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EDITORIAL
Arrhythmias

Personalized clinical management of patients with atrial fibrillation: is a biomarker-based strategy for prediction of sinus rhythm persistence ready for prime time?

Giuseppe Boriani [1,*], **Davide Antonio Mei** [1,2], **and Jacopo Francesco Imberti** [1,2]

[1]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Via del Pozzo 71, Modena 41121, Italy; and
[2]Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy

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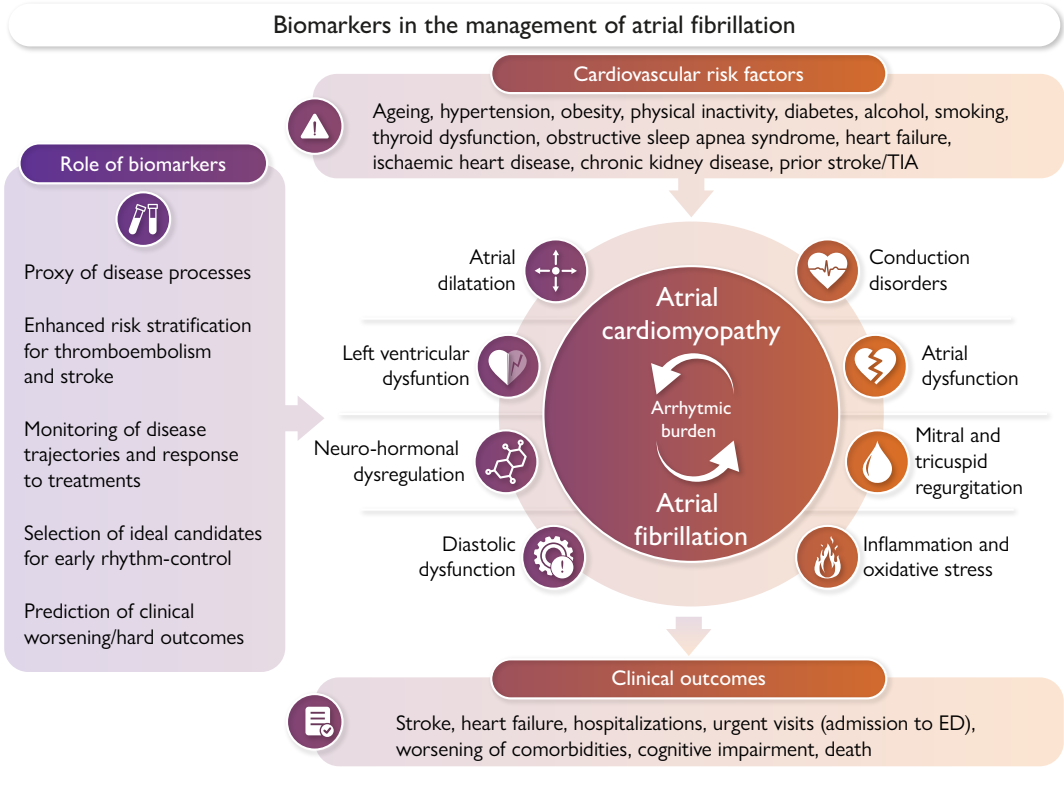
This editorial refers to 'Biomarker-based prediction of sinus rhythm in atrial fibrillation patients: the EAST-AFNET 4 biomolecule study', by L. Fabritz *et al.*, https://doi.org/10.1093/eurheartj/ehae611.

Graphical Abstract



The role of blood biomarkers in the complex interplay between atrial cardiomyopathy and atrial fibrillation. ED, emergency department; TIA, transient ischaemic attack.

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* Corresponding author. Tel: +39 059 4225836, Fax: + 39 059 4224498, Email: giuseppe.boriani@unimore.it

In the current issue of the *European Heart Journal*, Fabritz *et al.*[1] investigated the relationship between atrial fibrillation (AF)-related cardiovascular disease processes, as indicated by circulating biomarkers, and rhythm outcomes in 1586 patients enrolled in the EAST-AFNET4 randomized controlled trial (RCT) (mean age: 71 years, 46% women). Among 14 pre-specified biomarkers, higher baseline levels of angiopoietin 2 (ANGPT2; odds ratio [OR] 0.76; 95% confidence interval [CI] 0.65–0.89), bone morphogenetic protein-10 (BMP10; OR 0.83; 95% CI 0.71–0.97), and N-terminal-probrain natriuretic peptide (NT-proBNP; OR 0.73; 95% CI 0.60–0.88) were independently associated with a reduced likelihood of maintaining sinus rhythm at 12 and 24 months. The model was adjusted for multiple clinical variables, early rhythm control, and baseline rhythm status. Interestingly, NT-proBNP was found to be less predictive of rhythm outcomes in patients undergoing rhythm control therapy compared with those receiving usual care (OR 0.90; 95% CI 0.69–1.18 vs. OR 0.64; 95% CI 0.51–0.80, respectively). When added to a clinical risk score incorporating left atrial size >50 mm, persistent AF, or age >75 years (any two of these three features), these three biomarkers significantly improved the identification of patients with a low probability of maintaining sinus rhythm at 12-month follow-up. Additionally, the predictive value of these biomarkers was externally validated across three datasets (the AXAFA-AFNET 5 trial, the BBC-AF study, and the TRUST cohort snapshot), with confirmation of the findings in the AXAFA-AFNET 5 dataset. Interpretation of these very interesting findings should consider that, from a pathophysiological view, ANGPT2 is linked to vascular and endothelial dysfunction, BMP10 is associated with atrial metabolic dysfunction and stress, and NT-proBNP is indicative of increased cardiac load.

The present study highlights the interesting and novel concepts that multiple risk factors and disease processes, identified through blood biomarkers, underly AF development and progression, and may be associated with sinus rhythm maintenance (*Graphical Abstract*). Traditionally, biomarkers were sought for their ability to help the clinician in predicting clinical outcomes. However, the study by Fabritz *et al.*[1] reveals that these biomarkers do more than just provide prognostic information, since they underscore the complexity of AF pathophysiology, which is the result of systemic processes (e.g. inflammation, oxidative stress, neurohormonal dysregulation, and ageing), atrial electrical and/or structural remodelling (also linked to the complex processes of atrial cardiomyopathy), and ventricular dysfunction (with either preserved of reduced ejection fraction)[2] (*Graphical Abstract*). For these reasons, these biomarkers may be non-specific, and high concentrations of ANGPT2, NT-proBNP, and BMP10 have been found to be associated with diseases other than AF (e.g. heart failure, kidney disease, stroke, sepsis, acute pulmonary diseases, and pulmonary arterial hypertension), and it is well known that their concentrations can be influenced by patient characteristics (e.g. sex, body mass index, and age) and timing of sampling.[3–6]

In the field of AF, biomarkers have traditionally been integrated into clinical risk scores for improved stroke and bleeding prediction. These additions provided a modest but significant improvement in risk prediction, but at the cost of reduced simplicity (e.g. ABC-stroke, ATRIA, ABC-bleeding, and the inclusion of multiple biomarkers in the CHA_2DS_2-VASc and HAS-BLED scores). The primary clinical need driving these studies was the recognition that stroke and bleeding were the most critical (and known) determinants of clinical decision-making, as well as important elements conditioning clinical outcomes.

An important advancement in clinical management of patients with AF came in 2020, from the EAST-AFNET4 trial.[7] This randomized study showed that early rhythm control in patients with early AF (within 1 year before enrolment) reduced the composite endpoint of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome at a median of 5.1 years of follow-up per patient (hazard ratio [HR], 0.79; 96% CI 0.66–0.94). According to these results, it emerged that appropriate rhythm management should nowadays be considered as a primary requirement in appropriately selected patients, in parallel with stroke prevention and treatment of comorbidities.[2] Indeed, the clinical scenario significantly changed after EAST-AFNET4, with an evolution in the role of rhythm control therapeutic options (ablation and/or drug) from mere ways to improve symptoms and quality of life to an evidence-based way of preventing serious AF-related outcomes, especially in patients with recently diagnosed AF.

Patients with AF and associated risk factors and comorbidities (*Graphical Abstract*) are exposed to development and progression of atrial cardiomyopathy, i.e. a series of degenerative processes involving the cells of the atrial tissue, with derangements in atrial chamber architecture, as well as in contractile and electrophysiological properties that may evolve up to the stage of atrial failure.[8] In some patients with such an advanced degree of atrial derangement, usually after a long history of AF, sinus rhythm may no longer be maintained and therefore proper identification of these patients through reliable proxies of advanced atrial cardiomyopathy, atrial failure, and associated poorer clinical outcomes becomes an important goal, from both an individual and a societal perspective.[8–10]

The implementation of blood biomarkers, especially in combination, has the potential to improve a candidate's selection for early rhythm control using catheter ablation and/or antiarrhythmic drugs (AADs). Catheter ablation as the first-line rhythm control strategy was found to be associated with fewer arrhythmia recurrences as compared with AADs in patients with symptomatic paroxysmal AF and normal left ventricular systolic performance.[11] Of note, appropriate use of AADs may exert a favourable effect and act synergistically with catheter ablation, with the potential to slow AF progression to more sustained forms.[12]

Blood biomarkers may serve as indicators of treatment efficacy and patient response to specific interventions. However, in the context of AF, no biomarker has proven to be reliably suited for this purpose in large patient cohorts. In this regard, the study by Fabritz *et al.*[1] is an important step towards integration of biomarkers in clinical decision-making. However, some considerations are needed in translating these interesting findings to clinical practice. In this study, blood sampling was conducted exclusively at baseline, which precluded the assessment of potential changes during follow-up. Importantly, these biomarkers often reflect overlapping disease processes beyond AF. Consequently, their concentrations may not only fluctuate in relation to AF and atrial failure progression (or their regression), but may also be influenced by intercurrent conditions and disease-modifying therapies, further complicating their interpretation. For instance, Fabritz *et al.*[1] reported that the rhythm-predicting ability of NT-proBNP was reduced in patients receiving rhythm control therapy. Additionally, sampling conditions represent another potential confounding factor. Biomarker levels are known to exhibit spontaneous variability, which is also influenced by the cardiac rhythm at the time of sampling, typically showing higher concentrations when samples are collected during AF.

The practical implementation of biomarker measurements in daily clinical practice remains unclear. The availability and accessibility of these biomarkers may differ markedly across healthcare settings and socio-economic contexts. While some biomarkers, such as

NT-proBNP, are routinely available in clinical practice, others (such as ANGPT2 and BMP10) are limited to research use and have yet to be approved for widespread clinical application. Furthermore, biomarker assays are not fully standardized and can yield varying results across different laboratories, complicating their routine use. Standardization and validation of these assays are critical to ensuring consistency and reliability in clinical practice. Additionally, future research must evaluate the cost-effectiveness of using biomarkers as a tool for selecting candidates for rhythm control strategies. Without such an evaluation, the broad applicability of these biomarkers remains uncertain, particularly in resource-limited settings where healthcare budgets are a major consideration.

In conclusion, the study by Fabritz *et al.*[1] offers valuable insights into the complex pathophysiology of AF, suggesting that it is not solely an 'electrical disease'.[13] Furthermore, the underlying disease processes reflected by biomarker abnormalities, together with proteomic data potentially elaborated through artificial intelligence algorithms,[14,15] may lead to the identification of new potential targets for more personalized therapies, to be applied to properly identified groups of patients, at defined stages of AF progression and for specific amounts of AF burden. In this perspective, even at the time of modern, technologically advanced medicine, we should apply in our practice a personalized, holistic approach to patients with AF, in line with the famous aphorism of William Osler (1849–1919): 'Care more particularly for the individual patient than for the special features of the disease'.

Declarations

Disclosure of Interest

G.B. reports modest speaker fees from Bayer, Boehringer Ingelheim, Boston, Daiichi Sankyo, Microport, Janssen, and Sanofi outside of the submitted work. The other authors declare no disclosure of interest for this contribution.

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