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ORIGINAL RESEARCH

The Impact of Beta-Blockers and Renin-Angiotensin-Aldosterone System Inhibitors on the Prognosis of Atrial Fibrillation Patients with Chronic Obstructive Pulmonary Disease: A Nation-Wide Registry Study

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Purpose: The management of the coexistence of chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF) remains unclear due to a lack of evidence. This study aimed to find the effect of beta-blockers and renin-angiotensin-aldosterone system inhibitors (RAASi) in this special population.

Patients and Methods: We designed an observational real-world study that included 2016 AF patients from 20 hospitals across the country. The diagnosis of COPD was extracted from case report forms and confirmed by specialists. The study endpoint was all-cause mortality. Kaplan-Meier curves and Log rank test were used to analyse the prognosis of different treatments. Several multivariable Cox regression models were performed to identify the independent prognostic value of the medications.

Results: Approximately 30% of patients were prescribed beta-blockers or RAASi. Survival curves showed that beta-blockers did not affect all-cause mortality in AF patients with COPD (P=0.130). Patients with RAASi had a better prognosis than those without (P=0.011). After multivariable Cox regression analysis adjusting for demographics, other comorbidities and treatments, beta-blockers and angiotensin II receptor blockers (ARB) did not independently affect the endpoint. Angiotensin converting enzyme inhibitors (ACEI) remained a protective factor for overall survival in AF patients with COPD (model 1: HR=0.45, 95% CI 0.21–0.98, P=0.045; model 2: HR=0.41, 95% CI 0.18–0.93, P=0.034; model 3: HR=0.38, 95% CI 0.16–0.89, P=0.026).

Conclusion: Beta-blockers did not affect overall survival in patients with AF and COPD, whereas ACEI may be protective.

Keywords: atrial fibrillation, chronic obstructive pulmonary disease, beta-blockers, renin-angiotensin-aldosterone system

Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia and has a negative impact on patients' overall survival. Recent guidelines on AF strongly recommend the management of comorbidities as a central part of clinical practice.[1] Chronic obstructive pulmonary disease (COPD) has a strong and complex relationship with AF. From an etiological point of view, the imbalance in oxygen delivery caused by COPD may increase arterial blood pressure and cardiac remodeling, which is an important mechanism of AF.[2] From a treatment point of view, taking beta-blockers as an example, once AF patients are combined with COPD, this could be a thorny issue for both cardiologists and pulmonologists because of the

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side effect of airway spasm. It has also been reported that renin-angiotensin-aldosterone system inhibitors (RAASi) may improve lung function and slow the progression of emphysema, but this has not been widely recognized in practice.[3]

Our previous study had revealed the prevalence and survival of AF patients combined with COPD from a nation-wide cohort study.[4] We also found that RAASi was independently associated with less death and major adverse cardiovascular events in patients with AF and hypertension, but it has not been tested in AF patients with COPD.[5] Therefore, in this study, we try to analyze the effect of beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) on the prognosis of this specific population.

Materials and Methods

Study Design

Patients were enrolled from a multi-center, observational research in the real-world aimed to analyze the clinical characteristics, management and outcomes of AF patients in emergency departments. Data were post-hoc analyzed retrospectively. They were recruited from 20 different grade hospitals across China between November 2008 and October 2011. Inclusion criteria were individuals diagnosed with AF by electrocardiography and signed informed consent. The diagnosis of COPD was obtained from case report forms and confirmed by specialist cardiologists and pulmonologists at the time of enrolment. The study was approved by the ethics committee of each center (approval number: 2008–143) and adhered to the Declaration of Helsinki.

Baseline and Follow-Up

We collected baseline information including sex, age, body mass index (BMI), blood pressure, heart rate, previous medical history and medications. Data were recorded on standardized case report forms in all centers by interviewing patients, physicians or reviewing medical records. BMI, blood pressure and heart rate were measured in the first time of admission. Previous comorbidities included myocardial infarction, coronary artery disease, heart failure, hypertension, levy left ventricular hypertrophy (LVH) by electrocardiogram (ECG) or echocardiogram, previous stroke or transient ischemic attack (TIA), sleep apnea, tobacco use, left ventricular systolic dysfunction [LVSD, left ventricular ejection fraction (LVEF) <45%], dementia, hyperthyroidism, diabetes mellitus and prior major bleeding. Treatments, mainly related to AF and other cardiovascular comorbidities, included diuretics, beta-blockers, ACEI, ARB, calcium channel blockers, digoxin, aspirin, clopidogrel and warfarin. Follow-up was 1 year and was conducted by medical record review, telephone or outpatient visits. The study endpoint was all-cause mortality.

Statistical Analysis

Continuous variables were expressed as medians with interquartile ranges and analyzed using the Mann–Whitney *U*-test. Categorical variables were expressed as frequencies with percentages and compared by chi-squared test. Univariate and multivariate logistic regression and odds ratio (OR) were used to identify clinical factors associated with different treatments. Kaplan-Meier curves and Log rank test were used to compare the survival of AF patients with and without beta-blockers and RAASi. Univariate Cox proportional hazards regression was used for all-cause mortality. Variables that were considered clinically relevant to outcome were entered into multivariate Cox proportional-hazards regression model. Given the available sample size and number of events, variables for inclusion were carefully selected to ensure parsimony of the final model. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. All tests were two-sided, and P value <0.05 was considered statistically significant. R version 4.4.0 was used for statistical analysis and figures.

Results

A total of 2016 AF patients were recruited into our cohort and 236 AF patients with COPD were included in this study. Of these, 50.8% were male and the median age was 76 years. Seventy-three (30.9%) patients were prescribed beta-blockers and ninety (38.1%) patients were using RAASi. Baseline characteristics are shown in Tables 1 and 2. Both groups had a higher proportion of coronary artery disease (beta-blockers: 65.8%, RAASi: 72.2%) and hypertension (beta-

Table 1 Baseline Characteristics of AF and COPD Patients with and without Beta-Blockers

N	Overall 236	Without Beta-blockers 163	With Beta-blockers 73	*P*
Male [n (%)]	120 (50.8)	83 (50.9)	37 (50.7)	0.999
Age (year)	76.00 [71.00, 81.25]	77.00 [71.00, 82.00]	75.00 [70.00, 80.00]	0.336
BMI (kg/m2])	23.18 [20.77, 25.30]	22.86 [20.36, 25.03]	23.46 [21.97, 25.71]	0.083
SBP (mmHg)	137.00 [122.50, 150.00]	139.00 [124.00, 152.00]	134.00 [120.00, 150.00]	0.294
DBP (mmHg)	80.00 [70.00, 90.00]	80.00 [71.00, 90.00]	80.00 [70.00, 90.00]	0.297
Heart rate (beat/min)	100.00 [81.00, 120.50]	100.00 [82.00, 121.00]	100.00 [81.00, 120.00]	0.812
AF type [n (%)]				0.056
Persistent	48 (20.3)	39 (23.9)	9 (12.3)	
Paroxysmal	54 (22.9)	32 (19.6)	22 (30.1)	
Permanent	134 (56.8)	92 (56.4)	42 (57.5)	
Myocardial Infarction [n (%)]	21 (8.9)	8 (4.9)	13 (17.8)	0.003
Coronary artery disease [n (%)]	131 (55.5)	83 (50.9)	48 (65.8)	0.048
Heart failure [n (%)]	113 (47.9)	85 (52.1)	28 (38.4)	0.069
Hypertension [n (%)]	138 (58.5)	85 (52.1)	53 (72.6)	0.005
LVH [n (%)]	39 (16.5)	30 (18.4)	9 (12.3)	0.331
Previous stroke or TIA [n (%)]	53 (22.5)	29 (17.8)	24 (32.9)	0.016
Sleep apnea [n (%)]	8 (3.4)	7 (4.3)	1 (1.4)	0.448
Tobacco use [n (%)]	77 (32.6)	56 (34.4)	21 (28.8)	0.486
LVSD [n (%)]	51 (21.6)	35 (21.5)	16 (21.9)	0.999
Dementia [n (%)]	9 (3.8)	7 (4.3)	2 (2.7)	0.835
Diabetes mellitus [n (%)]	38 (16.1)	24 (14.7)	14 (19.2)	0.504
Hyperthyroidism [n (%)]	5 (2.1)	3 (1.8)	2 (2.7)	0.999
Prior major bleeding [n (%)]	7 (3.0)	4 (2.5)	3 (4.1)	0.781
CHA_2DS_2-VaSc score	4.00 [2.75, 5.00]	4.00 [2.00, 5.00]	4.00 [3.00, 5.00]	0.032
Diuretic [n (%)]	98 (41.5)	63 (38.7)	35 (47.9)	0.232
Digoxin [n (%)]	88 (37.3)	62 38.0)	26 (35.6)	0.834
Warfarin [n (%)]	26 (11.0)	17 (10.4)	9 (12.3)	0.837

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; LVH, levy left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; SBP, systolic blood pressure; TIA, transient ischemic attack.

Table 2 Baseline Characteristics of AF and COPD Patients with and without RAASi

N	Overall 236	Without RAASi 146	With RAASi 90	*P*
Male [n (%)]	120 (50.8)	76 (52.1)	44 (48.9)	0.735
Age (year)	76.00 [71.00, 81.25]	76.00 [71.00, 81.00]	76.00 [71.00, 82.00]	0.655
BMI (kg/m2])	23.18 [20.77, 25.30]	22.85 [20.34, 24.78]	23.44 [21.40, 25.95]	0.05
SBP (mmHg)	137.00 [122.50, 150.00]	139.50 [120.00, 151.50]	134.50 [126.50, 150.00]	0.968
DBP (mmHg)	80.00 [70.00, 90.00]	80.00 [70.00, 90.00]	80.00 [70.00, 90.00]	0.653
Heart rate (beat/min)	100.00 [81.00, 120.50]	100.00 [81.00, 120.00]	99.50 [82.25, 123.00]	0.954
AF type [n (%)]				0.083
Persistent	48 (20.3)	35 (24.0)	13 (14.4)	
Paroxysmal	54 (22.9)	36 (24.7)	18 (20.0)	
Permanent	134 (56.8)	75 (51.4)	59 (65.6)	
Myocardial Infarction [n (%)]	21 (8.9)	10 (6.8)	11 (12.2)	0.241
Coronary artery disease [n (%)]	131 (55.5)	66 (45.2)	65 (72.2)	<0.001
Heart failure [n (%)]	113 (47.9)	67 (45.9)	46 (51.1)	0.518
Hypertension [n (%)]	138 (58.5)	67 (45.9)	71 (78.9)	<0.001

(*Continued*)

Table 2 (Continued).

N	Overall 236	Without RAASi 146	With RAASi 90	*P*
LVH [n (%)]	39 (16.5)	21 (14.4)	18 (20.0)	0.343
Previous stroke or TIA [n (%)]	53 (22.5)	30 (20.5)	23 (25.6)	0.462
Sleep apnea [n (%)]	8 (3.4)	5 (3.4)	3 (3.3)	0.999
Tobacco use [n (%)]	77 (32.6)	45 (30.8)	32 (35.6)	0.542
LVSD [n (%)]	51 (21.6)	25 (17.1)	26 (28.9)	0.049
Dementia [n (%)]	9 (3.8)	8 (5.5)	1 (1.1)	0.176
Diabetes mellitus [n (%)]	38 (16.1)	16 (11.0)	22 (24.4)	0.011
Hyperthyroidism [n (%)]	5 (2.1)	2 (1.4)	3 (3.3)	0.581
Prior major bleeding [n (%)]	7 (3.0)	3 (2.1)	4 (4.4)	0.512
CHA_2DS_2-VaSc score	4.00 [2.75, 5.00]	3.00 [2.00, 4.00]	4.00 [3.00, 5.00]	<0.001
Diuretic [n (%)]	98 (41.5)	43 (29.5)	55 (61.1)	<0.001
Digoxin [n (%)]	88 (37.3)	45 (30.8)	43 (47.8)	0.013
Warfarin [n (%)]	26 (11.0)	16 (11.0)	10 (11.1)	0.999

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; LVH, levy left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; SBP, systolic blood pressure; TIA, transient ischemic attack.

blockers: 72.6%, RAASi: 78.9%). Patients with beta-blockers were more likely to have combined with myocardial infarction (4.9% vs 17.8%, *P*=0.003) and previous stroke or TIA (17.8% vs 32.9%, *P*=0.016), whereas patients with RAASi had higher BMI (22.85 vs 23.44, *P*=0.050), higher rates of LVSD (17.1% vs 28.9%, *P*=0.049) and diabetes mellitus (11.0% vs 24.4%, *P*=0.011).

In univariate logistic regression analysis, patients with beta-blockers were more associated with paroxysmal AF, coronary arterial disease, myocardial infarction, hypertension and stroke or TIA. However, in multivariate analysis, these associations were not statistically significant (Table 3). Patients with RAASi were significantly associated with more tobacco use (Table 4).

Table 3 Logistic Regression Analysis of Associated Factors of AF Patients with Beta-Blockers

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Female	1.01 (0.58–1.76)	0.973	1.13 (0.34–3.79)	0.840
Age	0.99 (0.96–1.02)	0.556	0.97 (0.91–1.04)	0.457
BMI	1.06 (0.99–1.14)	0.109	1.06 (0.97–1.15)	0.209
SBP	0.99 (0.98–1.00)	0.087	0.98 (0.97–1.00)	0.091
DBP	0.99 (0.97–1.00)	0.107	1.00 (0.97–1.02)	0.803
Heart rate	1.00 (0.99–1.01)	0.950	1.01 (0.99–1.02)	0.411
AF_type				
Paroxysmal	2.98 (1.24–7.67)	0.018	2.04 (0.73–5.93)	0.180
Permanent	1.98 (0.91–4.69)	0.099	1.95 (0.79–5.19)	0.161
Myocardial Infarction	4.20 (1.68–11.09)	0.002	4.20 (0.94–20.05)	0.064
Coronary artery disease	1.85 (1.05–3.32)	0.035	1.29 (0.62–2.68)	0.494
Heart failure	0.57 (0.32–1.00)	0.051	0.48 (0.15–1.56)	0.228
Hypertension	2.43 (1.35–4.50)	0.004	3.35 (0.93–12.52)	0.067
LVH	0.62 (0.27–1.34)	0.248	0.39 (0.12–1.13)	0.093

(*Continued*)

Table 3 (Continued).

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Previous stroke or TIA	2.26 (1.20–4.26)	0.011	2.10 (0.29–15.62)	0.465
Sleep apnea	0.31 (0.02–1.78)	0.277	0.22 (0.01–1.58)	0.198
Tobacco use	0.77 (0.42–1.39)	0.398	1.41 (0.64–3.15)	0.396
LVSD	1.03 (0.52–1.98)	0.939	1.90 (0.69–5.38)	0.217
Dementia	0.63 (0.09–2.67)	0.568	0.27 (0.03–1.75)	0.209
Diabetes mellitus	1.37 (0.65–2.81)	0.391	0.73 (0.20–2.60)	0.624
Hyperthyroidism	1.50 (0.19–9.25)	0.660	1.00 (0.09–8.56)	0.999
Prior major bleeding	1.70 (0.33–7.92)	0.493	2.80 (0.33–24.90)	0.339
CHA_2DS_2-VaSc score	1.20 (1.02–1.42)	0.030	0.87 (0.35–2.18)	0.768

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; LVH, levy left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; SBP, systolic blood pressure; TIA, transient ischemic attack.

Table 4 Logistic Regression Analysis of Associated Factors of AF Patients with RAASi

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Female	1.14 (0.67–1.92)	0.637	1.04 (0.32–3.40)	0.952
Age	1.01 (0.98–1.04)	0.461	0.97 (0.90–1.04)	0.374
BMI	1.07 (1.00–1.15)	0.066	1.04 (0.95–1.13)	0.384
SBP	1.00 (0.99–1.01)	0.765	1.00 (0.99–1.02)	0.703
DBP	1.00 (0.98–1.01)	0.746	0.98 (0.95–1.01)	0.129
Heart rate	1.00 (0.99–1.01)	0.790	1.01 (1.00–1.03)	0.036
AF_type				
Paroxysmal	1.35 (0.58–3.20)	0.494	0.90 (0.31–2.62)	0.840
Permanent	2.12 (1.05–4.49)	0.042	1.77 (0.74–4.40)	0.208
Myocardial Infarction	1.89 (0.77–4.74)	0.164	0.87 (0.19–4.05)	0.855
Coronary artery disease	3.15 (1.81–5.61)	<0.001	2.86 (1.39–6.08)	0.005
Heart failure	1.23 (0.73–2.09)	0.436	0.71 (0.22–2.29)	0.574
Hypertension	4.41 (2.45–8.21)	<0.001	3.51 (1.00–12.86)	0.053
LVH	1.49 (0.74–2.98)	0.261	0.68 (0.24–1.86)	0.459
Previous stroke or TIA	1.33 (0.71–2.47)	0.371	0.52 (0.07–3.98)	0.532
Sleep apnea	0.97 (0.20–4.06)	0.970	1.20 (0.20–6.34)	0.829
Tobacco use	1.24 (0.71–2.16)	0.452	3.68 (1.64–8.62)	0.002
LVSD	1.97 (1.05–3.70)	0.035	2.25 (0.90–5.78)	0.087
Dementia	0.19 (0.01–1.08)	0.125	0.04 (0.00–0.37)	0.022
Diabetes mellitus	2.63 (1.30–5.41)	0.007	1.51 (0.43–5.38)	0.523
Hyperthyroidism	2.48 (0.40–19.13)	0.324	8.39 (0.53–106.53)	0.098
Prior major bleeding	2.22 (0.48–11.48)	0.305	3.20 (0.20–90.24)	0.421
CHA_2DS_2-VaSc score	1.34 (1.14–1.59)	0.001	1.38 (0.55–3.50)	0.492

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; LVH, levy left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; SBP, systolic blood pressure; TIA, transient ischemic attack.

During one year, 8 participants were lost to follow-up and 228 patients were included for further analysis (our previous study included only 227 AF and COPD patients, as the age of the patients was limited to 22–96 years). Log-rank analysis showed that beta-blockers did not affect overall survival in AF patients with COPD, but there was a trend

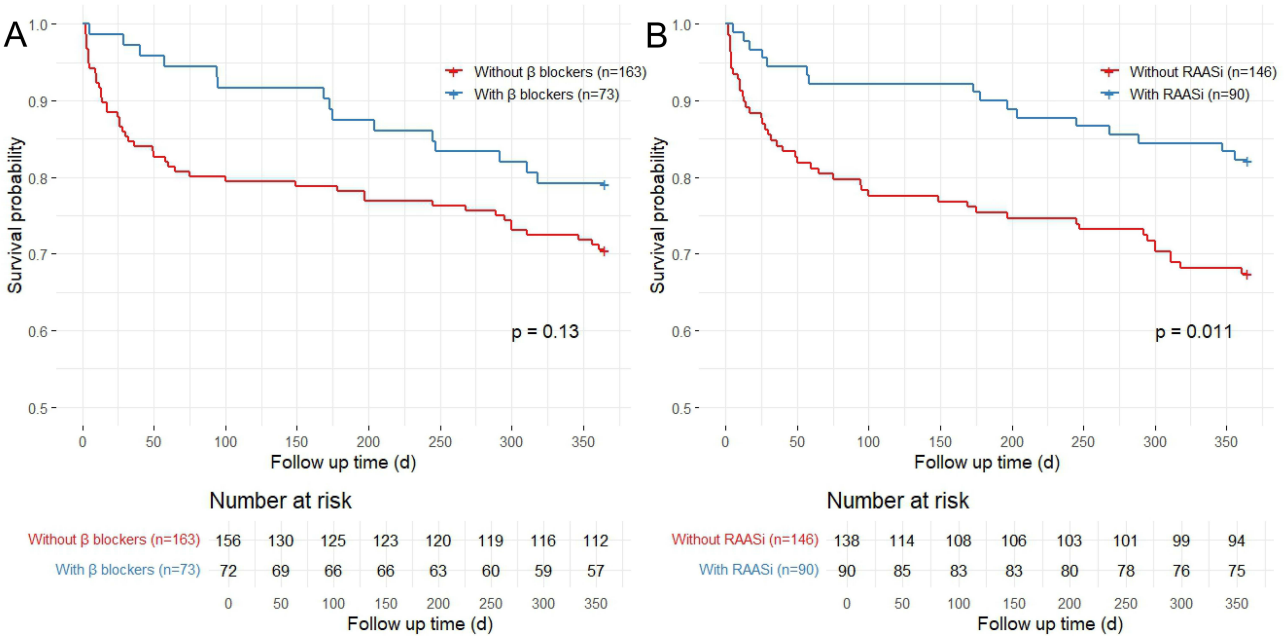

Figure 1 Kaplan–Meier curves comparing with and without beta blockers (**A**) and renin-angiotensin-aldosterone system inhibitors (RAASi) (**B**) in AF patients compared with COPD.

towards longer survival times (*P*=0.130, Figure 1A). The prognosis was significantly better in patients with RAASi (*P*=0.011, Figure 1B) compared to those without RAASi.

Several multivariable Cox models were conducted to find relationships between treatments and prognosis (Figure 2). Model 1 included sex, age, BMI, blood pressure and heart rate. Model 2 additionally adjusted for comorbidities including myocardial infarction, coronary artery disease, heart failure, hypertension, LVH, previous stroke or TIA, tobacco use, LVSD and diabetes mellitus. Model 3 additionally adjusted for other cardiovascular medications, such as diuretics, digoxin and anticoagulants. In these multi-adjusted models, beta-blockers and ARB showed no significant associations with all-cause mortality. ACEI was significantly associated with lower mortality (model 1: HR=0.45, 95% CI 0.21–0.98, *P*=0.045; model 2: HR=0.41, 95% CI 0.18–0.93, *P*=0.034; model 3: HR=0.38, 95% CI 0.16–0.89, *P*=0.026). Although

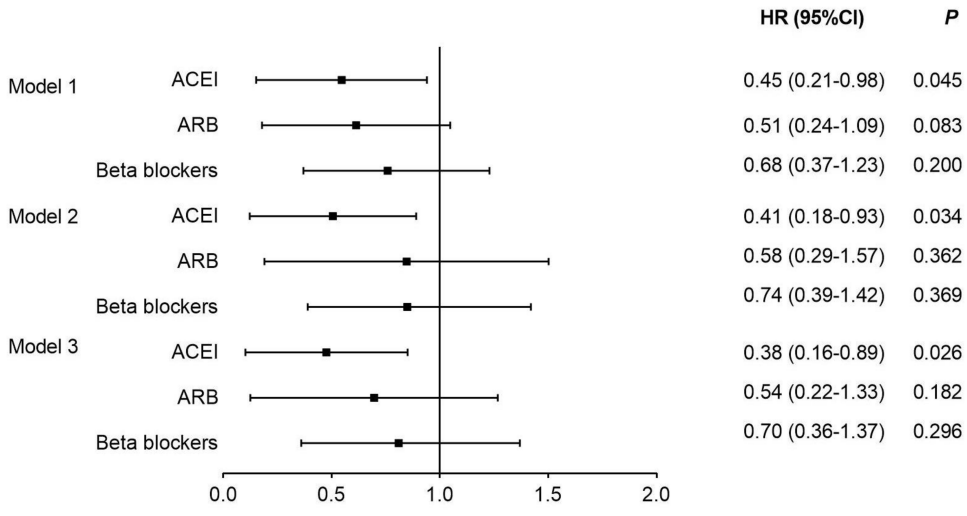

Figure 2 Multivariable adjusted Cox proportional hazard models to evaluate the associations between angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), beta blockers and endpoint. Model 1: Adjusting sex, age, body mass index, blood pressure and heart rate. Model 2: Adjusting sex, age, body mass index, blood pressure, heart rate and comorbidities. Model 3: Adjusting sex, age, body mass index, blood pressure, heart rate, comorbidities and treatments.

our database did not include specific medication adherence data, we conducted a sensitivity analysis to assess the potential impact of adherence on survival outcomes. Under the assumption of 70% adherence, we applied an inverse probability weighting (IPW) approach in a Cox regression model to evaluate the effects of beta-blockers and RAASi. The analysis yielded the HR of 0.64 (95% CI: 0.36–1.13, *P*=0.121) for beta-blockers, which is consistent with the primary analysis results (HR = 0.64, 95% CI: 0.36–1.14, *P*=0.132). Similarly, the HR for RAASi was 0.48 (95% CI: 0.27–0.84, *P*=0.011), aligning with the primary analysis (HR = 0.48, 95% CI: 0.27–0.85, *P*=0.012). These findings suggest that our main conclusions are robust to assumptions regarding medication adherence.

Discussion

In our study, we found that about 30% of AF patients with COPD used beta-blockers or RAASi and had more cardiovascular comorbidities such as hypertension and coronary arterial disease. Beta-blockers did not significantly affect overall survival, while ACEI may be beneficial in reducing all-cause mortality in this particular population.

Both COPD and AF bring heavy burdens and affect the quality of patients' life worldwide. In recent years, researchers have gradually realized their close association and the importance of managing comorbidities. Previously our group reported that 11.5% of AF patients had concomitant COPD,[4] the prevalence of which was similar to other cohorts.[6,7] The coexistence of COPD and AF would significantly worsen the prognosis of patients. Results from global registry studies have shown that COPD is associated with increased mortality, major adverse cardiovascular events and bleeding events.[8] However, randomized controlled studies of medications often exclude COPD patients with cardiovascular comorbidities by setting strict inclusion criteria. International expert consensus and recommendations for the pharmacological treatment of COPD in combination with AF are quite limited. Thus, we hope our work will fill this knowledge gap and have implications for both respiratory and cardiac physicians.

Beta-blockers are the first-line therapy for rate control in AF patients. In AF patients with COPD, the use of beta-blockers is limited by concerns about their side effect of airway spasm. The EORP-AF General Registry reported that beta-blockers were less likely to be prescribed when AF was combined with COPD.[9] However, we found that beta-blockers did not affect overall survival in patients with AF and COPD. It not only did not decrease mortality but also did not increase mortality, which has positive significance when worrying the side-effects of bronchoconstriction. A large-sample systematic review also showed that beta-blockers were not associated with adverse cardiovascular outcomes in patients with AF and COPD.[10] When the study endpoint was changed to severe exacerbation of COPD in patients with AF, beta-blockers were still effective compared with other standard treatments.[11] Unfortunately, the specific type of beta-blocker was not recorded in our database. In previous study, a post hoc analysis of MISOAC-AF trial reported that there was no difference in clinical outcomes between cardioselective and non-cardioselective beta-blockers in patients with AF and COPD after 4-year follow-up.[12] However, if COPD patients were combined with myocardial infarction, cardioselective beta-blockers were associated with a lower incidence of all-cause mortality and major adverse cardiac and cerebrovascular events.[13] In recent years, a number of randomised controlled trials have been conducted to investigate the effect of cardioselective beta-blockers in COPD patients with no established indication for such drugs. The BICS trial showed that bisoprolol did not reduce self-reported COPD exacerbations,[14] while the BLOCK COPD trial found that metoprolol was associated with more hospitalisations for exacerbations.[15] Therefore, based on our findings and the previous study, we believe that it may be a safe option to use cardioselective beta-blockers in patients with COPD and cardiovascular comorbidities, but evidence was still lacking in patients with COPD alone.

RAASi have been the cornerstone therapy in patients with heart failure, coronary heart disease and hypertension because of inhibiting cardiac remodeling and improving cardiac function. In AF patients, the protective effects of RAASi have also been reported in some studies despite the high burden of cardiovascular comorbidities.[5,16–18] In this research, we found that RAASi may bring a better prognosis in AF patients with COPD, especially ACEI. Notably, considering the side effect of airway hyperreactivity, the use of ACEI should be monitored carefully. The potential mechanism of ACEI to reduce mortality could be concluded from bench to bedside. As for the molecular mechanism, inflammation has been recognized as a central part of COPD progression, while the renin-angiotensin-aldosterone system is highly implicated in this pathogenesis. Angiotensin II (Ang II) upregulates pro-inflammatory mediators such as interleukin-6 (IL-6), reactive oxygen species (ROS) and transforming growth factor-β (TGF-β), which promote epithelial apoptosis and lung fibrosis.

Ang II also promotes bronchoconstriction, which worsens lung function.[19] ACEI has been reported to have immunomodulatory effects. It may help to inhibit the inflammatory response and improve lung function through the above pathways. As for clinical evidence, many studies have found a similar protective effect of ACEI. A retrospective nationwide study reported that ACEI significantly reduced mortality in patients hospitalized with a COPD exacerbation.[20] This benefit was also seen in COPD patients with acute respiratory failure.[21] In a large population-based study, slowed progression of percent emphysema was observed in COPD patients on ACEI.[22] A double-blind pilot study also showed that COPD patients on enalapril benefited from improved performance on cardiopulmonary exercise tests.[23] However, when combined with different levels of cardiovascular risk factors, the results may be different. A time-matched nested case-control study published in *JACC* showed that ACEI reduced mortality in COPD patients without myocardial infarction who were newly treated with nonsteroidal anti-inflammatory drugs (low risk). However, the protective effect was not statistically significant in COPD patients with prior revascularization (high risk).[24] We hope that our cohort of AF patients will provide additional evidence in COPD patients with cardiovascular comorbidities.

Due to the characteristics of a retrospective analysis, the database did not contain specific information on patient medication adherence. Therefore, we were unable to directly quantify the potential impact of adherence on outcomes. To our knowledge, no large-scale study has directly examined adherence to beta-blockers and RAASi in COPD patients, but similar patterns have been observed in cardiovascular populations. For example, Australian researchers found that it was common for heart failure patients to discontinue beta-blockers and RAASi after hospital discharge, while COPD was an independent predictor of poor adherence to beta-blockers.[25] In this elderly heart failure cohort (about 30% combined with COPD), increasing adherence to beta-blockers and RAASi reduces the risk of all-cause death and readmission.[26] The underuse of beta-blockers in heart failure patients with COPD has also been reported by British researchers.[27] We hope that our study will help physicians reduce concerns about side effects and improve adherence to guideline-based optimal therapy for this multi-comorbidity condition. In our future work, we will try to collect medication ownership rates, self-reported adherence or electronic monitoring data in our database and focus on this point.

We hope our study could influence decision-making for managing AF in COPD patients. Our findings will help to alleviate physicians' concerns about beta-blockers in the management of AF in COPD patients. Not only did beta-blockers not reduce mortality, but they also did not increase mortality, which is the clinical concern about the potential for increased bronchoconstriction with beta-blockers. If COPD patients were combined with indicators for RAASi due to cardiovascular comorbidities, adherence to RAASi may bring a better prognosis. We hope that our findings will inspire cardiologists and pulmonologists to work together to find an optimal choice for the management of these comorbidities.

Our study had several limitations. First, as the results were from an AF registry study, the results of lung function or blood gases were not recorded at baseline. Screening and treatment of airflow limitation have been shown to benefit patients with AF.[28] Considering the severity of COPD, existing evidence indicates that patients with severe COPD are less likely to be prescribed beta-blockers due to concerns about bronchospasm, despite their inherently higher mortality risk. Consequently, our analysis may underestimate the true protective effect of beta-blockers. In contrast, the use of RAAS inhibitors in severe COPD patients may be more frequently driven by the management of heart failure, potentially introducing confounding bias that could lead to an overestimation of their effect. Future studies incorporating pulmonary function data are warranted to more accurately evaluate the efficacy of these therapies. Second, treatment for COPD, such as inhaled beta-agonists, was also lacking in our study and requires further investigation. Third, the study sample and follow-up time were limited due to the available funding and resources. More rigorous randomized prospective studies would be conducted and deepen our understanding of the field. Despite these limitations, we hope our nation-wide study could help physicians be aware the importance of managing comorbid COPD in AF patients, consider comprehensive effects of beta-blockers and RAASi, and select effective medications for better prognosis.

Conclusion

Beta-blockers may be a safe therapeutic option for patients with AF and COPD, whereas ACEI may be associated with a better prognosis. Pulmonologists and cardiologists should recognize the importance of managing comorbidities and optimizing medical therapies.

Abbreviations

ACEI, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ECG, electrocardiogram; LVH, levy left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; RAASi, renin-angiotensin-aldosterone system inhibitors; SBP, systolic blood pressure; TIA, transient ischemic attack.

Ethics Approval and Informed Consent

The study was approved by the ethics committee of Fuwai hospital (approval number: 2008-143) and adhered to the Declaration of Helsinki.

Consent for Publication

Informed consent was obtained from all individual participants included in the study.

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Disclosure

The authors report no conflicts of interest in this work.

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