



International Journal of Gerontology

journal homepage: <http://www.sgecm.org.tw/ijge/>



Original Article

Dose-Dependent Efficacy of β -Blocker in Acute Reduced Ejection Fraction Heart Failure and Concomitant Chronic Obstructive Pulmonary Disease

Yu-Jou Hsieh ^{a,b}, Ying-Ju Chen ^c, Sheng-Yeh Shen ^d, Shin-Yi Tsai ^{e,f,g}, Hsien-Yu Peng ^{e,h}, Shih-Yi Lee ^{i,j}, Fa-Chang Yu ^k, Chung-Lieh Hung ^{h,k,#,*}, Han-Shui Hsu ^{a,l,#,**}

^a Institute of Emergency and Critical Care Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ^b Cardiovascular Center, MacKay Memorial Hospital, Taipei, Taiwan, ^c Telehealth Center, MacKay Memorial Hospital, Taipei, Taiwan, ^d Division of Chest Medicine, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan, ^e Department of Medicine, MacKay Medical College, New Taipei City, Taiwan, ^f Department of Laboratory Medicine, MacKay Memorial Hospital, Taipei, Taiwan, ^g Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA, ^h Institute of Biomedical Sciences, MacKay Medical College, New Taipei City, Taiwan, ⁱ Division of Pulmonary and Critical Care Medicine, MacKay Memorial Hospital, Taipei, Taiwan, ^j MacKay Junior College of Medicine, Nursing and Management, Taipei, Taiwan, ^k Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan, ^l Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan

ARTICLE INFO

Accepted 16 June 2025

Keywords:

heart failure, systolic, pulmonary disease, chronic obstructive, adrenergic beta-antagonists, hospital readmission, mortality

SUMMARY

Background: The use of beta-blockers in patients with heart failure with reduced ejection fraction (HFrEF) and coexisting COPD remains controversial. This study evaluated their feasibility, prognosis, and dose-dependent effects.

Methods: This retrospective study included 805 patients with HFrEF co-existed with COPD. 279 received beta-blockers and 526 did not. Beta-blocker users were stratified into < 25% and $\geq$ 25% of the recommended dose. Two- and five-year outcomes were assessed using Kaplan-Meier and Cox regression analyses.

Results: Patients on < 25% beta-blocker dose had significantly lower two- and five-year all-cause mortality than non-users (both $p < 0.05$). This benefit persisted after adjusting for age, ejection fraction, and bronchodilator use (HR 0.67; 95% CI 0.48–0.94; $p = 0.021$).

Conclusions: This study suggests that beta-blockers may be safely used in HFrEF patients with COPD, starting at low doses. Further studies should assess their effect on HF-related readmissions.

Copyright © 2025, Taiwan Society of Geriatric Emergency & Critical Care Medicine.

1. Introduction

Heart failure (HF) is a major cause of hospitalization in the elderly, with acute decompensated HF accounting for 50–70% of cases, a 6-month readmission rate near 50%, and a 5-year mortality rate of about 50%.¹ COPD a frequent HF comorbidity, has a 5-year mortality rate of 40–70%, further worsening patient outcomes and increasing healthcare burden.^{2–4}

HF can be classified as mildly-reduced LVEF ($50\% < \text{LVEF} < 40\%$), and HF with reduced LVEF (HFrEF, $\text{LVEF} \leq 40\%$).¹ According to 2021 European Society of Cardiology (ESC) guidelines, beta-blockers are a key therapy for HFrEF, improving heart function and survival.^{1,5,6} However, in patients with both HFrEF and COPD about one-third of cases beta-blockers are often underused due to concerns over respiratory side effects, especially in Asia.^{7–9} Recent studies have shown the benefit of even low-dose beta-blockers in this population.^{10–12}

This study aimed to evaluate the impact and dose-dependent effects of beta-blockers on outcomes in patients with acute decompensated HFrEF and concomitant COPD, providing evidence-based guidance for clinical use.

2. Methods

2.1. Participants

This study has been approved by the Institutional Review Board (IRB) of Mackay Memorial Hospital (IRB Number: 24MMHIS440e). Given the minimal risk involved, an exemption from informed consent was requested without impacting participants rights.

The study was a single-center, retrospective, observational cohort study conducted between January 2001 and December 2019 at the MacKay Memorial Hospital, Taipei and Tamsui branches, diagnosed HF history (prior HF admission history or worsening HF requiring oral or intravenous diuretic intervention). Eligible patients were aged ≥ 20 years with established COPD with concomitant ICD-10 diagnosis for HF (I502, I504), ACC/AHA stages C–D, $\text{LVEF} \leq 40\%$, and elevated natriuretic peptides (BNP ≥ 100 pg/mL or age-stratified NT-proBNP elevation as: NT-proBNP ≥ 450 pg/mL if age < 50 years; ≥ 900 pg/mL if age 50–75 years; ≥ 1800 pg/mL if age > 75 years).¹ COPD di-

* Corresponding author. Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei 104, Taiwan.

E-mail address: jotaro3791@gmail.com (C.-L. Hung)

** Corresponding author. Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan.

E-mail address: hsuhs@vghtpe.gov.tw (H.-S. Hsu)

Equal contributions.

agnosis was confirmed by ICD-10 codes (J42–J44), pulmonary physician assessment, FEV1/FVC < 70%, or the PUMA tool if PFTs were unavailable.^{13–15} Patients were divided into beta-blocker users and non-users. Among users, further subgrouping was based on discharge dosage per 2021 ESC HF guidelines < 25% or ≥ 25% of the recommended dose (bisoprolol, carvedilol, nebivolol).¹ Prescription and dosage information of β-blockers at discharge, as well as causes of rehospitalization and death at two and five years, were recorded. To avoid diagnostic overlap, prior heart disease was classified as CAD (ICD-10: I20, I25) or arrhythmias (ICD-10: I47, I49). Exclusion criteria included acute coronary syndrome, congenital heart valve disease, transfer to a respiratory care center without weaning off the ventilator, in-hospital death, or non-attendance after discharge. Data were collected retrospectively, including demographics, clinical parameters, lab results, imaging, PFTs, and outcomes such as readmissions

and mortality at 2 and 5 years (Figure 1).

Finally, a total of 1,428 cases of hospitalized patients or those requiring oral or intravenous diuretic intervention owing to symptoms or signs of HF and diagnosed with COPD were identified. After excluding patients with acute coronary syndrome (113 cases), congenital heart valve disease (71 cases), transfer to a respiratory care center without weaning off the ventilator (67 cases), in-hospital deaths (217 cases) and non-attendance after discharge (155 cases), 805 patients with HFrEF and COPD were included in our final analysis (Table 1A and 1B).

2.1. Clinical endpoints

The primary endpoints were all-cause mortality and HF re-hospitalization; secondary endpoints were HF-related death and all-

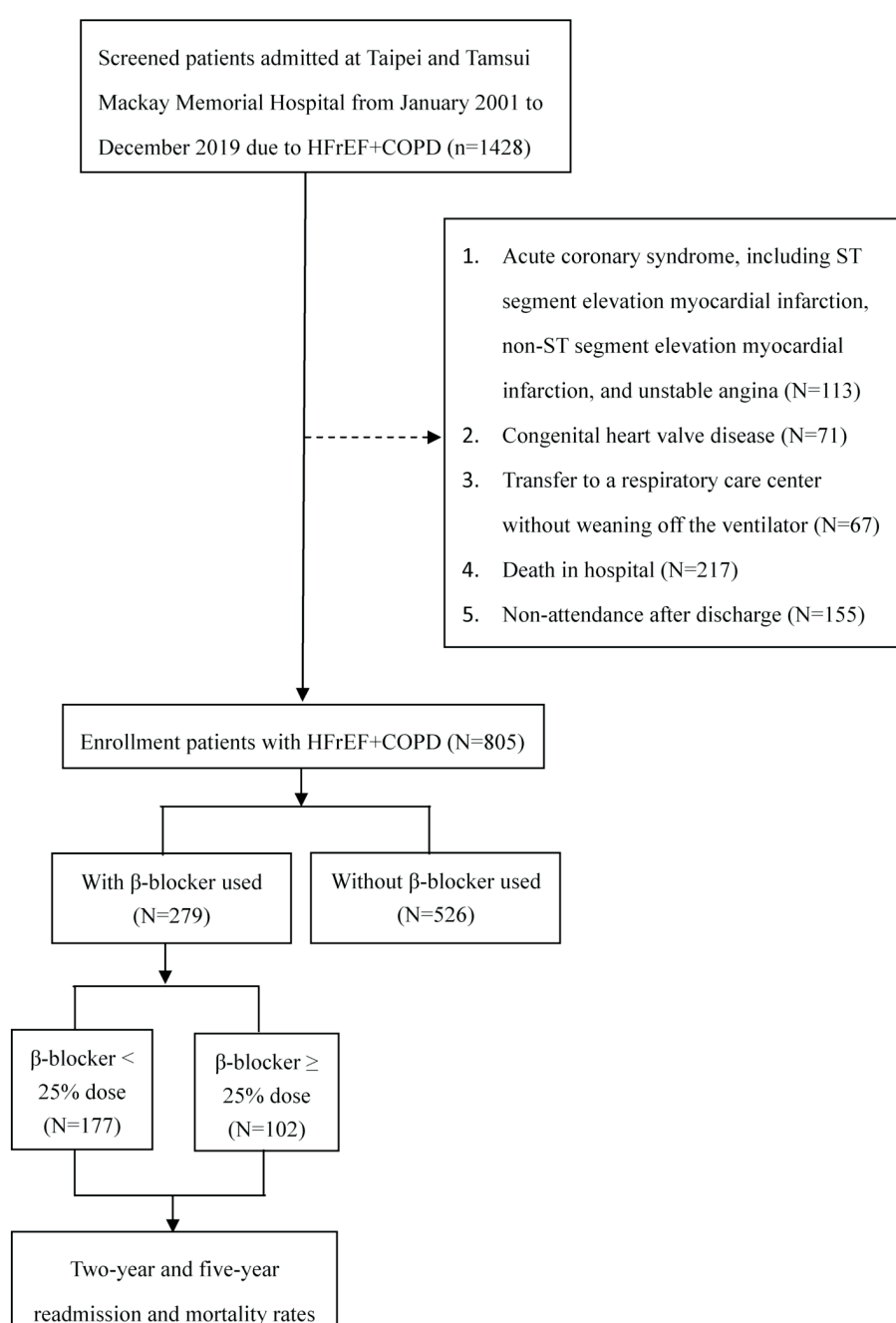


Figure 1. Schematic flowchart of current study. BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; HF, heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction.

Table 1A

Baseline patient demographics & previous medical history.

	All patients	Beta-blocker used	No beta-blocker used	p value
n	805	279	526	
Demographics				
Age (year), mean (SD)	72.3 ± 11.6	70.4 ± 11.4	73.2 ± 11.6	0.001*
Male (n, %)	592 (73.5%)	209 (74.9%)	383 (72.8%)	0.557
Body mass index (kg/m ²), mean (SD)	23.9 ± 4.6	24.2 ± 4.7	23.7 ± 4.6	0.218
Heart rate (beats/min), mean (SD)	88.5 ± 16.7	86.9 ± 15.5	89.3 ± 17.3	0.056
Systolic blood pressure (mmHg), mean (SD)	138.5 ± 24.0	136.2 ± 22.1	139.5 ± 25.0	0.081
Diastolic blood pressure (mmHg), mean (SD)	76.0 ± 13.8	75.9 ± 13.2	75.9 ± 14.1	0.988
NYHA class (n, %)				0.975
I	77 (9.6%)	27 (9.7%)	50 (9.5%)	
II	271 (33.7%)	96 (34.4%)	175 (33.3%)	
III	407 (50.6%)	138 (49.5%)	269 (33.4%)	
IV	50 (6.2%)	18 (6.5%)	32 (6.1%)	
Previous medical history				
Hypertension (n, %)	454 (56.4%)	162 (58.1%)	292 (55.5%)	0.487
Heart disease (n, %)	576 (71.6%)	209 (74.9%)	367 (69.8%)	0.124
Coronary artery disease (n, %)	449 (55.8%)	164 (58.8%)	285 (54.2%)	0.211
Atrial fibrillation (n, %)	286 (35.9%)	108 (38.7%)	178 (33.8%)	0.170
Diabetes mellitus (n, %)	346 (46.2%)	129 (46.2%)	217 (41.3%)	0.174
Chronic kidney disease (n, %)	255 (31.7%)	88 (31.5%)	167 (31.7%)	0.952
Chronic bronchitis (n, %)	321 (39.9%)	108 (38.7%)	213 (40.5%)	0.623

Table 1B

Baseline patient echocardiography, Post-bronchodilator lung function, laboratory and medication.

	All patients	Beta-blocker used	No beta-blocker used	p value
n	805	279	526	
Echocardiography				
Left ventricular ejection fraction (%), mean (SD)	31.8 ± 6.2	31.2 ± 6.4	32.2 ± 6.0	0.028*
Post-bronchodilator lung function				
FEV1/FVC, mean (SD)	62.2 ± 12.2	65.0 ± 12.4	60.7 ± 11.9	0.013*
FEV1, mean (SD)	72.0 ± 22.8	75.9 ± 23.6	70.0 ± 22.3	0.066
Laboratory				
Hemoglobin (g/dL), mean (SD)	12.4 ± 2.2	12.8 ± 2.2	12.1 ± 2.2	< 0.001*
BUN (mg/dL), mean (SD)	30.3 ± 22.3	28.6 ± 20.4	31.2 ± 23.2	0.117
Creatinine (mg/dL), mean (SD)	2.0 ± 2.0	2.0 ± 2.1	2.0 ± 1.9	0.863
eGFR (mL/min/1.73 m ²), mean (SD)	53.6 ± 35.8	54.0 ± 32.4	53.3 ± 36.5	0.810
Potassium (mEq/L), mean (SD)	4.0 ± 0.6	4.1 ± 0.6	4.0 ± 0.6	0.531
Sodium (mEq/L), mean (SD)	138.2 ± 4.3	138.1 ± 4.0	138.2 ± 4.5	0.829
BNP (pg/mL), mean (SD)	1255.0 ± 1260.5	1344.4 ± 1378.7	1156.8 ± 1184.3	0.083
NT-proBNP (pg/mL), mean (SD)	7620.8 ± 10540.3	7829.1 ± 10918.9	7430.1 ± 10219.6	0.765
Medication				
ACEI/ARB, (n, %)	393 (48.8%)	133 (47.7%)	260 (49.4%)	0.635
ARNI, (n, %)	70 (8.7%)	27 (9.7%)	43 (8.2%)	0.472
ACEI/ARB/ARNI, (n, %)	471 (58.5%)	168 (60.2%)	303 (57.6%)	0.475
MRA (n, %)	406 (50.4%)	151 (54.1%)	255 (48.5%)	0.056
I(f) inhibitor (n, %)	44 (5.5%)	19 (6.8%)	25 (4.8%)	0.308
Digoxin, (n, %)	213 (26.5%)	69 (27.7%)	144 (27.4%)	0.357
Diuretics, (n, %)	714 (88.7%)	255 (91.4%)	459 (87.3%)	0.078
Short-acting beta-agonist (SABA), (n, %)	490 (60.9%)	148 (53.0%)	342 (65.0%)	0.001*
Long-acting beta-agonist (LABA), (n, %)	166 (20.6%)	40 (14.3%)	126 (24.0%)	0.001*
Short-acting anti-muscarinic agent (SAMA), (n, %)	226 (28.1%)	53 (19.0%)	173 (32.9%)	< 0.001*
SABA/SAMA (n, %)	257 (31.9%)	74 (26.5%)	183 (34.8%)	0.017*
Methylxanthines, (n, %)	376 (46.7%)	113 (40.5%)	263 (50.0%)	0.012*
Ever used any COPD medication, (n, %)	593 (73.7%)	192 (68.8%)	401 (76.2%)	0.024*

Data are shown as n (%) or mean ± standard deviation

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitors; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; LABA, long-acting beta-agonist; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SABA, short-acting beta-agonist; SAMA, short-acting anti-muscarinic agent; SD, standard deviation.

cause hospitalization. Follow-up periods were two and five years.

2.2. Statistical analysis

Continuous variables were expressed as mean ± SD or median

(IQR) and compared using t-test or Wilcoxon rank-sum test. Categorical variables were shown as percentages and compared using chi-squared test. Associations between beta-blocker use and outcomes were assessed by uni- and multivariate Cox regression. Kaplan-Meier with log-rank tests compared outcomes between users and non-

users. Dose effects were analyzed by stratifying users into < 25% and ≥ 25% guideline dose, with non-users as reference.

All statistical analysis was performed using STATA 14. A 2-sided value of $p < 0.05$ was taken to indicate statistical significance for all analyses.

3. Results

Tables 1A and 1B listed the baseline characteristics by beta-blocker use. The cohort (mean age 72.3 ± 11.6 years; 73.5% male) had an average LVEF of 31.8% and FEV1/FVC ratio of 62.4%. About 50.6% were NYHA III, and 34.7% received beta-blockers. Significant differences were noted in age, LVEF, FEV1/FVC, hemoglobin, and bronchodilator use between users and non-users ($p < 0.05$). Some did not receive COPD treatment, likely due to mild symptoms (CAT < 10). At discharge, only 34.7% were prescribed beta-blockers. Significant differences in age, LVEF, FEV1/FVC, hemoglobin, and bronchodilator use were noted between beta-blocker users and non-users ($p < 0.05$).

Among 805 patients, 161 case (20.0%) died within 2 years (8.9% HF-related), and 65.3% were readmitted (38.3% due to HF). At 5 years, 255 case (37.7%) died (13.3% HF-related) and 47.0% were re-admitted for HF. Beta-blocker use reduced 2-year mortality (HR 0.62; CI 0.44–0.88; $p = 0.008$) and remained significant after adjustment. At 5 years, it was associated with lower mortality (HR 0.63; 95% CI 0.48–0.83; $p = 0.001$) and readmission (HR 0.83; 95% CI 0.72–1.00; $p = 0.034$); adjusted analysis confirmed mortality benefit (HR 0.69; 95% CI 0.52–0.92; $p = 0.01$). In addition, we analyzed the two- and five-year rehospitalization rates due to acute exacerbations of chronic obstructive pulmonary disease, a representative non-cardio-vascular event, and found no significant association with β-blocker use (HR 0.86; 95% CI 0.65–1.14; $p = 0.29$ and HR 0.89; 95% CI 0.69–1.13; $p = 0.32$, respectively) (Table 2 and Table 3). Kaplan-Meier curves (Figure 2A–H) illustrate these outcomes.

Clinical outcomes were compared among non-users, low-dose (< 25%), and high-dose (≥ 25%) beta-blocker users at 2-year and 5-year follow-up. At 2 years, low-dose users showed reduced mortality (HR 0.63; 95% CI 0.40–0.96; $p = 0.032$); the high-dose group showed borderline significance (HR 0.61; 95% CI 0.36–1.02; $p = 0.06$). Other outcomes were similar across groups. At 5 years, mortality was reduced in both low-dose and higher-dose groups (HR 0.63; $p = 0.006$; HR 0.64; $p = 0.028$), but after adjustment, significance remained only for the low-dose group (HR 0.67; 95% CI 0.48–

Table 2
Effect of beta-blocker use on mortality and heart failure-related hospitalization at two years.

Uni-variable analysis of beta-blocker use			
Primary endpoints	Hazard ratio	95% CI	p value
All-cause mortality	0.62	0.44–0.88	0.008*
HF mortality	0.66	0.40–1.11	0.115
All-cause readmission	0.87	0.73–1.05	0.148
HF readmission	0.98	0.78–1.24	0.90
COPD readmission	0.78	0.59–1.03	0.083
Multivariable analysis of beta-blocker use (adjusted for age, LVEF and bronchodilator use)			
Secondary endpoints	Hazard ratio	95% CI	p value
All-cause mortality	0.69	0.49–0.99	0.042*
HF mortality	0.76	0.45–1.28	0.30
All-cause readmission	0.92	0.77–1.11	0.39
HF readmission	1.05	0.83–1.33	0.67
COPD readmission	0.86	0.65–1.14	0.29

Table 3
Effect of beta-blocker use on mortality and heart failure-related hospitalization at five years.

Uni-variable analysis of beta-blocker use			
Primary endpoints	Hazard ratio	95% CI	p value
All-cause mortality	0.63	0.48–0.83	0.001*
HF mortality	0.70	0.46–1.06	0.10
All-cause readmission	0.83	0.72–1.00	0.03
HF readmission	0.93	0.76–1.15	0.52
COPD readmission	0.81	0.64–1.03	0.089
Multivariable analysis of beta-blocker use (adjusted for age, LVEF and bronchodilator use)			
Secondary endpoints	Hazard ratio	95% CI	p value
All-cause mortality	0.69	0.52–0.92	0.01*
HF mortality	0.77	0.50–1.17	0.22
All-cause readmission	0.89	0.75–1.05	0.17
HF readmission	1.01	0.82–1.25	0.93
COPD readmission	0.89	0.69–1.13	0.32

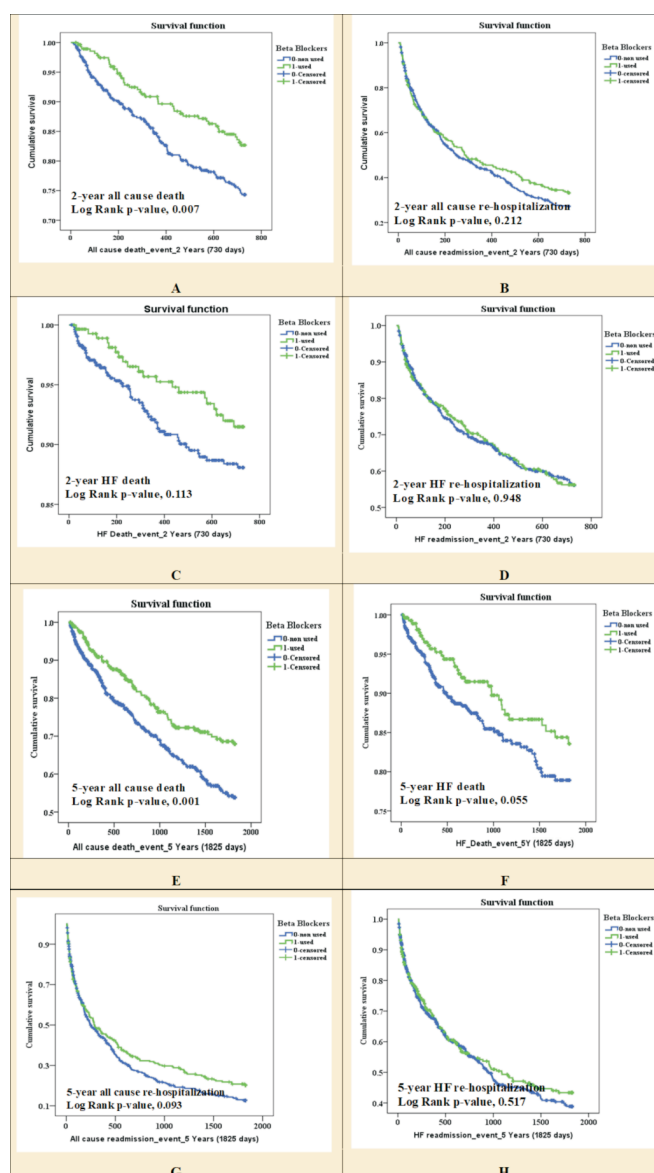


Figure 2. Kaplan-Meier curves for mortality and re-hospitalization rates in patients undergoing β-blocker treatment at two and five years, respectively. The blue line represents cases was non-used of beta-blockers, while the green line represents cases was used of beta-blockers. A–D. Mortality and re-hospitalization rates in patients undergoing β-blocker treatment versus non-users at two years. E–H. Mortality and re-hospitalization rates in patients undergoing β-blocker treatment versus non-users at five years.

0.94; $p = 0.021$). The other groups also did not show significant differences (Table 4 and Table 5). Kaplan-Meier curves (Figure 3A–H) illustrate these outcomes.

4. Discussion

Our study showed that β -blockers are underused in acute decompensated HFrEF patients complicated with COPD yet their use, even at low doses was linked to reduced all-cause mortality at two and five years. These findings support early β -blocker initiation at discharge, even in patients with COPD.

In Taiwan, cardiovascular disease is the second leading cause of death after cancer. For severe COPD, the 2-year mortality rate approaches 50%.³ Beta-blockers are often underused in HF patients with COPD due to concerns about respiratory side effects.^{3,16} In our cohort, only 34.7% received beta-blockers at discharge — much lower than in the ESC registry (62.8%) and EVEREST study (63%) —

likely reflecting physician caution, especially in Asian countries.^{16,17} Despite these concerns, our findings showed that even low-dose beta-blockers (< 25% of the recommended dose) were linked to better outcomes.

Several studies recommend standard dosage or $\geq 50\%$ beta-blocker doses for HFrEF with co-morbid COPD, but few analyze lower doses.^{3,8} Our study evaluated whether low-dose beta-blockers (< 25% of the guideline-recommended maximum) improve outcomes in HFrEF with COPD. We found lower all-cause mortality even with low-dose use at 5 years in both uni- and multivariate analyses. Similar findings were seen in the Asian-HF registry. Non-users in our cohort were older, used more bronchodilators, and had worse lung function, possibly reflecting physician concerns about prior drug reactions, respiratory status, and disease severity.⁹ Although multiple studies have indicated the substantial benefit of low dose β -blocker use (less than half recommended dose) for HFrEF, the clinical usage rate remains low in real-world clinical practice, particularly in COPD

Table 4
Effect of beta-blocker dosage on mortality and heart failure-related hospitalization at two years.

Univariable analysis of beta-blocker use			
Outcomes	Hazard ratio	95% CI	p value
All-cause mortality			
Not used	ref.		
< 25% maximum dose	0.63	0.42–0.96	0.032*
$\geq 25\%$ maximum dose	0.61	0.36–1.02	0.06
HF mortality			
Not used	ref.		
< 25% maximum dose	0.70	0.38–1.28	0.21
$\geq 25\%$ maximum dose	0.60	0.27–1.33	0.21
All-cause readmission			
Not used	ref.		
< 25% maximum dose	0.86	0.69–1.06	0.16
$\geq 25\%$ maximum dose	0.90	0.70–1.17	0.45
HF readmission			
Not used	ref.		
< 25% maximum dose	0.99	0.75–1.30	0.93
$\geq 25\%$ maximum dose	0.98	0.70–1.37	0.91
COPD readmission			
Not used	ref.		
< 25% maximum dose	1.19	0.68–2.06	0.54
$\geq 25\%$ maximum dose	0.52	0.25–1.08	0.08
Multivariable analysis of beta-blocker use (adjusted for age, LVEF and bronchodilator use)			
Outcomes	Hazard ratio	95% CI	p value
All-cause mortality			
Not used	ref.		
< 25% maximum dose	0.70	0.46–1.06	0.095
$\geq 25\%$ maximum dose	0.69	0.41–1.16	0.16
HF mortality			
Not used	ref.		
< 25% maximum dose	0.79	0.43–1.47	0.46
$\geq 25\%$ maximum dose	0.70	0.32–1.55	0.38
All cause readmission			
Not used	ref.		
< 25% maximum dose	0.90	0.73–1.12	0.36
$\geq 25\%$ maximum dose	0.96	0.74–1.24	0.74
HF readmission			
Not used	ref.		
< 25% maximum dose	1.05	0.79–1.39	0.73
$\geq 25\%$ maximum dose	1.05	0.75–1.48	0.76
COPD readmission			
Not used	ref.		
< 25% maximum dose	0.99	0.57–1.73	0.98
$\geq 25\%$ maximum dose	0.48	0.24–1.02	0.06

Table 5
Effect of beta-blocker dosage on mortality and heart failure-related hospitalization at five years.

Univariable analysis of beta-blocker use			
Outcomes	Hazard ratio	95% CI	p value
All-cause mortality			
Not used	ref.		
< 25% maximum dose	0.63	0.45–0.87	0.006*
$\geq 25\%$ maximum dose	0.64	0.43–0.95	0.028*
HF mortality			
Not used	ref.		
< 25% maximum dose	0.74	0.46–1.20	0.22
$\geq 25\%$ maximum dose	0.64	0.34–1.20	0.17
All-cause readmission			
Not used	ref.		
< 25% maximum dose	0.85	0.92–1.50	0.20
$\geq 25\%$ maximum dose	0.80	0.63–1.03	0.087
HF readmission			
Not used	ref.		
< 25% maximum dose	0.91	0.71–1.17	0.45
$\geq 25\%$ maximum dose	0.97	0.72–1.31	0.85
COPD readmission			
Not used	ref.		
< 25% maximum dose	1.26	0.77–2.07	0.36
$\geq 25\%$ maximum dose	0.77	0.42–1.41	0.40
Multivariable analysis of beta-blocker use (adjusted for age, LVEF and bronchodilator use)			
Outcomes	Hazard ratio	95% CI	p value
All-cause mortality			
Not used	ref.		
< 25% maximum dose	0.67	0.48–0.94	0.021*
$\geq 25\%$ maximum dose	0.73	0.48–1.09	0.12
HF mortality			
Not used	ref.		
< 25% maximum dose	0.79	0.48–1.29	0.34
$\geq 25\%$ maximum dose	0.74	0.39–1.39	0.35
All-cause readmission			
Not used	ref.		
< 25% used	0.90	0.74–1.10	0.20
$\geq 25\%$ used	0.86	0.67–1.10	0.24
HF readmission			
Not used	ref.		
< 25% maximum dose	0.98	0.76–1.27	0.89
$\geq 25\%$ maximum dose	1.06	0.78–1.43	0.72
COPD readmission			
Not used	ref.		
< 25% maximum dose	1.07	0.65–1.76	0.80
$\geq 25\%$ maximum dose	0.72	0.39–1.32	0.28

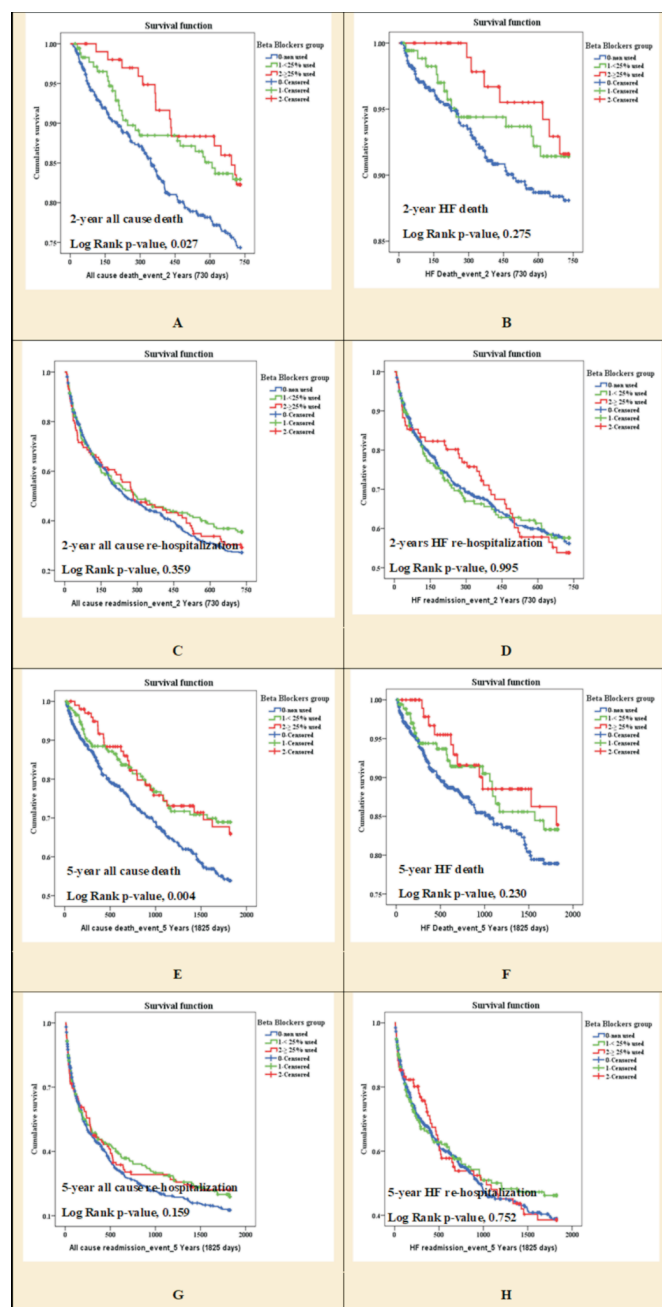


Figure 3. Patients were divided into two groups based on dose-stratified (< 25%, ≥ 25%) β-blocker use and non-use for comparisons tracked for all-cause mortality and heart failure (HF) readmission rates within two and five years, respectively. The blue line represents cases was non-used of beta-blockers, the green line represents cases was less than 25% usage of beta-blockers, and the red line represents cases was 25% or greater usage of beta-blockers. A–D. All-cause mortality and heart failure (HF) readmission rates in patients undergoing different dose of β-blocker treatment versus non-users at two years. E–H. All-cause mortality and heart failure (HF) readmission rates in patients undergoing different dose of β-blocker treatment versus non-users at five years.

population.^{3,7,8,10,11,16,18,19} Our study therefore extended the findings from STRONG-HF study and further provided numerical evidences about the precise dose range of beta-blocker use for beneficial outcomes among HFrEF patients complicated by COPD.²⁰

This retrospective study has limitations, including potential selection bias from 155 patients lost to follow-up and reliance on clinical symptoms rather than pulmonary function tests for COPD diagnosis. Unmeasured confounders may have affected outcomes. Pro-

spective studies with standardized follow-up and diagnostics are needed for more accurate evaluation.

5. Conclusions

Our present study indicated that concomitant COPD among HFrEF patients should not be a contraindication for the use of beta-blockers. Initiating at low doses, with careful escalation, showed significant reductions in HF hospitalization and mortality — even at doses below half the standard. These findings support β-blocker use in acute HFrEF with COPD, as benefits likely outweigh risks, and withholding them at discharge is not recommended.

Acknowledgements

I would like to express my sincere gratitude to my family, colleagues, mentors, friends, and all those who have supported me throughout the completion of this thesis.

Conflict of interest

None declared.

References

- McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726. doi:10.1093/eurheartj/ehab368
- Cheng SL, Lin CH, Chu KA, et al. Update on guidelines for the treatment of COPD in Taiwan using evidence and GRADE system-based recommendations. *J Formos Med Assoc*. 2021;120:1821–1844. doi:10.1016/j.jfma.2021.06.007
- Scrutinio D, Guida P, Passantino A, et al. Acutely decompensated heart failure with chronic obstructive pulmonary disease: Clinical characteristics and long-term survival. *Eur J Intern Med*. 2019;60:31–38. doi:10.1016/j.ejim.2018.11.002
- Wang CC, Chang HY, Yin WH, et al. TSOC-HFrEF registry: A registry of hospitalized patients with decompensated systolic heart failure: Description of population and management. *Acta Cardiol Sin*. 2016;32:400–411. doi:10.6515/acs20160704a
- Heidenreich PA, Fonarow GC, Breathett K, et al. 2020 ACC/AHA clinical performance and quality measures for adults with heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol*. 2020;76:2527–2564. doi:10.1016/j.jacc.2020.07.023
- van der Meer P, Gaggin HK, Dec GW. ACC/AHA versus ESC guidelines on heart failure: JACC guideline comparison. *J Am Coll Cardiol*. 2019;73:2756–2768. doi:10.1016/j.jacc.2019.03.478
- Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: A meta-analysis of observational studies. *PLoS One*. 2014;9:e113048. doi:10.1371/journal.pone.0113048
- Kubota Y, Tay WT, Asai K, et al. Chronic obstructive pulmonary disease and β-blocker treatment in Asian patients with heart failure. *ESC Heart Fail*. 2018;5:297–305. doi:10.1002/ehf2.12228
- Lipworth B, Skinner D, Devereux G, et al. Underuse of β-blockers in heart failure and chronic obstructive pulmonary disease. *Heart*. 2016;102:1909–1914. doi:10.1136/heartjnl-2016-309458
- Kubota Y, Asai K, Furuse E, et al. Impact of β-blocker selectivity on long-term outcomes in congestive heart failure patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2015;10:515–523. doi:10.2147/COPD.S79942
- Ouwkerk W, Zwinderman AH, Ng LL, et al. Biomarker-guided versus guideline-based treatment of patients with heart failure: Results from BIOSTAT-CHF. *J Am Coll Cardiol*. 2018;71:386–398. doi:10.1016/j.jacc.2017.11.041
- Güder G, Brenner S, Störk S, Hoes A, Rutten FH. Chronic obstructive pulmonary disease in heart failure: Accurate diagnosis and treatment. *Eur J*

- Heart Fail.* 2014;16:1273–1282. doi:10.1002/ejhf.183
13. Taiwan Society of Pulmonary and Critical Care Medicine. *2023 Taiwan Clinical Care Guidelines for COPD*. Taiwan Society of Pulmonary and Critical Care Medicine; 2023.
 14. Au-Doung PLW, Wong CKM, Chan DCC, Chung JWH, Wong SYS, Leung MKW. PUMA screening tool to detect COPD in high-risk patients in Chinese primary care-a validation study. *PLoS One*. 2022;17:e0274106. doi:10.1371/journal.pone.0274106
 15. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2021 report. Global Initiative for Chronic Obstructive Lung Disease; 2020.
 16. Canepa M, Straburzynska-Migaj E, Drozd J, et al. Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2018;20:100–110. doi:10.1002/ejhf.964
 17. Mentz RJ, Schmidt PH, Kwasny MJ, et al. The impact of chronic obstructive pulmonary disease in patients hospitalized for worsening heart failure with reduced ejection fraction: An analysis of the EVEREST trial. *J Card Fail.* 2012;18:515–523. doi:10.1016/j.cardfail.2012.04.010
 18. Sessa M, Mascolo A, Mortensen RN, et al. Relationship between heart failure, concurrent chronic obstructive pulmonary disease and beta-blocker use: A Danish nationwide cohort study. *Eur J Heart Fail.* 2018;20:548–556. doi:10.1002/ejhf.1045
 19. Su VY, Chang YS, Hu YW, et al. Carvedilol, bisoprolol, and metoprolol use in patients with coexistent heart failure and chronic obstructive pulmonary disease. *Medicine (Baltimore)*. 2016;95:e2427. doi:10.1097/MD.0000000000002427
 20. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): A multinational, open-label, randomised, trial. *Lancet.* 2022;400:1938–1952. doi:10.1016/S0140-6736(22)02076-1