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STATE-OF-THE-ART REVIEW

Direct Oral Anticoagulant Dosing in Patients With Atrial Fibrillation

An Asian Perspective

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ABSTRACT

Optimal dosing of direct oral anticoagulants (DOACs) for stroke prevention in "gray area" patients with atrial fibrillation (AF) remains a challenge for clinicians. In Asia, this is concerning in patients who are very elderly, have low body weight, and are at a high risk of bleeding. This review aims to summarize the dose reduction criteria for DOACs, discuss the evidence on dosing of DOACs across Asian regions, and collate opinions from authors across Asia. Nonrecommended dosing of DOACs is common in Asia, primarily due to the fear of bleeding, with the total clinical benefit of higher dosing being overlooked. The ELDERCARE-AF (Edoxaban Low-Dose for Elder Care-Atrial Fibrillation Patients) trial and real-world case studies provide some evidence on the use of low-dose DOACs in gray area patients. Opinions on dose adjustment guidance, concomitant medication adjustments, and therapeutic drug monitoring were collated. Research is needed to fill the evidence gaps on optimal DOAC doses for gray area patients. (JACC: Asia 2023;3:707–723) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Treatment with direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, is important for stroke prevention in patients with atrial fibrillation (AF).[1] A meta-analysis including 18 trials indicated that DOACs were more efficacious and safer than warfarin in real-world practice for stroke prevention in Asian patients with nonvalvular atrial fibrillation (NVAF).[2] Another meta-analysis of 6 studies involving 3,542 Asian and 23,481 non-Asian patients revealed that DOACs may be a safer treatment option in Asian patients, as analysis of safety endpoints significantly favored DOACs compared with vitamin K antagonists in Asian patients but not in non-Asian patients.[3] However, optimal dosing of DOACs is a challenge, as they require dose adjustment based on individual patient characteristics and concomitant medication use.[4] Off-label dosing with DOACs, defined as the use of DOACs not conforming to label dosing recommendations, is inadequate but common in the real-world clinical setting[5]; it can be categorized into nonrecommended low dosing (underdosing) and nonrecommended high dosing (overdosing).[5,6] While guidelines recommend that

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CG = Cockcroft-Gault

CrCl = creatinine clearance

DOAC = direct oral anticoagulant

HDER = higher-dose edoxaban regimen

IS = ischemic stroke

LDER = lower-dose edoxaban regimen

MDRD = Modification of Diet in Renal Disease

NAVL = nonvalvular atrial fibrillation

OD = once daily

RCT = randomized controlled trial

SE = systemic embolism

TDM = therapeutic drug monitoring

VLBW = very low body weight

DOACs be dosed according to the eligibility criteria established in pivotal randomized controlled trials (RCTs), not all patients with AF in real-world settings fit the eligibility criteria of these studies[7]; hence, whether the label dosing is appropriate or not for these patients remains uncertain.[8] In clinical practice, especially in Asia, clinicians tend to prescribe nonrecommended low doses of DOACs, mainly due to concerns about the risk of bleeding.[1] Although there are many observational and real-world reports on the nonrecommended dosing of DOACs in patients with AF, with substantial differences in findings among different studies, the efficacy and safety of these nonrecommended doses remain unclear.[1]

With a lack of dosing guidance, clinicians face difficulties in decision-making regarding the prescription of optimal on-label DOAC doses for these patients outside the eligibility criteria of pivotal RCTs (so-called gray area cases). This is especially challenging in Asia, as a higher proportion of Asian patients with AF are very elderly (defined as over 75 years of age or even older),[9] are frail, and have low body weight compared with non-Asian patients. To address the issue regarding the nonrecommended dosing of DOACs, we conducted a comprehensive and systematic review of the available literature on DOAC dosing in Asia by searching PubMed using the broad terms "non-vitamin K antagonist oral anticoagulant" or "direct oral anticoagulant therapy" or "NOAC" or "DOAC" in the title or abstract, along with the terms "prospective" or "prospectively," or "retrospective" or "retrospectively" and "observational" in all fields. The search included studies from Japan, South Korea, Taiwan, Hong Kong, and Thailand. Only articles in English published in the last 5 years were included. Prospective studies with <1,000 AF patient cases on anticoagulation treatment and retrospective studies with <3,000 AF patient cases on anticoagulation treatment were excluded. Focusing on large, observational studies provides valuable and robust insights into real-world prescribing practices and patient outcomes. Following an in-depth discussion and a collaborative scientific exchange of opinion, we have summarized the on-label DOAC dose reduction criteria across the treatment landscape, provided insights into the current clinical data on nonrecommended dosing in the Asian population, and identified the challenges faced by clinicians.

CURRENT DOSE REDUCTION CRITERIA ACROSS DOAC TREATMENT LANDSCAPE: AN ASIAN PERSPECTIVE

KEY CONSIDERATIONS IN DOAC DOSING. Twelve subgroups of high-risk patients with AF were identified following a risk stratification analysis of the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) RCT, which analyzed the relationship between risk factors and net clinical outcome, a composite of stroke/systemic embolism (SE) events, major bleeding, or death: 1) elderly (age ≥75 years); 2) increased risk of falls; 3) moderate renal dysfunction (creatinine clearance [CrCl] 30-50 mL/min); 4) prior cerebrovascular disease; 5) concomitant single antiplatelet therapy; 6) vitamin K antagonist naïve; 7) history of heart failure; 8) valvular heart disease; 9) malignancy; 10) prior coronary artery disease; 11) self-reported as Asian race; and 12) very low body weight (VLBW) (<55 kg).[7]

With respect to the Asian population, the 3 most relevant high-risk factors for patients with AF were identified as older age, high risk of bleeding, and low body weight based on the following findings:

AGE. Although Asia has a lower prevalence of AF,[10] the proportion of the elderly population is much higher and increasing compared with that in other regions.[11] The age category of >75 years is typically used to define the elderly[9]; however, Asian physicians typically consider >75 years not old enough in Asia and instead suggest that only patients with AF ≥85 years of age should be categorized as elderly with AF at high risk. The mean or median age of patients enrolled in previous landmark clinical trials of DOACs was 70 to 73 years, which is 5 to 10 years younger than the age of the general population with AF.[12-16] Therefore, the findings from these major trials cannot be easily extrapolated to older patients, especially those who are ≥85 years of age.[12]

RISK OF BLEEDING. It is necessary to assess all patient characteristics that are risk factors for bleeding, such as prior bleeding, age, cardiovascular disease, renal function impairment, anemia, and concomitant medications.[17] As clinicians are concerned about bleeding in their patients, they tend to prescribe a lower dose if deemed necessary. Low dosing in Asian

TABLE 1 Higher- and Lower-Dose Direct Oral Anticoagulants Based on RCTs, Guidelines, and Regional Labels

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban[a]
Higher dose	150 mg BID	20 mg OD[b]	5 mg BID	60 mg OD
Consideration of high-risk factors in Asian patients for dose reduction based on RCTs or local guidelines or labeling				
Age	+	+	+	-
Renal function	+	+	+	+
Concomitant medication	-	-	-	+
Weight	-	-	+	+
Lower dose	110 mg BID/75 mg BID[c]	15 mg OD[d]	2.5 mg BID	30 mg OD
Pivotal phase 3 RCTs	RE-LY (N = 12,091)[14] Patients aged ≥75 or 65-74 y with diabetes mellitus, hypertension, or coronary artery disease and CrCl ≥30 mL/min Patients randomized to 150 mg or 110 mg BID with no other specific dose reduction criteria	ROCKET-AF (N = 7,131)[15] Patients aged ≥75 y or the presence of diabetes mellitus. All patients with a CrCl of 30-49 mL/min randomized to 20 mg or 15 mg OD with no other specific dose reduction criteria	ARISTOTLE (N = 9,120)[16] At least 1 of the risk factors: age ≥75 y or a history of stroke, transient ischemic attack, or SE; symptomatic HF within the previous 3 mo or left ventricular ejection fraction of no more than 40%; diabetes mellitus; or hypertension requiring pharmacologic treatment Patients with ≥2 criteria received 2.5 mg BID: age ≥80 y, body weight ≤60 kg, or serum Cr level ≥1.5 mg/dL	ENGAGE AF-TIMI 48 (N = 14,069)[13] All patients aged ≥21 y Patients randomized to 60 mg or 30 mg OD Patients meeting any of the following criteria received 30 mg OD: CrCl 30-50 mL/min; body weight ≤60 kg; or concomitant use of verapamil, quinidine, or dronedarone

Continued on the next page

patients is frequently prescribed even though the patient meets higher dosing criteria. The rationale for this is based on an epidemiological study, which showed that the Asian population has a higher risk of intracranial hemorrhage than the Western population.[18] Therefore, clinicians believe that it is critical not to increase the risk of bleeding in this distinct population.

BODY WEIGHT. Body weight is another important risk factor that should be considered, as Asian patients tend to have VLBW. An analysis of baseline patient characteristics in the ENGAGE AF-TIMI 48 trial with Asian (n = 2,909) and non-Asian (n = 18,195) patients showed that Asian patients were 20 kg lighter on average.[19] Therefore, patients with a lower body weight may have higher drug exposure, placing them at risk of severe bleeding when treated with higher-dose DOACs.

DOSE REDUCTION CRITERIA FOR DOAC TREATMENT. The major treatment guidelines recommend dosing DOACs according to the doses tested in RCTs,[8] and are usually consistent with the prescribing information (Table 1). Each region has its own regulatory labeling, and physicians are advised to adhere to that labeling. The key points highlighting the dose reduction criteria for different DOACs are described subsequently.

Dabigatran. No dose reduction criteria were available for dabigatran in the pivotal RCT,[14] but the prescribing information and guidelines provide that information (Table 1).[20,21] Despite the 75-mg dose not being evaluated,[14] the U.S. Food and Drug Administration approved both the 150-mg BID higher dose and 75-mg BID lower dose.[20] The dose reduction criteria in the U.S. label are based on renal clearance only,[20] whereas the European Society of Cardiology and the European Medicines Agency consider patient age and risk of bleeding or the concomitant usage of medications.[21,22]

Rivaroxaban. The dose reduction criteria across regional labeling[23,24] vary slightly from the criteria established in the pivotal RCT[15] and primarily considers renal function (Table 1). Notably, the dose reduction is 25%—from 20 mg once daily (OD) to 15 mg OD—rather than 50%, as seen for edoxaban and apixaban (Table 1). As a result, some physicians may prefer to use rivaroxaban in a dose reduction setting, as it allows for a smaller dose reduction. However, whether the differences in the percentage of dosage reduction across different DOACs have an impact on clinical outcomes is currently unknown and is not supported by available evidence.

Apixaban. The 50% dose reduction criteria considered patients' age, body weight, and renal function (Table 1). It is worth mentioning that the approved dose reduction criteria for apixaban are the same globally, unlike those for other DOACs, which vary among countries.

TABLE 1 Continued

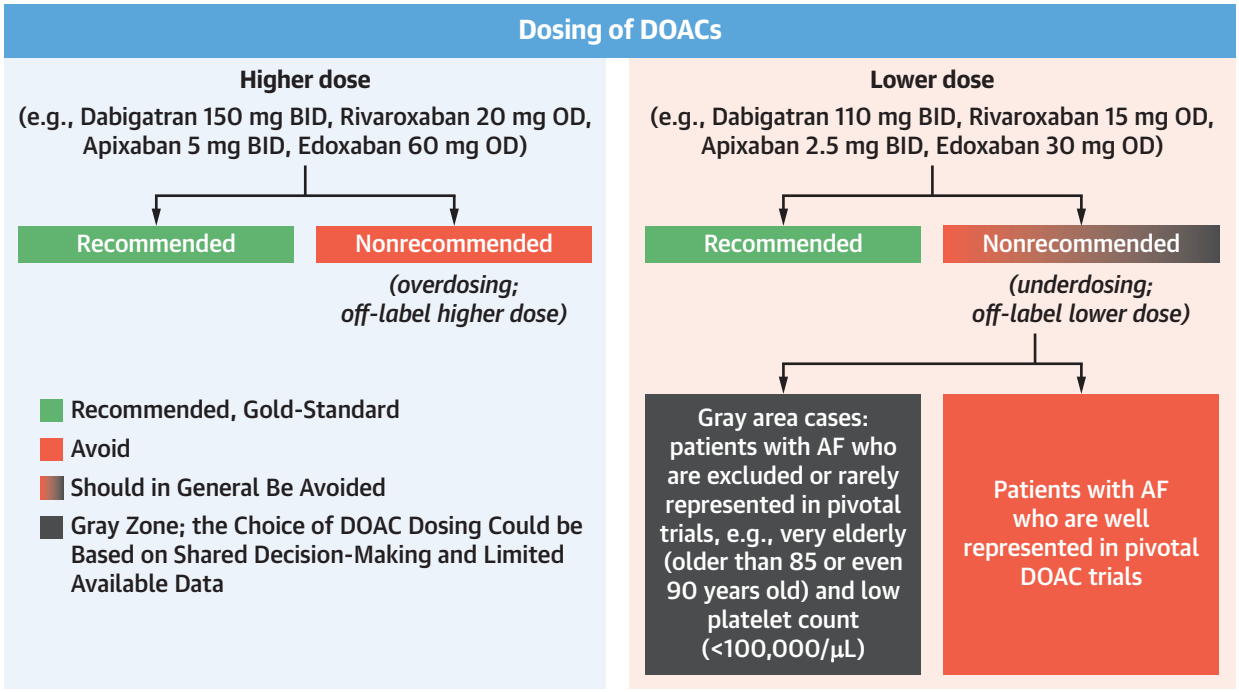
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban[a]
Region-specific dose-reducing criteria				
U.S. label	CrCl 15-30 mL/min: 75 mg BID CrCl <15 mL/min: no dosing recommendation[20]	CrCl ≤50 mL/min: 15 mg OD[24]	If ≥2 criteria met: 2.5 mg BID Age ≥80 y Weight ≤60 kg Cr ≥1.5 mg/dL[64-70]	CrCl 15-50 mL/min: 30 mg OD[71]
Europe label	If ≥1 criteria met: 110 mg BID Age ≥80 y Concomitant use of verapamil[21]	CrCl 15-49 mL/min: 15 mg OD[23]		If ≥1 criteria met: 30 mg OD CrCl 15-50 mL/min Weight ≤60 kg Concomitant use of dronedarone, cyclosporin, erythromycin, or ketoconazole[72]
Korea label	If ≥1 criteria met: 110 mg BID CrCl 30-50 mL/min Age ≥75 y Concomitant use of amiodarone, verapamil, or dronedarone Concomitant use of clopidogrel, aspirin, or NSAIDs Increased bleeding risk (coagulopathy, thrombocytopenia, platelet dysfunction, recent major trauma or biopsy, or infective endocarditis)[70]	Age ≥80 y CrCl 15-50 mL/min[70]		If ≥1 criteria met: 30 mg OD CrCl 15-50 mL/min Weight ≤60 kg Concomitant use of dronedarone, cyclosporin, erythromycin, or ketoconazole[70] 15 mg OD in elderly with a high risk of bleeding and CrCl 15-30 mL/min[26]
Hong Kong label	Same as EMA label[73]	Same as EMA label[73]		Same as EMA label[74]
Taiwan label	Patients at risk of bleeding: 110 mg BID Age ≥75 y $CHADS_2$ score >3 Weight <50 kg Previous gastrointestinal bleeding CrCl 30-50 mL/min[75]	CrCl 15-50 mL/min: 10-15 mg OD CrCl 15-30 mL/min: Use with caution[76]		If ≥1 criteria met: 30 mg OD CrCl 15-50 mL/min Weight ≤60 kg Concomitant use of dronedarone, cyclosporin, erythromycin, or ketoconazole 15 mg OD for elderly (defined as those age ≥80 y) and meeting both the following criteria: 1. If ≥1 criteria met: history of hemorrhage in important organs, weight ≤45 kg, CrCl 15-29 mL/min, regular use of NSAIDs, use of antiplatelet drugs 2. Unable to receive a usual dose or an approved dose of another oral anticoagulant due to the risk of hemorrhage[27]
Japan label	110 mg BID if age ≥70 y, CrCl 30-50 mL/min, a history of gastrointestinal bleeding, or concomitant use of oral P-glycoprotein inhibitors[77]	CrCl 15-49 mL/min: 10 mg OD[78]		If ≥1 criteria met: 30 mg OD CrCl 15-50 mL/min Weight ≤60 kg Concomitant use of drugs with a P-glycoprotein inhibitory effect 15 mg OD same as Taiwan[25]
Thailand label	110 mg BID Age ≥80 y[79]	CrCl 30-49 mL/min: 15 mg OD[80]		Same as EMA label[81]
China label	Same as EMA label[82]	If ≥1 criteria met: 15 mg OD Age >75 y Low body weight[83]	Not approved in China	Same as EMA label[84]

[a]15-mg OD is the approved dose for edoxaban in Japan, Taiwan, and South Korea for patients meeting the eligibility criteria of the ELDERCARE-AF study.[12] [b]15-mg OD is the higher dose for rivaroxaban in Japan and Taiwan. [c]The lower dose of dabigatran was not determined in the RE-LY trial. This was defined based on labeling in different countries. [d]10-mg OD is the lower dose for rivaroxaban in Japan and Taiwan only.

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events; BID = twice daily; Cr = creatinine; CrCl = creatinine clearance; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 (doubled), diabetes, previous stroke, or transient ischemic attack; ELDERCARE-AF = Edoxaban Low-Dose for Elder Care - Atrial Fibrillation Patients; EMA = European Medicines Agency; ENGAGE AF-TIMI 48 = Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48; HF = heart failure; NSAID = nonsteroidal anti-inflammatory drug; OD = once daily; RCT = randomized controlled trial; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SE = systemic embolism.

Edoxaban. The 50% dose reduction criteria considered patients' weight, renal function, and any concurrent medications that may increase edoxaban exposure (Table 1). A lower 15-mg dose was recently approved in a few Asian regions[25-27] based on the outcome of the ELDERCARE-AF (Edoxaban Low-Dose for Elder Care-Atrial Fibrillation Patients) study for high-risk patients who were not candidates for higher doses of oral anticoagulants, including those with low body weight of ≤45 kg (Table 1).

CENTRAL ILLUSTRATION Scenarios of DOAC Dosing



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This figure provides an overview of the direct oral anticoagulant (DOAC) prescribing scenarios. The green boxes represent the scenarios that are recommended, in which patients meet the criteria for the higher dose or they meet the criteria for the labeled lower dose based on patients' characteristics. The red/orange boxes are scenarios that physicians should avoid. The gray area box is for patients who are outside the eligibility criteria of pivotal randomized controlled trials. The choice of the DOAC dose needs to be carefully considered based on limited evidence. AF = atrial fibrillation; BID = twice daily; OD = once daily.

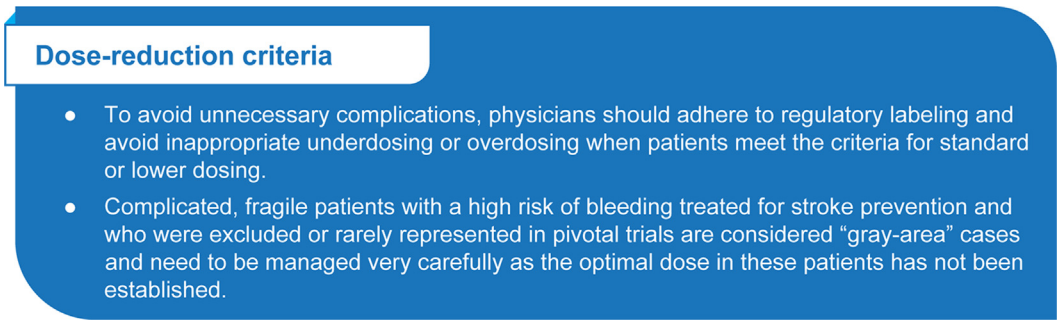
DOSE REDUCTION FOR DOAC TREATMENT CONCLUSIONS. In Asia, for very elderly patients with low body weight who do not meet the on-label criteria (referred to as gray area cases), adopting on-label dosing is difficult, leading to nonrecommended dosing, in which physicians are more likely to select a lower dose of DOACs. The recommended and nonrecommended dosing scenarios are outlined in the **Central Illustration**. Our summarized opinion for dose reduction criteria for DOAC treatment is presented in **Figure 1**.

DATA ON NONRECOMMENDED DOSING OF DOACs IN ASIA

PREVALENCE AND REASONS FOR NONRECOMMENDED DOSING. **Table 2** provides an overview of the prevalence of nonrecommended dosing across all DOACs as well as the characteristics of patients prescribed nonrecommended doses in various Asian regions based on observational, real-world studies.[28-36] According to a study that used the Taiwan National Health Insurance database in patients with NVAF, compared with warfarin, low-dose DOACs were mostly prescribed (edoxaban: 64%; apixaban: 64%; rivaroxaban: 94%; dabigatran: 89%), regardless of whether the patient met the higher or lower dose (on-label) criteria.[28]

Overall, the prevalence of nonrecommended (off-label) dosing with all DOACs ranged from 32% to 38% in these Asian regions, with nonrecommended underdosing being more prevalent at 22% to 36% than nonrecommended overdosing at 2% to 11%.[29,30,37] Two studies that specifically assessed nonrecommended dosing of edoxaban in Asia showed that the prevalence of nonrecommended/inappropriate use was 24% to 43%.[38,39] The XAPASS (Xarelto Post-Authorization Safety & Effectiveness Study in Japanese patients with AF) trial's 1-year follow-up study found that 36% of Japanese patients with AF treated with rivaroxaban were underdosed, with the top 3 reasons cited as high bleeding risk, elderly status, and renal impairment.[40]

FIGURE 1 Dose Reduction Criteria for Treatment With Direct Oral Anticoagulants



This figure represents the summarized opinion for dose reduction criteria for direct oral anticoagulant treatment. Avoid unnecessary complications by following regulatory labeling. Gray area patients, defined as patients outside the eligibility criteria of pivotal randomized controlled trials, need to be managed very carefully.

The prevalence of nonrecommended dosing of DOACs in these Asian regions, especially underdosing, was relatively higher than that reported in non-Asian regions.[41] Analysis of the prospective and multinational GARFIELD-AF (Global Anticoagulant Registry in the FIELD-AF) registry showed that a majority of patients (72.9%) received the recommended dosing, whereas 23.2% were underdosed and 3.8% were overdosed.[41] An analysis of the U.S. administrative database, Medicare, with 14,865 patients with NVAF who initiated apixaban, dabigatran, or rivaroxaban showed that among patients with renal indication for dose reduction, 43.0% of patients were potentially overdosed, whereas among patients with no renal indication for dose reduction, 13.3% were potentially underdosed.[42] Analysis of the ORBIT-AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II) registry in the U.S. with 7,925 patients with AF showed that 84% of patients received DOACs at the higher dose, whereas 16% of patients received the lower dose, although 57% of these did not meet the recommended dose reduction criteria.[43]

Most patients who were prescribed DOACs at the nonrecommended lower dose in Asia were elderly, had low body weight, had renal dysfunction, or were at a high risk of bleeding (Table 2).[28,29,31,33,35] As oral anticoagulation is usually a preventive strategy in Asian patients with NVAF, physicians tend to use low-dose DOACs to avoid the side effects of major bleeding, overlooking the total clinical benefits. The prevalence of nonrecommended dosing by individual DOACs in Asia is presented in Table 3.[39,40,44]

NONRECOMMENDED DOSING OF DOACS AND CLINICAL OUTCOMES. Several real-world global studies have shown that nonrecommended lower doses of DOACs are associated with decreased benefit, an increased risk of stroke, and an increased risk of all-cause mortality. The ORBIT-AF II registry showed that compared with patients receiving higher dosing, those receiving inappropriately lower-dose DOACs had higher unadjusted rates of thromboembolic events (HR: 1.56; 95% CI: 0.92-2.67) and death (HR: 2.61; 95% CI: 1.86-3.67). Analysis of the prospective multinational GARFIELD-AF registry showed that compared with recommended dosing, nonrecommended dosing (underdose and overdose combined) was associated with a higher risk of all-cause mortality (adjusted HR: 1.24; 95% CI: 1.04-1.48). The risks of stroke/SE and major bleeding were not significantly different based on the level of dosing, although underdosed patients had a significantly lower risk of bleeding and overdosed patients showed a trend toward higher risks of stroke/SE and major bleeding, although not statistically significant.[41] A few other studies have shown that among DOACs, underdosing of apixaban was associated with a higher risk of stroke[42,45] or all-cause mortality.[46] An analysis of the ENGAGE AF-TIMI 48 trial showed that the risk of stroke/SE was higher, but the risk of major bleeding was lower with the lower-dose edoxaban regimen (LDER) compared with the higher-dose edoxaban regimen (HDER). The risk of reaching the primary net clinical outcome (stroke/SE, major bleeding, or death) was significantly lower with the LDER compared with the HDER ($P = 0.014$). For patients with a history of cancer, it seemed that the risk of secondary net clinical outcomes (disabling stroke, life-threatening bleeding, or death) was lower with the LDER.[47] A meta-analysis of 16 studies with 130,609 patients showed that compared with on-label dosing, off-label underdosing of DOACs was

TABLE 2 Summary of Observational, Real-World Studies on Prevalence of Nonrecommended DOAC Dosing in Asia[a]

First Author (Year) Study	Location	Study Period	Design/ Patients	Prevalence of Nonrecommended Dose of DOACs	Characteristics of Patients/Factors Associated With Nonrecommended Dosing	Clinical Outcome Associated With Nonrecommended Dosing	Conclusion/ Main Message
Lee et al (2019)[29] Korea CODE-AF registry	Korea	June 2016 to May 2017	Prospective, multicenter, observational registry study: N = 3,080	On-label higher dose: 31.1% On-label lower dose: 30.8% Off-label underdose: 36.4% Off-label overdose: 1.6%	Compared with those with an on-label higher dosing, patients with an off-label lower dose of DOACs were older (≥75 y), were women, and had a lower body weight (≤60 kg), renal dysfunction (CrCl ≤50 mL/min), previous stroke, previous bleeding, hypertension, concomitant dronedarone use, and antiplatelet use	–	Considering the high risk of stroke with off-label lower dose, on-label use of DOAC is recommended
Murata et al (2019)[31] SAKURA AF registry	Japan	September 2013 to December 2015	Prospective multicenter registry study: N = 1,658 Edoxaban: n = 31 Apixaban: n = 424 Rivaroxaban: n = 754 Dabigatran: n = 449	Overdose: 4.0% Appropriate higher dose: 45.0% Appropriate low dose: 28.8% Underdose: 22.3%	Compared with the mean age of the higher-dose group (66.9 ± 9.0 y), patients were older in the appropriate low-dose (79.2 ± 6.0 y), underdose (71.2 ± 8.2 y), and overdose (76.0 ± 5.0 y) groups ($P < 0.001$)	The incidence of a stroke/SE event was higher in the overdose and appropriate low-dose groups compared with either the appropriate higher-dose or underdose groups ($P = 0.010$, log-rank test) The incidence of a major bleeding event was higher in the overdose group than in either the appropriate higher-dose or appropriate low-dose groups but was lower in the underdose group ($P = 0.042$, log-rank test)	Patients in the off-label overdose, underdose, and appropriate low-dose groups tended to be older and at higher risk for a stroke than those in the appropriate higher-dose group
Yamashita et al (2022)[32] ANAFIE registry	Japan	October 2016 to January 2020	Prospective, observational, multicenter registry: N = 21,585 Edoxaban: n = 4,790 Apixaban: n = 8,045 Rivaroxaban: n = 6,403 Dabigatran: n = 2,347	Appropriate higher-dose group: 17.7% Appropriate lower-dose group: 44.2% Inappropriate higher-dose group: 3.2% Inappropriate lower-dose group: 16.8%	Not reported	Not reported	Elderly and very elderly NVAF patients received DOACs, which resulted in significantly lower rates of stroke/SE, major bleeding, and all-cause death vs those who received well-controlled warfarin
Ohno et al (2021)[33] DIRECT registry	Japan	June 2011 to November 2017	Prospective, observational, single-center registry: N = 2,216 Edoxaban: n = 431 Apixaban: n = 599 Rivaroxaban: n = 538 Dabigatran: n = 648	Appropriate higher dose: 40.9% Appropriate lower dose: 37.6% Overdose: 5.3% Underdose: 15.3% Contraindication: 0.9%	Compared with the appropriate higher-dose group, the underdose and overdose groups had higher age; lower weight; lower CrCl; and higher ORBIT, HAS-BLED, $CHADS_2$, and CHA_2DS_2-VASc scores	Patients who received low-dose DOACs, irrespective of appropriate reduction or off-label reduction, reported worse baseline characteristics, resulting in worse clinical outcomes	Appropriate dose reduction was associated with a decrease in clinically significant bleeding and no significant impairment in efficacy endpoints

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associated with a higher risk of ischemic stroke (IS)/SE (HR: 1.22; 95% CI: 1.05-1.42; $P = 0.01$), and yet the incidence of major bleeding was similar (HR: 0.95; 95% CI: 0.82-1.11; $P = 0.48$). Off-label underdosing was associated with a higher risk of net clinical outcomes (HR: 1.19; 95% CI: 1.04-1.40; $P = 0.04$) and all-cause death (HR: 1.24; 95% CI: 1.04-1.48; $P = 0.02$) compared with on-label dosing.[48] These findings were similarly validated in studies conducted in Asia (Table 2). Underdosing of DOACs was found to be associated with a significantly higher risk of IS/SE,[30] while overdosing was found to be associated with a similar risk of major bleeding.[30,37] Incidence rates of stroke/non-central nervous system SE/myocardial

TABLE 2 Continued

First Author (Year) Study	Location	Study Period	Design/ Patients	Prevalence of Nonrecommended Dose of DOACs	Characteristics of Patients/Factors Associated With Nonrecommended Dosing	Clinical Outcome Associated With Nonrecommended Dosing	Conclusion/ Main Message
Nogami et al (2022)[34] RYOUMA registry	Japan	2017-2018	Prospective, observational, multicenter study: N = 2,844 Edoxaban: n = 917 Apixaban: n = 766 Rivaroxaban: n = 784 Dabigatran: n = 377	Off-label overdose: 4.7% On-label higher dose: 64.0% On-label lower dose: 18.1% Off-label underdose: 13.1%	Not reported	In the off-label overdose DOAC subgroup, the number of major bleeding events at 1 y after CA was significantly higher (3.03%; 95% CI: 1.15%-7.86%) than that in the on-label dose DOAC subgroup (0.94%, 95% CI: 0.61%-1.44%; $P = 0.0195$)	Off-label overdose of DOACs was a risk factor for major bleeding after CA
Chan et al (2019)[28] Taiwan NHI Database Note: This study did not discriminate on-label or off-label use of low-dose DOACs	Taiwan	June 2012 to December 2017	Retrospective database study Edoxaban: n = 4,577 Apixaban: n = 9,952 Rivaroxaban: n = 33,022 Dabigatran: n = 22,371	Low-dose prescription: Edoxaban (15 or 30 mg OD): 64% Apixaban (2.5 mg BID): 64% Rivaroxaban (10 or 15 mg OD): 94% Dabigatran (110 mg BID): 89%	The preference for low-dose DOAC prescription might be due to the high proportion of elderly patients with multiple comorbidities and poor renal function, high incidence of bleeding among Asian patients with NVAF taking oral anticoagulants, and the lower body weight of Asian patients compared with non-Asian patients	The effectiveness/safety outcomes with the 4 low-dose DOACs compared with warfarin were consistent with the main analysis	Inappropriate prescription of low-dose DOACs without following the "label-adherent" recommendations, especially for apixaban, may result in more thromboembolic events without reduction of major bleeding
Chan et al (2020)[30] Taiwan Multicenter Healthcare System	Taiwan	January 2010 September 2018	Retrospective database study: N = 11,275 Dabigatran: n = 2,068 Apixaban: n = 2,589 Rivaroxaban: n = 5,135 Edoxaban: n = 1,483	All DOACs: On-label dosing: 69% Off-label underdosing: 27% Off-label overdosing: 5%	Compared with the on-label dosing group, patients receiving underdosing of DOACs were younger, with lower mean CHA_2DS_2-VASc and HAS-BLED scores, whereas patients receiving overdosing of DOACs were older and had higher CHA_2DS_2-VASc and HAS-BLED scores. CrCl was higher in the underdosing group and lower in the overdosing group compared with the on-label dosing group	Compared with on-label dosing, underdosing of DOACs was associated with a significantly higher risk of IS/SE (adjusted HR: 1.59; 95% CI: 1.25-2.02; $P < 0.001$) with a similar risk of major bleeding, while overdosing of DOACs was associated with a significantly higher risk of major bleeding (adjusted HR: 2.01; 95% CI: 1.13-3.56; $P = 0.017$)	Even for Asian patients with AF at a higher risk for bleeding, DOACs should still be prescribed at the dosing based on clinical trial criteria and guideline recommendations
Lee et al (2020)[35]	Korea	Dabigatran, rivaroxaban, and apixaban from January 2013 to May 2017 and edoxaban from February 2016 to June 2018	Retrospective observational, single-center study: N = 3,733	All DOACs: On-label higher dose: 52% On-label lower dose: 21% Off-label higher dose: 6% Off-label lower dose: 20%	Off-label lower dosing was more frequent than off-label higher dosing and was associated with older age, concomitant antiplatelet drug use, and decreased renal function	Off-label lower dosing was associated with a higher thromboembolic risk	Off-label lower dosing resulted in decreased treatment effectiveness

Continued on the next page

infarction were higher for underdosed vs recommended doses of rivaroxaban in a population of patients with NVAF in Japan.[40] A few studies found no association between clinical outcomes and low-dose DOACs[28] or inappropriately prescribed edoxaban.[38] Analysis of the Korean National Health Insurance Service Database showed that among Korean adults <75 years of age without chronic kidney disease, the use of low-dose apixaban did not demonstrate a clinical benefit over warfarin with respect to thromboembolic events (HR: 0.99; 95% CI: 0.76-1.28) and mortality (HR: 0.85; 95% CI: 0.62-1.16).[49]

NONRECOMMENDED DOSING OUTCOMES CONCLUSION. Our summary of nonrecommended dosing of DOACs and clinical outcomes is shown in **Figure 2**.

TABLE 2 Continued

First Author (Year) Study	Location	Study Period	Design/ Patients	Prevalence of Nonrecommended Dose of DOACs	Characteristics of Patients/Factors Associated With Nonrecommended Dosing	Clinical Outcome Associated With Nonrecommended Dosing	Conclusion/ Main Message
Yu et al (2020)[36] Korean NHI System database	Korea	January 2013 to December 2016	Retrospective NHI database review: N = 53,649 Edoxaban: n = 5,194 Apixaban: n = 11,933 Rivaroxaban: n = 20,143 Dabigatran: n = 16,379	Underdosing: 31.2% Overdosing: 8.4% Labeled use: 60.4%	Patients taking dabigatran or apixaban were prescribed underdoses more frequently than those taking rivaroxaban or edoxaban, whereas patients taking rivaroxaban or edoxaban were more frequently prescribed overdoses than those taking dabigatran or apixaban	Significantly higher rate of stroke and SE, major bleeding, gastrointestinal bleeding, and all-cause death in patients with DOAC overdosing in comparison with labeled use or underdosing	Adverse clinical consequences were higher in the overdosing group compared with the on-label dosing group, and there was no safety benefit of underdosing compared with the labeled use/dosing of DOACs Label adherence of DOAC dosing is important to improve clinical outcomes in patients with AF

[a]All DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban).

AF = atrial fibrillation; ANAFIE = All Nippon AF In Elderly; CA = catheter ablation; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74 years, sex category (female); CODE-AF = Comparison Study of Drugs for Symptom Control and Complication Prevention of Atrial Fibrillation; CrCl = creatine clearance; DIRECT = Safety and effectiveness of 4 Different dIrect oRal anticoagulants, dabigatran, rivaroxaban, apixaban and edoxaban in the rEal-world Clinical pracTice: a single center prospective all-comer registry; DOAC = direct oral anticoagulant; HAS-BLED = hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol usage; IS = ischemic stroke; NHI = National Health Insurance; NVAF = nonvalvular atrial fibrillation; ORBIT-AF II = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II; RYOUMA = Real-world ablation therapY with anti-cOagUlants in Management of Atrial fibrillation; other abbreviations as in Table 1.

EVIDENCE OF THE USE OF LOW-DOSE DOACs FOR GRAY AREA PATIENTS

A subanalysis of the pivotal, randomized controlled ENGAGE AF-TIMI 48 trial comparing higher-dose edoxaban (60 mg OD), lower-dose edoxaban (30 mg OD), and warfarin found that dose reduction preserved the efficacy of edoxaban compared with warfarin and provided greater safety.[50] The findings validate the strategy that tailoring the edoxaban dose based on clinical factors achieves the dual goal of preventing excess drug concentrations and optimizing an individual patient's risk for ischemic and bleeding events, and also shows that the therapeutic window for edoxaban is narrower for major bleeding than for thromboembolism.

THE ELDERCARE-AF STUDY. Elderly individuals are at a higher risk of bleeding while using DOACs due to perceived risk factors such as renal failure, a history of bleeding, prior falls, polypharmacy, and/or frailty. In addition, due to a lack of data for this patient population, clinicians are hesitant to prescribe DOACs.[12] The ELDERCARE-AF trial fills a gap in the knowledge about the optimal anticoagulation strategy for very elderly patients at high risk of bleeding.[12] The objective of the ELDERCARE-AF trial was to provide evidence in support of an anticoagulant regimen for high-risk elderly patients. This was a phase 3 multicenter, randomized, double-blind, placebo-controlled, event-driven trial comparing an OD 15-mg dose of edoxaban with placebo in elderly Japanese patients (≥80 years of age) with NVAF who were deemed ineligible for oral anticoagulant therapy at doses approved for stroke prevention. A total of 984 patients were randomized in a 1:1 ratio to receive either a daily dose of 15 mg of edoxaban (n = 492) or a placebo (n = 492). The annualized rates of stroke or SE were 2.3% in the edoxaban group and 6.7% in the placebo group (HR: 0.34; 95% CI: 0.19-0.61; $P < 0.001$), and the annualized rates of major bleeding were 3.3% in the edoxaban group and 1.8% in the placebo group (HR: 1.87; 95% CI: 0.90-3.89; $P = 0.09$). No significant difference in death from any cause was observed between groups (9.9% in the edoxaban group and 10.2% in the placebo group; HR: 0.97; 95% CI: 0.69-1.36). The study concluded that an OD 15-mg dose of edoxaban was superior to placebo in preventing stroke or SE and did not result in a significantly higher incidence of major bleeding than the placebo in very elderly Japanese patients with NVAF who were not appropriate candidates for higher doses of oral anticoagulants. The edoxaban 15-mg OD dose is now approved in Japan and South Korea since August 2021 and in Taiwan since June 2022 for patients who meet the ELDERCARE-AF study eligibility criteria.[25-27]

This study provides important clinical evidence for the use of edoxaban in this high-risk population. However, whether the results of ELDERCARE-AF are limited to edoxaban or can be generalized to other

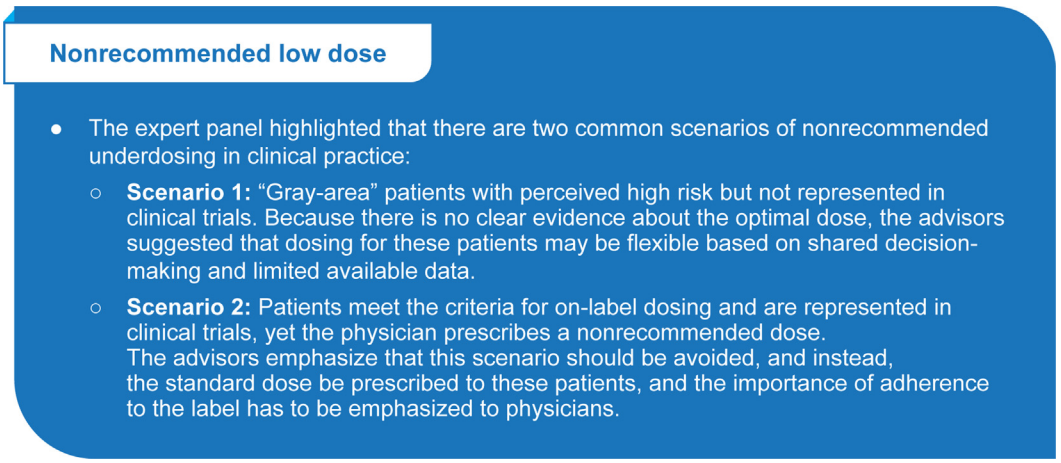
TABLE 3 Summary of Observational Studies on Prevalence of Nonrecommended Individual DOAC Dosing in Asia

First Author (Year) Study	Location	Study Period	Design/ Patients	Prevalence of Nonrecommended Dose of DOACs	Characteristics of Patients/Factors Associated With Nonrecommended Dosing	Clinical Outcome Associated With Nonrecommended Dosing	Conclusion/ Main Message
Edoxaban							
Chao et al (2021)[39] ETNA-AF program	Taiwan, South Korea	Taiwan: May 2017 to September 2020 Korea: February 2017 to May 2020	Prospective, observational noninterventional regional study: N = 2,677	Patients who should be on 60 mg per label: Recommended dose: 66.9% Nonrecommended dose: 33.1% Patients who should be on 30 mg per label: Recommended dose: 76.1% Nonrecommended dose: 23.9%	Compared with the recommended 60-mg group, the nonrecommended 30-mg group had a higher proportion of patients with baseline characteristics of age ≥75 y; higher stroke, IS, and bleeding risks; and a history of major bleeding The nonrecommended 60-mg group had a lower proportion of patients ≥75 years of age, a higher history of stroke, and lower history of bleeding compared with the recommended 30-mg group	NA	Physicians take patient clinical characteristics (eg, bleeding risks) into consideration when deviating from the dosing recommendation per label
Rivaroxaban							
Ikeda et al (2019)[40]	Japan	2012-2014	1-y follow-up of XAPASS, a real-world, Japanese, prospective, single-arm, observational study: N = 6,521	Recommended dose: 64.2% Nonrecommended underdose: 35.8%	The top reasons for using nonrecommended underdosing of DOACs were high bleeding risk, followed by elderly age, renal impairment, low body weight, and concomitant medications	Incidence rates of major bleeding were comparable between underdosed vs recommended-dose groups, although the incidence rates of stroke/non-CNS SE/MI were higher in the underdosed vs recommended-dose groups ($P = 0.009$)	Considering the total clinical benefit, the recommended dose may be preferable in terms of the balance between safety and effectiveness
Apixaban							
Lee et al (2021)[44] Korean Nationwide Claims database	Korea	January 2015 to December 2017	Retrospective database study: N = 7,084	On-label higher dosing: n = 4,194 Off-label underdosing: n = 2,890	Off-label lower dosed group were older; had higher mean $CHADS_2$ scores; had more comorbidities including hypertension, diabetes mellitus, heart failure, peripheral artery disease, chronic obstructive pulmonary disease, and cancer; and had lower mean body weight than those in the on-label higher-dose group	Patients prescribed off-label underdosed apixaban showed a higher risk of IS (adjusted HR: 1.38; 95% CI: 1.06-1.81), all-cause death (adjusted HR: 1.19; 95% CI: 1.01-1.39), and the composite outcome (adjusted HR: 1.17; 95% CI: 1.03-1.34) but with no significant differences in major bleeding between the 2 groups	Label adherence to apixaban dosing should be emphasized to achieve the best clinical outcomes for Asian patients with AF

CNS = central nervous system; ETNA-AF = Edoxaban Treatment in Routine Clinical Practice for Patients With Non Valvular Atrial Fibrillation; MI = myocardial infarction; NA = not available; XAPASS = Xarelto Post-Authorization Safety & Effectiveness Study in Japanese Patients with AF; other abbreviations as in Table 1.

DOACs remains unclear in the absence of other clinical trials. A retrospective cohort study conducted in Taiwan evaluated the clinical outcomes of DOACs in a population generally similar to the ELDERCARE-AF trial, with $CHADS_2$ (congestive heart failure, hypertension, age >80 years, diabetes, and a prior stroke or transient ischemic attack) score of ≥2 stratified into full-dose regimen or lower-dose regimen groups.[51] The results showed that the use of DOACs, regardless of the dose, was associated with a lower risk of IS (aHR: 0.77; 95% CI: 0.67-0.88) and all-cause mortality (aHR: 0.39; 95% CI: 0.37-0.42) compared with nonstandard oral anticoagulant use. Although these findings may

FIGURE 2 **Nonrecommended Low Dosing of Direct Oral Anticoagulants**



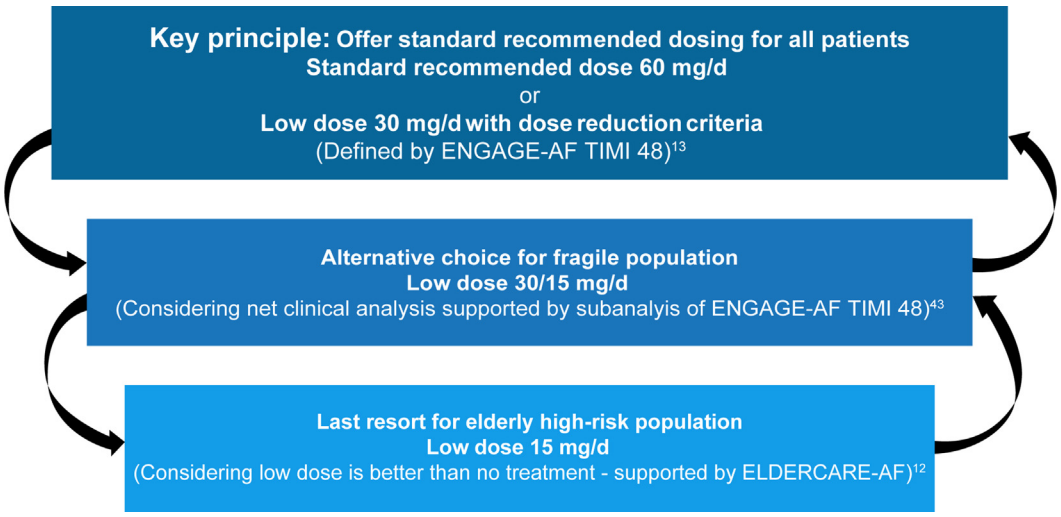
This figure represents the summarized opinion for dosing patients with a nonrecommended low dose. The 2 common scenarios are described. Scenario 1 represents the gray area patient in which no clear evidence is available. Scenario 2 represents the patients in which higher dosing needs to be prescribed and emphasizes the importance to physicians.

provide complementary data to support the generalizability of the results of the ELDERCARE-AF trial to other DOACs in daily clinical practice, this study is limited by the retrospective nature of the analysis of a claims database, and the potential for unmeasured confounders should be considered when interpreting the results.

In terms of labeled dose reduction criteria for DOACs in the elderly population, there is a need to consider factors beyond age alone, as chronological age is an insufficient criterion for determining the appropriate dosage of DOACs in the elderly population. Variations in cellular metabolism, daily activity, and cognitive functions exist among individuals of the same chronological age. Indeed, the choice and dosage of a treatment should be based on an individual's biological age rather than their chronological age.[52] For example, a cross-sectional study demonstrated that 58 patients with type 1 diabetes mellitus had a significantly older vascular age, with an 8.8-year difference ($P < 0.001$), and a higher cardiovascular disease risk stratification ($P < 0.001$) than chronological age control individuals.[53] Therefore, approved dose reduction criteria must consider various biological components or factors, such as renal function, concomitant medication usage, and weight, although regional variations do exist across the approved DOAC labels (**Table 1**). Further studies about how to accurately estimate the biological age and how it could redefine the dosing of DOACs and the subsequent impact on clinical outcomes are necessary.

CASE STUDY ON DOSE ADJUSTMENT OF DOACs IN CLINICAL PRACTICE (PROVIDED BY DR CHAO). An 85-year-old Taiwanese male with AF presented with a normal body weight of 64 kg, a serum creatinine level of 1.15 mg/dL, and an estimated glomerular filtration rate of 42.5 mL/min according to the Cockcroft-Gault (CG) equation and 60.4 mL/min according to the Modification of Diet in Renal Disease (MDRD) equation. His platelet count was low (73,500/μL), and he showed signs of mild anemia with a hemoglobin level of 11.3 g/dL. Additionally, he had a history of prior gastrointestinal bleeding. Very elderly patients with low platelet counts are typically excluded from trials[54] and therefore are not well represented in the pivotal DOAC RCTs. It should also be highlighted that there are differences in the estimated CrCl calculated using the CG equation and the estimated glomerular filtration rate calculated using the MDRD equation, and that the CG calculation should be used to determine the correct DOAC dose.[55-57] For this patient, different choices for on-label DOAC dosing for stroke prevention are available, including dabigatran 110 mg BID, rivaroxaban 15 mg/d (based upon the ROCKET-AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation] dosing),[15] rivaroxaban 10 mg/d (J-ROCKET AF [Japanese Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation]

FIGURE 3 Practical Considerations for Dosing in a Real-World Setting (e.g., Edoxaban)



This figure utilizes edoxaban as an example of dose adjustment in a real-world setting and considers how the dose may be adjusted (up- or downtitrated) according to the patients' characteristics as they change over time. For example, 60 mg/d is offered as a starting point to all patients unless they meet the criteria for dose reduction. For the elderly high-risk patient, 15 mg/d can be prescribed. When patient characteristics change (eg, the creatinine clearance improves and the risk of bleeding reduces), physicians should always consider to step up the lower dose to the higher dose. ELDERCARE-AF = Edoxaban Low-Dose for Elder Care-Atrial Fibrillation Patients; ENGAGE-AF TIMI 48 = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation Thrombolysis In Myocardial Infarction 48.

dosing),[58] apixaban 5 mg BID (as the patient did not fully meet the necessary dose reduction criteria), and edoxaban 30 mg/d. However, the patient and his family expressed concerns about the potential risk of bleeding due to the patient's low platelet count and past history of gastrointestinal bleeding. After discussing the options, the patient was prescribed edoxaban 15 mg/d. The decision was based on evidence from the ELDERCARE-AF study.[12] During subsequent follow-up, the patient's platelet count increased to 110,650/μL, and the physician uptitrated to adjust the edoxaban dose to 30 mg/d. Practical considerations for dosing in a real-world setting using edoxaban as an example are outlined in Figure 3. We believe that this approach is not intended to replace current dosing recommendations but rather is intended to provide a framework for individualizing DOAC dosing based on patient-specific factors. A similar approach may be applied to other DOACs in the future, depending on the availability of data, physicians' experience of the DOAC, and shared decision making with the patient.

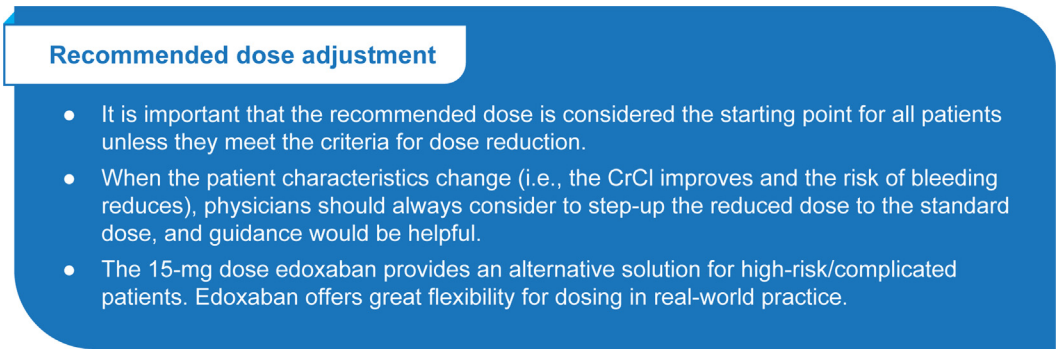
LOW-DOSE GRAY AREA PATIENT OUTCOMES CONCLUSION. The use of low-dose DOACs for gray area patients is summarized in Figure 4.

FUTURE PERSPECTIVE ON DOAC DOSING IN ASIA

GUIDANCE ON DOAC DOSING IN ASIA. The Asia Pacific Heart Rhythm Society recommends on-label dosing of DOACs in Asian patients with AF.[55] The key points in the consensus guidelines are as follows: 1) as DOACs are more effective and safer than warfarin in Asian patients with AF, DOACs are the recommended choice for oral anticoagulation in Asian patients with AF; 2) the CG equation should be adopted to calculate CrCl to determine the dosing of DOACs; and 3) on-label or guideline-adherent dosing of DOACs is recommended in Asian patients.

One of the most important Asia Pacific Heart Rhythm Society recommendations for DOAC dosing is regarding the determination of renal function. Patients with AF should have their CrCl measured using the CG equation, as used in the 4 major DOAC RCTs.[13-15,59] Compared with the CG equation, the MDRD or Chronic Kidney Disease Epidemiology Collaboration equations would overestimate the renal function of patients with AF, particularly the elderly (≥75 years) and those with low body weight (<50 kg), potentially leading to overdosing and attenuating the benefits of DOACs.[55]

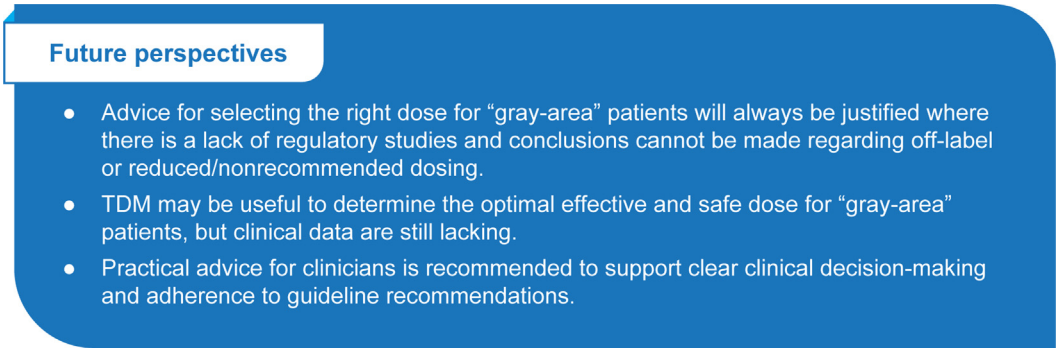
FIGURE 4 Dose Adjustment of Direct Oral Anticoagulants for Gray-Area Patients



This figure represents the summarized opinion for dose adjustment for all direct oral anticoagulants. CrCl = creatinine clearance.

THERAPEUTIC DRUG MONITORING AND PHARMACOKINETIC DATA. Treatment with DOACs typically does not require routine clinical monitoring due to their wide therapeutic index; however, it may be necessary to assess drug levels in specific situations to manage risks or side effects and confirm efficacy.[60] An 8-year retrospective, observational study monitoring DOAC levels in 236 patients in Poland concluded that therapeutic drug monitoring (TDM) is not necessary for the general population but should be considered in specific clinical settings, including patients with severe bleeding, obesity or VLBW, or impaired kidney function, and prior to emergent surgery to confirm the need for reversal agents.[60] Pharmacokinetic analysis of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study with 9,183 patients showed that dabigatran plasma concentrations increased with age and decreased with increasing body weight but were not affected by ethnicity and regional geographic variation.[61] Another study that assessed serum concentration of dabigatran in Asian patients with NVAF indicated that TDM should be considered for patients at risk of overexposure, including the elderly or those who have low body weight, impaired renal function, and high risk of thrombosis and bleeding.[62] In addition, a post hoc analysis of the ENGAGE AF-TIMI 48 trial assessed the differences in clinical outcomes and pharmacokinetic parameters between Asian (n = 2,909) and non-Asian (n = 18,195) patients and showed that the median trough concentration for edoxaban was 20% to 25% lower for Asians compared with non-Asians, resulting in lower trough anti-factor Xa activity, which may account for favorable clinical outcomes in Asian patients.[19] Taken together, the characteristics of patients with AF in Asia who may be prescribed nonrecommended dose of DOACs (elderly, low body weight, high risk of bleeding)

FIGURE 5 Future Perspectives on Dosing of Direct Oral Anticoagulants in Asia



This figure represents the summarized opinion for future considerations of direct oral anticoagulant dosing for Asian patients. TDM = therapeutic drug monitoring.

coincide with specific clinical settings in which TDM is recommended.[60]

Unfortunately, there are no specific guidelines for TDM intervals or periods and no evidence to recommend dose adjustments based on TDM findings. For example, for patients with recurrent bleeding, drug monitoring can be performed, but there are no detailed protocols to guide dose adjustments. The only recommendation that can be made is that the drug concentration is associated with the risk of adverse events. Specifically, higher DOAC plasma concentrations are associated with a higher risk of bleeding, whereas lower DOAC plasma concentrations are associated with a higher risk of ischemic events.[60,61]

CONSIDERATION OF ASIAN ETHNICITY AND RISK FACTORS. As Asian and non-Asian patients have participated in the pivotal RCTs for DOACs, DOACs are expected to be similarly effective regardless of race. Analysis of the ENGAGE AF-TIMI 48 trial demonstrates that higher-dose edoxaban significantly reduced intracranial hemorrhage while preserving the efficacy of stroke prevention in both Asian and non-Asian patients.[19] However, the risk factors tend to be different among these populations, as Asian patients tend to be older with lower body weight and a high risk of bleeding. It was shown that the reduction in the risk of net clinical outcomes (ie, stroke, SE, major bleeding, or death from any cause) with edoxaban compared with warfarin increases with the number of risk factors.[7] This finding may suggest that patients with higher risks will gain greater benefits from the use of low-dose DOACs than with warfarin.

CONCOMITANT MEDICATIONS. The use of antiplatelet agents in combination with anticoagulants increases the risk of bleeding events. The AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial showed that rivaroxaban monotherapy was noninferior to combination therapy with rivaroxaban plus antiplatelet therapy with respect to cardiovascular events and death from any cause and was superior with respect to major bleeding.[63] A high proportion of patients with AF may receive antiplatelet drugs unnecessarily. For patients being considered for a lower dose of DOACs, physicians should ensure reevaluation of antiplatelet therapy and reconsider the use of higher on-label doses accordingly.

UPTITRATING AND DOWNTITRATING. Currently, uptitration or downtitration of DOACs in clinical practice is often considered based primarily on the physician's discretion as a fact, and there is no evidence to provide guidance. More guidance on dose adjustment should be provided based on changes in clinical parameters/characteristics of patients on DOACs. To date, no study has conducted a risk-benefit analysis of uptitration and downtitration, and no information is currently available in the prescribing information of DOACs. Therefore, for inclusion of this type of information in the prescribing information, regulatory studies are required.

FURTHER STUDIES. Although the lowest recommended dose of edoxaban (15 mg/d) was superior to placebo in the ELDERCARE-AF trial, the HDER (60/30 mg) was not tested in this trial.[12] Therefore, we cannot ascertain whether HDER may perform better than the low dose of edoxaban (15 mg/d) in an ELDERCARE-AF population. Further investigations are needed to assess the optimal doses of DOACs and net clinical effects of off-label DOAC prescriptions in the Asian population with AF, especially for those with high bleeding as risk factors who were not well represented in clinical trials.

FUTURE DOSING INFORMATION CONCLUSION. Future perspectives on DOAC dosing in Asia are summarized in Figure 5.

HIGHLIGHTS

- Optimal dosing in very elderly gray area Asian patients is a challenge.
- Shared decision-making and a consideration of available evidence should be the basis for dosing choice.
- Avoid nonrecommended dosing where possible to mitigate unnecessary complications.
- Additional high-risk characteristics may be considered in future trials to further refine dose-reducing criteria.

CONCLUSIONS

Recommended dosing was associated with a better clinical outcome and therefore should be considered as the gold standard. However, nonrecommended doses of DOACs are commonly prescribed for Asian patients with AF. Based on demographics and clinical characteristics, there are more patients of Asian descent who are very elderly, with low body weight, and at a high risk of bleeding compared with non-Asian patients with AF. These patients may be candidates for lower dosage but do not fit into the

lower-dose criteria (gray area patients). The current challenge of DOAC dosing in gray area patients is an important issue. The ELDERCARE-AF trial provided evidence for the efficacy of low-dose DOACs in elderly Asian patients. Edoxaban 15 mg may be a promising management strategy for gray area patients, if indicated by the product label, and the DOAC dose can be adjusted based on changes in the patients' conditions. Key areas for improvement in treatment using DOACs in patients with AF in Asia are for physicians to avoid nonrecommended dosing where possible to mitigate unnecessary complications. Moreover, the dose reduction criteria may be refined to include additional high-risk characteristics relevant in clinical practice. Further research is needed to fill the gaps in the literature on the optimal DOAC doses for gray area patients.

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