were carried out using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA). A *p* value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

We identified a total of 23,116 COPD patients with first attack of AMI. The basic characteristics of these individuals are shown in Table 1. Among this population, 7609 (32.9%) were prescribed β-blocker therapy, while 15,507

Table 1 Characteristics of all patients with and without β-blockers (N = 23,116)

Characteristics	With β-blocker (n = 7609)	Selective β-blocker (n = 2859)		Non-selective β-blocker (n = 4750)			Without β-blocker (n = 15,507)		
	n (%)	n (%)		n (%)		p value[a]	n (%)		p value[b]
Sex									
Male	5621 (73.87)	2142	(74.92)	3479	(73.24)		11,478	(74.02)	0.8132
Female	1988 (26.13)	717	(25.08)	1271	(26.76)	0.1064	4029	(25.98)	
Age, mean (SD)	75.7 (10.04)	76.01	(10.06)	75.45	(10.02)	0.0181	77.63	(9.61)	<0.0001
Comorbidities									
Hypertension	5664 (74.44)	2239	(78.31)	3425	(72.11)	<0.0001	10,720	(69.13)	<0.0001
Diabetes mellitus	3259 (42.83)	1260	(44.07)	1999	(42.08)	0.0898	5850	(37.72)	<0.0001
Peripheral vascular disease	425 (5.59)	156	(5.46)	269	(5.66)	0.7037	835	(5.38)	0.5274
Heart failure	3241 (42.59)	1233	(43.13)	2008	(42.27)	0.4660	6507	(41.96)	0.3601
Heart failure (strict)[c]	1191 (15.65)	436	(15.25)	755	(18.89)	0.4535	2508	(16.17)	0.3101
STEMI	2465 (32.40)	782	(27.35)	1683	(35.43)	<0.0001	4009	(25.85)	<0.0001
NSTEMI	5159 (67.80)	2084	(72.89)	3075	(64.74)	<0.0001	11,519	(74.28)	<0.0001
End stage renal disease	324 (4.26)	125	(4.37)	199	(4.19)	0.7023	492	(3.17)	<0.0001
Previous stroke	2826 (37.14)	1076	(37.64)	1750	(36.84)	0.4879	5799	(37.40)	0.7055
Previous stroke (strict)[d]	329 (4.32)	131	(4.58)	198	(4.17)	0.3903	631	(4.07)	0.3617
Atrial fibrillation	1423 (18.70)	552	(19.31)	871	(18.34)	0.2930	3053	(19.69)	0.0745
PCI	3343 (43.93)	1303	(45.58)	2040	(42.95)	0.0253	4028	(25.98)	<0.0001
Medications									
Any antiplatelet	7047 (92.61)	2690	(94.09)	4357	(91.73)	0.0001	11,219	(72.35)	<0.0001
ACEI or ARB	5649 (74.24)	2142	(74.92)	3507	(73.83)	0.2925	6778	(43.71)	<0.0001
Statin	2484 (32.65)	1152	(40.29)	1332	(28.04)	<0.0001	2334	(15.05)	<0.0001
Calcium channel blocker	3686 (48.44)	1401	(49.00)	2285	(48.11)	0.4478	5901	(38.05)	<0.0001

Table 1 (continued)

Characteristics	With β-blocker (n = 7609)	Selective β-blocker (n = 2859)		Non-selective β-blocker (n = 4750)			Without β-blocker (n = 15,507)		
	n (%)	n (%)		n (%)		p value[a]	n (%)		p value[b]
Heparin or low molecular weight heparin	5843 (76.79)	2244	(78.49)	3599	(75.77)	0.0065	8217	(52.99)	<0.0001
Spironolactone	1440 (18.92)	599	(20.95)	841	(17.71)	0.0005	1932	(12.46)	<0.0001
Nitrate	6766 (88.92)	2543	(88.95)	4223	(88.91)	0.9550	10,671	(68.81)	<0.0001
Nicorandil	794 (10.44)	294	(10.28)	500	(10.53)	0.7370	1137	(7.33)	<0.0001
Xanthines	2306 (30.31)	863	(30.19)	1443	(30.38)	0.8588	6173	(39.81)	<0.0001
Corticosteroid	2355 (30.95)	1064	(37.22)	1291	(27.18)	<0.0001	4992	(32.19)	0.0567
SABA	3826 (50.28)	1476	(51.63)	2350	(49.47)	0.0689	8499	(54.81)	<0.0001
SAMA	2855 (37.52)	1011	(35.36)	1844	(38.82)	0.0025	5992	(38.64)	0.0999

[a]Comparison of the selective and the non-selective β-blockers groups among patients with β-blockers

[b]Comparison of patients with and without β-blockers

[c]Cases that had ever been admitted for heart failure before MI

[d]Cases that had ever been admitted for stroke or transient ischemic attack before MI

(67.1%) were not. The average (± standard deviation) age of patients with β-blockers was 75.70 (± 10.04) years, and that of patients without β-blockers was 77.63 (± 9.61) years. Patients with β-blockers had a higher prevalence of hypertension, diabetes mellitus, and end-stage renal disease than did patients without β-blockers. Moreover, a higher proportion of patients with β-blockers received PCI for AMI (43.93% vs. 25.98%, $p<0.0001$). In terms of medication, those who took β-blockers also received more antiplatelet, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARB), statin, calcium channel blockers, spironolactone, nitrate, and nicorandil. In contrast, those who did not take β-blockers were taking more xanthines and short-acting β antagonists (SABAs) (Table 1).

Among β-blocker users, 2,859 (37.57%) were given selective β-blockers and 4,750 (62.43%) were prescribed non-selective β-blockers (Table 1). Patients with selective β-blockers had a higher prevalence of hypertension and PCI than did patients with non-selective β-blockers. Regarding other medications, those took selective β-blockers had also received more antiplatelet, statin and spironolactone medications. In contrast, those who were taking non-selective β-blockers were taking more short-acting muscarinic antagonist (SAMA).

Multivariable analysis

After adjustment for all covariates, patients with β-blockers, both selective and non-selective, had significantly better short-term (1-, 3-, 6-, 9-, and 12-month) and long-term (2-, 4-, 6-, and 8-year) survival rates (selective β-blockers: 76.5%, 67.1%, 60.5%, 56.2%, 52.7%, 42.9%, 31.1%, 23.3% and 17.8%; non-selective β-blockers: 75.5%, 65.8%, 59.0%, 54.7%, 51.2%, 41.4%, 29.7%, 22.0% and 16.7%, respectively) as compared with patients without β-blockers, who had rates of 75.2%, 65.4%, 58.5%, 54.2%, 50.6%, 40.8%, 29.2%, 21.6% and 16.3%, respectively (Fig. 2). Patients with β-blockers showed a trend of reduced risk of mortality, as compared with patients without β-blockers (HR 0.97; 95% CI 0.93–1.00; $p=0.04$) (Table 2). Moreover, patients with selective β-blockers showed a reduced risk of mortality (HR 0.93; 95% CI 0.89–0.98; $p<0.01$) and non-selective β-blockers showed a non-inferior survival (HR 0.98; 95% CI 0.94–1.02; $p=0.38$) as compared with patients without β-blockers.

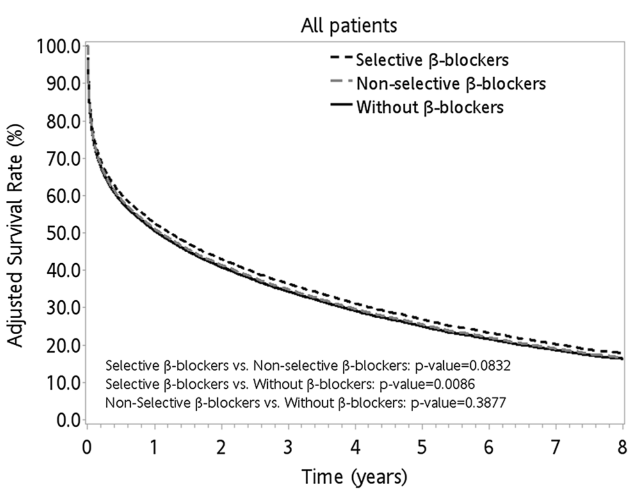

Fig. 2 Adjusted survival rate of all patients with and without β-blocker use ($N=23{,}116$)

Table 2 Cox proportional hazard regression of mortality in all patients ($N=23{,}116$)

Variables	Adjusted HR (95% CI)		*p* value
Without β-blockers	1.00	Ref.	
With β-blockers	0.97	(0.93, 1.00)	0.04
Non-selective β-blocker	0.98	(0.94, 1.02)	0.38
Selective β-blocker	0.93	(0.89, 0.98)	0.008

Sex, age, underlying diseases (hypertension, diabetes mellitus, peripheral vascular disease, heart failure, previous stroke, end-stage renal disease, and atrial fibrillation), AMI type (STEMI vs. non-STEMI), PCI and medication (antiplatelet, ACEI or ARB, statin, calcium channel blockers, xanthins, corticosteroids, SAMA and LAMA) are taken into adjustment for analysis

HR hazard ratio, *CI* confidence interval

Also, patients who underwent PCI (HR 0.58; 95% CI 0.56–0.61; $p<0.0001$), and those who took any antiplatelet (HR 0.76; 95% CI 0.73–0.79; $p<0.0001$) or ACEI/ARB (HR 0.79; 95% CI 0.76–0.81; $p<0.0001$) medications, demonstrated a lower risk of mortality (Supplement Table 1).

On the other hand, it is unsurprising that male gender (HR 1.15; 95% CI 1.11–1.19; $p<0.0001$); age (HR 1.04; 95% CI 1.04–1.04; $p<0.0001$); those with the presence of hypertension (HR 1.04; 95% CI 1.01–1.08; $p<0.0001$), diabetes mellitus (HR 1.23; 95% CI 1.19–1.26; $p<0.0001$), peripheral vascular disease (HR 1.34; 95% CI 1.26–1.42; $p<0.0001$), end-stage renal disease (HR 1.72; 95% CI 1.59–1.86; $p<0.0001$), and/or previous stroke (HR 1.17; 95% CI 1.13–1.21; $p<0.0001$); those who took corticosteroids (HR 1.06; 95% CI 1.02–1.10; $p=0.0001$), SABA (HR 1.26; 95% CI 1.21–1.32; $p<0.0001$) and/or short-acting muscarinic antagonists (SAMA) (HR 1.18; 95% CI 1.13–1.22; $p<0.0001$), were significantly associated with an increased risk of mortality (Supplement Table 1). All of these covariates were used for further multivariable analysis.

Variables	With β-blockers N	With β-blockers Death(%)	Without β-blockers N	Without β-blockers Death(%)	HR(95% CI)	p-value	p-value for interaction
Total	7609	68.20	15507	78.37	0.97(0.93- 1.00)	0.0444	
Subgroup							
Sex							
Male	5621	66.13	11478	77.90	0.94(0.90- 0.98)	0.0028	0.0115
Female	1988	74.04	4029	79.72	1.03(0.97- 1.10)	0.3133	
Hypertension							
No	1945	62.26	4787	75.20	0.97(0.91- 1.04)	0.3555	0.8827
Yes	5664	70.23	10720	79.79	0.96(0.93- 1.00)	0.0654	
Diabetes mellitus							
No	4350	65.33	9657	76.27	0.97(0.92- 1.01)	0.1425	0.8942
Yes	3259	72.02	5950	81.85	0.96(0.91- 1.01)	0.1414	
Peripheral vascular disease							
No	7184	67.23	14672	77.86	0.96(0.92- 0.99)	0.0188	0.0936
Yes	425	84.47	835	87.31	1.07(0.94- 1.22)	0.2867	
Heart failure							
No	4368	61.47	9000	73.72	0.96(0.91- 1.00)	0.0581	0.5456
Yes	3241	77.26	5518	84.80	0.98(0.93- 1.02)	0.3088	
STEMI							
No	5144	70.47	11498	80.18	0.95(0.91- 0.99)	0.0135	0.1428
Yes	2465	63.45	4009	73.19	1.00(0.94- 1.07)	0.9181	
NSTEMI							
No	2450	63.47	3988	73.14	1.00(0.94- 1.07)	0.9644	0.1643
Yes	5159	70.44	11519	80.18	0.95(0.91- 0.99)	0.015	
End stage renal disease							
No	7285	67.78	15015	78.06	0.97(0.93- 1.00)	0.0632	0.5589
Yes	324	77.47	492	88.01	0.92(0.79- 1.08)	0.3093	
Previous stroke							
No	4783	62.93	9708	74.69	0.96(0.91- 1.00)	0.0440	0.4779
Yes	2826	77.11	5799	84.53	0.98(0.93- 1.03)	0.4134	
Atrial fibrillation							
No	6186	66.60	12454	76.83	0.97(0.93- 1.01)	0.0905	0.7937
Yes	1423	75.12	3053	84.64	0.96(0.89- 1.03)	0.2315	
PCI							
No	4266	80.83	11479	84.78	0.98(0.94- 1.02)	0.2256	0.347
Yes	3343	52.08	4028	60.10	0.94(0.88- 1.00)	0.0572	

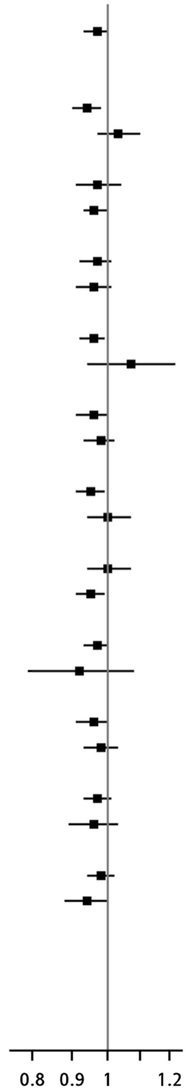

Fig. 3 Stratified multivariable analysis for risk of mortality between with and without β-blocker groups. *AMI* acute myocardial infarction, *COPD* chronic obstructive pulmonary disease, *PCI* percutaneous coronary intervention, *HR* hazard ratio, *CI* confidence interval

Stratified multivariable analysis

The use of β-blockers was associated with a lower risk of mortality (HR 0.97; 95% CI 0.93–1.00; $p < 0.05$) (Fig. 3). In addition, it was found to be associated with a reduced risk of mortality in most stratified analyses inCOPD patients after first AMI (Fig. 3), including in male patients (HR 0.94; 95% CI 0.90–0.98),in those with hypertension (HR 0.96; 95% CI 0.93–1.00), in those without peripheral vascular disease (HR 0.96; 95% CI 0.92–0.99), NSTEMI (HR 0.95; 95% CI 0.91–0.99), and in those without end-stage renal disease (HR 0.91; 95% CI 0.87–0.94) (Fig. 3).

Discussion

To our knowledge, this is currently the largest patient enrollment studied with respect to this condition. The results of this study indicated that β-blocker use, especially selective β-blocker, was associated with a reduced risk of mortality among COPD patients after first AMI. It was especially beneficial in male patients, as well as for those with hypertension, and NSTEMI. Furthermore, long-term survival of non-selective β-blocker group is not inferior to the group without β-blocker.

Beta-blockers are proved to decrease 30% of cardiovascular death and AMI among post-MI patients. COPD patients has higher post-discharge mortality after AMI. Traditionally, beta-blockers were thought to be related to bronchospasm, hence physicians would avoid using beta-blockers [6]. On the other hand, beta-blockers may not be absolute contraindication for COPD patients. More and more evidence pointed that beta-blockers reduce the rate of COPD exacerbation and mortality as well [12]. Bhatt et al. pointed that beta-blockers may lead to decrease in exacerbations of COPD, despite the severity of airflow obstruction [15]. Salpeter et al. demonstrated that cardio-selective beta-blockers revealed no significant adverse effects on pulmonary function test and respiratory symptoms for COPD patients [11]. Huang et al. indicated that COPD patients who were taking cardio-selective beta-blockers had lower risk of severe exacerbations compared to nonusers. However, for COPD patients who took nonselective beta-blockers, they were exposed to a higher risk of severe exacerbations compared to nonusers [16]. In reality, COPD patients with AMI have been advised to take cardio-selective beta-blockers if they are treated by inhaled steroids and long-acting beta-agonists [17, 18]. Several studies indicate beta-blockers can be beneficial to COPD patients with coronary artery disease. For example, one study revealed they could decrease re-admission rate in the emergency department [19]. In a brief summary, the previous studies indicated that for the patients with COPD and cardiovascular comorbidities, those who received blockers had lower mortality compared to those who never received beta-blockers. Cardio-selective beta-blockers tend to result in lower mortality compared with non-selective beta-blockers. This is compatible with the guidelines from GOLD strategy which emphasize on the importance of selective beta-blockers use for those patients who has ischemic heart disease, even when they have severe COPD [20].

Compared with previous studies [10, 21–23], the current study provides not only short-term follow-up data but also those of long-term follow-up. The median follow-up period of our study was 8 years, which is longer than the times of the previous studies of Gottlieb (2 years), Heller (4 years), Quint (2.9 years), Chen (1 year), and Andell (3 years) [8, 10, 21]. Although small-scale studies have shown that using β-blockers is beneficial in COPD patients with AMI, it has not been clear which type of β-blockers should be chosen for these individuals. It is a reasonable presumption that prescribing cardio-selective β-blockers is much safer than prescribing non-selective β-blockers, because cardio-selective β-blockers induce less bronchospasm in COPD patients [24, 25]. Our study showed that those who take selective β-blockers had a significantly better overall survival rate, compared with those who did not take β-blockers. Furthermore, this is the first study to compare the risk of overall mortality between COPD patients with AMI taking selective and non-selective β-blockers. No significant increased risk of mortality among them was observed.

The risk of cardiovascular disease is increased in COPD patients [26]. The rate can be worse in COPD patients with AMI as they have a low survival rate as compared with those without COPD [27]. Patients with MI and COPD constitute a high-risk group [21, 28, 29], and β-blockers are capable of improving the survival of all AMI patients and are thus considered to be the standard treatment. Thus, it is reasonable to routinely prescribe β-blockers for this high-risk group with a poor perspective outcome. However, our study and other studies reveal that β-blockers remain under-prescribed in the real world [22, 27, 30–32].

Interestingly, our findings indicate that members of the β-blocker group were receiving a more comprehensive panel of recommended post-MI medications, such as anti-platelet and ACEI/ARB drugs. Previous studies have also presented that COPD patients with AMI who took β-blockers received more aggressive medications [5, 27]. A possible explanation for this is that those patients who received β-blockers were those who were hemodynamically more stable, those without severe hypotension, those without bradycardia, or those who had a reduced bleeding tendency at present. Because of the limitations of the database, it is impossible to identify all relevant acute complications that present to the emergency room. However, the β-blocker group had a higher prevalence of underlying comorbidities, such as hypertension, diabetes mellitus, and end-stage renal disease. In other words, the β-blocker group has worse underlying characteristics than the non-β-blocker group. After adjusting for comorbidities and medication use, the use of β-blockers still proved to be beneficial for overall patient survival rate in our study.

The strength of our study is that the NHI database includes 99% of the Taiwanese population's medical records, including all patient's comorbidities and medications. Previous studies have analyzed relatively small samples, while our study enrolled 23,116 COPD patients with first AMI from the 23,000,000 participants of the nationwide database. Our average follow-up time was long and our sample size was large, so the results should be convincing.

Limitations

There were some limitations to our study. First, the findings derived from cohort studies are typically lower in methodological quality than those from randomized trials, because cohort studies are subject to certain biases related to adjusting for confounders. Second, we defined our patients according to ICD-9 codes, not laboratory data or test results, such as cardiac enzyme study, electrocardiogram findings, or pulmonary function test results. However, the National Health

Insurance Bureau has strict regulations for registration and payment, and our study method has been proved to be reliable, thus, the effects of these limitations may be restricted somewhat. Third, the use of beta-blocker was defined as the presence of prescription at any time point during hospitalization. In this study, we were not able to further analyze if β-blockers had been continued at long-term follow-up after discharge. On the other hand, the aim of this study is to investigate the impact of β-blockers in acute myocardial infarction which demonstrated the beneficial effect in both short-term and long-term follow-up. Future research regarding the relationship between clinical outcome and duration of β-blockers after being discharged is suggested.

β-blockers are a standard treatment for AMI patients, but are under-prescribed in patients with COPD with AMI, which might be due to the fear of acute exacerbation of COPD. We executed a nationwide cohort study, the first one of its kind, to focus on the use of β-blockers to improve long-term survival among COPD patients with AMI without increased complications. However, future randomized controlled trial studies are required to confirm our findings.

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Compliance with ethical standards

Conflict of interest All authors have declared that they have no potential conflicts (financial, professional, or personal) that are relevant to the manuscript.

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