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EDITORIAL

Risk-benefit ratio assessment for stroke prevention in intermediate risk atrial fibrillation patients: will TEE-based aspirin treatment fill the gap?

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Patients with atrial fibrillation (AF) have a 5% annual stroke risk depending on the presence of risk factors, i.e. prior stroke or peripheral embolism, age, hypertension, diabetes, impaired cardiac function, female gender, vascular disease and, echocardiographically, presence of mitral stenosis and moderate or severe left ventricular systolic dysfunction [1, 2]. These risk factors are incorporated into the previous and currently used risk scores, i.e. the $CHADS_2$ and CHA_2DS_2-VASc scores, respectively [1, 3]. Depending on these scores, it is decided whether to prescribe vitamin K antagonists (VKA), aspirin, nothing, or, in the future, the new oral anticoagulant drugs. Such decision-making requires careful consideration of pros and cons of anticoagulant therapy in the individual patient. On the one hand, during VKA therapy major bleeding may occur in up to 1.2–3.6% of patients yearly [4–7]. On the other hand, even with VKA therapy the residual stroke or systemic embolism rate in patients with AF remains relatively high, with a yearly incidence ranging between 1.1% and 2.4%, indeed depending on the presence of currently known risk factors [4, 6, 8].

Two decades ago, the Stroke Prevention in Atrial Fibrillation III investigators found that transoesophageal echocardiography (TEE) was a useful tool for refinement of the above-mentioned risk scores [9]. Using TEE, they showed that some of those patients classified as being at moderate or high risk for thromboembolic complications were actually at low risk. Furthermore, presence of stroke risk factors during TEE identified those patients with the highest risk of thromboembolic complications.

Since then, no prospective randomised trials have been performed assessing the clinical safety and feasibility of TEE-based risk assessment. In the present edition of the *Netherlands Heart Journal,* Dinh and colleagues present the design and baseline data of the **T**EE-gu**I**ded randomized comparison of **A**spi**R**in and vitamin K antagonists in patients with **A**F and an increased risk of stroke (TIARA) pilot study [10]. It is their hypothesis that a comprehensive strategy of TEE-based aspirin treatment is safe and feasible in AF patients who are eligible for VKA therapy on the basis of conventional risk assessment. The primary objective was to show that in patients who do not have predefined high-risk features on TEE, TEE-based aspirin treatment is safe compared with VKA therapy with respect to the composite endpoint of major cardiovascular and cerebrovascular events. The second objective was to assess whether TEE was feasible, i.e. whether it was possible to assess all four TEE features of increased stroke risk, being complex atheromatous plaques in the thoracic aorta and signs of atrial stasis including dense spontaneous echo contrast, thrombus, or low blood flow velocities in the left atrial appendage. Patients were eligible if they had documented paroxysmal or permanent AF and a conventional indication for treatment with VKA. Patients with a presumed very high risk of thromboembolic complications, i.e. previous stroke, systemic embolism, heart failure or significantly impaired left ventricular systolic function, mitral valve stenosis or hypertrophic cardiomyopathy, were excluded. After TEE, patients were randomised to aspirin 100 mg daily or VKA therapy (target INR 2.5–3.5) if TEE did not show high-risk abnormalities (i.e. one of the four TEE features of high stroke risk mentioned above). They included

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310 patients, of whom 69 were not eligible for randomisation because of non-visualisation (n=5), technical failure (n=1), or an abnormal TEE (n=63). The last-mentioned group predominantly consisted of only one TEE abnormality, most often being low left atrial appendage velocities and spontaneous echo contrast. A total of 241 patients (81%) were randomised. Patients who could be randomised were younger, less often had coronary artery disease and a previous transient ischaemic attack, had a higher ejection fraction, and a lower $CHADS_2$ score.

The authors are praised for their courage and effort in performing this innovative study. Awaiting the safety outcome, however, a number of limitations need to be borne in mind. The present study is a small pilot study, including 310 patients. Further support for the feasibility and, if positive, for the safety of this strategy warrants confirmation by a large-scale randomised study. Although the study shows a favourable answer to their second objective, i.e. feasibility of a TEE-based approach, it should be kept in mind that all centres were highly trained in performing TEE. This implies that such a strategy should and can not be translated as a feasible strategy in all cardiology centres. Before incorporation into new guidelines, it warrants further testing in a large number of centres. Furthermore, the study was performed in AF patients without a very high risk of stroke, with a mean $CHADS_2$ score of 1 which means that the results of the TIARA study only apply to this patient category. Undeniably, these are the patients in whom the pros and cons of each treatment strategy are carefully weighed and discussed, and in whom decision-making is most troublesome. Another point of concern is how to follow these patients. A TEE without risk factors at one time point does not implicate that the patient remains free of TEE risk factors in the future. A new prospective study has to investigate this issue. Finally, will the introduction of new oral anticoagulant drugs such as dabigatran, rivaroxaban and apixaban abolish the potential necessity of such a TEE-guided strategy? [4, 5, 7] It is our belief that it will not. Although VKA treatment and the new anticoagulant drugs are more effective for the prevention of thromboembolic complications as compared with aspirin, minor bleeding is observed at a lower rate during aspirin use, even when using the new generation of anticoagulant drugs [7].

We are looking forward to the safety results of the TIARA study. If positive, the outcome warrants confirmation in a large-scale prospective randomised study. Hopefully, we will be able to conduct such an innovative study on how to improve therapy and outcome in AF patients in the Netherlands.

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