Optimal Management of Anticoagulation Therapy in Asian Patients With Atrial Fibrillation

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Stroke prevention is the cornerstone of management of atrial fibrillation (AF), and non-vitamin K antagonist oral anticoagulants (NOACs) are commonly prescribed. Because routine monitoring of anticoagulant effects of NOACs is not necessary, appropriate dosing following the criteria of each NOACs defined in pivotal randomized trials is important. Real-world data demonstrate that underdosing NOACs is associated with a higher risk of ischemic stroke without a lower risk of major bleeding. Furthermore, renal function of AF patients should be assessed using the Cockcroft-Gault formula to prevent overestimation that could result in overdosing of NOACs. The assessment of bleeding risk is important, and the HAS-BLED score should be used to help identify patients at high risk of bleeding (HAS-BLED score ≥ 3). Moreover, the HAS-BLED score should be reassessed at periodic intervals to address potentially modifiable bleeding risk factors because bleeding risks of AF patients are not static. When managing NOAC-related bleeding episodes, the possibility of occult malignancies (e.g., gastrointestinal [GI] tract cancers for patients experiencing GI bleeding and bladder cancer for patients with hematuria) should be kept in mind. Addressing all of these issues is crucial to achieving better clinical outcomes for anticoagulated AF patients. More efforts are necessary to incorporate clear and easy-to-follow recommendations about optimal management of anticoagulation into the guidelines to improve AF patient care.

Key Words: Atrial fibrillation; Ischemic stroke; Malignancy; Non-vitamin K antagonist oral anticoagulation

Atrial fibrillation (AF), the most common arrhythmia in daily medical practice, could potentially cause blood stasis and increase the risk of thromboembolism, ischemic stroke (IS), dementia, heart failure, myocardial infarction (MI), and death compared with patients without AF.¹ In addition, AF-related stroke has higher morbidity/mortality rates.² Although the management of AF has changed markedly in the past 2 decades, stroke prevention with oral anticoagulants (OACs) remains the foundation of holistic care of AF.^{3,4}

Among the OACs, non-vitamin K antagonist OACs (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, have emerged as an alternative and effective choice for stroke prevention worldwide.^{5,6} Compared with warfarin, NOACs possess better efficacy/safety ratios without the need for routine drug concentration monitoring, and less food and drug interactions.⁷ In fact, the introduction of NOACs has changed the field of stroke prevention in Asia and improved the clinical outcomes of Asian AF patients.^{6,8} However, the appropriate use of NOACs still

remains unsatisfactory, and a considerable proportion of patients still do not receive OACs. Although current clinical guidelines have provided overall recommendations on the initiation and general principles of NOAC use,^{5,9} real-world analyses have revealed that several factors might cause underuse or improper use of NOACs.^{10,11} These factors include older age, worse renal function, and previous bleeding events,¹¹ and hinder optimal management of anticoagulation therapy.

Here we aim to provide an overview of optimal management of anticoagulation therapy in Asian AF patients, focusing on appropriate dosing of NOACs, adoption of the current renal function equations to determine the dosing of NOACs, and management of NOAC-related bleeding.

Importance of Prescribing On-Label Dosing of NOACs

Although the appropriate dosages of NOACs have been clearly defined by randomized controlled trials, real-world

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Table 1. Summary of Clinical Studies Regarding the Use of Non-Label Dosing of NOACS in Asian AF Patients

Clinical study	Study type	NOAC(s) studied	Definition of underdosing NOAC(s)	Age of the underdosing group	Total no. of patients receiving NOAC(s)	Main findings (underdosing group vs. appropriate dosing: Reference)
Murata et al (2019) ¹⁸	Prospective registry	Dabigatran Rivaroxaban Apixaban Edoxaban	Low-dose of NOACs despite standard dosage criteria being met	71.2±8.2 years	1,658 (Appropriate dosing: 1,223 [74%]; Underdosing: 369 [22%]; Overdosing: 66 [4%])	Stroke/SE: 1.02 event/100 patient-years; aHR: 0.851 (0.391–1.746) Major bleeding: 0.64 event/100 patient-years; aHR: 0.474 (0.185–1.071)
Ikeda et al (2019) ¹⁹	Prospective registry	Rivaroxaban	Rivaroxaban: 10 mg daily for patients with an eGFR >50 mL/min	68.0±21.2 years	6,521 (Appropriate dosing: 4,185 [64%]; Underdosing: 2,336 [36%])	Stroke/non-CNS SE/MI: 2.15 events/100 patient-years; HR: 1.45 (1.10–1.91) Major bleeding: 1.34 events/100 patient-years; HR: 0.82 (0.61–1.11)
Cheng et al (2019) ¹¹	Retrospective database	Rivaroxaban	Rivaroxaban: 10 mg daily for patients with an eGFR >50 mL/min	79.1±11.2 years	2214 (Appropriate dosing: 1,630 [74%]; Underdosing: 584 [26%])	IS: 2.82 events/100 patient-years; aHR: 2.75 (1.62–4.69) Intracranial hemorrhage: 1.16 events/100 patient-years; aHR: 0.62 (0.32–1.20)
Lee et al (2020) ²⁰	Retrospective database	Dabigatran Rivaroxaban Apixaban Edoxaban	The following dosing of NOACs without meeting the dosage reduction criteria Dabigatran: 110 mg twice daily Rivaroxaban: 15 mg once daily Apixaban: 2.5 mg twice daily Edoxaban: 30 mg twice daily	70.9±8.2 years	3,733 (Appropriate dosing: 2,650 [71%]; Underdosing: 733 [20%]; Overdosing: 226 [6%])	Thromboembolism: 2.73% patients/year; aHR: 3.12 (1.12–8.67) Major bleeding: 1.46% patients/year; aHR: 2.24 (0.62–8.17)
Chan et al (2020) ²¹	Retrospective database	Dabigatran Rivaroxaban Apixaban Edoxaban	Following dosing of NOACs without meeting the dosage reduction criteria. Dabigatran: 110 mg twice daily Rivaroxaban: 15 mg once daily with an eGFR >50 mL/min Apixaban: 2.5 mg twice daily Edoxaban: 30 mg twice daily or 15 mg once daily	71.7±69.4 years	11,275 (Appropriate dosing: 7,764 [69%]; Underdosing: 2,999 [27%]; Overdosing: 512 [4%])	IS/SE: 2.20% patients/year; aHR: 1.59 (1.25–2.02) Major bleeding: 0.46% patients/year; aHR: 0.80 (0.50–1.27)
Lee et al (2021) ²²	Retrospective database	Apixaban	Apixaban: 2.5 mg twice daily and did not fulfill the dose reduction criteria	73.7±7.7 years	7,084 (Appropriate dosing: 4,194 [59%]; Underdosing: 2,890 [41%])	IS: 2.11 events/100 patient-years; aHR: 1.38 (1.06–1.81) Major bleeding: 1.09 events/100 patient-years; aHR: 0.99 (0.70–1.42)

AF, atrial fibrillation; aHR, adjusted hazard ratio; CNS, central nervous system; eGFR, estimated glomerular filtration rate; IS, ischemic stroke; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism.

data reveal that underdosing is not uncommon, and has been reported in up to 50% of AF patients treated with NOACs.^{12–16} In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) II registry, nearly one-eighth of US patients were under-dosed with NOACs, resulting in more cardiovascular hospitalizations without significant declines in major bleeding.¹⁷

In Asia, underdosing of NOACs is even more common under concerns of the higher risk of bleeding for Asian AF patients. Published studies investigating the association between different dosing of NOACs and risk of clinical outcomes in Asian AF patients are summarized in **Table 1**.^{11,18–22} Most of these studies, except for that performed by Murata et al,¹⁸ consistently showed a higher risk of IS or systemic embolism (SE) for off-label underdosing

of NOACs, while overdosing NOACs was associated with a higher risk of bleeding (**Figure 1**). Taking the study performed by Chan et al, which enrolled 11,275 Taiwanese AF patients receiving NOACs, for example, ≈27% and ≈5% of them were treated with underdosing and overdosing of NOACs, respectively.²¹ Compared with on-label dosing, underdosing of NOACs was associated with a significantly higher risk of IS/SE (hazard ratio [HR] 1.59; 95% confidence interval [CI] 1.25–2.02; $P<0.001$), whereas overdosing NOACs was associated with a significantly higher risk of major bleeding (adjusted HR 2.01; 95% CI 1.13–3.56; $P=0.017$).²¹ Likewise, a study from a tertiary medical center in South Korea also demonstrated that underdosing of NOACs was associated with a 2.5-fold increased risk of thromboembolism compared with warfarin.²⁰

Figure 1. Risk of clinical events in Asian AF patients receiving on-labeling dosing, underdosing and overdosing of NOACs. Most studies demonstrate that underdosing is associated with a higher risk of ischemic stroke/systemic embolic events without a lower risk of major bleeding. On the other hand, overdosing is associated with a higher risk of major bleeding without a lower risk of ischemic events. The data used in the figure are from Cheng et al,¹¹ Murata et al,¹⁸ Ikeda et al,¹⁹ Lee et al,²⁰ Chan et al,²¹ and Lee et al.²² AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

The dosing issue of rivaroxaban is even more complicated in Asia, where the J-ROCKET dosing criteria (15mg/day for patients with an estimated glomerular filtration rate (eGFR) >50mL/min and 10mg/day for those having an eGFR <50mL/min) were approved by Japan and the Taiwan Food and Drug Administration according to results of the J-ROCKET AF study.²³ A prior study showed generally similar efficacy and safety profiles between the ROCKET-AF and J-ROCKET dosing regimens.²⁴ Although J-ROCKET dosing of rivaroxaban may be also regarded as on-label dosing for Asian AF patients,

off-label underdosing of rivaroxaban (10mg/day for patients with an eGFR >50mL/min) was associated with a higher risk of IS and should generally be avoided. Data from the XAPASS (Xarelto Post-Authorization Safety and Effectiveness Study in Japanese Patients with Atrial Fibrillation) registry disclosed that ≈35.8% of Japanese AF patients with an eGFR >50mL/min received underdosing of rivaroxaban (10mg/day), which was associated with a higher composite risk of IS/SE/MI compared with the recommended dose (2.15 vs. 1.48 events/100 patient-years, $P=0.009$).¹⁹ Of note, the incidence rates of major bleeding

Table 2. Summary of Clinical Studies Regarding the Effects of Different Renal Function Equations on NOAC Dosing in Asian Populations

Clinical studies	Definition of each renal function assessment equation	Study type	Total no. of patients	Main findings
Lee et al (2019) ²⁹	CG (mL/min) = (140 – Age) × Weight / (72 × SCr) × (0.85 if female) MDRD (mL/min/1.73 m ²) = 175 × SCr – 1.154 × Age – 0.203 × (0.742 if female) × (1.210 if African-American)	Retrospective	6,268	1. Among underweight and elderly patients, the CG formula underestimated renal function compared with the non-CG formulas 2. The concordant rate of drug indications between the CG and non-CG formulas was approximately 94% 3. The differences in eGFR and categorized dose indications are unlikely to affect the risk of thromboembolism or major bleeding in on-label use of a NOAC
Chan et al (2020) ³⁰	CKD-EPI (mL/min/1.73 m ²) = 141 × min (SCr/(0.7 if female; 0.9 if male), 1) (–0.329 if female; –0.411 if male) × max (SCr/(0.7 if female; 0.9 if male), 1) – 1.209 × 0.993 Age × (1.018 if female) × (1.159 if black)	Retrospective	39,239	1. Compared with the CG equation, the MDRD and CKD-EPI formulas overestimated eGFRs in older adult AF patients with low body weights 2. The adoption of MDRD or CKD-EPI, rather than CG, resulted in inappropriate dosing of DOACs, thus attenuating the advantages of DOACs compared with warfarin regarding the composite risks of IS/SE and major bleeding

CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine. Other abbreviations as in Table 1.

were similar between the underdosing and standard dosing groups (1.34 vs. 1.63 events/100 patient-years, $P=0.197$).¹⁹ Similar findings were reported by Cheng et al, showing that off-label low-dose rivaroxaban was associated with an increased risk of IS with an HR of 2.75 (95% CI 1.62–4.69; $P<0.001$), while the risk of intracranial hemorrhage did not differ significantly between the on-label and off-label low-dosing groups (HR 0.62; 95% CI 0.32–1.20; $P=0.213$).¹¹ A higher risk of IS was also observed for off-label underdosing of apixaban in a report from South Korea.²² Based on these studies, label-adherence to NOAC dosing should be emphasized to achieve the best clinical outcomes for Asian patients with AF.

NOAC Dosing in Patients With Renal Dysfunction: Do Different Renal Function Equations Matter?

Unlike warfarin, NOACs are prescribed at a fixed dose according to well-defined dosage reduction criteria of the individual NOAC. Therefore, the eGFR is crucial for the determination of the appropriate dose of NOAC. There are several equations (e.g., Cockcroft-Gault [CG], Modification of Diet in Renal Disease [MDRD] and the National Kidney Foundation recommended Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) that are commonly used to calculate eGFR in the daily practice, but only the CG method was adopted in 4 pivotal randomized clinical trials.^{25–28} The 2 studies investigating differences of eGFRs calculated using different equations and the effect on appropriate NOACs dosing and subsequent clinical outcomes are summarized in **Table 2**.^{29,30} Both studies showed that non-CG formulas would overestimate eGFR compared with the CG equation, especially for the elderly and patients with a low body weight. **Figure 2** demonstrates the eGFRs calculated using different equations for patients stratified by age and body weight based on data reported by Chan et al.³⁰ Taking patients aged 75–79 years for example, the mean eGFR is lower than 50 mL/min when calculated using CG, but higher than 50 mL/min calculated using the MDRD or CKD-EPI

equations.

Chan et al further reported that in comparison with the CG formula, both the MDRD and CKD-EPI formulas could cause inappropriate dosing of NOACs (mainly overdosing), which would attenuate the advantages of NOACs.³⁰ These findings were different from those reported by Lee et al, showing that despite the discrepancy in eGFR between the different equations, the risks of thromboembolic events and major bleeding were similar, irrespective of which formula was used.²⁹ In daily practice, the CG formula should be used to calculate eGFR to determine the dosage of NOACs as the randomized clinical trials did, unless more high-quality studies can prove the usefulness of the non-CG equations in the future.

Assessment of NOAC-Related Bleeding Risks

Although NOACs are vital for AF-related stroke prevention, they can confer excess risk of bleeding. To date, several bleeding risk scores have been published, such as the modified Hypertension, Age, Stroke, Bleeding tendency/predisposition, Labile international normalized ratios (INRs), Elderly age, Drugs or alcohol excess (HAS-BLED),^{31,32} the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA),^{33–35} and the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT) scores.^{35–37} Of these various risk scoring systems, HAS-BLED is recommended by important international guidelines,^{38–40} and is possibly the most validated scoring system, being applied for the prediction of bleeding risk whether AF patients are on no antithrombotic therapy, antiplatelet agents or OACs.^{35,41,42} Besides, the HAS-BLED score reliably performs the best by including labile INRs as a component for AF patients with warfarin therapy.³⁵

It is important to emphasize that a high bleeding risk score should not in itself guide treatment decisions to use OAC for stroke prevention, which has been clearly mentioned in the 2020 ESC AF guidelines.⁴⁰ The HAS-BLED score should be considered as an aid to addressing modifiable bleeding risk factors, and to identify patients at high

Figure 2. eGFRs calculated using different equations in different age and body weight strata. Compared with the CG formula, the MDRD and CKD-EPI equations overestimate the eGFR of AF patients, especially in the elderly and those with a low body weight. The data used in the figure are from Chan et al.³⁰ AF, atrial fibrillation; CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

risk of bleeding (HAS-BLED score ≥ 3) for early and more frequent clinical review and follow-up.⁴⁰ A recent study by Chao et al⁴³ investigated 24,990 AF patients aged ≥ 20 years with a CHA₂DS₂-VAsC score ≥ 1 (males) or ≥ 2 (females) and a HAS-BLED score of 0–2 who were treated with OACs. At end of 1 year, 5,229 (20.9%) patients had an increment of their HAS-BLED score to ≥ 3 and became a high-risk population for bleeding. Among 4,777 patients who consistently had a HAS-BLED score ≥ 3 , patients remaining on OACs (77.8%) even after their HAS-BLED score increased to ≥ 3 were associated with a lower risk of IS, major bleeding, all-cause death, and any adverse

events.⁴³ These findings support the concept that a high bleeding risk score should not be the only reason to withhold OACs, but reminds physicians to correct modifiable bleeding risk factors and follow up patients more closely.

The 2020 ESC guidelines also recommend that the bleeding risk should be reassessed at periodic intervals to address potentially modifiable bleeding risk factors,⁴⁰ because the bleeding risk of AF patients is not static.⁴⁴ In the mobile atrial fibrillation application (mAFA-II) randomized trial, dynamic risk monitoring using the HAS-BLED score, together with holistic App-based management using mAFA-II, significantly reduced bleeding events,

Table 3. Summary of Clinical Studies Regarding Coexistence of Malignancies Among AF Patients Receiving OACs With Presentation of Bleeding

Clinical study	Study type	No. of patients	OAC(s) studied	Main findings
Yu et al (2017) ⁶²	Retrospective	5,833 patients, 3,798 (65%) were on OACs (OAC (+) group) and 2,035 (35%) were not (OAC (–) group)	Warfarin	<ol style="list-style-type: none"> 1. GU cancer was more common in patients with OACs compared with those without, in the whole groups and after propensity score matching 2. Bladder cancer was the most common GU malignancy and was significantly more common in the OACs group 3. Patients with OACs were more likely to have bladder cancers of low pathologic grade, suggesting early detection of the malignancy 4. Age >75 years, male sex, and gross hematuria were associated with increased risk of GU cancer.
Flack et al (2017) ⁶³	Sub-analysis of prospective trial (RE-LY trial)	546 anticoagulated patients experiencing major GI bleeding	Warfarin Dabigatran	<ol style="list-style-type: none"> 1. Approximately 1 of every 12 major GI bleeding events was related to an occult cancer 2. Approximately two-thirds of cancer-related major GI bleeding presented with chronic bleeding, and morbidity, and resource utilization was high
Chang et al (2020) ⁶⁴	Retrospective	10,845 anticoagulated AF patients experiencing GI bleeding	Warfarin Dabigatran Rivaroxaban Apixaban	<ol style="list-style-type: none"> 1. At 1 year after GI bleeding, incident GI cancers were diagnosed in 1 in 37 patients treated with OACs 2. More patients treated with NOACs were diagnosed as having GI cancer than those treated with warfarin (3.87% vs. 2.44%; $P<0.001$; odds ratio 1.606; $P<0.001$) 3. Age and male sex were clinical factors associated with the diagnosis of GI cancer after GI bleeding 4. The 1-year risk of all-cause death after GI cancers was lower among NOACs users who experienced GI bleeding than among warfarin users
Raposeiras Roubín et al (2020) ⁶⁵	Retrospective	8,753 patients with AF aged ≥ 75 years. Of them, 2,171 (24.8%) experienced any clinically relevant bleeding, and 479 (5.5%) were diagnosed with cancer during a follow-up of 3 years	Warfarin Dabigatran Rivaroxaban Apixaban	<ol style="list-style-type: none"> 1. In patients with AF treated with OACs, any GI, GU, or bronchopulmonary bleeding was associated with higher rates of new cancer diagnosis

AF, atrial fibrillation; GI, gastrointestinal; GU, genitourinary; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

addressed modifiable bleeding risks, and increased the uptake of OACs.

Another important factor requiring regular re-evaluation is renal function. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial analysis, 24.2% patients were detected as having deteriorating renal function, which leads to higher risks of all-cause death and major bleeding.⁴⁵ Consistent with the RE-LY trial analysis, Fauchier et al further showed that bleeding events were accentuated with deteriorating renal function by quartiles.⁴⁶ Therefore, the 2018 European Heart Rhythm Association Practical Guide on the use of NOACs suggests follow up renal function at 6-month intervals for elderly or fragile patients.⁵ Furthermore, the suggested rechecking interval (months) equals “eGFR/10” for patients with a baseline eGFR <60 mL/min.⁵ Once a patient’s renal function has declined, we should try to survey for any correctable causes and adjust the dosing of NOACs if necessary based on the dosage reduction criteria of each NOAC.

Management of NOAC-Related Bleeding

Because NOACs have become more and more ubiquitous in AF patients, NOAC-related bleeding management is an important issue. When facing a NOAC-related bleeding event, closely and thoroughly reviewing the appropriate

NOAC’s dosing is crucial,⁵ and clinicians should also re-evaluate any modifiable bleeding risk factors, including suboptimally treated hypertension, excessive alcohol intake and potential drug-drug interactions.⁴⁷

Acute management of NOAC-related bleeding is mainly based on the severity and precise analysis of the patient’s condition, which can be further divided into (1) minor bleeding, (2) hemodynamically stable major bleeding, and (3) life-threatening major bleeding. General principles of acute NOAC-related bleeding management consist of withholding NOACs to wane, non-specific hemostasis treatment such as blood products transfusion and antifibrinolytics,⁴⁸ and specific NOAC reversal agents. Of note, neither vitamin K nor protamine has proven effective in dealing with NOAC-related bleeding.⁴⁷

Minor Bleeding

Minor bleeding often prompts localization of the bleeding foci, which can be then treated accordingly. For instances, clinicians may prescribe proton pump inhibitors for AF patients with a NOAC and ulcer-related bleeding. In addition, epistaxis and gum bleeds could be treated with local compression and antifibrinolytics.

For patients with recurrent minor bleeding, switching to another NOAC might be considered in order to maintain effective stroke prevention, although data are limited. Last

Figure 3. Optimal management of anticoagulation therapy in AF patients. Appropriate dosing of NOACs, assessment of renal function using the CG equation, bleeding risk assessment/re-assessment and correction of modifiable bleeding risk factors and being aware of potential malignancy when managing NOAC-related bleeding are all crucial to achieving better clinical outcomes for anticoagulated AF patients. AF, atrial fibrillation; CG, Cockcroft-Gault; NOAC, non-vitamin K antagonist oral anticoagulant.

but not the least, a detailed and systemic work-up of possible causes should always be conducted.

Hemodynamically Stable Major Bleeding

Best supportive treatment, including mechanical compression, surgical hemostasis, fluid/blood products replacement and other non-specific hemostatic medications, is the cornerstone of managing hemodynamically stable major bleeding. Because the half-lives of NOACs are relatively short, the clinical condition is likely to improve with time.⁴⁹

Another much-discussed issue is the effect of dialysis on NOAC-related bleeding, especially hemodynamically stable major bleeding. Several studies have proven the efficacy of dialysis when dealing with dabigatran-induced hemodynamically stable major bleeding,^{50,51} because approximately 80–85% of dabigatran is excreted by the kidney.⁵² On the other hand, dialysis is less likely to be beneficial for AF patients treated with factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), owing to the higher degree of protein-binding affinities.^{53,54}

Life-Threatening Major Bleeding

In addition to all aforementioned measures, administration of specific NOAC reversal agents has been proved to have better clinical outcomes.

• Idarucizumab

Idarucizumab is the first introduced reversal agent for the NOAC dabigatran. In the RE-VERSal Effects of Idarucizumab on Active Dabigatran (REVERSE-AD) study, idarucizumab demonstrated its efficacy in treating patients with life-threatening major bleeding events as it successfully and rapidly reversed the anticoagulation effect of dabigatran in all patients.⁵⁵ It is suggested that a total of 5 g idarucizumab be given intravenously in 2 bolus doses of 2.5 g less than 15 min apart.⁵⁵

• Direct reversal of factor Xa inhibitors

In the Anticoagulation Effects of Factor Xa Inhibitors-4 (ANNEXA-4) study, andexanet α showed its efficacy in treating patients with factor Xa inhibitor-related life-

threatening major bleeding events, as 82% of patients had excellent or good hemostatic efficacy at 12 h.⁵⁶ It is suggested that the drug be administered as a bolus over 15–30 min, followed by a 2-h infusion.⁵⁶

Pay Attention to Occult Malignancies When Managing NOAC-Related Bleeding

Although acute managements of NOACs-related bleeding is vital, an important issue that is easily overlooked is the existence of occult malignancies that are the cause/origin of the bleeding. In fact, in a pooled analysis of 4 randomized trials, malignancies were not uncommon in AF patients and accounted for $\approx 11\%$ of mortality.⁵⁷ In the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) registry, malignancy-related deaths accounted for 11.1% and 10.3% of all deaths at 1 year and 2 years, respectively.^{58,59} In a Danish Registry, Ostensfeld et al described a comparable rise of malignancies in AF patients.⁶⁰ Given that malignancies and AF are highly correlated, early stratification of AF patients with high risk of malignancy is essential. Hung et al reported that age, male sex, hypertension, diabetes, chronic obstructive pulmonary disease and liver cirrhosis are the main risk factors of malignancies among AF patients, and surveys for early detection of possible occult malignancies may be considered for high-risk patients.⁶¹

Interestingly, NOAC-related bleeding could be the clinical presentation of an underlying cancer. Published studies regarding this issue are summarized in **Table 3**.^{62–65} In sub-analyses of both the RE-LY and Cardiovascular Outcomes for People using Anticoagulation Strategies (COMPASS) trials, gastrointestinal (GI) bleeding was likely to be the first sign of GI malignancies in patients receiving NOACs.^{63,66} In a Taiwan nationwide study, incident GI cancers were diagnosed in 1 of 37 AF patients at 1 year after OAC-related GI bleeding, and were more common among patients treated with NOACs (1/26) compared with warfarin (1/41).⁶⁴ The risk of death was lower in patients treated with NOACs

than in those treated with warfarin (23.5% vs. 51.8%; $P < 0.001$), suggesting that NOACs may disclose occult cancers through the presentation of bleeding at an earlier stage than with warfarin, because the intensity of warfarin therapy is often suboptimal among Asians.⁶⁴ Similar findings have been reported for anticoagulated patients presenting with hematuria among whom the possibility of underlying bladder cancers should be kept in mind.⁶²

Conclusions

In this review article, we have highlighted several important issues about the optimal management of anticoagulation in AF patients, which are summarized in **Figure 3**. Appropriate dosing of NOACs, assessment of renal function using the CG equation, bleeding risk assessment/re-assessment and correction of modifiable bleeding risk factors, and being aware of potential malignancy when managing NOAC-related bleeding are all crucial to achieving better clinical outcomes for anticoagulated AF patients. More efforts are necessary to incorporate clear and easy-to-follow recommendations about optimal management of anticoagulation into the guidelines to improve AF patient care.

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None.

Data Availability

All data generated or analyzed during this study are included in this published article.

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