

## Rate-Control Treatment and Mortality in Atrial Fibrillation

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**Background**—Current American and European guidelines emphasize the importance of rate-control treatments in treating atrial fibrillation with a Class I recommendation, although data on the survival benefits of rate control are lacking. The goal of the present study was to investigate whether patients receiving rate-control drugs had a better prognosis compared with those without rate-control treatment.

**Methods and Results**—This study used the National Health Insurance Research Database in Taiwan. There were 43 879, 18 466, and 38 898 patients with atrial fibrillation enrolled in the groups receiving  $\beta$ -blockers, calcium channel blockers, and digoxin, respectively. The reference group consisted of 168 678 subjects who did not receive any rate-control drug. The clinical end point was all-cause mortality. During a follow-up of  $4.9 \pm 3.7$  years, mortality occurred in 88 263 patients (32.7%). After adjustment for baseline differences, the risk of mortality was lower in patients receiving  $\beta$ -blockers (adjusted hazard ratio=0.76; 95% confidence interval=0.74–0.78) and calcium channel blockers (adjusted hazard ratio=0.93; 95% confidence interval=0.90–0.96) compared with those who did not receive rate-control medications. On the contrary, the digoxin group had a higher risk of mortality with an adjusted hazard ratio of 1.12 (95% confidence interval=1.10–1.14). The results were observed consistently in subgroup analyses and among the cohorts after propensity matching.

**Conclusions**—In this nationwide atrial fibrillation cohort, the risk of mortality was lower for patients receiving rate-control treatment with  $\beta$ -blockers or calcium channel blockers, and the use of  $\beta$ -blockers was associated with the largest risk reduction. Digoxin use was associated with greater mortality. Prospective, randomized trials are necessary to confirm these findings. (*Circulation*. 2015;132:1604-1612. DOI: 10.1161/CIRCULATIONAHA.114.013709.)

**Key Words:** adrenergic beta antagonists ■ atrial fibrillation ■ calcium channel blockers ■ digoxin ■ heart rate

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with marked morbidity, mortality, and socioeconomic burden.<sup>1</sup> Uncontrolled rapid ventricular rate during AF could result in left ventricular systolic dysfunction and worsening heart failure. Because previous randomized trials did not show significant differences in prognosis between rate-control and rhythm-control strategies,<sup>2–4</sup> rate control has become front-line therapy in the management of AF. The American College of Cardiology, American Heart Association, and European Society of Cardiology have emphasized the importance of rate control with drugs ( $\beta$ -blockers [BBs], nondihydropyridine calcium channel antagonists [CCBs], or digoxin) in long-term AF management (Class I recommendation).<sup>5,6</sup> However, these recommendations were

based on previous evidence demonstrating that CCBs or BBs were efficacious for heart rate control without a clinically important decrease in exercise tolerance for patients with AF,<sup>7</sup> and data on the survival benefits of rate control are lacking. The goal of the present study was to investigate the risk of mortality in patients without rate-control treatments compared with those who received different rate-control drugs.

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### Methods

This study used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance system is a mandatory universal

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health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed healthcare data from >23 million enrollees, representing >99% of Taiwan's population. In this cohort data set, the patients' original identification numbers were encrypted to protect their privacy, but the encrypting procedure was consistent, so linkage of the claims belonging to the same patient was feasible within the NHIRD and can be followed continuously. Numerous scientific research articles have already been published using data from NHIRD (<http://nhird.nhri.org.tw/en/Research.html>). The large sample size of this database provides a good opportunity to study the risk of mortality between patients with AF with and without rate-control treatments. The study was approved by the Institutional Review Board at Taipei Veterans General Hospital, Taipei, Taiwan.

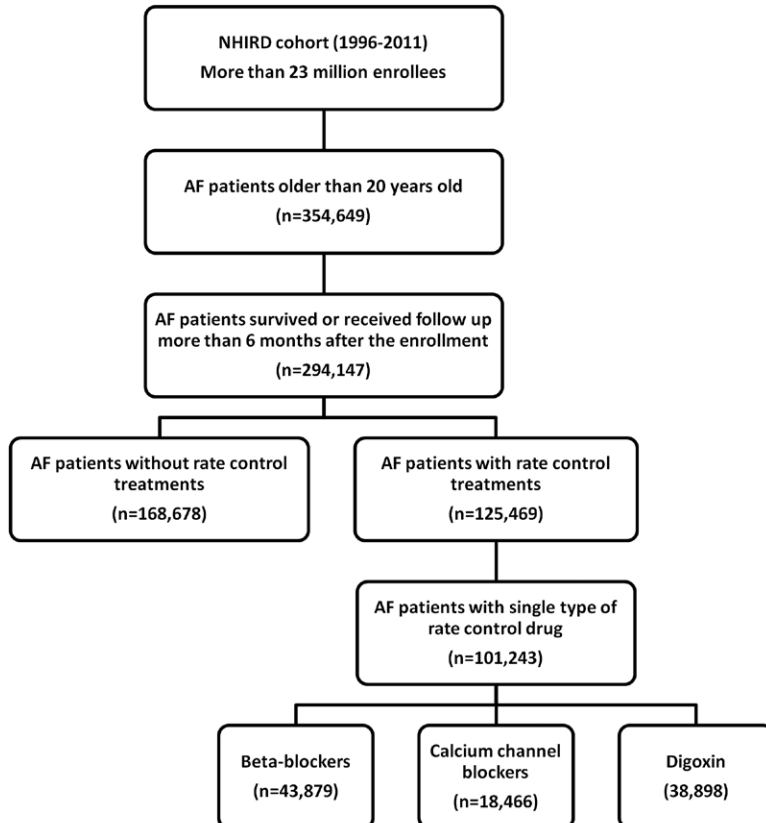
## Study Cohort

From January 1, 1996, to December 31, 2011, a total of 354 649 patients with AF who were  $\geq 20$  years of age were identified from the NHIRD as the study population. AF was diagnosed with the use of the *International Classification of Diseases, Ninth Revision, Clinical Modification* code (427.31). To ensure the accuracy of diagnosis, we defined patients with AF only when AF was a hospital discharge diagnosis or was confirmed on at least 2 occasions in the outpatient department.<sup>8</sup> We defined the date of discharge or the date of the second documented AF in the outpatient department as the index date. The diagnostic accuracy of AF using this definition in NHIRD has previously been validated.<sup>9,10</sup> Among the study population, we excluded patients who did not survive or did not receive follow-up for >6 months after the index date ( $n=60\,502$ ), resulting in 294 147 patients remaining in the study cohort.

## Definitions of Rate-Control Treatments and Study End Point

Prescriptions of BBs, CCBs, and digoxin, which were available in Taiwan for rate control, were identified for every patient. BBs included acebutolol, alprenolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, pindolol, propranolol, and timolol. CCBs included verapamil and diltiazem. Patients were assigned to each treatment group if they received 1 kind of drugs (BBs or CCBs or digoxin) for >90 days within 6 months after enrollment. With the use of this definition, a total of 168 678 subjects who did not receive any rate-control drug, including BBs, CCBs, and digoxin, were identified as the reference group. Of the 125 469 patients with AF receiving rate-control treatments, 24 226 subjects receiving >1 kind of rate-control drugs were excluded. Thus, there were 43 879, 18 466, and 38 898 patients enrolled in the BB, CCB, and digoxin groups, respectively. A flowchart of the enrollment of the study cohort is shown in Figure 1. The frequencies of use of BBs, CCBs and digoxin (days per year) were calculated for each patient by dividing the total days of drug prescriptions during the follow-up period (days) by follow-up duration (years).

Information about important comorbid conditions of each individual was retrieved from the medical claims based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. We defined patients with a certain disease only when it was a hospital discharge diagnosis or was confirmed on at least 2 occasions in the outpatient department. The diagnostic accuracies of important comorbidities in NHIRD such as hypertension, diabetes mellitus, heart failure, myocardial infarction, hyperlipidemia, and chronic obstructive pulmonary disease have been validated.<sup>11,12</sup> Insurance premiums, calculated according to the beneficiary's total income, were used to estimate monthly income. Monthly income was grouped into low income (monthly income <20 000 New Taiwan



**Figure 1.** Flowchart of the enrollment of the study cohort. From January 1, 1996, to December 31, 2011, a total of 168 678 patients with atrial fibrillation (AF) who did not receive rate-control medications were identified from the National Health Insurance Research Database (NHIRD) to constitute the reference group. Among the 101 243 patients with AF who received a single type of rate-control drug, 43 879 patients were taking  $\beta$ -blockers, 18 466 patients were taking calcium channel blockers, and 38 898 patients were taking digoxin.

**Table 1. Baseline Characteristics of Patients With AF Without Propensity Matching (Original Cohort)**

Variable	Without Rate-Control Treatments (n=168 678)	BBs (n=43 879)	CCBs (n=18 466)	Digoxin (n=38,898)	P Value
Age, mean (SD), y	71 (13)	68 (12)	72 (11)	71 (12)	<0.001
Male sex, n (%)	96 728 (57)	23 136 (53)	10 075 (55)	20 890 (54)	<0.001
Comorbidities, n (%)					
Congestive heart failure	58 840 (35)	15 560 (36)	7030 (38)	22 250 (57)	<0.001
Hypertension	107 820 (64)	35 763 (82)	14 373 (78)	24 428 (63)	<0.001
Diabetes mellitus	44 207 (26)	14 056 (32)	5659 (31)	9923 (26)	<0.001
Previous stroke/TIA	56 784 (34)	13 988 (32)	6467 (35)	12 044 (31)	<0.001
Vascular diseases	33 421 (20)	15 935 (36)	5624 (31)	6798 (18)	<0.001
Dyslipidemia	39 127 (23)	16 468 (38)	5402 (29)	6691 (17)	<0.001
Non-ESRD CKD	23 764 (14)	6365 (15)	2778 (15)	4567 (12)	<0.001
ESRD	3864 (2)	1077 (3)	293 (2)	239 (1)	<0.001
COPD	57 475 (34)	11 765 (27)	8238 (45)	13 203 (34)	<0.001
Malignancy	7673 (5)	2068 (5)	890 (5)	1447 (4)	<0.001
Autoimmune diseases	9236 (6)	2844 (7)	1096 (6)	1628 (4)	<0.001
Liver cirrhosis	5491 (3)	1170 (3)	528 (3)	1057 (3)	<0.001
Medications, n (%)					
Aspirin	44 176 (26)	21 196 (48)	8428 (46)	14 863 (38)	<0.001
Clopidogrel	5941 (4)	3768 (9)	1131 (6)	1165 (3)	<0.001
Warfarin	15 346 (9)	5921 (14)	2332 (13)	9287 (24)	<0.001
Class I AADs	5978 (4)	3561 (8)	1528 (8)	750 (2)	<0.001
Class III AADs (amiodarone or sotalol)	16 029 (10)	7160 (16)	2850 (15)	2451 (6)	<0.001
ACEI/ARB	42 842 (25)	19 722 (45)	6579 (36)	15 499 (40)	<0.001
Statins	6365 (4)	3032 (7)	910 (5)	1107 (3)	<0.001
Degree of urbanization, n (%)					0.001
Urban	85 165 (50)	24 750 (56)	9660 (52)	20 260 (52)	
Suburban	57 147 (34)	13 664 (31)	6064 (33)	12 732 (33)	
Rural	26 366 (16)	5465 (13)	2742 (15)	5906 (15)	
Income level, n (%)					0.002
Low	89 691 (53)	20 862 (48)	9537 (52)	20 996 (54)	
Median	57 234 (34)	16 323 (37)	6496 (35)	12 612 (32)	
High	21 753 (13)	6694 (15)	2433 (13)	5290 (14)	

AAD indicates antiarrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BB,  $\beta$ -blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; and TIA, transient ischemic attack.

Dollars), medium income (monthly income  $\geq 20\,000$  but  $< 40\,000$  New Taiwan Dollars), and high income (monthly income  $\geq 40\,000$  NTD).<sup>13</sup> Information about the degree of urbanization (urban, suburban, or

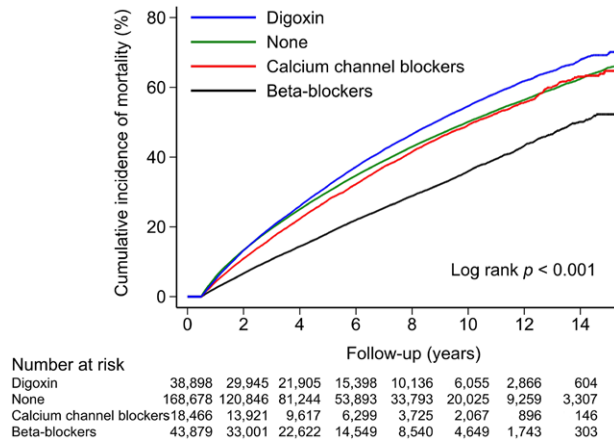
rural) of each patient was available in the Taiwan NHIRD on the basis of the townships where the patients lived. The stratifications of townships were based on the township population density (people per 1

**Table 2. Risk of Mortality in Patients With Different Rate-Control Medications Without Propensity Matching (Original Cohort)**

Rate-Control Treatments	Patients, n	Annual Mortality Rate, %	HR (95% CI)	P Value	Adjusted HF (95% CI)*	P Value
None (reference group)	168 678	6.99	1 (Reference)	...	1 (Reference)	...
BBs	43 879	4.15	0.59 (0.58–0.61)	<0.001	0.76 (0.74–0.78)	<0.001
CCBs	18 466	6.49	0.93 (0.90–0.95)	<0.001	0.93 (0.90–0.96)	<0.001
Digoxin	38 898	7.70	1.10 (1.08–1.12)	<0.001	1.12 (1.10–1.14)	<0.001

BB indicates  $\beta$ -blocker; CCB, calcium channel blocker; CI, confidence interval; and HR, hazard ratio.

\*Adjustment for all variables in Table 1, including age, sex, comorbidities, medications, degree of urbanization, and income level.



**Figure 2.** Cumulative incidence curves of mortality in patients with atrial fibrillation receiving different medications for rate control. The cumulative incidence curves with the log-rank test showed that the risk of mortality was lower in patients treated with  $\beta$ -blockers and higher in patients receiving digoxin.

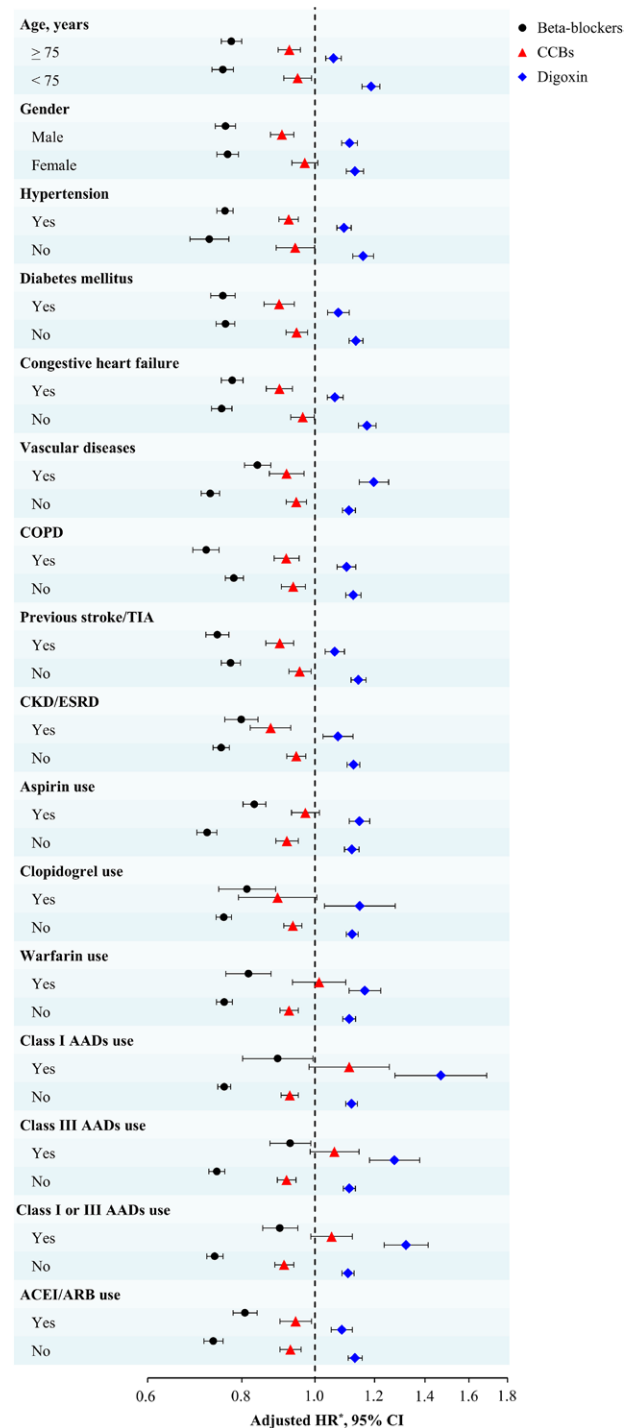
km<sup>2</sup>), population ratio of people with educational levels of college or above, population ratio of people >65 years of age, population ratio of agriculture workers, and the number of physicians per 100 000 people (<http://ntur.lib.ntu.edu.tw/bitstream/246246/176519/1/5.pdf>). The study end point was the occurrence of all-cause mortality.

### Propensity-Matched Analyses

We performed propensity score-matched analyses for 3 kinds of comparisons: BBs versus no rate-control treatment, CCBs versus no rate-control treatment, and digoxin versus no rate-control treatment. We calculated propensity scores for the likelihoods of using BBs, CCBs, and digoxin compared with no rate-control treatment by multivariate logistic regression analyses, conditional on all baseline covariates listed in Table 1. The results of the propensity score models for the probabilities of the use of BBs, CCBs, and digoxin are shown in Table 1 in the online-only Data Supplement. After that, we matched patients in the BB group to those in the no rate-control treatment group with a 1:1 ratio on the basis of age, sex, and the closest propensity score for the use of BBs within a threshold of  $\pm 0.01$ . If >1 patient in the reference group could be matched to the corresponding subject in the BB group, 1 patient from the reference group was selected randomly without repeat sampling. Similar matching processes were performed for the comparisons of CCBs and no rate-control treatment and of digoxin versus no rate-control treatment based on the propensity scores for the use of CCBs and digoxin, respectively. Figures I through III in the online-only Data Supplement show the distributions of propensity scores for study subjects for the use of BBs, CCBs, and digoxin before and after the propensity matching.

### Statistical Analysis

Data are presented as the mean and standard deviation for normally distributed continuous variables and as proportions for categorical variables. Differences between normally distributed continuous values were assessed with an unpaired 2-tailed *t* test or 1-way ANOVA with post hoc Bonferroni correction. Differences between nominal variables were compared by  $\chi^2$  test. The risk of mortality was assessed with Cox regression analysis. The cumulative incidence curve of mortality was plotted via the Kaplan-Meier method, with statistical significance examined by the log-rank test. Among propensity score-matched patients, the differences between the continuous variables were assessed with the paired *t* test, and the differences between nominal variables were compared by the McNemar test. Cox proportional hazards model accounting for frailty effects within matched pairs was



**Figure 3.** Rate-control medications and the risk of mortality in different groups of patients. In the subgroup analysis, the use of  $\beta$ -blockers for rate control consistently decreased and digoxin increased the risk of mortality in different groups of patients. The use of calcium channel blockers (CCBs) was associated with a survival benefit except for in female patients and those receiving treatment with aspirin, clopidogrel, warfarin, or Class I/III antiarrhythmic drugs (AADs). \*Adjustment for all variables in Table 1, including age, sex, comorbidities, medications, degree of urbanization, and income level. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; and TIA, transient ischemic attack.

**Table 3. Average Use of BBs, CCBs, and Digoxin in the Different Groups During the Follow-Up**

Groups of Rate-Control Treatments	BBs, Median (25th, 75th Percentiles), d/y	CCBs, Median (25th, 75th Percentiles), d/y	Digoxin, Median (25th, 75th Percentiles), d/y
None (reference group)	2 (0, 38)	0 (0, 8)	0 (0, 17)
BBs	223 (125, 326)	0 (0, 6)	0 (0, 4)
CCBs	3 (0, 49)	180 (82, 293)	0 (0, 13)
Digoxin	2 (0, 42)	0 (0, 8)	230 (123, 317)

BB indicates  $\beta$ -blocker; and CCB, calcium channel blocker.

used to assess the risk of mortality for different groups of patients. All statistical significance was set at a value of  $P < 0.05$ .

## Results

### Baseline Characteristics of Study Patients Without Propensity Matching

The baseline characteristics of the study patients without propensity matching are shown in Table 1. The mean age of patients

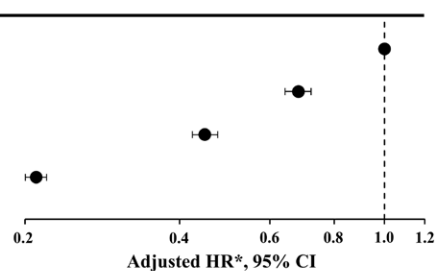
was  $70 \pm 13$  years, and 56% were male. The 4 groups of patients were significantly different from each other in age, sex, comorbidities, medications, degree of urbanization, and income level.

### Risk of Mortality in Patients With Different Rate-Control Medications Without Propensity Matching

During the follow-up of  $4.9 \pm 3.7$  years, mortality occurred in 88 263 patients (32.7%). The annual mortality rates of the 4 groups are shown in Table 2. After adjustment for baseline

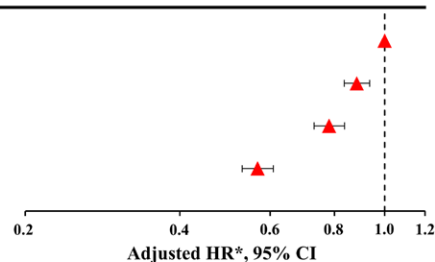
#### BBs

Frequency of usage	<i>n</i>	Adjusted HR* (95% CI)
First quartile (reference)	10,951	1
Second quartile	10,898	0.68 (0.64–0.72)
Third quartile	11,057	0.45 (0.42–0.47)
Fourth quartile	10,973	0.21 (0.20–0.22)



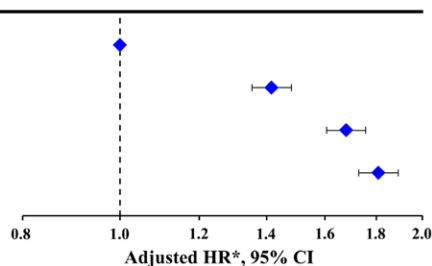
#### CCBs

Frequency of usage	<i>n</i>	Adjusted HR* (95% CI)
First quartile (reference)	4,634	1
Second quartile	4,604	0.88 (0.83–0.94)
Third quartile	4,581	0.78 (0.73–0.84)
Fourth quartile	4,647	0.57 (0.53–0.61)



#### Digoxin

Frequency of usage	<i>n</i>	Adjusted HR* (95% CI)
First quartile (reference)	9,690	1
Second quartile	9,731	1.42 (1.35–1.48)
Third quartile	9,778	1.68 (1.61–1.76)
Fourth quartile	9,699	1.81 (1.73–1.89)



**Figure 4.** Frequency of drug use and risk of mortality. Among the group of  $\beta$ -blockers (BBs) and calcium channel blockers (CCBs), patients receiving drugs more frequently had a lower risk of mortality compared with those with less frequent use. In contrast, the risk of mortality was higher among patients who received digoxin more frequently. \*Adjustment for all variables in Table 1, including age, sex, comorbidities, medications, degree of urbanization, and income level. CI indicates confidence interval; and HR, hazard ratio.



**Table 4. Baseline Characteristics of Patients With AF After Propensity Matching**

Variables	BBs vs No Rate-Control Treatments			CCBs vs No Rate-Control Treatments			Digoxin vs No Rate-Control Treatments		
	BBs (n=42 528)	Without Rate-Control Treatments (n=42,528)	P Value	CCBs (n=18 375)	Without Rate-Control Treatments (n=18 375)	P value	Digoxin (n=36 626)	Without Rate-Control Treatments (n=36 626)	P Value
Age, mean (SD), y	68 (12)	68 (12)	1.000	72 (11)	72 (11)	1.000	72 (12)	72 (12)	1.000
Male sex, n (%)	22 351 (53)	22 351 (53)	1.000	10 020 (55)	10 020 (55)	1.000	19 974 (55)	19 974 (55)	1.000
Comorbidities, n (%)									
Congestive heart failure	15 270 (36)	15 275 (36)	0.966	6 996 (38)	6 998 (38)	0.984	20 433 (56)	20 516 (56)	0.178
Hypertension	34 501 (81)	34 503 (81)	0.983	14 292 (78)	14 295 (78)	0.945	23 773 (65)	23 798 (65)	0.741
Diabetes mellitus	13 713 (32)	13 718 (32)	0.966	5 639 (31)	5 639 (31)	1.000	9 695 (26)	9 699 (26)	0.971
Previous stroke/TIA	13 874 (33)	13 884 (33)	0.915	6 453 (35)	6 455 (35)	0.979	11 754 (32)	11 782 (32)	0.727
Vascular diseases	15 058 (35)	15 063 (35)	0.961	5 572 (30)	5 570 (30)	0.979	6 669 (18)	6 713 (18)	0.517
Dyslipidemia	15 738 (37)	15 745 (37)	0.945	5 377 (29)	5 380 (29)	0.968	6 630 (18)	6 682 (18)	0.405
Non-ESRD CKD	6 264 (15)	6 270 (15)	0.950	2 767 (15)	2 767 (15)	1.000	4 490 (12)	4 526 (12)	0.564
ESRD	1 059 (2)	1 060 (2)	1.000	293 (2)	293 (2)	1.000	239 (1)	241 (1)	0.955
COPD	11 694 (28)	11 696 (28)	0.990	8 171 (44)	8 170 (44)	1.000	12 884 (35)	12 886 (35)	0.991
Malignancy	2 030 (5)	2 034 (5)	0.955	889 (5)	887 (5)	0.976	1 412 (4)	1 429 (4)	0.725
Autoimmune diseases	2 794 (7)	2 797 (7)	0.974	1 091 (6)	1 088 (6)	0.954	1 604 (4)	1 638 (4)	0.470
Liver cirrhosis	1 160 (3)	1 160 (3)	1.000	528 (3)	527 (3)	1.000	1 024 (3)	1 043 (3)	0.650
Medications, n (%)									
Aspirin	20 043 (47)	20 043 (47)	1.000	8 344 (45)	8 340 (45)	0.922	14 092 (38)	14 187 (39)	0.191
Clopidogrel	3 392 (8)	3 391 (8)	1.000	1 118 (6)	1 114 (6)	0.927	1 154 (3)	1 156 (3)	0.980
Warfarin	5 721 (13)	5 725 (13)	0.967	2 304 (13)	2 303 (13)	1.000	7 510 (21)	7 538 (21)	0.649
Class I AADs	3 162 (7)	3 157 (7)	0.947	1 468 (8)	1 461 (8)	0.830	745 (2)	778 (2)	0.305
Class III AADs (amiodarone or sotalolol)	6 827 (16)	6 829 (16)	0.991	2 830 (15)	2 827 (15)	0.959	2 407 (7)	2 471 (7)	0.205
ACEI/ARB	18 757 (44)	18 762 (44)	0.962	6 536 (36)	6 536 (36)	1.000	14 367 (39)	14 484 (40)	0.114
Statins	2 901 (7)	2 906 (7)	0.950	907 (5)	907 (5)	1.000	1 099 (3)	1 130 (3)	0.437
Degree of urbanization, n (%)									
Urban	23 684 (56)	23 677 (56)	0.841	9 602 (52)	9 598 (52)	1.000	18 806 (51)	18 773 (51)	0.981
Suburban	13 430 (32)	13 431 (32)		6 039 (33)	6 041 (33)		12 168 (33)	12 177 (33)	
Rural	5 414 (13)	5 420 (13)		2 734 (15)	2 736 (15)		5 652 (15)	5 676 (16)	
Income level, n (%)									
Low	20 257 (48)	20 249 (48)	0.489	9 492 (52)	9 487 (52)	0.696	19 683 (54)	19 661 (54)	0.904
Median	15 867 (37)	15 870 (37)		6 467 (35)	6 469 (35)		11 971 (33)	11 989 (33)	
High	6 404 (15)	6 409 (15)		2 416 (13)	2 419 (13)		4 972 (14)	4 976 (14)	
Propensity score	0.29 (0.14)	0.29 (0.14)	0.961	0.13 (0.06)	0.13 (0.06)	0.902	0.26 (0.14)	0.26 (0.14)	0.893

AAD indicates antiarrhythmic drug; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BB,  $\beta$ -blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; and TIA, transient ischemic attack.

differences, the risk of mortality was lower in patients receiving BBs (adjusted hazard ratio [HR]=0.76; 95% confidence interval [CI]=0.74–0.78;  $P<0.001$ ) and CCBs (adjusted HR=0.93; 95% CI=0.90–0.96;  $P<0.001$ ) compared with those who did not receive rate-control medications (Table 2). In contrast, the digoxin group had a higher risk of mortality with an adjusted HR of 1.12 (95% CI=1.10–1.14;  $P<0.001$ ) compared with the reference group (Table 2). The cumulative incidence curves of mortality of 4 groups are shown in Figure 2. In subgroup analyses, the use of BBs for rate control consistently decreased and digoxin increased the risk of mortality in different groups of patients (Figure 3). The association between CCB use and

mortality was not statistically significant in female patients and those receiving treatment with aspirin, clopidogrel, warfarin, or Class I/III antiarrhythmic drugs (Figure 3).

### Prescriptions of Drugs During the Follow-Up

To confirm whether the definition used for grouping based on the prescriptions of drugs within 6 months after the enrollment was appropriate, the frequencies of drug use (total days of drug prescriptions [days]/follow-up duration [years]) for BBs, CCBs, and digoxin during the follow-up period were calculated for each patient. The results are presented as median values (25th, 75th percentiles) in Table 3. These analyses

demonstrated that rate-control strategies adopted at baseline can be representative of the long-term treatment strategies in most patients.

### Frequencies of the Drug Use and Risk of Mortality

Among the group of BB users ( $n=43\,879$ ), patients were divided into 4 groups based on the quartile values of the frequency of the BB use shown in Table 3 (first quartile  $<125$  d/y; second quartile,  $125 - <223$  d/y; third quartile,  $223 - <326$  d/y; fourth quartile,  $\geq 326$  d/y). Patients receiving BBs more frequently had a lower risk of mortality compared with those with less frequent use (Figure 4). Similar analyses were performed for the groups of CCBs and digoxin (Figure 4).

### Results After Propensity Matching

The baseline characteristics after propensity matching for 3 comparisons (BBs versus no rate-control treatment, CCBs versus no rate-control treatment, and digoxin versus no rate-control treatment) are shown in Table 4. Propensity scores between 2 groups in each comparison were similar. Age, sex, comorbidities, and use of concomitant medications were not significantly different between the groups in each comparison. Compared with patients without rate-control treatment, mortality rates were lower in the BB and CCB groups and higher in the digoxin group. These results were consistent with that derived from the nonmatched cohort (Table 5).

## Discussion

### Main Findings

In this large-scale, nationwide study, we demonstrate that patients with AF receiving rate-control treatments with BBs or nondihydropyridine CCBs have a lower risk of mortality compared with those not taking rate-control drugs. The risk of mortality was lowest in the group taking BBs. In contrast, the use of digoxin was associated with a higher risk of mortality.

### Rate Control in AF: Rationale and Evidence

A sustained, uncontrolled tachycardia may lead to dilatation of left ventricle, increased ventricular wall stress, and left ventricular systolic dysfunction (so-called tachycardia-induced cardiomyopathy).<sup>14</sup> In AF-associated heart failure requiring

hospitalization, tachycardia-induced cardiomyopathy was the presumed cause in approximately one third of patients without previously known structural heart diseases.<sup>15</sup> Previous studies have demonstrated that improvements in and reversal of left ventricular dysfunction could be achieved by controlling AF-related rapid ventricular responses.<sup>16</sup> On the basis of the evidence mentioned above, rate control in AF is considered the cornerstone of managing AF patient symptoms and has been given a Class I recommendation in both US and European AF guidelines.<sup>5,6</sup> However, whether rate-control treatments with BBs or CCBs could improve the survival of patients with AF has not previously been investigated in large population-based cohorts.

In this nationwide study, we demonstrated that patients with AF receiving rate-control treatments of BBs or CCBs had a lower risk of mortality compared with those without rate-control drugs. Patients who received BBs as the rate-control drug had a 24% lower risk of mortality compared with those without rate-control treatments. Although these 4 groups were different in terms of their baseline characteristics, a lower risk of mortality was consistently observed among patients taking BBs even after adjustment for these potential confounders with multivariate Cox regression and propensity-matched analyses.

### The Survival Benefits of BBs in AF

In the rate-control arm of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, overall rate control was achieved in 70% of patients with BBs, in 54% with CCBs, and in 58% with digoxin.<sup>17</sup> The data suggest that BBs were the most effective drugs for controlling ventricular rates in AF, which may result in a better outcome. In addition to slowing heart rate, BBs have been reported to have several pleiotropic effects, including antioxidant activities,<sup>18,19</sup> improvements in endothelial function,<sup>20</sup> and anti-inflammatory potential,<sup>21</sup> which may provide some beneficial effects in addition to its rate-control activity. However, further study is necessary to investigate the precise mechanism(s) behind the observed lower risk of mortality of BB use compared with the use of other rate-control drugs.

In the recent meta-analysis by Kotecha et al<sup>22</sup> using data from 18 254 patients (3066 subjects had AF) enrolled in 10 trials of BBs in heart failure and reduced ejection fraction, the

**Table 5. Risk of Mortality in Patients With Different Rate-Control Medications After Propensity Matching**

Rate-Control Treatments	Patients, n	Annual Mortality Rate, %	HR (95% CI)	P Value	Adjusted HR (95% CI)*	P Value
BBs vs no treatments						
None (reference group)	42 528	5.13	1 (Reference)	...	1 (Reference)	...
BBs	42 528	4.23	0.83 (0.80–0.85)	<0.001	0.80 (0.78–0.82)	<0.001
CCBs vs no treatments						
None (reference group)	18 375	6.77	1 (Reference)	...	1 (Reference)	...
Calcium channel blockers	18 375	6.51	0.96 (0.92–0.99)	0.016	0.95 (0.92–0.99)	0.008
Digoxin vs no treatments						
None (reference group)	36 626	7.21	1 (Reference)	...	1 (Reference)	...
Digoxin	36 626	7.98	1.10 (1.07–1.13)	<0.001	1.11 (1.08–1.13)	<0.001

BB indicates  $\beta$ -blocker; CCB, calcium channel blocker; CI, confidence interval; and HR, hazard ratio.

\*Adjustment for all variables in Table 4, including age, sex, comorbidities, medications, degree of urbanization, and income level.

use of BBs did not reduce all-cause mortality in patients with AF with heart failure (HR=0.97; 95% CI=0.83–1.14). Another study performed by Lund et al<sup>23</sup> investigated the use of BBs and all-cause mortality in patients with heart failure with preserved ejection fraction using the Swedish heart failure registry. Lund and colleagues demonstrated that the use of BBs was associated with lower all-cause mortality, and subgroup analysis revealed that the benefits of BBs were observed only for patients with AF.<sup>23</sup> In the present study, we demonstrated that the association between BBs and a lower risk of mortality was consistent in patients with AF with or without heart failure. However, information on left ventricular ejection fraction was not available in our study. The discrepancies between our findings and those of previous studies could be explained partly by the different study designs and study populations (ie, heart failure with reduced versus preserved ejection fraction). Whether BBs could reduce mortality for patients with AF with heart failure remains unclear and should be studied in a prospective, randomized trial. It is also possible that patients receiving digoxin treatment may have a lower ejection fraction, which could account for the higher risk of mortality observed in the digoxin group.

### Study Limitations

Our study is the first population-based investigation demonstrating that rate-control treatment, especially BBs, was associated with a lower risk of mortality in patients with AF. The strength of our study was the use of a nationwide data set that enrolled a large sample of subjects. However, there are still some important limitations in our study. First, although we reported a significant association between mortality and different rate-control drugs, these results were derived from an observational database. Some important data such as baseline heart rate and blood pressure were not available, and we cannot exclude the possibility that significant bradycardia or hypotension, which prohibited the use of rate-control drugs for patients, was the reason why a higher mortality rate was observed in the group without rate-control treatments. We were not able to conclude whether different rate-control drugs were the direct causes of the differences in mortality; only a prospective, randomized trial can answer this question. Second, there were significant baseline differences between the 4 groups. Although we have tried to adjust for these differences using multivariate Cox regression and propensity-matched analyses, some unrecognized confounders may still be present. For example, the subtypes of AF (paroxysmal or nonparoxysmal) were not available from this nationwide data set. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, patients with persistent AF had a worse survival and were more likely to receive digoxin treatment compared with paroxysmal patients with AF.<sup>24</sup> Therefore, the higher risk of mortality observed in our digoxin treatment group may be attributable to more patients who received digoxin treatment being in persistent AF. However, the reliability of our findings was supported by the observed inverse relationship between exposure frequency of BBs and the risk of mortality. Finally, the present study enrolled only Asian patients; whether the results can be extrapolated to non-Asian populations remains

uncertain. Indeed, confounding by indication is an important limitation that could significantly confound the findings of the present study, and the results presented here should be interpreted carefully.

### Conclusions

In this nationwide AF cohort, the risk of mortality was lower for patients receiving rate-control treatments with BBs or CCBs, and the use of BBs was associated with the largest risk reduction. Digoxin use was associated with greater mortality. Prospective, large, randomized trials are necessary to confirm these findings.

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### Disclosures

None.

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## CLINICAL PERSPECTIVE

The current American and European guidelines emphasize the importance of rate control in treating patients with atrial fibrillation (Class I recommendation), although data on the survival benefits of rate control were lacking. This nationwide population-based study investigated the risk of mortality in 269 921 patients with atrial fibrillation stratified into 4 groups based on the different rate-control treatments they received, including  $\beta$ -blockers (n=43 879), calcium channel blockers (18 466), digoxin (38 898), and nontreatment (n=168 678). We found that the use of  $\beta$ -blockers or calcium channel blockers was associated with a lower risk of mortality with an adjusted hazard ratio of 0.76 and 0.93, respectively, compared with patients without rate-control treatments. In contrast, digoxin use was associated with a poor prognosis with a hazard ratio of 1.12. These results were consistently observed in the subgroup analysis, in sensitivity analysis based on the frequencies of the use of medications, and among the cohorts after propensity matching. Our findings support the current guidelines suggesting that rate-control treatments with  $\beta$ -blockers or calcium channel blockers should be performed for patients with atrial fibrillation. However, a prospective trial is necessary to confirm the findings presented in our study.

## Rate-Control Treatment and Mortality in Atrial Fibrillation

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## **Supplemental Material**

**Supplemental Table 1. Propensity score models of probabilities of the use of different rate control medications**

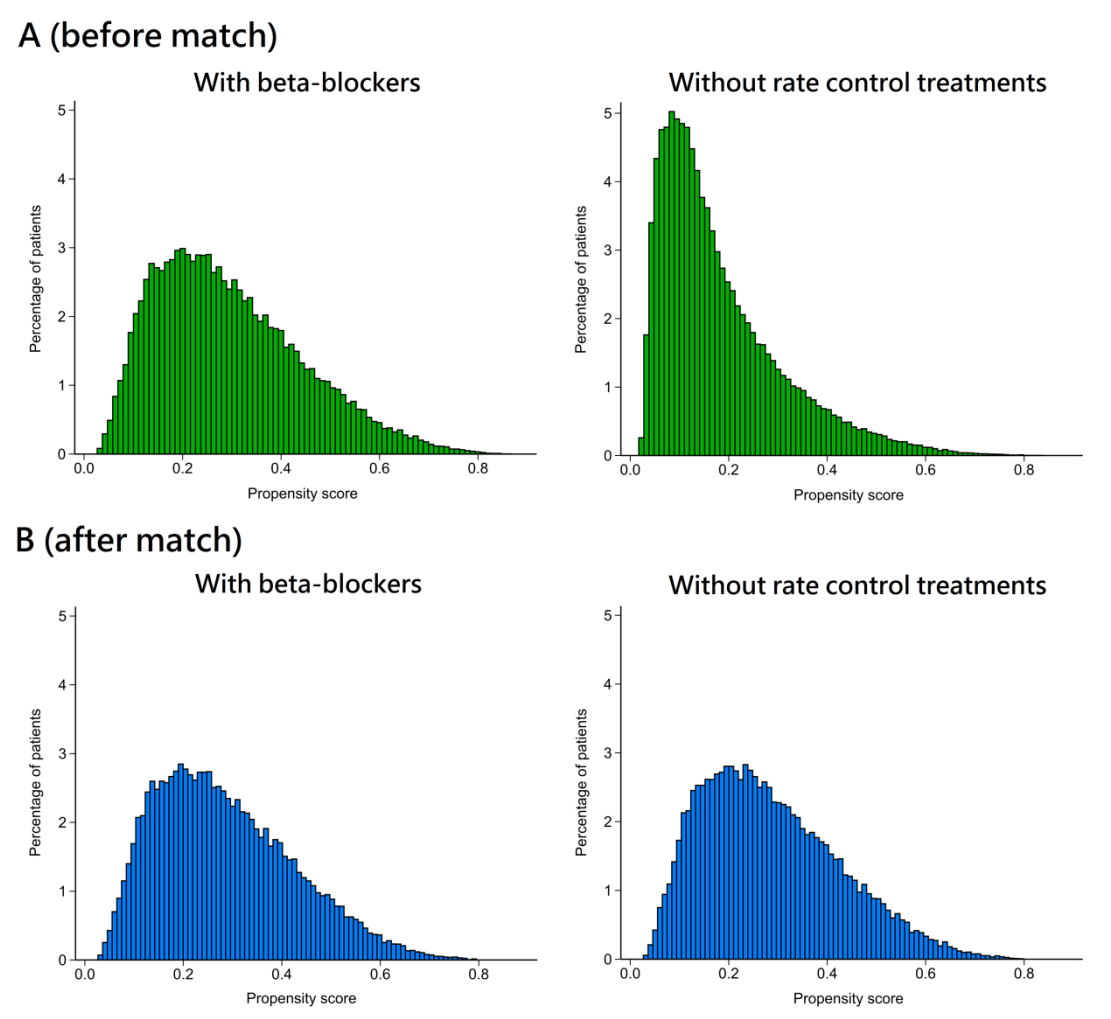
Variables	Beta-blockers vs. without rate control treatments			Calcium channel blockers vs. without rate control treatments			Digoxin vs. without rate control treatments		
	Estimate	Odds ratio (95% CI)	<i>P</i> value	Estimate	Odds ratio (95% CI)	<i>P</i> value	Estimate	Odds ratio (95% CI)	<i>P</i> value
Age, years	-0.024	0.98 (0.98–0.98)	< 0.001	0.005	1.00 (1.00–1.01)	< 0.001	0.001	1.00 (1.00–1.00)	0.125
Male gender	-0.276	0.76 (0.74–0.78)	< 0.001	-0.170	0.84 (0.82–0.87)	< 0.001	-0.148	0.86 (0.84–0.88)	< 0.001
Comorbidities									
Congestive heart failure	-0.049	0.95 (0.93–0.98)	< 0.001	-0.058	0.94 (0.91–0.98)	0.001	0.940	2.56 (2.50–2.62)	< 0.001
Hypertension	0.830	2.29 (2.22–2.36)	< 0.001	0.445	1.56 (1.50–1.63)	< 0.001	-0.205	0.81 (0.79–0.84)	< 0.001
Diabetes mellitus	-0.007	0.99 (0.97–1.02)	0.611	0.049	1.05 (1.01–1.09)	0.008	0.046	1.05 (1.02–1.08)	0.001
Previous stroke/TIA	-0.223	0.80 (0.78–0.82)	< 0.001	-0.190	0.83 (0.80–0.86)	< 0.001	-0.196	0.82 (0.80–0.84)	< 0.001
Vascular diseases	0.427	1.53 (1.49–1.57)	< 0.001	0.248	1.28 (1.24–1.33)	< 0.001	-0.307	0.74 (0.71–0.76)	< 0.001
Dyslipidemia	0.259	1.30 (1.26–1.33)	< 0.001	0.017	1.02 (0.98–1.06)	0.378	-0.387	0.68 (0.66–0.70)	< 0.001
Non-ESRD CKD	-0.031	0.97 (0.94–1.00)	0.067	-0.086	0.92 (0.88–0.96)	< 0.001	-0.252	0.78 (0.75–0.81)	< 0.001
ESRD	-0.253	0.78 (0.72–0.84)	< 0.001	-0.463	0.63 (0.56–0.71)	< 0.001	-1.185	0.31 (0.27–0.35)	< 0.001
COPD	-0.277	0.76 (0.74–0.78)	< 0.001	0.423	1.53 (1.48–1.58)	< 0.001	0.013	1.01 (0.99–1.04)	0.317
Malignancy	0.115	1.12 (1.06–1.18)	< 0.001	0.013	1.01 (0.94–1.09)	0.727	-0.069	0.93 (0.88–0.99)	0.025
Autoimmune diseases	0.064	1.07 (1.02–1.12)	0.007	-0.085	0.92 (0.86–0.98)	0.012	-0.249	0.78 (0.74–0.83)	< 0.001
Liver cirrhosis	-0.063	0.94 (0.88–1.00)	0.067	-0.076	0.93 (0.84–1.02)	0.107	-0.108	0.90 (0.84–0.96)	0.003
Medications									
Aspirin	0.759	2.14 (2.08–2.19)	< 0.001	0.750	2.12 (2.05–2.19)	< 0.001	0.770	2.16 (2.10–2.22)	< 0.001
Clopidogrel	0.598	1.82 (1.73–1.91)	< 0.001	0.354	1.43 (1.33–1.53)	< 0.001	0.108	1.11 (1.04–1.19)	0.002
Warfarin	0.484	1.62 (1.57–1.68)	< 0.001	0.515	1.67 (1.59–1.76)	< 0.001	1.328	3.77 (3.66–3.90)	< 0.001
Class I AADs	0.632	1.88 (1.80–1.97)	< 0.001	0.781	2.18 (2.05–2.32)	< 0.001	-0.718	0.49 (0.45–0.53)	< 0.001



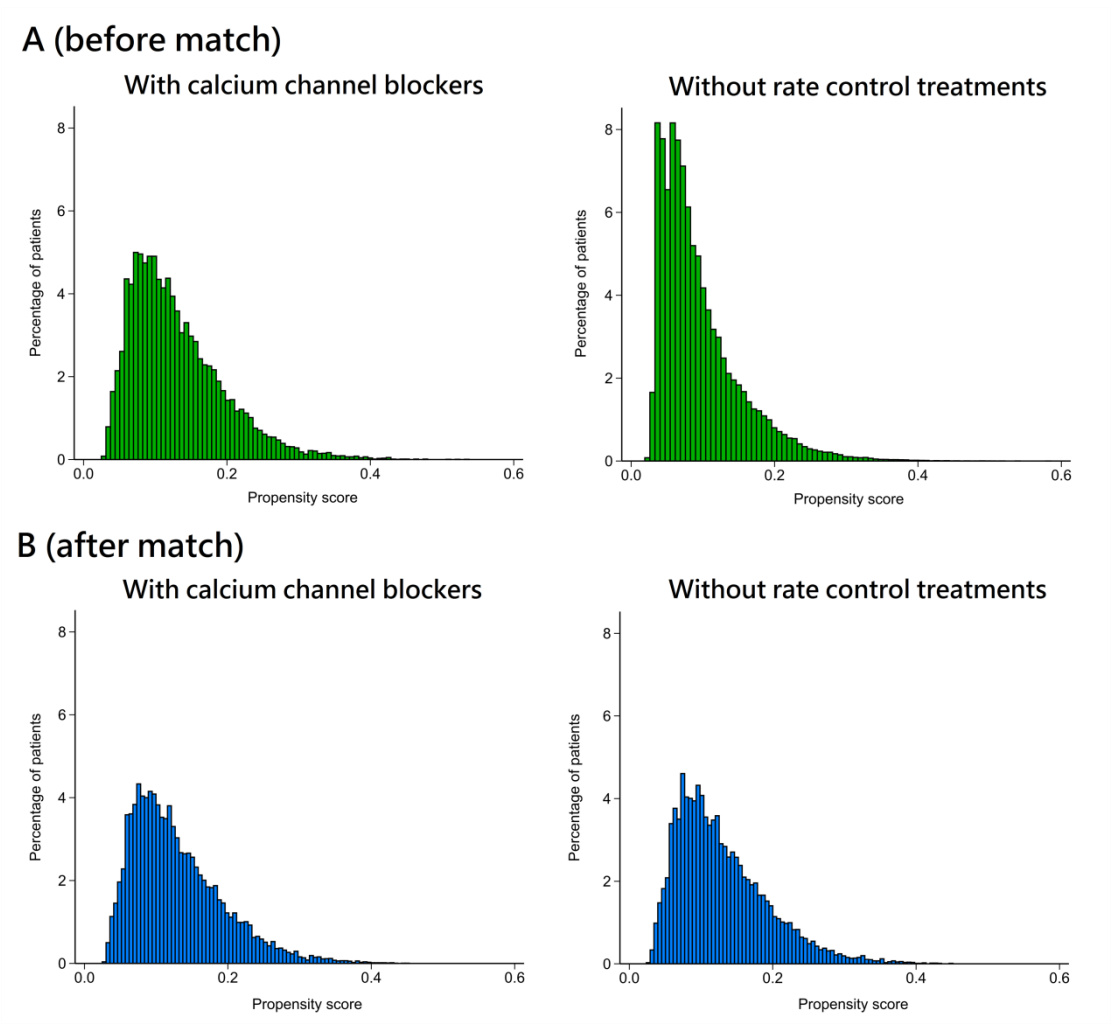
Class III AADs (Amiodarone or Sotalol)	0.211	1.23 (1.19–1.28)	< 0.001	0.304	1.36 (1.30–1.42)	< 0.001	-0.733	0.48 (0.46–0.50)	< 0.001
ACEI/ARB	0.407	1.50 (1.47–1.54)	< 0.001	0.063	1.07 (1.03–1.10)	< 0.001	0.523	1.69 (1.64–1.73)	< 0.001
Statins	-0.018	0.98 (0.93–1.03)	0.477	-0.096	0.91 (0.84–0.98)	0.013	-0.402	0.67 (0.62–0.72)	< 0.001
Degree of urbanization									
Urban	0.000	1 (reference)		0.000	1 (reference)		0.000	1 (reference)	
Suburban	-0.097	0.91 (0.88–0.93)	< 0.001	-0.053	0.95 (0.92–0.98)	0.003	-0.107	0.90 (0.87–0.92)	< 0.001
Rural	-0.183	0.83 (0.80–0.86)	< 0.001	-0.068	0.93 (0.89–0.98)	0.004	-0.120	0.89 (0.86–0.92)	< 0.001
Income level									
Low	0.000	1 (reference)		0.000	1 (reference)		0.000	1 (reference)	
Median	< 0.001	0.00 (0.00–0.00)	< 0.001	0.035	1.04 (1.00–1.07)	0.044	-0.091	0.91 (0.89–0.94)	< 0.001
High	0.059	1.06 (1.03–1.09)	< 0.001	0.048	1.05 (1.00–1.10)	0.052	0.061	1.06 (1.03–1.10)	0.001

AADs = anti-arrhythmic drugs; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II-receptor blocker; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; TIA = transient ischemic attack.

**Supplemental Figure 1.** Distributions of propensity scores of patients for the use of beta-blockers before (A) and after (B) propensity match



**Supplemental Figure 2.** Distributions of propensity scores of patients for the use of calcium channel blockers before (A) and after (B) propensity match



**Supplemental Figure 3.** Distributions of propensity scores of patients for the use of digoxin before (A) and after (B) propensity match

