Long-Term Effects of Apixaban Confirmed in the Open-Label Extension of AVERROES Trial

Tze-Fan Chao[1,2] Tatjana S. Potpara[3,4]

[1] Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[2] Institute of Clinical Medicine and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan
[3] School of Medicine, Belgrade University, Belgrade, Serbia
[4] Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia

Address for correspondence Tatjana Potpara, MD, PhD, School of Medicine, Belgrade University, dr Subotica 8, Cardiology Clinic, Clinical Centre of Serbia, Visegradska 26, 11000 Belgrade, Serbia (e-mail: tatjana.potpara@med.bg.ac.rs).

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The efficacy and safety of non-vitamin K antagonist (non-VKA) oral anticoagulants (NOACs) compared with warfarin have been shown in four pivotal randomized trials.[1–4] Thereafter, NOACs have been increasingly prescribed for stroke prevention in the daily practice, thus improving clinical outcome for atrial fibrillation (AF) patients.[5] The use of apixaban for AF-related stroke prevention has been studied in two randomized trials, the AVERROES (Apixaban Versus ASA to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation).[3,6] The AVERROES trial randomized AF patients considered unsuitable for VKA to receive aspirin or apixaban, and showed superiority of apixaban over aspirin for stroke prevention with comparable risks of intracranial hemorrhage and major bleeding.[6] Hence, apixaban is the only NOAC which has been compared with aspirin in a randomized trial for stroke prevention in AF. However, the median follow-up in the AVERROES trial was only 1 year, and data regarding the long-term outcome of apixaban versus aspirin are unknown.

In this issue of *Thrombosis and Haemostasis*, Benz and colleagues reported outcomes among 3,275 patients on apixaban during the open-label extension of the AVERROES trial.[7] After a 3-year median follow-up, the rate of stroke/systemic embolism (SE) was 1.0%/year, and the risk of major bleeding was 1.2%/year. These event rates were similar to those observed among patients receiving apixaban during the double-blinded phase of AVERROES. The findings of the present study confirm the long-term effectiveness and safety of apixaban for stroke prevention in AF patients.

Previous studies have reported the risk of stroke/SE and major bleeding among patients randomized to a NOAC during and after the respective double-blinded phase.[8–11] These data and those reported by Benz et al are summarized in ►**Fig. 1**. A higher risk of stroke/SE during the open-label phase was observed among patients randomized to NOACs and then transitioned to an open-label VKA in the ROCKET-AF (6.42%/year) and ARISTOTLE (4.02%/year) trials.[8,11] Of note, the event rate among nonanticoagulated AF patients with a mean $CHADS_2$ score of 3.5 was 5.9%/year for a score of 3 and 8.5%/year for a score of 4 in the study by Gage et al.[12]

Learning from the ROCKET-AF and ARISTOTLE trials, a delicate transition plan was set up in the ENGAGE-AF TIMI 48.[10] Owing to the aggressive monitoring and titration of VKA therapy, the median time to first therapeutic international normalized ratio (INR) $\geq$2 on open-label VKA was shorter in the ENGAGE AF-TIMI 48 (9 days) compared with ROCKET-AF (13 days).[8,10] Obviously, a 2-day "bridging" period with apixaban was too short to achieve a therapeutic INR among patients who transited from apixaban to open-label VKA in the ARISTOTLE trial.[11] By 30 days after the end of the trial, at least one therapeutic INR was achieved in around 99% of patients randomized to edoxaban and transitioned to open-label VKA in ENGAGE AF-TIMI 48, compared with only 52% in the ROCKET-AF trial. The risk of stroke/SE in patients randomized to edoxaban during the transition phase was similar to that in the double-blinded phase in ENGAGE-AF TIMI 48 (1.89%/year vs. 1.57% with high-dose edoxaban regimen; 1.85%/year versus 2.04%/year with low-dose edoxaban regimen).[10] These observations highlighted the importance of a comprehensive transition program when patients were shifted from a NOAC to VKA.

The RELY-ABLE study[9] (an open-label extension of the RE-LY trial) and the present report by Benz et al represent the body of evidence regarding long-term outcomes of NOAC use during open-label extension of landmark trials on stroke prevention in AF. The long-term risk of major bleeding with apixaban was consistently low (1.2%/year) even among patients who were considered unsuitable for VKA at the AVERROES trial entry, thus suggesting that NOACs could provide an easier and better

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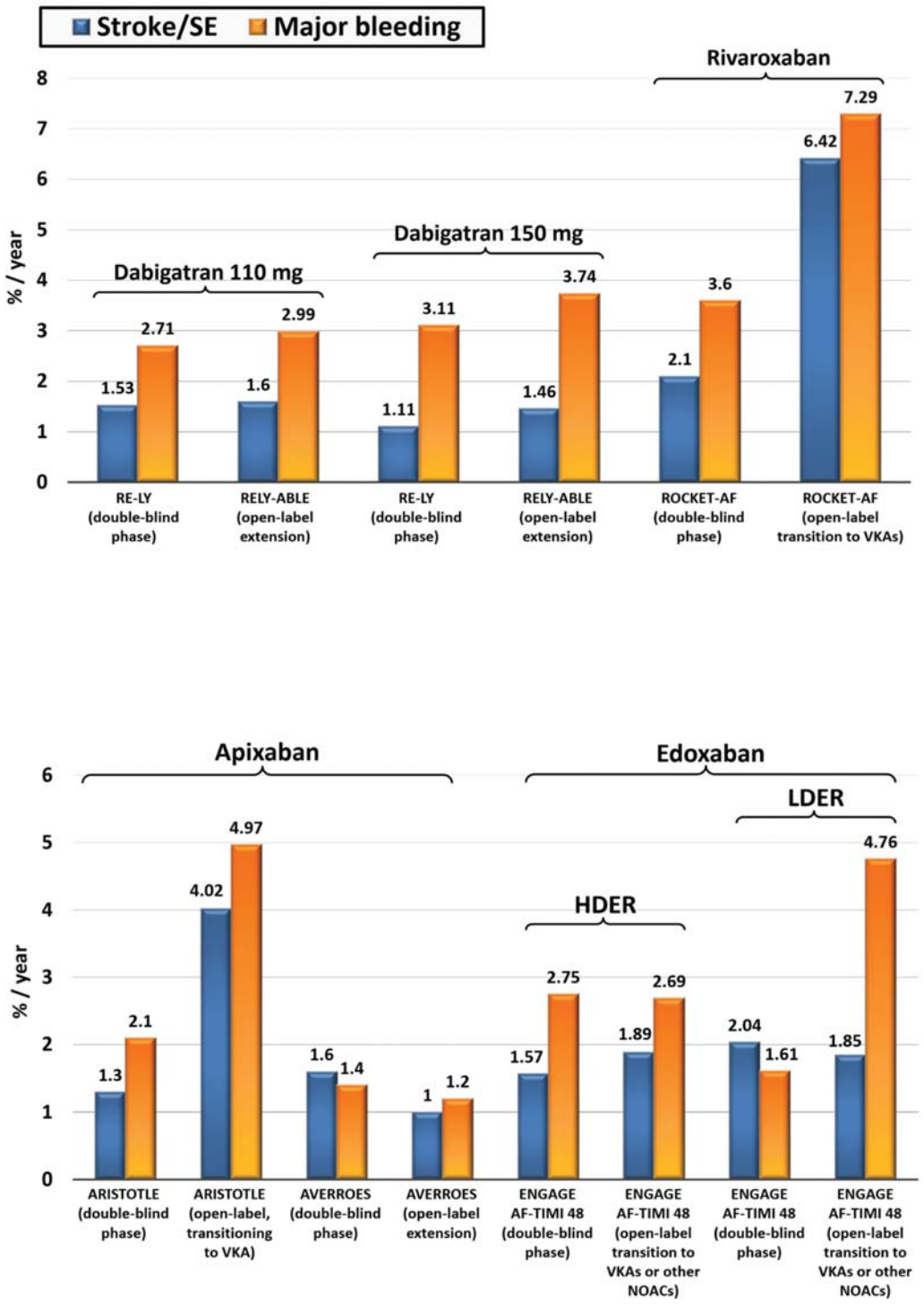

Fig. 1 Risks of stroke/SE and major bleeding of patients who had been randomized to an NOAC during and after the end of double-blind phase, and those reported in the open-label extension period of RE-LY (RELY-ABLE) and AVERROES trials. Data used in the figure were adopted from RE-LY,[1] ROCKET-AF,[2] AVERROES,[6] ARISTOTLE,[3] ENGAGE-AF TIMI 48 trials,[4] RELY-ABLE study,[9] and the studies by Mahaffey et al,[8] Ruff et al,[10] Granger et al,[11] and Benz et al.[7] HDER, high-dose edoxaban regimen; LDER, low-dose edoxaban regimen; NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism; VKA, vitamin K antagonist.

way than VKA to prevent stroke in AF patients. Actually, more and more patients who would be considered unsuitable for oral anticoagulant therapy with VKA only a few years ago now seem to do relatively well on NOACs, e.g., the extremely elderly and patients with prior history of intracranial hemorrhage.[13,14] The data from randomized trials seem to be well augmented and supported by a wealth of real-world data despite the higher risk profiles of patients in observational nontrial cohorts.[15,16]

When interpreting results of the open-label extension studies, we should realize that these patients were followed up regularly (e.g., 1, 6, and 12 months after entry into the open-label extension of AVERROES, and every 6 months thereafter),

and therefore, each participant was well managed. As emphasized in the 2020 European Society of Cardiology AF Guidelines,[17] careful evaluation and characterization of the patient,[18] as well as a regular follow-up, risk reassessment (even in those initially considered as low risk, given the dynamic nature of stroke and bleeding risks),[19,20] and management of modifiable bleeding risk factors are crucial for the care of anticoagulated AF patients. Indeed, the well-structured, easy-to-use ABC holistic pathway (A: Avoid stroke; B: Better symptom management; C: Cardiovascular and other comorbidity risk reduction), should be implemented into daily practice for the management of all AF patients.[21,22]

Conflict of Interest
None declared.

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