Clinical Chemistry 63:5
000–000 (2017)

Letters to the Editor

In Reply

In our manuscript, trimethylamine *N*-oxide (TMAO),[1] as the biomarker of focus, was analyzed retrospectively after previously understanding its prognostic ability in acute heart failure *(1)*, and we hypothesized that it might be prognostic for other acute cardiovascular conditions, namely acute myocardial infarction (MI). For this, we used a well-documented historical cohort that had been previously investigated for several biomarkers, including N-terminal pro B–type natriuretic peptide (NT-proBNP), and therefore would allow for comparison of the predictive ability of TMAO to the previously investigated/established biomarkers (e.g., proenkephalin) *(2)*. Previous analysis in this cohort has shown NT-proBNP to be a marker of adverse outcome when used alone *(3)* but not when combined with other contemporary markers (e.g., proenkephalin) *(2)*. The plasma concentrations of NT-proBNP were measured within 12–24 months of sample collection using an inhouse assay that has shown strong correlation with the Roche Diagnostics assay ($r = 0.90$) *(2)*.

In response to the present inquiry, additional analyses of the available NT-proBNP data over different time points (i.e., admission and discharge) were performed. Circulating concentrations at admission were approximately 20% higher than at later time points [median (interquartile range) 1075 (324–2692) pmol/L vs 812 (259–2199) pmol/L, respectively]. To investigate the prognostic ability of NT-proBNP, we used fully loaded Cox regression models including NT-proBNP, but excluding TMAO, which indicated that NT-proBNP concentrations at admission were not able to independently predict outcome at 6 months or 2 years ($P > 0.1$), with discharge samples prognostic at 6 months ($P \leq 0.048$) but not 2 years ($P > 0.1$). These results are consistent with a previous report using this cohort *(2)*.

As described within the manuscript, the patients in our study were representative of a patient population treated with a prior, more risk-averse approach to invasive revascularization procedures consistent with standard of care at the time. Statistical investigations were appropriately adjusted for the rates of revascularization. The mentioned manuscript by Heeschen et al. *(4)* used patients originating from the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study, which also showed similar rates of revascularization at 30 days (26% vs 21%, respectively) *(5)*. However, our cohort does reflect a much larger proportion of ST-elevation MI (47% vs 7%, respectively); but, as we did with revascularization, we adjusted our analyses by including ST-elevation MI class in the regression statistics.

In conclusion, plasma NT-proBNP concentrations in our cohort of acute MI patients were not able to independently predict outcome at 6 months or 2 years when included in a fully loaded Cox regression model including the biomarker of focus, TMAO. Exclusion of TMAO allowed prognostic prediction of adverse outcome at 6 months, but only in samples collected at discharge. Alternative demographics were observed in comparison to a previous cohort and did not follow similar prognostic qualities to previous reports, although the shortest term prediction we investigated was at 6 months, compared to previous investigation at 30 days *(4)*. Despite discrepancies among cohorts, BNP measurements have been collectively shown to predict outcome in acute coronary syndrome investigations and remain an important aspect of clinical practice.

[1] Nonstandard abbreviations: TMAO, trimethylamine *N*-oxide; MI, myocardial infarction; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

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Previously published online at DOI: 10.1373/clinchem.2017.272112