EDITORIAL

Seeking the “holy grail” of biomarkers to improve stroke risk prediction of clinical scores

Biomarkers are defined as “objective indications of medical state observed from outside the patient—which can be measured accurately and reproducibly.”

Biomarkers have 3 major potential roles in clinical practice: (1) to help the patient understand their risk of disease, which could lead to direct improvement of quality of life; (2) to direct the patient to make lifestyle changes that could improve health, such as restricting or improving dietary choices, becoming more active, and adhering to a plan laid out in collaboration with their physician; and (3) to direct a medical professional to make a (better) clinical decision based on known risk factors or disease(s) associated with a specific biomarker(s).

Given the complex pathophysiology of ischemic stroke, biomarkers that can stratify risk and identify those individuals most likely to have a cerebrovascular event are considered the “holy grail” of prognostic tools.

In the current issue of Neurology®, Shoamanesh et al.1 investigate the utility of measuring inflammatory, endothelial, and oxidative stress biomarkers in the prediction of incident ischemic stroke (IIS) risk. The authors assessed 15 biomarkers in 3,224 stroke-free Framingham Offspring Study (Framingham Heart Study [FHS]) participants attending exam cycle 7 between the years 1998 and 2001. Overall, 98 participants experienced IIS during a mean follow-up of 9.8 years (SD = 2.2). Utilizing survival analyses with Cox proportional hazard models, they calculated hazard ratios for IIS per SD increment of each biomarker in 2 different models. A basic model included age and sex as covariates and a full model additionally included the remaining variables of the Framingham Stroke Risk Profile, i.e., systolic blood pressure, hypertension treatment, current smoking, diabetes, cardiovascular disease, and atrial fibrillation.

The authors found that 4 inflammatory/endothelial biomarkers were associated with IIS in the FHS using their basic model. These included C-reactive protein (CRP), tumor necrosis factor receptor 2 (TNFR2), total homocysteine, and vascular endothelial growth factor. All associations, except for CRP, remained significant in the full model. Finally, addition of these 4 biomarkers to the clinical Framingham Stroke Risk Profile score improved stroke risk prediction with a net reclassification improvement of 0.34 (95% bootstrap confidence interval 0.12–0.57; p < 0.05). The net reclassification improvement has a range of −2 to +2 wherein a positive score indicates that some portion of participants were correctly reclassified.

This article addresses important questions in the search for biomarkers that could be used in both translational research and clinical practice to predict and prevent IIS. Testing multiple biomarkers, as this study did, could allow identification of different potential biological pathways involved in modulating the risk of ischemic stroke, given its extraordinarily complex and variable pathogenesis.4 The study by Shoamanesh et al. provides a platform to formulate future studies utilizing the full potential of circulating biomarkers, particularly in the related but independent area of primary prevention, which is even more complex. As an example, further prospective studies should validate sensitivity and specificity and replicate IIS-risk predictive performance of these biomarkers in the general population, and in the context of other biomarkers in this current era of -omics.5 In addition, large nonobservational studies specifically assessing the causal relationship of biomarker levels and stroke occurrence are needed to advance our knowledge and identify new molecular targets for translational research and development of novel specific management and therapeutic strategies.6

Regarding clinical practice, the multimarker approach1 and reclassification criteria8 used in this study helped to refine a well-established stroke risk clinical model, such as the Framingham Stroke Risk Profile score; it also helped to enhance individual stroke risk prediction, which has potential clinical implications. These methods, along with others,4 could improve the identification of subgroups of persons in the general population at highest risk of ischemic stroke, who should benefit from established and emerging personalized primary stroke preventive therapies. However, the benefit of systematically measuring these biomarkers for use in guidance of clinical decision-making, while also considering health care costs, should be further assessed...
in prospective investigations in order to fill the existing gaps and reconcile conflicting results in the literature.6

While Shoamanesh et al. present a well-executed analysis, the study has limitations. The main limitation relates to generalizability and thereby to broad clinical utility; participants of the FHS are almost entirely of European ancestry and application of these findings in other populations may not be tractable. In addition, as stated by the authors, they did not account for other clinical factors such as concurrent infection, renal impairment, chronic inflammatory/rheumatologic diseases, or malignancies that could affect measurements of all the biomarkers investigated. Furthermore, they did not account for preventive medications that affect stroke risk, such as statins or antithrombotic therapy, or underlying cerebral small vessel disease, which could have influenced the risk of IIS and inflammatory biomarker levels. The moderate sample size prevents us from drawing definitive conclusions on association between the identified biomarkers and stroke subtype, although exploratory analyses suggested an association among fibrinogen, interleukin 6, and TNFR2 and cardioembolic stroke and among CRP, TNFR2, total homocysteine, and vascular endothelial growth factor and atherosclerotic brain infarct. Biomarkers were only measured once, so we lack information on changes in their concentration over time. Finally, clinically relevant threshold values of these biomarkers were not explicitly identified for predicting the risk of IIS.

Considering the rich dataset available to FHS investigators, immediate future directions for this type of work are plentiful. Primarily, it would be of interest if the authors utilized genetic data to investigate not only the influence on the levels of these 15 biomarkers but also how genetic variants that are associated with biomarker levels directly influence risk of IIS. This could be a powerful approach, which in combination with the Framingham Stroke Risk Profile score, will be increasingly applicable as genomic information is transitioned into clinical care.

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DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES