Impact of Digitalis Use on Mortality in Japanese Patients With Non-Valvular Atrial Fibrillation
— A Subanalysis of the J-RHYTHM Registry —

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Background: Because the influence of digitalis use on the death of patients with non-valvular atrial fibrillation (NVAF) remains controversial, a subanalysis of the J-RHYTHM Registry was performed.

Methods and Results: A consecutive series of outpatients with AF from 158 institutions was enrolled and followed for 2 years or until the occurrence of an event. Among 7,406 patients with NVAF, 7,018 (age, 69.7±10.0 years; men, 71.1%) with information on antiarrhythmic drug and digitalis use at baseline were divided into 2 groups based on digitalis use. The influence of digitalis on death was investigated using a propensity score-matching model. In 802 patients treated with digitalis, all-cause death was significantly higher than in 6,216 patients with no digitalis use during the 2-year follow-up period (4.4% vs. 2.4%, unadjusted P=0.001). Digitalis use was significantly associated with all-cause death in the crude model (hazard ratio [HR] 1.85, 95% confidence interval [CI] 1.28–2.68, P=0.001). However, after propensity score-matching, the association was not significant (HR 1.31, 95% CI 0.70–2.46, P=0.405). Older age, male sex, heart failure, coronary artery disease, and lower body mass index were significantly associated with all-cause death in NVAF patients treated with digitalis.

Conclusions: Digitalis use was not independently associated with all-cause death, and several clinical confounding factors might contribute to increased mortality in NVAF patients treated with digitalis.

Key Words: Antiarrhythmic drugs; Atrial fibrillation; Digitalis; Digoxin; Mortality

Atrial fibrillation (AF) is a common arrhythmia and a known major risk factor for cardiogenic thromboembolism.1,2 In addition, AF itself is a risk factor for increased morbidity and mortality.3,4 In the Framingham Heart Study, mortality was 1.5-fold higher in men and 1.9-fold higher in women with AF than in either sex without AF.3 The number of AF-related deaths is increasing worldwide.5 Digitalis exerts a positive inotropic action by inhibiting the Na pump (Na+/K+-ATPase) and a negative chronotropic action via a parasympathomimetic action.6 Therefore, digitalis, mainly in the form of digoxin, has been used in the treatment of heart failure and for ventricular rate control in patients with AF.8 However, digitalis use is often harmful to patients because the effective therapeutic range of the serum concentration is narrow,9,10 and digoxin aggravates atrial remodeling.11 Several post hoc analyses of randomized controlled trials (RCTs) and retrospective cohort studies have indicated that digitalis use increased the long-term mortality in patients with AF,12–17 although conflicting results have been reported.18–23 Moreover, inconsistent results have even been found in the same study.12,19,20 The association between digitalis use and death has not yet been determined adequately in Asian patients with AF. Therefore, we investigated the influence of digitalis use on mortality in Japanese patients with non-valvular AF (NVAF) using data from the J-RHYTHM Registry.

Methods

Study Design of the J-RHYTHM Registry and Subanalysis
The J-RHYTHM Registry was conducted as a prospective observational study in order to investigate optimal anticoagulation therapy with warfarin in Japanese patients with

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Digitalis and Mortality in NVAF

The study design and baseline patient characteristics have been reported elsewhere. Briefly, the study protocol conformed to the Declaration of Helsinki principles and was approved by the ethics committee of each participating institution. A consecutive series of outpatients with AF of any type from 158 institutions was enrolled without any exclusion criteria regarding antiarrhythmic drug (AAD) and digitalis use. All participants gave written informed consent at the time of enrollment. All treatment strategies including the selection of AADs and digitalis, and the doses of these drugs were determined at the discretion of the treating cardiologists. Patients with valvular AF (those with mechanical valve replacement and mitral stenosis) were excluded from this subanalysis. Patients were followed for 2 years or until the occurrence of an event, whichever happened first. Primary endpoints were defined as thromboembolism, including symptomatic ischemic stroke, transient ischemic attack (TIA), and systemic embolic events; major hemorrhage, including intracranial hemorrhage, gastrointestinal hemorrhage, and other hemorrhages requiring hospitalization; or all-cause death. The diagnostic criteria for each event have been described elsewhere.

In this subanalysis, after surveying the status of AADs and digitalis use, patients were divided into 2 groups based on digitalis use at the time of enrollment (No-Digitalis group and Digitalis group). Baseline characteristics and event rates were compared between groups. Renal function, which affects mortality, was evaluated using creatinine clearance (CrCl) calculated by the Cockcroft-Gault formula.

**Statistical Analysis**

Data are presented as mean±standard deviation. Statistical significance of differences in mean values was analyzed using the Student’s t-test. Frequencies of parameters or events were compared using a chi-square test. Kaplan-Meier curves were used to compare time to events with log-rank tests. A Cox proportional hazard model was used to investigate the influence of digitalis use on events. Haz-

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Table 1. Antiarrhythmic Drugs and Digitalis in the J-RHYTHM Registry

| Vaughan Williams classification / Antiarrhythmic drugs* | No. of patients | Frequency in 7,018 patients (%) | Rate in class (%) |
|---------------------------------------------------------|----------------|-------------------------------|------------------|
| **Class I (Na channel blockers)**                       |                |                               |                  |
| Pilscainide                                             | 507           | 7.2                           | 33.6             |
| Cibenzoline                                             | 359           | 5.1                           | 23.8             |
| Flecaainide                                             | 229           | 3.3                           | 15.2             |
| Aprindine                                               | 180           | 2.6                           | 11.9             |
| Disopyramide                                            | 91            | 1.3                           | 6.0              |
| Propafenone                                             | 69            | 1.0                           | 4.6              |
| Pirmenol                                                | 33            | 0.5                           | 2.2              |
| Mexiletine                                              | 33            | 0.5                           | 2.2              |
| Procaainamide                                           | 6             | 0.1                           | 0.4              |
| Quinidine                                               | 1             | 0.0                           | 0.1              |
| **Subtotal**                                            | 1,508         | 21.5                          | 100              |
| **Class II (β-blockers)**                               |                |                               |                  |
| Carvedilol                                              | 451           | 6.4                           | 39.0             |
| Bisoprolol                                              | 391           | 5.6                           | 33.9             |
| Atenolol                                                | 186           | 2.7                           | 16.1             |
| Metoprolol                                              | 100           | 1.4                           | 8.7              |
| Propranolol                                             | 14            | 0.2                           | 1.2              |
| Others                                                  | 13            | 0.2                           | 1.1              |
| **Subtotal**                                            | 1,155         | 16.5                          | 100              |
| **Class III (K channel blockers)**                      |                |                               |                  |
| Bepridil**                                              | 780           | 11.1                          | 75.5             |
| Amiodarone                                              | 224           | 3.2                           | 21.7             |
| Sotalol                                                 | 29            | 0.4                           | 2.8              |
| **Subtotal**                                            | 1,033         | 14.7                          | 100              |
| **Class IV (Ca channel blockers)**                      |                |                               |                  |
| Verapamil                                               | 362           | 5.2                           | 73.6             |
| Diltiazem                                               | 130           | 1.9                           | 26.4             |
| **Subtotal**                                            | 492           | 7.0                           | 100              |
| **Digitalis**                                           |                |                               |                  |
| Digoxin                                                 | 521           | 7.4                           | 65.0             |
| Methyldigoxin                                           | 280           | 4.0                           | 34.9             |
| Digitoxin                                               | 1             | 0.0                           | 0.1              |
| **Subtotal**                                            | 802           | 11.4                          | 100              |

*Drugs in order of the rate in each class. **Bepridil was classified as a K channel blocker.
Calcium channel blockers. A propensity score for digitalis use was generated based on a multivariable logistic regression model using the variables listed above. Patients in the 2 groups were matched on a 1:1 basis with a 4-digit nearest neighbor algorithm. In addition, to identify significant factors for all-cause death, a multivariate Cox proportional hazard analysis using the stepwise forward method was performed. Two-tailed P-values <0.05 were considered statistically significant. All statistical analyses were performed with SPSS software version 23.0 (IBM Corporation).

Table 2. Baseline Characteristics of the Patients With Non-Valvular Atrial Fibrillation

| Overall | No-Digitalis | Digitalis | P value* |
|---------|-------------|-----------|---------|
| No. of patients | 7,018 | 6,216 | 802 |
| Age, years | 69.7±10.0 | 69.4±9.4 | 71.4±9.5 | <0.001 |
| Sex, male | 4,993 (71.1) | 4,459 (71.7) | 534 (66.6) | 0.003 |
| BMI, kg/m² | 23.6±3.9 | 23.7±3.6 | 23.2±5.9 | 0.001 |
| Type of atrial fibrillation | | | |
| Paroxysmal | 2,686 (38.3) | 2,578 (41.5) | 108 (13.5) |
| Persistent | 972 (13.9) | 876 (14.1) | 96 (12.0) | <0.001 |
| Permanent | 3,360 (47.9) | 2,762 (44.4) | 598 (76.6) |
| Comorbidities | | | |
| Coronary artery disease | 748 (10.7) | 655 (10.5) | 93 (11.6) | 0.393 |
| Cardiomyopathy | 604 (8.6) | 501 (8.1) | 103 (12.8) | <0.001 |
| Hypertrophic | 257 (3.7) | 237 (3.8) | 20 (2.5) | 0.076 |
| Dilated | 347 (4.9) | 264 (4.2) | 83 (10.3) | <0.001 |
| Congenital heart disease | 94 (1.3) | 81 (1.3) | 13 (1.6) | 0.566 |
| COPD | 128 (1.8) | 110 (1.8) | 18 (2.2) | 0.421 |
| Hyperthyroidism | 128 (1.8) | 107 (1.7) | 19 (2.4) | 0.247 |
| Risk factors for stroke | | | |
| Heart failure | 1,944 (27.7) | 1,593 (25.6) | 351 (43.8) | <0.001 |
| Hypertension | 4,251 (60.6) | 3,811 (61.3) | 440 (54.9) | <0.001 |
| Age (≥75 years) | 2,398 (34.2) | 2,075 (33.4) | 323 (40.3) | <0.001 |
| Diabetes mellitus | 748 (10.7) | 655 (10.5) | 93 (11.6) | <0.001 |
| Stroke/TIA | 951 (13.6) | 837 (13.5) | 114 (14.2) | 0.597 |
| CHADS₂ score | 1.7±1.2 | 1.6±1.2 | 1.9±1.2 | <0.001 |
| Clinical parameters | | | |
| Systolic BP, mmHg | 125.9±16.2 | 126.0±16.1 | 125.7±17.0 | 0.622 |
| Diastolic BP, mmHg | 73.5±17.2 | 73.6±17.8 | 72.6±12.0 | 0.122 |
| Heart rate, beats/min | 72.4±13.2 | 72.1±13.2 | 74.4±13.3 | <0.001 |
| CrCl, mL/min | 68.3±27.7 | 68.7±27.6 | 65.2±28.8 | 0.002 |
| Medications | | | |
| Warfarin | 6,064 (86.4) | 5,356 (83.2) | 708 (88.3) | 0.112 |
| Baseline PT-INR | 1.91±0.50 | 1.90±0.49 | 1.92±0.56 | 0.316 |
| TTR, %** | 59.2±29.1 | 59.2±29.3 | 59.3±29.2 | 0.934 |
| Antiplatelet drugs | 1,859 (26.5) | 1,621 (26.1) | 238 (29.7) | 0.033 |
| Aspirin | 1,609 (22.9) | 1,410 (22.7) | 199 (24.8) | 0.192 |
| Other | 422 (6.0) | 361 (5.8) | 61 (7.6) | 0.053 |
| Warfarin+antiplatelet | 1,333 (19.0) | 1,144 (18.4) | 189 (23.6) | <0.001 |
| Antiarrhythmic drugs | 3,373 (48.1) | 2,992 (48.1) | 381 (47.5) | 0.766 |
| Na channel blockers | 1,484 (21.1) | 1,405 (22.6) | 79 (9.9) | <0.001 |
| β-blockers | 1,148 (16.4) | 907 (14.6) | 241 (30.0) | <0.001 |
| K channel blockers*** | 1,028 (14.6) | 990 (15.9) | 38 (4.7) | <0.001 |
| Ca channel antagonists | 491 (7.0) | 374 (6.0) | 117 (14.6) | <0.001 |

Data are number of patients (%) or mean ± SD. *Comparison between No-Digitalis and Digitalis groups. **Target INR was 2.0–3.0 (<70 years) or 1.6–2.6 (≥70 years). ***Bepridil was classified as a K channel blocker. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHADS₂, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and history of stroke or TIA; TIA, transient ischemic attack; BP, blood pressure; CrCl, creatinine clearance; PT-INR, international normalized ratio of prothrombin time; TTR, time in therapeutic range.
Digitalis and Mortality in NVAF

Results

Among the 7,937 patients with AF who were enrolled in the J-RHYTHM Registry, 421 (5.3%) patients with valvular AF were excluded and 110 (1.5%) patients were lost to follow-up. Of the remaining 7,406 patients with NVAF, 388 patients with no information of AADs or digitalis at the time of enrollment were excluded. Consequently, a total of 7,018 patients constituted the study sample.

AADs and Digitalis

AADs, based on the Vaughan Williams classification, and digitalis at the time of enrollment in the J-RHYTHM Registry are listed in Table 1. A total of 3,794 (54.1%) patients received AADs, digitalis, or both. A single AAD was administered to 2,655 patients, 2 drugs to 634 patients, and ≥3 drugs to 84 patients. Pilsicainide, carvedilol, bepridil, and verapamil were used most frequently in each class (Table 1). Digitalis was administered to 802 (11.4%) patients in the form of digoxin in 521, methylidigoxin in 280, and digitoxin in 1. Of them, 421 patients received digitalis alone; digitalis was coadministered to 381 patients with a single AAD in 296, 2 drugs in 73, and ≥3 in 12.

Baseline Patient Characteristics and Medications

Baseline patient characteristics and medications used in the 2 groups are shown in Table 2. When compared with the No-Digitalis group, the Digitalis group had the following clinical characteristics: older age, higher CHADS 2 score (1 point for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and 2 points for history of stroke or TIA) and concomitant use of antiarrhythmic drugs (warfarin and antiplatelet drugs) and antiarrhythmic drugs (Na channel blockers, β-blockers, K channel blockers, and Ca channel blockers). BMI, CrCl, number of male patients, prevalence of hypertension, and concomitant use of Na and K channel blockers were significantly lower in the Digitalis group than in the No-Digitalis group (Table 2).

Event Rates and Digitalis Use

The 2-year event rates in the 2 groups are shown in Table 3. In the Digitalis group, all-cause death was significantly higher than in the No-Digitalis group (4.4% vs. 2.4%, P<0.001), but rates of thromboembolism and major hemorrhage were comparable between the 2 groups (Table 3).
Therefore, subsequent analyses were performed only for death. Noncardiovascular death in the Digitalis group was significantly higher than in the No-Digitalis group (3.4% vs. 1.5%, P<0.001), whereas cardiovascular death was comparable between the 2 groups (1.0% vs. 0.9%, P=0.823) (Table 3). Digitalis use was significantly associated with all-cause death in the unadjusted model (Model 1, HR 1.85, 95% CI 1.28–2.68, P=0.001) (Table 4). The Kaplan-Meier curves for all-cause death revealed a significant difference between the 2 groups on the log-rank test (P=0.001) (Figure A). When the HR was adjusted only for the use of AADs (Na channel blockers, β-blockers, K channel blockers, and Ca channel blockers), the association between digitalis use and all-cause death was still significant (Model 2, adjusted HR 1.77, 95% CI 1.21–2.59, P=0.003) (Table 4). There were no interactions for all-cause death between digitalis and each Vaughan Williams class of AAD (P for interaction=0.875, 0.389, 0.284, and 0.800, respectively). After adjusting for multiple covariates, digitalis use was no longer associated with all-cause death in the adjusted model (Model 3, adjusted HR 1.34, 95% CI 0.89–2.04, P=0.175) (Table 4).

**Mortality and Digitalis Use After Propensity Score-Matching**

After propensity score-matching, 1,006 patients (503 in each group) were included. Baseline patient characteristics and medications of the 2 matched groups are shown in Table 5. The groups matched well for all clinical variables except BMI (Table 5). The difference in all-cause death between the 2 groups became smaller and insignificant (4.4% vs. 3.4%, P=0.414), and digitalis use was not significantly associated with all-cause death after propensity score-matching (Model 4, HR 1.31, 95% CI 0.70–2.46, P=0.405) (Table 4). The Kaplan-Meier curves for all-cause death still revealed a lower survival rate in the Digitalis group, but the difference was insignificant on the log-rank test (P=0.404) (Figure B). When standard Cox proportional hazard analysis was performed using all 7,018 patients adjusted for full-digit propensity score as the sole covariate, digitalis use was not significantly associated with all-cause death (Model 5, adjusted HR 1.31, 95% CI 0.86–2.01, P=0.212) (Table 4).

**Independent Factors for All-Cause Death**

To identify the independent factors for all-cause death, multivariate Cox proportional hazard analysis using the stepwise forward method was performed. In the No-Digitalis group, male sex, heart failure, age (≥75 years), history of stroke or TIA, coronary artery disease, and lower CrCl were significantly associated with all-cause death (Table 6). In the Digitalis group, male sex, heart failure, age (≥75 years), coronary artery disease, and lower BMI were significantly associated with all-cause death (Table 6), although CrCl was significantly associated with all-cause death in univariate analysis (unadjusted HR 1.02/1-mL/min decrease, 95% CI 1.01–1.04, P=0.008).

**Discussion**

The major findings of the present study are summarized as follows. First, digitalis use was significantly associated with all-cause death in the crude model. However, the association was not significant in the adjusted models or propensity score-matched cohort. Second, in NVAF patients treated with digitalis, male sex, heart failure, age (≥75 years), coronary artery disease, and lower BMI were independently associated with all-cause death.

**Digitalis Use and Mortality in Previous Studies**

Inconsistent results have been reported concerning the association between digitalis use and mortality among
Digitalis and Mortality in NVAF

The difference in patient characteristics between the 2 groups (digoxin was mainly administered to an older and frailer subset of patients with AF). 38 However, another retrospective cohort study demonstrated that digoxin use was independently associated with higher risk of death (HR 1.71, 95% CI 1.52–1.93, P<0.001) even after propensity score-matching. 17 Moreover, post hoc analysis of prospective studies showed inconsistent results. 14,21,23 Even when the same data set was used, inconsistent results have been reported. A post hoc analysis of the AFFIRM (AF Follow-Up Investigation of Rhythm Management) trial showed that digoxin use was associated with a significant increase in all-cause death of AF patients (HR 1.41, 95% CI 1.19–1.67, P<0.001) after correcting for clinical charac-

| Table 5. Baseline Patient Characteristics After Propensity Score-Matching |
|-----------------------------|---------------------|---------------------|---------------------|
|                        | No-Digitalis | Digitalis | P value* |
| No. of patients | 503          | 503          |          |
| Age, years   | 70.6±9.6     | 71.2±9.7     | 0.334    |
| Sex, male   | 348 (69.2)   | 353 (70.2)   | 0.732    |
| BMI, kg/m²  | 23.7±3.7     | 23.1±3.4     | 0.004    |
| Type of atrial fibrillation |          |          |          |
| Paroxysmal   | 87 (17.3)    | 95 (18.9)    |          |
| Persistent   | 63 (12.5)    | 71 (14.1)    | 0.549    |
| Permanent    | 353 (70.2)   | 337 (67.0)   |          |
| Comorbidities |           |           |          |
| Coronary artery disease | 65 (12.9)   | 58 (11.5)    | 0.501    |
| Cardiomyopathy | 45 (8.9)    | 56 (11.1)    | 0.248    |
| Congenital heart disease | 5 (1.0)     | 7 (1.4)      | 0.561    |
| COPD         | 6 (1.2)      | 10 (2.0)     | 0.313    |
| Hyperthyroidism | 11 (2.2)    | 10 (2.0)     | 0.825    |
| Risk factors for stroke |         |           |          |
| Heart failure | 185 (36.8)   | 179 (35.6)   | 0.694    |
| Hypertension  | 297 (59.0)   | 304 (60.4)   | 0.653    |
| Age (≥75 years) | 192 (38.2)   | 199 (39.6)   | 0.651    |
| Diabetes mellitus | 116 (23.1)  | 112 (22.3)   | 0.763    |
| Stroke/TIA    | 69 (13.7)    | 74 (14.7)    | 0.652    |
| CHADS 2 score | 1.3±0.6      | 1.2±0.6      | 0.724    |
| Clinical parameters |          |           |          |
| Systolic BP, mmHg | 125.0±15.7   | 126.9±16.8   | 0.064    |
| Diastolic BP, mmHg | 73.9±11.0    | 72.8±12.2    | 0.116    |
| Heart rate, beats/min | 74.5±12.9    | 73.6±12.4    | 0.252    |
| CrCl, mL/min    | 66.9±27.1    | 66.1±27.6    | 0.638    |
| Medications     |           |           |          |
| Warfarin       | 438 (87.1)   | 447 (88.9)   | 0.383    |
| Baseline PT-INR | 1.92±0.57    | 1.92±0.52    | 0.908    |
| TTR, %**       | 60.9±28.0    | 59.1±28.6    | 0.373    |
| Antiplatelet drugs | 152 (31.2)  | 133 (26.4)   | 0.184    |
| Aspirin        | 131 (26.0)   | 113 (22.5)   | 0.185    |
| Other          | 30 (6.0)     | 33 (6.6)     | 0.696    |
| Warfarin+antiplatelet | 112 (22.3)  | 112 (22.3)   | 1.000    |
| Antiarrhythmic drugs | 185 (36.8)  | 189 (37.6)   | 0.794    |
| Na channel blockers | 62 (12.3)    | 63 (12.5)    | 0.924    |
| β-blockers     | 89 (17.7)    | 101 (20.1)   | 0.334    |
| K channel blockers*** | 30 (6.0)  | 35 (7.0)     | 0.521    |
| Ca channel blockers | 39 (7.8)    | 45 (8.9)     | 0.494    |

Data are number of patients (%) or mean±SD. *Comparison between No-Digitalis and Digitalis groups. **Target INR was 2.0–3.0 (<70 years) or 1.6–2.6 (≥70 years). ***Bepridil was classified as a K channel blocker. Abbreviations as in Table 2.

patients with AF. The Digoxin Investigation Group (DIG) determined the effects of digoxin on mortality and hospitalization in 6,800 patients with chronic heart failure and sinus rhythm in a randomized, controlled design. 18 Digoxin did not affect overall mortality, but significantly reduced the rate of hospitalization for worsening heart failure with a risk ratio (RR) of 0.72.

The Stockholm Cohort study of Atrial Fibrillation (SCAF) 31 found that all-cause death was significantly higher in patients treated with digoxin at baseline than in those without it (unadjusted HR 1.94, 95% CI 1.71–2.20, P<0.001). However, digoxin use had a neutral effect on mortality after propensity score-matching (HR 1.05, 95% CI 0.90–1.23, P=0.51). This discrepancy was explained by...
Characteristics or propensity score-matching in some studies with digitalis with death disappeared after adjusting for baseline analysis. For these reasons, the significant association of factors might not have been sufficient for the statistical founding factors, in other studies.

With increased mortality, even after adjusting for concomitant use of antithrombotic drugs (warfarin and antiplatelet drugs) and antiarrhythmic drugs (Na channel blockers, β-blockers, K channel blockers, and Ca channel blockers). Abbreviations as in Tables 2, 4.

### Digitalis Use and Mortality in the Present Study

Because the present study was observational in nature and yielded a negative result, the present results should be interpreted cautiously. We carefully analyzed our data using several statistical models (Models 3, 4, and 5: Table 4). Covariates to estimate propensity score were also carefully selected to balance the patients’ characteristics between the 2 groups after propensity score-matching (Table 5). Because BMI and CrCl are reportedly associated with all-cause death in patients with NVAF, they were also included as a covariate in the present study. The results were similar among the 3 different models and consistent with those of several previous studies. That is, digitalis use was significantly associated with all-cause death in the crude model (Model 1), but not in the adjusted models (Models 3 and 5) and propensity score-matching model (Model 4). After adjusting only for AAD use, digitalis use was still significantly associated with all-cause death (Model 2), indicating that AADs did not affect the death of these patients treated with digitalis (Table 4).

Recent systemic reviews and meta-analyses have revealed interesting and reasonable findings. In one meta-analysis that included 326,426 patients with heart failure and/or AF from 19 studies, digoxin use was associated with a 29% increase in mortality risk (HR 1.29, 95% CI 1.21–1.39) in patients with AF. However, this meta-analysis included only 1 RCT, the DIG trial, which excluded AF patients. In the other report including 621,845 patients from 52 studies, statistical models were considered, and digoxin use showed a neutral effect on mortality in randomized trials (RR 0.99, 95% CI 0.93–1.05). This suggests studies with better methods and lower risk of bias are more likely to report a neutral association of digoxin with mortality. Regardless of statistical analysis method, prescription biases limit the value of observational data, an unavoidable limitation of observational studies.

### Causes of Death and Risk Factors

As shown in Table 3, the causes of death in patients treated with digitalis were mainly noncardiovascular rather than cardiovascular. As expected, older age, male sex, heart failure, coronary artery disease, and lower BMI were significantly associated with all-cause death in patients treated with digitalis (Table 6). However, it was difficult to correlate these risk factors with noncardiovascular death in the present study, because the detailed cause of noncardiovascular death was unknown for many patients (i.e., 52% of 27 noncardiovascular deaths, Table 3) in the Digitalis group.

The influence of renal function on mortality in the Digitalis group deserves comment. Renal impairment is associated with all-cause death in patients with NVAF, and death in patients treated with digitalis. CrCl was significantly associated with all-cause death on univariate analysis in the present study, but was not an independent risk factor for all-cause death on multivariate analysis (Table 6). Because age and the prevalence of heart failure were higher in the Digitalis group than in the No-Digitalis group (Table 2), older age and heart failure could have exerted greater effects on all-cause death than did CrCl in the Digitalis group. Lower BMI might also have exerted a greater effect on mortality than CrCl in the Digitalis group.

Because most of the risk factors for all-cause death in patients treated with digitalis in the present study were treatable (Table 6), general management of these factors would be more important than digitalis use itself in NVAF patients.

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**Table 6. Significant Factors for All-Cause Death in Multivariate Analysis**

|                   | Overall |         | No-Digitalis |         | Digitalis |         |
|-------------------|---------|---------|-------------|---------|-----------|---------|
|                   | HR      | 95% CI  | P value     | HR      | 95% CI    | P value |
| Sex (male)        | 2.04    | 1.38–3.00 | <0.001     | 1.70    | 1.12–2.58 | 0.014   |
| Heart failure     | 3.14    | 2.22–4.44 | <0.001     | 2.88    | 1.96–4.23 | <0.001  |
| Hypertension      | –       | 0.67    | 0.47–0.96   | 0.030   | –         |
| Age (≥75 years)   | 1.99    | 1.36–2.93 | <0.001     | 1.81    | 1.18–2.76 | 0.006   |
| Stroke/TIA        | 1.49    | 1.02–2.17 | 0.038      | 1.58    | 1.04–2.40 | 0.034   |
| Coronary artery disease | 1.86 | 1.29–2.69 | 0.001      | 1.78    | 1.18–2.69 | 0.006   |
| Warfarin use      | 0.53    | 0.34–0.82 | 0.004      | 0.46    | 0.29–0.74 | 0.001   |
| BMI (/kg/m² decrease) | 1.07  | 1.01–1.12 | 0.013      | –       | –         |
| CrCl (/1-mL/min decrease) | 1.02  | 1.01–1.03 | <0.001     | 1.03    | 1.02–1.04 | <0.001  |

Multivariate Cox proportional hazard analysis with stepwise forward method using following variables: age group (<65, 65–74, or ≥75 years), sex, type of atrial fibrillation, heart rate, BMI, CrCl, comorbidities (heart failure, hypertension, diabetes mellitus, history of stroke/TIA, coronary artery disease, cardiomyopathy), and concomitant use of antithrombotic drugs (warfarin and antiplatelet drugs) and antiarrhythmic drugs (Na channel blockers, β-blockers, K channel blockers, and Ca channel blockers).
Study Limitations

The present study had several limitations. First, this study was a post hoc analysis of data from an observational study and was, therefore, hypothesis-generating in nature. Digitalis and AADs were administered at the discretion of the treating physicians. Although the patient characteristics of the 2 groups were comparable after propensity score-matching, unmeasured confounding factors could have affected the results. For instance, data on LVEF and the serum digoxin concentration were not available in the present study. There is no plan to collect them in future. Second, the participants were recruited from only 158 institutions in Japan and most of the participating physicians specialized in cardiology and the management of cardiac arrhythmias. Therefore, the present results cannot be generalized to other Japanese populations with NVAF. Third, because of missing data on AADs, 388 (5.2%) patients were excluded from the analysis. The status of AAD and digitalis use was determined only at the time of enrollment. Discontinuation of and change in these drugs during the follow-up period were not considered.

Conclusions

Digitalis use was not independently associated with all-cause death in Japanese patients with NVAF. Several clinical confounding factors might contribute in a complex way to increased mortality in NVAF patients treated with digitalis.

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