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EDITORIAL

It's a "Gut Feeling": Association of Microbiota, Trimethylamine N-Oxide and Cardiovascular Outcomes

Gopi K. Kolluru, PhD; Christopher G. Kevil, PhD

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. Major adverse cardiac and cerebrovascular events (MACE), including chronic heart failure, myocardial infarction (MI), and stroke, are a major cause of premature death.[1] Atherosclerosis is a classic hallmark of CVD and other associated complications, including coronary artery disease, peripheral artery disease, diabetes mellitus, stroke, hyperlipidemia, hypertension, and aging, which poses a substantial threat to human health.[2,3] Importantly, rupture of an atherosclerotic plaque results in occlusion of distal artery territories, thereby critically reducing blood flow to vital tissues.

See Article by Gencer et al.

Several established and novel emerging biomarkers of vascular disease, including hs-CRP (high-sensitivity C-reactive protein), hs-TnT (high-sensitivity troponin T), and NT-proBNP (N-terminal pro-B-type natriuretic peptide), indicate various pathophysiological associations of CVD, including cardiovascular ischemic events and platelet activation.[4] Prospective cohort studies have also suggested an increase in circulating trimethylamine N-oxide (TMAO), a microbe-dependent metabolite biomarker with enhanced thrombotic potential, to be associated with MACE.[5,6] Increasing evidence suggests a strong association between TMAO and cardiometabolic defects, atherosclerosis, platelet activation, proinflammatory signaling, and chronic kidney disease.[7–10] The effects of gut microbiota and subsequent changes in TMAO levels have been involved in the underlying mechanisms contributing to CVD risk. Various therapeutic strategies targeting TMAO metabolism have been explored with various degrees of success.[11] Despite the accumulating evidence, the question remains whether TMAO is critically involved with MACE, independently involved with MI as a risk factor, and has a higher risk reduction for MACE with prolonged protective drugs.

Previous observations from the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin Thrombolysis in Myocardial Infarction 54) trial, a randomized case–control study, suggests that ticagrelor reduces cardiovascular events among aspirin-treated individuals with prior MI.[12] This issue of the *Journal of the American Heart Association* (*JAHA*) includes a study by Gencer et al that analyzed data from the PEGASUS-TIMI 54 trial revealing a strong association between TMAO and cardiovascular death or stroke.[13] The authors reveal the prognostic value of TMAO as a biomarker for risk assessment in patients with CVD, and whether TMAO levels subside over prolonged treatment with ticagrelor after a MI. Interestingly, associations of TMAO were

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Correspondence to: Christopher G. Kevil, PhD, Department of Pathology and Translational Pathobiology, LSU Health Shreveport, 1501 Kings Hwy, Shreveport, LA 71103. E-mail: ckevil@lsuhsc.edu

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stronger for patients with normal renal function compared with those who had an estimated glomerular filtration rate of >60 mL/min per 1.73 m^2. While ticagrelor has shown consistent early and late beneficial effects for secondary prevention after MI, this study revealed that the efficacy of ticagrelor was independent of the baseline TMAO (N=1803).

Established reports suggest a positive correlation between increased TMAO and adverse cardiovascular effects.[14–16] This study used odds ratios to determine the association of TMAO quartiles with the incidence of cardiovascular events and death.[13] After adjustment for potential confounding variables, including baseline clinical characteristics such as age, sex, estimated glomerular filtration rate, region, body mass index, hypertension, hypercholesterolemia, diabetes mellitus, smoking, peripheral artery disease, index event, aspirin dosage, and treatment arm, the findings show a significant association between higher TMAO levels and incident cardiovascular death or stroke. However, further adjustment for cardiovascular biomarkers—hs-TnT, hs-CRP, and NT-proBNP—attenuated the significance of associations between TMAO and cardiovascular death or stroke. Importantly, a significant reduction in MACE with ticagrelor was observed across TMAO quartiles.

TMAO is a metabolite of gut microflora, generated from dietary choline, betaine, and L-carnitine.[11,16] As such, dietary components significantly influence the levels of TMAO. Animal-origin foods such as meat (especially red meat) and eggs are a rich source of L-carnitine, and choline can trigger proatherosclerotic conditions, thereby elevating TMAO production. Multiple studies have established the association between chronic red meat consumption to elevated TMAO levels and the risk of heart disease alike in both men and women.[17,18] Interestingly, γ-butyrobetaine, a metabolite of dietary L-carnitine, can convert L-carnitine to the TMAO that is pro-atherogenic.[19] Previous studies establish an association between increased plasma choline/betaine levels and the risk of MACE with elevated TMAO.[15,20] Conversely, in the current study no such significance was observed between plasma choline/betaine and the risks of MACE. It would be informative to identify the changes in precursor levels, including γ-butyrobetaine or L-carnitine levels that influence TMAO production, as it is evident that diet influences the association between TMAO and atherosclerosis. Subsequently, information on nutritional habits of the study population has to be considered to clarify the association between TMAO–diet–CV outcome, which was not identified in this study.

Overall, Gencer et al[13] establish a positive correlation between elevated TMAO and an increased risk of cardiovascular events. Their study further demonstrates prolonged ticagrelor treatment as an effective therapeutic measure with beneficial effects for cardiovascular outcomes, independent of TMAO levels. This study further establishes that elevated systemic TMAO levels in patients with prior MI could lead to increased risk of cardiovascular complications, including stroke and ultimately death. However, considering TMAO levels as a biomarker in the case of repeated MI is less robust compared with traditional clinical risk factors and previously established biomarkers.

ARTICLE INFORMATION

Affiliations

From the Department of Pathology and Translational Pathobiology, Louisiana State University Health Sciences Center at Shreveport, LA.

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Disclosures

None.

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