

## **SUPPLEMENTAL DATA**

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

Outcomes	Quintile	Unadjusted SHR/HR (CI)	Adjusted – Model 1* SHR/HR (CI)	Adjusted – Model 2** SHR/HR (CI)
Vascular Composite (CV Death, MI, HUA, MI, PVE, Stroke) <sup>§</sup>	Q2	1.20 (0.88-1.63)	1.08 (0.78-1.50)	1.10 (0.80-1.53)
	Q3	1.17 (0.86-1.60)	0.98 (0.71-1.36)	1.01 (0.73-1.39)
	Q4	1.08 (0.79-1.47)	1.03 (0.74-1.44)	1.09 (0.79-1.50)
	Q5	1.38 (1.03-1.84)	1.08 (0.78-1.50)	1.16 (0.86-1.57)
EVOLVE Primary Composite (All-cause Death, MI, HUA, HF, PVE)	Q2	1.12 (0.87-1.45)	1.06 (0.82-1.38)	1.07 (0.82-1.39)
	Q3	1.00 (0.77-1.31)	0.85 (0.64-1.12)	0.85 (0.65-1.12)
	Q4	1.01 (0.78-1.31)	0.99 (0.75-1.31)	1.00 (0.76-1.32)
	Q5	1.03 (0.80-1.34)	0.86 (0.64-1.14)	0.88 (0.67-1.15)
All-cause Mortality (HR)	Q2	1.22 (0.91-1.63)	1.18 (0.87-1.60)	1.20 (0.88-1.62)
	Q3	0.98 (0.72-1.34)	0.85 (0.62-1.18)	0.86 (0.63-1.19)
	Q4	1.06 (0.78-1.43)	1.03 (0.74-1.43)	1.06 (0.77-1.46)
	Q5	1.02 (0.75-1.38)	0.84 (0.60-1.17)	0.88 (0.64-1.20)
Cardiovascular Mortality (CV death) <sup>§</sup>	Q2	1.05 (0.71-1.55)	0.88 (0.57-1.34)	0.90 (0.59-1.37)
	Q3	1.00 (0.67-1.50)	0.90 (0.59-1.38)	0.93 (0.61-1.41)
	Q4	0.86 (0.57-1.29)	0.86 (0.55-1.33)	0.90 (0.59-1.38)
	Q5	1.24 (0.85-1.80)	0.97 (0.65-1.46)	1.05 (0.72-1.53)
Non-cardiovascular Mortality <sup>¥</sup>	Q2	1.39 (0.91-2.11)	1.43 (0.92-2.23)	1.44 (0.93-2.25)
	Q3	1.01 (0.64-1.58)	0.89 (0.55-1.45)	0.90 (0.55-1.46)
	Q4	1.37 (0.89-2.10)	1.36 (0.86-2.15)	1.40 (0.89-2.21)
	Q5	0.83 (0.52-1.32)	0.73 (0.44-1.21)	0.76 (0.46-1.24)

Myocardial Infarction (MI) <sup>+</sup>	Q2	1.34 (0.73-2.46)	1.23 (0.65-2.35)	1.28 (0.68-2.41)
	Q3	1.53 (0.85-2.76)	1.32 (0.69-2.54)	1.40 (0.75-2.61)
	Q4	1.26 (0.67-2.39)	1.30 (0.65-2.62)	1.40 (0.71-2.74)
	Q5	1.84 (1.04-3.27)	1.65 (0.86-3.17)	1.81 (0.99-3.32)
Peripheral Vascular Event (PVE) <sup>+</sup>	Q2	1.28 (0.74-2.22)	1.24 (0.68-2.27)	1.25 (0.68-2.28)
	Q3	0.89 (0.48-1.64)	0.83 (0.44-1.56)	0.83 (0.44-1.56)
	Q4	1.24 (0.73-2.10)	1.13 (0.63-2.03)	1.14 (0.64-2.03)
	Q5	1.27 (0.75-2.14)	1.15 (0.66-2.00)	1.17 (0.69-1.99)
Stroke <sup>+</sup>	Q2	1.59 (0.76-3.32)	1.66 (0.78-3.54)	1.62 (0.76-3.44)
	Q3	1.48 (0.68-3.23)	1.48 (0.66-3.30)	1.43 (0.64-3.20)
	Q4	1.46 (0.67-3.19)	1.66 (0.75-3.66)	1.58 (0.72-3.48)
	Q5	1.74 (0.83-3.62)	1.94 (0.95-3.96)	1.82 (0.90-3.66)
Hospitalization for Unstable Angina (HUA) <sup>+</sup>	Q2	0.20 (0.07-0.58)	0.18 (0.06-0.54)	0.19 (0.07-0.55)
	Q3	0.57 (0.25-1.30)	0.55 (0.22-1.35)	0.57 (0.24-1.33)
	Q4	0.38 (0.15-1.00)	0.41 (0.14-1.19)	0.43 (0.15-1.20)
	Q5	0.56 (0.26-1.22)	0.46 (0.19-1.10)	0.49 (0.21-1.13)

Quintile 1 (Q1) was used as the reference group for all analyses

Abbreviations: CI, confidence interval; SHR, subdistribution hazard ratio; HR, hazard ratio

\*Model 1 was adjusted for age, gender, BMI (categorized as <18, 18-25 and >25kg/m<sup>2</sup>), SBP (categorized as <130, 130-160, >160mmHg), albumin, race (black, non-black), dialysis duration, history of smoking, history of cardiovascular disease, history of percutaneous coronary intervention, history of stroke, history of MI, BUN, and the EVOLVE study design.

\*\* Model 2 was adjusted for same variables listed in model 1, except BUN

§ Adjusted for the competing risk of non-cardiac death

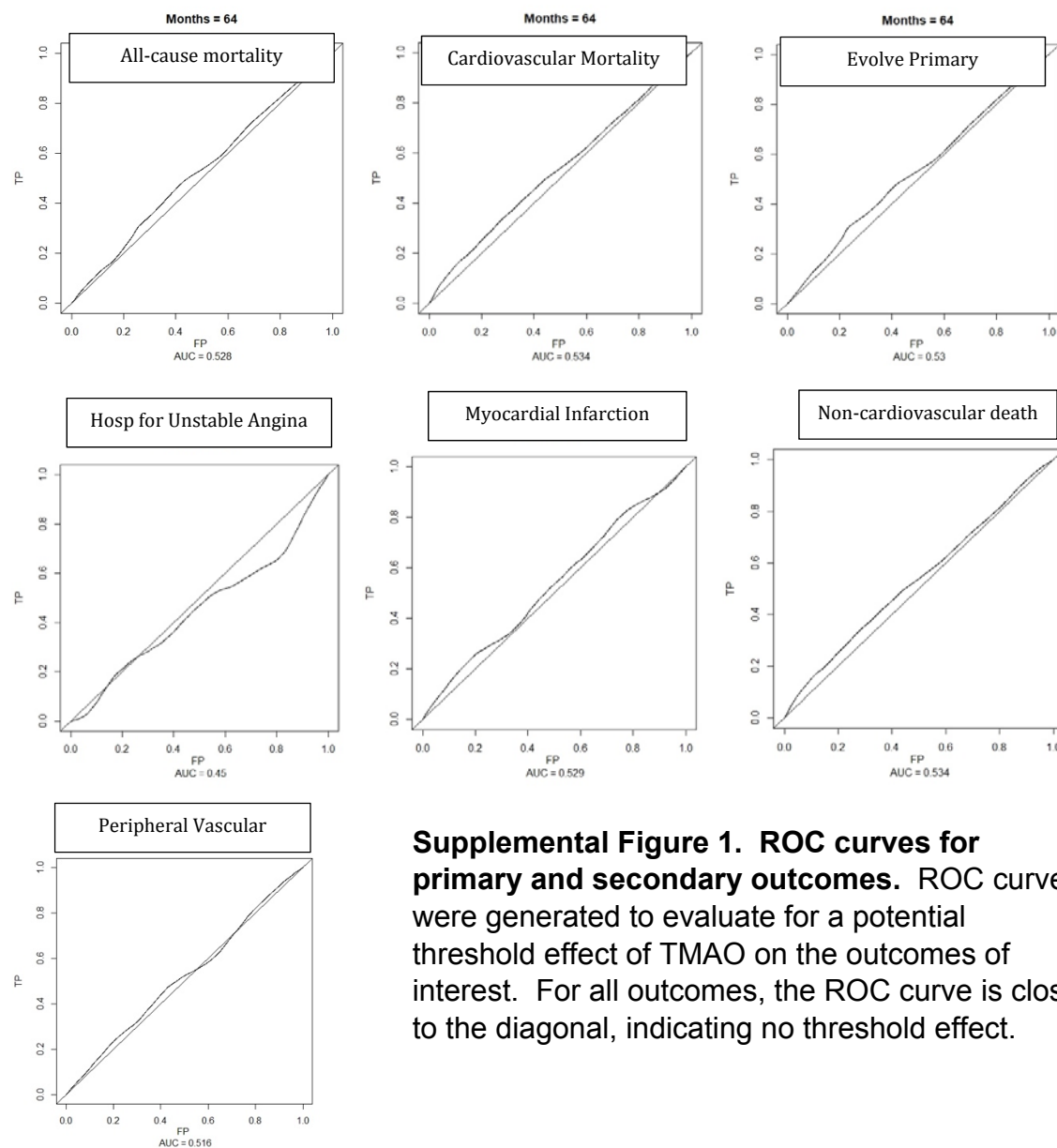
¥ Adjusted for the competing risk of cardiac death

+ Adjusted for the competing risk of all cause death

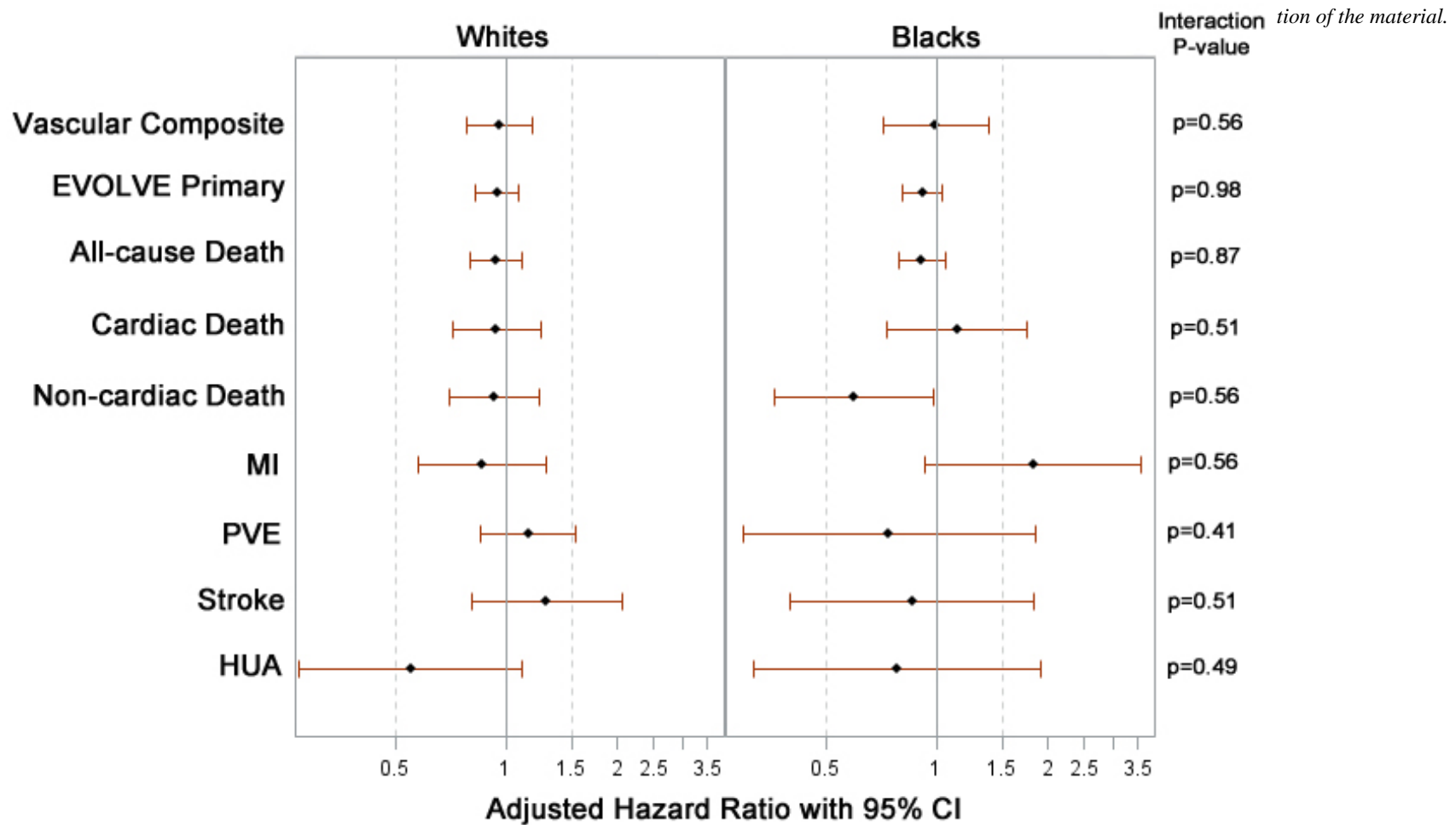
**Supplemental Table 2: Hazard/Subdistribution hazard ratio for each outcome and race (black vs. white) stratified by quintile of TMAO**

Outcomes	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Vascular Composite	<b>0.48</b> <b>(0.26-0.89)</b>	0.66 (0.30-1.41)	1.58 (0.41-6.13)	1.14 (0.43-3.00)	1.31 (0.67-2.56)
PRIMARY Composite	<b>0.41</b> <b>(0.24-0.72)</b>	0.85 (0.44-1.63)	0.48 (0.16-1.42)	1.79 (0.74-4.31)	1.69 (0.86-3.33)
All-cause Mortality	<b>0.46</b> <b>(0.24-0.87)</b>	1.79 (0.86-3.74)	1.39 (0.40-4.85)	0.96 (0.37-2.53)	1.39 (0.65-2.96)
Cardiovascular Mortality	<b>0.34</b> <b>(0.16-0.75)</b>	1.70 (0.58-5.02)	1.96 (0.26-14.6)	1.27 (0.34-4.69)	0.90 (0.40-2.04)
Non-cardiovascular Mortality	0.79 (0.27-2.37)	0.89 (0.32-2.44)	0.58 (0.10-3.32)	1.31 (0.39-4.41)	1.20 (0.39-3.64)
Myocardial Infarction	1.32 (0.42-4.17)	1.74 (0.49-6.16)	1.06 (0.18-6.34)	3.12 (0.53-18.4)	<b>4.43</b> <b>(1.26-15.5)</b>
Peripheral Vascular Event	0.69 (0.18-2.60)	0.52 (0.14-1.92)	0.14 (0.01-3.22)	3.29 (0.59-18.2)	1.22 (0.20-7.32)

\* Stroke and hospitalization for unstable angina (HUA) had too few events to be included in these analyses



**Supplemental Figure 1. ROC curves for primary and secondary outcomes.** ROC curves were generated to evaluate for a potential threshold effect of TMAO on the outcomes of interest. For all outcomes, the ROC curve is close to the diagonal, indicating no threshold effect.



**Supplemental Figure 2. Subgroup analysis of clinical outcomes stratified by race (whites and blacks only).**

Forest plot illustrates adjusted hazard ratios and confidence intervals for ln(TMAO) and each clinical outcome for whites (left, n=704) and blacks (right, n=256) included in our study cohort. Results are adjusted for the EVOLVE study design. Abbreviations: MI, myocardial infarction; PVE, peripheral vascular event; HUA, hospitalization for unstable angina