Comparison of prognostic impact of anticoagulants in heart failure patients with atrial fibrillation and renal dysfunction: direct oral anticoagulants versus vitamin K antagonists

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Abstract
Although high thromboembolic risk was assumed in elderly patients with heart failure (HF) and atrial fibrillation (AF), inadequate control of prothrombin time/international normalized ratio was often observed in patients using vitamin K antagonists (VKAs). We hypothesized that patients treated with direct oral anticoagulants (DOAC) would have a better outcome than those treated with VKAs. The aim of this study was to compare the efficacies of DOACs and VKAs in elderly patients with HF and AF. We retrospectively analyzed data from a multicenter, prospective observational cohort study. A total of 1036 patients who were hospitalized for acute decompensated HF were enrolled. We assessed 329 patients aged > 65 years who had non-valvular AF and divided them into 2 groups according to the anticoagulant therapy they received. A subgroup analysis was performed using renal dysfunction based on estimated glomerular filtration rate (eGFR; mL/min/1.73 m²). The primary outcome was all-cause mortality, and the secondary outcomes were non-cardiovascular death or stroke. The median follow-up period was 730 days (range 334–1194 days). The primary outcome was observed in 84 patients; non-cardiovascular death, in 25 patients; and stroke, in 14 patients. The Kaplan–Meier analysis revealed that all-cause mortality was significantly lower in the DOAC group than in the VKA group (log-rank *p* = 0.033), whereas the incidence rates of non-cardiovascular death (log-rank *p* = 0.171) and stroke (log-rank *p* = 0.703) were not significantly different in the crude population. DOAC therapy was not associated with lower mortality in the crude population (log-rank *p* = 0.146) and in the eGFR ≥ 45 mL/min/1.73 m² subgroup (log-rank *p* = 0.580). However, DOAC therapy was independently associated with lower mortality after adjustments for age, diabetes mellitus, and albumin level (hazard ratio, 0.55; 95% confidence interval, 0.30–0.99; *p* = 0.045) in the eGFR < 45 mL/min/1.73 m² subgroup. Compared with VKA therapy, DOAC therapy was associated with lower risk of all-cause mortality in the elderly HF patients with AF and renal dysfunction.

Keywords Vitamin K antagonist · Direct oral anticoagulants · Atrial fibrillation · Heart failure · Renal dysfunction

Introduction
Atrial fibrillation (AF) is a common form of cardiac arrhythmia in elderly patients. Moreover, heart failure (HF) or renal dysfunction frequently coexists with AF [1], and high thromboembolic risk was assumed in elderly patients with HF and AF [2]. Vitamin K antagonists (VKA) have been the standard therapeutic agents for patients with AF for decades, and a previous study reported that VKA reduced stroke risk by 64% and mortality by 26% as compared with placebo [3]. VKAs are effective and relatively safe drugs with an adequate time in therapeutic range (TTR) of > 70%, but inadequate control of prothrombin time/international normalized ratio was often observed in patients using VKAs. We hypothesized that patients treated with direct oral anticoagulants (DOAC) would have a better outcome than those treated with VKAs.
ratio is often observed in patients using VKAs [4]. A sub-
analysis of data from the ROCKET AF (Rivaroxaban Once
Daily Oral Direct Factor Xa Inhibitor Compared With Vita-
min K Antagonism for Prevention of Stroke and Embolism
Trial in Atrial Fibrillation) trial reported that renal dysfunc-
tion was associated with a lower TTR of VKA during the
administration period [5]. In the Outcomes Registry for Bet-
ter Informed Treatment of Atrial Fibrillation registry, mul-
tiple comorbidities such as frailty, HF, renal dysfunction,
chronic obstructive pulmonary disease, and diabetes were
identified as risk factors of lower TTR [6]. Patients with
multiple comorbidities tend to be given more concomitant
drugs, which are associated with low treatment adherence.
Direct oral anticoagulants (DOACs) have become common
therapeutic agents for preventing stroke or systemic embo-
ilism in patients with AF. Four DOACs are available for par-
oxysmal/persistent AF. Previous studies revealed that use of
DOACs as compared with VKAs was associated with lower
risks of stroke, systemic embolism, and major bleeding [7,
8], but the efficacy of DOACs in patients with renal dys-
function has not been fully discussed. Physicians sometimes
hesitate to prescribe DOACs for elderly patients with renal
dysfunction because of fear of hemorrhagic complications.
Recently, Makani et al. [9] reported the safety and efficacy
of DOAC use in patients with concomitant renal dysfunction
and AF. However, a meta-analysis of DOACs indicated that
the standard dose of DOACs as compared with that of VKAs
was safer and more effective in Asians than in non-Asians
[10]. We hypothesized that better outcomes can be obtained
using DOACs in high-risk patients with HF. The aim of this
study was to evaluate the efficacy of DOACs in HF patients
with AF and renal dysfunction in the Japanese population.

Materials and methods

Patient population

This study was a post hoc analysis of a multicenter, pro-
spective observational cohort study. In this study, 1036 con-
secutive patients who were admitted at 13 institutions in
Nagano Prefecture, Japan, between July 2014 and December
2018 because of acute decompensated HF (ADHF) were
enrolled. The diagnosis of HF was based on the criteria
used in the Framingham study [11]. The exclusion criteria
were patients aged < 20 years, those who were impossible
to follow-up, those from whom informed consent was dif-
ficult to obtain, and those with acute coronary syndrome.
After admission, medical therapy was initiated at the discre-
tion of the physician. Clinical data, including patient demo-
graphics, past medical history, drug usage, echocardiogra-
phy findings, electrocardiography findings, and laboratory
data, were collected during the compensated state of HF.

Echocardiography was performed in accordance with the
recommendations of the American Society of Echocardiog-
raphy [12]. After the patients’ discharge, follow-up data were
collected from their medical records or through telephone
interview. The clinical events were all-cause death, cardio-
vascular death, acute coronary syndrome, stroke, hospitaliz-
ation for acute decompensated HF, and hospitalization for
any cardiovascular disease. This study was approved by the
ethics committees of the hospitals and performed in accord-
ance with the tenets of the 1975 Declaration of Helsinki for
clinical research protocols. Informed consent was obtained
from all the patients.

Study protocol

We screened 541 patients aged > 65 years who had parox-
ysmal/persistent AF and excluded 212 patients who had
undergone surgery, had severe valvular disease, and had not
received anticoagulant therapy. The remaining 329 patients
were assessed as having non-valvular AF (NVAF) and
divided into 2 groups according to the anticoagulant therapy
they received (Fig. 1). A subgroup analysis was performed
using renal dysfunction based on estimated glomerular filtra-
tion rate (eGFR; mL/min/1.73 m²). The cutoff value was set
at 45 mL/min/1.73 m² as an approximate value of median
eGFR (46 mL/min/1.73m²) and as the boundary of chronic
kidney disease (CKD) grade between G3a and G3b. The
primary outcome was all-cause mortality, and the secondary
outcomes were non-cardiovascular death and stroke.

Statistical analyses

Continuous variables are expressed as mean ± standard
deviation when normally distributed and as median and
interquartile range when non-normally distributed. Normal-
ity was assessed using the Shapiro–Wilk W test. Categori-
cal variables are expressed as number and percentage. The
patients’ baseline characteristics were compared using a

- 1036 patients with decompensated HF
- 495 patients under 65 years old and/or without AF
- Excluded 212 patients
  - Post-operative state
  - Severe valvular disease
  - Not prescribed anticoagulant therapy
- Leaving 329 patients
- 119 VKA
- 210 DOAC

Fig. 1 Study flow diagram. AF atrial fibrillation, DOAC direct oral
anticoagulant, HF heart failure, VKA vitamin K antagonists
Table 1  Baseline characteristics of the crude population and subgroups

|                  | Crude population n = 329 | eGFR < 45 (mL/min/1.73 m²) n = 159 | eGFR ≥ 45 (mL/min/1.73 m²) n = 170 |
|------------------|--------------------------|-----------------------------------|-----------------------------------|
|                  | VKA n = 119              | DOAC n = 210                       | VKA n = 65                        | DOAC n = 94                        |
| Age (years)      | 82 (76, 86)              | 83 (76, 87)                        | 84 (80, 88)                       | 81 (72, 85)                       |
| Female, n (%)    | 57 (48.3%)               | 104 (49.3%)                        | 91 (50.8%)                        | 46 (48.9%)                        |
| Body mass index  | 20.2 (18.8, 23.5)        | 21.4 (19.1, 24.2)                 | 111 (20.5, 24.5)                 | 21.8 (19.1, 24.7)                |
| Heart rate (beats per minute) | 70 (60, 80) | 72 (63, 83) | 0.062 | 66 (60, 77) | 0.018 | 75 (60, 82) | 0.883 |
| Systolic blood pressure (mmHg) | 0.062 | 66 (60, 77) | 0.018 | 75 (60, 82) | 0.883 |
| Hypertension, n (%) | 80 (66.7%)   | 136 (65.1%)                        | 77.4 | 65 (69.1%) | 0.332 | 29 (53.7%) | 0.358 |
| Dyslipidemia, n (%) | 29 (24.2%)   | 52 (24.9%)                         | 0.880 | 28 (27.6%) | 0.847 | 11 (20.3%) | 0.861 |
| Diabetes mel-litus, n (%) | 40 (33.3%) | 48 (23.2%)                        | 0.041 | 22 (23.4%) | 0.324 | 19 (35.2%) | 0.079 |
| Hyperuricemia, n (%) | 26 (21.7%)   | 40 (19.1%)                         | 0.583 | 25 (26.6%) | 0.745 | 6 (11.1%) | 0.737 |
| COPD, n (%)      | 8 (6.7%)                | 11 (5.3%)                          | 0.604 | 4 (4.3%) | 0.688 | 6 (11.1%) | 0.246 |
| Hemodialysis, n (%) | 0 (0%)           | 0 (0%)                             | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Coronary artery disease, n (%) | 24 (20.0%) | 39 (18.7%)                        | 0.782 | 24 (23.4%) | 0.414 | 11 (20.4%) | 0.350 |
| Stroke, n (%)    | 13 (10.8%)              | 40 (19.1%)                         | 0.049 | 20 (21.3%) | 0.041 | 7 (13.0%) | 0.477 |
| Neoplasm, n (%)  | 6 (5.0%)                | 20 (9.6%)                          | 0.142 | 9 (9.6%) | 0.432 | 2 (3.7%) | 0.187 |
| Laboratory data  | < 0.001                 | < 0.001                            | < 0.001 | < 0.001 | < 0.001 | 2.07 ± 0.53 | 0.821 |
| Albumin (g/dL)   | 3.4 ± 0.5               | 3.4 ± 0.5                           | 3.4 ± 0.4 | 3.4 ± 0.5 | 3.4 ± 0.5 | 0.805 |
| Hemoglobin (g/dL) | 11.4 (10.2, 13.1)      | 12.4 (11.0, 13.9)                  | < 0.001 | 11.0 (10.0, 12.4) | 1.17 | 10.6, 13.6 | 0.011 |
| eGFR (mL/min/1.73 m²) | 43.9 (30.8, 56.8)    | 46.2 (36.0, 60.0)                  | 0.057 | 33.0 (25.4, 39.0) | 0.105 | 58.0 (51.0, 68.0) | 0.624 |
| BNP (pg/mL)      | 302 (144, 544)          | 258 (138, 451)                     | 0.264 | 363 (166, 645) | 0.155 | 216 (117, 424) | 0.812 |
| CRP (mg/dL)      | 0.33 (0.10, 0.69)       | 0.30 (0.10, 0.96)                  | 0.675 | 0.19 (0.10, 0.67) | 0.424 | 0.39 (0.09, 0.74) | 0.784 |
| PT-INR           | 1.89 ± 0.46             | 1.21 ± 0.14                        | < 0.001 | 1.77 ± 0.36 | 1.20 ± 0.12 | < 0.001 | 2.07 ± 0.53 | 0.821 |
| CHADS2 score     | 3 (2, 4)                | 3 (2, 4)                           | 0.981 | 3 (2, 4) | 0.862 | 3 (2, 4) | 0.821 |
| Medication       | < 0.001                 | < 0.001                            | < 0.001 | < 0.001 | < 0.001 | 2.07 ± 0.53 | 0.821 |
| Antiplatelet drugs, n (%) | 33 (28.3%) | 52 (24.9%)                        | 0.499 | 17 (26.2%) | 0.607 | 16 (29.6%) | 0.350 |
| ACEi/ARB, n (%)  | 83 (69.2%)              | 147 (70.3%)                        | 0.826 | 40 (61.5%) | 0.394 | 42 (77.8%) | 0.392 |
| Beta-blocker, n (%) | 84 (70.0%)   | 167 (79.9%)                        | 0.042 | 44 (67.7%) | 0.063 | 39 (72.2%) | 0.306 |
| MRA, n (%)       | 60 (50.0%)              | 118 (56.4%)                        | 0.268 | 30 (46.1%) | 0.459 | 30 (55.6%) | 0.629 |
| SGLT2 inhibitor, n (%) | 0 (0%)           | 7 (3.3%)                           | 0.051 | 0 (0%) | 0.237 | 0 (0%) | 0.121 |

ACEi angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, BNP brain natriuretic peptide, COPD chronic obstructive pulmonary disease, CRP C-reactive protein, DOAC direct oral anticoagulant, eGFR estimated glomerular filtration rate, MRA mineralocorticoid receptor antagonist, SGLT sodium glucose cotransporter, VKA vitamin K antagonist
contingency table and t test for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and the chi-square test for categorical variables. P values of <0.05 were considered statistically significant. The cumulative incidence of the end point was analyzed using the Kaplan–Meier method, and differences were assessed with the log-rank test. Cox proportional hazard analysis was performed to adjust for baseline differences and assess whether the variables were independent predictors of outcome. Following univariate analysis, covariates that were associated with outcome (p < 0.1) were included in the multivariate model. The SPSS version 27.0 statistical software (SPSS Inc., Chicago, Illinois) was used in the analysis.

**Results**

**Patients’ characteristics**

Among the 329 patients, 119 were treated with VKA and 210 were treated with DOACs. The patients’ baseline characteristics are shown in Table 1. The median age was 82 years (interquartile range: 76–86 years), and 49% (n = 161) of the patients were female. Among the comorbidities, diabetes mellitus was more frequently observed in the VKA group, but history of stroke was more prevalent in the DOAC group. Laboratory data indicated that hemoglobin level was lower in the VKA group, but serum albumin level, eGFR, brain natriuretic peptide level, and C-reactive protein level were not significantly different between the two groups. Whereas β-blocker was more frequently prescribed in the DOAC group, the use frequencies of antiplatelet and conventional drugs for HF, including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and mineralocorticoid receptor antagonist were not markedly different between the two groups.

**Outcomes**

The median follow-up period was 730 days (interquartile range 334–1194 days). The primary outcome was observed in 84 patients (25.5%). Non-cardiovascular death occurred in 25 patients (7.6%), and stroke occurred in 14 patients (4.3%). The hazard ratio (HRs) and 95% confidence interval (CIs) for the primary and secondary outcomes are shown in Table 2. The incidence of non-cardiovascular death and stroke were not statistically significantly different between the two groups, but all-cause death was more frequently observed in the VKA group. The Kaplan–Meier analyses for the primary and secondary outcomes are shown in Fig. 2. All-cause mortality was significantly lower in the DOAC group than in the VKA group (log-rank p = 0.033), while the incidence rates of non-cardiovascular death and stroke were not significantly different between the two groups. DOAC use was not significantly associated with all-cause mortality (HR, 0.71; 95% CI 0.45–1.13; p = 0.146) in multivariate analysis of the crude population, although it was associated with a lower incidence of the primary outcome (HR, 0.63; 95% CI 0.41–0.97; p = 0.035) in univariate analysis (Table 3).

The subgroup analysis for renal dysfunction is shown in Fig. 3. DOAC administration was associated with lower mortality rates in the eGFR < 45 mL/min/1.73 m² subgroup (log-rank p = 0.036) but not in the eGFR ≥ 45 mL/min/1.73 m² subgroup (log-rank p = 0.581). The Cox proportional hazard analysis revealed that DOAC therapy was independently associated with lower mortality after adjustments for age, diabetes mellitus, and albumin level (HR, 0.55; 95% CI 0.30–0.99; p = 0.045) in the eGFR < 45 mL/min/1.73 m² subgroup (Table 4) but not associated in the eGFR ≥ 45 mL/min/1.73 m² subgroup (HR, 1.27; 95% CI 0.60–2.67; p = 0.533).

**Discussion**

The major finding of our study was that DOAC therapy was independently associated with lower mortality rate in patients with renal dysfunction in the Japanese population. Previous studies showed that use of DOACs was associated with lower risks of stroke and systemic embolism, but its association with all-cause mortality has not been fully evaluated especially in patients with renal dysfunction. Four
Fig. 2 Kaplan–Meier analysis for the incidence of all-cause mortality, non-cardiovascular death, stroke. All-cause mortality was significantly lower in the DOAC group than in the VKA group, but non-cardiovascular death and stroke were not statistically significantly different between the two groups. DOAC direct oral anticoagulant, VKA vitamin K antagonists.
mega studies were conducted for each DOAC; however, three studies (ROCKET AF, RE-LY [Randomized Evaluation of Long-term Anticoagulant Therapy], and ENGAGE AF-TIMI 48 [Effective Anticoagulation with Factor XA Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction study 48]) excluded patients with creatinine clearance values <30 mL/min. The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial excluded patients with creatinine clearance values <25 mL/min. Recently, Makani et al. reported the safety and efficacy of DOAC use in patients with concomitant renal dysfunction and AF. In this study, the patients were classified into three groups according to eGFR (>60, 30–60, and <30 mL/min/1.73 m²), and DOAC administration was associated with lower risk of mortality across all stages of renal dysfunction [9]. However, the efficacy of DOACs in the patients with renal dysfunction was not equal across races and ethnicity because the meta-analysis of five mega studies revealed that the usual DOAC dose as compared with that of VKA was effective for the prevention of stroke or systemic prevention and safer in terms of reducing the risk of major bleeding in Asians than in non-Asians [10]. The difference in the efficacy of DOACs between the populations remains an unsolved problem.

In the Japanese population, three major observational studies were conducted in patients with AF [13–15]. The J-RHYTHM Registry 2, a multicenter observational study, revealed that the incidence of all-cause death in the DOAC group was extremely low as compared with those in the non-OAC and VKA groups. However, this study expanded the follow-up period in the J-RHYTHM Registry, which enrolled patients from January 2010 to July 2010. At baseline, the antithrombotic therapy was VKA only (5737 patients), but 923 patients were switched from VKA to DOAC, and the exact follow-up time after the switch was unknown. The Fushimi AF registry was a prospective, observational multicenter cohort study conducted between March 2011 and November 2015. In this registry, DOAC use was not statistically associated with stroke or systemic embolism \( (p = 0.70) \) or major bleeding \( (p = 0.34) \) after propensity score matching, but all-cause mortality was not evaluated [15]. The Shinken Database is a single-hospital-based cohort that was started in 2004, and the 9-year trends of anticoagulation therapy and thromboembolic events or major bleeding

| Table 3  | Cox multivariate analysis for all-cause death in the crude population |
|----------|--------------------------------------------------------------------|
|          | Crude population                                                   |
|          | Unadjusted HR (95% CI)     | p value | Adjusted HR (95% CI) | p value |
| Age      | 1.07 (1.03–1.11)           | < 0.001  | 1.04 (1.00–1.08)    | 0.044   |
| Female   | 0.70 (0.45–1.08)           | 0.105    |                     |         |
| BMI      | 0.90 (0.85–0.96)           | 0.001    | 0.92 (0.87–0.98)    | 0.010   |
| Hypertension | 0.86 (0.55–1.33)       | 0.494    |                     |         |
| Dyslipidemia | 0.93 (0.57–1.53)       | 0.782    |                     |         |
| Diabetes mellitus | 1.24 (0.78–1.96)   | 0.358    |                     |         |
| Hyperuricemia | 0.76 (0.50–1.32)       | 0.180    |                     |         |
| COPD     | 2.22 (1.15–4.30)           | 0.018    | 2.24 (1.10–4.56)    | 0.026   |
| CAD      | 1.34 (0.82–2.20)           | 0.241    |                     |         |
| Stroke   | 0.78 (0.40–1.51)           | 0.456    |                     |         |
| Neoplasms| 1.21 (0.56–2.62)           | 0.635    |                     |         |
| Albumin  | 0.39 (0.24–0.62)           | < 0.001  | 0.48 (0.27–0.84)    | 0.010   |
| Hemoglobin | 0.82 (0.74–0.92)         | < 0.001  | 0.94 (0.83–1.07)    | 0.371   |
| eGFR     | 0.99 (0.97–1.00)           | 0.055    | 0.99 (0.98–1.01)    | 0.275   |
| BNP      | 1.00 (1.00–1.01)           | 0.111    |                     |         |
| CRP      | 1.06 (0.94–1.18)           | 0.355    |                     |         |
| Antiplatelet drugs | 1.06 (0.66–1.70) | 0.805    |                     |         |
| DOAC     | 0.63 (0.41–0.97)           | 0.035    | 0.71 (0.45–1.13)    | 0.146   |
| ACEi/ARB | 0.91 (0.57–1.44)           | 0.676    |                     |         |
| Beta-blocker | 0.73 (0.46–1.17)    | 0.190    |                     |         |
| MRA      | 1.36 (0.88–2.11)           | 0.167    |                     |         |

ACEi angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, BMI body mass index, BNP brain natriuretic peptide, CAD coronary artery disease, CI confidence interval, COPD chronic obstructive pulmonary disease, CRP C-reactive protein, DOAC direct oral anticoagulant, eGFR estimated glomerular filtration rate, HR hazard ratio, MRA mineralocorticoid receptor antagonist
were analyzed, but the incidence of all-cause death was not evaluated.

Recently, the SAKURA-AF registry was established to compare the safety and efficacy of DOACs and VKAs in the Japanese AF population and revealed that the incidence rates of stroke/systemic embolism, major bleeding, and all-cause mortality were not statistically significantly different between the VKA and DOAC groups after adjustment by propensity score matching.

Our study represents a real-world analysis of the efficacy of DOACs in elderly NVAF patients with renal dysfunction. As compared with VKA administration, the use of DOACs was associated with lower mortality rates among patients with AF and renal dysfunction. Although this was a retrospective analysis, our findings suggest that DOACs do not appear to be inferior to VKA, and physicians should not hesitate to prescribe DOACs for patients with concomitant renal dysfunction and AF.
Two hypotheses may explain the association of DOAC use with the lower risk of mortality in our registry. First, the SAKURA-AF registry included TTR, which was relatively high (65.4% ± 31.1%) as compared with those in other recent randomized controlled trials (mean TTR: 55–68%) [16–18]. The better TTR in the VKA users would result in a low clinical event rate as in the DOAC users. Although our registry did not include TTR, it would be lower in the eGFR < 45 mL/min/1.73 m² subgroup than in the eGFR ≥ 45 mL/min/1.73 m² subgroup because renal dysfunction was identified as risk factor of lower TTR [6]. Moreover, Lin et al. reported that VKA was associated with higher incident of significant bleeding and myocardial infarction in patients with stage 3–5 CKD [19]. Second, the mean CHADS² score in our registry was 3.0 in both subgroups, which was relatively higher than those in other registries in Japan, ranging from 1.8 to 2.1 [15, 20, 21], or the SAKURA-AF registry, ranging from 1.7 to 1.9 [22]. Patients with high CHADS² scores have more comorbidities and are associated with the use of more concomitant drug treatments, that is, polypharmacy. A previous study reported that adverse clinical outcomes such as death and bleeding complications occurred more frequently in patients with polypharmacy [23–25]. These outcomes could be derived from the increasing risk of drug-to-drug interactions with the use of many concomitant drug treatments. Although our registry did not analyze the number of drugs used, having more comorbidities would be associated with the incidence of stroke or other adverse clinical events and lead to high mortality in patient with renal dysfunction. Further randomized control trials are needed to certify our hypotheses.

Limitations

This study has several limitations. First, the sample size was relatively small and it would not be enough to represent the general population. Second, we did not evaluate TTR in the VKA group. Third, we did not specify the kinds of DOACs used. In the 2019 AHA/ACC guideline, only VKA and apixaban are recommended for patients with severe CKD, and other DOACs are not recommended [26]. Safety and efficacy would differ between DOACs.

Table 4  Cox multivariate analysis for all-cause death in subgroups

|                          | eGFR < 45 (mL/min/1.73 m²) | eGFR ≥ 45 (mL/min/1.73 m²) |
|--------------------------|---------------------------|---------------------------|
|                          | Unadjusted HR (95% CI)    | p value                   | Adjusted HR (95% CI)  | p value | Unadjusted HR (95% CI)    | p value                   | Adjusted HR (95% CI)  | p value |
| Age                      | 1.05 (0.99–1.10)          | 0.076                     | 1.03 (0.97–1.09)       | 0.346   | 1.08 (1.03–1.13)          | 0.001                     | 1.04 (0.99–1.10)       | 0.165   |
| Female                   | 0.85 (0.48–1.50)          | 0.570                     |                          |         | 0.51 (0.25–1.01)          | 0.054                     | 0.50 (0.22–1.11)       | 0.088   |
| BMI                      | 0.96 (0.89–1.03)          | 0.258                     |                          |         | 0.77 (0.68–0.87)          | <0.001                    | 0.78 (0.68–0.90)       | <0.001  |
| Hypertension             | 0.83 (0.45–1.55)          | 0.565                     |                          |         | 0.75 (0.39–1.44)          | 0.390                     |                          |         |
| Dyslipidemia             | 1.02 (0.55–1.87)          | 0.962                     |                          |         | 0.69 (0.29–1.66)          | 0.406                     |                          |         |
| Diabetes mellitus        | 1.71 (0.95–3.07)          | 0.072                     | 1.83 (0.98–3.40)        | 0.057   | 0.79 (0.37–1.68)          | 0.537                     |                          |         |
| Hyperuricemia            | 1.50 (0.79–3.72)          | 0.221                     |                          |         | 0.88 (0.31–2.48)          | 0.801                     |                          |         |
| COPD                     | 1.67 (0.52–5.39)          | 0.388                     |                          |         | 3.04 (1.33–6.95)          | 0.008                     | 1.86 (0.64–5.37)       | 0.255   |
| CAD                      | 1.30 (0.69–2.45)          | 0.427                     |                          |         | 1.32 (0.60–2.89)          | 0.492                     |                          |         |
| Stroke                   | 0.70 (0.30–1.65)          | 0.414                     |                          |         | 0.84 (0.30–2.39)          | 0.750                     |                          |         |
| Neoplasm                 | 1.39 (0.50–3.89)          | 0.529                     |                          |         | 1.07 (0.33–3.50)          | 0.908                     |                          |         |
| Albumin                  | 0.49 (0.26–0.93)          | 0.028                     | 0.49 (0.25–0.95)        | 0.036   | 0.30 (0.15–0.59)          | <0.001                    | 0.50 (0.22–1.12)       | 0.091   |
| Hemoglobin               | 0.89 (0.76–1.04)          | 0.131                     |                          |         | 0.78 (0.67–0.93)          | 0.004                     | 0.90 (0.73–1.11)       | 0.340   |
| eGFR                     | 0.99 (0.95–1.02)          | 0.429                     |                          |         | 0.99 (0.97–1.02)          | 0.748                     |                          |         |
| BNP                      | 1.00 (1.00–1.01)          | 0.109                     |                          |         | 1.00 (1.00–1.01)          | 0.443                     |                          |         |
| CRP                      | 0.96 (0.77–1.20)          | 0.707                     |                          |         | 1.25 (1.03–1.52)          | 0.026                     | 1.20 (0.94–1.54)       | 0.153   |
| Antiplatelet drugs       | 0.92 (0.50–1.72)          | 0.803                     |                          |         | 1.20 (0.58–2.48)          | 0.629                     |                          |         |
| DOAC                     | 0.54 (0.30–0.95)          | 0.036                     | 0.55 (0.30–0.99)        | 0.045   | 0.83 (0.43–1.61)          | 0.580                     | 1.27 (0.60–2.67)       | 0.533   |
| ACEi/ARB                 | 1.27 (0.68–2.37)          | 0.448                     |                          |         | 0.63 (0.31–1.25)          | 0.185                     |                          |         |
| Beta-blocker             | 0.77 (0.42–1.44)          | 0.420                     |                          |         | 0.70 (0.34–1.42)          | 0.320                     |                          |         |
| MRA                      | 1.20 (0.68–2.13)          | 0.522                     |                          |         | 1.75 (0.86–3.57)          | 0.121                     |                          |         |

ACEi angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, BMI body mass index, BNP brain natriuretic peptide, CAD coronary artery disease, CI confidence interval, COPD chronic obstructive pulmonary disease, CRP C-reactive protein, DOAC direct oral anticoagulant, eGFR estimated glomerular filtration rate, HR hazard ratio, MRA mineralocorticoid receptor antagonist.
Fourth, the HAS-BLED (hypertension, abnormal renal/liver function, previous stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly and drugs/alcohol consumption) score could not be determined because information on alcohol dependency was unavailable. Fifth, only three patients had severe renal dysfunction (eGFR < 15 mL/min/1.73 m²), and we could not perform a sufficient evaluation for these patients.

Conclusion

DOAC therapy for HF patients with NVAF and renal dysfunction is associated with lower mortality than VKA therapy.

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Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

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