EDITORIAL

Biomarkers in atrial fibrillation: a constant search for simplicity, practicality, and cost-effectiveness

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The way we look at atrial fibrillation (AF) has radically changed in the last decade, switching from a mere arrhythmic conception to a complex nosological entity subtending structural and ultrastructural cardiac changes.[1] Together with this acquisition, the concept of atrial cardiomyopathy has progressively matured and several circulating factors have been identified as markers of atrial disease and, by association, are assumed to be reliable in AF clinical assessment.[2]

However, despite the undebatable usefulness of biomarkers in many settings, their excessive or inappropriate use can lead to unnecessary and even harmful procedures as well as to a waste of healthcare resources. Thus, given the increasing number of available biomarkers and their several possible clinical applications, there is a need to clarify which ones are clinically effective and cost effective at the same time, and can substantially optimize the clinical decision-making process even in busy daily settings, representing a valuable "add-on" to physicians' practice (FIGURE 1).[3,4]

In the present issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Cichoń et al[5] aimed to evaluate the impact of basal and 4-week follow-up concentrations of biomarkers of left atrial overload on electrical cardioversion (CVE) efficacy. The study population included 82 patients with persistent AF undergoing successful CVE and was divided into an obese and nonobese group with no significative difference in the distribution of the main features. Increased high-sensitivity C-reactive protein (hs-CRP) levels were found in the obese compared with the nonobese group, both at baseline and follow-up measurements. However, no relevant relation was highlighted between all the tested biomarkers (hs-CRP, N-terminal pro B-type natriuretic peptide [NT-proBNP], growth differentiation factor 15 [GDF-15], galectin 3, renalase, and copeptin) and the 4-week efficacy of CVE.[5]

Although the small study sample and the monocentric setting limit the generalization of the results, the present study[5] enriches the open debate on the practical utility of biomarkers in the AF population.

As we know, AF pathophysiology articulates on a complex interplay between atrial remodelling (atrial enlargement and fibrosis), inflammatory substrate, and oxidative stress. All these factors are entwined in a bidirectional relation in which each one influences others' appearance, maintenance, and arrhythmia progression. Nowadays, the recommended approach to AF management is a holistic and integrated process that encompasses both patient and arrhythmia characteristics, in line with an individual-oriented clinical model resumed by the ABC approach (A, avoid stroke; B, better symptoms control; C, cardiovascular and comorbidity risk factor control).[6] From this perspective, and due to their dynamic nature, biomarkers may serve as an extra tool for an individualized decision-making process with the aim to provide a more targeted care.[7]

Many biomarkers have been evaluated with these purposes, from traditional markers of inflammation or atrial stretching (hs-CRP, NT-proBNP) and routinely available assays (eg, red blood cell distribution width [RDW])[8] to extremely specific tests not currently employed

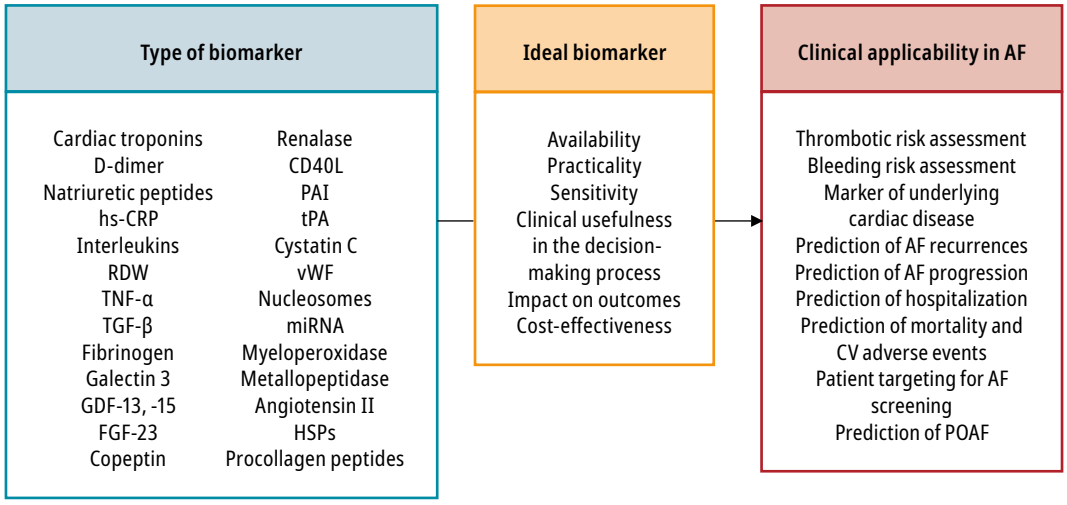

FIGURE 1 Biomarkers in atrial fibrillation: type, ideal characteristics, and clinical applicability

Abbreviations: AF, atrial fibrillation; CD40L, cluster of differentiation 40 ligand; FGF-23, fibroblast growth factor 23; GDF-13, growth differentiation factor 13; hs-CRP, high-sensitivity C-reactive protein; HSPs, heat shock proteins; miRNA, microRNA; PAI, plasminogen activator inhibitor; POAF, postoperative atrial fibrillation; RDW, red blood cell distribution width; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; tPA, tissue-type plasminogen activator; vWF, von Willebrand factor

or accessible (eg, peptides from collagen subtypes, microRNAs, nucleosomes, etc).

In the AF setting, biomarkers already entered some integrated risk scores for stroke and bleeding prediction (ABC-stroke, ATRIA, and ABC-bleeding), adding a modest, albeit statistically significant, improvement to conventional clinical-based scores and with a net clinical advantage limited to selected cases.[9] Moreover, individual biomarkers cannot predict specific outcomes per se, and the need to integrate them with clinical items may lead to a further complication rather than simplification of clinical decision making. On the other hand, the actual evidence on biomarkers' role in predicting AF recurrences / progression is not homogenous and is often conflicting. In a large retrospective cohort of 1410 patients undergoing catheter ablation, BNP, hs-CRP, and estimated glomerular filtration rate were independent predictors of AF relapse after ablation with incremental predicting value when combining all 3 markers.[10] Similarly, in a smaller cohort of patients with AF, Carballo et al[11] found that basal values of hs-CRP and an immediate postablation assessment of NT-proBNP were related to a higher risk of AF recurrences, supporting the role of inflammation in triggering AF pathogenesis and relapse. Conversely, in other studies, no significant relationships were found between basal concentrations of various biomarkers and AF recurrences.[12] It is noteworthy that Merino-Merino et al[13] recently proposed that follow-up assessments rather than basal measurements may reflect those pathophysiological changes related to arrhythmic relapses and may be useful in patients' monitoring.

Thus, a question spontaneously arises: would a biomarker really change the daily management of AF patients? While research on biomarkers certainly contributes to uncover pathophysiologic aspects that lead us to a deeper comprehension of the arrhythmic substrate and its clinical manifestations, to date, no circulating factor alone seems to be able to substantially tip the balance in the clinical decision-making process, neither for patient rule-in nor rule-out.

In the setting of AF, the potential value of combining several biomarkers in order to achieve an integrated assessment is still not fully established, as well as the precise impact of sex, age, and ethnicity on thresholds for specific decisions and interventions. To date, evidence supporting their role in guiding a clinicians' decision-making process is controversial, thus the clinical-based evaluation, pivoted on the medical history, physical examination, 12-lead electrocardiography, and cardiac imaging reports, remains the cornerstone of AF assessment.[3,5,6,14]

In conclusion, additional knowledge is needed to provide a daily clinical approach based on precision medicine and including biomarkers as an important reference for decision making.[15]

ARTICLE INFORMATION

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