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Review

Asian Patients with Stroke plus Atrial Fibrillation and the Dose of Non-Vitamin K Oral Anticoagulants

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After recent randomized control trials (RCTs), non-vitamin K oral anticoagulants (NAOAs) are now widely being used in patients with atrial fibrillation (AF) worldwide. However, current guidelines for the use of NOACs in patients with AF are derived mostly using a Caucasian population and non-stroke patients. Relatively few Asian patients with AF and stroke are included in the recent RCTs. As a result, the optimal use of NOACs in this particular group of patients is remains to be settled. The optimal dose of NOACs and response to current dose of NOACs of Asian patients with AF and stroke may differ from those of westerners and patients without stroke. We reviewed available research on NOACs by searching PubMed and ClinicalTrials.gov published in English up to December 2015. In this review, the characteristics of Asian AF patients with prior stroke/transient ischemic attack, which might influence the efficacy and safety profiles of NOACs, are discussed. In addition, we summarize the risk factors for bleeding complications on NOACs, which are related or unrelated with the blood level of NOACs. Lastly, we provide recent data of reduced dose of NOACs from RCTs or large cohorts. The results reviewed herein call for clinical trials to test whether a reduced dose of NOACs is beneficial in Asian patients with AF and stroke. In the meantime, further researches are needed to establish the safety and efficacy of dose-adjusted NOACs considering both blood levels of NOACs and fragility of patients in Asian patients with AF and stroke.

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Introduction

Large randomized controlled trials (RCTs) consistently showed that non-vitamin K antagonist oral anticoagulants (NOACs) were at least as effective and safe as (regarding intracranial bleeding, much safer than) warfarin for stroke prevention in atrial fibrillation (AF),[1-4] and regulatory authorities in many countries have approved NOACs. As a result, NOACs are now increasingly and widely being used worldwide. However, even with NOACs, the risk of major bleeding complication is not negligible; the annual major bleeding rates in the landmark RCTs were 2.71% and 3.11% with low and high dose dabigatran, 3.13% with rivaroxaban, 2.8% with apixaban, and 1.61% and 2.75% with low and high dose edoxaban.[1-4]

Patients enrolled in RCTs are only partly representative of patients with AF in clinical practice.[5] Furthermore, Asian AF patients with prior stroke or transient ischemic attack (TIA) constituted the minority of patients enrolled in the RCTs; 10.7% were Asians (from 6.5% of the ROCKET-AF trial to 15.4% of the RE-LY trial),[6-9] 20.3% were patients with prior stroke or TIA (from 18.9% in the ARISTOTLE trial to 52.4% of the ROCKET-AF trial),[10-12] and thereby only 3.7% were Asian patients with prior stroke or TIA.[13]

The relative efficacy and safety of NOACs over warfarin appear to be greater in Asians than in non-Asians,[13-15] but the bleeding rates with NOACs were higher in Asians than in non-Asians. Therefore, the optimal dose and response to the currently recommended dose of NOACs in Asian AF patients with prior stroke/TIA may differ from those in non-Asians and those without prior stroke/TIA.

In this review, we will discuss the characteristics of Asian AF patients with prior stroke/TIA, which might influence the efficacy and safety profiles of NOACs. In addition, we will summarize the risk factors for bleeding complications on NOACs, which are related or unrelated with the blood level of NOACs. Lastly, we will provide recent data of reduced dose of NOACs from RCTs or large cohorts.

Search strategy and selection criteria

We identified references for this review by searching PubMed and ClinicalTrials.gov published in English up to December 2015, with the search terms of AF, anticoagulation, Asians, stroke, cerebral infarction, bleeding, and hemorrhage. Additional relevant articles were identified from manual searches of relevant articles and reviews and were solicited from the authors. The final reference list was generated on the basis of originality and relevance to this topic. Because of space limitation, we were not able to include the results of small cohort studies and we described the results of RCTs only briefly.

Summary of efficacy and safety findings from representative studies

Table 1 summarizes the findings of efficacy and safety endpoints from representative RCTs, cohort studies, and meta-analyses.

In a meta-analysis of overall populations including Asians and non-Asians enrolled in 4 major RCTs,[16] high-dose NOACs compared to warfarin significantly reduced stroke or systemic embolism by 19% (risk reduction 0.81, 95% CI 0.73-0.91; $P<0.001$)

Table 1. Summary of risk of stroke/thromboembolism and major bleeding with and without dose reduction of non-vitamin K oral anticoagulants and warfarin

NOAC vs. warfarin	No. of patients	Primary end point HR (95% CI)	Bleeding complications HR (95% CI)		
		Stroke or SE	Major bleeding	ICH	G-I bleeding
RE-LY trial					
Dabigatran 150 mg	6,076	0.66 (0.53-0.82)	0.93 (0.81-1.07)	0.40 (0.27-0.60)	1.50 (1.19-1.89)
Dabigatran 110 mg	6,015	0.91 (0.74-1.11)*	0.80 (0.55-0.83)*	0.31 (0.20-0.47)	1.10 (0.86-1.41)*
U.S. Medicare data (propensity-matched)					
Dabigatran 150 mg	56,576	0.70 (0.57-0.85)	N/A	0.30 (0.21-0.42)	1.51 (1.32-1.73)
Dabigatran 75 mg	10,522	0.88 (0.60-1.27)	N/A	0.46 (0.26-0.81)	1.01 (0.78-1.31)
Taiwan national health insurance data (propensity-matched)					
Dabigatran 150 mg	1,168	0.61 (0.37-1.00)	N/A	0.22 (0.06-0.76)	1.05 (0.29-3.76)
Dabigatran 110 mg	8,772	0,62 (0.52-0.75)*	N/A	0.47 (0.34-0.65)	0.99 (0.64-1.52)
ROCKET-AF trial					
Rivaroxaban (20 mg in 79.4%)	7,081	0.79 (0.66-0.96)	1.04 (0.90-1.20)	0.67 (0.47-0.93)	N/A
Rivaroxaban (15 mg J-ROCKET)	1,280	0.49 (0.24-1.00)	0.85 (0.50-1.43)	0.73 (0.16-3.25)	N/A
ARISTOTLE trial (Apixaban)	9,120	0.79 (0.66-0.95)	0.68 (0.61-0.75)	0.42 (0.30-0.58)	0.89 (0.70-1.15)
ENGAGE AF-TIMI 48 trial					
Edoxaban 60 mg	5,251	0.87 (0.73-1.04)	0.80 (0.71-0.91)	0.47 (0.34-0.63)	1.23 (1.02-1.50)
Edoxaban 30 mg	1,784	1.13 (0.96-1.34)*	0.47 (0.41-0.55)*	0.30 (0.21-0.43)*	0.67 (0.53-0.83)*
Meta-analysis (Ruff et al. 2014)					
High-dose NOACs	29,287	0.81 (0.73-0.91)	0.86 (0.73-1.00)	0.48 (0.39-0.59)	1.25 (1.01-1.25)
Low-dose NOACs	13,049	1.03 (0.84-1.27)	0.65 (0.43-1.00)	0.31 (0.24-0.41)	0.89 (0.57-1.37)
Meta-analysis (Wang et al. 2015)					
Standard dose of NOACs in Asians	3,035	0.65 (0.52-0.83)	0.57 (0.44-0.74)	0.33 (0.22-0.50)	0.79 (0.48-1.32)
Low dose of NOACs in Asians	2,216	0.93 (0.71-1.21)	0.52 (0.32-0.86)	0.28 (0.16-0.49)	0.67 (0.39-1.15)
Standard dose of NOACs in non-Asians	26,277	0.85 (0.77-0.93)	0.89 (0.76-1.04)	0.52 (0.42-0.64)	1.44 (1.12-1.85)
Low dose of NOACs in non-Asians	11,473	1.07 (0.93-1.24)	0.64 (0.38-1.09)	0.32 (0.24-0.44)	0.87 (0.56-1.35)

The meta-analysis for standard vs. low dose NOACs included data of dabigatran 150 vs. 110 mg, edoxaban 60 vs. 30 mg, and rivaroxaban 20 vs. 15 mg.
NOAC, non-vitamin K oral anticoagulant; HR, hazard ratio; CI, confidence interval; SE, systemic embolism; ICH, Intracranial bleeding; G-I, Gastrointestinal; N/A, not assessed.
*Significant difference between two dose groups.

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and intracranial hemorrhage by 52% (0.48, 0.39-0.59; $P<0.001$), and there were no heterogeneity across the trials. However, the reduction of major bleeding with high-dose NOACs was non-significant (0.86, 0.73-1.00; $P=0.06$), and there was significant heterogeneity across the trials. Gastrointestinal bleeding was significantly increased with high-dose NOACs (1.25, 1.01-1.55; $P=0.043$), but significant heterogeneity was noted. In contrast, low-dose NOACs (110 mg dabigatran and 30/15 mg edoxaban) compared to warfarin had similar risk of stroke or systemic embolism (1.03, 0.84-1.27; $P=0.74$) and higher risk of ischemic stroke (1.28, 1.02-1.0; $P=0.045$), but had comparable risk of gastrointestinal bleeding (0.89, 0.57-1.37; $P=0.58$), non-significant reduction in major bleeding (0.65, 0.43-1.00; $P=0.05$), and substantial reduction in intracranial hemorrhage (0.31, 0.24-0.41; $P<0.001$).

The relative safety and efficacy of NOACs compared to warfarin may be greater in Asians than in non-Asians, especially in stroke patients.[14,15] In a recent meta-analysis,[17] Asians had greater benefits of high-dose NOACs over warfarin than non-Asians for the endpoints of stroke or systemic embolism (odds ratio [95% CI], 0.65 [0.52-0.83] vs. 0.85 [0.77-0.93]; P interaction = 0.045), major bleeding (0.57 [0.44-0.74] vs. 0.89 [0.76-1.04], P interaction = 0.004), and hemorrhagic stroke (0.32 [0.19-0.52] vs. 0.56 [0.44-0.70], P interaction = 0.046). While the risk of gastrointestinal bleeding was higher with high-dose NOACs than with warfarin in non-Asians (1.44 [1.12-1.85]), but not in Asians (0.79 [0.48-1.32]) (P interaction = 0.041). In contrast, when comparing low-dose NOACs compared to warfarin, Asians and non-Asians did not differ in the results of efficacy and safety endpoints (Table 1).

In patients randomized to NOACs, Asians versus non-Asians had numerically lower rates of major bleeding except for those on edoxaban 60 mg (Figure 1). However, the risks of intracranial hemorrhage, the most devastating complication, were higher in Asians than in non-Asians (the annual risk difference from 0%/year to 0.37%/year) and greater in patients with prior stroke/TIA than in those without (the annual risk difference from 0.2%/year to 0.26%/year) (Figure 2).[6-9] Therefore, these results suggest that intracranial hemorrhage rather than major bleeding (including gastrointestinal bleeding) is a major concern in selection and dosing of NOACs in Asians. Asian AF patients with prior stroke/TIA who are likely to have fragile cerebrovascular bed might have greater risk of intracranial hemorrhage, but until now no analysis has been specifically conducted for these patients.

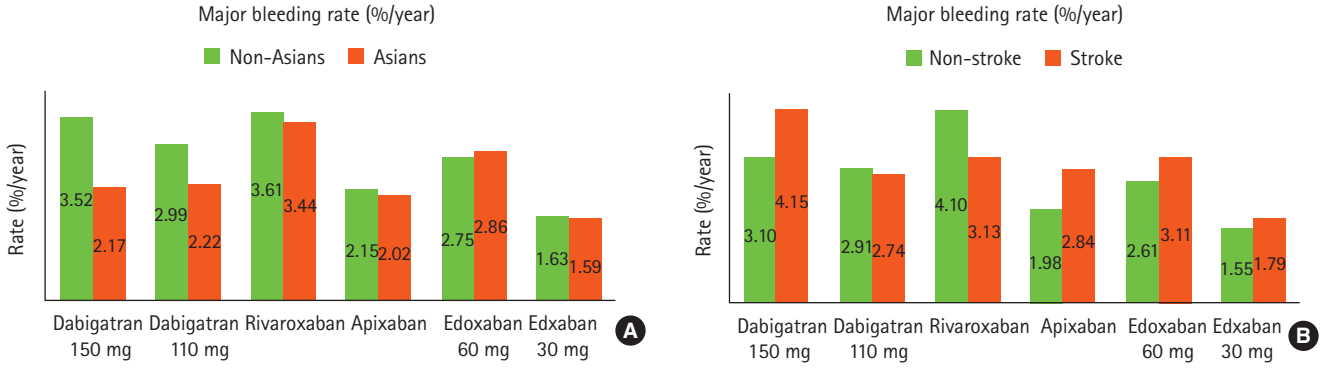

Figure 1. Annual rates of major bleeding with NOACs in (A) Asians vs. non-Asians and (B) patients with prior stroke/TIA vs. patients without from AF RCTs.

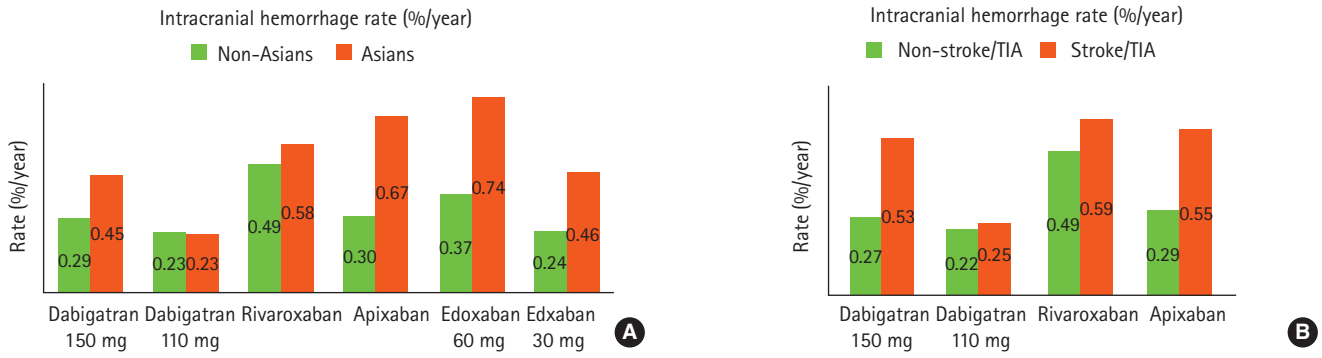

Figure 2. Annual rates of intracranial hemorrhage with NOACs in (A) Asians vs. non-Asians and (B) patients with prior stroke/TIA vs. patients without from AF RCTs.

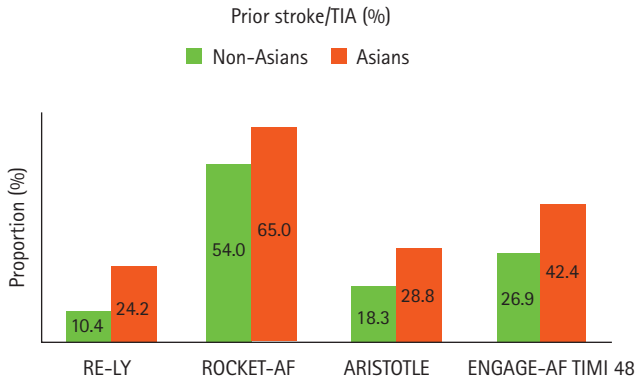

Figure 3. Patients with a prior stroke/TIA enrolled in NOACs RCTs.

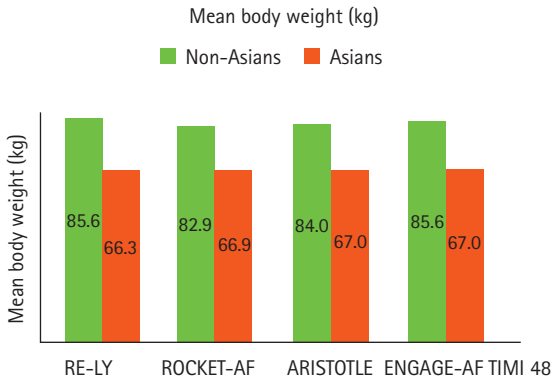

Figure 4. Body weight of patients enrolled in NOACs RCTs.

Characteristics of Asians patients with stroke and atrial fibrillation

In multinational survey or cohort studies, Asian AF patients were more likely to have a history of prior stroke/TIA and lower body weights (or less obesity) than non-Asian AF patients.[18-21] In a Japanese community-based registry of AF patients, the mean age was 74.2 years, the mean body weight was 58.5 kg, 21.8% had a history of stroke/TIA, and the mean creatinine clearance (CrCl) was 63.4 mL/min and 35.6% had moderate to severe renal impairment (<30 mL/min in 11.4% and 30-50 mL/min in 24.2%).[22] Similarly, among patients enrolled in 4 RCTs of NOACs, Asians had more history of stroke/TIA (despite the comparable CHADS2 score) and substantially lower body weights than non-Asians (Figures 3 and 4).[6-9] The difference in body weight between Asians and non-Asians was 20 kg in RE-LY, 16 kg in ROCKET-AF, 17 kg in ARISTOTLE, and 20 kg in ENGAGE-AF TIMI 48. Body weight, along with serum creatinine level, age and sex determines CrCl, which significantly influence NOACs metabolism. Of note, the proportions of patients with mild (CrCl 50-80 mL/min) or moderate (CrCl 30-50 mL/min) renal impairment were higher in Asians than in non-Asians.[6-9,23]

Among Asian patients with AF, characteristics are likely to differ between patients with a history of stroke/TIA and those without, but no study has conducted formal comparison. In a Japanese multicenter registry of acute ischemic stroke patients with AF, the mean age was 77.7 years, the mean body weight was 56.3 kg, and the mean CrCl was 56.6 mL/min.[24] Despite the limitation of indirect comparison, Japanese AF patients with stroke/TIA compared to Japanese overall AF patients appear to have higher age, lower body weight, and lower renal function.[22,24] In a single center study of Korea, AF patients with stroke/TIA had a mean age of 73.9 years and CrCl of 56.8 mL/min,[5] which were similar to those of Japanese AF patients with stroke/TIA. In this study, when the enrollment criteria of four RCTs were applied to Korean patients with AF, the proportion of patients excluded from trials were expected to be higher in patients with stroke/TIA (27.2%-42.6%, depending on individual trial's criteria) vs. those without stroke/TIA (18.5%-27.2%). The main reasons for ineligibility for RCTs in patients with stroke/TIA were high of bleeding risk (15.2%-20.8%) and low CrCl (5.6%-9.2%).[5]

Compared to non-Asians, Asians are at higher risk of warfarin-related intracranial bleeding,[25] and the prevalence of intracranial macro- and microangiopathy also appears to be high.[26-28] For example, cerebral microbleeds, which are high prevalent in Asians and stroke patients, increase the risk of intracranial bleeding with warfarin use.[29-31] Individualized antithrombotic therapy, e.g., use of NOACs, was proposed depending on the presence of and increase in the number of cerebral microbleeds on brain MRI.[32,33]

Previous ischemic stroke or TIA is the most powerful independent risk factor for stroke in patients with AF.[34] The early period after acute ischemic stroke or TIA is particularly at high risk of recurrent stroke, but also at high risk of intracranial bleeding. Furthermore, a large population-based study showed an increased risk of stroke during the early period of warfarin initiation,[35] possibly due to prothrombotic activity of warfarin at treatment initiation.[36] For anticoagulation in acute cerebral ischemia, NOACs might be better than warfarin. However, patients with recent stroke/TIA were largely excluded in the landmark NOAC AF trials: the cut-off time point for eligibility from stroke onset to randomization was 30 days in ENGAGE-AF, 14 days in RE-LY and ROCKET-AF, and 7 days in ARISTOTLE. As a result, data about the use of NOACs in patients with recent stroke are lacking. Currently, a randomized trial is ongoing to examine the safety and efficacy of early initiation (within 5 days from stroke onset) of rivaroxaban in patients with AF and acute ischemic stroke (TripleAXEL, NCT02042534).[37]

In patients with AF, stroke is not always caused by cardiogenic embolism (AF-unrelated mechanism). Since macro- and microangiopathies are more prevalent in Asians than in non-Asians,

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AF-unrelated stroke/TIA is more likely to occur in Asian AF patients than in non-Asian AF patients. In a Korean study, among AF patients with recent ischemic stroke, 17.2% of ischemic strokes were classified as AF-unrelated strokes.[38] Moreover, compared to patients with AF-related stroke, patients with AF-unrelated stroke experienced more recurrent strokes even with adequate anticoagulation, and 87.5% of their recurrent strokes were AF-unrelated strokes.[38] Therefore, it would be of clinical relevance to differentiate stroke mechanism in AF patients. A recent multidetector cardiac computed tomography study showed that morphometric and volumetric changes of left atrial appendage was not prominent in AF-unrelated stroke.[39] For patients with AF-related stroke, antiplatelet drugs should be discontinued at the time of NOACs initiation unless there is a strong indication other than secondary stroke prevention for their continuous use. However, antiplatelet therapy might be often needed in patients with AF-unrelated stroke, particularly during the early period after acute cerebral ischemia.

Annual risk of stroke in individuals with AF is a continuum and increases with risk factors. The $CHADS_2$ and CHA_2DS_2-VASc schemes are most widely used model for stratification of AF-related stroke risks, but a high score would also indicate a higher atherosclerotic burden. Previous studies showed that high $CHADS_2$ and CHA_2DS_2-VASc scores were associated with subsequent stroke, cardiovascular events, and death in stroke patients without AF[40] and in acute coronary syndrome patients.[41] Thereby, AF patients with high $CHADS_2$ or CHA_2DS_2-VASc scores might have a higher risk of AF-unrelated stroke (macro- or microangiopathy).[42,43] A large Chinese cohort of AF patients showed that although net benefit favor warfarin over antiplatelet for patients at high risk of stroke, the benefit of warfarin decreased with the increase in the CHA2DS2-VASc scores.[44]

Therefore, concomitant use of antiplatelet agents are often needed in Asian stroke patients with AF. In the RE-LY trial, Asians had a higher rate of previous stroke (24.2% vs. 10.4%) and use of antiplatelet agents (47.1% vs. 38.1%) than non-Asians.[6] Concomitant use of antiplatelet agents and anticoagulants increase the bleeding risks. A meta-analysis of patients receiving antiplatelet therapy after an acute coronary syndrome showed that the use of NOACs is associated with a dramatic increase (~3 times) in major bleeding events.[45]

Dose of NOACs: serum level vs. fragility of patients

Renal function, a major determinant of serum NOAC levels

Based on the study design and results of subgroup analysis of RCTs of NOACs, current guidelines of AF management recommended dose reduction according to the serum level of NOACs.[46] Because NOACs are predominantly or partially excreted by the kidneys, only patients with CrCl ≥ 30 mL/min (dabigatran and rivaroxaban) or ≥ 25 mL/min (apixaban) were included in the trials. The studies with apixaban and rivaroxaban used reduced doses for patients with CrCl < 50 mL/min. Age (> 80 years) for dabigatran and apixaban, body weight (≤ 60 kg) for apixaban and edoxaban, and the use of P-glycoprotein antagonist (e.g., dronedarone) were also considered in selection of NOAC dose. Both age and body weight are parameters used to estimate CrCl by Cockcroft-Gault equation, and absorption of NOACs is dependent on the intestinal P-glycoprotein system.

However, the benefits of the NOACs seem to be larger in chronic kidney disease stages.[47] In the ARISTOTLE trial, relative reduction in major bleeding was greater in patients with renal dysfunction.[48] For Asian patients with stroke, data about bleeding risk depending on the renal function is limited. In Asian patients in the RE-LY trial, bleeding rate was increased with renal impairment, but relative benefits of dabigatran over warfarin were preserved regardless of renal function.[49]

Comorbid conditions of patients, major determinants of bleeding complications

Safe use of NOACs needs understanding of when to reduce the dose of NOACs. In this context, it is possible that fragility of patients (clinical and radiological features) may be as important as serum NOAC levels (related to renal function) in the development of major bleeding during the use of NOACs.

Post-hoc analysis of RCTs showed determinants of major bleeding in NOAC users. Elderly, prior stroke, prior gastrointestinal bleeding/anemia, aspirin use, renal dysfunction, and multiple cerebral microbleeds were commonly associated with major bleeding.[50-52] Patients with AF and stroke often have comorbid conditions and take multiple medications. In ROCKET AF, two-thirds of enrolled patients were on ≥ 5 medications, and the bleeding risk increased as the medication numbers increased.[53] In RE-LY, concomitant antiplatelet drugs increased the risk of major bleeding, and the major bleeding risk was higher with dual antiplatelet therapy than with single antiplatelet therapy. Of patients who had concomitant antiplatelet use, the major bleeding risk was lowest in low dabigatran user (dabigatran 110 mg, BID).[54]

It is interesting that many of the factors are relatively unrelated to the degree of renal impairment, suggesting the importance of consideration of 'non-renal' factors as well as renal factor when considering the dose of NOACs (Figure 5).

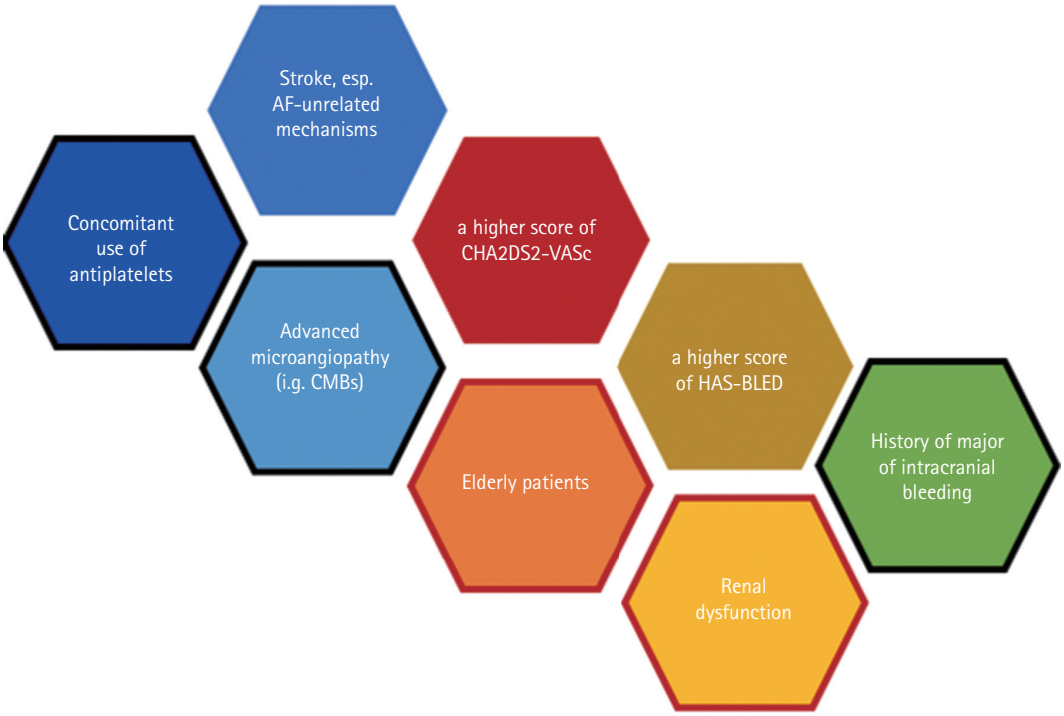

Figure 5. Factors associated with major or intracranial bleeding in RCTs of NOAC trials and their relationships. Black outlines represent fragility in Asian patients with stroke, whereas red outlines represent factors that determined serum levels of NOACs. CMBs, cerebral microbleeds.

Results of low doses of warfarin and non-vitamin K oral anticoagulants

Need for a low level of anticoagulation in frail patients

Anticoagulation therapy is needed even in frail patients with AF who have an increased risk of bleeding. A Japanese community-based survey (Fushimi AF registry) showed that features suggesting fragility of patients (i.e., advanced age, underweight, previous stroke, heart failure, chronic kidney disease, and anemia) were independently associated with risk of stroke and death in non-anticoagulated patients.[55] In post-hoc analysis of ROCKET-AF, renal dysfunction was a strong, independent predictor of stroke and systemic embolism and a risk estimation scheme incorporating renal dysfunction (R_2CHADS_2 score) better predicted the risk of stroke or systemic embolism in ROCKET-AF and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) populations.[56]

A Japanese study (J-RHYTHM registry) showed that warfarin could have beneficial effects even in very old patients with AF if INR is kept between 1.6 and 2.59, suggesting importance of a lower level of anticoagulation in frail patients.[57]

The benefits of NOACs compared with warfarin in the elderly individuals with multiple comorbid conditions were consistently observed among the trials.[58] NOACs appear promising and help overcome some if not all of the limitations of warfarin in early frail patients.[58] In fact, the clinical benefits of NOACs may be greater in patients with high bleeding risk.[59] Proposals for decision-making in NOACs use for these frail/high bleeding risk patients were recently suggested.[58-60] However, in the real world, NOACs were underutilized in these patients (e.g., elderly).[61,62] Our results of Korean patients with AF and stroke showed that there was a negative correlation between CrCl and ATRIA score (a scheme for bleeding-risks), and patients who had features favoring NOAC use (i.e., a high ATRIA score) were more likely to have contraindications for NOACs use (i.e., a low CrCl).[5]

Evidences from randomized controlled trial

RCTs and large cohort studies have evaluated the safety and efficacy of different doses of NOACs in patients with AF. In particular, the RE-LY and ENGAGE AF-TIMI 48 trials formally tested two different doses of NOACs (Table 1).

In the J-ROCKET-AF study, 15 mg rivaroxaban instead of 20 mg was used,[63] because 15 mg rivaroxaban dose in Japanese patients yield exposures comparable to 20 mg dose in white patients.[64] The trial results demonstrated noninferiority of 15 mg rivaroxaban and less intracranial bleeding over warfarin, which supports the use of a reduced dose of rivaroxaban (15 mg) for evaluation in Japanese patients with AF.[63]

The ENGAGE AF-TIMI 48 trial evaluating the efficacy of edoxa-

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ban vs. warfarin in patients with AF provided the evidence of supporting the use of a lower dose of NOAC in fragile patient population.[4,65] In this study, low-dose (30 mg vs. 60 mg) edoxaban was associated with a 41% increase in ischemic stroke, which is counterbalanced by a 53% reduction in hemorrhagic stroke, suggesting an Importance of the low dose of NOACs in fragile patient populations that present with greater risk of hemorrhagic stroke. Despite the lower anti-factor Xa activity, dose reduction preserved the efficacy of edoxaban compared with warfarin, suggesting that the therapeutic window for edoxaban is narrower for major bleeding than thromboembolism.[65] One recent Japanese study showed that bleeding rate, plasma edoxaban concentration and biomarkers of blood coagulation and fibrinolysis were similar between patients with severe renal impairment receiving low dose edoxaban (15 mg) and those with normal renal function receiving a higher dose edoxaban (30 or 60 mg).[66]

Similar results were also observed in the RE-LY trial that showed dose reduction of dabigatran significantly increased in stroke or systemic embolism but a significant reduction in major bleeding.[1] However, further studies are needed because, in the recent study of propensity score matched elderly patients enrolled in Medicare, neither stroke/systemic embolism nor intracranial/major gastrointestinal bleeding were significantly different between patients received dabigatran 150 mg vs. 75 mg twice daily.[67] Very recently, the Taiwan national health insurance research database showed that 88% patients took 110 mg dabigatran and the magnitude of effect for outcomes of 110 mg was comparable with those of 150 mg dose in real-world practice.[68]

A recent meta-analysis of RCTs of NOACs comparing efficacy and safety of NOACs between patients enrolled in Asian and non-Asian countries showed that standard-dose NOACs are preferred over warfarin in Asians patients, whereas low-dose NOACs are effective and safe alternative to warfarin.[17]

Perspectives and conclusions

Current guidelines for the use of NOACs in patients with AF are largely derived from Caucasian and non-stroke patients. Asian patients with AF and stroke might be 'specific' AF population due to 'specific' profiles of higher risks of both thromboembolic and bleeding events, and both patients and physicians are often reluctant to use NOACs as well as warfarin due to fear of bleeding complications. However, no specific guidelines exist regarding the dose of NOACs in these patients.[69,70] Measurement of serum levels of NOACs and anti-IIa or anti-Xa activity may improve safety during NOAC therapy, but not available in clinical practice yet. Several clinical and radiological features related bleeding complications may provide additional information to current guideline (dose reduction according to renal function to achieve optimal serum NOAC levels) in the selection of dose of NOACs.

Available data reviewed herein suggest that anticoagulation with NOACs could be promising and help overcome limitations of warfarin, especially in elderly frail patients, such as Asian patients with AF and stroke. Although the dose of NOACs should be used under the current guidelines for NOAC use in patients with AF, emerging evidences suggested that a reduced dose of NOACs could be helpful in these patients. To date, no studies have been conducted to test whether a reduced dose of NOACs is beneficial in Asian patients with AF and stroke. Because head-to-head comparisons of NOACs regarding their efficacy in preventing stroke in these particular patients are lacking, a recommendation for a preferred use of any of the NOACs can not be made. In the meantime, further researches are needed to establish the safety and efficacy of dose-adjusted NOACs considering both blood level of NOACs and fragility of patients in Asian patients with AF and stroke.

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