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CASE SERIES

Early experiences with edoxaban for stroke prevention in atrial fibrillation in the Southeast Asia region

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Abstract

Edoxaban, a once-daily, direct-acting oral anticoagulant, is approved to prevent stroke or systemic embolism in non-valvular atrial fibrillation (NVAF) and treat venous thromboembolism. The clinical benefit of edoxaban for stroke prevention in Asian patients with NVAF has been demonstrated in clinical and real-world studies. We share early clinical experiences with once-daily edoxaban and discuss its evidence-based use in patients with NVAF in Southeast Asia through several cases of patients at high risk, including frail patients, elderly patients with multiple comorbidities and patients with increased bleeding risk. These cases demonstrate the effectiveness and safety of once-daily edoxaban in patients with NVAF in Southeast Asia.

Keywords: atrial fibrillation, edoxaban, Southeast Asia, stroke.

Citation

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Introduction

With the ageing of the world population, the incidence and prevalence of atrial fibrillation (AF) have been increasing over the past decade, posing a significant global health challenge. The estimated worldwide prevalence of AF in 2017 was 46.3 million,[1] with a future projection of a more than 60% increase by 2050.[2] With a larger and rapidly ageing population in Asia, about 72 million people will be diagnosed with AF by 2050, with approximately 3 million experiencing AF-related stroke.[3]

Stroke prevention with oral anticoagulants is the cornerstone of AF management.[4] Warfarin has been widely used for many years given its significant effect in reducing the risk of ischaemic stroke compared with placebo.[5] However, warfarin presents with several practical limitations, such as a slow onset of action, narrow therapeutic margins, several drug and food interactions, and the need for frequent laboratory monitoring, which may lead to less than optimal treatment or its discontinuation.[6,7] This is especially more severe in Asia due to the reduced availability of good medical facilities for monitoring and frequent use of traditional medications, which may interact with warfarin.

Direct-acting oral anticoagulants (DOACs) have emerged as alternatives to warfarin, offering comparable efficacy and superior safety without the need for routine monitoring and with fewer food and drug interactions.[8] Large randomized controlled trials (RCTs) in patients with AF have demonstrated that, when compared with warfarin, DOACs are at least non-inferior in preventing thromboembolic complications, with a lower incidence of severe bleeding, especially intracranial bleeding.[9–12] International and regional guidelines and consensus from the American College of Cardiology/American Heart Association and Heart Rhythm Society, the European Society of Cardiology, the Asia Pacific Heart Rhythm Society and the Asian Pacific Society of Cardiology have recommended the use of DOACs over warfarin for stroke prevention in non-valvular AF (NVAF).[13–16]

Edoxaban is a selective, direct inhibitor of coagulation factor Xa.[17] Once-daily edoxaban is the fourth DOAC to gain approval for the prevention of stroke or systemic embolism in NVAF and for the treatment of venous thromboembolism.[18,19] Edoxaban approval was based on the data from the pivotal ENGAGE AF-TIMI 48 trial.[12] To complement the findings from the pivotal trial, the largest global real-world study of edoxaban, the Edoxaban Treatment in routiNe clinical prActice for patients with non-valvular atrial fibrillation (ETNA-AF) program, is currently ongoing.[20] Additionally, other real-world studies of edoxaban (including observational and meta-analysis studies) in the Asian population provide further evidence for the use of edoxaban in clinical practice.[21–26]

As edoxaban has only been recently approved in Southeast Asia (SEA), there is limited clinical experience with edoxaban in this region. As such, this article aims to share early clinical experiences with edoxaban and discuss its evidence-based use and benefit in improving outcomes in patients with NVAF in SEA. The cases described herein will add to the real-world evidence for edoxaban and further define its place in the management paradigm for NVAF.

Methods

Seven real-world AF cases managed with edoxaban in the SEA region (Malaysia, the Philippines and Singapore) are described in this article. The authors presented and discussed these cases at an expert meeting held virtually in May 2022. Patient details have been de-identified such that the identity of the patients could not be ascertained in any way. The authors are cardiologists and neurologists practicing in the SEA region who manage patients with AF in their clinical practice.

To summarize the relevant clinical trial and real-world studies of edoxaban for stroke prevention in NVAF, a targeted literature review was conducted using the search terms "edoxaban", "ENGAGE AF-TIMI 48", "ETNA-AF", "real-world", "clinical practice" and "Asian". Relevant publications evaluating the efficacy and safety of edoxaban, particularly in Asian patients and those at high risk, were included in this article.

Case reports

Edoxaban has become available in Malaysia, the Philippines and Singapore since mid-2021. The real-world cases described here demonstrate the early clinical experiences and benefits of using edoxaban in managing specific patient populations with NVAF in this region. Table 1 summarizes key information about the clinical cases presented.

Case 1 – AF with frailty

A 65-year-old right-handed man was admitted within 2 hours of sudden onset of incoherent speech. He was an ex-smoker with essential tremor, AF, hypertension and gastritis and had had a mild stroke 5 years earlier. He had a family history of stroke – his father had a stroke at the age of 50+ years. The patient had experienced occasional dizziness and falls; he was not keen to take any medications. He was frail (FRAIL score of 3/5). Upon examination, he had well-controlled blood pressure with a regular pulse rate. He was dysphasic; had no gaze deviation, anopia or neglect; had full eyes, palate and tongue movements with a drooped right angle of mouth; had normal limb tone, power, reflexes and coordination; and had normal pain sensation. He was diagnosed with left cortical stroke. His brain computed tomography (CT) showed an old right occipital infarct and no hyperacute changes. He had a normal brain CT angiogram and normal electrocardiogram (ECG). Telemetry confirmed AF. His echocardiogram showed a mildly dilated left atrium. He subsequently received intravenous recombinant tissue plasminogen activator therapy, as he was within the thrombolysis window, and his dysphasia improved. His other medications included atorvastatin 20 mg every night (ON), amiodarone 200 mg three times a day, bisoprolol 2.5 mg every morning (OM) and piracetam 2.4 g twice daily (BID). He also received speech therapy and physiotherapy. His CHA_2DS_2-VASc score was 4, and his HAS-BLED score was 3. A detailed discussion on antithrombotic therapy was conducted with the patient. He wanted an effective medication but was not keen on one that required frequent dosing, preferring a once-daily (OD) formulation. He was also concerned about his falls and was fearful of bleeding if he were to sustain further injuries after a fall, wanting a proven medication. OD edoxaban 60 mg was prescribed for secondary stroke prevention. Medications to control lipid levels and arrhythmia were continued. The patient was closely followed up in the clinic. There were no side-effects or recurrence of cerebrovascular events.

This patient had a history of stroke and was diagnosed with left cortical stroke at admission. He had a history of falls and was considered frail based on a simple frailty screening tool.[27] Meta-analysis data suggests that DOACs have broadly similar efficacy in secondary stroke prevention.[28] A sub-analysis of the ENGAGE AF-TIMI 48 trial has demonstrated that edoxaban is at least as effective and safer than warfarin in those with prior stroke or transient ischaemic attack (TIA).[29] In patients at an increased risk of falls, edoxaban was associated with a greater absolute reduction in severe bleeding events and mortality compared with warfarin.[30] Furthermore, a *post hoc* analysis of the ENGAGE AF-TIMI 48 trial found

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Table 1. Summary of real-world cases of non-valvular atrial fibrillation from South-East Asia.

	Patient profile	Age, sex	Previous history	Current presentation, examination and diagnosis	Concurrent medications	Current treatment for stroke prevention	Outcomes of treatment for stroke prevention (efficacy and safety)
Case 1	AF with frailty	65, M	• Ex-smoker with essential tremor; AF; hypertension and gastritis; had mild stroke 5 years earlier • His father had stroke in his late 50s • Did not want to take any medications • Experiences occasional dizziness and has had falls	• Body weight: 75kg • CrCl (Cockcroft–Gault): 79 mL/min • Admitted for incoherent speech; FRAIL score[a] 3/5 • Well-controlled BP; regular pulse rate • Dysphasic; left cortical stroke • Brain CT: old right occipital infarct • Telemetry confirmed AF; echocardiogram showed mildly dilated left atrium • Received IV rTPA and dysphasia improved • CHA_2DS_2-VASc: 4; HAS-BLED: 3	Atorvastatin 20 mg ON; amiodarone 200 mg TDS; bisoprolol 2.5 mg OM and piracetam 2.4 g BID; P-glycoprotein inhibitor: atorvastatin, amiodarone	Edoxaban 60 mg OM	Follow-up period: 12 months No side-effects or recurrence of cerebrovascular events
Case 2	AF with hemiplegia due to ICH	72, M	• Hypertension • Chronic AF maintained on aspirin (80 mg) and triflusal (300 mg), later switched to dabigatran 150 mg BID • Continued with aspirin 80 mg OD	• Body weight: 58kg • CrCl (Cockcroft–Gault): 56.4 mL/min • Admitted to ED due to right hemiplegia • Cranial CT: left capsule-ganglionic hematoma with intraventricular extension • Expressive dysphasia; dysarthria; right central facial palsy; grade 1-2/5 MRC motor strength right upper extremity and right lower extremity; right hemisensory impairment; NIHSS: 10 • ECG confirmed AF • CHA_2DS_2-VASc: 3; HAS-BLED: 2	Irbesartan 150 mg OD; amlodipine 5 mg OD; P-glycoprotein inhibitor: none	Edoxaban 30 mg OD	Follow-up period: 21 months Had good compliance with no reported adverse events; good outcome of mRS 1 on 3rd month of follow-up; remains well

(*Continued*)

Table 1. (Continued)

	Patient profile	Age, sex	Previous history	Current presentation, examination and diagnosis	Concurrent medications	Current treatment for stroke prevention	Outcomes of treatment for stroke prevention (efficacy and safety)
Case 3	Elderly with AF and multiple comorbidities	85, F	• AF; hypertension; diabetes mellitus; diabetic retinopathy • Has frequent falls with a history of left wrist fracture	• Body weight: 45kg • CrCl (Cockcroft–Gault): 30 mL/min • CHA_2DS_2-VASc: 5	Insulin therapy; amlodipine 10 mg OD; P-glycoprotein inhibitor: none	Edoxaban 30 mg OD	Follow-up period: 18 months Had responded well and no stroke or any bleeding events
Case 4	Elderly with AF and multiple comorbidities	83, M	• Hypertension; hyperlipidaemia; benign prostatic hypertrophy • Experienced postural giddiness (2018) • Admitted to hospital for chest discomfort and received clopidogrel (2019) • Continued treatment with clopidogrel and statin (2020)	• Body weight: 68.3 kg • CrCl (Cockcroft–Gault): 47 mL/min • Admitted due to feeling unwell • AF detected • BP: 130/80 mmHg with irregular heart rate (100) but not in heart failure • Creatinine level: 101 µmol/L • CHA_2DS_2-VASc:3; HAS-BLED: 3	Amiodarone 100 mg OD; bisoprolol 5 mg OD; amlodipine/valsartan 5/80 mg OD; atorvastatin 20 mg ON; P-glycoprotein inhibitor: atorvastatin, amiodarone	Edoxaban 30 mg OD	Follow-up period: 36 months No bleeding events and side-effects reported
Case 5	Elderly with AF and multiple comorbidities	88, M	• Coronary artery disease; hypertension; dyslipidaemia and chronic obstructive pulmonary disease • Mild renal impairment (2020) • First degree atrioventricular block and right bundle branch block (2020) • Sick sinus syndrome (2021) • Heart failure with preserved ejection fraction (2021)	• Body weight: 84 kg • CrCl (Cockcroft–Gault): 55 mL/min • CHA_2DS_2-VASc:4; HAS-BLED: 2 • Ambulatory ECG: multiple sinus pauses (2021) • Left bundle branch block pacing performed (2021) • AF detected on remote home monitoring (lasting for 12 hours)	Famotidine 40 mg OM; dronedarone 200 mg BD; frusemide 20 mg OM; rosuvastatin 20 mg OM; ezetimibe 10 mg ON; sacubitril/valsartan 75 mg BD; empagliflozin 10 mg OM; P-glycoprotein inhibitor: dronedarone	Edoxaban 30 mg OD	Follow-up period: 19 months Remains well with no evidence of any bleeding events

	Patient profile	Age, sex	Previous history	Current presentation, examination and diagnosis	Concurrent medications	Current treatment for stroke prevention	Outcomes of treatment for stroke prevention (efficacy and safety)
Case 6	AF with increased bleeding risk	70, F	• Hypertension; hyperlipidaemia • Mitral valve repair (2016); right parietal infarct (2017) and treated with clopidogrel 75 mg OM • AF detected (2020); received rivaroxaban 15 mg OM; experienced gross haematuria and had cystitis • Switched to apixaban 2.5 mg BID but unable to tolerate • OGD: mild gastritis and gastric polyps • Retried apixaban post-OGD; had bleeding from polypectomy site • Successful AF ablation; received rivaroxaban 15 mg OM but dose reduced to EOD due to intermittent haematuria	• Body weight: 46.1 kg • CrCl (Cockcroft–Gault): 81 mL/min • Presented with a change in behaviour and short-term memory lapse • Experienced new stroke despite on rivaroxaban 15 mg EOD and was in sinus rhythm • CHA_2DS_2-VASc:5; HAS-BLED: 4	Sotalol 40 mg BID; losartan 50 mg OM; esomeprazole 40 mg OD; P-glycoprotein inhibitor: none	Edoxaban 60 mg OM but dose reduced to 30 mg OM due to decrease in body weight (<50 kg)	Follow-up period: 19 months Had tolerated edoxaban 30 mg well. No reported episodes of bleeding tendency or gross haematuria
Case 7	AF with increased bleeding risk	72, M	• Ischaemic heart disease; diabetes mellitus; hypertension; chronic kidney disease • History of cerebral vascular accident	• Body weight: 56 kg • CrCl (Cockcroft–Gault): 28 mL/min • Palpitation and abnormal ECG after surgery for gangrenous diabetic foot ulcer	Valsartan/amlodipine (80/5mg) 1 tab OD; rosuvastatin 10 mg ON; gliclazide MR 60 mg OD;	Edoxaban 30 mg OD	Follow-up period: 11 months Remains well without any adverse events

(*Continued*)

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Table 1. (Continued)

	Patient profile	Age, sex	Previous history	Current presentation, examination and diagnosis	Concurrent medications	Current treatment for stroke prevention	Outcomes of treatment for stroke prevention (efficacy and safety)
			• Recent history of upper gastrointestinal bleeding (OGD: D1 ulcer)	• Haemoglobin: 10.2 gm/dL • ECG: left ventricular ejection fraction 30%, mild dilated left ventricle/left atrium • Coronary angiography: patent grafts, severe three-vessel disease • Foot X-ray: osteomyelitis of digits • CHA_2DS_2-VASc:6; HAS-BLED: 5	dapagliflozin 10 mg OD; metformin XR 1 g OD; bisoprolol 2.5 mg OD; P-glycoprotein inhibitor: none		

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[a]Frailty was based on Fatigue, Resistance, Ambulation, Illness, and Loss (FRAIL) screening score.[27]

AF, atrial fibrillation; BID, twice daily; BP, blood pressure; CrCl, creatinine clearance; CT, computed tomography; ECG, electrocardiogram; ED, emergency department; EOD, every other day; ICH, intracerebral haemorrhage; IV, intravenous; MR, modified release; MRC, Medical Research Council; mRS, modified Rankin score; NIHSS, NIH stroke scale/score; OD, once-daily; OGD, oesophagogastroduodenoscopy; OM, every morning; ON, every night; rTPA, recombinant tissue plasminogen activator; TDS, three times daily; XR, extended release.

that edoxaban was as effective as warfarin across different frailty statuses (fit, pre-frailty, mild-to-moderate frailty and severe frailty) and had lower rates of bleeding compared with warfarin, except in those with severe frailty.[31] The concomitant use of potent P-glycoprotein inhibitors, such as dronedarone, necessitates dose reduction of edoxaban.[32] However, in the case of amiodarone, edoxaban 60 mg resulted in a significant reduction in ischaemic events with a favourable bleeding profile and minimal concern for safety, though the plasma level of edoxaban was increased.[33] Atorvastatin was also shown to have minimal effects on edoxaban exposure.[34] As such, there is no concern with the concomitant use of edoxaban 60 mg and amiodarone and atorvastatin in this patient.

Case 2 – AF with hemiplegia due to ICH

A 72-year-old man was admitted to the emergency department with right hemiplegia. Cranial CT showed left capsule-ganglionic haematoma with intraventricular extension. His weight was 58 kg, and he had a history of hypertension. The patient had chronic AF and was previously maintained on aspirin (80 mg) and triflusal (300 mg), which was later switched by his cardiologist to dabigatran 150 mg BID as triflusal was no longer available. A different physician continued prescribing aspirin (80 mg OD). He had been taking combined DOAC and aspirin for some time prior to his admission to the emergency department. Upon admission, the patient had expressive dysphasia, dysarthria, right central facial palsy, grade 1–2/5 Medical Research Council scale for motor strength, right upper extremity and right lower extremity, and right hemisensory impairment. His NIH stroke scale/score (NIHSS) was 10. His ECG confirmed AF. His CHA_2DS_2-VASc score was 3, and his HAS-BLED score was 2. His creatinine clearance (CrCl) was 56.4 mL/min. He was admitted to the hospital for 15 days. During hospitalization, he received general medical and organized stroke care, including physical therapy and rehabilitation. A repeat plain cranial CT scan was conducted on day 12, which showed clearing of the intracerebral haemorrhage (ICH). Edoxaban 30 mg OD was initiated after 2 weeks post-ICH stroke and clearing of ICH on follow-up cranial CT exam, as his body weight was 59 kg at treatment initiation. After discharge, he was followed through telemedicine once a week, then twice a month and later monthly. He had good compliance with treatment with no reported adverse events. The patient showed good outcomes, achieving a modified Rankin score of 1 at subsequent follow-ups through telemedicine and clinic visits.

The patient, in this case, experienced hemiplegia secondary to ICH from previous combined DOAC and antiplatelet therapy. With the clearing of haemorrhage on repeat CT 2 weeks after the ictus, edoxaban 30 mg OD was initiated 14 days post-ICH, as his body weight was <60 kg at the point of reinitiating anticoagulation. Existing observational data supports the benefit of restarting anticoagulants in patients with AF after ICH to prevent thromboembolic events, depending on the cause of ICH; restarting of the anticoagulant should be considered after careful assessment of benefits and risks in each patient.[15,35] However, the optimal timing for restarting anticoagulants remains uncertain — guidelines and expert input suggest avoiding anticoagulant or antithrombotic agents for at least 2–8 weeks after ICH.[15,35,36] The patient responded well to edoxaban with good compliance and reported no adverse events.

Cases 3–5 – elderly patients with AF and multiple comorbidities

Case 3 describes an 85-year-old woman who was 45 kg in weight and experienced frequent falls with a history of fracture of the left wrist. She has a history of AF, hypertension, diabetes mellitus and diabetic retinopathy. Her CHA_2DS_2-VASc score was 5, and her CrCl was 30 mL/min. Edoxaban 30 mg OD was prescribed, as the patient had a high CHA_2DS_2-VASc score and a high risk of falls. The patient responded well and had no stroke or any bleeding events following edoxaban use.

Case 4 involves an 83-year-old man who was admitted for generally feeling unwell — AF was detected at this admission. He was 68.3 kg and had a history of hypertension, dyslipidaemia and benign prostatic hypertrophy. In 2018, he experienced postural giddiness, which was managed by adjusting his antihypertensive medications. In 2019, he was admitted to the hospital for chest discomfort, and clopidogrel was initiated. He had his follow-up and tests in 2020 and continued treatment with clopidogrel and a statin. One month after his current admission, blood pressure was 130/80 mmHg with an irregular heart rate (100), but he was not in heart failure. His creatine level was 101 µmol/L (CrCl 47 mL/min). His CHA_2DS_2-VASc score was 3, and his HAS-BLED score was 3. He was on concomitant medications: amiodarone 100 mg OD, bisoprolol 5 mg OD, amlodipine/valsartan 5/80mg OD and atorvastatin 20 mg ON. Since the patient was concerned about the risk of stroke, edoxaban 30 mg OD was prescribed in accordance with the recommended dosing criteria of edoxaban. He did not have any side-effects or any bleeding events following edoxaban use.

Case 5 describes an 88-year-old man with multiple comorbidities — coronary artery disease (percutaneous coronary intervention in 2005 and repeated for in-stent restenosis in 2020), hypertension, dyslipidaemia and chronic obstructive pulmonary disease. He had mild renal impairment (creatinine 134 µmol/L in 2020). In

September 2020, Holter monitoring showed first-degree atrioventricular block and right bundle branch block. In June 2021, he was diagnosed with heart failure with preserved ejection fraction. His CrCl was 55 mL/min in July 2021. His CHA_2DS_2-VASc score was 4. An ambulatory ECG in September 2021 showed multiple sinus pauses related to sick sinus syndrome. Left bundle branch block pacing was conducted in late September 2021. In October 2021, AF, which lasted for 12 hours, was detected on remote home monitoring. His HAS-BLED score was 2. His medication was switched from clopidogrel to edoxaban 30 mg OM. His other medications included famotidine 40 mg OM, dronedarone 200 mg BID, frusemide 20 mg OM, rosuvastatin 20 mg OM, ezetimibe 10 mg ON, sacubitril/valsartan 75 mg BID and empagliflozin 10 mg OM. The patient has remained well with no evidence of bleeding whilst on edoxaban.

The patients with AF in Cases 3, 4 and 5 were very elderly (>80 years old), with mild-to-moderate renal impairment and multiple comorbidities requiring polypharmacy. Edoxaban demonstrated similar efficacy with warfarin in the elderly population (≥75 years) in the ENGAGE AF-TIMI 48 trial but with a significant reduction of major bleeding.[37] As such, edoxaban provides greater safety in the elderly population compared with warfarin. These patients were prescribed OD edoxaban 30 mg in accordance with dosing recommendations – the recommended edoxaban dosing for patients with CrCl 15–50 mL/min is 30 mg.[32] The clinical benefit and safety of edoxaban compared with warfarin were also seen in patients with moderate renal function (CrCl 30–50 mL/min).[38] Additionally, the patient in Case 3 also had low body weight (45 kg) – a sub-group analysis of the ENGAGE AF-TIMI 48 trial has shown that edoxaban had similar efficacy as warfarin in patients with body weight ≤55 kg but with a more favourable safety profile in terms of major bleeding.[39] The patient in Case 5 was receiving dronedarone concomitantly, which could increase edoxaban exposure and thus requires dose reduction to reduce the potential risk of bleeding.[34] Furthermore, rivaroxaban is not recommended for concomitant use with dronedarone.[40]

Case 6 and 7 – AF with increased bleeding risk

Case 6 describes a 70-year-old woman with hypertension and dyslipidaemia. She had undergone mitral valve repair in 2016. She first presented with a right parietal infarct in 2017 and was treated with clopidogrel as there was no documented AF. AF was first documented in September 2020, and her treatment was switched to rivaroxaban 15 mg OM. However, the patient was admitted for gross haematuria in October 2020 and was diagnosed with cystitis. Her treatment was then switched to apixaban 2.5 mg BID as she was concerned about recurrent haematuria. However, she had gastric side-effects and was unable to tolerate apixaban. Her oesophagogastroduodenoscopy (OGD) showed mild gastritis and gastric polyps. She tried apixaban again after OGD but experienced bleeding from the polypectomy site. Her ECG indicated fast AF; she then underwent successful AF ablation. Rivaroxaban 15 mg was initiated post-ablation but had to be administered every alternate day as the patient continued to experience intermittent haematuria. The patient remained well until October 2020, when she presented to the clinic with a change in behaviour and memory lapse. She was found to have a new stroke despite being in sinus rhythm and on rivaroxaban 15 mg every alternate day. Her CHA_2DS_2-VASc score was 5, and her HAS-BLED score was 4. The patient received edoxaban 60 mg OM after her stroke. She tolerated the treatment well but needed a dose reduction to 30 mg OM as her weight subsequently dropped to below 50 kg. The patient has since remained well, with no new episodes of TIA or new neurological deficits. She did not report any episodes of bleeding or haematuria since switching to edoxaban.

Case 7 is a 72-year-old man who presented with a diabetic foot ulcer (gangrenous fourth and fifth digits) and underwent surgery. Post-surgery, he experienced palpitations and an abnormal ECG. He had multiple comorbidities: ischaemic heart disease with coronary artery bypass surgery in 2009; diabetes mellitus and hypertension with chronic kidney disease; history of cerebral vascular accident (with residual right-sided hemiparesis); and a recent history of upper gastrointestinal (GI) bleeding (OGD: D1 ulcer). His CrCl was 28 mL/min, and the haemoglobin level was 10.2 gm/dL. ECG showed a reduced left ventricular ejection fraction of 30% with mild dilated left ventricle/left atrium and global hypokinesia. A recent coronary angiography revealed patent grafts with underlying severe three-vessel disease. His foot X-ray showed osteomyelitis of the digits. In summary, his CHA_2DS_2-VASc score was 6, and HAS-BLED score was 5. He had moderate renal impairment, complications from diabetes, poor cardiac function, and a history of bleeding (upper gastrointestinal tract) with mild anaemia. The patient was managed with edoxaban 30 mg OD and remains well without any adverse events.

Cases 6 and 7 describe patients with AF with a prior history of bleeding. The patient in Case 6 had experienced bleeding complications and gastric side-effects with apixaban and rivaroxaban. Despite continuing with rivaroxaban at a reduced dose post-AF ablation, the patient experienced a stroke. Anticoagulant therapy is generally continued for 2 months following AF ablation, and a decision to continue anticoagulant therapy beyond this period depends on the risk of stroke.[15] As such, contin-

uing DOAC treatment in this patient, who remained at high risk despite successful AF ablation, was warranted. Compared with warfarin, edoxaban has been associated with a reduced risk of stroke and major bleeding in the real-world Asian population.[22] In the head-to-head comparison between edoxaban and rivaroxaban in real-world Asian patients, edoxaban showed overall comparable outcomes in terms of efficacy and safety but tended to be associated with a lower GI bleeding risk compared with rivaroxaban albeit this was not statistically significant.[23] Given that the patient had a history of bleeding with other DOACs and experienced a new stroke despite being on rivaroxaban, edoxaban is a reasonable option for this patient, and she was managed with edoxaban 30 mg according to the dose reduction criteria.

The patient in Case 7 had a prior stroke, a CHA_2DS_2-VASc score of 6, and a HAS-BLED score of 5, with multiple comorbidities and moderate renal impairment. Despite the high bleeding risk, it was necessary to prescribe DOAC in this patient for secondary prevention of stroke. To reduce the burden of polypharmacy, an OD dose of DOAC was preferred. The ENGAGE AF-TIMI 48 trial showed that edoxaban demonstrated a 20% relative risk reduction of major bleeding and a similar risk of upper GI bleeding compared with warfarin.[12] In real-world Asian patients with NVAF, OD edoxaban demonstrated a lower rate of ischaemic stroke and a lower rate of GI bleeding and major bleeding compared with OD rivaroxaban,[24] rendering edoxaban a suitable option in this patient.

Review

Table 2 summarizes the clinical data of edoxaban from the pivotal ENGAGE AF-TIMI 48 trial and its sub-group analyses of patients at high risk and Asian patients. The ENGAGE AF-TIMI 48 trial, a large, randomized, double-blind, multicentre, placebo-controlled trial, demonstrated that edoxaban 60/30 mg (high-dose edoxaban regimen) was non-inferior to warfarin for the prevention of stroke and systemic embolism, and was superior to warfarin in reducing the risk of major bleeding (Table 2).[12] In the trial, edoxaban dose reduction by half was required for CrCl of 30–50 mL/min, or body weight ≤60 kg, or concomitant use of potent P-glycoprotein inhibitors (i.e. verapamil, quinidine or dronedarone).

Table 2. Clinical data from ENGAGE AF-TIMI 48 trial and sub-group analyses of patients at high risk and Asian patients.

Patient population	Efficacy (stroke/SEE) HR (95% CI; *p* value)		Safety (major bleeding) HR (95% CI; *p* value)	
	HDER *vs* warfarin	LDER *vs* warfarin	HDER *vs* warfarin	LDER *vs* warfarin
Main analysis				
Modified intention-to-treat[12]	0.79 (0.63–0.99; <0.001[a])	1.07 (0.7–1.31; 0.005[a])	0.80 (0.71–0.91; <0.001)	0.47 (0.41–0.55; <0.001)
Sub-group analyses				
East Asian patients[41]	0.53 (0.31–0.90; 0.02)	0.98 (0.63–1.54; 0.93)	0.61 (0.41–0.89; 0.011)	0.34 (0.21–0.54; <0.001)
Asian patients[42]	0.74 (0.51–1.08)	1.03 (0.73–1.46)	0.77 (0.56–1.06)	0.37 (0.25–0.55)
Elderly (≥75 years)[37]	0.83 (0.66–1.04)	1.12 (0.91–1.37)	0.83 (0.70–0.99)	0.47 (0.38–0.58)
Increased risk of falling[30]	0.96 (0.53–1.75)	0.84 (0.45–1.58)	0.96 (0.59–1.56)	0.56 (0.31–1.00)
Low body weight (≤55 kg)[39]	1.08 (0.61–1.88; 0.8)	1.03 (0.59–1.79; 0.92)	0.55 (0.31–0.97; <0.05)	0.27 (0.13–0.54; <0.0005)
Moderate renal impairment (CrCl 30–50 mL/min)[38]	0.87 (0.65–1.18; 0.37)	–	0.76 (0.58–0.98; 0.036)	–
Prior stroke/transient ischaemic attack[29]	0.86 (0.67–1.09; 0.20)	1.10 (0.88–1.38)	0.84 (0.67–1.06; 0.14)	0.52 (0.4–0.67)
Frail[b] (mild-moderate frailty)[31]	0.84 (0.61–1.15)	1.17 (0.87–1.56)	0.75 (0.57–0.98)	0.47 (0.35–0.64)

[a]Non-inferiority; [b]Unadjusted HR compared with warfarin.
CrCl, creatinine clearance; HDER, high-dose edoxaban regimen (60/30 mg dose reduced); LDER, low-dose edoxaban regimen (30/15 mg dose reduced); SEE, systemic embolic event.

The efficacy of edoxaban compared with warfarin in terms of risk reduction of stroke or systemic embolism was also seen consistently across various sub-groups of patients at high risk, including in patients who are elderly (≥75 years),[37] with moderate renal impairment (CrCl 30–50 mL/min),[38] with low body weight (≤55 kg),[39] with increased risk of falling,[30] frail[31] and with prior stroke/TIA.[29] Furthermore, edoxaban demonstrated a more favourable safety profile compared with warfarin in these patients who were at high risk.[29–31,37–39] A recent comprehensive secondary analysis of 12 high-risk sub-groups of patients in the ENGAGE AF-TIMI 48 trial supports the favourable net clinical outcomes with both edoxaban regimens compared with warfarin in these patients.[43] Higher-dose edoxaban compared with warfarin was effective in stroke prevention and was associated with a favourable safety profile in Asian[41] and East Asian populations[40] of the ENGAGE AF-TIMI 48 trial.

Complementing the findings from the clinical trial, data from the ongoing real-world ETNA-AF program thus far confirm the safety and effectiveness of edoxaban in real-world settings (Table 3). The 1-year follow-up global analysis of the ETNA-AF program reveals low event rates for stroke and bleeding in patients with AF prescribed with edoxaban in routine clinical practice.[44] Similarly, low rates of stroke and bleeding events were also observed in patients from Europe[45] and Asia[46,47] in the ETNA-AF program.

Table 4 summarizes other real-world studies evaluating the effectiveness and safety of DOACs in Asian patients. Compared with warfarin, edoxaban was associated with a lower risk of ischaemic stroke and major bleeding.[21–26] In Korean patients, edoxaban demonstrated similar effectiveness and safety outcomes compared with rivaroxaban; edoxaban tended to be associated with a lower GI bleeding risk compared with rivaroxaban, but it was not statistically significant.[23] The superior safety profile of edoxaban compared with other DOACs in Asian patients was also shown in a meta-analysis of RCTs and observational cohort studies.[25] A recent meta-analysis suggests that apixaban and edoxaban may be a relatively more well-balanced DOAC for Asian patients with NVAF.[26]

Discussion

RCTs remain the gold standard for evaluating treatment efficacy and safety; however, the stringent criteria employed for patient enrolment means that the patient population enrolled in RCTs does not reflect the real-world population. Real-world studies are thus essential for complementing RCT data and providing evidence in clinical scenarios from routine practice. In the absence of direct head-to-head RCTs between DOACs, data from real-world practice may be used to compare the effectiveness and safety of DOACs indirectly. The clinical cases presented here further add to the accumulating evidence for the clinical efficacy and safety of edoxaban in Asian patients.

As described in our case reports, OD edoxaban was used for the treatment of patients with NVAF with different profiles (frail, elderly and with increased bleeding risk) and was found to be effective and safe in these real-world patients who were at high risk. Edoxaban was selected based on its well-documented efficacy and safety in

Table 3. Reported clinical events from real-world ETNA-AF program.

	No. of patients	Received recommended dose (%)	Annualized clinical event rate (%)				
			Any stroke/systemic embolism	Ischaemic stroke	Major bleeding	Major gastrointestinal bleeding	Intracerebral haemorrhage
Global, 1-year follow-up[44]	26,823	82.6	1.12	0.87	1.12	0.57	0.31
Europe, 1-year follow-up[45]	13,092	83	0.82	0.56	1.05	0.40	0.24
Japan, 2-year follow-up[46]	11,569	86.3	1.08[a]	1.03	1.02	0.47	0.33
Taiwan and Korea, 1-year follow-up[47]	2677	70.8	–	0.90	0.78	0.23	0.27

[a]Ischaemic stroke/systemic embolism.

Table 4. Other real-world studies of edoxaban in Asian population.

Study type	Comparison (*vs* reference)	HR (95% CI; *p* value)				
		Ischaemic stroke/systemic embolism	Ischaemic stroke	Major bleeding	Major gastrointestinal bleeding	Intracerebral haemorrhage
Retrospective cohort (Korean National Health Insurance Service Database)[22]	Edoxaban *vs* warfarin	–	0.693 (0.487–0.959; 0.033)	0.532[a] (0.352–0.773; 0.001)	0.597[b] (0.363–0.930; 0.030)	0.407 (0.182–0.785; 0.014)
Retrospective cohort (Korean National Health Insurance Service Database)[23]	Edoxaban *vs* rivaroxaban	–	0.951 (0.658–1.338; 0.78)	0.775[a] (0.515–1.124; 0.197)	0.732[b] (0.442–1.149; 0.198)	0.844 (0.405–1.582; 0.622)
Retrospective cohort (Korean Health Insurance Review and Assessment Database)[24]	Edoxaban *vs* warfarin	–	0.629 (0.532–0.740)	0.556 (0.462–0.665)	0.630 (0.510–0.774)	0.375 (0.254–0.537)
	Edoxaban *vs* rivaroxaban	–	0.768 (0.651–0.902)	0.713 (0.593–0.851)	0.772 (0.625–0.946)	0.547 (0.373–0.779)
	Edoxaban *vs* apixaban	–	0.915 (0.765–1.092)	0.973 (0.799–1.180)	1.194 (0.948–1.501)	0.563 (0.379–0.815)
	Edoxaban *vs* dabigatran	–	0.786 (0.652–0.944)	0.841 (0.678–1.040)	0.852 (0.665–1.089)	0.790 (0.508–1.209)
Retrospective cohort study (Taiwan's National Health Insurance Research Database)[21]	Edoxaban *vs* warfarin	0.67 (0.49–0.93; 0.0177)	0.71 (0.50–1.00; 0.049)	0.42 (0.28–0.64; <0.0001)	0.32 (0.16–0.65; 0.0019)	0.41 (0.21–0.80; 0.0089)
	Rivaroxaban *vs* warfarin	0.72 (0.55–0.94; 0.0164)	0.76 (0.57–1.01; 0.0557)	0.55 (0.41–0.75; 0.0001)	0.65 (0.41–1.02; 0.0609)	0.54 (0.34–0.88; 0.0127)
	Apixaban *vs* warfarin	0.65 (0.49–0.87; 0.0036)	0.71 (0.52–0.95; 0.023)	0.34 (0.23–0.50; <0.0001)	0.24 (0.12–0.47; <0.0001)	0.44 (0.26–0.75; 0.0027)
	Dabigatran *vs* warfarin	0.77 (0.59–1.01; 0.0554)	0.82 (0.62–1.08; 0.162)	0.56 (0.41–00.77; 0.0003)	0.78 (0.50–1.21; 0.2653)	0.48 (0.29–0.80) 0.0048)
Meta-analysis of RCTs and observational cohorts[25]	Edoxaban *vs* warfarin	0.90 (0.66–1.53)	0.54 (0.37–0.77)	0.34 (0.24–0.49)	0.38 (0.19–0.76)	0.24 (0.16–0.36)
	Rivaroxaban *vs* edoxaban	0.80 (0.57–1.13)	1.61 (1.07–2.44)	1.92 (1.29–2.85)	1.97 (0.88–4.45)	2.20 (1.41–3.45)
	Apixaban *vs* edoxaban	0.62 (0.44–0.89)	1.46 (0.95–2.23)	1.42 (0.94–2.14)	1.02 (0.44–2.32)	1.86 (1.17–2.94)
	Dabigatran *vs* edoxaban	0.85 (0.60–1.19)	1.68 (1.11–2.55)	1.63 (1.09–2.45)	1.83 (0.86–3.89)	1.84 (1.19–2.84)
Meta-analysis of observational cohorts[26]	Edoxaban *vs* warfarin	0.71 (0.60–0.84)	0.56 (0.49–0.64)	0.56 (0.49–0.64)	0.69 (0.56–0.86)	0.42 (0.35–0.50)
	Edoxaban *vs* rivaroxaban	0.97 (0.80–1.18)	0.81[c] (0.74–0.88)	0.76[c] (0.65–0.88)	0.8 (0.63–1.03)	0.61 (0.50–0.73)
	Edoxaban *vs* apixaban	–	–	1.01 (0.85–1.22)	0.83 (0.67–1.04)	–

[a]Hospitalization for major bleeding; [b]Hospitalization for GI bleeding; [c]Statistically significant

patients with NVAF, including in Asian patients.[21,22,24,41,42,46,47] Importantly, edoxaban has demonstrated a better safety profile compared with other DOACs[25] and is a more well-balanced DOAC for Asian patients.[26] Given that the risks of ischaemic stroke and bleeding tend to be higher in Asian populations, edoxaban may be a more suitable choice for DOAC in this population. Furthermore, the use of edoxaban in Asian patients is also supported by the recent consensus clinical recommendations from JACC: Asia on stroke prevention in AF.[48]

We observed the clinical benefit of edoxaban in patients at high risk, including frail patients (Cases 1 and 2), elderly patients with multiple comorbidities (Cases 3–5), and patients with increased bleeding risk (Cases 6 and 7). Sub-analyses of the ENGAGE AF-TIMI 48 trial have demonstrated the consistent efficacy and safety of edoxaban compared with warfarin across various high-risk sub-groups of patients (Table 2). This was further reinforced in a recent comprehensive secondary analysis of 12 high-risk sub-groups in the ENGAGE AF-TIMI 48 trial.[43]

Amongst the OD DOACs, edoxaban was shown to have a better safety profile than rivaroxaban in Asian patients (Table 4).[23,25,26] An OD regimen promotes treatment adherence and is an important attribute, especially in elderly patients who tend to have multiple comorbidities requiring polypharmacy, as illustrated in all the cases we have described. A simple treatment regimen of a DOAC that reduces pill burden and promotes adherence should therefore be considered, as non-adherence to DOAC has been associated with ~40% increased risk of stroke.[49] Taken together, the evidence supports the use of OD edoxaban in these Asian patients at high risk.

Our case reports also highlight several considerations for determining the appropriate treatment dosing to achieve and maintain optimum anticoagulation effectiveness and safety in patients with NVAF in routine clinical practice. This includes renal function, body weight and drug–drug interactions. Renal function and body weight change over time, hence requiring dose adjustment to ensure the efficacy and safety of DOAC treatment. Although relatively less common than warfarin, there is increasing evidence for drug–drug interactions with DOAC use.[40] This is particularly important when dronedarone is used, as it is contraindicated in patients taking rivaroxaban. In this context, edoxaban provides clear guidance in dosing strategy based on renal function, body weight and concomitant use of a potent P-glycoprotein inhibitor. It is important that DOAC dosing adheres to the recommended strategy and criteria as defined in the RCTs to ensure optimal efficacy and safety.

Conclusion

Clinical trial data and real-world evidence have demonstrated the clinical benefits of edoxaban for stroke prevention in Asian patients with NVAF. Amongst the OD DOACs, edoxaban has similar efficacy outcomes but a better safety profile than rivaroxaban in Asian patients. Consistent with real-world evidence thus far, early clinical experience from SEA also suggests the utility of OD edoxaban in Asian patients with NVAF.

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