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Outcomes of Rate-Control Treatment in Patients With Atrial Fibrillation and Heart Failure

— A Nationwide Cohort Study —

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Background: Rate control is now a front-line therapy in the management of atrial fibrillation (AF). However, the survival benefits of different rate-control medications remain controversial, so we assessed the efficacy of rate-control medications in AF patients with concomitant heart failure (HF).

Methods and Results: From January 2002 to December 2008, a total of 7,034 AF patients with a single type of rate-control drug or without rate-control treatment were enrolled from the Korea National Health Insurance Service database. The death rates over a mean follow-up of 4.5±1.2 years were 12.6% (580 of 4,593) and 29.0% (709 of 2,441) in non-HF and HF patients, respectively. Among the total subjects, the risk of death was lower in patients receiving β-blockers (adjusted hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.64–0.88) and calcium-channel blockers (adjusted HR 0.74, 95% CI 0.55–0.98) compared with those who did not receive rate-control medications. In patients without HF, use of rate-control medications did not affect the risk of death. In patients with HF, β-blockers significantly decreased the mortality risk (adjusted HR 0.63, 95% CI 0.50–0.79), whereas use of calcium-channel blockers or digoxin was not associated with death. The results were observed consistently among the cohorts after propensity matching.

Conclusions: Use of β-blockers was associated with a reduced mortality rate for AF patient with HF but not for those without HF. These findings should be examined in a large randomized trial.

Key Words: Atrial fibrillation; Beta-blockers; Calcium-channel blockers; Digoxin; Heart failure

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide and is associated with increased morbidity and mortality.[1] In our previous report on a Korean nationwide semi-dynamic cohort, hospital visits and costs for AF increased with the increase in comorbidities during the past decade.[2] Uncontrolled rapid ventricular rate during AF can lead to left ventricular systolic dysfunction and consequent heart failure (HF). In addition, AF and HF affect each other, contributing to increased cardiovascular morbidity and mortality.[3] Randomized trials have not identified significant differences between rate-control and rhythm-control strategies with respect to prognosis;[4] thus, rate control has become a front-line therapy for managing AF. Indeed, for long-term AF management, the American College of Cardiology, American Heart Association, Heart Rhythm Society, and European Society of Cardiology all emphasize the importance of rate control with medication (β-blockers [BBs], non-dihydropyridine calcium-channel blockers [CCBs], or digoxin).[5,6]

The use of digoxin has recently declined[7–9] due in part to safety concerns following the publication of observational studies that found increased mortality rates with digoxin.[10–12] In addition, digoxin is associated with a significant increase in all-cause death in patients with AF after correcting for clinical characteristics and comorbidities, regardless of sex or the presence or absence of HF.[13] Nevertheless, digoxin is particularly prone to prescription bias, as clinicians have been trained to use digoxin in patients with more severe illness. Statistical adjustment of observational data does not remove all confounding factors, and even techniques such as propensity-score matching cannot replace randomized allocation.[14,15] However, a recent meta-analysis reported that digoxin has a neutral effect on mortality in randomized

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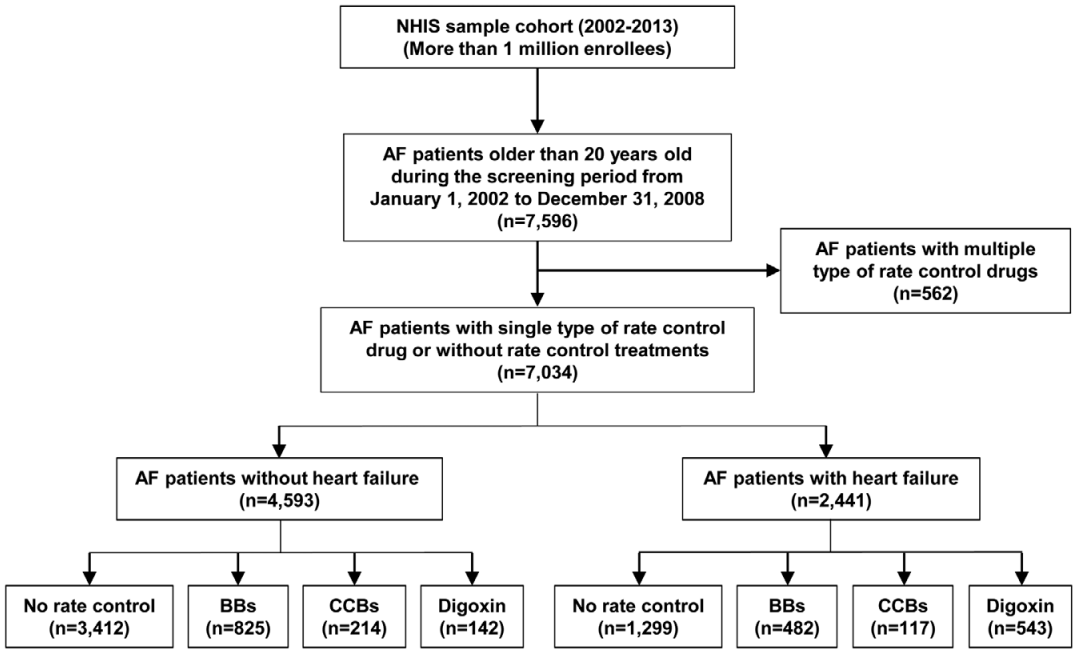

Figure 1. Flowchart of the enrollment of the study cohort. AF, atrial fibrillation; BBs, β-blockers; CCBs, calcium-channel blockers; NHIS, National Health Insurance Service.

trials and a lower rate of hospital admission across all study types. Regardless of the method of statistical analysis, prescription biases limit the value of observational data.[16]

The use of BBs does not improve morbidity or mortality in patients with HF and concomitant AF in contrast with patients in sinus rhythm, who experience substantial reductions in admission to hospital and all-cause death with BBs.[17] Irrespective of age or sex, patients with HF in sinus rhythm should receive BBs to reduce the risk of death and admission to hospital.[18] In a Taiwanese nationwide AF cohort, the risk of death was lower for patients receiving rate-control treatment with BBs or CCBs, and the use of BBs was associated with the largest risk reduction. On the other hand, digoxin was associated with increased deaths.[19]

Data on the survival benefits of rate control continue to be debated. The aim of the present study was to assess the efficacy of rate-control medications in AF patients according to concomitant HF in a nationwide Korean AF cohort.

Methods

Study Population

A national health insurance system in Korea was established in 1963 according to the National Health Insurance Act, and participation is compulsory for all citizens in South Korea. Currently, the National Health Insurance Service (NHIS) maintains and manages all Korean health service databases. The database is open to researchers, whose study protocols are approved by the official review committee. Based on this NHIS database, the Korean National Health Insurance Dataset Sample Cohort (K-NHID-Sample Cohort) was created and released in 2014, and contains 1,025,340 individuals representing the general Korean population. The database amounts to 2.2% of the entire population of the Korean NHIS and consists of data from the beginning of 2002 through 2013.[2,20] The database is a semi-dynamic cohort database; the cohort has been followed up to either the time of the participant's disqualification of health services due to death or emigration or to the end of the study period. Samples of newborn infants are included annually. The database contains eligibility and demographic information about health insurance and medical aid beneficiaries, medical bill details, medical treatment, disease histories, and prescriptions. The data were constructed after converting insurance claim information to the first day of medical treatment.

A total of 7,596 patients with AF age ≥20 years were identified from the Korea NHIS sample cohort database during the screening period from January 2002 to December 2008; 562 patients receiving multiple types of rate-control medications were excluded. A final total of 7,034 AF patients were enrolled in the study cohort and were followed up until December 2013 (**Figure 1**). AF was diagnosed using the International Classification of Disease (ICD)-10 code (ICD-10:I48). To ensure accurate diagnosis, we defined patients with AF only when it was a discharge diagnosis or confirmed more than twice in the outpatient department.[21–23] To evaluate the accuracy of our definition of AF, we conducted a validation study in 2 hospitals with 628 randomly chosen patients with the ICD-10 code I48; the positive predictive value was 94%.[24] Past history including congestive HF, hypertension, diabetes, strokes, and vascular disease was analyzed by the presence of medical claim data with ICD codes I50, I10–I15, E10–E14, I60–I69, I20–I25, I71, and I72, respectively. The study protocol was approved by the Institutional Review Board of Severance Cardiovascular Hospital, and adhered to the principles of the Declaration of Helsinki.

Table 1. Baseline Characteristics of Atrial Fibrillation Patients With and Without HF

	Total (n=7,034)	Without HF (n=4,593)	With HF (n=2,441)	P value
Age, years	63.6±15.5	60.2±15.9	70.0±12.4	<0.001
Male sex, %	52.3	54.8	47.6	<0.001
Comorbidities, %				
Hypertension	77.1	67.9	94.3	<0.001
Diabetes mellitus	19.5	17.2	23.9	<0.001
Stroke/TIA	25.4	21.6	32.7	<0.001
Vascular disease	21.0	16.4	29.6	<0.001
CKD	5.6	3.5	9.5	<0.001
ESRD	1.4	0.8	2.5	<0.001
Dyslipidemia	52.4	47.8	61.2	<0.001
Malignant neoplasm	20.8	20.0	22.1	0.039
CHA_2DS_2-VASc score	3.3±2.1	2.6±1.8	4.8±1.7	<0.001
Medications, %				
Aspirin	31.2	28.5	36.4	<0.001
$P2Y_{12}$ inhibitors	8.9	7.8	11.1	<0.001
Warfarin	14.6	10.0	23.4	<0.001
BBs	18.6	18.0	19.7	0.067
CCBs	4.7	4.7	4.8	0.801
Digoxin	9.7	3.1	22.2	<0.001
Class Ic AADs	3.4	3.9	2.5	0.003
Class III AADs	3.1	2.8	3.5	0.109
Statins	19.3	17.5	22.7	<0.001

AADs, antiarrhythmic drugs; BBs, β-blockers; CCBs, calcium-channel blockers; CKD, chronic kidney disease; ESRD, endstage renal disease; HF, heart failure; TIA, transient ischemic attack.

Definitions of Rate-Control Treatments and Study Outcomes

Patients with AF were analyzed in terms of treatment pattern, including medication for stroke prevention, rate control, and rhythm control. We identified 7,034 AF patients over 20 years of age with (n=2,441) or without (n=4,593) HF. Prescriptions for BBs, CCBs, and digoxin, which were available in Korea for rate control, were identified for every patient. BBs included acebutolol, arotinolol, atenolol, bevantolol, bisoprolol, carvedilol, celiprolol, labetalol, metoprolol, nadolol, nebivolol, and propranolol. CCBs included verapamil and diltiazem. Patients were assigned to each treatment group if they received 1 type of medication (BBs or CCBs or digoxin) for >90 days within the 6 months after enrollment.[19] There were 1,307 (18.6%), 331 (4.7%), and 685 (9.7%) patients enrolled in the groups receiving BBs, CCBs, and digoxin, respectively. A flowchart of the enrollment strategy for the study cohort is shown in **Figure 1**. The primary outcomes were all-cause death based on ICD-10 codes during the 5 years of follow-up period (January 2009 to December 2013).

Statistical Analysis

Data are presented as mean±standard deviation (SD) for continuous variables and as proportion for categorical variables. Continuous variables were compared using Student's t-test. Analysis of categorical variables was performed with the Chi-square test. Continuous variables were compared using one-way analysis of variance and Chi-square test or Fisher's exact test as a posthoc test for each medication group. The risk of death according to rate-control medication was assessed with Cox regression analysis. The covariates selected for adjustment were age, sex, and history of hypertension, diabetes mellitus, congestive HF, transient ischemic attack (TIA) or stroke, chronic kidney disease, endstage renal disease (ESRD), dyslipidemia, and malignant neoplasms. The cumulative incidence curve of death was analyzed by the Kaplan-Meier method, and statistical significance was examined with the log-rank test.

In addition, we performed propensity-score matched analysis for 3 comparisons: BBs vs. no rate-control treatment, CCBs vs. no rate-control treatment, and digoxin vs. no rate-control treatment. The propensity scores for the likelihood of using BBs, CCBs, or digoxin compared with no rate-control treatment were calculated by multivariate logistic regression analyses, conditional on all the baseline covariates listed in **Table 1**. Statistical significance was set at $P<0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 23.0, SPSS Inc., Chicago, IL, USA) and R statistical software package (R 3.2.3, R studio, Boston, MA, USA).

Results

Baseline Characteristics of the Study Patients

A total of 7,034 patients with AF were included in this study, of which 4,593 (65.3%) did not have HF (no-HF), and 2,441 (34.7%) had HF at baseline. **Table 1** shows the baseline characteristics of the AF patients according to the presence or absence of HF. Compared with no-HF patients, those with HF were 10 years older, and a higher percentage were women. Patients with HF had a higher prevalence of comorbidities such as hypertension, diabetes mellitus,

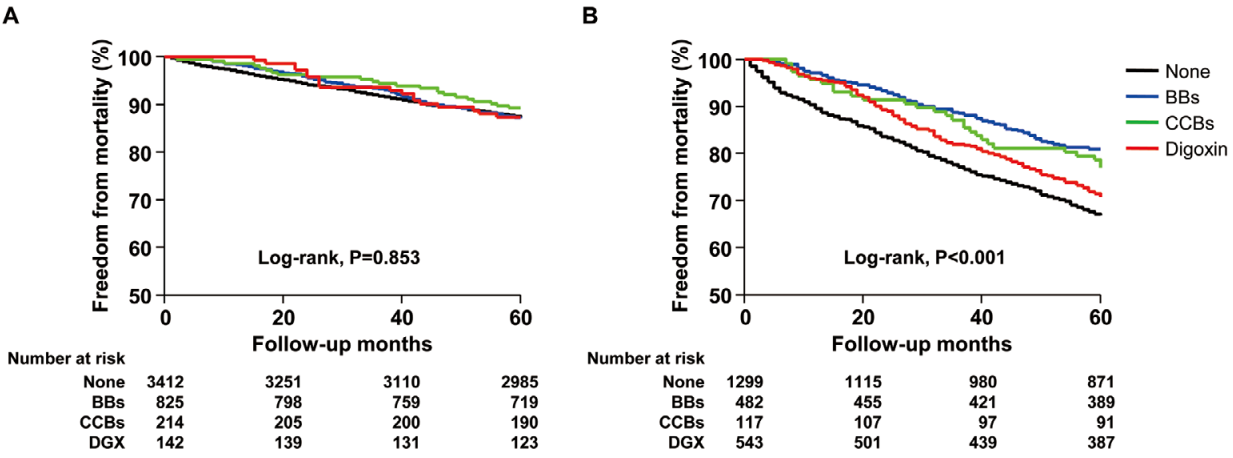

Figure 2. Kaplan-Meier curves for mortality in AF patients receiving different medications for rate control. Survival from all-cause death was plotted for AF patients without (**A**) and with (**B**) heart failure. Abbreviations as in Figure 1.

Table 2. Risk of All-Cause Death in Patients With Different Rate-Control Medications

	Patients, n	Annual rate, %	HR (95% CI)	P value	Adjusted* HR (95% CI)	P value
Total						
None	4,711	4.07	1 (Ref.)		1 (Ref.)	
BBs	1,307	3.25	0.80 (0.69–0.94)	0.005	0.75 (0.64–0.88)	<0.001
CCBs	331	3.25	0.80 (0.60–1.06)	0.120	0.74 (0.55–0.98)	0.036
Digoxin	685	5.87	1.44 (1.22–1.69)	<0.001	1.01 (0.86–1.19)	0.928
Without HF						
None	3,412	2.72	1 (Ref.)		1 (Ref.)	
BBs	825	2.72	1.00 (0.81–1.24)	0.980	0.86 (0.69–1.07)	0.169
CCBs	214	2.25	0.83 (0.55–1.26)	0.383	0.74 (0.48–1.12)	0.154
Digoxin	142	2.69	0.99 (0.62–1.58)	0.950	0.68 (0.43–1.10)	0.116
With HF						
None	1,299	8.17	1 (Ref.)		1 (Ref.)	
BBs	482	4.21	0.52 (0.41–0.65)	<0.001	0.63 (0.50–0.79)	<0.001
CCBs	117	5.19	0.64 (0.43–0.94)	0.024	0.71 (0.48–1.05)	0.087
Digoxin	543	6.80	0.83 (0.70–1.00)	0.049	0.90 (0.75–1.08)	0.255

*Adjustment for all variables including age, sex and comorbidities listed in Table 1. HR, hazard ratio. Other abbreviations as in Table 1.

stroke or TIA, vascular disease, chronic kidney disease, ESRD, and dyslipidemia at baseline than those without HF (**Table 1**). More patients with HF used aspirin, $P2Y_{12}$ inhibitors, warfarin, digoxin, or statins.

Digoxin was used in 3.1% and 22.2% in the no-HF and HF groups, respectively. The use of BBs or CCBs was comparable between the 2 groups. The 4 medication subgroups of AF patients with and without HF were significantly different from each other with respect to age, sex, comorbidities, and medications (**Table S1**).

Risk of Death in Patients With Different Rate-Control Medications

The crude death rates over a mean follow-up of 4.5±1.2 years were 12.6% (580 of 4,593) in the no-HF and 29.0% (709 of 2,441) in the HF patients. **Figure 2** shows the Kaplan-Meier curves for all-cause death for the 4 medication groups in AF patients with and without HF. In patients without HF, there was no significant difference in the risk of death among the 4 medication subgroups (**Figure 2A**). In the HF patients, the curves of the log-rank test showed that the risk of death was lower in patients treated with BBs or CCBs, whereas there was no significant difference between patients treated with digoxin or not being treated with rate-control medication (**Figure 2B**).

After adjustment for baseline differences, the risk of death was lower in patients receiving BBs (adjusted hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.64–0.88) or CCBs (adjusted HR 0.74, 95% CI 0.55–0.98) compared with those who did not receive rate-control medications among the total AF patients (**Table 2**). However, use of rate-control medications did not affect the risk of death in

Table 3. Characteristics of Atrial Fibrillation Patients After Propensity-Score Matching

Without HF	BBs vs. No rate-control			CCBs vs. No rate-control			Digoxin vs. No rate-control		
	None (n=2,634)	BBs (n=804)	P value	None (n=1,443)	CCBs (n=212)	P value	None (n=1,162)	Digoxin (n=140)	P value
Age, years	64.0±15.5	64.2±11.9	0.814	63.6±13.2	63.8±10.1	0.719	66.5±13.8	66.7±11.2	0.776
Male sex, %	46.9	46.5	0.791	62.8	63.2	0.681	55.4	55.5	0.905
Comorbidities, %									
Hypertension	88.9	90.3	0.617	87.5	87.8	0.843	87.0	87.2	0.889
Diabetes mellitus	21.9	22.2	0.860	20.6	20.9	0.893	19.5	19.6	0.965
Stroke/TIA	22.8	22.9	0.945	22.9	23.0	0.911	27.9	28.1	0.912
Vascular disease	24.8	25.1	0.892	22.9	23.1	0.827	16.7	16.8	0.977
CKD	3.8	3.9	0.954	2.5	2.4	0.954	1.0	0.8	0.806
ESRD	0.6	0.4	0.808	0.7	0.5	0.712	0.4	0	0.296
Dyslipidemia	60.9	61.5	0.648	66.0	66.3	0.798	54.6	54.8	0.850
Malignant neoplasm	19.5	19.3	0.903	23.0	23.3	0.831	20.3	20.4	0.974
CHA_2DS_2-VASc score	3.0±1.7	3.1±1.7	0.245	2.7±1.6	2.8±1.6	0.202	3.0±1.7	3.1±1.7	0.345
With HF	**None (n=1,074)**	**BBs (n=442)**	**P value**	**None (n=643)**	**CCBs (n=111)**	**P value**	**None (n=1,128)**	**Digoxin (n=517)**	**P value**
Age, years	69.4±12.7	69.0±10.9	0.670	70.5±12.0	70.6±9.8	0.843	70.1±13.0	70.0±12.3	0.913
Male sex, %	49.1	50.2	0.860	47.8	47.8	0.996	44.5	44.3	0.868
Comorbidities, %									
Hypertension	97.1	97.5	0.845	98.0	98.2	0.866	94.1	94.3	0.909
Diabetes mellitus	23.0	23.4	0.772	26.4	26.5	0.951	24.5	24.6	0.941
Stroke or TIA	31.7	30.3	0.601	38.3	38.4	0.915	29.0	28.6	0.712
Vascular disease	32.6	33.9	0.539	35.1	35.8	0.566	25.3	25.2	0.837
CKD	9.9	9.5	0.822	7.2	6.9	0.713	5.6	5.4	0.811
ESRD	1.0	0.7	0.715	1.3	1.0	0.698	0.6	0.2	0.566
Dyslipidemia	71.7	72.1	0.794	75.7	76.0	0.832	58.0	58.1	0.954
Malignant neoplasm	21.5	20.6	0.694	22.4	22.3	0.934	19.4	19.0	0.798
CHA_2DS_2-VASc score	4.8±1.7	4.7±1.6	0.157	4.9±1.7	5.0±1.5	0.297	4.7±1.8	4.7±1.7	0.682

Abbreviations as in Table 1.

Table 4. Risk of All-Cause Death in Patients With Different Rate-Control Medications After Propensity-Score Matching

	Patients, n	Annual rate, %	HR (95% CI)	P value	Adjusted* HR (95% CI)	P value
Without HF						
BBs vs. none						
None	2,634	2.76	1 (Ref.)		1 (Ref.)	
BBs	804	2.74	0.99 (0.80–1.22)	0.967	0.88 (0.71–1.10)	0.187
CCBs vs. none						
None	1,443	2.69	1 (Ref.)		1 (Ref.)	
CCBs	212	2.26	0.84 (0.56–1.27)	0.412	0.76 (0.49–1.18)	0.143
Digoxin vs. none						
None	1,162	2.65	1 (Ref.)		1 (Ref.)	
Digoxin	140	2.70	1.02 (0.64–1.63)	0.899	0.94 (0.60–1.35)	0.692
With HF						
BBs vs. none						
None	1,074	7.70	1 (Ref.)		1 (Ref.)	
BBs	442	4.24	0.55 (0.43–0.67)	<0.001	0.64 (0.49–0.82)	<0.001
CCBs vs. none						
None	643	7.76	1 (Ref.)		1 (Ref.)	
CCBs	111	5.20	0.67 (0.44–0.95)	0.030	0.73 (0.49–1.09)	0.104
Digoxin vs. none						
None	1,128	7.60	1 (Ref.)		1 (Ref.)	
Digoxin	517	6.84	0.90 (0.72–1.08)	0.265	0.96 (0.76–1.13)	0.790

*Adjustment for all variables including age, sex and comorbidities listed in Table 1. Abbreviations as in Tables 1,2.

AF patients without HF. In AF patients with HF, BBs significantly decreased the risk of death (adjusted HR 0.63, 95% CI 0.50–0.79), whereas use of CCBs or digoxin was not associated with death in these patients.

Results After Propensity-Score Matching

The baseline characteristics after propensity-score matching for 3 comparisons (BBs vs. no rate-control treatment, CCBs vs. no rate-control treatment, and digoxin vs. no rate control treatment) in AF patients with and without HF are shown in **Table 3**. Age, sex, and other comorbidities were not significantly different between the groups in each comparison. The risk of death was observed consistently among the cohorts after propensity-score matching. In patients without HF, use of rate-control medications did not affect the risk of death. In patients with HF, BBs significantly decreased the risk of death (adjusted HR 0.64, 95% CI 0.49–0.82), whereas use of CCBs or digoxin was not associated with death (**Table 4**).

Discussion

Main Findings

The main finding of this study was that BBs significantly decreased the risk of death in AF patients, especially in those with HF. The use of CCBs was also associated with a decreased risk of death in the overall AF patient group. In the current study, however, digoxin use was not associated with an increased risk of death in AF patients. The results were observed consistently among the cohorts after propensity-score matching.

Rationale and Evidence of Rate Control in AF

AF can have significant symptomatic and hemodynamic effects. During AF, the atria fail to properly eject blood and they do not contribute to the stroke volume, significantly reducing cardiac output.[25] An irregular and rapid ventricular rate further reduces ventricular filling and stroke volume,[26] and the reduction in stroke volume can become even more significant at faster heart rates.[27] Reduced cardiac output is substantial in patients with HF and can cause serious clinical symptoms.[28] For example, sustained tachycardia can lead to dilatation of the left ventricle and left ventricular systolic dysfunction, resulting in tachycardia-induced cardiomyopathy.[29] In patients with AF-associated HF requiring hospitalization, tachycardia-induced cardiomyopathy is presumably the cause in approximately one-third of the patients without any known structural heart disease.[30] Previous studies have demonstrated that improving and restoring left ventricular function can be achieved by controlling rapid ventricular responses.[31] Based on these reports, rate control is considered central to the management of symptoms in AF patients and was given a Class I recommendation in recent AF guidelines.[5,6] However, whether rate-control treatment with BBs or CCBs improve the survival of patients with AF continues to be debated. Recently, in a Taiwanese nationwide AF cohort, Chao et al showed that the risk of death was lower for patients receiving rate-control treatment with BBs or CCBs.[19] In the present study, we showed that patients with BBs had a lower risk of death compared with those without rate-control drugs, especially in the HF group. CCBs also conferred a lower risk of death in AF patients.

There is a evidence that digoxin may increase the risk of death,[32,33] but other studies have reported no change in mortality associated with digoxin use.[16,34] In the present study of a Korean sample cohort population, the effect of digoxin use on mortality in AF patients with and without HF appeared to be neutral. The reasons for the different effects of digoxin on the mortality of AF patients remain unclear. Well-designed randomized trials of digoxin are strongly recommended to identify the place of this treatment in the management of AF patients with or without HF.

Study Limitations

This study was a retrospective observational study that was performed using nationwide sample cohort data. First, important clinical information such as blood pressure, heart rate, type of AF, or ejection fraction determined by echocardiography were not available from the NHIS database. Therefore, it is difficult to state whether the drug itself affected the outcome or the drug affected blood pressure and thus had an effect on the outcome. Although it seems that there will be a difference in outcomes according to the presence of HF with preserved ejection fraction or HF with reduced ejection fraction, it is difficult to analyze the effect of such differences with the current data. Second, because the study population was a semi-dynamic cohort with a 12-year follow-up, the comorbidity and demographic data of patients do not accurately represent those of the general population with respect to time. However, this cohort does show the effect of ageing on patients with AF over a 12-year follow-up period. In addition, all patients with AF were identified according to diagnosis, not ECG, and patients with atrial flutter were included in the AF population.

Conclusions

In AF patients, use of BBs was associated with reduced mortality for those with HF but not for those without HF. A well-designed trial of rate-control medications in patients with AF and HF is greatly needed.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Files

Supplementary File 1

Table S1. Characteristics of atrial fibrillation patients with and without HF receiving different medications for rate control

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