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MEETING REPORT

Risk of gastrointestinal bleeding in Asian patients receiving oral anticoagulants for stroke prevention in atrial fibrillation

Alejandro Bimbo Diaz[1], Jeremy Chow[2], Fan Kee Hoo[3], Gary Lee Chin Keong[4], Narayanaswamy Venketasubramanian[5], Nannette Rey[6], Gregorio Rogelio[7], Radhika Mehta[8]

[1]University of Santo Tomas Hospital, Manila, Philippines; [2]Asian Heart & Vascular Centre, Singapore, Singapore; [3]University Putra Malaysia, Serdang, Malaysia; [4]Thomson Hospital Kota Damansara, Petaling Jaya, Malaysia; [5]Raffles Hospital, Singapore, Singapore; [6]de La Salle Medical and Health Sciences Institute, Dasmarinas Cavite, Philippines; [7]St Luke's Medical Center, Quezon City, Philippines; [8]Menarini Asia-Pacific Pte Ltd, Singapore, Singapore

Abstract

Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly used for stroke prevention in atrial fibrillation. At the Asia Pacific Advancing Patient care with EdoXaban 2023 meeting, experts shared insights on gastrointestinal bleeding with NOACs for stroke prevention in atrial fibrillation in Asian clinical practice, where NOACs have gained widespread acceptance due to their favourable profiles. Gastrointestinal bleeding risk varies amongst NOACs, emphasizing the importance of diligent patient assessment, dosage selection and vigilant monitoring. Edoxaban emerged as a viable option with a low gastrointestinal bleeding risk profile in Asian compared with non-Asian patients, supporting its continued clinical utilization for appropriate patients.

Keywords: Asian patients, atrial fibrillation, edoxaban, gastrointestinal bleeding, non-vitamin K oral anticoagulant, Southeast Asia, stroke.

Citation

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Box 1. Key summary points.

Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly used for stroke prevention in atrial fibrillation in Asia.
Relative to warfarin, NOACs offer a favourable risk-benefit profile and convenience.
Data from the large, randomized ENGAGE TIMI-AF trial and the real-world Global ETNA-AF registry clearly show a lower risk of major gastrointestinal (GI) bleeding in Asian compared with non-Asian patients with atrial fibrillation treated with edoxaban, which is associated with a lower plasma concentration.
Clinical characteristics may be associated with the risk of GI bleeding events in patients with atrial fibrillation treated with oral anticoagulants, and attention should be paid to occult GI cancer when managing oral anticoagulant-related bleeding.
GI bleeding risk varies amongst NOACs, emphasizing the importance of diligent patient assessment (e.g. caution is advised when administering higher edoxaban doses to elderly patients), dosage selection and routine, vigilant monitoring (e.g. for urinary tract bleeding, particularly in elderly patients).
Tailored approaches, guided by individual bleeding histories and underlying GI conditions, are advocated.

Introduction

The Menarini Asia Pacific Advancing Patient care with EdoXaban (APEX) 2023 Expert Meeting convened in Kuala Lumpur, Malaysia, and provided a forum for experts to explore the occurrence of gastrointestinal (GI) bleeding linked to non-vitamin K antagonist oral anticoagulants (NOACs) in Asian clinical practice for stroke prevention in atrial fibrillation (SPAF). This report amalgamates insights from two segments of the meeting.

The first segment centred on a review of GI bleeding data from key NOAC trials including the ENGAGE trial and the Edoxaban Treatment in routiNe clinical prActice (ETNA)-AF (South Korea and Taiwan). These trials compared edoxaban and warfarin for SPAF, with particular attention to the differences in outcomes between Asian and non-Asian patients with atrial fibrillation (AF), and the factors that influence the variance. The following part of the meeting featured a panel discussion devoted to managing GI bleeding in Asian patients undergoing treatment with NOACs for non-valvular AF. The panel addressed four key areas: disparities in GI bleeding risk between Asian and non-Asian patients, implications for treatment strategies, considerations, and strategies to enhance detection and treatment outcomes.

Summary of GI bleeding data from key NOAC trials

Increasing OAC use and outcomes in Taiwan

During the era when warfarin and other vitamin K antagonists were the only available class of oral anticoagulants (OACs) to reduce the risk of stroke in newly diagnosed patients with non-valvular AF,[1] prescription rates were low, particularly in Asia.[2] This is most likely because warfarin requires regular laboratory monitoring to maintain the international normalized ratio within the therapeutic range and is associated with an increased risk of intracranial haemorrhage.[3] Following the availability of NOACs from 2009 onwards, use of the OACs dabigatran, rivaroxaban, apixaban and edoxaban (which inhibit thrombin (FIIa) or factor Xa (FXa),[4] have predictable pharmacokinetics, and do not require continuous anticoagulant monitoring[5,6]) for SPAF has increased.[7,8]

In Taiwan alone, the initiation rates of OACs for SPAF increased almost three-fold from 2008 (13.6%) to 2015 (35.6%).[7] Edoxaban is the most recent NOAC to have received regulatory approval for SPAF in Taiwan,[9] following dabigatran, rivaroxaban and apixaban.[4] Importantly, along with the temporal increase in NOAC prescription rates since 2011, there has been a gradual decrease in the 1-year risk of ischaemic stroke for patients with incident AF in Taiwan,[7] suggesting that the introduction of NOACs has had a positive influence on patient outcomes. A similar temporal trend in prescribing patterns of OACs was seen in elderly patients (aged ≥85 years) with newly diagnosed AF in Taiwan.[8] From 2009 to the end of 2011, OAC initiation rates ranged from 9.5% to 13.2%, and from 2012 to 2015 these increased to 34.3%, largely driven by increased use of NOACs (0–26.2%) (Figure 1).[10] Additionally, there was an associated decrease in the risk of ischaemic stroke, with no significant increase in the risk of major bleeding (defined as intracranial haemorrhage or GI, genitourinary or respiratory tract bleeding requiring hospitalization), supporting the safety of NOACs in elderly populations.[8,10]

Efficacy and safety of NOACs compared with warfarin

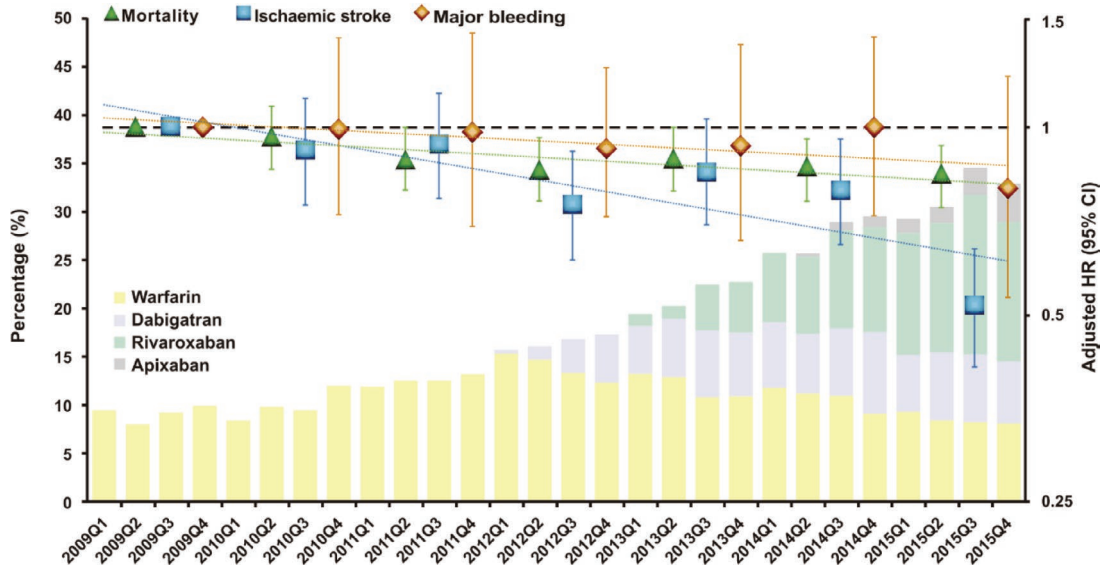
Further to previous NOAC trial-level meta-analyses that showed a favourable risk-benefit profile,[11] meta-analyses of patient-level data from the Collaboration between Multiple institutions to Better Investigate Non-vitamin K antagonist oral anticoagulant use in Atrial Fibrillation (COMBINE AF) database evaluated the collective efficacy and safety of NOACs (standard dose and lower dose) relative to warfarin for SPAF.[12] The COMBINE AF database includes data for all patients (*n*=71,683) with AF randomized in the four pivotal phase III trials of NOACs *versus* warfarin, including Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY);[13] Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF);[14] Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE);[15] and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48)[16,17] (Table 1).

The principal findings of the patient-level analyses are shown in Figure 2.[12] Compared with warfarin, collectively, pooled standard-dose (but not all lower-dose) NOACs significantly reduced the risk of stroke/systemic embolic events, intracranial bleeding and all-cause death as well as all bleeding events, with the exception of GI bleeding. Relative to warfarin, the risk of GI bleeding was higher with standard-dose but not with lower-dose NOACs, suggesting differences in safety outcomes according to NOAC dose.[12]

NOACs and bleeding risk

The results from individual phase III NOAC trials confirm the differences in the risk of GI bleeding, relative to warfarin, for each NOAC by dose (Table 2).[13–15,17] In the ROCKET-AF trial, the risk of GI bleeding was significantly increased

Figure 1. Temporal trends in initiation rates of oral anticoagulants in elderly patients with atrial fibrillation and 1-year risk of adverse events.



CI, confidence interval; HR, hazard ratio; Q, quarter.
Reprinted with permission from Liao et al.[10]

Table 1. Pivotal randomized trials of NOACs *versus* adjusted-dose warfarin in patients with atrial fibrillation.

Trial	NOAC	*N*	MoA	Standard dose	Lower dose
RE-LY[13]	Dabigatran	18,113	Thrombin inhibitor	150 mg bid	110 mg bid
ROCKET AF[14]	Rivaroxaban	14,264	Direct factor Xa inhibitor	20 (15[a]) mg/day	
ARISTOTLE[15]	Apixaban	18,201	Direct factor Xa inhibitor	5 (2.5[a]) mg bid	
ENGAGE AF-TIMI 48[16,17]	Edoxaban	21,105	Direct factor Xa inhibitor	60 (30[a]) mg/day	30 (15[a]) mg/day

[a]If dose-reduction criteria were met.
bid, twice daily; MoA, mechanism of action; NOAC, non-vitamin K antagonist oral anticoagulant.

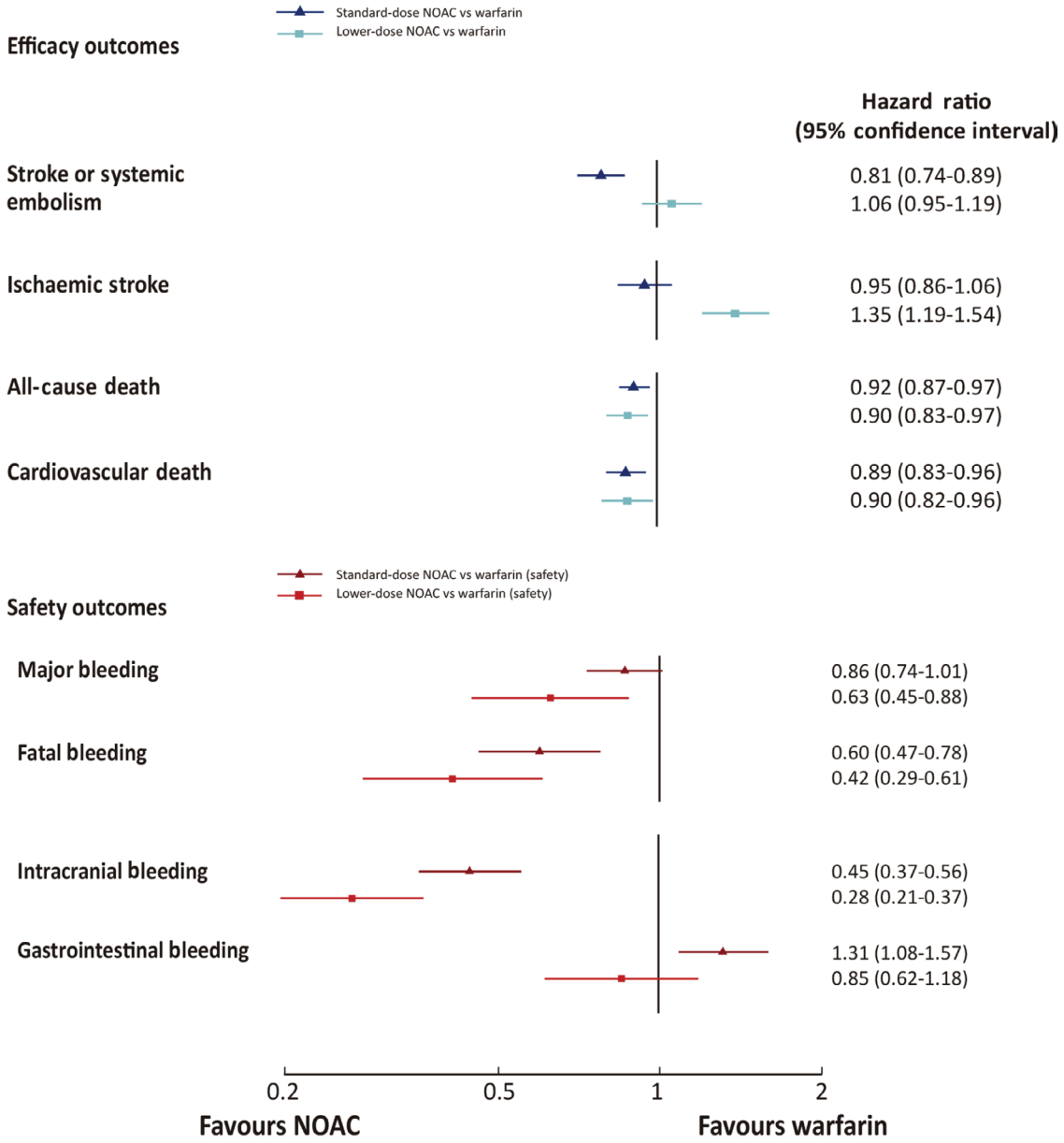
with rivaroxaban 20 or 15 mg/day.[14] In ENGAGE AF-TIMI 48, the risk of GI bleeding was significantly increased with edoxaban 60 mg/day; however, dose reduction to 30 mg/day did not increase the risk, which was lowest in the low-dose regimen for edoxaban.[17] Similarly, in the RELY trial,[13] the risk was significantly higher with dabigatran 150 mg bid but was similar for the low-dose, 110 mg bid, arm; in ARISTOTLE,[15] the risk of GI bleeding did not differ between apixaban 5 or 2.5 mg bid and warfarin.

NOAC dose and risk of major bleeding

In the randomized, double-blind ENGAGE AF-TIMI 48 trial in 21,105 patients with AF within the past 12 months and a $CHADS_2$ score ≥2, over a median follow-up of 2 years, two edoxaban treatment strategies, standard dose (60 mg/day) and low dose (30 mg/day), were non-inferior to adjusted-dose warfarin for the primary efficacy endpoint, the composite of first stroke or systemic embolic events.[16,17] Edoxaban doses were halved (60 mg/day reduced to 30 mg/day; 30 mg/day reduced to 15 mg/day) at randomization or during the trial if patients had estimated creatinine clearance 30–50 mL/min or body weight ≤60 kg or required concomitant medication with potent P-glycoprotein interaction. These dose-reduction criteria were applied to adjust for anticipated increased drug exposure in the presence of such characteristics.[17]

For the primary safety endpoint (major bleeding), both the standard and the low-dose edoxaban regimens showed a significantly greater risk reduction than warfarin (0.80, 95% CI 0.71–0.91; $p<0.001$ and 0.47, 95%

Figure 2. Forest plots showing efficacy and safety outcomes of standard-dose and lower-dose NOACs *versus* warfarin.



NOAC, non-vitamin K antagonist oral anticoagulant.
Adapted from Carnicelli et al.[12]

CI 0.41–0.55; $p<0.001$, respectively).[17] Analysis of the primary efficacy and safety data by standard-dose edoxaban dose-reduction status showed that, for ischaemic stroke, there was no difference in risk compared with warfarin for patients who received no dose reduction and those who did (Table 3).[18] Nevertheless, compared with warfarin, the risk of major bleeding and GI bleeding was lower for patients who met dose-reduction criteria and received edoxaban 30 mg/day.

NOAC dose and severity of GI bleeding

A subsequent analysis of the ENGAGE AF-TIMI 48 trial investigated the risk factors for major GI bleeding with standard-dose and low-dose edoxaban or well-managed warfarin.[19] During 2.8 years of follow-up, there were 579 major GI bleeding events (1.22% per year) and, amongst these, 63 were life-threatening or fatal (0.13% per year). Overall, only 10% of all major GI bleeding events were life-threatening and 2% were fatal. Additionally, certain baseline clinical characteristics were associated with the increased risk of major GI, including advanced age, prior GI bleeding and concomitant use of aspirin. When considering the risk of major GI bleeding over time (Figure 3), the risk was higher for the standard-dose edoxaban arm than with warfarin, though there was no significant

Table 2. Risk of major gastrointestinal bleeding with NOACs *versus* adjusted-dose warfarin in patients with atrial fibrillation.[13–15,17]

Trial	NOAC, dose	TTR	Median $CHADS_2$ score; 3–6, %	Rate/year		HR (95% CI)	*p* value
				Warfarin	NOAC		
ROCKET AF[14]	Rivaroxaban 20/15 mg/day	58%	3.5; 87%	1.24	2.0	1.66 (1.34–2.05)	<0.001
ENGAGE AF-TIMI 48[17]	Edoxaban 60/30 mg/day	68%	2.8; 53%	1.25	1.53	1.23 (1.02–1.48)	0.033
	60 mg/day			1.18	1.56	1.32 (1.06–1.61)	
	30 mg/day			1.48	1.44	1.00 (0.67–1.47)	
	30/15 mg/day			1.25	0.87	0.70 (0.86–1.41)	<0.001
RELY[13]	Dabigatran 150 mg bid	64%	2.1; 33%	1.02	1.51	1.50 (1.19–1.89)	<0.001
	110 mg bid			1.02	1.12	1.10 (0.86–1.41)	0.43
ARISTOTLE[15]	Apixaban 5/2.5 mg bid	66%	2.1; 30%	0.86	0.76	1.89 (0.70–1.15)	0.37

bid, twice daily; CI, confidence interval; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; TTR, time in the therapeutic range.

Table 3. Efficacy and safety of standard-dose edoxaban compared with warfarin by dose-reduction status.[18]

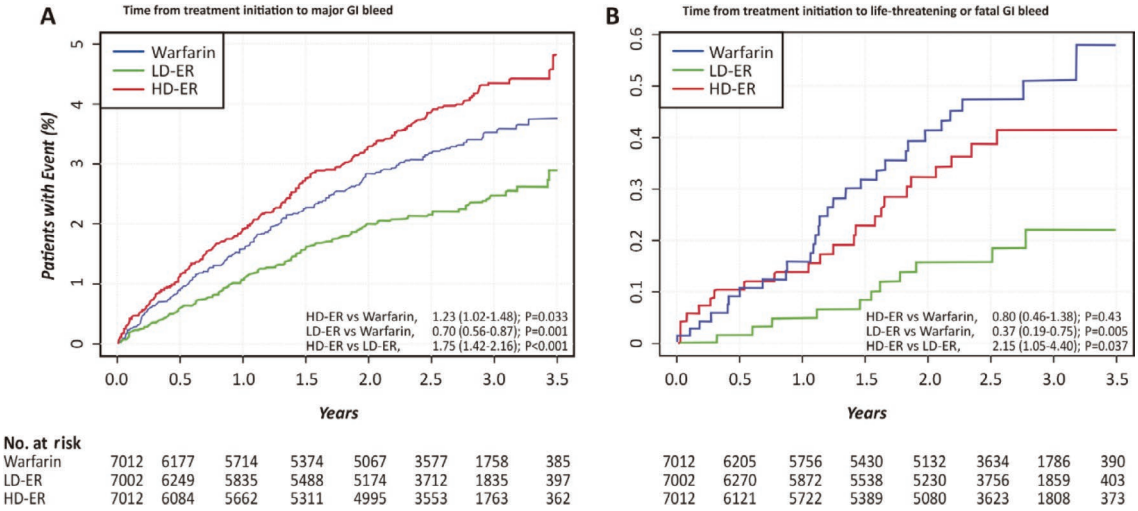
	No dose reduction, 60 mg/day	Dose reduction, 30 mg/day	
	HR (95% CI)		$P_{interaction}$
Stroke or systemic embolic events	0.78 (0.61–0.99)	0.81 (0.58–1.13)	0.85
Ischaemic stroke	0.94 (0.70–1.24)	0.96 (0.63–1.46)	0.91
All-cause mortality	0.94 (0.76–1.17)	0.85 (0.62–1.17)	0.59
Major bleed	0.88 (0.76–1.03)	0.63 (0.50–0.81)	0.023
Fatal bleed	0.61 (0.35–1.07)	0.46 (0.23–0.92)	0.54
Intracranial haemorrhage	0.47 (0.32–0.68)	0.46 (0.27–0.78)	0.94
Gastrointestinal bleed	1.32 (1.06–1.65)	1.00 (0.67–1.47)	0.21

CI, confidence interval; HR, hazard ratio.

difference in the risk of life-threatening or fatal GI bleeding between the standard-dose edoxaban regimen and warfarin.[19]

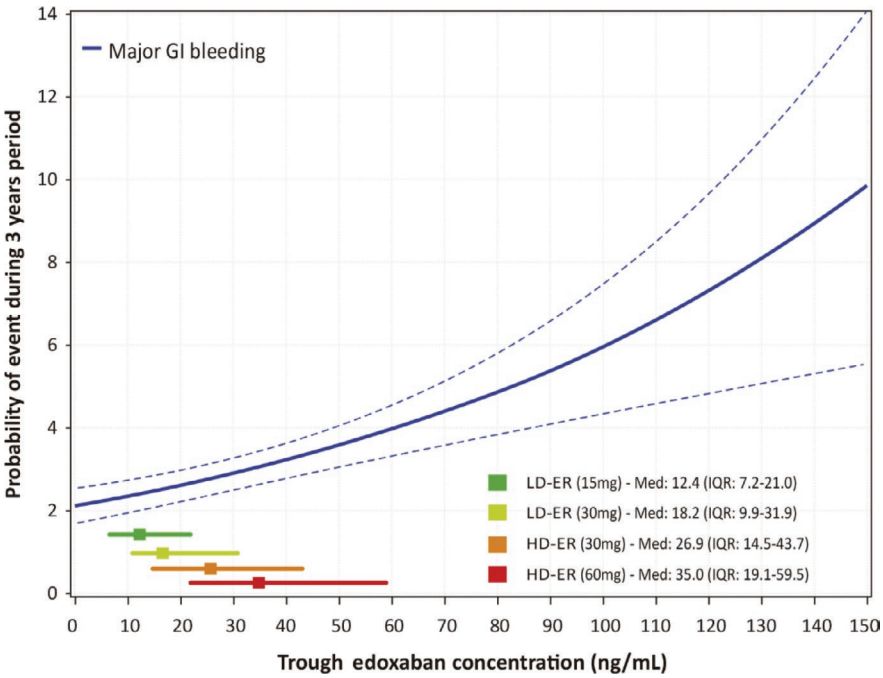
Patients who received standard-dose edoxaban had a significantly lower risk of major GI bleeding requiring surgical intervention (HR 0.37, 95% CI 0.16–0.88; p=0.025) and were significantly more likely than warfarin recipients to have a major GI bleed associated with none of the five potential markers of bleeding severity evaluated (HR 1.69, 95% CI 1.05–2.73; p=0.03), demonstrating that the severity of the major GI bleeding was mild.[19] Importantly, the risk of major GI bleeding correlated with edoxaban concentration; increasing plasma trough edoxaban concentrations on day 29 was associated with a higher risk of major GI bleeding over the course of 3 years (Figure 4). In patients who received standard-dose edoxaban and experienced major GI bleeding, the median trough edoxaban concentration was about 25% higher than that in patients without major GI bleeding (40.5 ng/mL, IQR 20.7–63.4 and 32.4 ng/mL, IQR 17.8–55.0, respectively).[19]

Figure 3. Time from treatment initiation with warfarin or edoxaban to first GI bleeding event for (A) patients with a major gastrointestinal bleeding event or (B) patients with a life-threatening or fatal GI bleeding event.



GI, gastrointestinal; HD-ER, higher dose edoxaban regimen (60 mg/day); LD-ER, lower-dose edoxaban regimen (30 mg/day). Reprinted with permission from Aisenberg et al.[19]

Figure 4. Probability of a major GI bleeding event as a function of trough edoxaban concentration at day 29.



GI, gastrointestinal; HD-ER, higher dose edoxaban regimen (60 mg/day); LD-ER, lower-dose edoxaban regimen (30 mg/day). Reprinted with permission from Aisenberg et al.[19]

These results show that, though there was an increased risk of major GI bleeding with standard-dose edoxaban compared with warfarin, the rates of life-threatening or fatal GI bleeding were low and similar between standard-dose edoxaban and warfarin; essentially, the excess in major GI bleeding events seen with edoxaban relative to warfarin were of the least severe type. Additionally, there was a clear correlation between edoxaban dose, trough level and the risk of GI bleeding, demonstrating that the risk of major GI bleeding is associated with the edoxaban plasma concentration.

Efficacy and safety in Asian and non-Asian patients with AF

Two *post hoc* secondary analyses of the ENGAGE AF-TIMI 48 trial showed that the risk of thromboembolic and bleeding events differs between Asian and non-Asian patients with AF. The studies used data from the Asian population in the trial, including 1943 patients from East Asia (Japan, China, Taiwan and South Korea)[20] and 2909 patients of Asian[21] race.

In East Asian patients, the risk of GI bleeding with standard and low-dose edoxaban was not greater than that seen with warfarin.[20] By contrast, in non-East Asian patients, compared with warfarin, though the risk of GI bleeding was lower with low-dose edoxaban, the risk was higher with standard-dose edoxaban.[20] Analysis of key efficacy and safety data from the patients of Asian race in ENGAGE AF-TIMI 48 treated with warfarin or standard-dose edoxaban showed no significant interaction *p* values, supporting the efficacy and safety of standard-dose edoxaban in this population; notably, the risk of major GI bleeding was not higher with standard-dose edoxaban compared with warfarin (Table 4).[21] Thus, compared with non-Asian patients with AF, the risk of GI bleeding seems not to be a concern for Asian patients with AF treated with standard-dose edoxaban, though potential factors influencing this outcome have not been established.

Edoxaban concentration in Asian and non-Asian patients with AF

In the overall population in the ENGAGE AF-TIMI 48 trial, the relationship between the edoxaban concentration and the probability of events was such that, as the edoxaban trough concentration increased, the risk of major bleeding increased, the risk of ischaemic events decreased and the risk of intracranial haemorrhage showed a relatively flat association, even at a high edoxaban trough concentration.[18] Comparison of the risk of events and the edoxaban trough concentration in Asian and non-Asian patients showed that, as the edoxaban concentration increased, the risk of intracranial haemorrhage increased more sharply for the Asian than for the non-Asian population as did the risk of major bleeding (Figure 5),[21] suggesting that Asian patients may be more sensitive than the overall population to edoxaban concentrations. Therefore, when treating Asian patients with edoxaban, there may be a

Table 4. Efficacy and safety outcomes of Asian and non-Asian patients with atrial fibrillation treated with edoxaban 60 mg/day compared with warfarin.[21]

Clinical outcome	Study population	Edoxaban *versus* warfarin HR (95% CI)	$P_{Interaction}$
Efficacy endpoints			
Ischaemic stroke	Asians	0.83 (0.52–1.32)	0.40
	Non-Asians	1.03 (0.85–1.25)	
Stroke/systemic embolic events	Asians	0.74 (0.51–1.08)	0.37
	Non-Asians	0.90 (0.76–1.07)	
All-cause death	Asians	0.75 (0.57–0.99)	0.13
	Non-Asians	0.95 (0.85–1.05)	
Safety endpoints			
Intracranial haemorrhage	Asians	0.57 (0.32–1.00)	0.41
	Non-Asians	0.43 (0.30–0.62)	
Life-threatening or fatal bleeding	Asians	0.57 (0.34–0.97)	0.70
	Non-Asians	0.51 (0.38–0.68)	
Major bleeding	Asians	0.77 (0.56–1.06)	0.79
	Non-Asians	0.81 (0.70–0.93)	
Major gastrointestinal bleeding	Asians	1.27 (0.72–2.21)	0.92
	Non-Asians	1.23 (1.00–1.51)	

CI, confidence interval; HR, hazard ratio.

'sweet spot', namely a relatively lower trough edoxaban concentration, that could be targeted to minimize the risk of GI bleeding and achieve a favourable safety profile without compromising efficacy.

Observations in patients who met dose-reduction criteria in ENGAGE AF-TIMI 48 showed that edoxaban dose reduction from 60 to 30 mg/day was associated with greater relative reductions in edoxaban trough concentrations (25.2% and 20.3%) and anti-FXa activity (50% and 16.7%) in Asian than in non-Asian patients.[21] Despite receiving the same edoxaban dose, the edoxaban trough concentration was lower in Asian than in non-Asian patients, which essentially shifts the event rate curve to align with a lower trough edoxaban concentration that fits the 'sweet spot' (Figure 5).[21] Importantly, the lower edoxaban plasma concentration and anti-FXa activity observed in Asian patients than in non-Asian patients treated with standard-dose edoxaban may contribute to the efficacy for stroke prevention with a lower risk of major GI bleeding than warfarin in Asian patients.

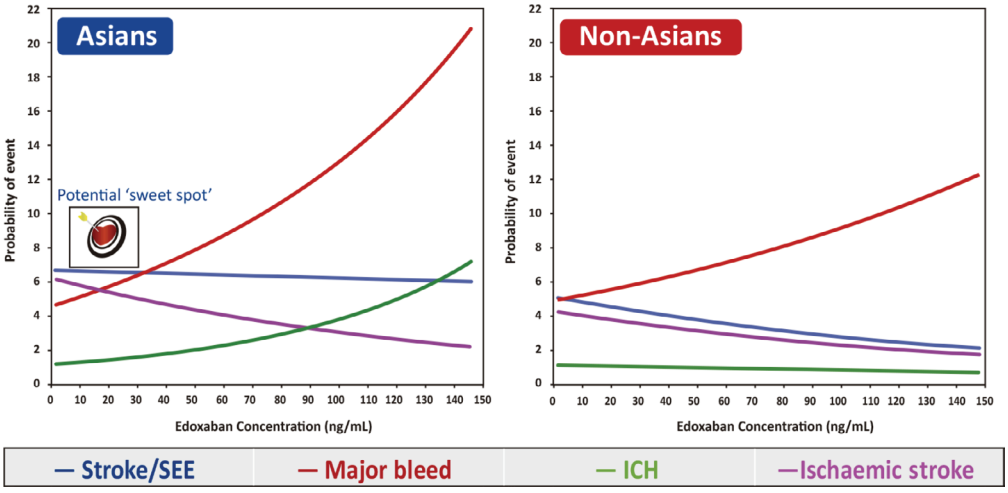
Dosing and safety in routine clinical practice — globally

Edoxaban dosing and outcomes in routine clinical practice were investigated in the largest (*n*=26,823) phase IV post-regulatory single NOAC registry, the Global ETNA-AF non-interventional programme in patients with AF from Europe (*n*=13,092), Asia (Japan (*n*=11,054), and Korea and Taiwan (*n*=2677)).[22]

Globally, dosing with edoxaban 60 or 30 mg/day was similar (53.5% and 46.5%, respectively) but dosing differed by region: Europe, 76.3% and 23.7%; Japan, 27.6% and 72.4%; and Korea and Taiwan, 48.7% and 51.3%.[22] The risk of major GI bleeding in the different dosing groups in this real-world setting, where patients may be prescribed different doses based on patient characteristics, highlighted divergence from the clinical trial setting. The risk of major GI bleeding was lower (0.27%/year) for patients who received the recommended edoxaban dose of 60 mg/day but higher (0.76%/year) for patients who received the non-recommended dose of 30 mg/day despite not meeting any dose-reduction criteria (i.e. underdosed patients). In patients with ≥1 dose-reduction criteria, the risk of major GI bleeding was higher (0.98%/year) for those who received the recommended edoxaban dose of 30 mg/day and lower (0.39%/year) for patients who received the non-recommended dose of 60 mg/day (i.e. overdosed patients).[22]

Surprisingly, the highest risk of major GI bleeding in the Global ETNA-AF programme was observed in patients who received low-dose edoxaban, which may be attributed to differences in patient clinical characteristics and physician prescribing decisions. For example, for patients who met dose-reduction criteria, the physician may have recognized them as fragile, hence, low-dose edoxaban was prescribed, yet such patients may have been at a higher risk of major GI bleeding. Patients who received the recommended edoxaban dose of 30 mg/day

Figure 5. Association between the trough edoxaban concentration and the probability of events (%) at 3 years in Asian and non-Asian patients with atrial fibrillation in the ENGAGE TIMI-AF 48 trial.



The x-axis represents the trough concentration of edoxaban at day 29.
ICH, intracranial haemorrhage; SEE, systemic embolic events.
Reprinted with permission from Chao et al.[21]

following dose reduction may have had a lower body weight or poor renal function and were thus at a higher risk of major GI bleeding.

Dosing and safety in routine clinical practice — in South Korea and Taiwan

An analysis from the Global ETNA-AF programme that focused on the 2677 patients with AF from Korea and Taiwan, showed that 1-year clinical event rates were low compared with those of the global population, again supporting the effectiveness and safety of edoxaban in Asian patients.[9] Not only were the annualized event rates of all-cause mortality (1.17%), stroke/systemic embolic events (1.08%), major bleeding (0.78%) and cardiovascular mortality (0.51%) low in patients with AF from Korea and Taiwan but a regional difference in the 1-year risk of GI bleeding was also observed.[9] The 1-year risk of GI bleeding was lowest in South Korea (0.12%), followed by Taiwan (0.47%) and Japan (0.50%), and was highest in the overall Global ETNA-AF population (0.57%).[9,23,24] This finding is in agreement with the data from the ENGAGE TIMI-AF trial, which showed that the risk of GI bleeding may not be of concern for Asian patients with AF treated with edoxaban.[20]

Efficacy and safety of NOACs in routine clinical practice in Taiwan

In the largest real-world retrospective cohort study of Asian patients in Taiwan with non-valvular AF that investigated the effectiveness and safety of the four NOACs *versus* warfarin, patients had received standard or low-dose regimens of edoxaban (*n*=4577), apixaban (*n*=9952), rivaroxaban (*n*=33,022), dabigatran (*n*=22,371) or warfarin (*n*=19,761).[25] Although each NOAC was associated with a comparative or lower risk of thromboembolism and a lower risk of bleeding than warfarin, there were differences between the NOACs in effectiveness and safety outcomes.[25] The NOACs were associated with a comparative or lower risk of ischaemic stroke/systemic embolic events than warfarin, with a trend in favour of the lowest risk with edoxaban (Table 5). The cumulative risk of intracranial haemorrhage

Table 5. Risks and trends of effectiveness and safety outcomes, relative to warfarin, amongst patients with atrial fibrillation treated with standard-dose NOACs.[25]

	Incidence rate (%/100 patient-years)	HR (95% CI)	*p* value
Ischaemic stroke			
Warfarin	2.81 (2.28–3.35)		
Edoxaban	2.19 (1.39–2.99)	0.68 (0.45–1.02)	0.0645
Apixaban	2.38 (1.71–3.05)	0.83 (0.59–1.16)	0.2731
Rivaroxaban	2.16 (1.69–2.63)	0.77 (0.57–1.03)	0.0732
Dabigatran	2.31 (1.85–2.83)	0.82 (0.61–1.10)	0.1845
Intracranial haemorrhage			
Warfarin	1.20 (0.86–1.55)		
Edoxaban	0.53 (0.21–1.09)	0.41 (0.18–0.90)	0.0274
Apixaban	0.56 (0.23–0.88)	0.46 (0.24–0.87)	0.0176
Rivaroxaban	0.64 (0.39–0.90)	0.53 (0.33–0.87)	0.0122
Dabigatran	0.61 (0.35–0.88)	0.51 (0.30–0.86)	0.0107
Major gastrointestinal bleeding			
Warfarin	1.19 (0.85–1.54)		
Edoxaban	0.38 (0.12–0.88)	0.27 (0.11–0.69)	0.0060
Apixaban	0.32 (0.12–0.67)	0.26 (0.11–0.59)	0.0013
Rivaroxaban	0.75 (0.48–1.03)	0.63 (0.40–1.01)	0.0549
Dabigatran	0.92 (0.60–1.24)	0.77 (0.49–1.21)	0.2584

Standard-dose NOAC: edoxaban 60 mg/day; apixaban 5 mg bid, rivaroxaban 20 mg/day, and dabigatran 150 mg bid) *versus* warfarin.
bid, twice daily; NOAC, non-vitamin K antagonist oral anticoagulant.

was significantly lower with each NOAC than with warfarin and was comparable between the four NOACs. All NOACs had a lower risk of major bleeding than warfarin, with edoxaban and apixaban showing a statistically significant lower risk of major GI bleeding than warfarin (Table 5).[25]

PPI cotherapy and risk of GI bleeding

In clinical practice, clinicians may consider whether proton pump inhibitor (PPI) cotherapy would reduce the risk of GI bleeding in Asian patients. Using real-world data from South Korea, the effect of PPI cotherapy on the risk of GI bleeding was evaluated in 42,048 Asian patients with AF and a prior history of upper GI bleeding who were treated with OACs (warfarin, rivaroxaban, dabigatran, apixaban or edoxaban).[26] Amongst patients who did not receive PPI cotherapy, compared with warfarin, the risk of major GI bleeding was lower with edoxaban and apixaban and comparable with rivaroxaban and dabigatran. Relevant to PPI non-use, PPI cotherapy was associated with a significantly lower (with rivaroxaban and warfarin groups) or comparable risk (dabigatran, apixaban and edoxaban groups) of major GI bleeding; in clinical practice, PPI cotherapy may reduce the risk of GI bleeding.

Risk of cancer in patients with AF

Although the risk of major GI bleeding is paramount in the management of patients with incident AF, evidence suggests that patients with AF may be at a higher risk of GI tract cancer than the general population, particularly due to the presence of coexisting risk factors.[27] In a population-based cohort study in Taiwan in 332,555 patients with AF with no past history of cancer, during follow-up, there were 22,911 incident cancers (1.65%/year). Factors significantly associated with the development of cancer in patients with AF were age ≥65 years, male sex, hypertension, diabetes, chronic pulmonary disease and liver cirrhosis.[27]

In patients receiving OACs, GI bleeding can be a result of occult malignancies. Data from the large global RELY trial in 18,113 patients with AF showed that, amongst 546 major GI bleeding events, 44 (8.1%, ~1 of every 12) events were associated with an occult cancer.[28] Colorectal cancer accounted for 80% of all the cancers that were identified. Statistically more colorectal cancer-associated major GI bleeding events were reported in the dabigatran group (30/34) than in the warfarin group (5/10) (p=0.02), whilst significantly more gastric cancer-associated major GI bleeding events were reported in the warfarin group (5/10) than in the dabigatran group (1/34) (p=0.001).

In a nationwide cohort study in Taiwan, amongst 10,845 patients with AF who received OACs and were hospitalized due to GI bleeding, incident GI cancers (n=290, 2.67%) were diagnosed in 1 of 37 patients within 1 year.[29] Significantly more patients treated with NOACs (1/26) were diagnosed with incident GI cancer than those treated with warfarin (1/41; p<0.001). Prudent examination for occult GI cancers is necessary in patients with AF with OAC-related GI bleeding.

Panel discussion

The following section summarizes the discussion amongst the panel members on the topics covered in the analysis of GI bleeding with NOACs for SPAF in Asian patients described above, with a focus on four main areas.

NOACs — disparities in the risk of GI bleeding between Asian and non-Asian patients with AF?

Key observations from clinical trials included variations in GI bleeding risk across NOACs and between Asian and non-Asian patients. Despite receiving the same dose, the trough concentration of edoxaban tends to be lower in Asian than in non-Asian patients with AF, and edoxaban exhibited a reduced risk of GI bleeding;[21] however, if patients are under-dosed following an intentional dose reduction, then efficacy may be affected. The panel discussed that the efficacy of edoxaban is maintained with dose reduction. A comparison across pivotal trials of the risk of ischaemic stroke in Asian and non-Asian patients treated with NOACs showed that, despite similar baseline $CHADS_2$ or CHA_2DS_2-VASc scores, the residual risk of ischaemic stroke was higher for Asian patients treated with dabigatran in the RELY trial,[13] with rivaroxaban in ROCKET AF,[14] and with apixaban in ARISTOTLE.[15] By contrast, in the ENGAGE trial,[17] the risk of ischaemic stroke was similar between Asian and non-Asian patients; the lower edoxaban plasma concentration observed in Asian patients did not result in lower clinical efficacy for SPAF.

Across the ENGAGE trials, patients on standard-dose edoxaban tended to have a higher risk of GI bleeding compared with warfarin.[19] Age can be a risk factor for GI bleeding and the risk of GI bleeding is associated with the edoxaban plasma concentration; hence, caution was advised when administering higher edoxaban doses to elderly patients. Nevertheless, many older patients have lower body weight and lower creatinine clearance and meet the criteria for dose reduction to edoxaban 30 mg/day, for which the risk of GI bleeding is relatively lower.

How does the risk of GI bleeding impact the treatment strategy with NOACs for AF management in the Asian context?

In Japan, there is an almost 70/30 division in the percentage use of the low-dose and standard-dose edoxaban

regimens.[22] According to data from the ETNA-AF trial,[22] Japanese patients with AF had the lowest body weight and many met the dose-reduction criteria, which may explain the higher prescription rate of edoxaban 30 mg/day in Japan.

Major GI bleeding is rarely encountered in routine clinical practice; haematuria is a more common observation. The definition for major GI bleeding in the four NOAC trials is based on International Society of Thrombosis and Hemostasis criteria,[30] which specify a drop in haemoglobin of 2 g/dL; other criteria specify a drop of >5 g/dL which, in the ENGAGE trial,[17] would classify most of the major GI bleeding events as mild. With a history of NOAC use in the absence of any major GI bleeding, experience with a NOAC antidote, in particular, the anti-FXa antidote, is scarce. Usually, a reversal agent is not used as it could reverse the coagulation effect too rapidly and expose the patient to a risk of an ischaemic event. If the patient is haemodynamically stable, stopping the NOAC, treating the bleeding and waiting several days until the bleeding has resolved, then reinitiating the NOAC, may be appropriate.[4] Compared with an intracranial bleed, a GI bleed is not considered to be a significant issue. A reversal agent is mainly used for an intracranial bleed or if a patient requires thrombolysis. GI bleeds are generally seen either with dabigatran or aspirin. In the clinic, major bleeds are not frequent, but a lot of bleeds are seen due to antiplatelet therapy use instead of anticoagulation.

Additionally, gastric symptoms, for example, gastritis, can be precursors for a bleed. With major GI bleeding, the nature of whether it is upper or lower GI bleeding is unknown, yet the pathophysiology is different. PPIs are often prescribed to prevent upper GI bleeds as they prevent gastric ulcers. Often, the main reason for upper GI bleeding is erosion into one of the major prominent vessels. If there is an untreated diverticular disease, acute diverticulitis or haemorrhoids, there could be pronounced GI bleeding, resulting in a drop in haemoglobin.

The panel discussed that, in a series of studies that assessed the distribution of GI bleeds with different NOACs, dabigatran was associated with more upper than lower GI bleeding, edoxaban with a mix of upper and lower, whereas rivaroxaban and apixaban tended to have more lower than upper GI bleeds. NOACs have different mechanisms of action,[6] and hence a different distribution of GI bleeds. Prior to a GI bleed, patients often have gastric symptoms if they are on dabigatran. PPIs are not effective, but a switch to a NOAC that has a lower propensity for upper GI bleeding events, such as edoxaban or apixaban, can dissipate the GI gastritis symptoms prior to a bleed.

Given that GI bleeding is higher amongst Asian than non-Asian patients with AF, should advice be provided on how to reduce the risk of GI bleeding? The panel concurred that GI bleeding is not the main concern. If a patient presents with GI bleeding, the concern is the risk of ischaemic events because the NOAC has to be interrupted to treat the bleeding, which places the patient at a high risk of ischaemic stroke. If there is grade 3 peptic ulcer disease or GI bleeding, a PPI can be prescribed together with a NOAC. Patients with stage III cancer on chemotherapy are at an increased risk for GI bleeding; in such situations, PPIs can be prescribed. Often, these patients can be started on low-dose edoxaban, which, if tolerated, can be increased to the standard dose. Dosing can be flexible – a physician can choose the appropriate dose based on decision-making at different times for the same patient.

A panel member advised that, for an anticoagulation-naive patient, he initially screens for a history of bleeding aside from the HAS-BLED score and a history of pre-existing/previous GI disease, both upper and lower. If previous GI disease is suspected, the patient is referred to a gastroenterologist to assess for cancer. If the risk factor for GI bleeding is correctible/curable, it is prudent to wait until this is achieved before starting low-dose or standard-dose NOAC; however, if the disease is not correctible, a lower NOAC dose is preferable. It is better to settle for a level of effectiveness that is comparable to that of warfarin rather than not provide a low-dose NOAC at all and leave the patient with a high $CHADS_2$-VASc risk unprotected.

What are the potential limitations and considerations in managing GI bleeding in Asian patients on NOACs for AF management?

There are some patients who lie in a grey zone, such as those undergoing chemotherapy or with a history of GI bleeding, that were not included in NOAC trials and for whom the guidelines do not provide dosing recommendations; hence, based on the clinician's judgement, a suitable dose should be chosen. For patients with AF well-represented in the NOAC trials, the gold standard is to follow on-label dosing and dose-reduction criteria to avoid under-dosing. A patient undergoing chemotherapy or with a history of GI bleeding should be prescribed a NOAC with up-titration to the standard dose, if possible.

Regarding the duration of PPI treatment when a patient is receiving antiplatelet therapy, generally, when a patient is on double antiplatelets, it is a routine to prescribe a PPI regimen. For those on a single antiplatelet, the tendency is to also prescribe PPIs. Once a patient is taken off two and given only one antiplatelet, PPI use may be stopped if there are no further gastric symptoms or there is a past history of GI bleeding.

Are major bleeds seen with combined antiplatelet therapy and anticoagulants? With advances in coronary interventions, triple therapy is hardly used currently and, if it is used, then aspirin use is limited to a week or a month. Dual therapy usually means clopidogrel plus NOACs, with which major clinically relevant bleeding is seldom seen.

Are concomitant medications a concern? Several guidelines, including those of the Asia Pacific Heart Rhythm Society (APHRS),[31] focus on the concomitant use of some medications. It is rare to have to maintain aspirin use together with an NOAC, unless the patient has just had a percutaneous coronary intervention. Nevertheless, stopping aspirin is sometimes overlooked or its use is unknown to the physician. Non-steroidal anti-inflammatory drugs are classified as a risk factor for bleeding in the HAS-BLED scoring scheme,[31] and it is recommended to avoid the use of aspirin if possible. Polypharmacy has been demonstrated to be a high risk for bleeding.[31]

When should NOAC treatment be resumed after a bleed? In general, no later than 5 days. There are no data regarding when to reinitiate NOACs, but there are data regarding warfarin, which can be initiated within 1–2 weeks after GI bleeding. Any later, then the patient may experience ischaemic events; earlier, and the patient may experience rebleeding. An attempt to reinitiate the NOAC after 3 days was advised, starting with a lower dose, such as edoxaban 30 mg/day, then if the patient is stable, titrate up to 60 mg/day. After a major bleed, two options can be considered: either use a lower dose if available or shift to another NOAC,[32] particularly for patients unwilling to stay on the same medication, even at a lower dose. When a surgeon or a gastroenterologist is involved, there is normally a discussion about risk-benefit and then a general acceptance and agreement about when to restart NOAC therapy.

What strategies can be implemented to improve the detection, monitoring and treatment outcomes of GI bleeding in NOAC-treated Asian patients with AF?

Predicting the bleeding and stroke risk for patients with AF is difficult and the difficulty in predicting bleeding is greater than that for a stroke. It is paramount to choose a NOAC with the least concern for GI bleeding for the patient based on the available data. Although it is not possible to accurately predict if someone is going to bleed, the risk can be minimized. For instance, for patients with gastritis, testing for *Helicobacter pylori* may be conducted and, if positive, eradication to lower the risk of related peptic ulcer disease can be considered. If the patient has symptoms, they could be sent for a gastroscopy.

A panel member asked whether the risk of GI bleeding is continuous over the duration of treatment or front loaded. Studies have reported a transient peak or higher risk of bleeding events at the initiation of OAC treatment.[33] Compared to those who encounter problems with the drug, patients who have been stable on OAC for years are less likely to experience bleeding events. The transient higher risk of bleeding events at the start of medication could be like a screening process that reveals underlying medical conditions that were previously unnoticed by the patient such as peptic ulcers. Most discontinuations of OAC treatment occur within a year of treatment initiation.

Major GI bleeds are very rarely encountered in routine clinical practice; haematuria is a more common observation, yet urine is not routinely checked for microscopic haematuria until gross haematuria is seen. At this point, antiplatelet and anticoagulant treatment is stopped and restarted after a period of at least 14 hours of no bleeding.[32] More urinary tract bleeding than GI bleeding is generally seen in the clinic, especially in elderly male patients with prostatitis or other urinary tract diseases. It is important to consider structural diseases, such as renal stones or cystitis, as well as cancer. Gross haematuria in elderly patients should be monitored closely, and platelet count and creatinine should be checked before adjusting anticoagulant dosage.

Regarding the edoxaban dosing regimen used in routine daily practice, the general consensus amongst the panel members was standard-dose edoxaban (60 mg/day). Factors reported to influence dosing include weight and a concern that, when FXa inhibitors are inappropriately under-dosed, a higher risk of ischaemic stroke may not be seen but signals of cardiovascular or all-cause mortality may be seen. Care is required to not under-dose inappropriately, whether for a short or protracted period of time, before titrating up to 60 mg.

The dosing terminology was clarified:

- Standard-dose (also referred to as high-dose) edoxaban: 60 mg, as specified by the label.
- Low-dose edoxaban: 30 mg, as specified for patients who meet specific criteria for dose reduction, for example, low weight.
- Off-label low-dose edoxaban: 30 mg or lower, for patients who do not meet the specific criteria for dose reduction.

The key observations from the discussion earlier included variations in GI bleeding risk across NOACs and between Asian and non-Asian patient populations. Despite lower plasma concentrations in Asians, edoxaban exhibited a reduced risk of GI bleeding. However, caution was

advised when administering higher edoxaban doses to elderly patients. Additionally, the panel emphasized on the significance of GI bleeding, notably its potential to disrupt NOAC treatment and elevate the risk of ischaemic events, especially in high-risk cases. Tailored approaches, guided by individual bleeding histories and underlying GI conditions, were advocated. The panel also highlighted a transient peak in bleeding risk at the onset of oral anticoagulant treatment, which could serve as an early detection opportunity for underlying medical issues. Routine monitoring for urinary tract bleeding, particularly in elderly patients, was underscored.

Conclusions

In conclusion, in the last decade, OAC prescription rates for SPAF have increased in Asia, largely driven by the introduction of NOACs, which offer a favourable risk-benefit profile and convenience relative to warfarin. Data from the large, randomized ENGAGE TIMI-AF and the real-world Global ETNA-AF registry clearly show a lower risk of major GI bleeding in Asian than in non-Asian patients with AF treated with edoxaban, which were associated with a lower plasma concentration. Clinical characteristics may be associated with the risk of GI bleeding events in patients with AF treated with OACs, and attention should be paid to occult GI cancer when managing OAC-related bleeding. Nevertheless, GI bleeding risk varies amongst NOACs, emphasizing the importance of diligent patient assessment, dosage selection and vigilant monitoring. Edoxaban emerged as a viable option with a low GI bleeding risk profile in Asian patients, supporting its continued clinical utilization; hence, in clinical practice, at-risk patients with AF should not be left untreated.

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Correspondence: Alejandro Bimbo Diaz, Department of Neurosciences and Behavioural Medicine, University of Santo Tomas Hospital, Espana Street, Manila 1108, Philippines. Email: afdiaz@ust.edu.ph

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