The influence of frailty under direct oral anticoagulant use in patients with atrial fibrillation

Takashi Yamamoto,1 Kentaro Yamashita,1 Kiichi Miyamae,1 Yuichiro Koyama,1 Masataka Izumimoto,1 Yoshihiro Kamimura,1 Satoko Hayakawa,1 Kazutaka Mori,1 Takaaki Yamada,1 Yasushi Tomita,1 Toyoaki Murohara2

ABSTRACT

Background Frailty is a prognostic factor in patients with atrial fibrillation (AF). However, there is no report on the associations between frailty and clinical adverse events in patients with AF taking direct oral anticoagulants (DOAC). The factors related to the occurrence of clinical adverse events are still under discussion. Therefore, we examined the associations between frailty and clinical adverse events in patients with AF taking DOAC in daily clinical practice.

Methods We retrospectively evaluated 240 consecutive patients with AF who had been newly prescribed DOAC in our hospital from April 2016 through May 2017. Data collected included Clinical Frailty Scale (CFS) scores, laboratory results and basic demographic information.

Results During the mean follow-up period of 13.4 months, 20 patients died (7.6 per 100 person-years), stroke or systemic embolism occurred in seven patients (2.6 per 100 person-years) and major bleeding occurred in 11 patients (4.2 per 100 person-years). We defined these adverse events as composite end points, and we estimated adjusted HRs and 95% CIs for risk factors using the Cox proportional hazard regression model. Frailty (defined as a CFS score of 5 or more; HR: 3.71; 95% CI: 1.59 to 8.65), female sex (HR: 3.49; 95% CI: 1.73 to 7.07), serum albumin level (HR: 0.47; 95% CI: 0.28 to 0.79) and malignancy (HR: 4.02; 95% CI: 1.83 to 8.84) were independent predictors of the composite end points.

Conclusions Frailty, female sex, hypoalbuminaemia and malignancy were associated with clinical adverse events in patients with AF who were prescribed DOAC.

INTRODUCTION

Both the number of elderly people and the prevalence of atrial fibrillation (AF) are increasing worldwide.1,2 Anticoagulation therapy for elderly patients with AF is important because of the high embolic risk in this population.3 The efficacy and safety of direct oral anticoagulants (DOAC) in patients with AF have been proven in large-scale clinical trials.4,5 The risk of bleeding or death is increased in elderly patients with AF.6-8 In addition, we sometimes observe cases in which clinically serious adverse events (eg, bleeding, stroke and death) occur over a short period of time after DOAC administration. However, it is not appropriate to dichotomise people solely based on age. Therefore, it remains controversial whether DOAC should be prescribed for this group.

In recent years, frailty status has drawn attention as being a strong predictor of mortality in elderly people.9 There have also been reports that AF is associated with frailty.10 Frailty is a prognostic factor in patients with AF,11 but to our knowledge, there are no reports on the prognostic potential of frailty in patients with AF who are taking DOAC. Therefore, we examined the associations between frailty and clinical adverse events in patients with AF taking DOAC in daily clinical practice.

MATERIALS AND METHODS

Study patients

Using the data warehouse and search functions of the electronic medical records (HOPE Life-Mark-HX, FUJITSU), we retrospectively evaluated 240 consecutive patients with AF who had been newly prescribed DOAC in our hospital from April 2016 through May 2017. All patients were screened using the ICD-10 (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems) code I48, and then AF was confirmed by an ECG or Holter ECG. Patients who had previously received anticoagulants including DOAC were excluded. This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board of Nagoya Medical Centre.

To cite: Yamamoto T, et al. Heart Asia 2019;11:e011212. doi:10.1136/heartasia-2019-011212
trolled hypertension is an independent risk factor for stroke.13

Blood pressure greater than 160 mm Hg, because even well-con-
trained physicians based on the records of nurses who directly
met with each patient. Patients were classified into one of two
categories based on CFS scores: frail (a score of 5–9) or non-frail
(a score of 1–4).12 We included a history of hypertension, rather than
female sex and prior stroke or transient ischaemic attack (TIA; two points).12
We included a history of hypertension, rather than blood pressure greater than 160 mm Hg, because even well-con-
trolled hypertension is an independent risk factor for stroke.13
Diabetes mellitus was defined as a fasting plasma glucose concentra-
tion >126 mg/dL and/or a glycosylated haemoglobin concentra-
tion ≥6.5% (National Glycohemoglobin Standardisation Programme), or intake of any antidiabetic agents. Current and
ex-smokers were defined as ‘smoker’.

The estimated glomerular filtration rate (eGFR) was calculated using the equation for Japanese subjects recommended by the Japanese Society of Neph-
rology: eGFR (mL/min/1.73 m²) = 194 × Scr −1.094 × Age −0.287 × 0.739 (if female).14 Cancer was defined as malignancy diagnosed
within the previous 6 months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment had
ever been administered within 6 months prior to DOAC prescription; or haematological cancer that was not in complete remission.

Clinical Frailty Scale
The Clinical Frailty Scale (CFS) was developed and validated by Rockwood et al.15 Patients are assigned a score of 1–9 (1: very
fit; 2: well; 3: managing well; 4: vulnerable; 5: mildly frail; 6: moderately frail; 7: severely frail; 8: very severely frail and 9:
terminally ill) based on a semiquantitative evaluation of their symptoms, level of inactivity, exhaustion and basic or instru-
mental activities of daily living. CFS scores were determined by
trained physicians based on the records of nurses who directly
met with each patient. Patients were classified into one of two
categories based on CFS scores: frail (a score of 5–9) or non-frail
(a score of 1–4).

Clinical outcomes
Follow-up patient data were obtained from the medical records
on 2 May 2019. We defined all-cause mortality, stroke or systemic
embolism (SE) confirmed by imaging, or major bleeding that
occurred during the follow-up period as composite end points.
Major bleeding was defined as a reduction in haemoglobin by at
least 2 g/dL, transfusion of at least 2 units of blood, or sympto-
matic bleeding in a critical area or organ using definitions set out by
The International Society on Thrombosis and Haemostasis.16

Statistical analyses
Categorical data are presented as percentages (%), and consecu-
tive patient data are presented as mean±SD or median (range),
depending on their distribution. We compared categorical vari-
ables using the χ² test when appropriate; otherwise, we used
Fisher’s exact test. We compared continuous variables using the
Student’s or Welch’s t-test on the basis of the dispersion when
appropriate; otherwise, we used the Mann-Whitney U test on
the basis of distribution. The incidence rate of each composite
end point was calculated as the number per 100 person-years
with 95% CIs. A Cox proportional hazards regression analysis
was used to assess the association between factors and composite
end points. Any statistically significant covariates (ie, p<0.05)
in the univariate analysis were included in the multivariate anal-
ysis using a downward stepwise regression method. The thresh-
olds for entry and removal were 0.05 and 1.0, respectively. We
also analysed the incidence rate of the composite end points in
each group stratified by frailty status as determined using CFS
scores (frail: 5–9; and non-frail: 1–4), and assessed the differ-
ence between them using a log-rank test. All statistical analyses
were done using JMP V9.0 (SAS Institute, Cary, NC, USA), and
all tests were two-tailed with the statistical significance set at
p<0.05.

RESULTS
We enrolled 240 patients, as shown in figure 1. Table 1 shows
the baseline characteristics of these patients. The mean age of the
patients was 76.1±10.0 years and 42.9% of them were women.
The median CHA2DS2-VASc score was 4, and the median
HAS-BLED score (Hypertension, Abnormal renal/liver function,
Stroke, Bleeding history or predisposition, Labile international
normalization ratio, Elderly (>65 years), Drug/alcohol concom-
antly) score was 2. An under-dose of DOAC was observed in
8.33% of patients. The median eGFR and serum albumin level
was 63.8 mL/min/1.73 m² and 3.60 g/dL, respectively. Frail
patients constituted 50.0% of the total patient population.
The frail group had a higher proportion of women (55.8% vs
30.0%; p<0.001), and was older (81.2±7.9 years vs 71.0±10.0
years; p<0.001) and lighter in weight (52.5 kg vs 60.5 kg;
0.001), compared with the non-frail group. The median CFS
(6 vs 3; p<0.001), CHA2DS2-VASc score (5 vs 3; p<0.001) and
HAS-BLED score (2 vs 1; p<0.001) were higher in frail group
compared with the non-frail group. History of stroke was more
common in the frail group (58.3% vs 27.5%; p<0.001). Serum
albumin (3.3 g/dL vs 4.0 g/dL; p<0.001) and haemoglobin (12.3
mg/dL vs 13.7 mg/dL; p<0.001) levels were lower in the frail
group.

During the median follow-up period of 9.2 months (IQR:
1.5–25.5 months), seven patients had a stroke or SE, 11 had a
major bleed and 2 died. In total, 37 patients had a composite
disease point event (14.0 per 100 person-years). The incidence of
stroke or SE, major bleeding, all-cause mortality, and stroke, SE
or all-cause mortality in the frail group were 6.2 per 100 person-
years, 8.3 per 100 person-years, 16.6 per 100 person-years and
30.2 per 100 person-years, respectively (table 2).

In the univariate analysis, age, female sex, weight, heart
failure, haemoglobin, serum albumin, frailty, malignancy,
Table 1  Baseline characteristics of the patients

| Characteristics                  | Total (n=240) | Frail (n=120) | Non-frail (n=120) | P value* |
|----------------------------------|---------------|---------------|-------------------|----------|
| Female, n (%)                    | 103 (42.9)    | 67 (55.8)     | 36 (30.0)         | <0.001   |
| Age, years                       | 76.1±10       | 81.2±7.8      | 71.0±10           | <0.001   |
| Weight, kg                       | 57.0 (48.4–64.9) | 52.5 (44.3–60.0) | 60.5 (53.5–67.0) | <0.001   |
| CFS                              | 4.5 (3.0–6.0) | 6.0 (6.0–7.0) | 3.0 (3.0–4.0)     | <0.001   |
| Hypertension, n (%)              | 147 (61.3)    | 78 (65.0)     | 69 (57.5)         | 0.233    |
| Diabetes mellitus, n (%)         | 42 (17.5)     | 22 (18.3)     | 20 (16.7)         | 0.734    |
| Smoking, n (%)                   | 118 (49.2)    | 49 (40.8)     | 69 (57.5)         | 0.101    |
| Heart failure, n (%)             | 101 (42.1)    | 53 (44.2)     | 48 (40.0)         | 0.513    |
| Bleeding history, n (%)          | 14 (5.8)      | 9 (7.5)       | 5 (4.2)           | 0.271    |
| Stroke/TIA, n (%)                | 103 (42.9)    | 70 (58.3)     | 33 (27.5)         | <0.001   |
| Paroxysmal AF, n (%)             | 126 (52.9)    | 56 (46.7)     | 70 (58.3)         | 0.070    |
| CHA2DS2-VASc score               | 4 (3–5)       | 5 (4–6)       | 3 (2–4)           | <0.001   |
| HAS-BLED score                   | 2 (1–2)       | 1 (1–2)       | 2 (1–2)           | <0.001   |
| BUN (mg/dL)                      | 17 (13–21)    | 17 (12–21)    | 16 (13–20)        | 0.855    |
| eGFR (mL/min/m²)                 | 63.8 (51.7–78.1) | 67.0 (51.8–82.6) | 62.7 (51.7–72.0) | 0.124    |
| Albumin (g/dL)                   | 3.6 (3.1–4.0) | 3.3 (2.7–3.7) | 4.0 (3.5–4.2)     | <0.001   |
| Hb (mg/dL)                       | 12.9 (11.2–14.2) | 12.3 (10.7–13.3) | 13.7 (12.2–14.7) | <0.001   |
| DOAC under-dosed (%)             | 20 (8.3)      | 8 (6.7)       | 12 (10)           | 0.350    |
| DOAC over-dosed (%)              | 13 (5.4)      | 5 (4.2)       | 8 (6.7)           | 0.392    |
| β-blocker, n (%)                 | 118 (49.2)    | 56 (46.7)     | 62 (51.7)         | 0.439    |
| ACE-I/ARB, n (%)                 | 87 (36.3)     | 38 (31.7)     | 49 (40.8)         | 0.140    |
| Mineralocorticoid receptor antagonist, n (%) | 37 (15.4) | 23 (19.2) | 14 (11.7)         | 0.108    |
| Antiplatelet drugs, n (%)        | 39 (16.3)     | 19 (15.8)     | 20 (16.7)         | 0.861    |
| Malignancy, n (%)                | 20 (8.3)      | 13 (10.8)     | 7 (5.8)           | 0.161    |

Values are presented as mean±SD, median (IQR) or n (%).

*D value for comparison between frail and non-frail from log-rank test.

ACE-I, ACE inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BUN, blood urea nitrogen; CFS, Clinical Frailty Scale; DOAC, direct oral anticoagulants; TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate.

Table 2 Incidence of clinical events during follow-up (per 100 person-years)

|                  | Total (n=240) | Frail (n=120) | Non-frail (n=120) | P value* |
|------------------|---------------|---------------|-------------------|----------|
| Stroke/SE/Major bleeding /all-cause mortality | 14.0 | 30.2 | 4.8 | <0.001 |
| Stroke/SE        | 2.6           | 6.2           | 0.6               | 0.024    |
| Major bleeding   | 4.2           | 8.3           | 1.8               | 0.038    |
| All-cause death  | 7.6           | 16.6          | 2.4               | <0.001   |
| Cardiac death    | 1.5           | 2.1           | 1.2               | 0.583    |
| Non-cardiac death| 6.0           | 14.6          | 1.2               | <0.001   |

Frail, CFS 5–9; non-frail, CFS 1–4.

*D value for comparison between frail and non-frail from log-rank test.

CHAD2-VASc score and HAS-BLED score were significantly associated with the composite end points. In the multivariate analysis, frailty (HR: 3.71, 95% CI: 1.59 to 8.65), female sex (HR: 3.49, 95% CI: 1.73 to 7.07), serum albumin level (HR: 0.47, 95% CI: 0.28 to 0.79) and malignancy (HR: 4.02, 95% CI: 1.83 to 8.84) were confirmed as statistically significant factors associated with an increased risk of the composite end points (table 3). The Kaplan-Meier curves stratified by frailty category are shown in figure 2. The cumulative incidence rate was significantly higher in the frail group compared with the non-frail group (log-rank test; p<0.001).

DISCUSSION

In this study, frailty, hypoalbuminaemia, female sex and malignancy were associated with a higher incidence rate of the composite end points, which included all-cause mortality, stroke or SE, and/or major bleeding. The incidence rate of the composite end points was high and many patients had events shortly after DOAC administration (the median number of months before the occurrence of an adverse event was 5.5 (IQR: 1.8–11.5) months in all patients, and 3.6 (IQR: 1.3–9.3) months in the frail patient group).

In a previous cohort study of Japanese patients with AF, the incidence rate of adverse events (death or stroke/SE) was 8.7 per 100 person-years. In addition, when the previous study focused on patients weighing less than 50 kg, the incidence rate of adverse events increased to 16.1 per 100 person-years. In our study, 50% of patients were frail and their mean body weight was 52.5 kg, so the incidence rate observed in this study was not surprising. Furthermore, the incidence rate of non-cardiovascular events was also consistent with past reports (eg, cardiac death in 1.1 per 100 person-years, non-cardiac death in 5.7 per 100 person-years and 66% of patients dying due to non-cardiovascular events). Although the median CHAD2-VASc score in the frail group was 5 and the incidence of stroke or other thromboembolic events was expected to be 6.7% per year, ischaemic stroke occurred in 6.2% of frail patients. In addition, although the median HAS-BLED score in the frail group was 2 and the incidence of major bleeding was expected to be 1.88% per year, major bleeding occurred in 8.3% of frail patients. Therefore, it is possible that death and bleeding act as competing events against the decrease in incidence of cerebral infarction in our study. In the frail group, we found that non-cardiac death...
Table 3  Indicators of Stroke/Systolic Embolism/Major Bleeding/All-Cause Mortality

| Factor                        | Univariate       | Multivariate      |
|-------------------------------|------------------|-------------------|
|                               | HR (95% CI)      | P value           |
| Age                           | 1.08 (1.04 to 1.13) | <0.001            | - | - |
| Female                        | 3.36 (1.71 to 6.62) | <0.001            | 3.49 (1.73 to 7.07) | 0.001 |
| Weight                        | 0.96 (0.93 to 0.99) | 0.004             | - | - |
| Hypertension                  | 2.00 (0.94 to 4.24) | 0.067             | - | - |
| Diabetes mellitus             | 0.67 (0.26 to 1.73) | 0.408             | - | - |
| Heart failure                 | 2.25 (1.17 to 4.33) | 0.012             | - | - |
| Stroke/TIA                    | 1.43 (0.75 to 2.73) | 0.274             | - | - |
| Bleeding history              | 1.93 (0.59 to 6.30) | 0.270             | - | - |
| eGFR                           | 0.99 (0.98 to 1.01) | 0.348             | - | - |
| Albumin                       | 0.73 (0.62 to 0.86) | <0.001            | - | - |
| Frail                          | 0.40 (0.26 to 0.63) | <0.001            | 0.47 (0.28 to 0.79) | 0.005 |
| Malignancy                    | 5.77 (2.60 to 12.6) | <0.001            | 3.71 (1.59 to 8.65) | 0.002 |
| Under-dosed                   | 3.37 (1.59 to 7.16) | 0.001             | 4.02 (1.83 to 8.84) | 0.001 |
| Over-dosed                    | 2.46 (0.74 to 8.23) | 0.130             | - | - |
| eGFR                           | 0.57 (0.08 to 4.16) | 0.574             | - | - |
| Hb                             | 1.41 (1.17 to 1.71) | <0.001            | - | - |
| HAS-BLED score                | 1.57 (1.12 to 2.20) | 0.009             | - | - |

Frail: CFS score of 5–9.
Hb, haemoglobin; TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate.

Increased significantly compared with the non-frail group. In past reports, mortality due to undetermined cause increased substantially in accordance with age, and non-cardiovascular death was most strongly associated with anaemia. This report may indicate that more careful follow-up of major bleeding events is necessary after DOAC administration in older patients.

Frailty is a complex syndrome of decreased stress tolerance that arises from impairments in multiple organ systems, and it is considered a factor in the difference between biological and chronological age. In general, frailty leads to a higher risk of disability, hospital admission and death, and this higher risk has been reported in patients with AF. In this study, it is interesting that frailty remained a risk factor for the composite end points despite accounting for established risk factors such as age, CHA2DS2-VASc score and HAS-BLED score in the multivariate analysis. On the contrary, there is also a report that AF is associated with frailty, and it is possible that stress tolerance had become considerably low in these frail patients at the time of AF development. Therefore, frailty could be a strong indicator of these adverse events in patients with AF.

Previous studies have reported that hypoalbuminaemia is an important marker of clinical adverse events such as major bleeding and death, and our study had similar results. Hypoalbuminaemia has several aetiologies that include decreased synthesis in the liver, lack of intake, systemic inflammation and loss of albumin (nephritic syndrome or protein-losing enteropathy). However, a detailed pathophysiological mechanism has not been proposed to explain the association between hypoalbuminaemia and clinical events. An association between hypoalbuminaemia and frailty has also been reported. However, the pathophysiology underlying the relationship between hypoalbuminaemia and frailty is also unclear. The presence of a third factor that can affect both hypoalbuminaemia and frailty has been suggested and includes a decrease in muscle mass, poor dietary intake and chronic inflammation. In our study, we did not measure muscle mass, dietary intake or inflammatory markers, so we could not determine the detailed relationship between hypoalbuminaemia and frailty.

Past reports have also associated with anaemia with frailty, and anaemia has been associated with clinical adverse events in patients with AF. In this study, univariate analysis showed that anaemia was significantly associated with the composite end points, but the multivariate analysis did not show this significant association. Therefore, it may be clinically important to comprehensively understand the patient’s condition instead of only evaluating haemoglobin levels. In patients not eligible for randomised controlled trials after starting DOAC, more careful follow-up is necessary, and a more comprehensive approach is required.

Contrary to existing evidence, stroke or TIA and bleeding history were not predictive of composite end points in the univariate analysis in our study. Bleeding history was an indicator
of major bleeding, but not stroke or SE. This could explain why major bleeding was not a predictor of composite end points. In our study, bleeding history was a predictor of major bleeding in the univariate analysis (HR: 4.70, 95% CI: 1.00 to 22.1). Stroke or TIA history is also a predictor of stroke, but not a significant predictor of major bleeding. Moreover, our hospital actively performs emergent endovascular treatment of acute ischaemic stroke (about 60 cases a year). These factors may explain why stroke or TIA history was not predictive of composite end points in our study.

Our study has some limitations. First, this study had a small sample size. Second, this study was a retrospective single-centre study, and we could not determine causality. Further studies are needed to address whether improvement in frailty leads to a reduced risk of adverse events in patients with AF. Third, there are several other methods that may be used to evaluate frailty status. In clinical practice, CFS is superior in its simplicity, and several studies have used this scale score as a prognostic factor for adverse events. Fourth, follow-up periods were short. Fifth, patients who did not receive DOAC were not studied.

CONCLUSIONS
Frailty, hypoalbuminaemia, female sex and malignancy were associated with clinical adverse events in patients with AF who were prescribed DOAC.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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