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

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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

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. Nonetheless, low-dose initiation and gradual uptitration are recommended in the guidelines. In Asia, ageing populations and large increases in cardiovascular risk factors have contributed to a high burden of HF. Patients with HFRF from Asia may differ in clinical characteristics from patients elsewhere. 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 HFRF enrolled from 1 October 2012 to 31 December 2015, with special reference to COPD and its treatment.

Methods

Study design

The ASIAN-HF registry was a prospective observational registry of symptomatic patients with HFRF 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. HFRF 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). 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. 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, χ² 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 HFRF 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...
| Demographics | Overall cohort | 1:2 matched cohort | Japanese cohort |
|--------------|---------------|--------------------|-----------------|
| Age (years)  | 63.9 ± 13.7   | 64.2 ± 12.7        | 64.6 ± 13.7     |
| Male         | 347 (80.0)    | 330 (80.5)         | 50 (79.4)       |
| Geographical region | 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 | 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 (22.5) |
| Presenting characteristics | NYHA class, I/II/III/IV (%) 11/45/33/8 | 12/44/33/11 13/52/30/5 |
| Shortness of breath on exertion | 349 (80.4) 3567 (74.4) | 328 (80.0) 608 (74.2) |
| Reduction in exercise tolerance | 318 (73.3) 3346 (69.8) | 301 (73.4) 553 (67.5) |
| Nocturnal cough | 115 (26.5) 841 (17.5) | 109 (26.6) 174 (21.2) |
| Orthopnoea   | 137 (31.6) 1046 (21.8) | 132 (32.2) 4 (7.9) |
| Paroxysmal nocturnal dyspnoea | 116 (26.7) 878 (18.3) | 112 (27.3) 156 (19.0) |
| Angina       | 67 (15.5) 530 (11.1) | 62 (15.2) 93 (11.3) |
| Systolic blood pressure (mmHg) | 119.4 ± 19.0 118.3 ± 20.3 | 119.3 ± 19.0 118.8 ± 19.9 |
| Diastolic blood pressure (mmHg) | 83.3 ± 18.9 81.3 ± 19.0 | 83.3 ± 18.9 81.3 ± 19.0 |
| Heart rate (b.p.m.) | 74.7 ± 18.1 73.6 ± 15.9 | 74.7 ± 18.1 73.6 ± 15.9 |
| Body mass index (kg/m²) | 24.8 ± 6.2 24.9 ± 5.0 | 24.8 ± 6.2 24.9 ± 5.0 |
| eGFR (mL/min/1.73 m²) | 63.8 ± 10.8 64.1 ± 30.4 | 63.8 ± 10.8 64.1 ± 30.4 |
| LVEF (%)     | 27.8 ± 7.2 27.3 ± 7.0 | 27.8 ± 7.2 28.2 ± 6.6 |
| Medical history | Aetiology HF, ischemic 213 (49.1) 2245 (46.8) | 201 (49.0) 418 (51.0) |
| Ventricular tachycardia/fibrillation | 44 (10.1) 362 (7.5) | 40 (9.8) 70 (8.6) |
| Coronary artery disease | 214 (49.3) 2411 (50.3) | 200 (48.8) 457 (55.8) |
| Atinal fibrillation/flutter | 83 (19.1) 851 (17.7) | 79 (19.3) 188 (23.0) |
| Hypertension | 236 (54.4) 2475 (51.6) | 227 (55.4) 467 (57.0) |
| Diabetes     | 167 (38.5) 1948 (40.6) | 158 (38.5) 374 (45.7) |
| Stroke       | 31 (7.1) 305 (6.4) | 30 (7.3) 58 (7.1) |
| Peripheral arterial vascular disease | 26 (6.0) 152 (3.2) | 25 (6.1) 55 (5.4) |
| Renal artery stenosis | 10 (2.3) 36 (0.8) | 10 (2.4) 8 (0.1) |
| Smoking, current or ex | 261 (60.1) 2093 (42.1) | 254 (62.0) 388 (47.4) |
| Alcohol, current or ex | 153 (35.3) 1359 (28.4) | 156 (38.1) 234 (28.6) |
| 12-lead ECG | ECG rhythm, SR/AF/others or unknown (%) | 64/11/25 70/12/18 | 64/12/24 66/15/19 |
| ECG heart rate (b.p.m.) | 83.3 ± 19.0 81.3 ± 19.0 | 83.3 ± 19.1 80.1 ± 18.8 |
| Left bundle brunch block | 63 (15.0) 628 (13.8) | 58 (14.6) 97 (12.5) |
| Right bundle brunch block | 39 (10.5) 350 (8.7) | 35 (10.0) 60 (8.9) |
| QRS duration (ms) | 117.6 ± 32.2 115.1 ± 32.4 | 117.6 ± 32.0 116.8 ± 32.4 |
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 left ventricular ejection fraction, left ventricular end diastolic 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 II 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, \( \beta \)-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 (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.

**Table 2**: 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 (\( P < 0.001 \)). Similarly, 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 (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.
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 in the COPD group.

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    | 1.82 (1.30, 2.54) | <0.001 | 1.81 (1.33, 2.47) | <0.001 |
| High income     | 0.79 (0.62, 1.00) | 0.054 | 0.50 (0.26, 0.96) | 0.038 |
| Middle income   | 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 |
| NYHA            | 1.37 (1.08, 1.74) | 0.010 | 2.12 (0.63, 7.14) | 0.228 |
| Diagnoses       | 0.93 (0.72, 1.20) | 0.594 | 0.93 (0.72, 1.20) | 0.594 |
| β-Blockers      | 0.47 (0.37, 0.61) | <0.001 | 0.47 (0.37, 0.61) | <0.001 |

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.

| 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 matcheda cohort | Japanese cohort |
| N       | With COPD | Without COPD | P-value | With COPD | Without COPD | P-value | With COPD | Without COPD | P-value |
| Any β-blockers | 434 (8.3%) | 4798 (91.7%) | 0.001 | 273 (66.3%) | 3692 (79.9%) | <0.001 | 236 (57.3%) | 3200 (69.2%) | <0.001 |
| HF guidelines β-blockersb | 236 (57.3%) | 3200 (69.2%) | <0.001 | 235 (57.3%) | 3200 (69.2%) | <0.001 | 236 (57.3%) | 3200 (69.2%) | <0.001 |
| Any cardioselective β-blockersc | 153 (37.1%) | 1695 (36.7%) | 0.849 | 152 (37.1%) | 311 (38.0%) | 0.759 | 152 (37.1%) | 311 (38.0%) | 0.759 |
| HF guidelines cardioselective β-blockersd | 149 (36.2%) | 1651 (35.7%) | 0.854 | 148 (36.1%) | 305 (37.2%) | 0.695 | 148 (36.1%) | 305 (37.2%) | 0.695 |
| 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 |

aPropensity matched for age, sex, geographical region, income level, and ethnic group.
bBisoprolol, metoprolol, nebivolol, and carvedilol.
cBisoprolol, metoprolol, nebivolol, and atenolol.
dBisoprolol, metoprolol, and nebivolol.

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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 Registry18 (27%), Get with the Guidelines registry19 (26.7%), United States Veterans20 (26.6%), and Olmsted County21 (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 up titration 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.

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Conflict of interest

None declared.

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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 β-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, Prada 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 β-blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; 63: 301–305.

7. Short PM, Lipworth S1, Elder DH, Schembri S, Lipworth BJ. Effect of β-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, Lindenauner 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, Shigahara 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, Siawanto 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.

15. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbi 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.

16. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, Takahashi K, Nishimura K, Ishioka S, Aizawa H, Zaker C. COPD in Japan: the Nippon COPD Epidemiology study. *Respirology* 2004; 9: 458–465.

17. 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 ADHERE National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006; 47: 76–84.

18. 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.

19. Ather S, Chan W, Bozkurt B, Aguilar D, Ransamubbi 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: 1005–1015.

20. 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: 1498–1504.