

## EDITORIAL

## Leaving no stone unturned: the search for stroke associated with atrial fibrillation

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The diagnosis of paroxysmal atrial fibrillation (AF) continues to be a main priority in stroke patients. After the clinical trials that evaluated anticoagulation versus antiplatelet treatment in patients with embolic stroke of undetermined source (ESUS) showed that there is no benefit of anticoagulation in the absence of a diagnosis of AF, diagnosing paroxysmal AF continues to be an essential part of the etiological investigation of stroke patients.<sup>1,2</sup> However, finding paroxysmal AF may be challenging.

It is well known that longer heart rhythm monitoring is associated with a higher probability of detecting paroxysmal AF and the longer the duration of monitoring the higher is the probability of actually finding AF.<sup>3</sup> However, performing long term heart rhythm monitoring with insertable cardiac monitors in all stroke patients is currently not feasible due to resources constraints. Therefore, an effective pre-selection of patients with a higher likelihood of having AF would be very useful in clinical practice. In the last years, several studies reported biomarkers associated with an increased risk of developing AF. These biomarkers include morphological cardiac features (atrial fibrosis, left atrial volume,<sup>4</sup> blood velocity in the left atrial appendage<sup>5</sup>), electrocardiographic characteristics (P-wave duration and morphology<sup>6</sup>) and blood analytical determinations (NT-proBNP, MR-proANP<sup>7,8</sup>). Evidence suggests that these biomarkers may actually be features of an atrial cardiopathy characterized by morphological and structural changes in the atria with associated remodeling that ultimately contributes to the development of AF.<sup>9</sup> Atrial cardiopathy has even been associated with stroke risk in the absence of AF.<sup>9</sup>

In the current study, the authors evaluated if a cardiac morphological parameter, periatrial epicardial adipose tissue thickness (pEATT), could be used as a new potential biomarker of AF-associated stroke.<sup>10</sup> pEATT has previously been shown to be associated with the presence of AF, its severity, and recurrence in patients in general.<sup>11</sup> pEATT may contribute to AF due to the secretion of inflammatory mediators, increased oxidation stress, and promotion of fibrosis with consequent disruption of the heart conduction system.<sup>11</sup> In the current study, Edsen

et al. retrospectively included 121 patients with AF-related acute stroke and 94 patients with acute non-cardioembolic stroke with large vessels occlusion that had been prospectively consecutively collected.<sup>10</sup> pEATT was evaluated using data from the admission computed tomographic angiographies that routinely included the supra-aortic vessels as well as the heart. After data analysis, patients with AF-related stroke were shown to have increased right and left sided pEATT. In a multivariate analysis adjusted for potential confounders including coronary heart diseases, age, body mass index, left atrial enlargement and NT-proBNP, left sided pEATT was found to be an independent marker of AF-related stroke. This study has evident limitations like a retrospective design, a small sample size, a lack of external validation of the results, and an absence of evaluation of the biomarker in patients with cryptogenic stroke. Nevertheless, it adds one more piece of data that may help us to further improve our knowledge of cardioembolic stroke. A better comprehension of the features associated with cardioembolic stroke may help to refine the selection of stroke patients that are more likely to have AF.

Still, some steps have to be taken, prior to the use of these biomarkers in clinical practice. In the future, it would be interesting to know which biomarkers or combinations of biomarkers have the highest accuracy for the diagnosis of AF. Also, currently, there is weak evidence of a useful role for blood, ECG, and brain imaging biomarkers for the identification of patients at high risk of AF mainly because there is a lack of clinical trials evaluating their effectiveness to select patients that may benefit the most from AF monitoring.<sup>3</sup> A pioneer clinical trial (The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial—ARCA-DIA) is suppressing this step of searching for AF and directly using biomarkers that have been associated with atrial cardiomyopathy (NT-proBNP, P-wave terminal force >5000  $\mu\text{V} \times \text{ms}$  in ECG lead V<sub>1</sub>, serum NT-proBNP >250 pg/mL, and left atrial diameter index  $\geq 3 \text{ cm/m}^2$  on echocardiogram) to select patients to test if anticoagulant therapy reduces stroke recurrence in patients with atrial cardiopathy but no known AF.<sup>12</sup> This

is a clear example of how precision medicine can be used to improve the selection of patients that may benefit the most from certain treatments.

Step by step, we are getting closer to better identify patients with AF-associated stroke and therefore to be able to provide these patients with the best prevention treatment to reduce stroke recurrence.

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