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The effect of frailty in older community-dwelling outpatients with atrial fibrillation: a new score HAS-BLED-F (rail)

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Abstract. – OBJECTIVE: This study aims to determine the effect of frailty on thromboembolic events (TEE) and bleeding in older patients with non-valvular atrial fibrillation (AF).

PATIENTS AND METHODS: Patients aged ≥65 years who were diagnosed as having non-valvular AF in a geriatric outpatient clinic between June 2015 and February 2021 were included in the study. Frailty, the risk of thrombosis secondary to AF, and the risk of bleeding as a complication of AF treatment were evaluated using the FRAIL scale, and CHA2DS2-VASc and HAS-BLED scores, respectively.

RESULTS: Out of 83 patients included in the study, 72.3% were frail and 21.7% were pre-frail. TEE was observed in 14.5% (n=12) and bleeding was observed in 25.3% (n=21) of the patients. A total of 21 (25.3%) patients had a history of bleeding. There was no difference between the normal, pre-frail, and frail groups in terms of TEE and bleeding history (p=0.112 and p=0.571, respectively). In multivariate analysis, mortality decreased with the use of apixaban; frailty and malnutrition were found to increase mortality (p=0.014, p=0.023, and p=0.020, respectively). HAS-BLED-F score was obtained as a result of the sum of the patients' HAS-BLED and FRAIL scores to predict the bleeding risk. A HAS-BLED-F score of ≥6 predicted the risk of bleeding with 90.5% sensitivity and 40.3% specificity.

CONCLUSIONS: Frailty is not associated with a statistically significant increase in the risk of thromboembolic events or bleeding in patients with non-valvular AF. HAS-BLED-F score can be used to better predict the risk of bleeding in frail patients.

Key Words:
Atrial Fibrillation, Bleeding, Frailty, Older adults, Thromboembolic events.

Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia[1]. The global prevalence rate of AF per 100,000 population is estimated to be 596 for men and 373 for women[1]. The national prevalence of AF in Turkey is also high (475-550 per 100,000 population) and increases with advancing age[1]. Due to the increasing life expectancy, it is estimated that the geriatric patient population with AF will quadruple by 2050[2]. AF accompanies various cardiac and chronic comorbidities such as hypertension (HT), cerebrovascular events (CVE), diabetes mellitus (DM), congestive heart failure (CHF), and chronic kidney disease (CKD)[3]. AF is also associated with a decrease in the quality of life, an increase in health service use and healthcare costs, and an increased risk of mortality and stroke[4,5]. Anticoagulant therapy is the basic method to prevent ischemic stroke and systemic thromboembolism (TE) for patients with AF. Warfarin and its derivatives have been used for many years as a vitamin K-dependent oral anticoagulant (VKA) for anticoagulation in the treatment of AF, and the use of direct vitamin K-independent oral anticoagulants (DOACs) has changed treatment approaches in recent guidelines[4]. Current guidelines recommend the use of CHA_2DS_2-VASc and HAS-BLED score, respectively, to evaluate the risk of embolism and bleeding to reduce thromboembolic complications and the adverse effects of drugs used in patients with AF[6,7].

Frailty is an increased sensitivity that causes an abnormal response to stressors such as acute illness or trauma, due to the decline in functions of many organs and systems due to biologic ag-

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ing, and a decrease in daily activities and functional reserve that creates homeostatic capacity. For this reason, it is more appropriate to use frailty in the treatment decision of older people because it is more related to biologic age compared with chronologic age[4]. Frailty is associated with adverse clinical outcomes, such as increased incidence of stroke and mortality in patients with AF, and long hospital stays[8]. Frailty affects both the management and prognosis of AF in the geriatric population, and AF can worsen frailty.

Anticoagulant therapy is not used adequately due to the use of antiplatelet therapy, advanced age, increased risk of falling, and staying in a nursing home[9]. Decision making is especially challanging in older adults with multiple comorbidities. This study aims to determine the effect of frailty, a geriatric syndrome, on arterial thromboembolic events and bleeding in patients with non-valvular AF.

Patients and Methods

The patients admitted to geriatric outpatient clinic of the Marmara University Hospital, Istanbul, Turkey, were evaluated retropectively and cross-sectionally by a geriatrician using the patients' records. We recruited the study patients among the patients admitted between June 2015 and February 2021. The study protocol was approved by the Clinical Research Ethics Committee of the Marmara University Hospital (approval number: 09.2020.12). Informed consent was obtained from all individual participants included in the study, and those not giving consent were excluded. The sample size was determined assuming a type 1 error of 0.05, a type 2 error of 0.2 and a power of 80%. A minimum sample size of 68 was calculated to detect a proportion difference of 10%. A total of 83 patients aged ≥65 years who were diagnosed as having non-valvular AF or developed AF during their outpatient follow-up formed the study population. Demographic data, comorbidities, frailty status, medications and doses, history of falling in the last year, and fear of falling were recorded at the initial presentation.

The FRAIL (fatigue, resistance, ambulation, illnesses, loss of weight) scale, CHA_2DS_2-VASc score and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, Elderly, drugs/alcohol concomitantly (HAS-BLED) score were used to evaluate the frailty status of patients, the risk of thrombosis secondary to AF, the risk of bleeding as a complication of AF treatment, respectively. The FRAIL scale developed by Morley et al[10] is a validated screening scale that stands out with its ease of application. Polypharmacy was defined as the regular use of at least five medications. The Mini Nutritional Assessment-short form (MNA-SF) was used to assess their nutritional status, the Katz activity of daily living (ADL) and Lawton-Brody instrumental daily living activities scale (IADL) were used to evaluate functional status. According to the FRAIL scale, 0 points are categorized as normal, 1-2 points as pre-frail, 3-4-5 points as frail[10]. According to the CHA_2DS_2-VASc score, the risk of stroke is categorized as 0 = low risk, 1 = moderate risk, and 2 and above = high risk[11]. In the evaluation of bleeding risk, a score of ≥3 according to the HAS-BLED score was accepted as "high risk"[7]. In the MNA-SF questionnaire, 12 points and above are considered as normal nutritional status, 8-11 points as malnutrition risk, and 7 points and below as malnutrition[12]. In the Katz ADL test, 13-18 points indicate independence, 7-12 points mean some assistance needed, and 0-6 points define the dependent patient population[13]. The Lawton IADL test shows the patient population with 0-8 points as dependent, 9-16 points as some assistance needed, and 17-24 points as independent[14]. Gait speed was calculated according to how long it took to complete 4 meters with the usual gait speed; slow speed was accepted as <0.8 m/sec[15].

Thromboembolic event (TEE) was accepted as the development of ischemic CVE, transient ischemic attack (TIA), acute coronary syndrome (ACS), pulmonary thromboembolism (PTE), or deep vein thrombosis (DVT) during follow-up. Major bleeding was defined as fatal bleeding and/or bleeding to a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial or intramuscular bleeding with compartment syndrome) and/or a ≥2 g/dL decrease in hemoglobin (Hb) or clinically significant bleeding resulting in two or more red blood cell transfusions according to the recommendations of the International Society for Thrombosis and Hemostasis (ISTH). The mortality status of the patients was evaluated from the electronic database of the national death notification system.

Statistical Analysis

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) 22.0 program (IBM Corp., Armonk, NY, USA). The conformity of the descriptive variables

of continuous data to normal distribution was evaluated using Kolmogorov-Smirnov/Shapiro-Wilk tests, mean and standard deviation (SD) were given for normally distributed variables, and median and minimum-maximum (min-max) values were given for non-normally distributed variables. Student's *t*-test was used when appropriate for the comparison of normally distributed continuous variables, and the Mann-Whitney U test was used for non-normally distributed variables. The comparison of categorical variables was performed using Chi-square or Fisher's exact tests. Variables that were found to be significant in univariate analyses were analyzed using regression analyses. Multiple correlations between possible regression analyses and independent variables were checked for tau-b correlation analyses using Pearson, Spearman, or Kendall correlation tests. Multivariate logistic regression analysis was used to evaluate the relationship between frailty and variables that reached statistical significance in univariate logistic regression analysis such as Katz ADL, MNA, CHA_2DS_2-VASc, HAS-BLED score, and the number of drugs. All statistical tests were bidirectional and *p*-values lower than or equal to 0.05 were considered statistically significant.

Results

A total of 690 patients presented to the geriatric outpatient clinic between June 2015 and February 2021. Eighty-three patients who fullfilled the inclusion criteria formed the study population. Fifty-three (63.9%) of the 83 patients were female, with a median age of 84 (range, 67-101) years. Fifty-nine percent of the patients had elementary school education, 10% had high school education and 22% had university education. The mean follow-up period was 23.4±17.9 months, with a median of 17 (1-64) months. A total of 64 patients (77%) had AF diagnosis at presentation while 19 patients (23%) received diagnosis during follow-up. Twelve patients were treated with warfarin, 37 with apixaban (11 patients at 2*5 mg and 26 patients at 2*2.5 mg doses), 18 with rivaroxaban (5 at 1*20 mg and 13 at 1*15 mg doses), four with edoxaban (three patients at 1*60 and one patient at 1*30 doses), three with 2*110 mg dabigatran, and six with 1 mg/kg low-molecular-weight heparin.

Based on the FRAIL scale, 72.3% (n=60) of the patients, 21.7%, and 6% were frail, pre-frail, and normal, respectively. TEE was observed in 14.5% (n=12) and bleeding was observed in 25.3% (n=21) of the patients during follow-up. A total of 21 (25.3%) patients had a history of bleeding [16 (9.3%) cases of minor and 5 (6.0%) cases of major bleeding]. More specifically, five patients had a history of gastrointestinal bleeding, five had hematuria, four had cranial bleeding, two had epistaxis, and one had hemoptysis. The mean age of the patients with a history of bleeding was 85±6 years. The mean age was 83±7 years for those without a bleeding history. The mortality rate was 24.6% (n=20). Table I shows the characteristics of the participants.

Most of the patients with frailty were female (81.1%, p=0.024), older (p=0.003) and had elementary school education or less (p=0.002). The number of drugs they used was higher (6±2.1 *vs.* 8.3±3.6 *vs.* 10.3±3.7, p=0.011), and they were functionally more dependent (p<0.001). Patients with frailty were more likely to have a fear of falling (p<0.001), to have malnutrition and/or malnutrition risk (p<0.001), and to walk more slowly (p<0.001). According to the HAS-BLED classification, the majority of patients with frailty were in the high bleeding risk group (p=0.043). Around three-quarters (73.3%) of those with frailty were using DOACs, 13.3% were using warfarin, and 8.3% were using low-molecular-weight heparin. Among the DOAC group drugs, the most preferred, regardless of the frailty status, was apixaban with a frequency of 65.9%. There was no difference between the normal, pre-frail, and frail groups in terms of TEE and bleeding history (p=0.112 and p=0.571, respectively). There was no difference between the DOAC preferences in terms of bleeding (p=0.530).

There was no difference in mortality according to gender (seven males, 13 females, p=0.452) or frailty (pre-frail n=2, frail n=18, p=0.330). More apixaban (p=0.02), rivaroxaban (p=0.031), and antihypertensive treatment use (p=0.014) were observed in survivors, and higher FRAIL score (p=0.004), lower MNA (p=0.003), and lower chronic obstructive pulmonary disease (COPD) diagnoses were more common in non-survivors (p=0.014).

Factors related to bleeding risk were evaluated using univariate analysis. Falling (33.9% *vs.* 61.9%, p=0.023), fear of falling (75.8% *vs.* 100%, p=0.009), the HAS-BLED score (2.9±1.0 *vs.* 3.4±0.9, p=0.044) were significantly associated with bleeding. Although not statistically significant, total AF duration, frailty status, and gait speed were examined in multivariate analysis as independent risk factors because they were thought to be clinically relevant. Spearman's cor-

Table I. Demographic characteristics of patients with AF.

	Mean ± SD or n (%)		Mean ± SD or n (%)
Total number of participants	83	ADL, n (%)	
Gender, n (%)		Independent	21 (25.3)
Female	53 (63.9)	Some assistance needed	46 (55.4)
Male	30 (36.1)	Dependent	16 (19.3)
Age (years), (mean ± SD)	83.6 ± 6.9	IADL, n (%)	
Age (years), n (%)		Independent	21 (25.3)
65-74	8 (9.6)	Some assistance needed	46 (55.4)
75-84	36 (43.4)	Dependent	16 (19.3)
> 85	39 (47.0)	Falls, n (%)	34 (41.0)
Residence, n (%)		Fear of Falling, n (%)	68 (81.9)
Living in own home	43 (51.8)	Gait speed (<0.8 m/s)i n (%)	68 (81.9)
Living with family members	40 (48.2)	FRAIL score (min-max)	3 (0-5)
Number of comorbidities (min-max)	6 (1-12)	Frailty, n (%)	
Comorbidities, n (%)		Normal	5 (6.0)
HT	69 (83.1)	Pre-frail	18 (21.7)
CKD	49 (59.0)	Frail	60 (72.3)
CAD	37 (44.6)	Anticoagulants, n (%)	
DM	35 (42.2)	Apixaban	37 (44.6)
CVE	25 (30.1)	Rivaroxaban	18 (21.7)
CHF	22 (26.5)	Warfarin	12 (14.5)
Dementia	21 (25.3)	Edoxaban	4 (4.8)
Malignancy	18 (21.7)	Dabigatran	3 (3.6)
PTE	7 (8.4)	LMWH	6 (7.2)
AF status, n (%)		No anticoagulation	3 (3.6)
Diagnosed AF	64 (77.1)	CHA_2DS_2-VASc score (mean + SD)	5.4 ± 1.4
AF detected during follow-up	19 (22.9)	HAS-BLED score (mean + SD)	3.1 ± 1.0
Total AF time (month, min-max)	48 (4-236)	HAS-BLED risk group, n (%)	
Number of medications (min-max)	9 (3-18)	High risk	62 (74.7)
Polypharmacy, n (%)	74 (89.2)	Low risk	21 (25.3)
Nutritional status (MNA), n (%)		Complications, n (%)	
Normal nutrition	18 (21.7)	TEE	12 (14.5)
Risk of malnutrition	41 (49.4)	Bleeding	21 (25.3)
Malnutrition	24 (28.9)	Hospitalization, n (%)	32 (38.6)
		Mortality, n (%)	20 (24.6)

ADL: Activities of Daily Living, AF: Atrial Fibrillation, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, CKD: Chronic Kidney Disease, CVE: Cerebrovascular Event, HT: Hypertension, *IADL: Instrumental Activities of Daily Living*, LMWH: Low-molecular-weight Heparin, MNA: Mini Nutritional Assessment, PTE: Pulmonary Thromboembolism, TEE: Thromboembolic Event.

relation test determined a correlation between gait speed and frailty, hence the two variables were not used in the same model.

Three different models were built for multivariate analysis. In model 2 and 3, HAS-BLED score was significantly related to bleeding [odds ratio (OR):1.81, confidence interval (CI): (1.01-3.24); p=0.047 and OR:1.82, CI: (1.00-3.30); p=0.05, respectively], whereas frailty was not found to be an independent risk factor for bleeding (Table II).

To better predict the bleeding risk, HAS-BLED-F score was obtained using the sum of the patients' HAS-BLED and FRAIL scores. In the receiver operating characteristics (ROC) analysis, the area under the ROC curve (AUC) was calculated as 0.708 and the confidence interval was calculated as 0.590-0.825. A HAS-BLED-F score of ≥6 predicted the risk of bleeding with 90.5% sensitivity and 40.3% specificity. When we evaluated the mortality determinants in multivariate analysis; apixaban use [OR: 7.35, CI: (1.50-35.92);

Table II. Multivariate analysis of variables associated with bleeding.

	Model 1		Model 2		Model 3	
	OR*	p	OR*	p	OR*	p
HAS-BLED score	1.74 (0.96-3.14)	0.069	1.81 (1.01-3.24)	**0.047**	1.82 (1.00-3.30)	**0.050**
Falls	0.55 (0.18-1.71)	0.299	0.49 (0.16-1.51)	0.214	0.48 (0.15-1.58)	0.228
Fear of falling	0.00	0.998	0.00	0.998	0.00	0.998
Total AF time	1.01 (1.00-1.03)	0.053	1.01 (1.00-1.02)	0.075	1.01 (1.00-1.02)	0.750
Frailty	0.37 (0.06-2.37)	0.577				
Gait speed					0.89 (0.08-10.40)	0.928

AF: Atrial Fibrillation, OR: Odds Ratio; *(95%) with confidence interval.

p=0.014] and FRAIL score [OR: 1.98, CI: (1.09-3.56); p=0.023] in multivariate analysis were statistically significant in Model 1. Apixaban use (p=0.008) and nutritional status (p=0.020) were statistically significant in Model 3 (Table III).

Discussion

In the present study, frailty was not associated with a significant increase in the risk of thromboembolic events or bleeding in older patients with non-valvular AF. Our prevalence of pre-frailty/frailty was higher compared with the literature[16], which can be explained by the fact that the study was conducted in a tertiary care university hospital. A possible explanation for the association of AF and frailty is that the clinical manifestations of AF may worsen the frail state of the patient, and renin-angiotensin system-mediated remodeling may correspondingly predispose the frail individual to the development of AF. Similarly, Bo et al[17] reported that 75% of patients with AF were frail. In the current study, frail patients were older, malnourished, functionally more dependent, and had a slower gait speed, as expected. They also had a lower education level, used more drugs, and had higher bleeding risk score. People with a lower level of education may lead an unhealthy lifestyle due to financial difficulties. They may have more frequent exposure to environmental stressors or lack psychosocial resources. We found female patients to be more frail. Frailty is more common in women compared with men because of the lower mean lean body mass and muscle strength. Women also have a longer life expectancy compared with men, hence age-associated syndromes are more frequently seen[18].

In a study by Nguyen et al[19], the most common comorbidities occurring with AF were HT, coronary artery disease (CAD) and CHF. In this study, the most common chronic disease associated with AF was HT, possibly due to its high prevalence in the general population.

Grymonprez et al[20] studied the efficacy and safety of oral anticoagulant treatment in older adults and showed that increasing age, multimorbidity, polypharmacy, high risk of falling, frailty, and dementia were not absolute contraindicions to DOACs. Nevertheless, in the FRAIL-AF study[2], the rate of anticoagulation was reported as 69.6%. Patients who were not prescribed anticoagulants

Table III. Multivariate analysis of mortality predictors.

	Model 1		Model 2		Model 3	
	OR*	p	OR*	p	OR*	p
Apixaban	7.35 (1.50-35.92)	**0.014**	8.23 (1.88-35.97)	**0.005**	9.55 (1.79-50.93)	**0.008**
Rivaroxaban	0.76 (0.18-3.25)	0.705			0.98 (0.23-4.18)	0.974
COPD	0.32 (0.08-1.26)	0.104	0.32 (0.08-1.32)	0.095	0.43 (0.11-1.73)	0.233
Antihypertensive treatment	3.47 (0.98-12.29)	0.054	3.56 (1.01-12.49)	**0.048**	3.49 (0.97-12.52)	0.055
FRAIL score	1.98 (1.09-3.56)	**0.023**	1.97 (1.09-3.54)	**0.024**		
Nutritional Status					0.31 (0.11-0.83)	**0.020**

COPD: Chronic Obstructive Pulmonary Disease, OR: Odds Ratio; *(95%) with confidence interval.

were older, had a history of major bleeding, lived in nursing homes, and had anemia. Determining the patient's bleeding risk before initiating anticoagulant treatment is an important step in the management of AF. Fang et al[21] showed that the risk of major bleeding in patients with non-valvular AF increased with age. In the present study, however, no statistically significant difference was found between the groups with and without bleeding. No correlation was found regarding gender, educational status, number of drugs, use of anticoagulants, smoking, glomerular filtration rate, dementia, nutritional status, or gait speed. Nguyen et al[22] found no significant difference between frail and normal groups in terms of major bleeding. In the Swiss-AF study[23], however, bleeding risk was higher in the frail group. Similarly, in a study by Ohta et al[24] in patients with AF, in which 60% of the patients were pre-frail and 28.6% were frail, the rate of major bleeding was shown to be associated with frailty. However, there was no relationship regarding age, gender, presence of CKD, HAS-BLED scores, or OAC use[24]. In the current study, a higher rate of bleeding was observed in the frail group in accordance with the literature, but this difference was not statistically significant. The lack of statistical significance may be due to our patient population, which had a high prevalence of frail patients. HAS-BLED has limitations and may lead to under or overestimation of bleeding risk[25]. To better predict the risk of bleeding, we developed HAS-BLED-F, the validation of which requires further research.

Both AF and frailty are associated with increased mortality and morbidity. In a prospective study, mortality was found to be higher in frail patients with AF over a 6-month follow-up[19]. In the Swiss-AF study, being pre-frail and frail were associated with death from all causes[23]. Studies[26,27] have also shown that malnutrition is associated with mortality. In this study, the use of apixaban, the use of rivoraxaban, and the use of antihypertensive drugs decreased mortality and frailty increased mortality. The lower rate of mortality with apixaban was in line with the frail subgroup analysis of the ARISTOPHANES study[28]. Wide confidence intervals for the mortality determinants in multivariate analysis are likely due to small sample size. MNA scores were found to be statistically significant in univariate analysis, but not in multivariate analysis, which may also be due to small sample size. Likewise, COPD was not significantly related to mortality in multivariate analysis.

We found the incidence of anemia to be higher in patients with a history of bleeding. Occult gastrointestinal bleeding may account for this finding and anemia may warrant further investigation in this patient group.

Falls are a major cause of morbidity, disability, and decreased activity in older adults. In the present study, the rate of falls was found as 25%. AF is considered to be an independent risk factor for falls[29]. It is also of note that patients with a history of falls have a higher rate of major and intracranial bleeding[30]. In the present study, although the history of falling was found to be statistically significant in univariate analysis, no significance was observed in multivariate analysis. Therefore, although fall risk management is of utmost importance, a history of falls should not lead to the cessation of anticoagulant therapy. However, given the small sample size of the study, we acknowledge that further research is needed to validate our findings.

Limitations and Strenghts

This study has several limitations. First, it was a single-center study with a small sample, which limits the generalizability of the study findings to the wider population. Second, a study with a longer follow-up period is warranted to support our findings. Third, this was a retrospective, cross-sectional study. A randomized controlled trial comparing frail and non-frail AF patients, adjusting for potential confounders that could influence the bleeding risk, would give more accurate results.

The strength of our study is that the study population consists mostly of adults with frailty. To the best of our knowledge, this is also the first study in Turkey to investigate the relationship between frailty, TE, and bleeding in older adults with AF. Our results indicate that frailty alone should not lead to avoiding anticoagulant treatment. However, patients at high risk for bleeding should be monitored frequently and closely with special attention to fall precautions, drug interactions, and dose adjustments.

Conclusions

We have shown that frailty is not associated with a statistically significant increase in the risk of thromboembolic events or bleeding in patients with non-valvular AF, most of whom have multiple geriatric syndromes. Patients with frailty with high CHA_2DS_2-VASc scores were under anticoagulant treatment with no significant risk of TE, which indicates that patients with frailty benefit from

treatment. HAS-BLED-F, which is a new tool that needs to be validated with future research, may be used to better predict the risk of bleeding.

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Conflict of Interest
The authors declare that they have no conflict of interest.

Ethics Approval
This study was performed in line with the principles of the Declaration of Helsinki. Approval for the study was granted by the Clinical Research Ethics Committee of the hospital (approval number: 09.2020.12).

Informed Consent
All participants provided written consent for their inclusion.

Data Availability
The datasets generated during the study are available from the corresponding author upon request.

Authors' Contributions
Conceptualization: YY, NŞD, BC, and AT; methodology: YY, NŞD, BC, CI, Bİ, and AT; data acquisition: YY, NŞD, BC and AT; statistical analysis: YY, CI, Bİ, and AT; writing-original draft preparation: YY, NŞD, BC, and CI; writing-review and editing: NŞD, BC, Bİ, and AT; interpretation of the results and approval of the final manuscript: all authors.

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