Article

Trimethylamine *N*-Oxide and Cardiovascular Outcomes in Patients with End-stage Kidney Disease Receiving Maintenance Hemodialysis

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Abstract

Background and objectives Trimethylamine *N*-oxide (TMAO), a compound derived from byproducts of intestinal bacteria, has been shown to accelerate atherosclerosis in rodents. To date, there are conflicting data regarding the association of serum TMAO with cardiovascular outcomes in patients with ESKD, a population exhibiting both high serum TMAO and excessive atherosclerosis.

Design, setting, participants, & measurements We measured baseline serum TMAO concentrations in a subset of participants (n=1243) from the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial and conducted *post hoc* analyses evaluating the association between baseline serum TMAO and cardiovascular outcomes.

Results We observed a wide distribution of serum TMAO in our cohort, with approximately 80% of participants exhibiting TMAO concentrations ≥56 μM and a maximum TMAO concentration of 1103.1 μM. We found no association between TMAO and our primary outcome, a composite of cardiovascular mortality, myocardial infarction, peripheral vascular event, stroke, and hospitalization for unstable angina. Moreover, in unadjusted and adjusted analyses, we observed no relation between TMAO and all-cause mortality, the independent components of our composite outcome, or the original EVOLVE primary outcome. Although we did observe higher TMAO concentrations in white participants, further subgroup analyses did not confirm the previously identified interaction between TMAO and race observed in a prior study in patients receiving dialysis.

Conclusions We found no evidence linking TMAO to adverse clinical outcomes in patients receiving maintenance hemodialysis with moderate to severe secondary hyperparathyroidism.
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Patients with CKD demonstrate a disproportionate burden of atherosclerosis compared with individuals with normal or near normal kidney function (1–5), which is largely responsible for the excessive morbidity and mortality in this group. Moreover, a higher prevalence of traditional risk factors for the development of atherosclerosis, such as diabetes and hypertension, does not fully account for the accelerated atherosclerosis observed in patients with CKD, implying that unique risk factors must be present in this population (6,7).

Evolving evidence suggests that toxins that are byproducts of intestinal bacteria may facilitate the development of multiple pathologic processes commonly associated with impaired kidney function, including atherosclerosis (8). One such bacterial byproduct is trimethylamine *N*-oxide (TMAO), an organic compound derived from the metabolism of dietary L-carnitine and choline by intestinal bacteria (9–12). Interestingly, published evidence from our group and others suggests that circulating concentrations of

TMAO increase in early CKD and become substantially elevated in more advanced stages of disease (13–16), potentially supporting a role of TMAO in the promotion of cardiovascular disease that accompanies CKD progression.

To date, there are limited data on the association of serum TMAO with cardiovascular outcomes in patients receiving dialysis (17,18), a population exhibiting both a marked elevation in serum TMAO and an exceedingly high risk for cardiovascular morbidity and mortality. Thus, in this study, we performed a *post hoc* analysis to investigate the association between baseline serum TMAO and cardiovascular outcomes in participants from the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial (19), a large, international, randomized, clinical trial that tested the effects of cinacalcet versus placebo on mortality and cardiovascular events in patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism.

Materials and Methods

Study Participants and Design

EVOLVE was a global clinical trial that included 3883 patients receiving maintenance hemodialysis with moderate to severe secondary hyperparathyroidism enrolled from 22 countries. Patients were randomized to receive cinacalcet or placebo (on top of standard of care therapies, typically including phosphate binders and vitamin D analogs) and were followed longitudinally to determine effects on mortality and cardiovascular events (19). A detailed description of the EVOLVE trial design and end point adjudication is summarized in the supplemental materials that accompanied the original EVOLVE trial publication (19). EVOLVE trial participants consented for storage of serum samples collected at prespecified intervals throughout the study.

We obtained stored baseline serum samples (of sufficient quality) from 1243 placebo-treated patients for measurement of TMAO concentrations. The primary outcome was a vascular composite outcome defined as a composite of cardiovascular death, myocardial infarction (MI), peripheral vascular event, stroke, and hospitalization for unstable angina. Secondary outcomes included the individual components of the primary outcome, along with all-cause death, noncardiovascular death, and the primary composite outcome from the original EVOLVE trial (all cause death, MI, hospitalization for unstable angina, heart failure, and peripheral vascular event) (19).

TMAO Quantification

We measured serum TMAO concentrations by ultra-high-performance liquid chromatography-tandem mass spectrometry using heated electrospray ionization (positive mode) and selected reaction monitoring as previously described (20). The standard curve ranged from 0.010 to 5.00 μg/ml (0.13–66.6 μM). Samples that were above the upper limit of the standard curve were diluted in PBS to within the assay range. The within-run and between-run precision (percent coefficient of variation) was <10%.

Statistical Analyses

We measured TMAO in a subset (*n*=1243) of the 1935 (64%) patients randomized to the placebo arm in the EVOLVE trial. The EVOLVE trial randomized patients within strata defined by diabetes and country; all analyses accounted for the stratification factors. Descriptive statistics (means and SD, medians and interquartile ranges or ranges, or frequencies and percentages) were reported for each patient characteristic by quintile of TMAO, along with a test for trend across quintiles. Each test for trend was estimated by including TMAO quintile as a continuous predictor of the demographic in a generalized estimating equations model that adjusted for the clustering within strata.

The primary explanatory measure for all survival models was the natural log of TMAO, or ln(TMAO), and we used Cox proportional hazards models to estimate the hazard of all-cause mortality from ln(TMAO). For all other outcomes, such as cardiac death and MI, we adjusted for potential competing events (other-cause or all-cause death) using Fine and Gray's subdistribution hazard model (21). For all hazard models, time was measured in months beginning at entry into the trial with a maximum follow-up time of 64 months. Patients were censored if they were lost to follow-up or reached the end of the study without observing the outcome of interest. We further adjusted these models for important baseline covariates, including age, sex, body mass index (categorized as <18.5, 18.5–25, and >25 kg/m^2), systolic BP (categorized as <130, 130–160, and >160 mm Hg), albumin, race (black versus nonblack), dialysis vintage, BUN, history of smoking, MI, stroke, other cardiovascular disease, and percutaneous coronary intervention. To examine the interaction between TMAO and race for the outcomes of interest, we included a multiplicative term in the original models and in separate models compared subgroup estimates in black versus white race. We performed a complete case analysis for the models where five (0.4%) patients were dropped from the original cohort because of missing data. A total of 33 patients had incomplete follow-up. For all models, we checked the proportional hazards assumption by examining the Schoenfeld residuals and found that no covariates violated the assumption.

Results

Participant Demographic Characteristics

In Table 1, we compare the demographic characteristics of the study population at baseline across quintiles of TMAO. The study population was predominantly men, 50–60 years of age, and white, with a mean dialysis vintage of approximately 4 years. An extraordinarily wide range of TMAO concentrations was observed, from a minimum value of 2.5 μM, up to a maximum value of 1103.1 μM. When subdivided by quintiles, patients in the lowest quintile exhibited a TMAO cut-off of ≤56.6 μM, whereas the TMAO range for the highest quintile was 155–1103 μM.

Risk of Cardiovascular Outcomes

In our evaluation of the association between baseline serum ln(TMAO) and risk of cardiovascular outcomes during the follow-up period (Table 2), we found no significant associations between TMAO and cardiovascular outcomes in unadjusted and adjusted analyses. We also considered the association between TMAO and risk of all-cause mortality (the sum of cardiac and noncardiac death) and found no significant association. Additional analyses evaluating the association between TMAO quintiles and cardiovascular outcomes yielded similar findings to our models utilizing ln(TMAO) (Supplemental Table 1). The adjusted cumulative incidence of the vascular composite, cardiac death, and noncardiac death for each quintile of TMAO are graphically displayed in Figure 1. Receiver operating classification curves were generated to evaluate for a potential threshold effect of TMAO on the outcomes of interest (Supplemental Figure 1). For all outcomes, the receiver operating classification curve is close to the diagonal, indicating no threshold effect.

Subgroup Analyses

On the basis of a prior report suggesting an interaction between race and TMAO in a separate ESKD cohort (18), we performed additional subgroup analyses to determine if

Table 1. Demographics by TMAO quintile

Group ID	All	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
No. per group	n=1243	n=248	n=249	n=249	n=249	n=248
(TMAO range)	(2.5–1103.1 μM)	(≤ 56.6 μM)	(56.7–79.5 μM)	(79.6–107.8 μM)	(107.9–155.2 μM)	(>155.2 μM)
(ln[TMAO] range)	(0.91–7.01)	(0.91–4.04)	(4.04–4.37)	(4.37–4.68)	(4.68–5.04)	(5.05–7.01)
Age, yr, mean (SD)	54 (14)	53 (15)	53 (15)	54 (14)	53 (13)	56 (13)
Women	495 (40%)	104 (42%)	102 (41%)	96 (39%)	102 (41%)	91 (37%)
Race						
Black	256 (21%)	84 (34%)	58 (23%)	42 (17%)	33 (13%)	39 (16%)
White	704 (57%)	116 (47%)	126 (77%)	152 (61%)	155 (62%)	155 (63%)
Other	283 (23%)	48 (19%)	65 (26%)	55 (22%)	61 (25%)	54 (22%)
Dialysis vintage, mo, median (IQR)[a]	48 (23–88)	39 (19–75)	46 (22–87)	57 (21–105)	50 (26–86)	51 (25–82)
Smoking status						
Never smoker	704 (57%)	137 (55%)	138 (55%)	137 (55%)	149 (60%)	143 (58%)
Current smoker	326 (26%)	66 (27%)	68 (27%)	64 (26%)	66 (27%)	62 (25%)
Former smoker	213 (17%)	45 (18%)	43 (17%)	48 (19%)	34 (14%)	43 (17%)
Systolic BP, mm Hg						
<130	348 (28%)	74 (30%)	71 (29%)	66 (27%)	66 (27%)	71 (29%)
130–160	622 (50%)	107 (43%)	107 (43%)	125 (50%)	141 (57%)	122 (49%)
>160	273 (22%)	67 (27%)	51 (21%)	58 (23%)	42 (17%)	55 (22%)
Body mass index, kg/m2[b]						
<18	24 (2%)	6 (2%)	5 (2%)	4 (2%)	5 (2%)	4 (2%)
18–25	456 (37%)	92 (37%)	94 (38%)	100 (40%)	92 (37%)	78 (32%)
>25	718 (58%)	146 (59%)	141 (57%)	136 (55%)	139 (56%)	156 (63%)
Abnormal baseline ECG	736 (59%)	144 (58%)	149 (60%)	146 (59%)	148 (59%)	149 (60%)
Diabetes (type 1/2)	391 (32%)	88 (36%)	73 (29%)	66 (27%)	77 (31%)	87 (35%)
Chronic atrial fibrillation	76 (6%)	11 (4%)	12 (5%)	17 (7%)	16 (6%)	20 (8%)
Arrhythmia of any type	183 (15%)	32 (13%)	30 (12%)	43 (17%)	34 (14%)	44 (18%)
Hypertension	1137 (92%)	237 (96%)	222 (89%)	226 (91%)	223 (90%)	229 (92%)
Coronary artery bypass graft	91 (7%)	15 (6%)	22 (9%)	16 (6%)	18 (7%)	20 (8%)
Myocardial infarction	148 (12%)	29 (12%)	27 (11%)	30 (12%)	31 (12%)	31 (13%)
Heart failure	276 (22%)	58 (23%)	64 (26%)	47 (19%)	51 (21%)	56 (23%)
Stroke	132 (11%)	23 (9%)	28 (11%)	26 (10%)	28 (11%)	27 (11%)
Peripheral arterial disease	201 (16%)	40 (16%)	34 (14%)	45 (18%)	37 (15%)	45 (18%)
Amputation	80 (6%)	21 (9%)	15 (6%)	15 (6%)	14 (6%)	15 (6%)
Baseline drug use						
Calcium-based phosphate binders	673 (54%)	126 (50.8%)	135 (54%)	129 (52%)	151 (61%)	132 (53%)
Baseline vitamin D	750 (60%)	157 (63.3%)	152 (61%)	155 (62%)	125 (50%)	161 (65%)
Baseline laboratory values						
Corrected calcium, mg/dl, mean (SD)	9.8 (0.7)	9.8 (0.7)	9.9 (0.7)	9.8 (0.7)	9.8 (0.7)	9.8 (0.6)
Phosphorus, mg/dl, mean (SD)	6.5 (1.4)	6.2 (1.5)	6.4 (1.4)	6.5 (1.3)	6.7 (1.4)	6.5 (1.4)
Intact PTH, pg/ml, median (IQR)	690 (477–1122)	632 (482–1068)	646 (457–937)	790 (496–1197)	786 (471–1170)	709 (480–1160)
FGF23, pg/ml, median (IQR)	5570 (1740–12,700)	4305 (1125–13,225)	4980 (1690–11,770)	6385 (1885–12,740)	6650 (2350–12,970)	5440 (1720–12,050)
Hemoglobin, g/dl	11.9 (1.5)	11.8 (1.6)	11.8 (1.5)	12.0 (1.6)	11.8 (1.5)	11.9 (1.5)
BUN, mg/dl	62 (19)	52 (17)	57 (17)	63 (18)	68 (18)	70 (19)
Albumin, g/dl, mean (SD)	3.7 (0.4)	3.7 (0.4)	3.7 (0.4)	3.7 (0.4)	3.7 (0.3)	3.6 (0.3)
Baseline dialysis dose, spKt/V, mean (SD)	1.5 (0.3)	1.5 (0.3)	1.5 (0.3)	1.5 (0.3)	1.4 (0.3)	1.5 (0.3)

All data are shown as n (%) unless otherwise indicated. TMAO, trimethylamine N-oxide; IQR, interquartile range; ECG, electrocardiogram; PTH, parathyroid hormone; spKt/V, single-pool Kt/V; FGF23, fibroblast growth factor 23.
[a]One patient missing dialysis vintage, six patients missing FGF23, 96 patients missing hemoglobin, four patients missing BUN.
[b]3.6% of patients were missing BMI.

there was an interaction between race and TMAO on the measured outcomes in our cohort. We stratified the models for cardiovascular outcomes by race (restricted to black and white, n=960) and observed no interaction between race and TMAO in our models (P>0.05 for the interaction between race and TMAO for all outcomes; Supplemental Figure 2). In all cases, except for noncardiac death in black participants, the confidence intervals for the TMAO-related hazard ratios/subdistribution hazard ratios cross the null

(null, 1), indicating no statistical association (Supplemental Figure 2). In separate analyses, we stratified the models by TMAO quintile and examined the hazard ratio of black compared with white participants within each quintile (Supplemental Table 2). In these analyses, black participants had a significantly lower risk of cardiovascular outcomes compared with white participants in the lowest quintile of TMAO, and in the higher quintiles the association was reversed (NS).

Table 2.   Association between log(TMAO) and adverse clinical outcomes

Outcomes	Events (n)	Unadjusted SHR/ HR (95% CI)	Adjusted, Model 1[a] SHR/HR (95% CI)	Adjusted, Model 2[b] SHR/HR (95% CI)
Vascular composite (CV death, MI, HUA, PVE, stroke)[c]	434	1.14 (0.99 to 1.31)	1.03 (0.89 to 1.21)	1.07 (0.93 to 1.24)
EVOLVE primary composite (all-cause mortality, MI, HUA, HF, PVE)	604	1.01 (0.89 to 1.14)	0.94 (0.82 to 1.08)	0.95 (0.84 to 1.08)
All-cause mortality	458	1.02 (0.88 to 1.17)	0.94 (0.80 to 1.10)	0.96 (0.83 to 1.11)
Cardiovascular mortality (CV death)[c]	249	1.14 (0.93 to 1.39)	1.05 (0.85 to 1.29)	1.09 (0.89 to 1.32)
Noncardiovascular mortality[d]	209	0.91 (0.76 to 1.09)	0.86 (0.71 to 1.05)	0.88 (0.73 to 1.06)
Myocardial infarction (MI)[e]	117	1.25 (0.95 to 1.64)	1.18 (0.87 to 1.60)	1.24 (0.93 to 1.66)
Peripheral vascular event (PVE)[e]	129	1.13 (0.90 to 1.42)	1.10 (0.86 to 1.40)	1.10 (0.87 to 1.39)
Stroke[e]	71	1.16 (0.84 to 1.60)	1.25 (0.89 to 1.70)	1.20 (0.88 to 1.64)
Hospitalization for unstable angina (HUA)[e]	48	0.75 (0.51 to 1.10)	0.68 (0.43 to 1.06)	0.69 (0.45 to 1.06)

TMAO, trimethylamine N-oxide; SHR/HR, subdistribution hazard ratio/hazard ratio; 95% CI, 95% confidence interval; HF, heart failure; MI, myocardial infarction.
[a]Model 1 was adjusted for age, sex, body mass index (categorized as <18, 18–25, and >25 kg/m^2), systolic BP (categorized as <130, 130–160, and >160 mm Hg), albumin, race (black and nonblack), dialysis duration, history of smoking, history of cardiovascular disease, history of percutaneous coronary intervention, history of stroke, history of MI, BUN, and the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events study design.
[b]Model 2 was adjusted for same variables listed in model 1, except BUN.
[c]Adjusted for the competing risk of noncardiac death.
[d]Adjusted for the competing risk of cardiac death.
[e]Adjusted for the competing risk of all-cause death.

Discussion

Recent reports support an independent association between serum TMAO and cardiovascular outcomes in patients with nondialysis-requiring CKD; however, similar studies exploring the relation between TMAO and cardiovascular outcomes in patients receiving dialysis, the population demonstrating the highest chronic systemic exposure (i.e., highest serum concentrations) of TMAO, have thus far yielded conflicting conclusions (17,18). Our current investigation further explored the relation between TMAO and cardiovascular outcomes in a relatively large sample of patients on hemodialysis with moderate to severe secondary hyperparathyroidism, with the hope of confirming or refuting previously published findings. The EVOLVE trial participants represented a nearly ideal cohort for our analysis on the basis of several factors, which included relatively large trial enrollment, an international distribution of recruitment centers, the inclusion of patients exhibiting a broad range of TMAO concentrations and a high rate of cardiovascular outcomes, significant racial and ethnic diversity, meticulous adjudication of cardiovascular end points, and a placebo arm receiving no active therapy.

Our first notable observation was a vast distribution of serum TMAO concentrations among the 1243 participants included in our study, with a minimum concentration of 2.5 μM (comparable with someone with normal kidney function) to a maximum concentration of 1103.1 μM. After stratifying our TMAO data by quintiles (Table 1), we found several baseline clinical attributes associated with TMAO concentrations. Of the baseline demographic data, both age and race demonstrated a significant trend across TMAO quintiles. We observed the highest TMAO quintile to contain a slightly older population (56 years versus 53 years for quintile 1; P=0.005 for trend) that was skewed toward the inclusion of more white patients (63% versus 47% for

quintile 1; P=0.02 for trend). Additionally, several laboratory parameters appeared to trend across TMAO quintiles, with patients in the highest quintile exhibiting higher serum phosphate and BUN concentrations. The relation between TMAO, phosphate, and BUN may be explained by variations in diet. One of the primary precursors to TMAO formation is L-carnitine, an amino acid that is found at high concentrations in red meat, which also serves as a significant dietary source for urea and phosphate. Alternatively, these associations could be explained by one or more complex alterations in metabolic pathways responsible for TMAO formation in the setting of uremia, including production of TMA from dietary precursors by gut microbiota and conversion of TMA to TMAO by hepatic flavin-containing monooxygenases (22). As such, TMAO has been demonstrated to protect living organisms from the protein denaturing effects produced by high concentrations of urea (23,24); thus, it is plausible that patients exhibiting higher circulating concentrations of BUN may possess a propensity toward greater TMAO formation to counteract the effects of azotemia.

We performed analyses examining the relationship between TMAO and our primary outcome of interest (composite of cardiovascular death, MI, peripheral vascular event, stroke, and hospitalization for unstable angina), as well as the association with secondary outcomes, including all-cause mortality, noncardiac mortality, the individual components of our primary outcome, and the original EVOLVE trial composite outcome, and showed no significant associations. When evaluating the relation between the cumulative incidence of our primary outcome and individual quintiles of TMAO, we observed no obvious association between the cumulative incidence of the primary outcome and elevated TMAO concentrations. It is plausible that the extreme increases in serum TMAO
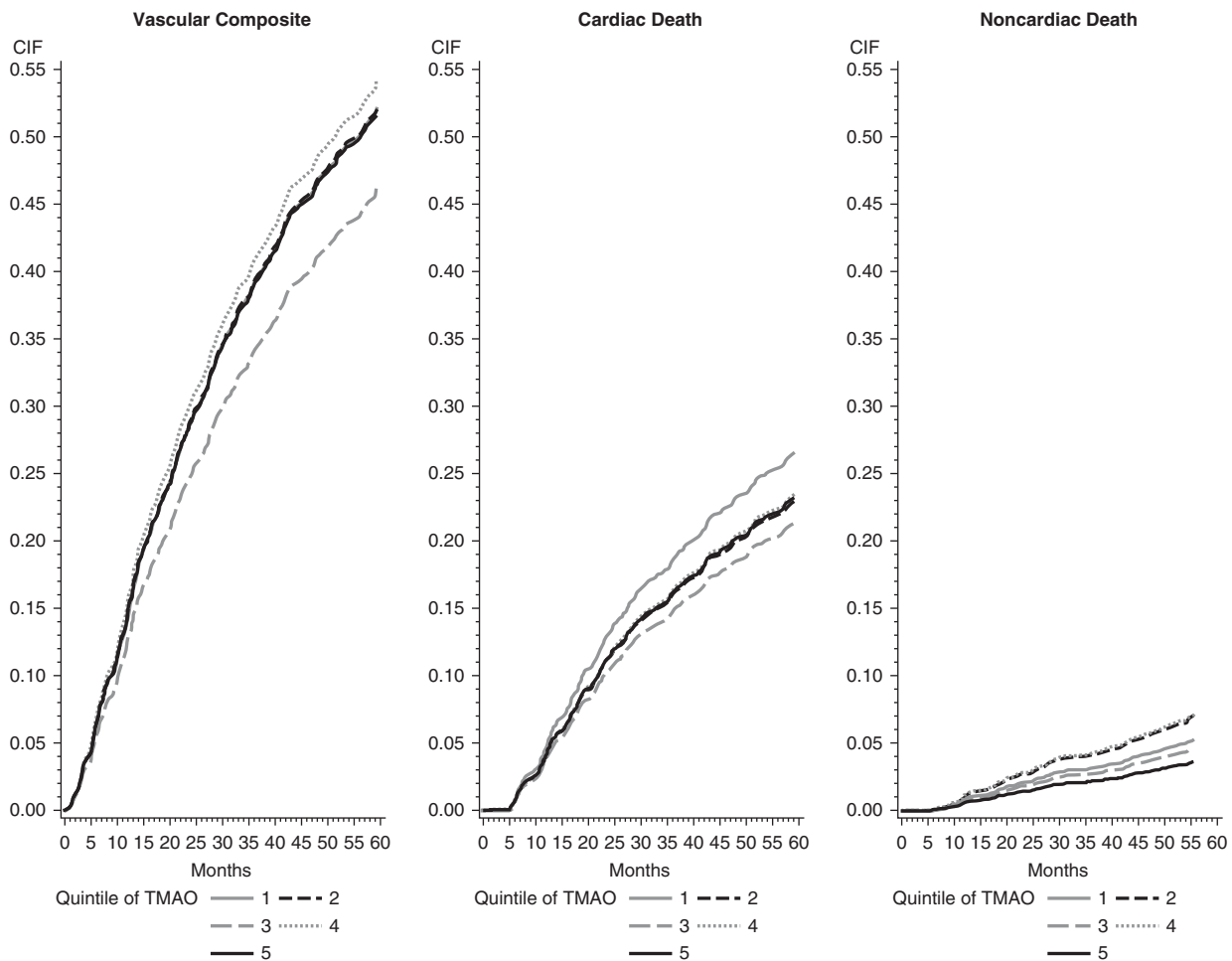
Figure 1. | **Association between TMAO and select cardiovascular and noncardiovascular outcomes.** Adjusted cumulative incidence of the vascular composite (left), cardiac death (middle), and noncardiac death (right), by TMAO quintile ($P>0.05$ for all listed outcomes).

observed in patients with ESKD could still possess incremental cardiovascular risk; however, this risk may be counterbalanced by some protective effects of TMAO in the setting of uremia (*i.e.*, protein stabilization).

It is important to contrast our findings with those of other groups. To date, only two prior publications exist that have examined the relation between TMAO and cardiovascular outcomes specifically in patients receiving dialysis. Kaysen *et al.* (17) explored the association between baseline TMAO and all-cause or cardiovascular mortality, as well as cardiovascular hospitalizations, in 235 participants from the Comprehensive Dialysis Study (CDS), a prospective, multicenter cohort study (a special study of the US Renal Data System [USRDS]) evaluating the relation between nutritional status and adverse outcomes in patients new to dialysis. No independent association was observed between baseline TMAO concentrations and either all-cause mortality, cardiovascular death, or cardiovascular hospitalization. Because the USRDS only includes hospitalization data for Medicare beneficiaries, data on cardiovascular hospitalization were only available on a subset of the CDS cohort (*n*=152, 65%). Thus, the power to detect associations between serum TMAO concentrations and outcomes was limited in this investigation.

Most recently, Shafi *et al.* performed a *post hoc* analysis of TMAO concentrations (obtained from samples collected 3–6 months postrandomization) in 1232 participants from the HEMO study (18), a randomized trial sponsored by the National Institutes of Health, comparing higher versus standard urea clearance and high versus low flux dialyzers on all-cause mortality and a series of secondary outcomes, including cardiovascular and noncardiovascular hospitalization, changes in serum albumin, and health-related quality of life. The investigators found white patients exhibited a higher risk of cardiovascular events compared with black patients for a given TMAO concentration. In the highest TMAO quintile (>135 μM), white patients demonstrated a four-fold higher risk of cardiac death compared with black patients. Although this finding is intriguing, particularly given the previously described lower risk of death for black patients receiving dialysis relative to white patients with comparable comorbidities (25,26), we were unable to confirm these findings within a restricted sample (black and white race only, *n*=960) of EVOLVE trial participants (Supplemental Figure 2).

Our current investigation has several important limitations. First, we did not have information on dietary

habits of individuals in the EVOLVE trial cohort. Moreover, in addition to the types of foods consumed by study participants, the temporal relation between food consumption and blood sampling and how this may have acutely altered serum TMAO concentrations is unclear. Second, limited time and resources prevented us from performing repeat TMAO measurements at additional study time points to reduce misclassification related to the single baseline TMAO value. Third, EVOLVE trial participants had moderate to severe secondary hyperparathyroidism, so the results observed may not be generalizable to patients receiving hemodialysis who exhibit lesser severity of secondary hyperparathyroidism, or patients receiving peritoneal dialysis. Finally, information on residual kidney function was not collected in the EVOLVE trial. Because patients with residual kidney function could exhibit improved solute clearance and less severe interdialytic fluid retention, this could be an important confounder to studies examining cardiovascular outcomes in patients receiving chronic dialysis. Important strengths of our investigation include a relatively large sample size, a precise and well described method of TMAO quantification, a racially and clinically diverse international cohort, the inclusion of participants receiving placebo therapy (which avoided modifying effects of calcimimetic therapy), and most importantly, adjudication of all cardiovascular endpoints.

In conclusion, although evidence suggests that TMAO may be an independent risk factor for adverse cardiovascular outcomes in patients with nondialysis-requiring CKD and in persons with normal or near normal kidney function, we observed no significant associations between serum TMAO and cardiovascular outcomes in patients on hemodialysis with moderate to severe secondary hyperparathyroidism. Although this study does not exclude a role for TMAO in cardiovascular disease in uremia, it does not support interventions aimed solely at reduction of TMAO once patients have reached ESKD.

Disclosures

The original EVOLVE trial was funded by Amgen. G.M.C. served on the Academic Executive Committee for the EVOLVE trial and currently serves on the Publication Committee for the EVOLVE trial. G.M.C. has received funding from Amgen to conduct secondary analyses of the EVOLVE trial.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.06190518/-/DCSupplemental.

Supplemental Table 1. Association between quintiles of TMAO and adverse clinical outcomes.

Supplemental Table 2. Hazard/subdistribution hazard ratio for each outcome and race (black versus white) stratified by quintile of TMAO.

Supplemental Figure 1. Receiver operating classification curve for primary and secondary outcomes.

Supplemental Figure 2. Subgroup analysis for clinical outcomes stratified by race.

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