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EDITORIAL COMMENT

Coagulation Biomarkers for Predicting Clinical Outcomes Among Patients With Atrial Fibrillation

Piecing Together the Biomarkers*

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Over the past decade, the CHA_2DS_2-VASc score has become the standard for assessing stroke risk in patients with atrial fibrillation (AF).[1,2] Its simplicity allows rapid application and guides treatment decisions while maintaining high performance. However, the hegemony of the CHA_2DS_2-VASc score has been challenged by numerous efforts to improve risk stratification by incorporating biomarkers. Circulating biomarkers may enhance the risk prediction of stroke/systemic embolism and bleeding when used with or instead of clinical risk assessment.[3] This concept is based on the pathophysiology of thromboembolism in patients with AF and is involved in the onset and maintenance of AF. Atrial myopathy, myocardial injury, and coagulation activity are the biological mechanisms of thromboembolic risk. We propose a biomarker triad for stroke/systemic embolism, analogous to Virchow's triad for thrombosis (**Figure 1**). N-terminal pro-B-type natriuretic peptide is a well-known biomarker secreted by cardiomyocytes in response to increased wall tension and is strongly associated with ischemic stroke. Cardiac troponin levels also show a significant gradient in the risk of stroke/systemic embolism, independent of clinical risk factors. D-dimer, a fibrin degradation product most frequently used for venous thromboembolic risk stratification, is an unambiguous indicator of thrombogenesis risk in patients with AF. Other biomarkers indicating inflammation (eg, C-reactive protein and interleukin-6) or renal dysfunction (eg, estimated glomerular filtration rate and cystatin C) are also associated with thromboembolism risk. Incorporating circulating biomarkers into clinical risk assessment tools can potentially improve stroke/systemic embolism risk prediction by capturing important pathophysiological pathways better than dichotomous clinical risk factors. The ABC (Age, Biomarker, Clinical history) stroke score, which includes age, high-sensitivity cardiac troponin (I or T), N-terminal pro-B-type natriuretic peptide, and prior history of stroke or transient ischemic attack, outperforms the CHA_2DS_2-VASc score.[4] However, there is limited information on coagulation biomarkers for risk stratification in patients with AF.

In this issue of *JACC: Asia*, Koretsune et al[5] examined the role of coagulation biomarkers in the clinical outcomes of patients with nonvalvular AF. This study used a subcohort of 3,194 elderly Japanese patients with nonvalvular AF from the ANAFIE (All Nippon AF In the Elderly) registry. The study evaluated the association between clinical outcomes and coagulation biomarkers, including D-dimer, thrombin-antithrombin complex (TAT), prothrombin fragment 1+2 (F1+2), and soluble fibrin monomer complex. Among more than 3,000 study patients, two-thirds were prescribed direct oral anticoagulants (DOACs), 23% were prescribed warfarin, and 5% were not prescribed oral anticoagulants (OACs). Compared with the OAC group, the non-OAC group showed higher levels of D-dimer, TAT, and F1+2 and was more likely to have positive soluble fibrin monomer complex. Overall, higher biomarker levels were associated with poorer clinical outcomes, although some disparities

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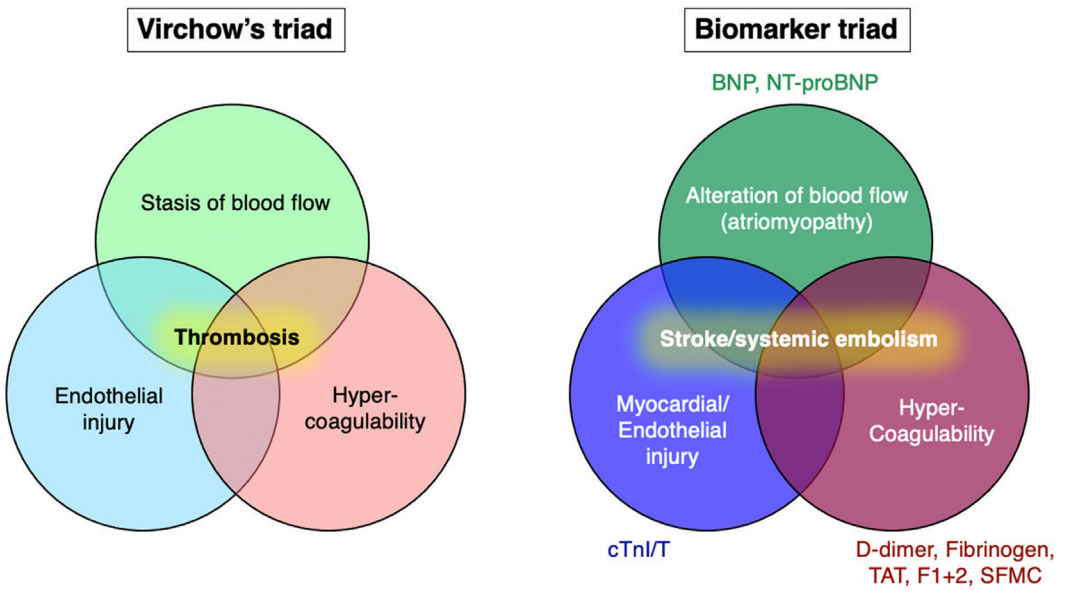
FIGURE 1 **A Biomarker Triad for Stroke/Systemic Embolism**



In analogy to Virchow's triad for thrombosis, biomarkers for stroke and systemic embolism would be summarized as a triad. BNP = B-type natriuretic peptide; cTNI/T = cardiac troponin I/T; F1+2 = prothrombin fragment 1+2; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SFMC = soluble fibrin monomer complex; TAT = thrombin-antithrombin complex.

were observed between patients taking DOACs and those taking warfarin.

However, there are several points needed to be mentioned. First, the 4 coagulation biomarkers did not show a statistically significant association with each outcome among the groups consistently. Some clinical outcomes did not show a statistically significant association between higher D-dimer and TAT levels in the DOAC and warfarin groups. In contrast with previous reports, patients with DOACs showed a higher risk of intracranial hemorrhage when they had negative soluble fibrin monomer complexes compared with those with warfarin. Additionally, previous studies indicated that higher D-dimer levels were associated with an increased risk of stroke/systemic embolism, but could not be reproduced in this study. Second, there remain unanswered questions regarding the importance of coagulation biomarkers for thrombogenesis in patients with AF. Changes in biomarker levels during the follow-up period may have affected the risks of thromboembolism and bleeding. The association between TAT and F1+2 levels and the severity of AF remains questionable. Another limitation is that this study investigated only 9.9% of patients from the original ANAFIE registry, potentially introducing a selection bias. Interpreting the results needs caution because biomarker levels can depend on various factors. Patient age and comorbidities may also contribute to biomarker levels. Although AF is associated with elevated levels of coagulation biomarkers,[6] the relationship between AF severity and biomarker levels is not yet fully understood.

The addition of biomarkers may improve the performance of clinical risk scores in patients with AF.[4,7,8] However, using biomarker-based risk scores may not always improve risk stratification in patients already assessed using the CHA_2DS_2-VASc score,[7] and real-world validation data suggest some controversies regarding its efficacy compared with previous clinical risk scores.[9] For the clinical application of biomarkers, the refinement of further risk stratification of clinical outcomes, particularly for those initially classified as low-risk with a nonsex CHA_2DS_2-VASc score of 0 or 1, would be noteworthy.[10,11] Therefore, the use of biomarkers may uncover truly low-risk patients with AF among those previously identified as at low risk of stroke.

Overall, biomarkers have recently accumulated their efficacy and usefulness for better management of patients with AF. To enhance their clinical usefulness, we need not only highly predictive

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biomarkers, but also their laboratory standardization, cost effectiveness, and the ability to surmount intra-individual or interindividual variability. The reliability of biomarkers in clinical settings is crucial,[12] and clinically useful biomarkers require less variability over repeated measurements.[13] Moreover, further evidence is required to determine whether biomarker-guided AF management is more beneficial than usual care. An ongoing randomized controlled trial (ABC-AF [ABC-Scores for Reduction of Stroke and Mortality in Atrial Fibrillation]; NCT03753490) is evaluating the clinical usefulness of biomarker-based score (ABC scores)-guided management in reducing stroke and mortality in patients with AF. With a concerted effort to overcome these challenges, biomarker-guided management of AF could provide substantial benefits for physicians and patients. Again, it is now time to piece biomarkers together for making a more tailored strategy for stroke prevention in patients with AF.

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