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ORIGINAL ARTICLE

Managements and outcomes of hospitalized heart failure patients with paroxysmal vs nonparoxysmal atrial fibrillation in Taiwan

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Abstract

Background: The prognostic significance and the optimal treatment strategy for patients with atrial fibrillation (AF) and heart failure (HF) remain controversial.

Methods: We extracted data from a large prospective national database involving Taiwanese patients with AF who were hospitalized for acute HF with reduced ejection fraction. Baseline characteristics, AF types, medications, and 1-year outcomes of the patients were analyzed.

Results: At baseline, 393 (26%) patients had AF, including 117 (29.8%) patients with paroxysmal AF (PAF) and 276 (70.2%) with nonparoxysmal AF (N-PAF). Patients with PAF were more likely to have ischemic cardiomyopathy (47.3% vs 29.7%, $p = 0.021$), chronic kidney disease (46.2% vs 29.0%, $p = 0.001$), and higher CHA_2DS_2-VASc score (4.0 vs 3.6, $p = 0.033$) compared with patients with N-PAF; however, patients with N-PAF had larger left atrial diameter (50.5 vs 47.3 mm, $p = 0.004$) than patients with PAF. Patients with PAF were more likely to receive treatment with amiodarone (31.6% vs 13.8%, $p < 0.001$) and antiplatelet agents (54.1% vs 42.5%, $p = 0.041$) but less likely to receive treatment with renin–angiotensin system blockers (52.3% vs 64.9%, $p = 0.021$) and anticoagulants (33.3% vs 50%, $p = 0.003$) compared with patients with N-PAF at discharge. The 1-year mortality (26.2% vs 16.5%, $p = 0.024$) and non-HF-related death rates (13.1% vs 5%, $p = 0.005$) were significantly higher in patients with PAF, whereas HF and arrhythmic death rates were similar in both groups (13.1% vs 11.5%).

Conclusion: Among patients with HF complicated with AF, those with PAF were more likely to receive antiarrhythmic agents, less likely to receive guideline-recommended therapy, but developed worse 1-year outcome compared with patients with N-PAF. These findings further emphasize the importance of optimal guideline-recommended medical therapy in patients with HF.

Keywords: Atrial fibrillation; Heart failure; Registry; Taiwan

1. INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) are the two major cardiovascular diseases with a rapidly increasing prevalence worldwide. The prevalence of both diseases increases dramatically with aging.[1,2] AF and HF not only frequently coexist but also increase the risk for one another. Both systolic and diastolic dysfunction could result in an increase in atrial pressure and volume overload, cellular hypertrophy, myocardial fibrosis, and conduction disturbances, and they have also been shown to be associated with a higher risk for AF. The prevalence of AF in published large clinical trials varies between 9.7% and 49.8%, depending on the severity of HF.[3–7] On the contrary, AF can aggravate HF, leading to hemodynamic compromise via the mechanism of inappropriate acceleration of ventricular rate, loss of atrial contraction, and elevated filling pressures. Previous population-based studies have reported that between 59% and 76% of patients with AF and HF develop AF either before or concurrently with onset of HF.[8,9] The recent ORBIT-AF registry showed that incident HF developed in 3.6% of patients with AF during the 2-year follow-up period.[10]

Although the interrelationships between AF and HF could be associated with a vicious cycle, there is no consensus regarding whether AF is an independent prognostic risk factor for HF or only a marker of merely more advanced disease. In the COMET study, patients with HF and permanent AF developed worse outcomes than patients in sinus rhythm, whereas after multivariate adjustment, AF alone did not predict a higher mortality.[11] In contrast, the results of the SOLVD trial, which enrolled 6500 patients with left ventricular ejection fraction (LVEF) <35%, demonstrated that baseline AF was an independent predictor of all-cause mortality, progressive pump failure, and the composite end point of death or hospitalization due to HF.[12] Treatment strategies of AF in patients with HF remain controversial. Results of the AF-CHF trial demonstrated that rhythm-control strategy failed to reduce death due to cardiovascular causes compared with rate-control strategy in patients with both AF and HF.[13] Potential benefits occurring via the maintenance of sinus rhythm might be neutralized by the adverse effects of antiarrhythmic drugs.

The Taiwan Society of Cardiology-Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry specifically enrolled

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decompensated hospitalized patients with LVEF <40%. This is the largest national database till date involving patients with acute decompensated HFrEF in Taiwan.[14] Using the TSOC-HFrEF database, we conducted this study to evaluate the characteristics, treatment, and outcomes of patients with HF with different AF classifications.

2. METHODS

2.1. Study design and patient characteristics

The TSOC-HFrEF registry was a prospective, multicenter, observational survey of patients who were hospitalized with either acute new-onset HF or acute decompensation of chronic HFrEF from 21 hospitals between 2013 and 2014 in Taiwan. The institutional review board of each hospital agreed to participate in the registry. The enrollment of patients, the overall characteristics of the patient population, and the management during index hospitalization and follow-up have been described in previous articles.[14,15]

There were no specific exclusion criteria, except that all patients should be aged >18 years and their LVEF had to be documented at <40% before enrollment. There were no specific protocols or recommendation for evaluation and management of HF during this observational study.

Information about AF was based on medical history. Investigators were asked to state whether there was a history of AF, and if yes, whether the AF was paroxysmal or persistent or permanent. For analysis, patients with a history of AF were divided into the following two groups according to their AF status: patients with paroxysmal AF (PAF group) and patients with nonparoxysmal AF (N-PAF group). Baseline characteristics, comorbidities, in-hospital management, discharge medications, and 1-year outcomes were analyzed in both groups. Specific 1-year outcomes included readmission for worsening HF, HF-related mortality (either due to refractory progressive HF, arrhythmic death, or sudden death), and non-HF-related mortality. Data were collected centrally using an electronic, standardized case report form and sent electronically to the data collection center.

2.2. Electrocardiogram, echocardiography, and laboratory studies

Electrocardiogram (ECG) and echocardiographic examinations were performed for all patients. Complete 12-lead ECG was done by a standard method with a paper speed of 25 mm per second. The first ECGs (either in the emergency room or at admission) of each patient were collected for analysis. Rhythm, heart rate, and QRS duration were recorded, and specific ECG findings such as left bundle branch block, left ventricular hypertrophy, and pathologic Q wave were marked. Echocardiographic images were acquired and measured in each institute. Left ventricular end-diastolic diameter was measured at end-diastole, and left ventricular end-systolic diameter and left atrial anteroposterior dimension were measured at end-systole on parasternal views. LVEF was calculated using the biplane Simpson's method on apical 4-chamber and 2-chamber views.

Baseline laboratory data (either in the emergency room or at admission) were collected for analysis, except for serum blood urea nitrogen and creatinine levels, which were collected before discharge. Glomerular filtration rate (GFR) was calculated using the modification of diet in renal disease formula.

2.3. Statistical analysis

Quantitative data were expressed as mean ± SD or as median and interquartile range, and categorical variables were presented as percentages. Descriptive summaries were presented for different groups of patients. The Student's *t*-test or the Mann–Whitney *U* test was used for comparisons between continuous data, and a χ^2 test was used for comparisons between categorical data. A Kaplan–Meier survival analysis was used to plot the survival curves. Multivariate Cox regression analysis with forward selection was performed to assess the predictability of variables on 1-year outcome presented as hazard ratios (HRs) and 95% CIs using $p < 0.1$ in univariate analyses for inclusion. $p < 0.05$ was considered to be statistically significant. All tests were two-sided. All the statistical analyses were performed using the SPSS Statistics 17.0 software (Chicago, IL, USA).

3. RESULTS

3.1. General information

A total of 1509 hospitalized patients (aged 63.9 ± 16.1 years) were included in the TSOC-HFrEF registry from May 2013 to October 2014. Among these patients, 393 (26%) had AF. These patients were further divided into the following two groups based on their AF status: 117 patients with PAF and 276 patients with non-PAF.

3.2. Differences in baseline characteristics

The differences in baseline characteristics of patients in the TSOC-HFrEF registry based on their AF status are shown in Table 1. In general, age and gender were similar in both groups. Regarding the etiology of HF, patients with PAF more frequently presented with ischemic cardiomyopathy (47.3% vs 29.7%, $p = 0.021$). Medical history revealed that patients with PAF more frequently presented with a history of myocardial infarction (29.9% vs 20.3%, $p = 0.039$), peripheral arterial disease (46.2% vs 29.0%, $p = 0.001$), and chronic kidney disease (46.2% vs 29.0%, $p = 0.001$). However, the incidence rates of a prior stroke were similar (14.5%) in both groups. Patients in the PAF group showed a slightly increased prevalence of hypertension (35% vs 27.9%) and diabetes mellitus (47.9% vs 38%) compared with those in the N-PAF group, which was not statistically different. Patients with PAF had higher a CHA_2DS_2-VASc score (4.0 vs 3.6, $p = 0.033$) and a higher HASBLED score (3.1 vs 2.6, $p = 0.015$) than patients with N-PAF.

3.3. Differences in cardiovascular examinations and laboratory tests

Differences in cardiovascular examinations of patients in the current registry based on their AF status are presented in Table 2, and differences in their laboratory tests are shown in Table 3. Regarding the ECG parameters, the mean heart rate, QRS duration, the percentages of left bundle branch block, left ventricular hypertrophy, and pathologic Q wave were comparable in both groups. The 24-hour Holter monitor data demonstrated that the PAF group had a significantly higher percentage of baseline sinus rhythm than the N-PAF group ($p < 0.001$). However, the mean 24-hour heart rate, ventricular premature beats counts, atrial premature beats counts, and the percentage of nonsustained ventricular tachycardia were similar in both groups. Echocardiographic examinations revealed that both groups had similar LVEF and left ventricular diameters, whereas patients with N-PAF had significantly larger left atrial diameter (50.5 vs 47.3 mm, $p = 0.004$), compared with those of patients with PAF. The percentages of moderate or severe mitral regurgitation, aortic regurgitation, tricuspid regurgitation, and aortic stenosis were comparable in both groups.

Patients with PAF had higher blood urea nitrogen and creatinine levels and lower estimated GFR and hemoglobin levels than patients with N-PAF. The levels of electrolytes, blood glucose, liver function, uric acid, natriuretic peptides, and cardiac troponin-I were similar in both groups.

3.4. Differences in in-hospital managements and guideline-recommended medications at discharge

Results of the comparisons of in-hospital management and discharge medications between both groups are shown in Table 4.

Vital signs at admission and discharge were comparable in both groups. Approximately 30% to 40% of patients admitted in the intensive care unit and patients in the PAF group were more likely to receive endotracheal tube intubation and mechanical ventilator support compared with patients with N-PAF (19.7% vs 10.1%, $p = 0.031$). In-hospital mortality rates were 5.1% in the PAF group and 2.5% in the N-PAF group of patients ($p = 0.22$).

At discharge, patients with PAF were more likely to receive treatment with amiodarone (31.6% vs 13.8%, $p < 0.001$) and antiplatelet agents (54.1% vs 42.5%, $p = 0.041$) but less likely to receive renin–angiotensin system (RAS) blockers (52.3% vs 64.9%, $p = 0.021$), digoxin (26.1% vs 46.6%, $p < 0.001$), and anticoagulants (33.3% vs 50%, $p = 0.003$) compared with patients in the N-PAF group. The prescription rates of beta-blockers, mineralocorticoid receptor antagonists, and diuretics were comparable between patients in both groups.

3.5. One-year outcomes and predictors

At 6 and 12 months after hospital discharge, the all-cause mortality rates were 11.5% and 19.3% and the HF-related mortality rates were 7.8% and 12.0%, respectively. The 1-year all-cause mortality (26.2% vs 16.5%, $p = 0.024$) and non-HF-related mortality rates (13.1% vs 5.0%, $p = 0.005$) were significantly higher in patients with PAF, whereas the HF-related mortality rates were similar in both groups (13.1% vs 11.5%, $p = 0.701$). The Kaplan–Meier survival curves are shown in the Figure.

Among all patients with AF in the TSOC-HFrEF registry, the rates of rehospitalization for worsening HF were 30.7% and 37.1% at 6 and 12 months after index hospitalization, respectively. The 1-year readmission rates for HF in both groups were similar (39.4% in PAF and 36.2% in N-PAF patients, $p = 0.55$). The numbers of HF rehospitalizations were comparable in both groups (1.8 ± 1.2 times in PAF vs 1.7 ± 0.9 times in N-PAF patients, $p = 0.447$).

To further clarify the impact of AF type on the 1-year outcome, multivariate Cox regression analysis of factors associated with 1-year mortality was performed, and the results are shown in Table 5. Model 1 included baseline characteristics such as age, AF types, CHA_2DS_2-VASc score, underlying diseases, and body mass index. AF type (PAF vs N-PAF, HR 1.62, 95% CI 1.02-2.59, $p = 0.044$) and higher CHA_2DS_2-VASc score (HR 1.16, 95% CI 1.01-1.33, $p = 0.038$) could predict the 1-year mortality in this model. In model 2, the same baseline characteristics used in model 1 were included, as well as the medical therapy. Model 2 demonstrated that prescription of less than two types of guideline-recommended medical therapy (including RAS blockers, beta-blockers, and mineralocorticoid receptor antagonists, HR 1.96, 95% CI 1.24-3.11, $p = 0.004$) and a history of chronic kidney disease (HR 1.77, 95% CI 1.12-2.80, $p = 0.014$) could independently predict the 1-year outcome, and PAF was no longer associated with 1-year mortality.

4. DISCUSSION

4.1. Prevalence of AF in HF studies

The prevalence of AF among patients with HF varies in previously published HF studies, depending on the trials' inclusion criteria, age, gender, HF severity, and comorbidities. In the CONSENSUS trial, which enrolled patients with the most severe HF (NYHA class IV), AF was detected in 49.8% of patients.[7] On the contrary, previous large-scale HF registries, including the ADHERE registry from the United States of America,[16] the EHFS II survey from Europe,[17] and the ATTEND registry from Japan,[18] enrolled not only HFrEF but also 34% to 47% of patients with HF with preserved LV ejection fraction. Consequently, patients included in these three international registries were significantly older and the prevalence rates of female gender and hypertension were significantly higher than those among patients in our TSOC-HFrEF registry.[13] Since AF was largely associated with old age, female gender, and diastolic dysfunction, the prevalence of AF from these three registries ranged from 31% to 40% and was therefore higher than the prevalence in our current registry (26%). Our registry enrolled only hospitalized patients with HFrEF.

4.2. Baseline characteristics and potential effects on treatment

Ischemia was universally the most common cause of HF among the registries.[14,17,18] In the TSOC-HFrEF registry, we found that patients with PAF had a significantly higher prevalence of atherosclerotic disease, such as ischemic cardiomyopathy, history of myocardial infarction, and peripheral arterial disease than patients with N-PAF. The prevalence of a previous stroke was about 14.5% and was similar in both groups. The CHA_2DS_2-VASc scores were high in both groups. Although we did not classify stroke as atherosclerotic or embolic, according to the underlying disease and scoring system, the risk of future stroke was very high; hence, aggressive medical treatment to prevent stroke in our patient population was mandatory.

Analysis of discharge medications revealed that patients with PAF were more likely to receive antiplatelet agents (54.1% vs 42.5%, $p = 0.041$) but less likely to receive anticoagulants (33.3% vs 50%, $p = 0.003$) compared with patients with N-PAF. Although current guidelines recommend anticoagulants for the prevention of thromboembolism for all patients with AF with a CHA_2DS_2-VASc score ≥ 2, except in case of contraindications,[19,20] physicians in the current registry preferred to prescribe fewer anticoagulants and more antiplatelet agents, especially for patients with PAF who also had a high prevalence of atherosclerotic disease. In parallel to the CHA_2DS_2-VASc scores, the HASBLED scores were high in the registry population and were even higher in patients with PAF than in patients with N-PAF (3.1 ± 1.6 vs 2.6 ± 1.6, $p = 0.015$), indicating that patients with PAF had a higher risk of bleeding than those with N-PAF. We were not aware whether the nonprescription of anticoagulants was due to neglect of stroke risk, fear of bleeding, or other

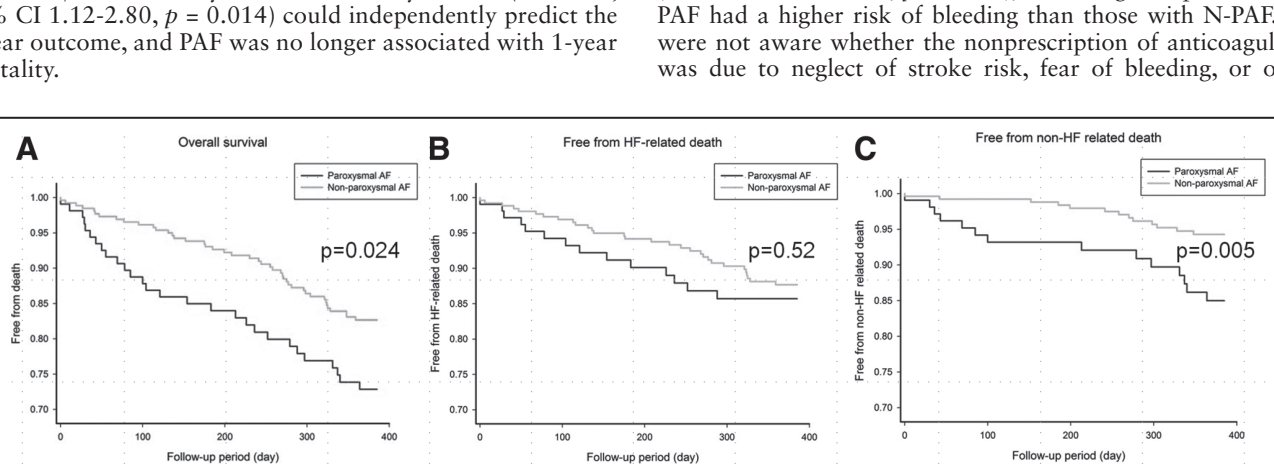

Fig. 1 Kaplan–Meier survival curves in the registry patients presenting with different atrial fibrillation status. A, All-cause mortality. B, HF-related mortality. C, Non-HF-related mortality.

Table 1

Baseline characteristics of patients with heart failure grouped according to the type of atrial fibrillation

	PAF (n = 117)	N-PAF (n = 276)	*p*
Age, y	70.0 ± 13.2	68.9 ± 14.7	0.488
Male	69.2%	73.2%	0.424
Etiology of heart failure			
Ischemic cardiomyopathy	47.3%	29.7%	0.021
Dilated cardiomyopathy	34.2%	39.1%	
Valvular heart disease	10.2%	14.1%	
Past and personal history			
Current smoker	19.7%	18.1%	0.719
Ex-smoker	31.6%	31.2%	0.915
Alcohol consumption	31.6%	38.0%	0.351
Previous hospitalization for heart failure	47.0%	46.4%	0.909
Coronary artery disease	46.2%	37.7%	0.117
Old myocardial infarction	29.9%	20.3%	0.039
Valvular surgery	6.8%	8.7%	0.538
Peripheral arterial disease	9.4%	4.0%	0.033
Previous stroke	14.5%	14.5%	0.992
Hypertension	35.0%	27.9%	0.158
Diabetes mellitus	47.9%	38.0%	0.070
Hypercholesterolemia	17.9%	15.2%	0.500
Chronic kidney disease	46.2%	29.0%	0.001
Cardiac resynchronization therapy and/or implantable cardioverter-defibrillator	3.4%	4.0%	1.000
Chronic obstructive pulmonary disease/asthma	19.7%	14.9%	0.238
Cancer with chemotherapy	2.6%	4.0%	0.766
Hypothyroidism	4.3%	2.9%	0.540
Hyperthyroidism	1.7%	5.4%	0.097
Sleep apnea	2.6%	4.7%	0.412
CHA_2DS_2-VASc score	4.0 ± 1.6	3.6 ± 1.7	0.026
CHA_2DS_2-VASc score ≥ 2	93.2%	86.2%	0.051
HASBLED score	3.1 ± 1.6	2.6 ± 1.6	0.015

N-PAF = nonparoxysmal atrial fibrillation; PAF = paroxysmal atrial fibrillation.

adverse drug events because the reasons for nonprescription were not collected in our current registry.

The majority of past history findings and patient characteristics, including smoking, alcohol consumption, histories of previous HF hospitalization, valvular heart disease, hypertension, diabetes, and previous device implantation, were similar in both groups. However, patients with PAF had a significantly higher prevalence of chronic kidney disease than those with N-PAF. Because of this, patients with PAF had higher blood urea nitrogen and creatinine levels and lower estimated GFR than patients

Table 2

Cardiovascular examinations of patients with heart failure grouped according to the type of atrial fibrillation

	PAF (n = 117)	N-PAF (n = 276)	*p*
Electrocardiogram findings			
Heart rate, bpm	101 ± 29	106 ± 29	0.149
QRS duration, msec	118 ± 31	113 ± 32	0.193
Left bundle branch block	11.4%	7.4%	0.202
Left ventricular hypertrophy	12.3%	13.3%	0.779
Pathologic Q wave	2.6%	1.9%	0.699
24-h Holter findings			
Numbers of examination	21	25	
Sinus rhythm as baseline rhythm	76.2%	4.0%	<0.001
Mean heart rate, bpm	78.4 ± 17.9	88.0 ± 22.8	0.137
Daily VPC counts	3481 ± 7016	2402 ± 5573	0.568
Daily APC counts	3099 ± 8362	361 ± 1661	0.165
Nonsustained VT	28.6%	16.0%	0.560
Echocardiographic findings			
LVEF, %	27.9 ± 7.6	29.2 ± 8.0	0.165
Left atrial diameter, mm	47.3 ± 9.5	50.5 ± 9.0	0.004
Left ventricular end-diastolic diameter, mm	60.2 ± 9.8	59.3 ± 9.0	0.360
Left ventricular end-systolic diameter, mm	50.4 ± 10.2	49.7 ± 9.6	0.519
Left ventricular mass, g	272 ± 80	281 ± 102	0.645
Moderate/severe mitral regurgitation	36.8%/14.2%	44.7%/11.4%	0.362
Moderate/severe tricuspid regurgitation	36.8%/8.5%	35.2%/14.4%	0.301
Moderate/severe aortic regurgitation	14.2%/1.9%	14.0%/1.5%	0.855
Moderate/severe aortic stenosis	0.9%/0.9%	1.1%/0.4%	0.649

APC = Atrial premature complex; N-PAF = nonparoxysmal atrial fibrillation; PAF = paroxysmal atrial fibrillation; VPC = ventricular premature complex.

Table 3

Mean values of the laboratory tests according to the type of atrial fibrillation

	PAF (n = 117)	N-PAF (n = 276)	*p*
Laboratory findings			
Blood urine nitrogen, mg/dL	41.1 ± 28.5	32.4 ± 23.7	0.017
Creatinine, mg/dL	1.8 ± 1.2	1.5 ± 1.3	0.029
Estimated GFR, mL/min/m^2	54.2 ± 31.5	66.1 ± 37.5	0.003
Sodium, mEq/L	137.0 ± 4.8	137.4 ± 4.5	0.438
Potassium, mEq/L	4.1 ± 0.7	4.1 ± 0.7	0.793
Magnesium, mg/dL	2.0 ± 0.4	2.0 ± 0.3	0.917
Hemoglobin, g/dL	12.2 ± 2.4	13.2 ± 2.2	<0.001
Fasting blood glucose, mg/dL	147 ± 66	140 ± 63	0.413
HbA1c, %	6.6 ± 1.3	6.8 ± 1.6	0.524
Total bilirubin, mg/dL	1.9 ± 2.7	1.3 ± 0.9	0.117
Aspartate aminotransferase, U/L	203 ± 708	70 ± 180	0.094
Alanine aminotransferase, U/L	146 ± 425	57 ± 139	0.052
Brain natriuretic peptide, pg/mL	1859 ± 1994	1321 ± 1174	0.093
N-terminal pro-brain natriuretic peptide, pg/mL	6436 ± 7585	4514 ± 4334	0.232
Uric acid, mg/dL	8.4 ± 3.5	8.7 ± 2.9	0.574
Troponin-I, ng/mL	1.9 ± 10.3	1.1 ± 9.0	0.518

GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; N-PAF = nonparoxysmal atrial fibrillation; PAF = paroxysmal atrial fibrillation.

with N-PAF. The prevalence of renal impairment and end-stage renal disease in patients in Taiwan is very high. A report from Taiwan Renal Registry Data System demonstrated that the prevalence of renal replacement therapy was 2926 per million of the population in 2012.[21] The overall prevalence of chronic renal failure in the TSOC-HFrEF registry was 31.5%,[14] which was much higher than the data reported in the previous European and Asian national surveys.[17,22–24] Renal dysfunction was found to be associated with underutilization of RAS blockers in the current registry,[25] and patients with PAF were less likely to receive RAS blockers (52.3% vs 64.9%, p = 0.021) compared with patients with N-PAF at discharge.

4.3. Rhythm control vs rate control for AF and HF

Although a routine strategy of rhythm control does not reduce the rate of cardiovascular mortality compared with a rate-control strategy,[13] the CAFÉ-II study reported that restoration to sinus rhythm was associated with improvement in quality of life and LVEF.[26] These conflicting findings suggest that the benefits of rhythm control could be counterbalanced by the adverse effects of antiarrhythmic therapy.[27] Since dronedarone and class I antiarrhythmic agents are not recommended for patients with HF,[19] and sotalol and dofetilide are not available in most of the hospitals in Taiwan, amiodarone was the only effective drug for rhythm control in our registry.

Table 4

Comparison of in-hospital management and discharge medication of patients with heart failure based on different atrial fibrillation type

	PAF (n = 117)	N-PAF (n = 276)	*p*
Admission and discharge profiles			
Admission HR, bpm	97.1 ± 24.5	93.8 ± 27.7	0.262
Admission SBP, mmHg	129.5 ± 24.6	127.6 ± 24.1	0.480
Admission BW, kg	63.9 ± 14.1	66.6 ± 16.0	0.113
Admission BMI, kg/m^2	24.3 ± 4.5	25.0 ± 4.9	0.169
Discharge HR, bpm	78.5 ± 15.3	77.3 ± 14.7	0.449
Discharge SBP, mmHg	120.0 ± 20.3	117.4 ± 15.4	0.222
Discharge BW, kg	60.9 ± 1 2.9	63.5 ± 15.0	0.121
In-hospital management			
ICU admission	39.3%	29.3%	0.053
Intravascular inotropic agents	47.0%	35.1%	0.027
Intravascular vasodilators	35.0%	26.1%	0.073
Intravascular diuretics	76.1%	69.2%	0.120
Mechanical ventilator	19.7%	10.1%	0.031
IABP or ECMO support	2.6%	1.8%	0.432
Implantation of CRT and/or ICD	0.9%	2.9%	0.290
In-hospital mortality	5.1%	2.5%	0.220
Discharge medication			
Renin–angiotensin system blocker	52.3%	64.9%	0.021
Beta blocker	48.6%	56.3%	0.171
Mineralocorticoid receptor antagonist	44.1%	48.9%	0.401
Diuretics	81.1%	88.4%	0.058
Digoxin	26.1%	46.6%	<0.001
Antiplatelet	54.1%	42.5%	0.041
Anticoagulant	33.3%	50.0%	0.003
Both antiplatelet and anticoagulant	9.0%	12.3%	0.356
Amiodarone	33.3%	14.1%	<0.001

BMI = body mass index; BW = body weight; CRT= cardiac resynchronization therapy; ECMO = extra-corporeal membrane oxygenation; HR = hazard ratio; IABP = intraaortic balloon pumping; ICD = implantable cardioverter defibrillator; N-PAF = nonparoxysmal atrial fibrillation; PAF = paroxysmal atrial fibrillation; SBP = systolic blood pressure.

Table 5

Multivariate analysis for factors associated with 1-year mortality

	Univariate analysis			Multivariate analysis	
	Morality	Alive	*p*	HR (95% CI)	*p*
Model 1 (baseline characteristics)					
Age, y/o	72.5 ± 13.7	68.3 ± 14.4	0.029	…	NA
Paroxysmal atrial fibrillation	39.4%	26.9%	0.038	1.62 (1.02-2.59)	0.044
CHA_2DS_2-VASc score	4.2 ± 1.6	3.6 ± 1.7	0.007	1.16 (1.01-1.33)	0.038
Chronic kidney disease	46.5%	30.0%	0.008	…	NA
Chronic obstructive pulmonary disease/asthma	22.5%	14.5%	0.096	…	NA
Body mass index, kg/m^2	24.1 ± 4.5	25.0 ± 4.8	0.086	…	NA
Hospital length, d	15.5 ± 12.9	12.1 ± 13.4	0.091	…	NA
Model 2 (baseline characteristics + medical therapy)					
Age, y/o	72.5 ± 13.7	68.3 ± 14.4	0.029	…	NA
Paroxysmal atrial fibrillation	39.4%	26.9%	0.038	…	NA
CHA_2DS_2-VASc score	4.2 ± 1.6	3.6 ± 1.7	0.007		NA
Chronic kidney disease	46.5%	30.0%	0.008	1.77 (1.12-2.80)	0.014
Chronic obstructive pulmonary disease/asthma	22.5%	14.5%	0.096	…	NA
Body mass index, kg/m^2	24.1 ± 4.5	25.0 ± 4.8	0.086	…	NA
Hospital length, d	15.5 ± 12.9	12.1 ± 13.4	0.091	…	NA
Renin–angiotensin system blockade	54.9%	62.9%	0.163		
Beta blocker	45.1%	56.8%	0.059	…	NA
Mineralocorticoid receptor antagonist	42.3%	48.6%	0.330		
Guideline-recommended medical therapy ≤1 types	54.9%	41.2%	0.025	1.96 (1.24-3.11)	0.004
Anticoagulants	39.4%	44.6%	0.447		
Digoxin	42.9%	38.8%	0.547		
Amiodarone	25.4%	17.7%	0.135		
Antiplatelet agents	42.9%	47.3%	0.545		

HR = hazards ratio; NA = not available.

At discharge, prescription rates of beta-blockers were similar in both groups, but patients with PAF were more likely to receive amiodarone (31.6% vs 13.8%, $p < 0.001$) and less likely to receive digoxin (26.1% vs 46.6%, $p < 0.001$) compared with patients in the N-PAF group, indicating that more physicians applied rhythm-control strategy on patients with HF with PAF. Although amiodarone could reduce the incidence of AF, induce pharmacological cardioversion, and more efficiently maintain sinus rhythm in patients with HF and AF,[28] the notorious side effects, including thyroid, pulmonary, and corneal complications, limit its usage. At baseline, 4.7% of patients in the TSOC-HFrEF registry had either hyperthyroidism or hypothyroidism, which may have been further deteriorated after treatment with amiodarone.[14]

4.4. Prognostic significance of AF

The prognostic significance of AF in patients with HF remains controversial. In the V-HeFT study, the presence of AF was not associated with a worse outcome in 1427 patients with mild-to-moderate HF.[4] In contrast, the SOLVD trial demonstrated that the odds ratio for total mortality among patients with HF with AF compared with patients in sinus rhythm was 1.81 ($p < 0.0001$).[12] In a retrospective analysis of the COMET study, which included 3029 patients with LVEF < 35%, baseline AF was found to significantly increase the risk for death and HF readmission. However, after adjustment for other predictors, AF was no longer an independent risk factor for mortality.[11] In the TRACE study, long-term mortality was increased in all subgroups of patients with AF, except in those with the most advanced disease (LVEF < 25%), suggesting that the independent effect of AF on mortality is inversely related to the severity of HF.[29]

Few HF studies have compared the outcomes of patients with different AF types. In the current study, we found that patients with PAF had significantly higher 1-year mortality than patients with persistent or permanent AF. This result appeared to be paradoxical from the point of view of disease progression, as patients with PAF have less advanced atrial disease and smaller left atrial size than patients with N-PAF. After multivariate adjustment of baseline characteristics, PAF was found to be still associated with higher 1-year mortality. Similar to our findings, the PARADIGM-HF and ATMOSPHERE trials showed that patients with PAF had higher risks for primary composite endpoint, HF hospitalization, and stroke than patients with N-PAF after multivariate adjustment, although cardiovascular death rates were similar in both groups.[30] Regarding the baseline characteristics in these two large-scale randomized trials, patients with PAF presented more frequently with ischemic HF etiology (63.6% vs 50.6%, $p < 0.001$), history of myocardial infarction (49.2% vs 30.0%, $p < 0.001$), renal disease (21.8% vs 17.3%, $p < 0.001$), and higher CHA_2DS_2-VASc score (4.1 vs 3.9, $p = 0.005$) compared with patients with N-PAF; these results were similar to the findings in our registry. Even in the randomized controlled trials, medical treatments were not equally prescribed; patients with PAF were more likely to receive amiodarone and antiplatelet agents but less likely to receive digoxin and anticoagulants compared with patients with N-PAF.[30] Hence, in the current registry data, if guideline-recommended treatments were taken into consideration in the multivariate analysis, PAF would no longer be associated with 1-year mortality, whereas prescription of less than two types of guideline-recommended medical therapy could predict a worse 1-year outcome. Considering these findings together, we noticed that there is a gap between guideline-recommended therapy and real-world practices, which applies to both the randomized controlled trials and our observational registry. The importance of anticoagulants and other evidential HF treatments in patients with concurrent AF and HF should not be neglected.

4.5. Study limitations

Several limitations were present in this study. First, the design of the current registry was an observational, prospective survey that included only hospitalized patients with reduced ejection fraction. Despite covariate adjustment, other measured or unmeasured factors might also affect outcomes. Second, according to the study design, we collected patients' death mode as follows: death

due to refractory HF, death due to arrhythmia or sudden cardiac death and noncardiac death. Fatal stroke could be categorized into non-HF-related death in this study, but it is an important endpoint for those patients with HF with AF. Hospitalization due to stroke and systemic embolism was not recorded; hence, it was difficult to describe the effect of under-usage of guideline-recommended treatment, especially anticoagulants.

In conclusion, The TSOC-HFrEF registry is the largest national database till date involving patients with acute decompensated HFrEF in Taiwan. In this observational, real-world registry, patients with PAF and HFrEF were less likely to receive anticoagulant therapy and more likely to receive antiarrhythmic agents but they had worse 1-year outcome than their N-PAF counterparts. Our study findings further emphasize the importance of optimal guideline-recommended medical therapy in patients with HFrEF, regardless of the underlying AF types.

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