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Biomarkers (plasma trimethylamine-N-oxide) to predict atrial fibrillation: Are we there yet?

Mihail G. Chelu^{a,b} and Na Li^{c,d,e,*}

^aComprehensive Arrhythmia and Research Management (CARMA) Center, USA

^bCardiovascular Medicine Division, Section of Cardiac Electrophysiology, University of Utah, School of Medicine, Salt Lake City, UT, USA

^cDepartment of Medicine (Section of Cardiovascular Research), Baylor College of Medicine, Houston, TX, USA

^dCardiovascular Research Institute, Baylor College of Medicine, Houston, TX, USA

^eDepartment of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX, USA

Atrial fibrillation (AF) is the most prevalent arrhythmia and is projected to rise from 2.7–6.1 million in 2010 to 12.1 million by 2030 [1]. AF portends a 4–5 fold risk of ischemic stroke in non-anticoagulated patients, and is an independent risk factor for ischemic stroke severity, recurrence, and mortality [1]. Due to the alarming increase in global prevalence with the attached increase in morbidity, mortality, and cost there has been increased effort to identify risk factors in the hope that prevention would turn the tide of this disease [1,2]. However, none of the clinical factors or combination of clinical factors identified demonstrate a better or superior accuracy in the risk prediction: aging, hypertension, congestive heart failure, coronary artery disease, valvular heart disease, diabetes mellitus, male sex, left ventricular hypertrophy, obesity, excessive alcohol use, sleep apnea, physical inactivity and poor cardiorespiratory fitness [1,2]. Therefore, the focus has been directed toward identifying biomarkers that may refine the accuracy of predicting development of AF.

In this issue of the International Journal of Cardiology, Svingen et al. [3] investigated the association between plasma trimethylamine-N-oxide (TMAO) and incidence of subsequent AF in two cohorts of patients: Western Norway Coronary Angiography Cohort (WECAC; 3797 patients with suspected angina pectoris) and Hordaland Health Study (HUSK; 3143 elderly community participants). Plasma TMAO correlated with incident AF in both cohorts, albeit the correlation was weaker when correcting for multiple confounders. Similarly, the correlation was weaker in the HUSK than the WECAC cohort. It is important to note that one plasma TMAO measurement was linked to incident AF noted over a long period of time, median 7.3 (6.3–8.6) and 10.8 (8.3–11.1) years for the in WECAC and HUSK, respectively. Addition of TMAO to a model including clinical risk factors refined the net reclassification improvement (NRI) calculations but did not improve the C-statistics. Interestingly, although

*Corresponding author at: Department of Medicine (Section of Cardiovascular Research), Baylor College of Medicine, One Baylor Plaza, BCM285, Houston, TX 77030, USA. nal@bcm.edu (N. Li).

imperfect in estimation of dietary precursors, plasma TMAO had no or weak association with intake of betaine and choline, two known precursors of TMAO. Accounting for these precursors in the statistical models did not affect the correlation between plasma TMAO and incident AF. These findings suggest that dietary intake of precursor may have little influence on plasma TMAO. Thus, the plasma level of TMAO may be a stand-alone predictor for AF incidence.

The biogenesis of TMAO relies on gut metabolism [4,5]. First, the gut microbiota metabolizes dietary phosphatidylcholine and carnitine from red meat to trimethylamine (TMA) [4,5]. Then, absorbed TMA is transported through the portal circulation to the liver where it is oxidized by flavin containing monooxygenases to TMAO [4,5]. Without further modification, TMAO is almost entirely excreted into the urine by glomerular filtration [5]. Although the mechanisms are not elucidated, TMAO appears to provide a link between a typical Western diet and many of its unfavorable and undesirable consequences including obesity, metabolic syndrome, cardiovascular disease, and chronic kidney disease [5]. Indeed, TMAO has been identified as both biomarker and pathogenesis link in cardiovascular diseases including atherosclerosis, diabetic cardiovascular disease, and heart failure [4–7].

Although this epidemiological study by Svingen et al. [3] cannot establish a causal relationship between plasma TMAO and incident AF, the potential mechanistic link between TMAO and AF has been explored previously by others [8,9]. To date, two main mechanisms have been proposed to be contributing to the TMAO's proarrhythmic action in AF development: 1) an altered autonomic nerve input via ganglionated plexi (GP) modulation, and 2) an enhanced activation of $\text{NF}\kappa\text{B}$ -mediated inflammatory pathway signaling [8,9]. Hou et al. has shown in a dog model of AF induced by the atrial tachycardia pacing that application of TMAO to atrial GP directly can increase expression of nerve growth factors and exacerbate atrial electrical remodeling, creating a substrate for AF [8]. On the other hand, the involvement of inflammatory signaling in AF pathophysiology has been gaining research interests. Yu et al. have demonstrated that TMAO may promote an AF-substrate by evoking inflammatory response via activating the proinflammatory $\text{NF}\kappa\text{B}$ -p65 signaling pathway [9]. The latter may further influence the cardiac inflammasome signaling and promote AF by promoting ectopic activity and shortening of atrial effective refractory period as recently shown by Yao and colleagues [10]. However, it remains unknown whether the altered plasma level of TMAO due to either dietary intake or gut microbiota changes is sufficient to directly modulate the cardiac the autonomic nervous system or activate the inflammasome pathway in cardiomyocytes. Moreover, whether TMAO can serve as a pathologic link between gut microbiota/metabolism changes due to co-morbid conditions and the pathogenesis of AF remains elusive. Despite the limitations, the work by Svingen et al. [3] provides a potential path between gut metabolism and cardiac electrophysiology. Future work is needed to further establish the practical utility of TMAO as a biomarker refining the predictive value of current clinical risk factors for AF development.

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