ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 297–305
Published online 21 October 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12228

ORIGINAL RESEARCH ARTICLE

Chronic obstructive pulmonary disease and β-blocker treatment in Asian patients with heart failure

Yoshiaki Kubota[1]*, Wan Ting Tay[2], Kuniya Asai[1], Koji Murai[1], Ikutaro Nakajima[3], Nobuhisa Hagiwara[4], Takanori Ikeda[5], Takashi Kurita[6], Tiew-Hwa Katherine Teng[2,7], Inder Anand[8], Carolyn S.P. Lam[2,9,10], Wataru Shimizu[1] and on behalf of the ASIA-HF Study investigators[†]

[1]*Department of Cardiovascular Medicine, Nippon Medical School, Bunkyō, Tokyo, Japan;* [2]*National Heart Centre Singapore, Singapore, Singapore;* [3]*Division of Cardiology, Department of Internal Medicine, National Cerebral and Cardiovascular Center Hospital, Suita, Osaka, Japan;* [4]*Department of Cardiology, School of Medicine, Tokyo Women's Medical University, Shinjuku, Tokyo, Japan;* [5]*Division of Cardiovascular Medicine, Department of Internal Medicine, Toho University Omori Hospital, Ōta, Tokyo, Japan;* [6]*Division of Cardiology, Department of Internal Medicine, Kinki University School of Medicine, Higashiōsaka, Osaka, Japan;* [7]*School of Population Health, University of Western Australia, Perth, WA, Australia;* [8]*VA Medical Center, University of Minnesota, Minneapolis, MN, USA;* [9]*Cardiovascular Research Institute, National University Heart Centre, Singapore, Singapore;* [10]*Duke–National University of Singapore, Singapore, Singapore*

Abstract

Aims Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are increasingly frequent in Asia and commonly coexist in patients. However, the prevalence of COPD among Asian patients with HF and its impact on HF treatment are unclear.

Methods and results We compared clinical characteristics and treatment approaches between patients with or without a history of COPD, before and after 1:2 propensity matching (for age, sex, geographical region, income level, and ethnic group) in 5232 prospectively recruited patients with HF and reduced ejection fraction (HFrEF, <40%) from 11 Asian regions (Northeast Asia: South Korea, Japan, Taiwan, Hong Kong, and China; South Asia: India; Southeast Asia: Thailand, Malaysia, Philippines, Indonesia, and Singapore). Among the 5232 patients with HFrEF, a history of COPD was present in 8.3% (n = 434), with significant variation in geography (11.0% in Northeast Asia vs. 4.7% in South Asia), regional income level (9.7% in high income vs. 5.8% in low income), and ethnicity (17.0% in Filipinos vs. 5.2% in Indians) (all $P < 0.05$). Use of mineralocorticoid receptor antagonists and diuretics was similar between groups, while usage of all β-blockers was lower in the COPD group than in the non-COPD group in the overall (66.3% vs. 79.9%) and propensity-matched cohorts (66.3% vs. 81.7%) (all $P < 0.05$). A striking exception was the Japanese cohort in which β-blocker use was high in COPD and non-COPD patients (95.2% vs. 91.2%).

Conclusions The prevalence of COPD in HFrEF varied across Asia and was related to underuse of β-blockers, except in Japan.

Keywords Chronic obstructive pulmonary disease; Heart failure; β-Blocker

Received: 6 June 2017; Revised: 21 August 2017; Accepted: 1 September 2017
**Correspondence to: Wataru Shimizu, Department of Cardiovascular Medicine, Nippon Medical School, 1-1-5, Sendagi, Bunkyō, Tokyo 113-0022, Japan. Tel: +81- 3- 3822- 2131; Fax: +81- 3- 5814- 6050. Email: wshimizu@nms.ac.jp*
†A list of investigators is provided in the Acknowledgements.

Introduction

Chronic obstructive pulmonary disease (COPD) is present in approximately one-third of patients with heart failure (HF) and reduced ejection fraction (HFrEF).[1] Because of concern regarding respiratory deterioration, COPD is an important cause of underuse and underdosing of β-blockers.[1–4] The mechanistic relationship between COPD and HFrEF is complex, multifactorial, and not fully understood. Hyperinflation and greater changes in intrathoracic pressure during respiration might enhance ventricular pre-load and afterload, resulting in left ventricular (LV) dysfunction and HF.[5] Despite increasing evidence that β-blockers are safe and beneficial in patients with COPD,[6,7] they are often underused in this group worldwide.[8] The reason is most likely related to concerns that β-blockers may induce bronchospasm in COPD patients. The National Institute for Health and Care Excellence and European Society of Cardiology guidelines state that COPD is not a contraindication for the use of β-blockers, and mild deterioration in pulmonary

function and symptoms should not indicate the necessity for prompt discontinuation.[9,10] Nonetheless, low-dose initiation and gradual uptitration are recommended in the guidelines.[9,10] In Asia, ageing populations and large increases in cardiovascular risk factors have contributed to a high burden of HF.[11] Patients with HFrEF from Asia may differ in clinical characteristics from patients elsewhere.[12,13] The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry was established to bridge the knowledge gap regarding the burden associated with chronic HF in Asian patients. In the present study, we report data on co-morbidities of Asian patients with HFrEF enrolled from 1 October 2012 to 31 December 2015, with special reference to COPD and its treatment.[14,15]

Methods

Study design

The ASIAN-HF registry was a prospective observational registry of symptomatic patients with HFrEF from 44 centres in 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand) that enrolled patients between 2010 and 2015. Detailed methods have been previously published.[14] HFrEF was defined as patients >18 years of age with symptomatic HF (at least one episode of decompensated HF in the previous 6 months that resulted in a hospital admission or was treated in an outpatient clinic) and LV systolic dysfunction (ejection fraction ≤40% on baseline echocardiography).[14] Ethics approval was obtained from the local institutional review board of each participating centre, and the study complied with the Declaration of Helsinki.

For this study, patients from the ASIAN-HF registry with both HF and COPD were identified, and health data including vital signs and other diagnosed illnesses were analysed. Heart rate was measured at rest using electrocardiography. Hypertension was defined as the presence of a clinical diagnosis of hypertension (blood pressure ≥ 140/90 mmHg) or treatment with anti-hypertensive medications. Diabetes was defined as the presence of a clinical diagnosis of diabetes (fasting plasma glucose ≥ 7 mmol/L or random plasma glucose ≥ 11.1 mmol/L or HbA1C ≥ 6.5%) or treatment with anti-diabetic therapy. COPD was diagnosed in accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria.[16] The usage of β-blocker was defined at first visit.

Statistical analyses

The primary analysis compared the clinical characteristics of HF patients with or without COPD in the overall cohort. Secondary analyses were conducted in a 1:2 propensity-matched cohort and the Japanese cohort separately. Propensity matching for age, sex, geographical region, income level, and ethnic group was performed to produce the matched cohort (with a ratio of COPD to non-COPD patients of 1:2). Patients were categorized on the basis of geographic region of recruitment, income level, and ethnic group, with groups defined as follows:

(1) Geographic region (by United Nations; Northeast Asia: South Korea, Japan, Taiwan, Hong Kong, and China; South Asia: India; Southeast Asia: Thailand, Malaysia, Philippines, Indonesia, Singapore)
(2) Income level (by World Health Organization; high: Japan, Singapore, Hong Kong, Taiwan, South Korea; middle: China, Malaysia, Thailand; low: Philippines, Indonesia, India)
(3) Ethnicity (Chinese, Indian, Malay, Japanese, Korean, Thai, and Indigenous Southeast Asians)

Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as number (percentage). To compare baseline characteristics in HF patients with or without COPD, χ^2 tests and independent *t*-tests were used for categorical and continuous variables, respectively. Multivariable logistic regression to assess those factors associated with the diagnosis of COPD, including variables with *P*-values <0.10 in univariable analysis as well as clinical and demographic variables from a prior knowledge. A *P*-value ≤0.05 was considered statistically significant. Stata software version 14 (StataCorp., TX) was used for statistical analyses.

Results

Baseline characteristics of the overall population

In the overall HFrEF cohort, 434 (8.3%) patients had a diagnosis of COPD, whereas 4798 (91.7%) did not. *Table 1* shows the clinical characteristics of the groups categorized by the presence or absence of COPD. There was signification variation in the prevalence of COPD by geographical region and income level (all $P < 0.05$). The highest prevalence of COPD was found in Northeast Asians (11.0%), who were significantly older than patients in other areas (mean age: 62 ± 14 years vs. 58 ± 12 years in other regions), while COPD prevalence was lowest in South Asians (4.7%) (*Table S1*). COPD was also more prevalent in high- and middle-income regions than in low-income regions (*Table S1*). The prevalence of COPD varied widely among ethnicities, ranging from 17.0% in Filipinos to 5.2% in Indians (*Table S2*). Overall, the COPD group was significantly older, had a greater severity of HF as assessed with the New York Heart Association

Table 1 Baseline characteristics of heart failure patients with and without chronic obstructive pulmonary disease

	Overall cohort			1:2 matched[a] cohort			Japanese cohort		
	With COPD	Without COPD	*P*-value	With COPD	Without COPD	*P*-value	With COPD	Without COPD	*P*-value
N	434 (8.3%)	4798 (91.7%)		410	820		63 (11.8%)	471 (88.2%)	
Demographics									
Age (years)	63.9 ± 13.7	59.3 ± 12.9	<0.001	63.9 ± 13.7	64.2 ± 12.7	0.666	68.5 ± 12.6	64.6 ± 13.7	0.033
Male	347 (80.0)	3742 (78.0)	0.343	330 (80.5)	666 (81.2)	0.758	50 (79.4)	363 (77.1)	0.683
Geographical region			<0.001			0.556			
Northeast Asia	181 (41.7)	1471 (30.7)		175 (42.7)	360 (43.9)				
South Asia	68 (15.7)	1368 (28.5)		60 (14.6)	134 (16.3)				
Southeast Asia	185 (42.6)	1959 (40.8)		175 (42.7)	326 (39.8)				
Income level			<0.001			0.547			
High income	218 (50.2)	2020 (42.1)		214 (52.2)	444 (54.2)				
Middle income	111 (25.6)	1077 (22.5)		103 (25.1)	183 (22.3)				
Low income	105 (24.2)	1701 (35.4)		93 (22.7)	193 (23.5)				
Presenting characteristics									
NYHA class, I/II/III/IV (%)	11/45/33/11	13/53/28/6	<0.001	12/44/33/11	13/52/30/5	0.001	8/67/23/2	6/73/18/3	0.621
Shortness of breath on exertion	349 (80.4)	3567 (74.4)	0.005	328 (80.0)	608 (74.2)	0.023	45 (71.4)	343 (72.8)	0.815
Shortness of breath at rest	104 (24.0)	860 (17.9)	0.002	95 (23.2)	151 (18.4)	0.049	9 (14.3)	59 (12.5)	0.694
Reduction in exercise tolerance	318 (73.3)	3346 (69.8)	0.128	301 (73.4)	553 (67.5)	0.034	38 (60.3)	311 (66.0)	0.371
Nocturnal cough	115 (26.5)	841 (17.5)	<0.001	109 (26.6)	136 (16.6)	<0.001	5 (7.9)	22 (4.7)	0.267
Orthopnoea	137 (31.6)	1046 (21.8)	<0.001	132 (32.2)	174 (21.2)	<0.001	3 (4.8)	28 (5.9)	0.706
Paroxysmal nocturnal dyspnoea	116 (26.7)	878 (18.3)	<0.001	112 (27.3)	156 (19.0)	0.001	3 (4.8)	21 (4.5)	0.913
Angina	67 (15.5)	530 (11.1)	0.006	62 (15.2)	93 (11.3)	0.057	2 (3.2)	6 (1.3)	0.243
Systolic blood pressure (mmHg)	119.4 ± 19.0	118.3 ± 20.3	0.317	119.3 ± 18.8	118.8 ± 19.9	0.688	114.2 ± 18.3	112.7 ± 19.7	0.571
Diastolic blood pressure (mmHg)	71.4 ± 12.1	72.5 ± 12.6	0.087	71.2 ± 12.1	71.7 ± 12.3	0.545	66.7 ± 11.3	66.1 ± 12.9	0.708
Heart rate (b.p.m.)	80.5 ± 15.0	79.6 ± 16.3	0.275	80.2 ± 14.9	77.9 ± 15.5	0.015	72.5 ± 10.7	72.6 ± 14.5	0.937
Body mass index (kg/m^2)	24.8 ± 6.2	24.9 ± 5.0	0.709	24.8 ± 6.0	24.5 ± 4.9	0.403	23.4 ± 3.9	22.8 ± 4.2	0.255
eGFR (mL/min/1.73 m^2)	63.8 ± 10.8	65.1 ± 28.6	0.403	64.1 ± 30.4	63.1 ± 27.9	0.610	67.1 ± 32.9	65.0 ± 28.8	0.603
LVEF (%)	27.8 ± 7.2	27.3 ± 7.0	0.207	27.8 ± 7.1	28.2 ± 6.6	0.305	28.6 ± 7.5	27.9 ± 7.6	0.542
Medical history									
Aetiology HF, ischaemic	213 (49.1)	2245 (46.8)	0.389	201 (49.0)	418 (51.0)	0.734	16 (25.4)	129 (27.4)	0.373
Ventricular tachycardia/fibrillation	44 (10.1)	362 (7.5)	0.053	40 (9.8)	70 (8.6)	0.484	18 (28.6)	115 (24.4)	0.474
Coronary artery disease	214 (49.3)	2411 (50.3)	0.698	200 (48.8)	457 (55.8)	0.020	23 (36.5)	172 (36.5)	0.999
Atrial fibrillation/flutter	83 (19.1)	851 (17.7)	0.472	79 (19.3)	188 (23.0)	0.139	22 (34.9)	183 (38.9)	0.547
Hypertension	236 (54.4)	2475 (51.6)	0.274	227 (55.4)	467 (57.0)	0.581	31 (49.2)	226 (48.0)	0.855
Diabetes	167 (38.5)	1948 (40.6)	0.383	158 (38.5)	374 (45.7)	0.017	13 (20.6)	156 (33.1)	0.045
Stroke	31 (7.1)	305 (6.4)	0.522	30 (7.3)	58 (7.1)	0.880	7 (11.1)	51 (10.8)	0.946
Peripheral arterial vascular disease	26 (6.0)	152 (3.2)	0.002	25 (6.1)	55 (5.4)	0.606	3 (4.8)	17 (3.6)	0.651
Renal artery stenosis	10 (2.3)	36 (0.8)	0.001	10 (2.4)	8 (0.1)	0.044	2 (3.2)	3 (0.6)	0.050
Smoking, current or ex	261 (60.1)	2093 (43.7)	< 0.001	254 (62.0)	388 (47.4)	< 0.001	38 (60.3)	252 (53.6)	0.316
Alcohol, current or ex	153 (35.3)	1359 (28.4)	0.001	156 (38.1)	234 (28.6)	0.001	31 (49.2)	200 (42.6)	0.317
12-lead ECG									
ECG rhythm, SR/AF/others or unknown (%)	64/11/25	70/12/18	< 0.001	64/12/24	66/15/19	0.057	32/11/57	41/15/44	0.172
ECG heart rate (b.p.m.)	83.3 ± 18.9	81.3 ± 19.0	0.048	83.3 ± 19.1	80.1 ± 18.8	0.007	74.7 ± 18.1	73.6 ± 15.9	0.616
Left bundle brunch block	63 (15.0)	628 (13.8)	0.732	58 (14.6)	97 (12.5)	0.516	9 (14.8)	38 (8.1)	0.086
Right bundle brunch block	39 (10.5)	350 (8.7)	0.247	35 (10.0)	60 (8.9)	0.566	6 (9.7)	41 (8.8)	0.811
QRS duration (ms)	117.6 ± 32.2	115.1 ± 32.4	0.138	117.6 ± 32.0	116.8 ± 32.4	0.684	136.9 ± 37.4	128.3 ± 34.3	0.069

(*Continues*)

Table 1 (continued)

	Overall cohort			1:2 matched[a] cohort			Japanese cohort		
	With COPD	Without COPD	*P*-value	With COPD	Without COPD	*P*-value	With COPD	Without COPD	*P*-value
Echocardiography									
LV end diastolic volume (mL)	182.9 ± 78.0	179.7 ± 67.2	0.460	182.1 ± 77.4	178.8 ± 66.1	0.538	202.0 ± 88.2	203.1 ± 72.7	0.916
LV end systolic volume (mL)	133.5 ± 67.1	130.4 ± 57.4	0.392	133.0 ± 67.0	126.4 ± 55.7	0.140	147.7 ± 80.2	141.6 ± 66.0	0.545
LA volume (mL)	75.1 ± 35.8	70.8 ± 42.3	0.135	75.4 ± 36.0	78.8 ± 54.9	0.411	97.0 ± 42.9	96.4 ± 66.4	0.954
ICD and medications									
ICD/pacemaker/CRT	87 (20.1)	661 (13.8)	<0.001	83 (20.2)	154 (18.8)	0.546	42 (66.7)	242 (51.4)	0.022
ICD/CRT	66 (15.2)	507 (10.6)	0.003	62 (15.1)	119 (14.5)	0.782	33 (52.4)	220 (46.7)	0.397
Pacemaker	21 (4.8)	154 (3.2)	0.071	21 (5.1)	35 (4.3)	0.501	9 (14.3)	22 (4.7)	0.002
ACE-I or ARB	292 (70.9)	3503 (75.8)	0.028	292 (71.2)	605 (73.8)	0.341	48 (77.4)	386 (83.0)	0.278
β-Blockers	273 (66.3)	3692 (79.9)	< 0.001	272 (66.3)	670 (81.7)	< 0.001	59 (95.2)	423 (91.2)	0.287
Diuretics	330 (80.1)	3772 (81.6)	0.454	328 (80.0)	658 (80.2)	0.919	40 (64.5)	340 (73.1)	0.156
Aldosterone antagonists	240 (58.3)	2751 (59.5)	0.619	239 (58.3)	479 (58.4)	0.967	34 (54.8)	270 (58.1)	0.629

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SR, sinus rhythm. Mean ± standard deviation.
[a]Propensity matched for age, sex, geographical region, income level, and ethnic group.

(NYHA) classification, and had higher prevalence of renal artery stenosis and smoking than the non-COPD group (all $P < 0.05$). The most common presenting symptoms in the COPD group were breathlessness on exertion, orthopnoea, and paroxysmal nocturnal dyspnoea. No significant differences were found between the COPD and non-COPD groups for body mass index, ischaemic aetiology, or the prevalence of hypertension, diabetes mellitus, and atrial fibrillation/flutter or echo parameters, including LV ejection fraction, LV end diastolic volume, LV end systolic volume, and left atrium volume. The average heart rate on electrocardiogram of the COPD group (83 ± 19 b.p.m.) was significantly higher than that of the non-COPD group (81 ± 19 b.p.m.; $P = 0.048$). HF medications were significantly underused in the COPD group. Angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blockers (ARB) were used in 70.9% and 75.8% of patients in the COPD and non-COPD groups, respectively ($P = 0.028$). Similarly, β-blockers were used in 66.3% and 79.9% of patients in the COPD and non-COPD groups, respectively ($P < 0.001$). Conversely, the use of mineralocorticoid receptor antagonists and diuretics was approximately the same between the two groups. HF device therapy (defibrillator, pacemaker, or cardiac resynchronization therapy) was more frequently employed in the COPD group than in the non-COPD group (20.1% vs. 13.8%, respectively, $P < 0.001$), which might be attributed to a more severe HF condition assessed by the NYHA classification in the COPD group.

Independent correlates of chronic obstructive pulmonary disease

Table 2 shows the multivariable associations with COPD after adjustment for the variables listed. Compared with low-income regions, the middle- and high-income regions had 1.81 [95% confidence interval (CI), 1.33–2.47] and 1.82 (95% CI, 1.30–2.54) times higher odds of having COPD, respectively (*Table 2*). COPD was significantly associated with older age, high NYHA classification, renal artery stenosis, smoking, and a high average heart rate on electrocardiography. The prevalence of COPD might lead to the underuse of β-blockers in the overall cohort, but not in the Japanese cohort.

Propensity-matched and Japanese cohorts

Because of significant differences in the baseline characteristics, HFrEF patients were 1:2 matched into a COPD group ($n = 410$) and non-COPD group ($n = 820$) using propensity matching for age, sex, geographical region, income level, and ethnic group as a secondary analysis (*Table 1*). As noted

Table 2 Multivariable associations with chronic obstructive pulmonary disease

Characteristics	Whole cohort		Japanese cohort	
	Adjusted odds ratio (95% confidence intervals)	*P*-value	Adjusted odds ratio (95% confidence intervals)	*P*-value
Age (years)	1.031 (1.021, 1.040)	<0.001	1.025 (1.003, 1.047)	0.026
Income level				
High income	1.82 (1.30, 2.54)	<0.001		
Middle income	1.81 (1.33, 2.47)	<0.001		
Low income	Reference			
NYHA				
Class III/IV	1.37 (1.08, 1.74)	0.010		
Class I/II	Reference			
Diabetes	0.79 (0.62, 1.00)	0.054	0.50 (0.26, 0.96)	0.038
Renal artery stenosis	3.49 (1.60, 7.66)	0.002	6.12 (0.86, 43.44)	0.070
Smoking, current or ex	2.27 (1.75, 2.95)	< 0.001	1.29 (0.74, 2.26)	0.370
ECG heart rate (b.p.m.)	1.007 (1.001, 1.013)	0.016		
ACE-I or ARB	0.93 (0.72, 1.20)	0.594		
β-Blockers	0.47 (0.37, 0.61)	< 0.001	2.12 (0.63, 7.14)	0.228

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; NYHA, New York Heart Association.
Adjusted for female, nocturnal cough, ventricular tachycardia/fibrillation, coronary artery disease, and variables listed.

in the overall cohort, the COPD group had a higher average heart rate and lower usage of β-blockers than the non-COPD group (83 ± 19 b.p.m. vs. 80 ± 19 b.p.m., $P = 0.007$; and 66.3% vs. 81.7%, $P < 0.001$).

Among the Japanese cohort, usage of β-blockers was remarkably high (COPD group: 95.2% vs. non-COPD group: 91.2%, $P = 0.287$) and the average heart rate (COPD group: 75 ± 18 b.p.m. vs. non-COPD group: 74 ± 16 b.p.m., $P = 0.616$) was lower than other cohort data (*Table 1*). No significant differences were found between the COPD and non-COPD groups with respect to other parameters in this cohort.

Proportion of cardioselective and non-cardioselective β-blocker treatment

Table 3 shows usage of cardioselective and non-cardioselective β-blocker treatment for the COPD and non-COPD groups. In all cohorts, the non-COPD group had a higher usage of carvedilol, a non-cardioselective β-blocker, than the COPD group. Whereas in the overall cohort and 1:2 matched cohort, cardioselective β-blockers were used equally in the COPD and non-COPD groups, in the Japanese cohort, the usage of cardioselective β-blockers was twofold higher in the COPD group as compared with the non-COPD group.

Discussion

This analysis of the multi-national ASIAN-HF registry shows that a history of COPD was present in only 8.3% of the overall cohort, with significant variation in geography, regional income level, and ethnicity. The COPD group was significantly older, had higher NYHA classification scores, had higher average heart rate, and had a greater rate of HF device therapy than the non-COPD group in the overall and matched cohorts. Furthermore, β-blockers were significantly underused

Table 3 Proportion of cardioselective and non-cardioselective β-blocker treatment for heart failure patients with and without chronic obstructive pulmonary disease

	Overall cohort			1:2 matched[a] cohort			Japanese cohort		
	With COPD	Without COPD	*P*-value	With COPD	Without COPD	*P*-value	With COPD	Without COPD	*P*-value
N	434 (8.3%)	4798 (91.7%)		410	820		63 (11.8%)	471 (88.2%)	
Any β-blockers	273 (66.3)	3692 (79.9)	<0.001	272 (66.3)	669 (81.7)	<0.001	59 (95.2)	423 (91.2)	0.287
HF guidelines β-blockers[b]	236 (57.3)	3200 (69.2)	<0.001	235 (57.3)	569 (69.5)	<0.001	59 (95.2)	419 (90.1)	0.198
Any cardioselective β-blockers[c]	153 (37.1)	1695 (36.7)	0.849	152 (37.1)	311 (38.0)	0.759	30 (48.4)	108 (23.2)	<0.001
HF guidelines cardioselective β-blockers[d]	149 (36.2)	1651 (35.7)	0.854	148 (36.1)	305 (37.2)	0.695	30 (48.4)	108 (23.2)	<0.001
Carvedilol only	89 (21.6)	1605 (34.7)	<0.001	89 (21.7)	277 (33.8)	<0.001	30 (48.4)	319 (68.6)	0.002

[a]Propensity matched for age, sex, geographical region, income level, and ethnic group.
[b]Bisoprolol, metoprolol, nebivolol, and carvedilol.
[c]Bisoprolol, metoprolol, nebivolol, and atenolol.
[d]Bisoprolol, metoprolol, and nebivolol.

in the COPD group when compared with the non-COPD group in both the overall and propensity-matched cohorts. COPD was significantly correlated with the lower usage of β-blockers in the overall and matched cohorts, but not in the Japanese cohort. The presence of COPD influenced the use of cardioselective β-blockers in the Japanese cohort, with usage being twofold higher in COPD patients than in non-COPD patients.

The high prevalence of smoking, coupled with an ageing population, threatens to further increase the burden of COPD. In addition, a previous report in Japan suggested that COPD is underdiagnosed.[17] The ASIAN-HF registry found a lower rate of COPD diagnosis in the HF cohort than in other studies such as the Acute Decompensated Heart Failure National Registry[18] (27%), Get with the Guidelines registry[19] (26.7%), United States Veterans[20] (26.6%), and Olmsted County[21] (30%). Whether COPD is being underdiagnosed in these countries is unclear, but the findings suggest the need for enhanced screening efforts for COPD in Asians with HF.

COPD is a systemic inflammatory disease characterized by airflow limitation that is not fully reversible.[22] Up to one-third of all deaths in patients with COPD can be attributed to cardiovascular disease, and for every 10% decrease in the forced expiratory volume in 1 s, the risk of cardiovascular mortality reportedly increases by 28%.[23] COPD is a key cause of β-blocker underuse, largely owing to concerns regarding the precipitation of respiratory deterioration in HF patients.[4] Indeed, results from this contemporary study of the ASIAN-HF registry showed significant underuse of β-blockers in HF patients with COPD compared with those without COPD. Furthermore, the mean heart rate of COPD patients was significantly higher than that of non-COPD patients. It is also possible that the relatively high heart rate observed in the COPD group was reflective of increased HF severity, as indicated by more severe NYHA classification relative to the non-COPD group. Importantly, heart rate is directly related to overall risk of death, risk of cardiovascular death, and hospitalization risk in patients with HF,[24] while heart rate reduction is associated with improved outcomes.[25]

In the past, β-blockers were thought to be potentially harmful in patients with COPD. However, several recent studies have demonstrated significant benefits of the use of β-blockers in COPD patients.[26,27] One of these studies showed that β-blockers might reduce the risk of mortality and respiratory exacerbation in patients with COPD.[26] Similarly, a systematic review and meta-analysis of nine retrospective cohort studies reported a reduction in COPD-related mortality of 31% with β-blocker use.[28] Another study clearly demonstrated the safety of β-blockers during COPD exacerbation.[8] Furthermore, the use of β-blockers when started either at the time of hospital admission for myocardial infarction or before myocardial infarction has been shown to be associated with improved survival after myocardial infarction in patients with COPD.[29] We have also reported on the effectiveness of β-blockers in Japanese HF patients with COPD.[30]

The ACE-I or ARB was significantly underused in the COPD group in the overall cohort. The use of ACE-I or ARB might be influenced by the discretion of the treating physicians, because the renal artery stenosis was significantly higher in the COPD group than in the non-COPD group.

Evaluating prospective multi-national data from the ASIAN-HF registry has shown the important influence of both ethnicity and regional income level on the characteristics of HF patients with COPD. Our data suggest that the very high use of β-blockers in Japanese HFrEF patients with COPD shows that these agents may be used safely in Asian patients with these two conditions. Further studies should evaluate long-term data from the ASIAN-HF registry for patients with COPD.

Study limitations

Several limitations associated with the present study warrant consideration. These baseline registry data were cross-sectional in nature, and we were unable to exclude the possibility of selection bias. Bias is inevitable in the selection of sites in each region, and the willingness of patients to participate in a prospective protocol influences enrolment. In previous objective data on the prevalence of COPD in Asia, the COPD prevalence rates were 6.3%.[31] According to the Global Burden of Disease Study, not only each region but also multi-ethnicity in the same country influenced the prevalence rates of COPD.[32] Our results may therefore still underestimate the true burden of HF with COPD in Asia. Furthermore, the use of β-blockers was left to the discretion of the treating physicians in each nation, and the β-blocker doses and COPD grades were unclear. The usage rate of β-blockers in each region might be influenced by different understanding of the safety and usefulness of the β-blockers. This study cohort comprised only HFrEF patients in the ASIAN-HF registry. Owing to the specificity of this population, β-blockers should be considered as standard therapy. However, in patients with severe COPD, low-dose initiation and gradual uptitration are recommended. In the overall cohort, the number of patients with COPD was relatively small. We therefore confirmed the results observed in the overall cohort using the propensity-matched cohort as a way of minimizing confounding factors. It is noted that the prevalence of COPD in the Japanese cohort was low.

Conclusions

In the Asian HF registry, COPD prevalence showed significant variation according to geography, regional income level, and

ethnicity. The prevalence of COPD was strongly related to the underuse of β-blockers, in patients with both HF and COPD.

Acknowledgements

Current site investigators of the ASIAN-HF study are as follows.

China

Ruijin Hospital, Shanghai Jiao Tong University School of Medicine: Liqun Wu. Fuwai Hospital: Shu Zhang. Jiangsu Province People's Hospital: Xinli Li. Zhongshan Hospital Fudan University: Yangang Su.

Hong Kong

The Chinese University of Hong Kong: Cheuk Man Yu.

India

Sir Ganga Ram Hospital: Jitendra Sawhney. West Fort Hi-Tech Hospital Ltd: Mohanan Padinhare Purayil. Dayanand Medical College and Hospital: Gurpreet Singh Wander. Medanta The Medicity: Vijay Chopra. Care Institute of Medical Sciences: Ajay Naik. Care Hospital: Narasimhan Calambur.

Indonesia

Rumah Sakit Khusus Jantung Binawaluya: Muhammad Munawar. Rumah Sakit Hasan Sadikin: Pintoko Tedjokusumo. Harapan Kita National Cardiovascular Center: Bambang Budi Siswanto. Siloam Karawaci Hospital: Antonia A. Lukito.

South Korea

Korea University Anam Hospital: Jaemin Shim. Korea University Guro Hospital: Jin Oh Na. Severance Hospital, Yonsei University Health System: Boyoung Joung. Chonnam National University Hospital: Hyung-Wook Park. Hyewon Medical Foundation Sejong General Hospital: Suk Keun Hong. Korea University Ansan Hospital: Seong Hwan Kim.

Malaysia

Institut Jantung Negara: Razali Omar. University Malaya Medical Centre: Imran Zainal Abidin. Hospital Queen Elizabeth II: Houng Bang Liew. Sarawak General Hospital: Tiong Kiam Ong.

Philippines

Philippine Heart Center: Eleanor Lopez. Makati Medical Center: Raul Lapitan. Manila Doctors Hospital: Eugenio Reyes.

Singapore

National Heart Centre: Kheng Leng David Sim. Tan Tock Seng Hospital: Poh Shuan Daniel Yeo. Changi General Hospital-Parent: Kui Toh Gerard Leong. Singapore General Hospital-Parent: Fazlur Rehman Jaufeerally. Khoo Teck Puat Hospital: Hean Yee Ong.

Taiwan

Mackay Memorial Hospital: Chung-Lieh Hung. National Taiwan University Hospital: Juey-Jen Hwang. Taipei Veterans General Hospital: Wen-Chung Yu. China Medical University Hospital: Hsin-Yueh Liang.

Thailand

Phramongkutklao Hospital: Waraporn Tiyanon. Maharaj Nakorn Chiang Mai Hospital: Wanwarang Wongcharoen. Ramathibodi Hospital: Tachapong Ngarmukos.

Japan

National Cerebral and Cardiovascular Center: Takashi Noda, Mitsuru Wada, Kohei Ishibashi. Tokyo Women's Medical University: Atsushi Suzuki, Takeshi Suzuki. Kinki University: Ryoubun Yasuoka. Toho University Omori Medical Center: Sinji Hisatake, Shunsuke Kiuchi, Takayuki Kabuki. Nippon Medical School Hospital: Yuki Izumi.

Conflict of interest

None declared.

Funding

The ASIAN-HF study is funded by the Investigator-Sponsored Research Program of Boston Scientific, via a competitive grant for investigator-initiated studies awarded to the Cardiovascular Research Institute, Singapore. Recruitment of

patients in Singapore is partially supported by the Singapore Heart Failure Outcomes and Phenotypes study, funded by the National Medical Research Council of Singapore [centre grant principal investigator (PI): A.M.R, theme PI: C.S.P.L]. C.S.P.L is supported by a Clinician Scientist Award from the National Medical Research Council.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Prevalence of COPD and usage of β-blockers by region and stage of economic development.
Table S2. Prevalence of COPD and usage of β-blockers by ethnicity.

References

1. Lainscak M, Cleland JG, Lenzen MJ, Follath F, Komajda M, Swedberg K. International variations in the treatment and co-morbidity of left ventricular systolic dysfunction: data from the EuroHeart Failure Survey. *Eur J Heart Fail* 2007; **9**: 292–299.
2. Sin DD, McAlister FA. The effects of beta-blockers on morbidity and mortality in a population-based cohort of 11,942 elderly patients with heart failure. *Am J Med* 2002; **113**: 650–656.
3. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, Dietz R, Gavazzi A, Van Gilst WH, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, Widimsky J, Freemantle N, Eastaugh J, Mason J. The EuroHeart Failure Survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. *Eur Heart J* 2003; **24**: 464–474.
4. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009; **11**: 130–139.
5. Holguin F, Folch E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005; **128**: 2005–2011.
6. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; **63**: 301–305.
7. Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *BMJ* 2011; **342**: d2549.
8. Stefan MS, Rothberg MB, Priya A, Pekow PS, Au DH, Lindenauer PK. Association between β-blocker therapy and outcomes in patients hospitalised with acute exacerbations of chronic obstructive lung disease with underlying ischaemic heart disease, heart failure or hypertension. *Thorax* 2012; **67**: 977–984.
9. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; **29**: 2388–2442.
10. Al-Mohammad A, Mant J. The diagnosis and management of chronic heart failure: review following the publication of the NICE guidelines. *Heart* 2011; **97**: 411–416.
11. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015; **17**: 884–892.
12. Atherton JJ, Hayward CS, Wan Ahmad WA, Kwok B, Jorge J, Hernandez AF, Liang L, Kociol RD, Krum H. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International-Asia Pacific). *J Card Fail* 2012; **18**: 82–88.
13. Mentz RJ, Roessig L, Greenberg BH, Sato N, Shinagawa K, Yeo D, Kwok BW, Reyes EB, Krum H, Pieske B, Greene SJ, Ambrosy AP, Kelly JP, Zannad F, Pitt B, Lam CS. Heart failure clinical trials in East and Southeast Asia: understanding the importance and defining the next steps. *JACC Heart Fail* 2016; **4**: 419–427.
14. Lam CS, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto B, Ling LH, Richards AM. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. *Eur J Heart Fail* 2013; **15**: 928–936.
15. Lam CS, Teng TK, Tay WT, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto BB, Hung CL, Ling LH, Yap J, MacDonald M, Richards AM. Regional and ethnic differences among patients with heart failure in Asia: the Asian Sudden Cardiac Death in Heart Failure registry. *Eur Heart J* 2016; **37**: 3141–3153.
16. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013; **187**: 347–365.
17. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, Takahashi K, Nishimura K, Ishioka S, Aizawa H, Zaher C. COPD in Japan: the Nippon COPD Epidemiology study. *Respirology* 2004; **9**: 458–465.
18. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006; **47**: 76–84.
19. Cheng RK, Cox M, Neely ML, Heidenreich PA, Bhatt DL, Eapen ZJ, Hernandez AF, Butler J, Yancy CW, Fonarow GC. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. *Am Heart J* 2014; **168**: 721–730.
20. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XH, Deswal A. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 2012; **59**: 998–1005.
21. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and

diastolic heart failure in the community. *JAMA* 2006; **296**: 2209–2216.
22. Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008; **31**: 204–212.
23. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; **32**: 962–969.
24. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J* 2006; **27**: 65–75.
25. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol* 2008; **101**: 865–869.
26. Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2010; **170**: 880–887.
27. 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.
28. Etminan M, Jafari S, Carleton B, FitzGerald JM. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. *BMC Pulm Med* 2012; **12**: 48.
29. Quint JK, Herrett E, Bhaskaran K, Timmis A, Hemingway H, Wedzicha JA, Smeeth L. Effect of beta blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ* 2013; **347**: f6650.
30. Kubota Y, Asai K, Furuse E, Nakamura S, Murai K, Tsukada YT, Shimizu W. Impact of beta-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.
31. Regional COPD Working Group. COPD prevalence in 12 Asia-Pacific countries and regions: projections based on the COPD prevalence estimation model. *Respirology* 2003; **8**: 192–198.
32. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020:global burden of disease study. *Lancet* 1997; **349**: 1498–1150.