Gut Microbiota-Dependent TMAO and Cardiovascular Outcomes in Patients with Prior Myocardial Infarction: a Nested Case-Control Study from the PEGASUS-TIMI 54 Trial

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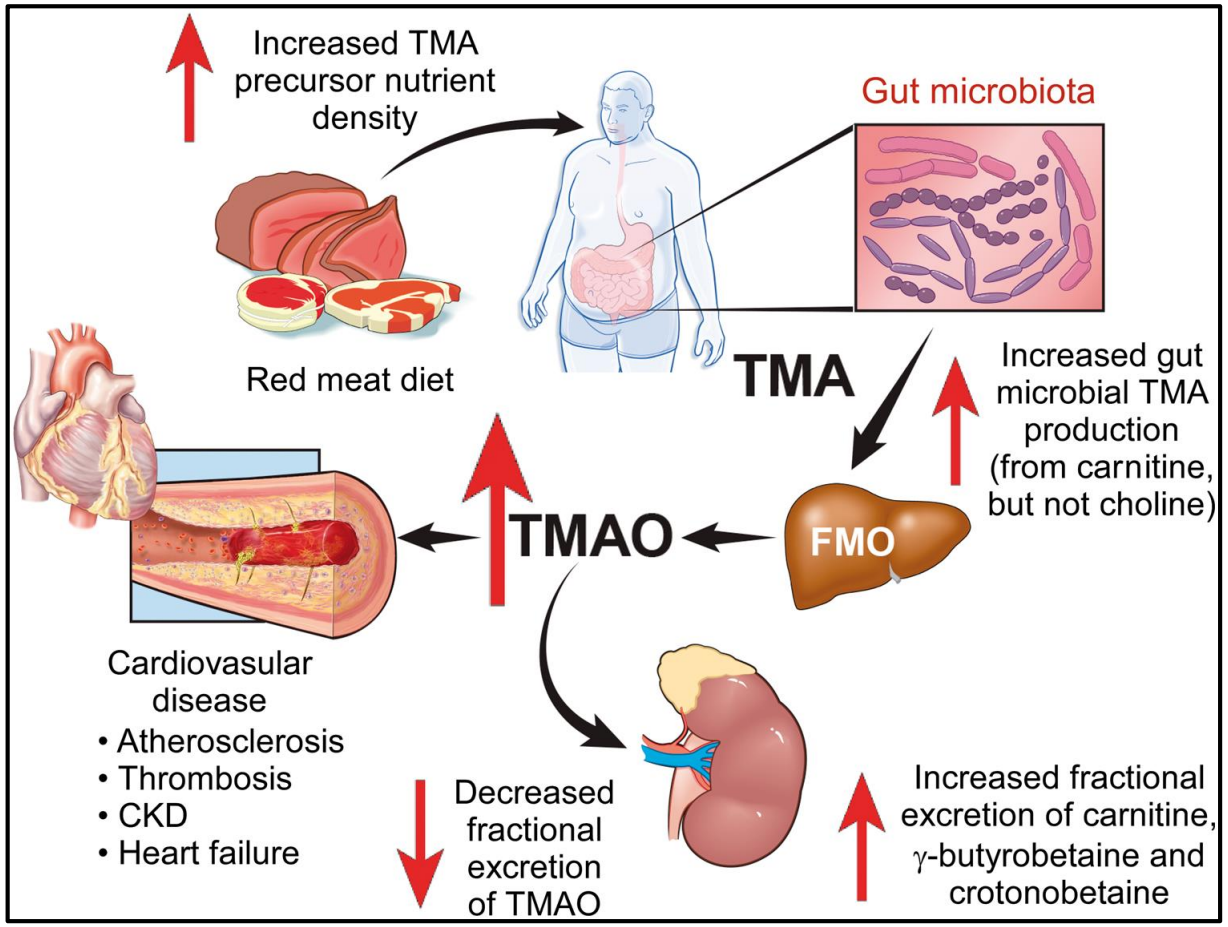
Monday November 18, 2019

Relevant Disclosures

- PEGASUS-TIMI 54 trial was supported by a grant from AstraZeneca.

- This work was supported in part by the National Institute of Health and the Office of Dietary Supplements (P01HL147823, HL103866, and HL126827 to S.L.H.; R01 HL130819 to Z.W.) and the Leducq Foundation (to S.L.H.).

TMAO and CV Health



TMAO: Trimethylamine N-oxide

TMAO is a plasma biomarker produced by gut microbiota metabolism.

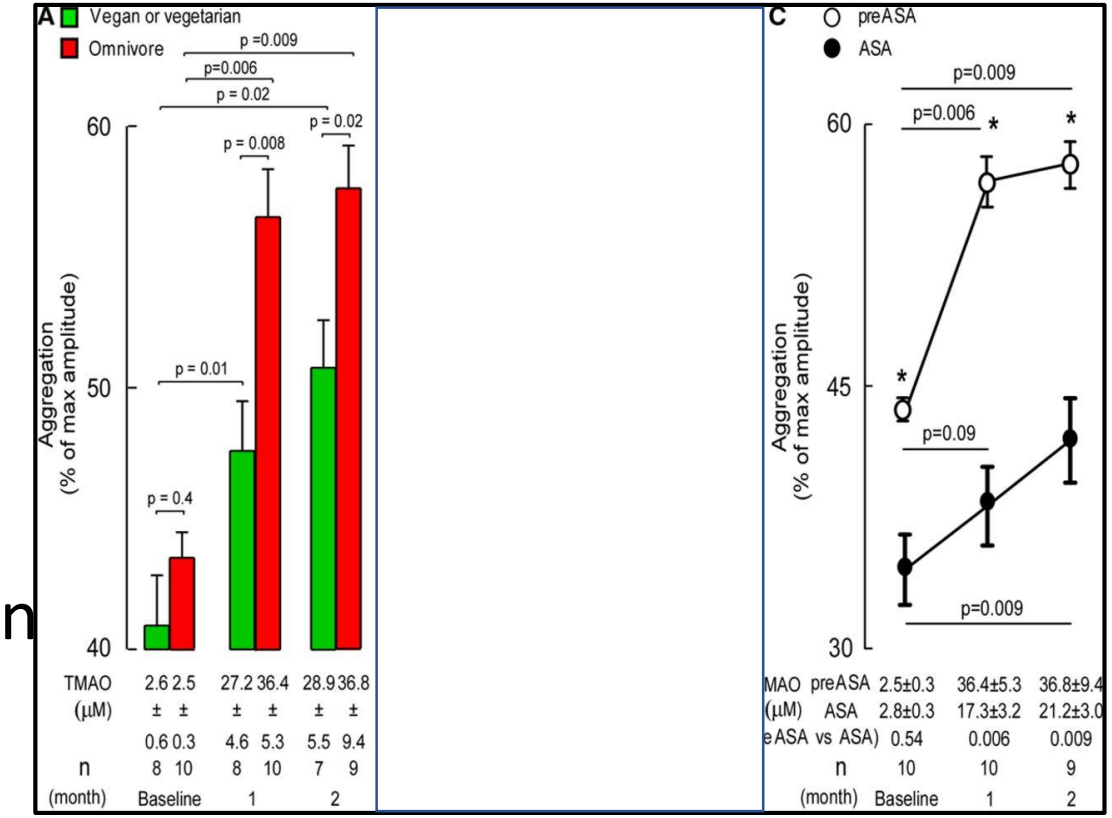
TMAO may have pro-atherogenic and pro-thrombotic properties.

Wang Z et al., Eur Heart J 2019 (40) 583–594.

TMAO and Platelet Activity

Red meat diet increases TMAO

TMAO levels correlated with platelet aggregation



TMAO-associated platelet aggregation reversible with aspirin

Zhu W et al., Circulation 2017 135(17):1671-1673.

Aims

- To evaluate the prognostic value of TMAO levels in patients with prior myocardial infarction (MI).

- To determine if baseline plasma TMAO levels can identify patients who have a greater risk reduction of major adverse cardiovascular events (MACE) with prolonged use of ticagrelor.

PEGASUS-TIMI 54 Trial

Trial Schema

PEGASUS TIMI 54

N ~ 21,000

Stable patients with history of MI 1-3 yrs prior
+ ≥ 1 additional atherothrombosis risk factor*

* Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction

RANDOMIZE
DOUBLE BLIND

Planned treatment with ASA 75 – 150 mg &
Standard background care

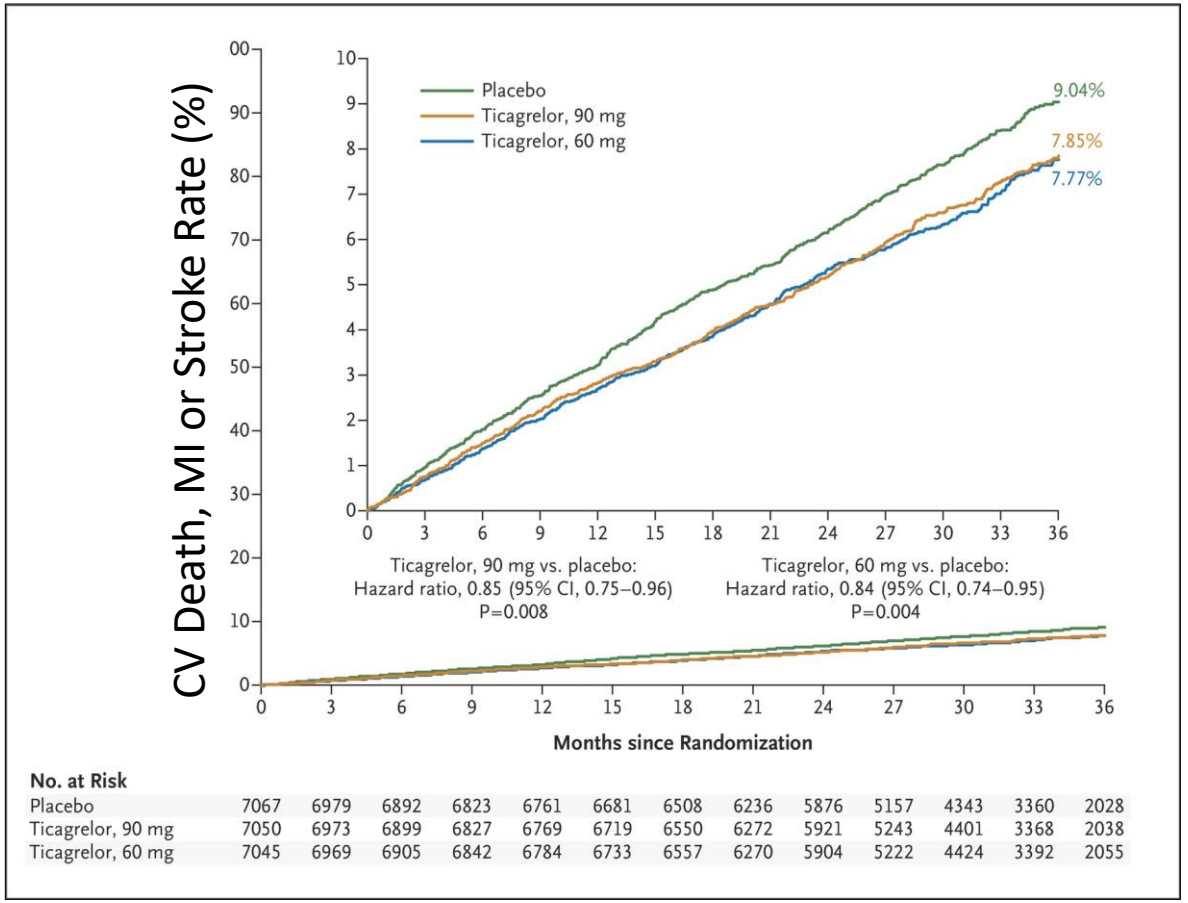
- Ticagrelor 90 mg bid
- Ticagrelor 60 mg bid
- Placebo

Follow-up Visits
Q4 mos for 1st yr, then Q6 mos

Min 12 months of Follow Up
Event-driven trial

Primary Efficacy Endpoint: CV Death, MI, or Stroke
Primary Safety Endpoint: TIMI Major Bleeding

Bonaca MP et al., Am Heart J. 2014 Apr;167(4):437-444.



No. at Risk

Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
Ticagrelor, 90 mg	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
Ticagrelor, 60 mg	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

Bonaca MP et al., N Engl J Med. 2015 May 7;372(19):1791-800.

Study Design

- Nested case control study within the PEGASUS-TIMI 54 Trial.
- 8635 random participants had collection of blood samples for biomarkers.
- Cases were defined as the primary efficacy endpoint (PEP) of composite of CV death, MI and any stroke at the end of the follow-up.
- Controls were free from the PEP and were matched to cases for age (range ±3 years), sex and eGFR (range ±5 ml/min/1.73m^2) with a ratio 2:1.
- Final sample size with available TMAO: 597 Cases vs. 1194 Controls.

Statistical Analysis

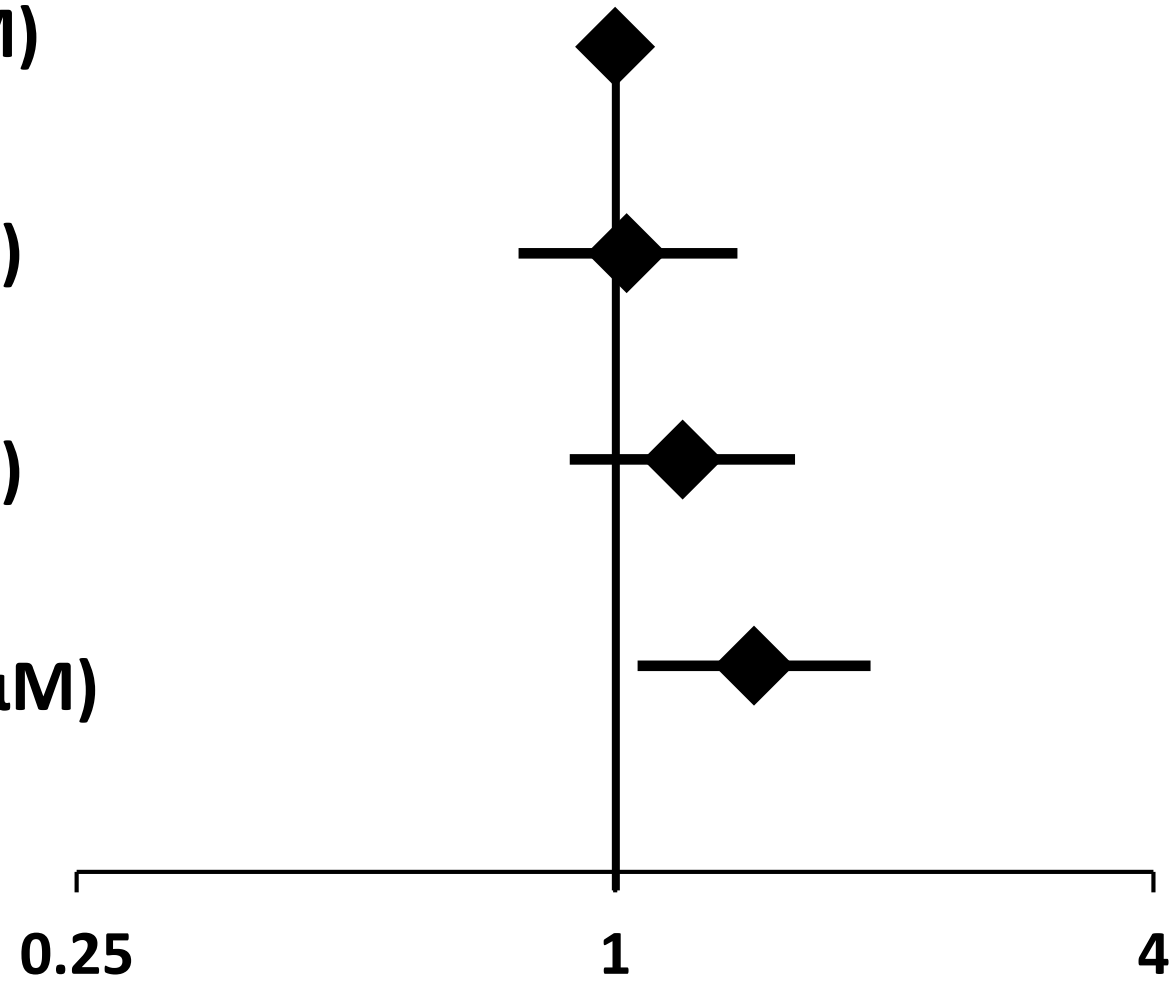
- Conditional logistic regression model (for matched paired data) to assess the association between the exposure (TMAO quartiles) and the binary outcome (cases vs. controls) matching for age, gender and eGFR.
    1. Adjustment for baseline CVD clinical risk factors (diabetes, BMI, hypertension, hypercholesterolemia, smoking, PAD, region, type of index event).
    2. Further adjustment for hsTnT, hsCRP, and NTproBNP.
    3. Statistical interaction by treatment arm.

Baseline characteristics

Variables	Q1 TMAO (N=452) (0.12-3.24 µM)	Q2 TMAO (N=450) (3.25-4.75 µM)	Q3 TMAO (N=450) (4.76-7.20 µM)	Q4 TMAO (N=451) (7.22-157.37 µM)	P-value
Median age (years)	64	66	69	69	< 0.001
Female, %	21	22	26	34	< 0.001
Median eGFR (ml/min/1.73m^2)	76	72	64	55	< 0.001
Median BMI (kg/m^2)	28	28	28	30	< 0.001
Current smoking, %	25	21	18	15	0.002
Hypertension, %	75	79	80	86	0.001
Diabetes mellitus, %	22	30	34	50	< 0.001
Qualifying STEMI event, %	51	49	50	38	< 0.001
Median hsTnT (ng/L)	6.9	8.0	9.3	12.3	< 0.001
Median NTproBNP (pg/mL)	131	163	181	277	< 0.001
Median hsCRP (mg/dL)	1.5	1.6	1.5	2.0	0.003

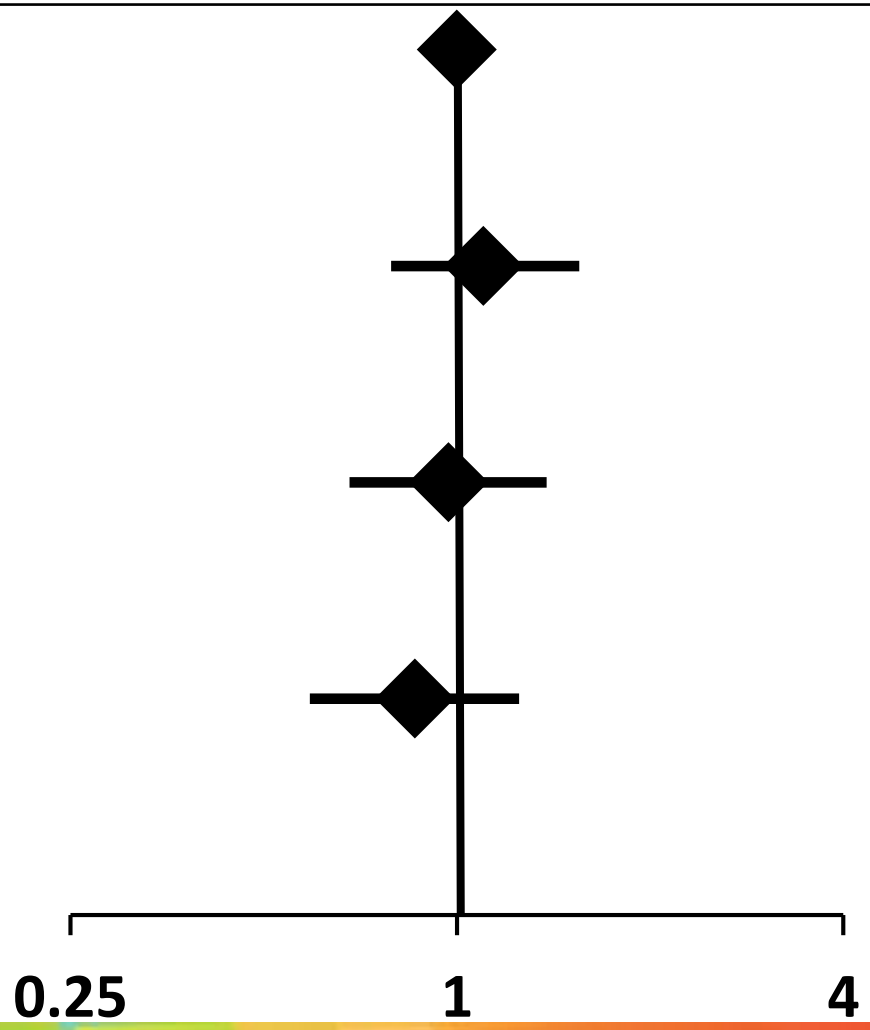
TMAO and MACE

TMAO Quartiles	CV Death, MI and Stroke	Matched OR (95% CI)
Q1 (0.12-3.24 µM)		1 (Ref)
Q2(3.25-4.75 µM)		1.03 (0.78-1.37)
Q3(4.76-7.20 µM)		1.19 (0.89-1.59)
Q4(7.22-157.37 µM)		1.43 (1.06-1.93)
P for trend		*P=0.015*



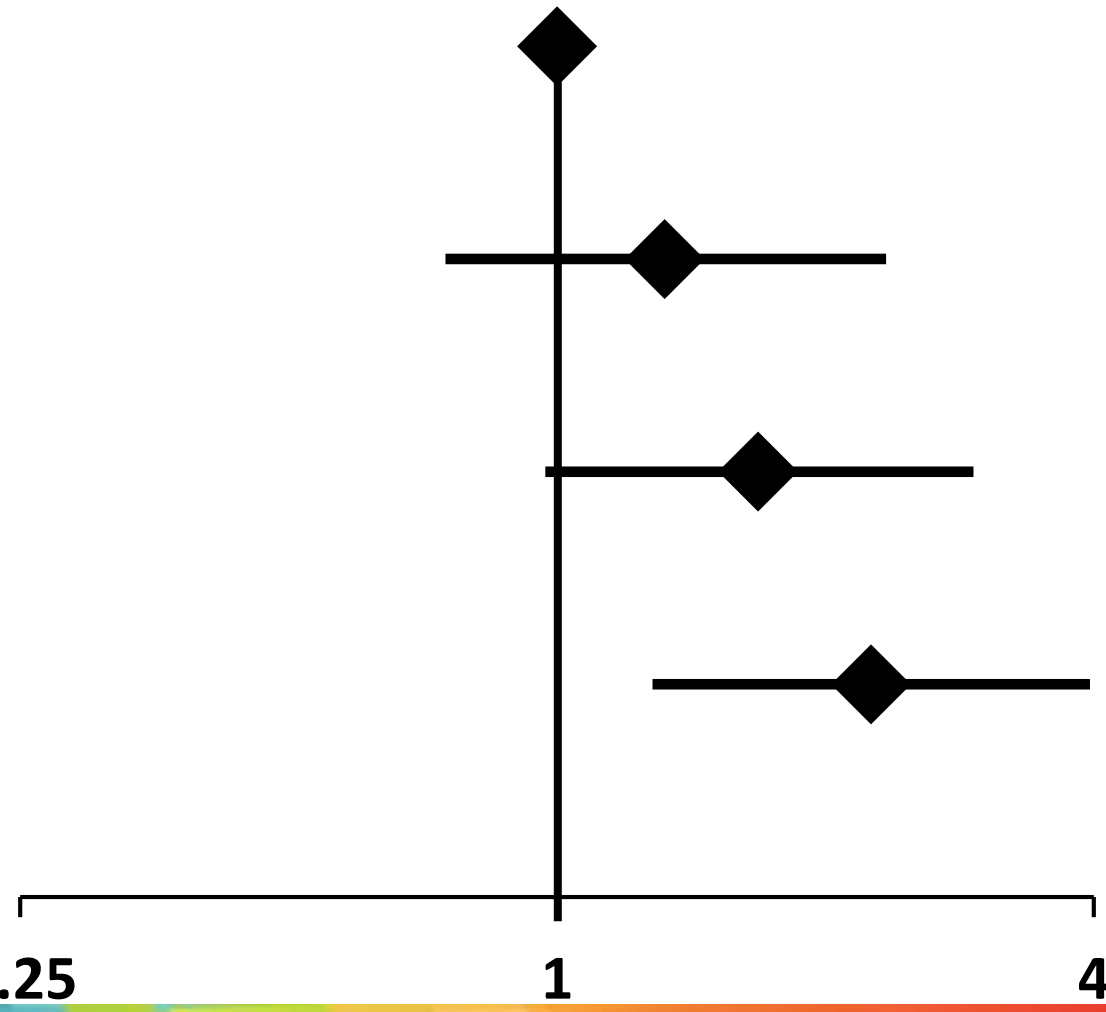
TMAO and Recurrent MI

TMAO Quartiles	Recurrent MI	Unadj OR (95% CI)
Q1		1 (Ref)
Q2		1.10 (0.79-1.55)
Q3		0.97 (0.68-1.38)
Q4		0.86 (0.59-1.25)
P for trend		P=0.59



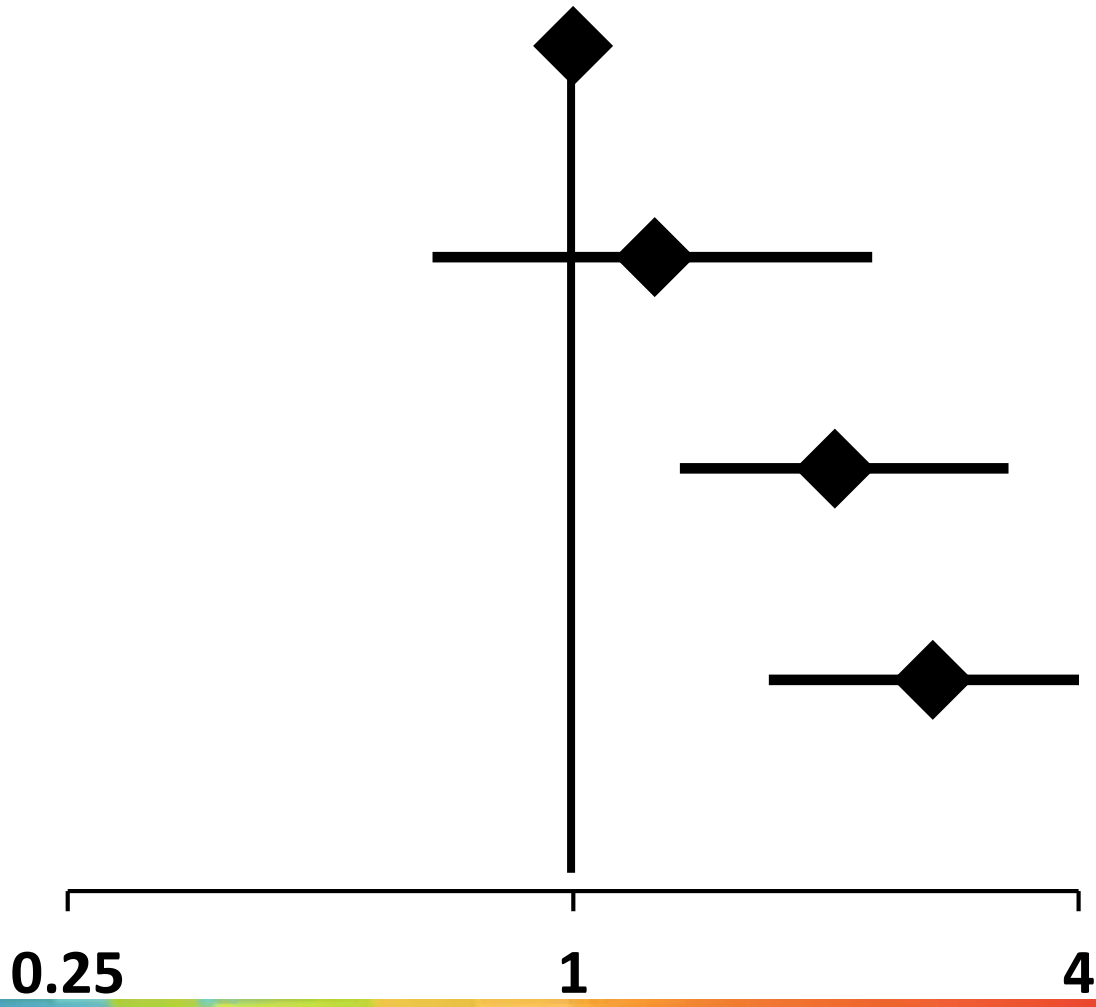
TMAO and CV Death

TMAO Quartiles	CV Death	Unadj OR (95% CI)
Q1		1 (Ref)
Q2		1.32 (0.75-2.34)
Q3		1.68 (0.97-2.93)
Q4		2.25 (1.28-3.96)
P for trend		*P=0.003*



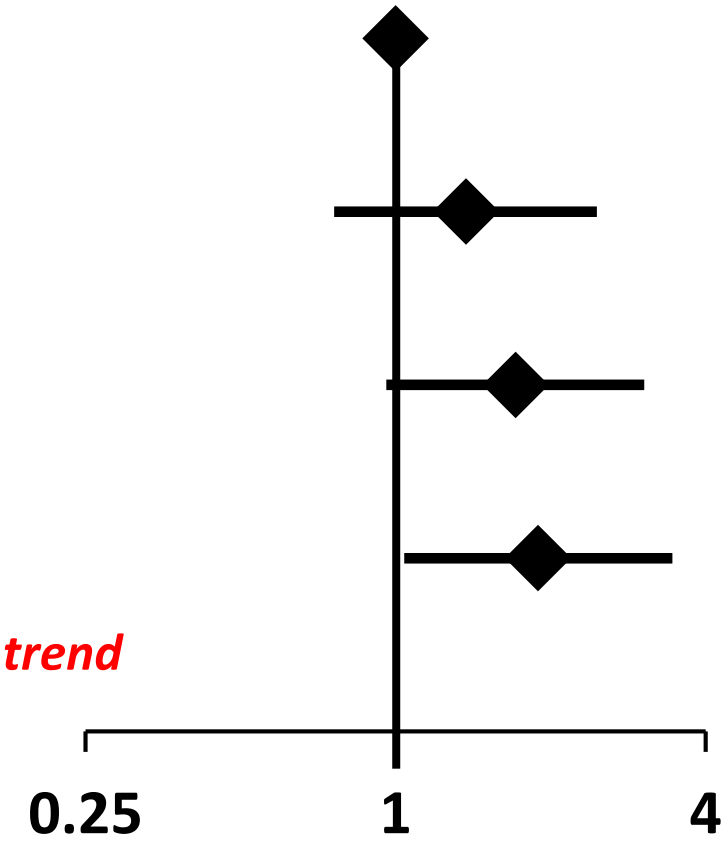
TMAO and Any Stroke

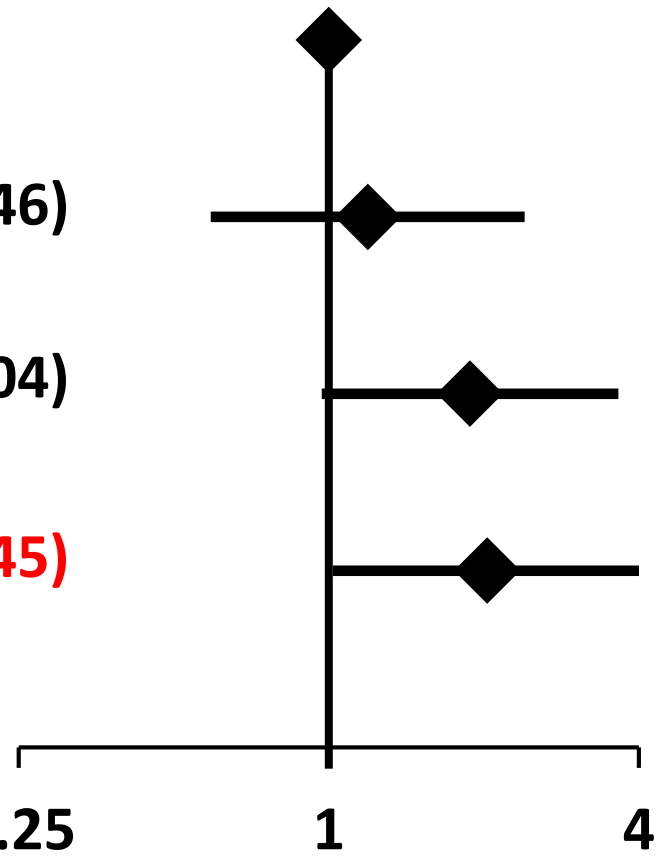
TMAO Quartiles	Stroke	Unadj OR (95% CI)
Q1		1 (Ref)
Q2		1.25 (0.62-2.52)
Q3		2.05 (1.07-3.93)
Q4		2.68 (1.39-5.17)
P for trend		*P<0.001*



Adjusted for Clinical Variables*

TMAO Quartiles	CV Death	Adj OR (95% CI)	Any Stroke	Adj OR (95% CI)
Q1		1 (Ref)		1 (Ref)
Q2		1.37 (0.76-2.46)		1.19 (0.59-2.40)
Q3		1.71 (0.96-3.04)		1.88 (0.97-3.65)
Q4		1.89 (1.04-3.45)		2.03 (1.02-4.04)
P for trend		*P=0.029*		*P=0.019*

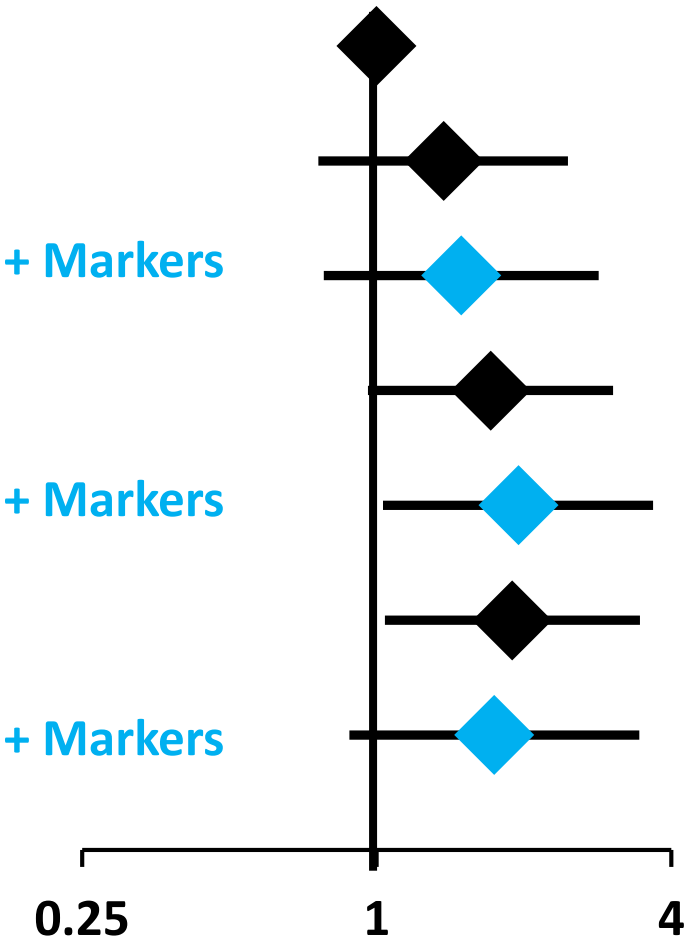


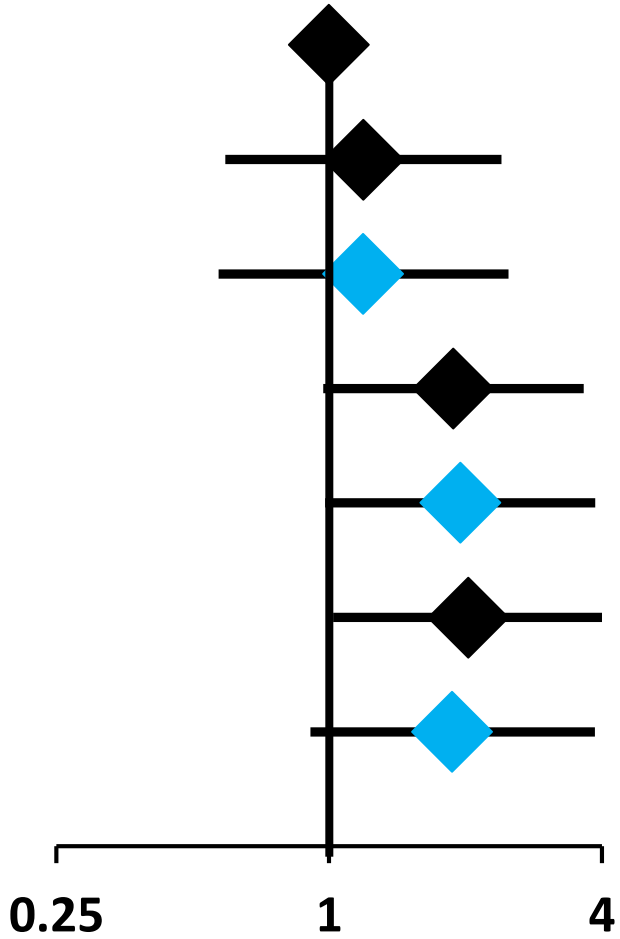


* Adjustment for age, gender, eGFR, diabetes, BMI, hypertension, hypercholesterolemia, smoking, PAD, region, type index event

Adjusted for Clinical* + CV Markers#

TMAO Quartiles	CV Death Adj OR (95% CI)	Any Stroke Adj OR (95% CI)
Q1	1 (Ref)	1 (Ref)
Q2 Clin	1.37 (0.76-2.46)	1.19 (0.59-2.40)
Q2 Clin + Markers	1.49 (0.78-2.84)	1.19 (0.57-2.49)
Q3 Clin	1.71 (0.96-3.04)	1.88 (0.97-3.65)
Q3 Clin + Markers	1.95 (1.03-3.67)	1.95 (0.98-3.87)
Q4 Clin	1.89 (1.04-3.45)	2.03 (1.02-4.04)
Q4 Clin + Markers	1.74 (0.88-3.44)	1.87 (0.91-3.86)
	P trend=0.09	*P trend=0.044*

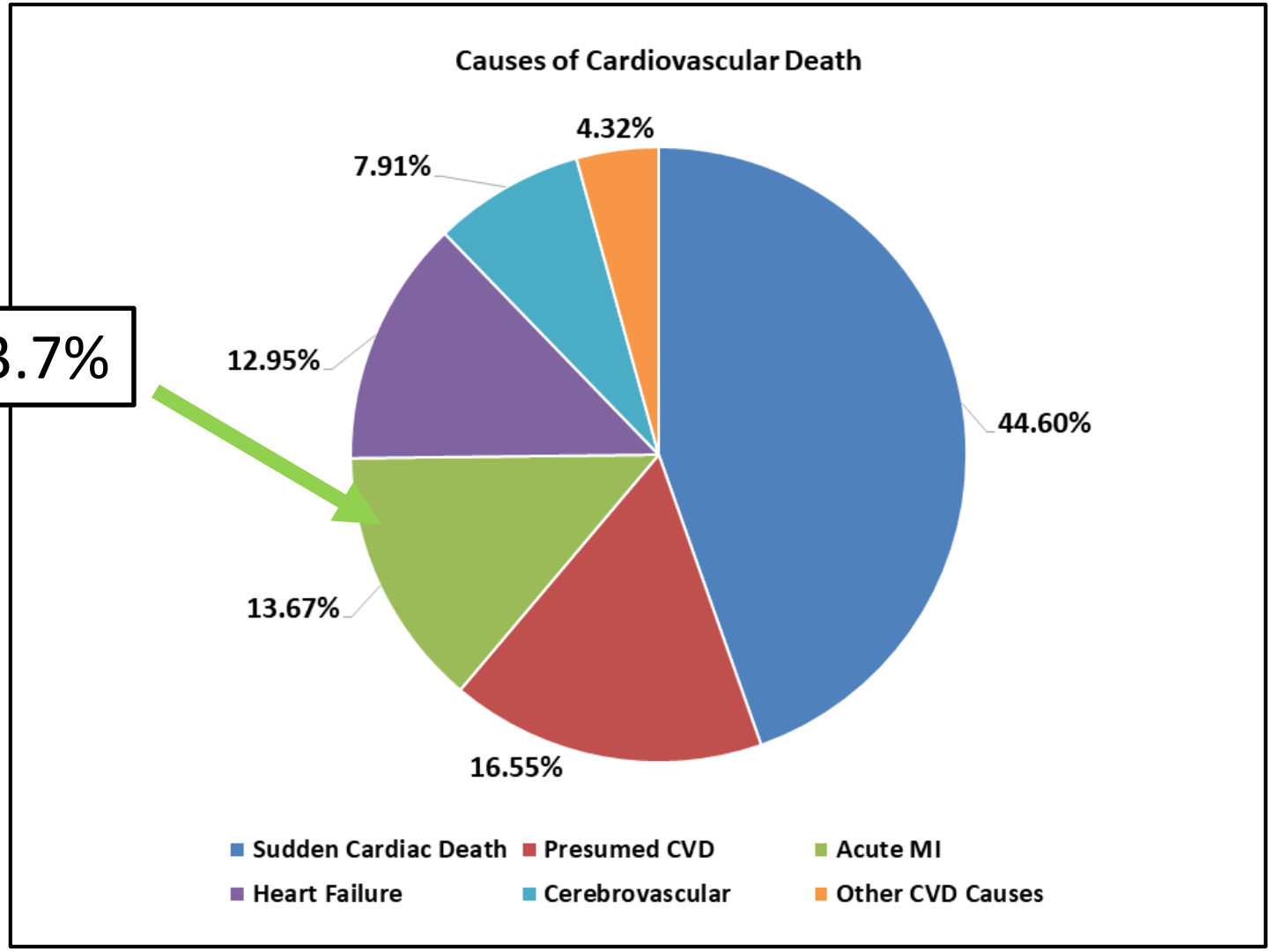




** Clinical adjustment for age, gender, eGFR, diabetes, BMI, hypertension, hypercholesterolemia, smoking, PAD, region, index event.*
 # Further adjustment clinical + hsCRP, hsTnT and NTpro BNP.

Causes of CV Death

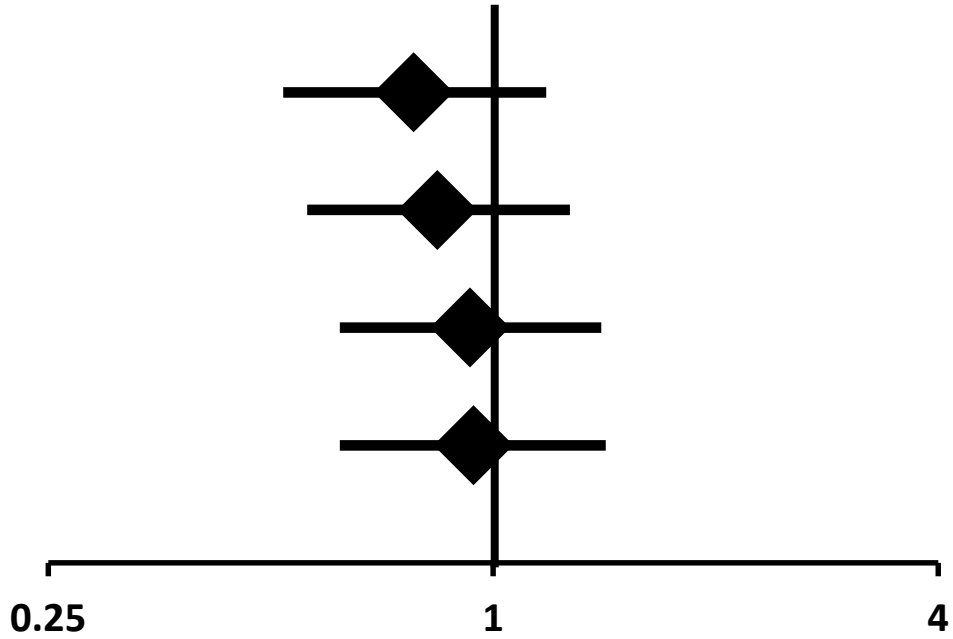
Acute MI only 13.7%



TMAO and Ticagrelor Effect

CV Death, MI or Stroke Events

TMAO Quartiles	Unadj OR (95% CI)
Q1	0.78 (0.52-1.18)
Q2	0.84 (0.56-1.27)
Q3	0.93 (0.62-1.40)
Q4	0.94 (0.62-1.42)
P for interaction	*P=0.92*



Ticagrelor Better ⟷ Placebo Better

Limitations

- Nested case-cohort for cost efficiency.
- Applicable to a stable population with a previous MI.
- All patients were on aspirin.
- No data collection for nutritional habits or prior use of antibiotics.

Summary

- In patients with prior MI, those with higher TMAO levels had higher risks of CV death or stroke.
- The association had a borderline significance after adjustment for clinical factors and traditional CV biomarkers.
- We did not observe an association between TMAO levels and recurrent MI events.
- The benefit of ticagrelor was consistent regardless of TMAO levels.

Future directions

- Further studies should clarify the mechanisms increasing the risk of CV death and stroke not attributable to atherothrombosis (e.g. heart failure, sudden cardiac death, fatal stroke, atrial fibrillation, hypertension) in patients with high TMAO levels.

Thank you!

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