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EDITORIAL COMMENT

Novel Markers for Adverse Events in Atrial Fibrillation*

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The prevalence of atrial fibrillation (AF) in adults >65 years of age in the U.S. population is about 10% (1). The hemodynamic impairment of AF is rarely disabling when the ventricular response rate is controlled. However, chronic AF is associated with formation of thrombi in the atrial appendage and thereby increases the risk of thromboembolic events. To avoid life-threatening embolic events, patients with chronic AF are routinely placed on anticoagulants. Whereas such therapy is demonstrably effective in reducing the risk of stroke, the anticoagulated patient is now at increased risk of intracranial and extracranial bleeding. Accordingly, the clinician must weigh the risk and benefits of anticoagulant therapy for the patient with AF. To this end, algorithms for risk prediction have been developed to aid clinicians in their management decisions.

The algorithms to stratify patients according to their risks for thromboembolism or bleeding primarily utilize clinical observational data rather than biochemical markers, and the relative impact of each component is not weighted (2). Not surprisingly, these risk stratification schemes overall have modest predictive value, because each scheme is developed in very different patient populations or clinical settings (3). Identification of new biochemical markers may improve the performance of risk stratification.

2 NEW MARKERS FOR RISK STRATIFICATION

In this issue of the *Journal,* Horowitz et al. (4) investigated 2 new biochemical markers that show promise for risk stratification of chronic AF patients on anticoagulant therapy. These markers were measured in plasma samples from 5,004 participants in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. In this trial, subjects were randomized to warfarin or apixaban; the latter was superior in preventing stroke or systemic embolism (hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.66 to 0.95), caused less bleeding (HR: 0.69; 95% CI: 0.60 to 0.80), and resulted in lower mortality (HR: 0.51; 95% CI: 0.35 to 0.75) over a median follow-up of 1.8 years.

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Horowitz et al. (4) describe a prospective substudy of ARISTOTLE to evaluate associations between major AF outcomes and plasma biomarkers, including asymmetric dimethylarginine (ADMA) or symmetric dimethylarginine (SDMA). The major AF outcomes included stroke or systemic embolism, acute myocardial infarction, International Society on Thrombosis and Hemostasis major bleeding, cardiovascular death (excluding hemorrhagic stroke), and all-cause mortality.

Plasma ADMA levels predicted thromboembolic events, whereas plasma SDMA levels predicted hemorrhagic events in AF patients on anticoagulants during a median follow-up period of 1.9 years. Incorporating these markers into the corresponding risk assessment schemes (CHA_2DS_2-VASc and HAS-BLED) improved the predictive value of these algorithms. Furthermore, high levels of both dimethylarginines were associated with increased mortality in those patients.

THE BIOLOGY OF ADMA AND SDMA

ADMA and SDMA are methylated derivatives of arginine residues in cellular proteins. Free dimethylarginines are released as a result of protein turnover

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and are detectible in the blood at high nanomolar concentrations (5). It is well known that dimethylarginines are able to suppress nitric oxide (NO) production by endothelium. ADMA is a competitive inhibitor of NO synthase (6). Both ADMA and SDMA can interfere with transport of arginine into the endothelium (reducing the availability of this NO precursor) (7). Furthermore, ADMA can increase the degradation of NO by increasing the generation of reactive oxidative species (8). Thus, an increase in plasma dimethylarginines (especially ADMA) in the circulation can suppress NO generation by the endothelium, increasing the risk for vascular inflammation, lesion formation, and thrombosis (9).

The primary elimination route for SDMA is renal excretion, and it may be a more sensitive marker of renal function than creatinine clearance (10). As impaired renal function is associated with an increase in major adverse cardiovascular events (MACE), this may explain the relationship between plasma SDMA levels and adverse events in patients with stable coronary heart disease or chronic kidney disease (11).

By contrast, renal clearance of ADMA plays a minor role in regulation of its plasma levels. The clearance of ADMA is primarily due to the activity of the enzyme dimethylarginine dimethylaminohydrolase, which is ubiquitously expressed in many cells (12).

PLASMA ADMA AS A RISK MARKER

In patients with cardiovascular risk factors, plasma ADMA levels are elevated, in large part due to reduced dimethylarginine dimethylaminohydrolase activity (13). This enzyme is very sensitive to oxidative stress, and therefore, its activity is diminished under conditions accompanied by increased reactive oxidative species formation, such as smoking, hyperglycemia, or high low-density lipoprotein levels (14).

Whereas plasma ADMA is elevated in the presence of cardiovascular risk factors, prior studies have revealed an independent association between blood ADMA and the risk for MACE in the general population, in patients with cardiovascular disease, or in those with renal insufficiency (15–18). Thus, plasma ADMA provides additional information regarding the risk of MACE. With respect to patients with AF, an increase in plasma ADMA increases the risk of ischemic stroke and cardiovascular death (19). This small cohort study (n = 141) is now confirmed in the current study in a much larger population.

ADMA AND ENDOTHELIAL DYSFUNCTION: A MECHANISM FOR THROMBOSIS IN AF

Because ADMA inhibits endothelial synthesis of NO (an endogenous antiplatelet agent and anti-inflammatory molecule), it is possible that high ADMA levels promote thrombus formation in the left atrial appendage in chronic AF patients by interfering with the homeostatic effects of NO. Thrombus formation is more likely in the presence of Virchow's triad: hypercoagulability, hemodynamic disturbance, and "injury" to the luminal wall (i.e., endothelial or endocardial damage or dysfunction), each of which are present in AF (20). An elevated plasma level of ADMA in AF would impair NO generation, causing an "injury" to the luminal cells that would favor platelet and leukocyte adherence and thrombus formation. Previous studies have demonstrated that AF patients have reduced endothelial NO synthase expression in the endocardium as well as decreased NO synthesis, as reflected by decreased NO metabolite levels, and impaired endothelium-dependent vasodilation in the peripheral vasculature (21).

It is still unclear whether endothelial dysfunction is a cause or a result of AF. Intriguingly, patients with lone AF have impaired flow-mediated endothelium-dependent vasodilation of the brachial artery, which could be improved by cardioversion (22). This finding suggests that AF may engender an impairment in endothelial function. However, it is also possible that impaired endothelial function may engender AF. Because NO is an important determinant of vascular resistance, and as ADMA may elevate systemic resistance and is elevated in hypertensive patients (23,24), it is possible that ADMA could contribute to hypertension-induced AF. In support of this hypothesis, the recurrence of AF after cardioversion or ablation is predicted by ADMA levels in several reports (19,25). However, a recent prospective study failed to show an association between the incidence of AF and plasma dimethylarginine levels (26).

SDMA AND RISK OF ADVERSE EVENTS

The correlation between plasma ADMA and thromboembolic events is consistent with its effect to reduce the generation of NO, an endogenous inhibitor of platelet adherence and aggregation. The association between SDMA and bleeding in AF patients is more difficult to explain. To our knowledge, the existing published data on SDMA and arrhythmias is limited to a single paper that describes a lack of relationship between AF incidence and SDMA