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Optimizing Anticoagulation in Older Patients with Nonvalvular Atrial Fibrillation

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Abstract

Purpose of Review We sought to review the current issues on optimization of anticoagulation in elderly patients with nonvalvular atrial fibrillation (NVAF).

Recent Findings Advanced age is a risk factor for stroke and as one advances in age, the risk of stroke also increases. One of the many challenges of oral anticoagulation for stroke prevention in the elderly patients with NVAF is the underutilization of anticoagulants. Commonly cited reasons for hesitation by physician in prescribing oral anticoagulants are advanced age, increase risk of bleeding, and the difficulty in maintaining an adequate time in therapeutic range and the need for frequent monitoring for those who are given warfarin. The non-vitamin K antagonist oral anticoagulants (NOAC) have been shown to have similar or superior efficacy, and a better safety profile compared with warfarin due to its wider therapeutic window, low interaction with food, and less frequent monitoring of anticoagulation levels. It is also important to note that renal dysfunction is becoming increasingly common in elderly patients with AF. This poses a therapeutic challenge for physicians due to a higher bleeding risk; thus, renal function should be taken into consideration when prescribing NOACs. Warfarin, on the other hand, remains to be a viable therapeutic option in certain clinical scenarios.

Summary In elderly patients, the choice of oral anticoagulants for stroke prevention in NVAF should be individualized and should include considerations for the best estimate of absolute benefit weighed against bleeding risks in order to optimize anticoagulation.

Keywords Atrial fibrillation · Oral anticoagulant · Elderly · Chronic kidney disease · Warfarin

Abbreviations

AF	Atrial fibrillation
CrCl	Creatinine clearance
ICH	Intracranial hemorrhage
INR	International normalized ratio
NOAC	Non-vitamin K antagonist oral anticoagulants
NVAF	Nonvalvular AF
OAC	Oral anticoagulant
RCT	Randomized controlled trial
SPAF	Stroke prevention in atrial fibrillation
TTR	Time within therapeutic range
VKA	Vitamin K antagonist

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Introduction

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in clinical practice causing a 2-fold increase in mortality and a 5-fold increase in stroke [1–3]. The overall prevalence of AF is predicted to increase significantly due to the population aging [4, 5] and the risk of ischemic stroke related to AF increases with age, from 4.6% (ages 50 to

59 years) to 20.2% (ages 80 to 89 years) [6]. Furthermore, the risk for ischemic stroke is not homogeneous and is influenced by the patient's clinical characteristics and associated comorbidities [5]. Strokes related to AF are also associated with higher mortality, greater disability, longer hospital stays, poorer functional outcome, and lower chance of being discharged home [7]. Thus, the cornerstone of effective stroke prevention in AF (SPAF) is using oral anticoagulants (OAC) regardless whether a rate or rhythm control management approach was employed [8].

Clinical risk stratification schemes have been developed to assess the patient's stroke and bleeding risk for the initiation of oral anticoagulation. The risk stratification scheme widely used in most guidelines that can better discriminate stroke risks in AF patients, and for the initiation of OACs in men with a score of 1 or higher and women with a score of 2 or higher, is the CHA_2DS_2-Vasc (congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65–74 years, sex category [female]) score (Table 1) [9]. Stroke risk reduction should also be balanced against the increased risk of bleeding, especially intracranial hemorrhage (ICH). Among the several scoring systems available, the HAS-BLED bleeding score offers better prediction of bleeding compared with other bleeding risk scores and has been recommended as a simple clinical score to predict relevant bleeding in AF patients (Table 2) [1, 10]. A HAS-BLED score ≥ 3 indicates a high risk of bleeding but does not preclude initiation of OAC. In such patients, addressing the modifiable bleeding-risk factors (i.e., uncontrolled hypertension, labile international normalized ration (INR), and concomitant use of aspirin, NSAIDs, or alcohol excess/abuse) is recommended [1].

Warfarin has been the mainstay for stroke prevention in AF since the 1940s. Studies have shown that it reduces the risk of stroke by 65–68% compared with placebo, and by 32–47% compared with aspirin [11]. Additionally, its effectiveness in reducing stroke risk requires a patient to be maintained at therapeutic levels of the international normalize ration (INR) (between 2 and 3) 70% of the time (time within therapeutic range, TTR) to reduce the risk of stroke by 79% compared to those whose TTR is ≤ 30% [12•]. However, warfarin is associated with increased risk for bleeding, especially ICH, with major bleeding rates varying from 1.40 to 3.40% per year across studies [13]. Furthermore, the use of warfarin possesses certain limitations, including food and drug interactions, the need for close laboratory monitoring to ensure the prothrombin time–INR is maintained within a narrow therapeutic range, and a high risk of bleeding when the high end of this range is exceeded [14]. Recently, the non-vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, have been shown in large randomized controlled trials (RCTs) to be at least as effective as warfarin for stroke prevention with better safety profile [1]. Thus, NOACs have been regarded as the preferred agents for SPAF and have been used extensively over the past few years [15]. Warfarin, on the other hand, still remains to be a viable option in certain clinical scenarios [1].

Despite the plethora of evidence, the use of OAC in patients with NVAF has been suboptimal especially in patients with advanced age. Advanced age has been the most common demographic factor associated with underuse of OAC due to the fear of bleeding and other complications [16], thus posing a major public health issue on initiation of anticoagulation. Therefore, in this review, our objective is to summarize the recent available data for optimization of oral anticoagulation in the elderly population.

Advancing Age and Stroke Risk

Advanced age is a critical determinant of AF-related ischemic stroke. Recent studies based on "real-world" registries have established advanced age as an independent risk factor for

Table 1 Assessment of stroke risk in atrial fibrillation patients using CHA_2DS_2-Vasc [8]

CHA_2DS_2-Vasc risk	Description	Score
Congestive heart failure	Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	1
Hypertension	Resting blood pressure > 140/90 mmHg on at least two occasions or current antihypertensive treatment	1
Age	75 years or older	2
Diabetes mellitus	Fasting glucose > 125mg/dl (7 (mmol/l) or treatment with oral hypoglycemic agent and/or insulin	1
Stroke	Previous history of stroke, transient ischemic attack or thromboembolism	2
Vascular disease	Previous myocardial infarction, peripheral artery disease, or aortic plaque	1
Age	65–74 years	1
Sex category	Female	1

Table 2 Assessment of bleeding risk in atrial fibrillation patients using HASBLED [8]

HAS-BLED	Definition	Score
Hypertension	SBP ≥ 160 mmHg	1
Abnormal renal or liver function (1 score each)	Renal: dialysis, transplantation, or creatinine ≥ 2.3mg/dl	1 or 2
	Liver: chronic hepatitis, cirrhosis, bilirubin > 2 ULN, with ALT > 3 ULN	
Stroke	Previous history, particularly lacunar	1
Bleeding history or predisposition	Recent bleed, anemia, etc.	1
Labile INR	Unstable/high INR, or TTR < 60% in patients on warfarin	1
Elderly	Age > 65 years, extreme frailty	1
Drugs or alcohol	Drugs: concomitant antiplatelet or NSAID use	1 or 2
	Alcohol excess (8 or more drinks/week)	

ALT alanine transaminase, *INR* international normalized ratio, *NSAID* nonsteroidal anti-inflammatory drugs, *TTR* time in therapeutic range, *ULN* upper limit of normal

stroke [17–19]. It is also an individual risk factor that is included in the CHA_2DS_2-Vasc risk stratification scheme wherein an age between 65 and 74 years will have a score of 1 and an age of ≥ 75 years will garner a score of 2. This group of patients also represents the fastest growing segment of the population in many countries due to the advent of newer medical technologies and improved healthcare system, access to better medical treatment, education, and quality of life. As the population ages, the burden of AF is also projected to increase substantially. The Framingham study reported the increase in incidence of AF, with a prevalence of about 0.1% in people younger than 55 years [20] and increasing to 6%, 12%, and 16% in people aged 65–74 years, 75–84 years, and ≥ 85 years, respectively [21]. Additionally, in patients with NVAF, the risk of ischemic stroke increases by 5-fold and the proportion of AF-related strokes was found to increase progressively with age, from 6.7% for ages 50 to 59 years to 36.2% for ages 80–89 years [22]. With advancing age, there is also a substantial increase in the comorbidities of the patient, thereby further increasing the risk for ischemic stroke. Chao et al. [23•] demonstrated that as one ages, approximately 51.9% of patients would accumulate at least 1 new-onset comorbidity, the most common being hypertension (37.2%), congestive heart failure (27%), or diabetes mellitus (13%). Since stroke prevention is the priority for AF management, long-term OAC therapy is critical in achieving effective stroke prevention.

Underutilization of Oral Anticoagulation Therapy Among Elderly Patients

Underutilization of OAC for stroke prevention in NVAF has been a major problem worldwide. A substantial number of patients whom OAC therapy is indicated do not receive appropriate treatment. A systematic review on the numerous cohort studies of individuals who had AF and a prior history of stroke demonstrated the underuse (less than 60% in most of the population studied) of OAC therapy for real-world AF patients with an elevated risk of stroke [24]. Several studies reporting demographic factors in the underutilization of OAC found that overall age has been the most common demographic factor. In a study conducted recently in 807 frail elderly outpatients, advancing age was the only item independently associated with the likelihood of not receiving VKAs in the multivariate analysis [25]. No other single factor, including the presence of contraindications to OAC, influenced prescription of OAC significantly. Other studies also consistently found that older patients are less likely to receive warfarin than younger patients [26–28]. The reasons often cited in most studies for the underuse of OAC therapy in the elderly population were high bleeding risk and difficulties in maintaining the INR in the target range during warfarin treatment. Additionally, the strongest risk factors for stroke in AF, namely, prior stroke and increasing age, were also the reasons for withholding appropriate OAC therapy [29]. Several studies and survey data also showed that elderly patients (≥ 75 years) with AF have lower prescription rates for OAC and more likely to receive aspirin [30••, 31, 32]. Thus, despite studies showing that elderly patients benefit as much from OAC therapy and a net clinical benefit compared with aspirin therapy [33–36], they still do not receive adequate OAC therapy. Furthermore, many are still treated with aspirin which has been shown to be ineffective and strongly discouraged by the present guidelines [37].

Frailty, which invariably affects 11% of the elderly over the age of 65 years old and 25% over the age of 85 years old, is another reason for underutilization of OAC therapy in this population [38, 39]. The fear of bleeding is often the cause for hesitation among physicians when prescribing OACs among frail elderly patients. However, among these patients, the underuse of evidence-based drug treatment was found to be the more frequent and important cause of rehospitalization rather than due to adverse drug reactions [40]. A recent real-world, observational study concerning very elderly patients (≥ 85 years old) demonstrated that OAC use for SPAF was associated with 36% relative reduction in thromboembolic complications versus antiplatelet or no antithrombotic therapy [41]. Importantly, they demonstrated that OAC use did not increase the risk for major bleeding compared to treatment with antiplatelet. These findings were confirmed in a subgroup of extremely frail patients (aged ≥ 90 years old) showing the highest absolute benefit of OAC use among these patients. Thus, in frail elderly patients, OACs may be prescribed with great consideration for various factors that may increase the risk for stroke and bleeding. This includes the propensity to falling, impairment of cognitive function, low body weight due to malnutrition, decline in renal function, and regimen complexity [42]. In order to provide safe and effective OAC therapy for these patients, individualized assessment of frailty and balancing potential benefits and risks is crucial.

Another important demographic factor that has been found to have an impact on the decision-making to initiate anticoagulation for SPAF is gender. It is known that the stroke risk is higher in men across all age groups before the age of 85 years old. However, this incidence reverses dramatically with women (age more than 65 years old) being much more at risk, and with a longer life expectancy, the majority of stroke deaths now occur in women [43]. In spite of studies demonstrating the association between AF, female gender, and stroke risk, underrecognition of the higher thromboembolic risk in this group still remains [44]. A possible reason could be that women who were previously categorized as intermediate risk using the $CHADS_2$ scoring system (score = 1) are now categorized as high risk using the CHA_2DS_2-Vasc score (score ≥ 2) [44] but were not recategorized on follow-up; thus, appropriate anticoagulation was not prescribed. Clinical reassessment of stroke risk of AF patients has to be emphasized since patients tend to develop additional comorbidity as one ages [23•]. Another reason for underutilization of OAC in elderly women is adverse drug reaction. A study have shown that women were prescribed more medications than men but were found to be less adherent due to the higher incidence of adverse drug reactions, with more severe bleeding noted in elderly women who were prescribed with oral anticoagulants [45]. Women tend to have smaller body type, older age, higher prevalence of comorbidities, and have different drug metabolism and distribution compared to men. They are also underrepresented in large clinical trials as shown in a Cochrane review of 258 clinical trials where women comprised only 27% of the population and accounting for only 25 to 40% of the study population in recent large-scale trials of NOACs [44]. Furthermore, there is no currently available gender-specific recommendation for OAC treatment for SPAF. Whether or not dose adjustment to minimized adverse drug reactions among female AF patients should be done still remains to be investigated. These issues could influence physician perception of bleeding risks and may also cause hesitation on the part of the patient to initiate or continue OAC treatment. Despite the challenges faced in OAC treatment in elderly women, the risk for stroke associated with female gender cannot be overemphasized. A recent observational cohort study from 3 Danish nationwide registries involving 239,671 patients has demonstrated that female gender is a risk modifier for stroke in patients with AF [46]. The study found that female patients with AF who have no additional risk factor (i.e., score = 1 due to female gender alone) have similar thromboembolic risk in comparison with male patients with no stroke risk factor (i.e., score = 0). However, an excess risk for women was noted among those ages more than 65 years old or those who developed additional stroke risk factor. Female gender was found to modify and accentuate the stroke risk among women.

Oral Anticoagulation for Stroke Prevention in the Elderly

Warfarin vs Aspirin and Other Combinations for Stroke Prevention in the Elderly

Currently, warfarin remains the most commonly used OAC for SPAF. A meta-analysis of randomized trials has demonstrated the efficacy of adjusted-dose warfarin for prevention of ischemic stroke in patients with AF with an overall relative risk reduction (RRR) for all stroke of 64% (95% CI, 49 to 74%) and 25% RRR for mortality [47]. Although clinical studies are more readily applicable in real life in geriatric patients with AF, still there are many physicians who hesitate in prescribing OACs. Variations in the clinical practice and concerns over the prescription of OACs in the elderly were probably partly due to the underrepresentation of elderly patients in these studies [48]. Presently, there are two RCT that compared the efficiency and superiority of warfarin over aspirin in elderly patients (≥ 75 years of age), the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) [33] and the Warfarin versus Aspirin for Stroke Prevention in Octogenarians (WASPO) trial [32]. The BAFTA trial included 973 elderly patients ≥ 75 years old (mean age 81.5 ± 4.2 years). The trial demonstrated the superior efficacy of warfarin in reducing the annual risk for ischemic stroke and intracranial hemorrhage (ICH) compared to aspirin (RR 0.48, [95% CI 0.28–0.80], $p = 0.003$; absolute yearly risk reduction 2%, [95% CI 0.7–3.2]) [33]. There was no difference in the safety profile between warfarin and aspirin even at ages ≥ 85 years old (rates of all major hemorrhages including ICH: RR 0.96%, [95% CI, 0.53–1.75] and annual risk of extracranial hemorrhage: warfarin 1.4% vs aspirin 1.6%, RR 0.87 [95% CI 0.43–

1.73]). Additionally, the efficacy of warfarin was similar in people aged ≥ 85 years vs younger people as well as those with low stroke risk vs those with high stroke risk (classified based on $CHADS_2$ scoring system). The WASPO trial also included a very old cohort of patients (mean age 83.9 years) with NVAF showing a similar results. Anticoagulation control was achieved in the octogenarian cohort with 69% in TTR (target INR range 2.0–3.0). Aspirin, on the other hand, was less tolerated with more adverse events (including 3 serious bleeding) compared to the adjusted-dose warfarin (no serious bleeding occurred). Furthermore, all combinations of warfarin, aspirin, and clopidogrel were associated with increased risk of nonfatal bleeding compared with warfarin monotherapy [49, 50]. When compared with no antithrombotic therapy or with the use of antiplatelet drugs, warfarin therapy even in very old patients (≥ 90 years old) with NVAF was associated with lower risk of ischemic stroke and a positive net clinical benefit [30••].

The efficacy of warfarin lies on maximizing the time in the therapeutic range (INR 2.0 to 3.0) and was shown to provide the most benefit for preventing stroke, major hemorrhage, and death. Greater TTR correlates with improved patient outcomes for patients treated with warfarin for AF [51]. Although there has been no definite consensus for the minimum target threshold for TTR, a TTR between 58 and 65% was suggested in order for warfarin to be beneficial over antiplatelet therapy [49]. Clinical parameters summarized in the SAMe-TT_2R_2 score [52–54] can also help identify patients who are likely to achieve a decent TTR on warfarin therapy [37]. Additionally, in one study, the percentage of time spent in target INR has also been shown to be similar in different age groups of patients with NVAF even in those ≥ 84-year-olds and it was not difficult to maintain INR in the therapeutic range as persons get older [55].

Non-vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in the Elderly

In recent years, four NOACs (one direct thrombin inhibitor—Dabigatran, and three factor Xa inhibitors—Rivaroxaban, Apixaban, and Edoxaban) tested separately in RCTs were found non-inferior to warfarin for AF stroke prophylaxis has been introduced to clinical practice [56–59]. Their more predictable pharmacokinetics and pharmacodynamics, and set dosing schedule without the need for regular anticoagulation monitoring, makes them an attractive alternative to warfarin. Furthermore, these RCTs included subjects ≥ 75 years of age with substantial evidence for their safety and efficacy for older patients (summarized in Table 3). However, it is important to note that the combination of AF and chronic kidney disease (CKD) is becoming increasingly common in the elderly patients due to the physiological decline of renal function that goes with aging and the increasing prevalence of shared risk factors, i.e., hypertension and diabetes. There is a bidirectional pathophysiological relationship between the AF and CKD and subjects with CKD are at a higher risk of developing AF and the presence of AF increases the risk of developing renal dysfunction [64]. Thus, patients with AF with renal dysfunction pose a therapeutic challenge for physicians due to a higher bleeding risk and renal function should be taken into consideration when prescribing NOACs.

Dabigatran

In the RE-LY trial [45], dabigatran (110 mg and 150 mg) which involved 7258 (40%) who were ≥ 75 years of age demonstrated that age did not affect the benefits of treatment with dabigatran vs warfarin for ischemic stroke. In patients < 80 years of age, there was a significant decrease in extracranial bleeding in patients taking dabigatran compared to those taking warfarin (HR 0.78 for 150 mg dabigatran; HR 0.72 for 110 mg twice daily) [65••]. However, in patients ≥ 80 years of age, the rates of extracranial bleeding were similar (HR 1.50 for 110 mg twice daily) or higher (HR 1.68 for 150 mg twice daily) between dabigatran and warfarin. Thus, while age does not affect the benefits of dabigatran against warfarin, lower doses of dabigatran (110 mg) twice daily for patients ≥ 80 years due to the age-dependent extracranial major bleeding were recommended in a subgroup analysis of the RE-LY trial [60].

As dabigatran is highly dependent on renal excretion (80% renal elimination) [64], it is contraindicated in severe renal disease (Creatinine Clearance (CrCl) < 30 mg/min). It is the only dialyzable NOAC and a 4-h hemodialysis session will remove 50 to 60% of plasma dabigatran, with a 10% rebound in dabigatran levels post-dialysis [66]. Although the Food and Drug Administration (FDA) approved a low dose of dabigatran at 75 mg twice daily for patients with CrCl between 15 and 30 ml/min [67], this was based on a phase I pharmacokinetic study of 29 patients, 11 of whom have a CrCl < 30 ml/min [65••]. However, studies have demonstrated the rate of major hemorrhage among dabigatran-treated patients accelerated and surpassed warfarin when the CrCl fell below 50 ml/min [68] and a 6-fold increase in dabigatran exposure in patients with CrCl < 30 ml/min compared with healthy subjects [66]. Thus, in elderly patients, closer monitoring of renal function is warranted as they are prone to overdosing.

Rivaroxaban

In contrast to the other novel anticoagulants, rivaroxaban is dosed once daily. Rivaroxaban was compared with warfarin in the ROCKET AF trial [55] which includes 6229 (44%) patients ≥ 75 years of age. Rivaroxaban was found to be non-inferior to warfarin for prevention of ischemic stroke and ICH

Table 3 Comparison of phase III trials subgroup analysis of non-vitamin K antagonist oral anticoagulants vs warfarin in the elderly patients

	Dabigatran [54, 60]	Rivaroxaban [55, 61]	Apixaban [56, 62]	Edoxaban [57, 63]
Drug class	Direct thrombin inhibitor, factor IIa	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Phase 3 study design	RE-LY ($n = 18{,}113$)	ROCKET-AF ($n = 14{,}264$)	ARISTOTLE ($n = 18{,}201$)	ENGAGE AF-TIMI ($n = 21{,}105$)
Study population	AF and a risk for stroke	AF with at least 2 risk factors for stroke	AF and at least 1 risk factor for stroke	AF with at least 2 risk factors for stroke
Subjects ≥ 75 years old	$n = 7258$ (40%)	$n = 6229$ (44%)	$n = 5672$ (31%)	$n = 8474$ (40%)
Renal Dose Adjustments				
> 50 ml/min	150 mg BID*	20 mg QD	5 mg BID	60 mg QD
50 ml/min 30 ml/min 15 ml/min	75 mg BID*	15 mg QD	2.5 mg BID [2 of 3: ≥ 80 years old, serum Cr > 1.5 mg/dl, weight ≤ 60 kg]	30 mg QD
< 15 ml/min	Avoid use*	Avoid use	Avoid use	Avoid use
Efficacy (% events/year, HR or RR vs warfarin, 95% CI and *p*-int values**)				
Ischemic stroke and/or systemic embolism	*150 mg dosing*: 75–79 years: 1.14 vs 1.76, HR 0.65 (0.42–1.01); 80–84 years: 1.73 vs 2.58, HR 0.67 (0.41–1.10); ≥ 85 years:2.15 vs 3.09, HR 0.70 (0.31–1.57); *p*-int = 0.50 *110 mg dosing*: 75–79 years: 1.90 vs 1.76, HR 1.08 (0.73–1.60); 80–84 years: 1.95 vs 1.76, HR 0.75 (0.46–1.23); ≥ 85 years: 1.61 vs 3.09, HR 0.532 (0.21–1.29); *p*-int = 0.25	2.29 vs 2.85, HR 0.80 (0.63–1.02), *p*-int = 0.31	1.56 vs 2.19, HR 0.71 (0.53–0.95); *p*-int = 0.11	1.9 vs 2.3, HR 0.83 (0.66–1.04), *p*-int = 0.84
Hemorrhagic Stroke	–	0.34 vs 0.49, HR 0.70 (0.39–1.28); *p*-int = 0.36	–	0.3 vs 0.5, HR 0.58 (0.35–0.97), *p*-int = 0.31
Safety (% events/year, HR or RR vs warfarin, 95% CI and *p* values)				
Major Bleeding	*150 mg dosing*: 75–79 years: 4.28 vs 4.16, HR 1.04 (0.81–1.35); 80–84 years: 5.91 vs 4.28, HR 1.41 (1.02–1.94); ≥ 85 years:7.29 vs 5.96, HR 1.22 (0.74–2.02); *p*-int < 0.001 *110 mg dosing*: 75–79 years: 3.87 vs 4.16, HR 0.93 (0.71–1.21); 80–84 years: 5.01 vs 4.28, HR 1.18 (0.84–1.65); ≥ 85 years: 6.00 vs 7.29, HR 1.10 (0.59–1.73); *p*-int < 0.001	4.86 vs 4.40, HR 1.11 (0.92–1.34); *p*-int = 0.34	3.33 vs 5.19, HR 0.64 (0.52–0.79); *p*-int = 0.43	4.0 vs 4.8, HR 0.83 (0.70–0.99), *p*-int = 0.78
Intracranial Hemorrhage	*150 mg dosing*: 75–79 years: 0.18 vs 0.79, HR 0.23 (0.09–0.60); 80–84 years: 0.64 vs 1.16, HR 0.55 (0.25–1.21); ≥85 years: 1.07 vs 1.77, HR 0.61 (0.20–1.87); *p*-int = 0.55 *110 mg dosing*: 75–79 years: 0.40 vs 0.79, HR 0.51 (0.25–1.04); 80–84 years: 0.35 vs 1.16, HR 0.30 (0.11–0.82); ≥ 85 years:0.23 vs 1.77, HR 0.13 (0.02–1.04); *p*-int 0.67	0.66 vs 0.73, HR 0.80 (0.50–1.28); *p*-int = 0.26	0.43 vs 1.29, HR 0.34 (0.20–0.57), *p*-int = 0.20	0.5 vs 1.2, HR 0.40 (0.26–0.62), *p*-int = 0.11

*US labeling

***p*-int value, interaction *p* values between age and treatment based on continuous age

[57]. A sub-analysis of ROCKET AF [67] comparing the safety and efficacy of rivaroxaban 20 mg once daily (or 15 mg once daily for CrCl<50 ml/min) between older (≥75 years) and younger (<75 years) age groups found that there was no interaction between age and treatment on the composite endpoint of stroke/systemic embolism, major bleeding or mortality. Although elderly patients may have higher stroke and bleeding rates than younger patients, the efficacy and safety of rivaroxaban relative to warfarin did not differ with age [61].

Two-thirds of rivaroxaban is metabolized in the liver and 36% is eliminated by the kidneys. In the ROCKET AF trial, only patients with moderate renal function were recruited and given reduced dose of rivaroxaban (15 mg daily) while those with several renal disease were excluded [57]. The trial demonstrated that in these groups of patients, the rates of stroke and systemic embolism were significantly higher than those with normal or better renal function. Major bleeding was also more frequently observed compared to the other treatment groups showing that rivaroxaban had no significant benefit for stroke prevention compared to warfarin in patients with moderate renal failure. Furthermore, rivaroxaban has also not been studied in patients with severe renal impairment [57, 69].

Apixaban

In the ARISTOTLE trial comparing apixaban with warfarin, 5672 (31%) subjects were ≥ 75 years old [58]. The trial demonstrated that apixaban was more effective than warfarin in preventing stroke and systemic embolism, ICH, and reducing mortality across all age groups. Apixaban also demonstrated significantly reduced risk for major bleeding. In a sub-analysis of the trial demonstrated that apixaban reduced the rate of major bleeding compared with warfarin with a consistent treatment effect across age groups (interaction with continuous age, $P = 0.63$) [69]. Treatment with apixaban compared with warfarin reduced the rate of ICH in patients 65–74 years, as well as in patients ≥ 75 years of age. The results were also consistent for the 13% of patients ≥ 80 years [62, 69].

The benefits of apixaban compared with warfarin were shown to be consistent across the range of estimated glomerular filtration rate and also in the elderly (≥ 75 years old) with no significant interaction between the treatment effect and the level of renal dysfunction [62, 69]. The drug label was amended in 2014 for patients with renal impairment, including those with end-stage renal disease (ESRD) who were on maintenance hemodialysis with no dose reduction (5 mg twice daily) unless the patients were ≥ 80 years old or had a body weight < 60 kg. In a retrospective, prognostic score-matched analysis of the US Medicare beneficiaries with ESRD on dialysis and AF [70], apixaban was found to have lower rates of major bleeding compared with warfarin, whereas there was no difference in the rates of stroke and systemic embolism. The study also found that standard-dose apixaban (5 mg) had lower rates of stroke and death compared with those on reduced dose apixaban (2.5 mg). However, it is important to note that since only 27% of apixaban is eliminated by the kidneys and only 6.7% can be cleared by a 4-h hemodialysis session, in patients who have overdosed or having life-threatening bleeding, dialysis would not be effective [65]. Additionally, in a post-hemodialysis administration of 5 mg apixaban resulted a 36% higher drug exposure compared with healthy subjects with normal renal function [71]. Since patients with creatinine > 2.5 mg/dl or < 1.5 mg/dl, or on long-term dialysis were excluded in the trial, further studies are needed to establish the optimal apixaban dose and dosing schedule for patients with ESRD and on maintenance hemodialysis [62, 65, 71].

Edoxaban

Among the four, edoxaban is the most recently approved NOAC and the ENGAGE AF TIMI 48 trial involved 8474 (40%) subjects who were (≥ 75 years old [59]. Both once-daily regimens of edoxaban were non-inferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. No interactions between age group and randomized treatment in the primary efficacy and safety outcomes using edoxaban in the elderly compared with warfarin were also found in a subgroup analysis [63].

Approximately 50% of edoxaban is cleared by the kidneys and it is poorly cleared by hemodialysis [65]. In the ENGAGE AF TIMI 48 trial, subjects with CrCl between 30 and 50 ml/min were given 30 mg edoxaban (low-dose regimen). The subgroup analysis showed that this dose was comparable to warfarin for the prevention of stroke and systemic embolism and resulted in lower rates of major bleeding and a more favorable net clinical outcome [72].

Conclusion

NOACs have been shown to have similar or superior efficacy, and a better safety profile compared with warfarin due to its predictable pharmacokinetics and pharmacodynamics, and set dosing schedules allowing optimization of anticoagulation for stroke prevention in the elderly patients with AF. However, renal function should be taken into consideration when choosing NOACs as renal dysfunction may increase the risk of bleeding in these patients posing a therapeutic challenge for physicians. Warfarin, on the other hand, remains to be a viable option in certain clinical scenarios. Finally, in elderly patients, the choice of oral anticoagulants for stroke prevention in NVAF should be individualized and should include considerations for the best estimate of absolute benefit weighed against bleeding risks in order to optimize anticoagulation.

Compliance with Ethical Standards

Conflict of Interest Drs. Te, Chao and Chen declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
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1. Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Lim TW, et al. 2017 Consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythm. 2017;33(4):345–67.
2. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998;82(8A):2N–9N.
3. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham heart study. Circulation. 2003;107:2920–5.
4. Chugh SS, Haymoeller R, Narayan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014;129:837–47.
5. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, et al. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan nationwide AF cohort study. Chest. 2018;153(2):453–66.
6. Lip GY, Nieuwlaat R, Pisters R. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263–72.
7. Lip GY. Stroke and bleeding assessment in atrial fibrillation: when, how, and why? Eur Heart J. 2013;34(4):1041–9.
8. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. Lancet. 2016;388(10046):806–17.
9. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093–100.
11. Maringh R, Lip GY, Lane DA. Stroke prevention in atrial fibrillation patients. Expert Opin Pharmacother. 2010;11(14):2331–50.
12.• Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risk of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost. 2011;106(5):968–77 **Gallagher et al. emphasize on the importance of optimal anticoagulation for stroke reduction and that mortality rates were significantly lower with warfarin when the time spent within therapeutic range is at least 70%.**
13. Agarwal S, Hachamovitch R, Menon V. Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis. Arch Intern Med. 2012;172(8):623–31.
14. Björck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. Stroke. 2013;44:3103–8.
15. Chao TF, Chiang CE, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Evolving changes of the use of oral anticoagulants and outcomes in patients with newly diagnosed atrial fibrillation in Taiwan. Circulation. 2018;138(14):1485–7.
16. Chiong JR, Cheung RJ. Long-term anticoagulation in the extremely elderly with the newer antithrombotics: safe or sorry? Korean Circ J. 2013;43(5):287–92.
17. Stöllberger C, Chnupa P, Abzieher C, Länger T, Finsterer J, Klem I, et al. Mortality and rate of stroke or embolism in atrial fibrillation during long term follow-up in the embolism in left atrial thrombi (ELAT) study. Clin Cardiol. 2004;27:40–6.
18. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke. 2009;40:1410–6.
19. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. Stroke. 1999;30:1223–9.
20. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA. 2001;285(18):2370–5.
21. Fitzmaurice DA, Hobbs FD, Jowett S, Mant J, Murray ET, Holder R, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomized controlled trial. BMJ. 2007;335:383.
22. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987;147:1561–4.
23.• Chao TF, Lip GY, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Relationship of aging and incident co-morbities to stroke risk in patients with atrial fibrillation. J Am Coll Cardiol. 2018;71:122–32 **Chao et al demonstrated that most AF patients would developed at least 1 new stroke risk factor as they age. The Delta CHA_2DS_2-VASc score may be used to predict risk for ischemic stroke, which demonstrate the dynamic nature of stroke risk due to aging and incident comorbidities.**
24. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010;123:638–645.e4.
25. Tulner LR, van Campen JP, Kuper IM, Gijsen GJ, Koks CH, Mac Gillavry MR, et al. Reasons for undertreatment with oral anticoagulants in frail geriatric outpatients with atrial fibrillation: a prospective, descriptive study. Drugs Aging. 2010;27:39–50.
26. Gandolfo C, Balestrino M, Burrone A, Del Sette M, Finocchi C. Stroke due to atrial fibrillation and the attitude to prescribing anticoagulation prevention in Italy. A prospective study of a consecutive stroke population admitted to a comprehensive stroke unit. J Neurol. 2008;255:796–802.
27. Lin LJ, Cheng MH, Lee CH, Wung DC, Cheng CL, Kao Yang YH. Compliance with antithrombotic prescribing guidelines for patients with atrial fibrillation – a nationwide descriptive study in Taiwan. Clin Ther. 2008;30:1726–36.
28. Walker AM, Bennett D. Epidemiology and outcomes in patient s with atrial fibrillation in the United States. Heart Rhythm. 2008;5:1365–72.
29. Arts DL, Visscher S, Opstelten W, Korevaar JC, Abu-Hanna A, van Weert HC. Frequency and risk factors for under- and over-treatment in stroke prevention for patients with non-valvular atrial fibrillation in general practice. PLoS One. 2013;8:e67806.

30.•• Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: A nationwide cohort study. Circulation. 2018;138:37–47 **Chao et al compared the risk of ischemic stroke and ICH in elderly patients (≥90 years old) (1) with and without AF without antithrombotic therapy; (2) among AF patients between those without treatment, those taking antiplatelet agents, warfarin; (3) among AF patients taking warfarin and NOACs. The authors found that warfarin was associated with lower risk of ischemic stroke but no difference in ICH risk compared with nontreatment while a positive net clinical benefit was found using warfarin when compared with no antithrombotic therapy or with antiplatelet therapy. When comparing warfarin vs NOAC in elderly patients with AF, there was no significant difference between risks for ischemic stroke but NOAC was found to lower the risk of ICH. They concluded that OACs may be considered for stroke prevention in the elder, with NOACs being a favorable choice.**

31. Biteker M, Basaran Ö, Dogan V, Altun I, Özpamuk Karadeniz F, Tekkesin AI, et al. Real-world clinical characteristics and treatment patterns of individuals aged 80 and older with nonvalvular atrial fibrillation: results from the ReAl-life Multicenter Survey Evaluation Stroke Study. J Am Geriatr Soc. 2017;65:1684–90.

32. Yamashita Y, Hamatani Y, Esato M, Hun YH, Tsuji H, Wada H, et al. Clinical characteristics and outcomes in extreme elderly (age ≥85 years) Japanese patients with atrial fibrillation: the Fushimi AF Registry. Chest. 2016;149:401–12.

33. Mant J, Hobbs FDR, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomized controlled trial. Lancet. 2007;370:493–503.

34. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomized controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age Ageing. 2007;36(2):151–6.

35. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med. 2009;151: 297–305.

36. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the stroke prevention investigators. Stroke. 2009;40:1410–6.

37. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37: 2893–962.

38. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol. 2014;63: 747–62.

39. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc. 2012;60:1487–92.

40. Ekerstad N, Bylin K, Karlson BW. Early re-hospitalizations of frail elderly patients – the role of medications: clinical, prospective, observational trial. Drug Healthc Patient Saf. 2017;9:77–88.

41. Patti G, Lucerna M, Pecen L, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: a sub-analysis from the PREFER in AF (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation). J Am Heart Assoc. 2017;6:e005657.

42. Perera V, Bajorek BV, Matthews S, Hilmer SN. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. Age Ageing. 2009;38:156–62.

43. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol. 2008;7:915–26.

44. Thompson LE, Maddox TM, Lei L, et al. Sex differences in the sue of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR) PINNACLE registry. J Am Heart Assoc. 2017;6:1–10.

45. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. Eur Heart J Cardiovasc Pharmacother. 2017;3:163–82.

46. Nielsen PB, Skjoth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-Vasc? Circulation. 2018;137:832–40.

47. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–67.

48. Fawzy A, Lip GYH. Anti-coagulation in elderly patients with nonvalvular atrial fibrillation: a balancing act. Heart Rhythm. 2018. https://doi.org/10.1016/j.hrthm.2018.09.011.

49. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008;118:2029–37.

50. Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010;170:1433–41.

51. Gateman D, Trojnar ME, Agarwal G. Warfarin anticoagulation for atrial fibrillation in community-based practice. Can Fam Physician. 2017;63:e425–31.

52. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. Chest. 2013;144:1555–63.

53. Lip GY, Haguenoer K, Saint-Etienne C, Fauchier L. Relationship of the SAMe-TT(2)R(2) score to poor-quality anticoagulation, stroke, clinically relevant bleeding, and mortality in patients with atrial fibrillation. Chest. 2014;146:719–26.

54. Gallego P, Roldan V, Marin F, Galvez J, Valdes M, Vicente V, et al. SAMe-TT2R2 score, time in therapeutic range, and outcomes in anticoagulated patients with atrial fibrillation. Am J Med. 2014;127:1083–8.

55. Hylek E, Go A, Chang Y. Increasing age is not associated with poorer anticoagulation control in outpatients with nonvalvular atrial fibrillation. J Am Geriatr Soc. 2000;48:S58.

56. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.

57. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.

58. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban and warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.

59. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.

60. Lauw MN, Eikelboom JW, Coppens M, Wallentin L, Yusuf S, Ezekowitz M, et al. Effects of dabigatran according to age in atrial fibrillation. Heart. 2017;103:1015–23.

61. Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, oral, Direct Factor Xa Inhibition

Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). Circulation. 2014;130:138–46.
62. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J. 2014;35:1864–72.
63. Kato ET, Giugliano RP, Ruff CT, Koretsune Y, Yamashita T, Kiss RG, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIM 48 trial. J Am Heart Assoc. 2016;5:e003432.
64. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: Niigata preventive medicine study. Am Heart J. 2009;158:629–36.
65.•• Chan KE, Giugliano RP, Patel MR, Abramson S, Jardine M, Zhao S, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. J Am Coll Cardiol. 2016;67:2888–99 **Chan et al. reviewed the pharmacokinetic data on NOACs in patients with severe renal impairment and those on hemodialysis. They presented the data in terms of safety and efficacy of NOACs for stroke prevention in this group of patients with AF especially that the randomized controlled trial of each NOACs excluded patients with severe renal impairment and those on hemodialysis.**
66. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet. 2010;49:259–68.
67. Hariharan S, Madabushi R. Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment. J Clin Pharmacol. 2012;52:1195–255.
68. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation. A RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial analysis. Circulation. 2014;129: 961–70.
69. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J. 2011;32:2387–94.
70. Siontis K, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation. 2018;138:1519–29.
71. Wang X, Tirucherai G, Marbury TC, Wang J, Chang M, Xhang D, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol. 2016;56:628–36.
72. Bohula EA, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, Antman EA, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF TIME 48 trial. Circulation. 2016;134:24–36.