Pathophysiological Types and Biomarkers of Acute Myocardial Infarction

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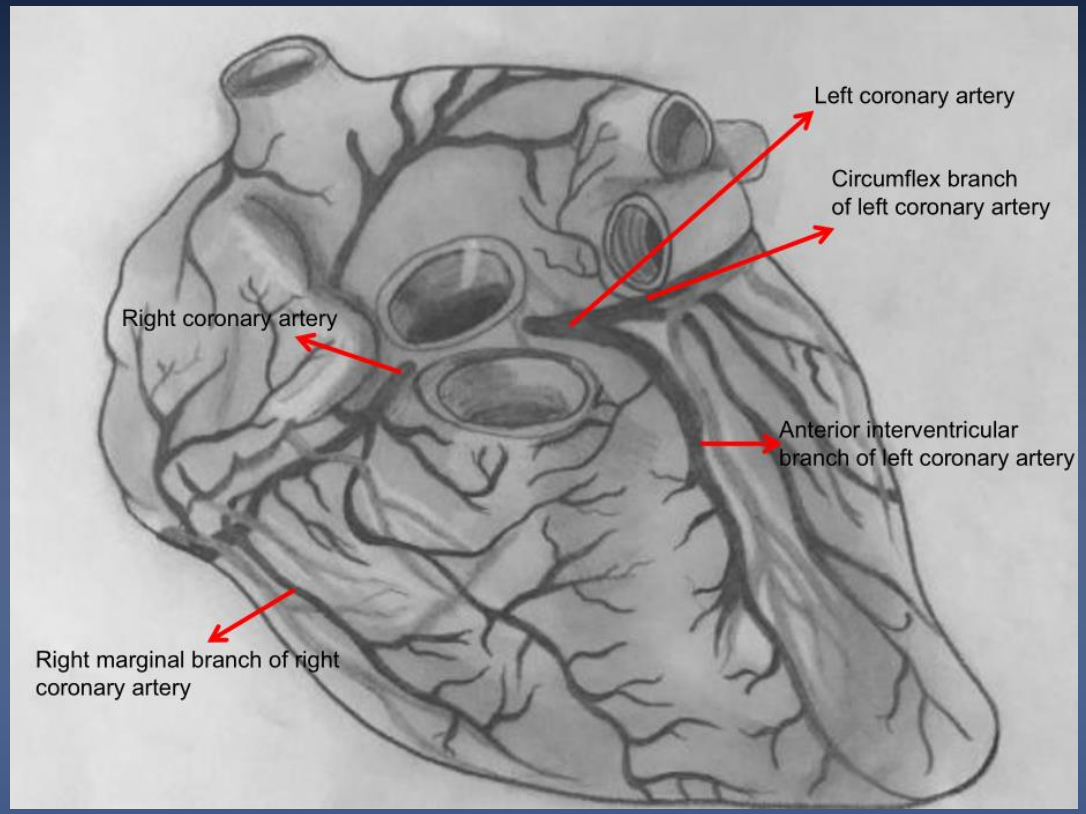
Disclosure : no conflicts

Background

- Acute myocardial infarction (AMI) is one of the major causes of mortality and morbidity worldwide.
- About 10% of patients who are admitted to emergency departments with chest pain every year are diagnosed with heart attack.
- The most common cause of AMI is an atherosclerotic plaque ruptures and thrombus occluding the coronary artery totally or partially, restricting blood access to the heart.
- As the sensitivity and specificity of ECG are low in diagnosing AMI, cardiac biomarkers are frequently used in diagnosing AMI and determining prognosis.



Vascular Health and Risk Management 2019:15 1–10

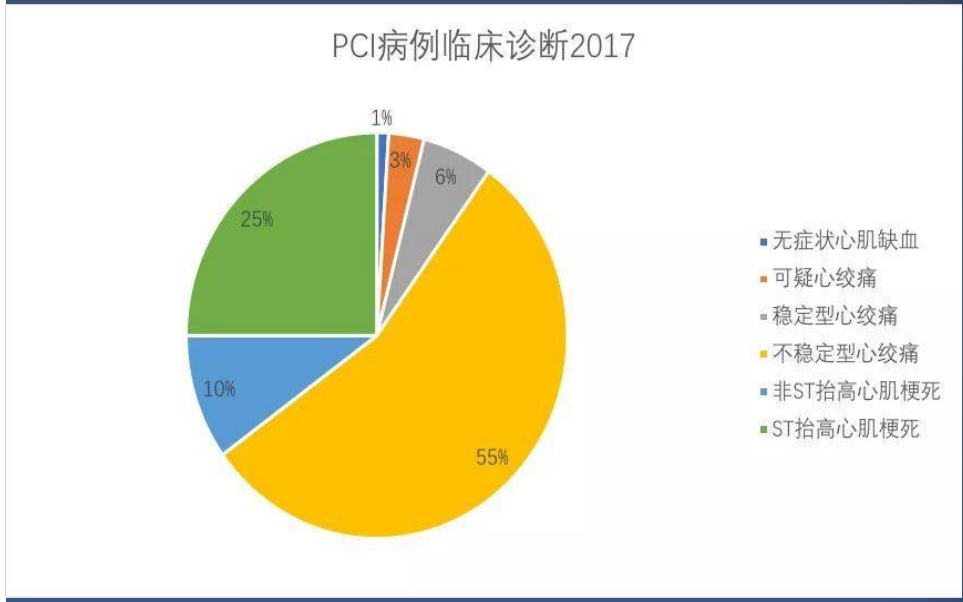
The incidence of AMI in China

- Fifty AMI patients/100000 people;
- STEMI:NSTEMI=1:3;
- Estimated 210 000 new STEMI patients per year in China.

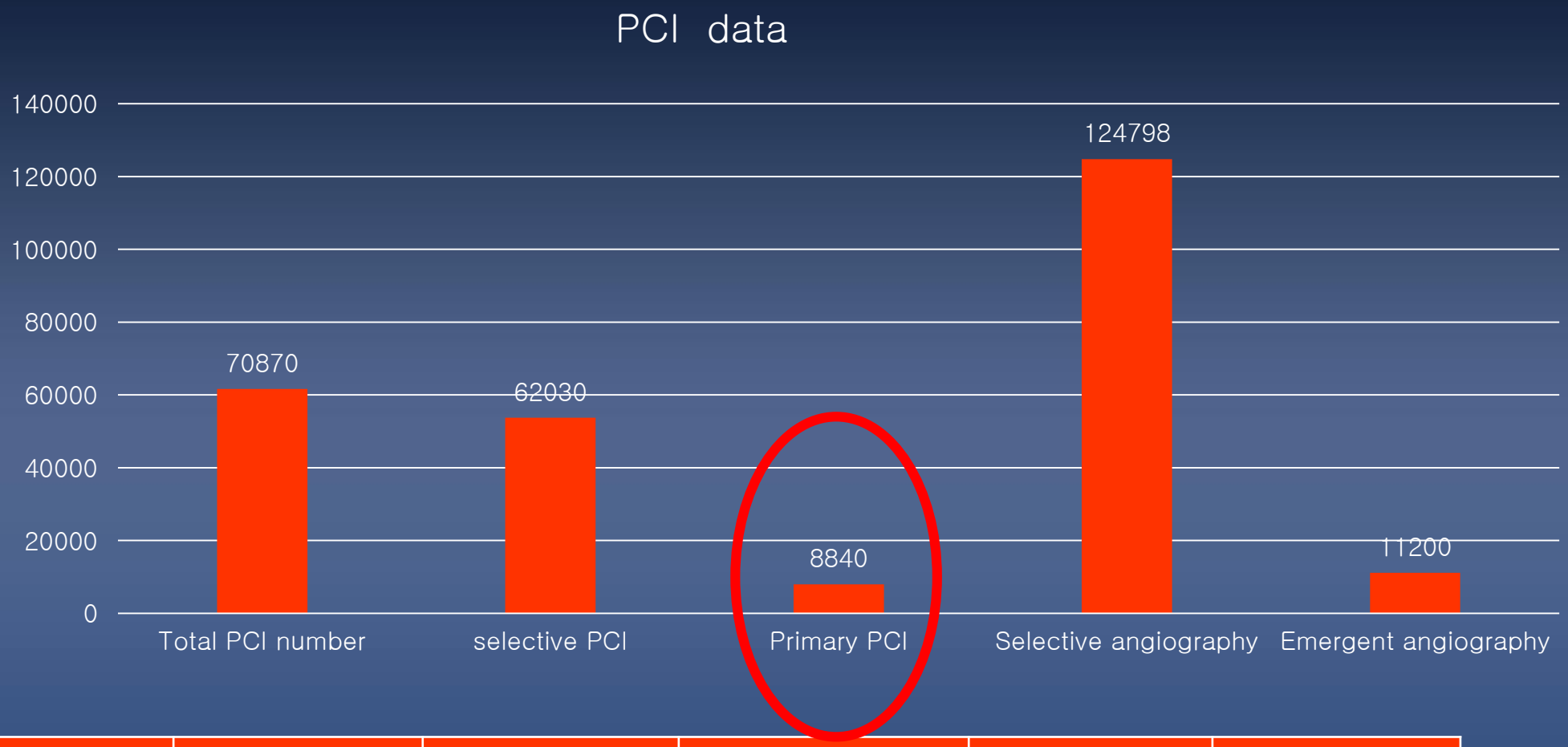
Lancet,2015,385:441-451.
Chin J Cardiol,2019,47(2):82-84

Total PCI number from 2009 to 2017 in China

Total PPCI number 69889 cases, less than 10% AMI patients were received PPCI therapy

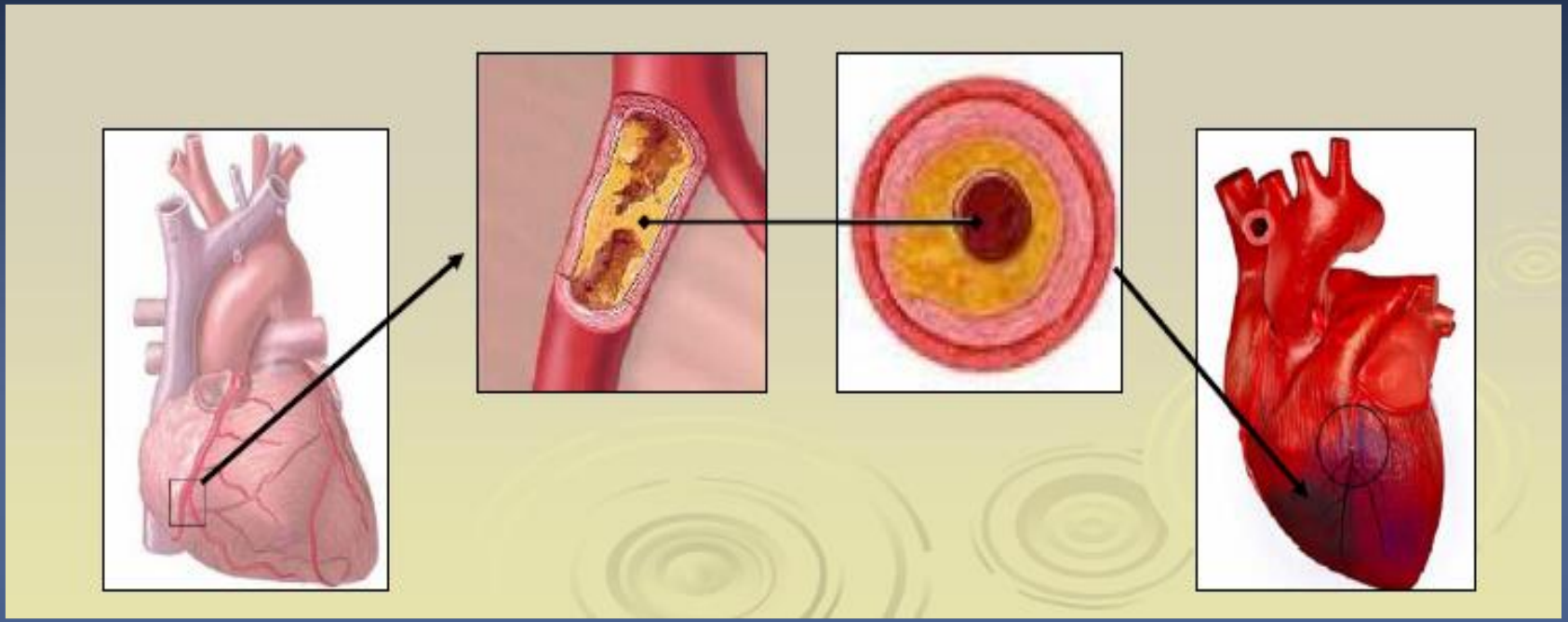


PCI in Beijing,2018



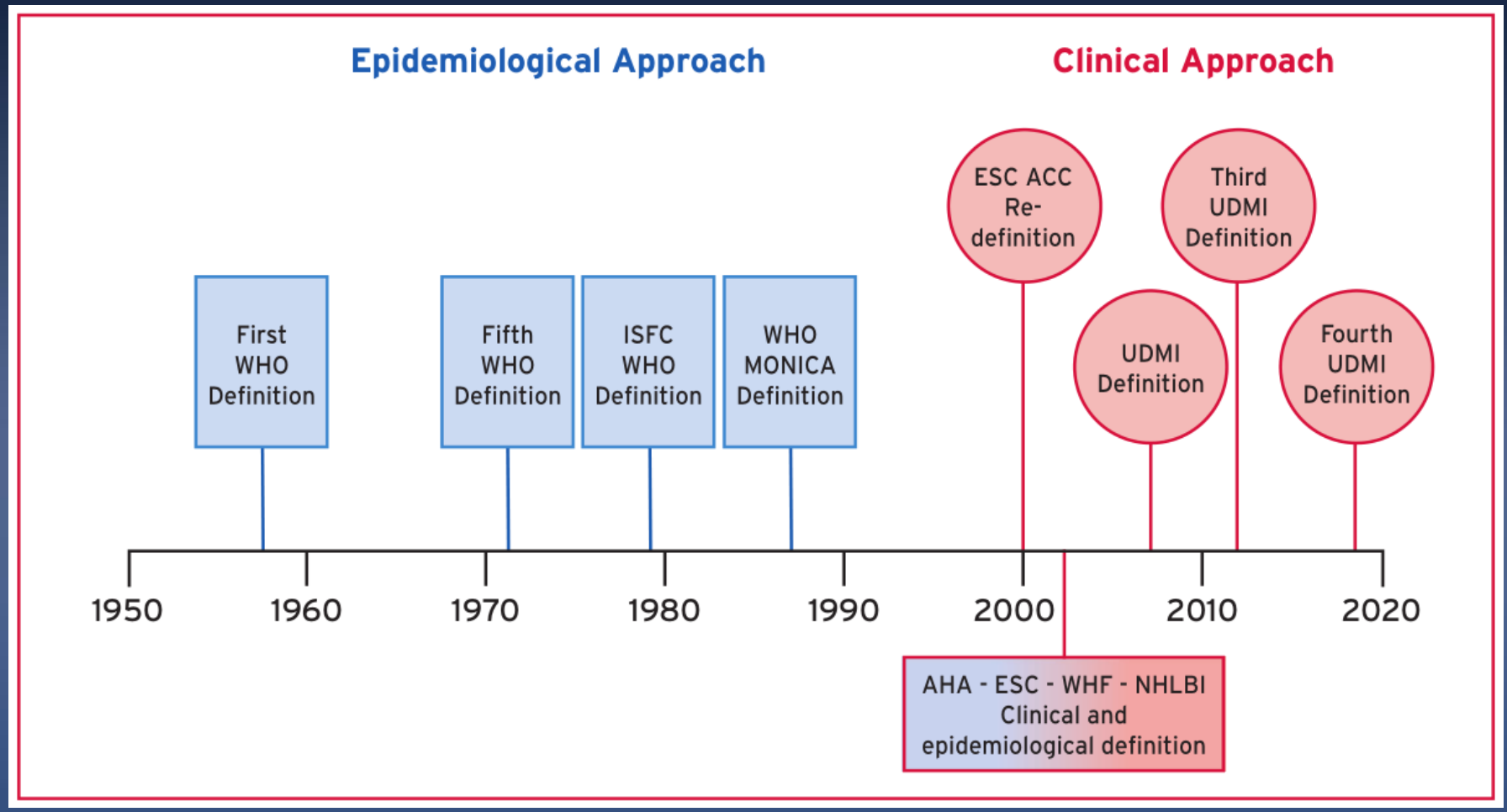
Total death number	292	55	237	20	62
Death rate(%)	0.41%	0.09%	2.68%	0.016%	0.55%

What are new pathophysiological types of AMI?



Acute thrombotic occlusion of coronary artery leading to myocardial injury.
But……?

Fourth universal definition of myocardial infarction (2018):ESC/AHA/ACC/WHF



Eur Heart J,2019 ,40(3):237-269

Fourth universal definition of myocardial infarction (2018)

- Type 1 MI
- Type 2 MI
- Type 3 MI
- Type 4:Type 4a,type 4b,type 4c
- Type 5

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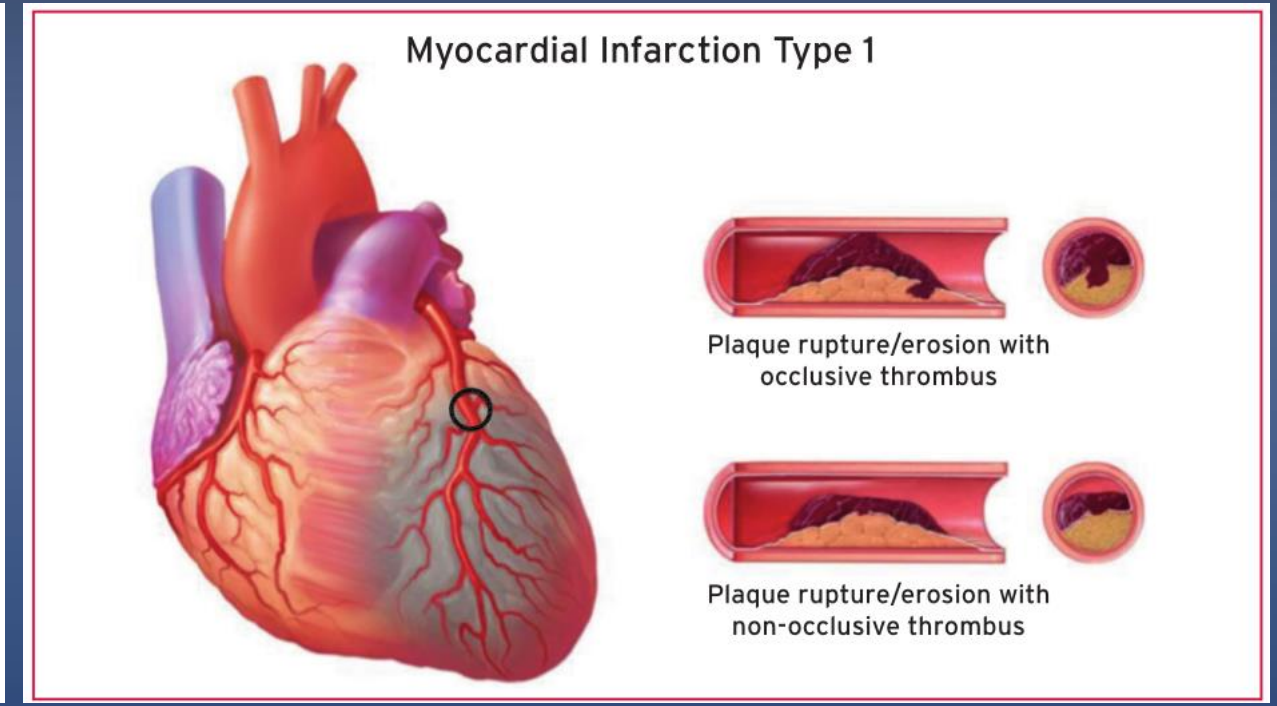
Type 1 MI

- MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion).

Criteria for type 1 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.[a]



Eur Heart J,2019 ,40(3):237-269

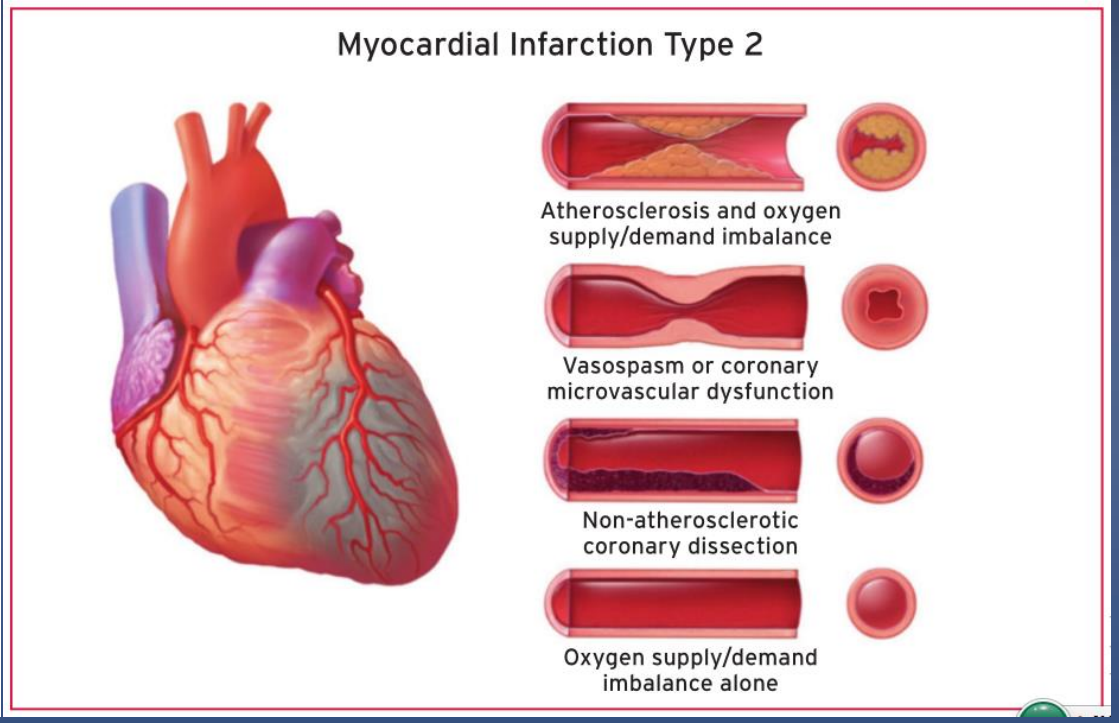
Type 2 MI

- Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis.

Criteria for type 2 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.



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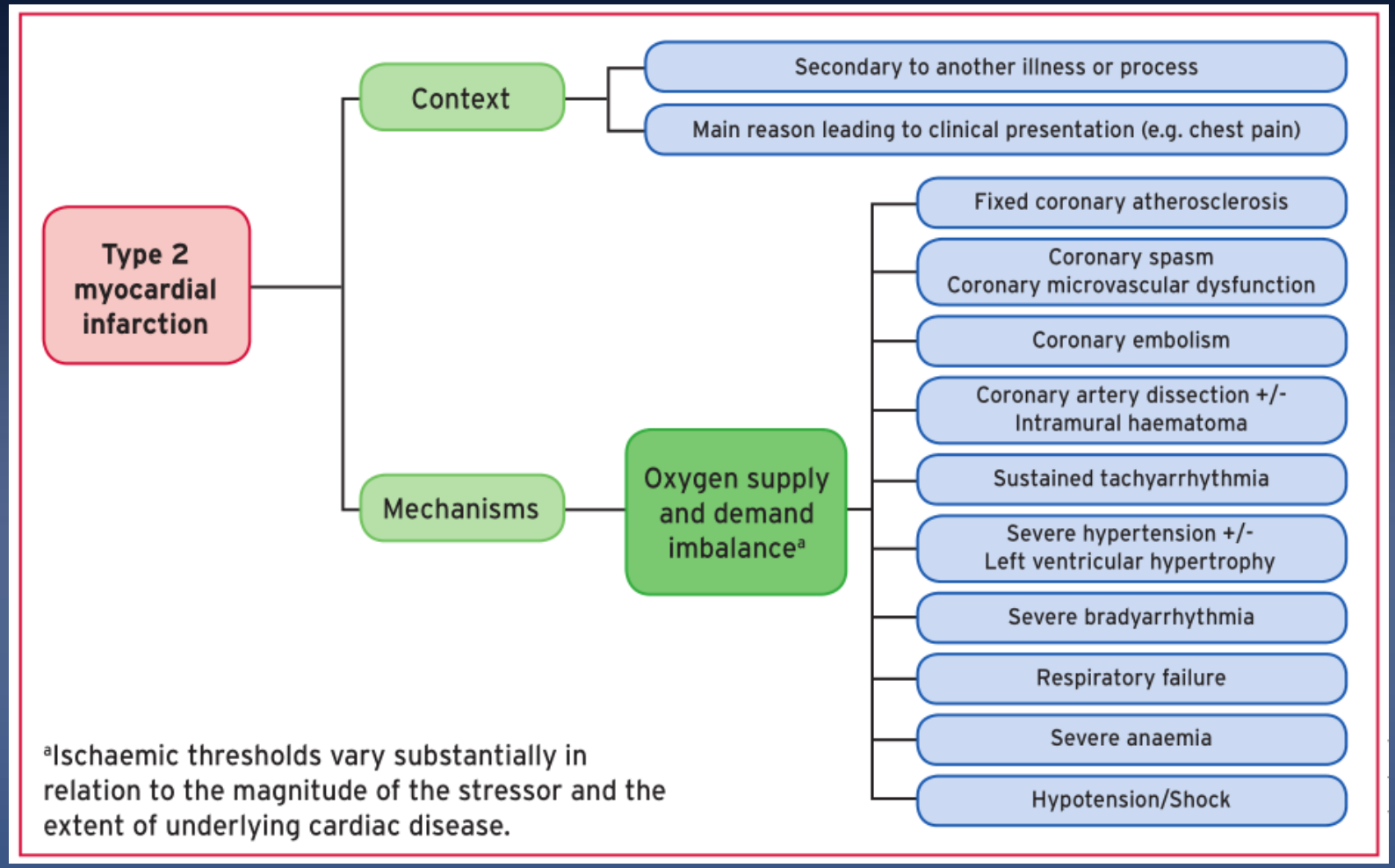
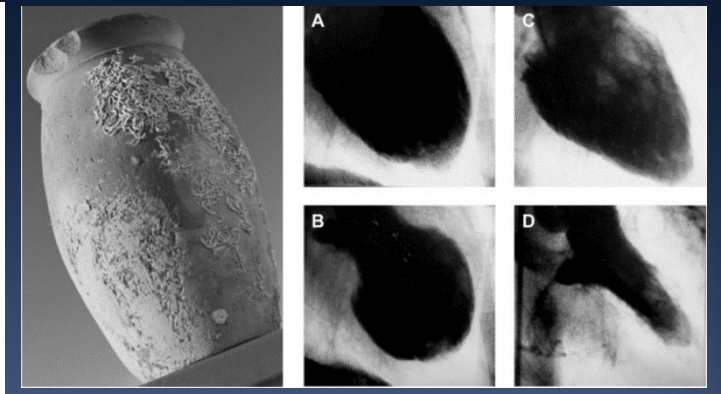
Framework for type 2 myocardial infarction





- Takotsubo syndrome.
- MINOCA.

J Am Cardiol Coll 2017;70:1569–1572.
European Heart Journal (2018) 39, 2032–2046

Type 3 MI

Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal.

Criteria for type 3 MI

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

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Type 4 MI

- Type 4a: MI associated with PCI;
- Type 4b: Stent/scaffold thrombosis associated with PCI;
- Type 4c: Restenosis associated with PCI.

Criteria for PCI-related MI ≤ 48 h after the index procedure (type 4a MI)

Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (≤ 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves;[a]
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.[b]

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Type 5 MI

- Type 5: MI associated with CABG.

Criteria for CABG-related MI ≤ 48 h after the index procedure (type 5 MI)

CABG-related MI is arbitrarily defined as elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value still must be > 10 times the 99th percentile URL. In addition, one of the following elements is required:

- Development of new pathological Q waves;[a]
- Angiographic documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

[a]Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.

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What is an ideal cardiac biomarker of acute myocardial infarction?

1. must be sensitive enough to detect a small degree of damage to the heart;
2. should be specific to the heart ;
3. should give information regarding the severity of the infarct and the prognosis of the disease;
4. should also show the result of reperfusion therapy in AMI;
5. needs to distinguish between reversible and irreversible damage;
6. ought not to be detected in patients showing no myocardial damage;
7. should help in early and late diagnosis;
8. should be easy to measure, fast, cheap, and quantitative;
9. should have long-term storage conditions and be stable under them.

Cardiac biomarkers of acute myocardial infarction

1. Myocardial necrosis
2. Neuroendocrine
3. Inflammation
4. Other novel cardiac biomarkers

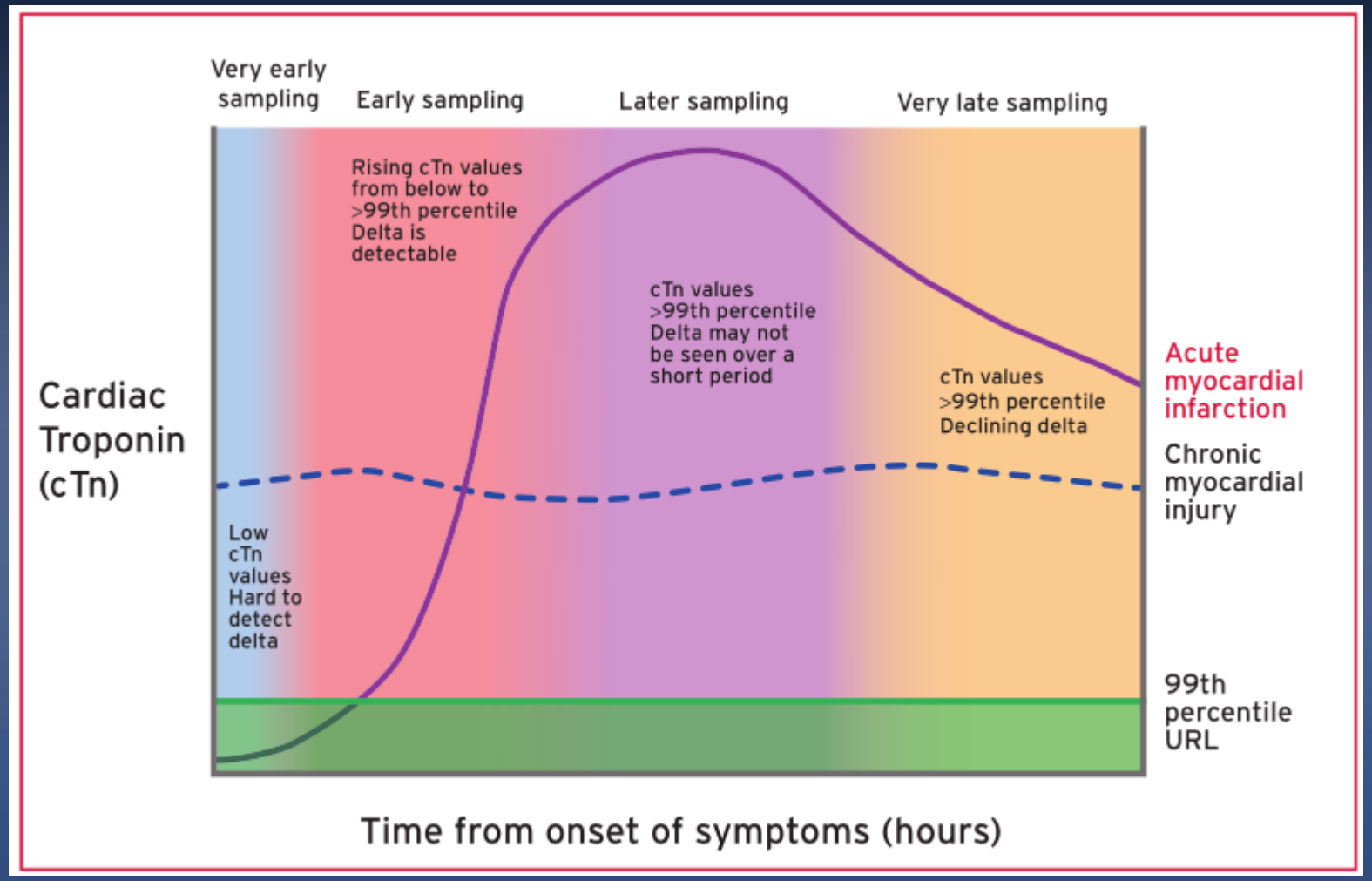
Biomarkers in acute myocardial infarction
Myocardial necrosis

Biomarkers	Diagnostic value	Prognostic value
AST	First biomarker of AMI but lacks specificity (Ladue et al in 1954)	No data
CK/CK-MB	Not as sensitive or specific as cTn (in 1970)	Not consistently predictive of adverse events
Troponin	Highly sensitive and specific, current 'gold s tandard' for AMI diagnosis	Independent predictor of adverse events
Myoglobin	Sensitive early after symptom onset, negativ e predictive value, but lacks specificity (in 1958)	Predictive of mortality in renal insufficiency
IMA	Less sensitive than cTn and lacks specificity	Possibly predictive of adverse events
hFABP	Sensitive early after symptom onset, but lacks specificity	Predictive of mortality

Postgrad Med J 2019;0:1–7

IMA:ischemia-modified albumin, hFABP:heart-type fatty acid binding protein

Illustration of early cardiac troponin kinetics in patients after acute myocardial injury including acute myocardial infarction



Eur Heart J,2019 ,40(3):237-269

Reasons for the elevation of cardiac troponin values because of myocardial injury

- Myocardial injury related to acute myocardial ischaemia
  - Atherosclerotic plaque disruption with thro mbosis.

- Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance

Reduced myocardial perfusion

1. Coronary artery spasm, microvas cular dysfunction
2. Coronary embolism
3. Coronary artery dissection
4. Sustained bradyarrhythmia
5. Hypotension or shock
6. Respiratory failure
7. Severe anaemia

Increased myocardial oxygen demand

1. Sustained tachyarrhythmia
2. Severe hypertension with or witho ut left ventricular hypertrophy

Possible causes of troponin elevation,except in AMI

Cardiac causes	Noncardiac causes
Acute and chronic heart failure	Acute pulmonary edema
Acute inflammatory myocarditis, endocarditis/pericarditis	Acute pulmonary embolism
Aortic dissection	Cardiotoxic drugs
Aortic valve disease	COPD
Apical balloon syndrome	Chronic renal failure
Bradyarrhythmia, heart block	Difficult exercise/excessive effort
Cardiac contusion	Infiltrative diseases (amyloidosis)
Cardiac surgery, post–percutaneous coronary intervention, endomyocardial biopsy	Nonacute critical cardiac disease
Cardioversion	Pulmonary hypertension
Hypertrophic cardiomyopathy	Rhabdomyolysis
Myocardial trauma	Sepsis
Tachycardia/tachyarrhythmia	Stroke, subarachnoid hemorrhage

Vascular Health and Risk Management 2019:15 1–10

Biomarkers in acute myocardial infarction: Neuroendocrine

Biomarkers	Diagnostic value	Prognostic value
BNP/NT-proBNP	Not sensitive or specific	Highly predictive of heart failure and mortality
Adrenomedullin	Not as sensitive or specific as cTn	Possibly predictive of adverse events
RAAS		

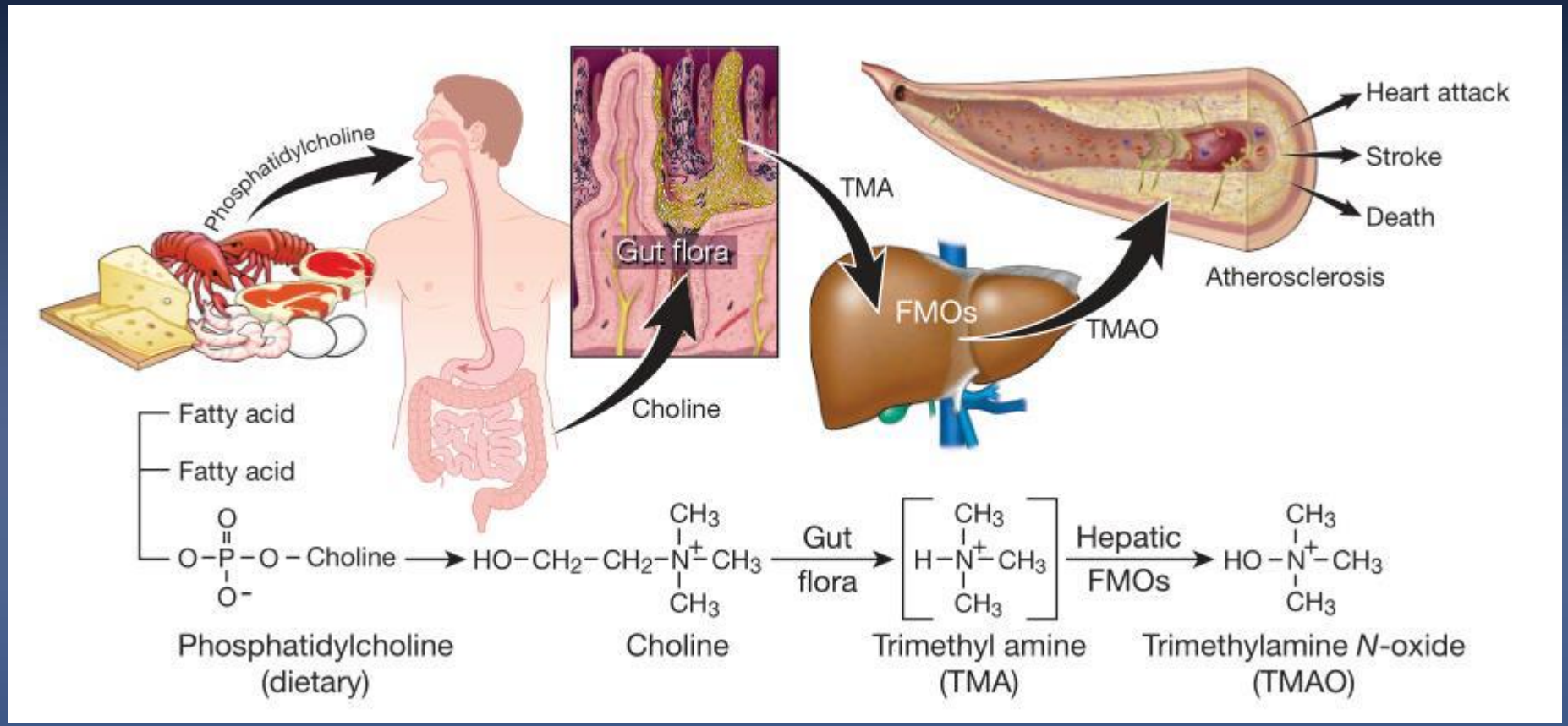
Biomarkers in acute myocardial infarction : Inflammation

Biomarkers	Diagnostic value	Prognostic value
CRP IL-6 TNF-α PCT MPO MMP sCD40L PGF 6	Not sensitive or specific. The diagnostic accuracy of cTn can be increased when combining with some of these Inflammatory biomarkers	Possibly predictive of heart failure and mortality

Biomarkers in acute myocardial infarction
Other novel cardiac biomarkers

Biomarkers	Diagnostic value	Prognostic value
miRNAs	Raised but not sensitive or specific for AMI	Possibly predictive of mortality and heart failure
ST2	Raised but not sensitive or specific for AMI	Predictive of mortality and heart failure
GDF-15	Raised but not sensitive or specific for AMI	Predictive of mortality and ischaemia
Gal-3	Raised in AMI but insufficient data	Possibly predictive of adverse events
TMAO		

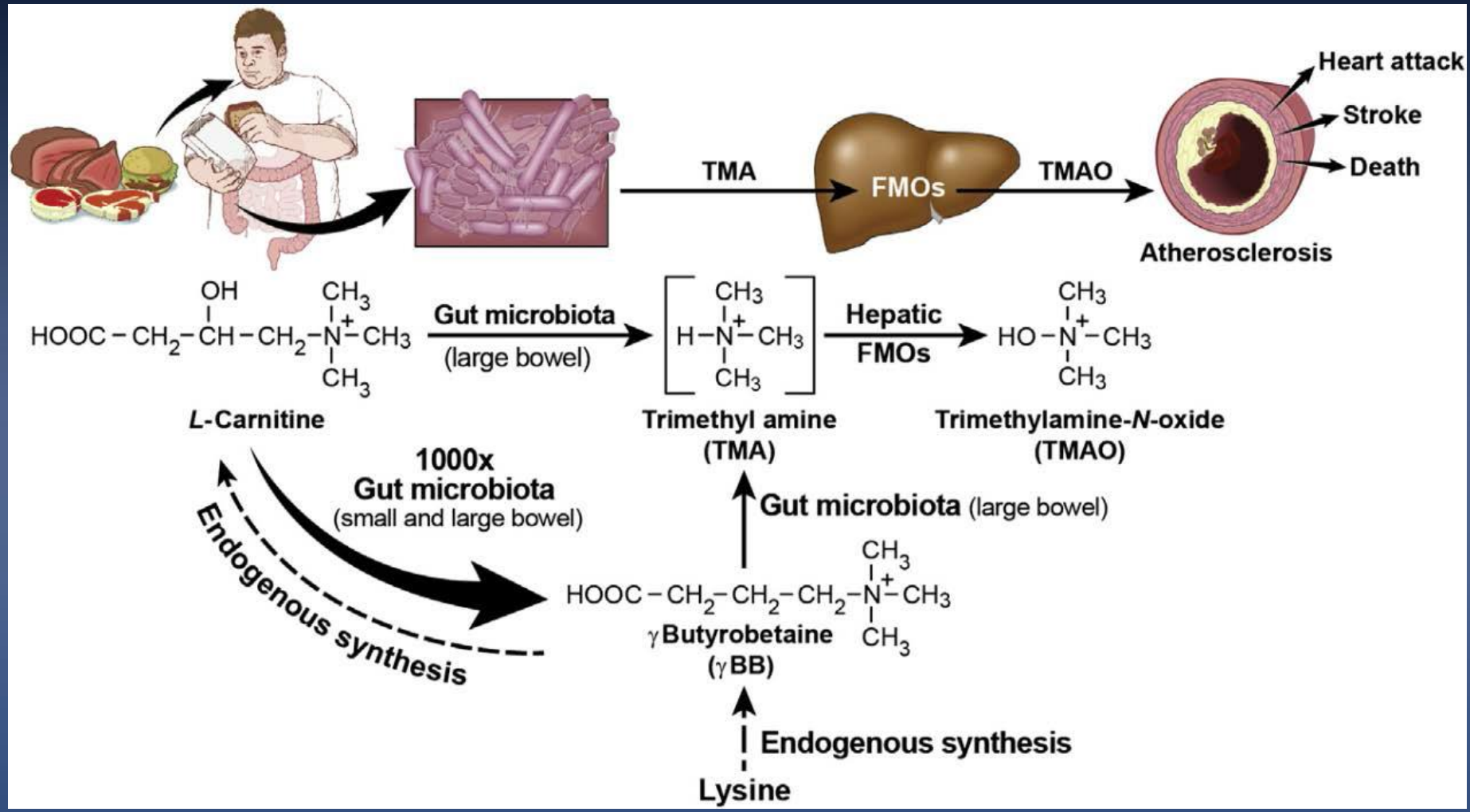
Gut Microbial Metabolite:TMAO



Gut-flora-dependent metabolism of dietary PC and atherosclerosis

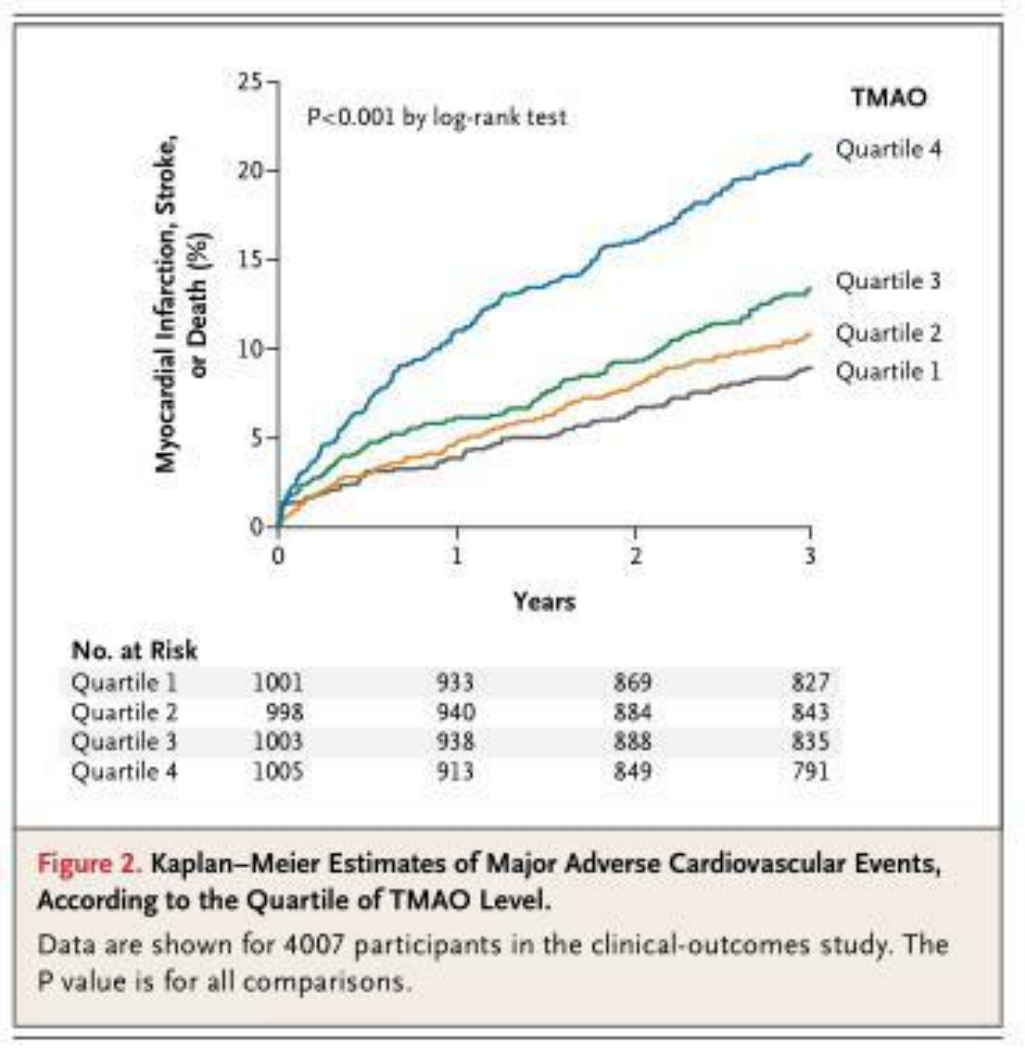
Wang Z,et al. Nature,2011,472(7341):57-63

Gut Microbial Metabolite:TMAO



Koeth RA,etal.Nat Med,2013,19(5):576-585

Intestinal microbial metabolism of phosphatidycholine and cardiovascular risk



No. at Risk				
Quartile 1	1001	933	869	827
Quartile 2	998	940	884	843
Quartile 3	1003	938	888	835
Quartile 4	1005	913	849	791

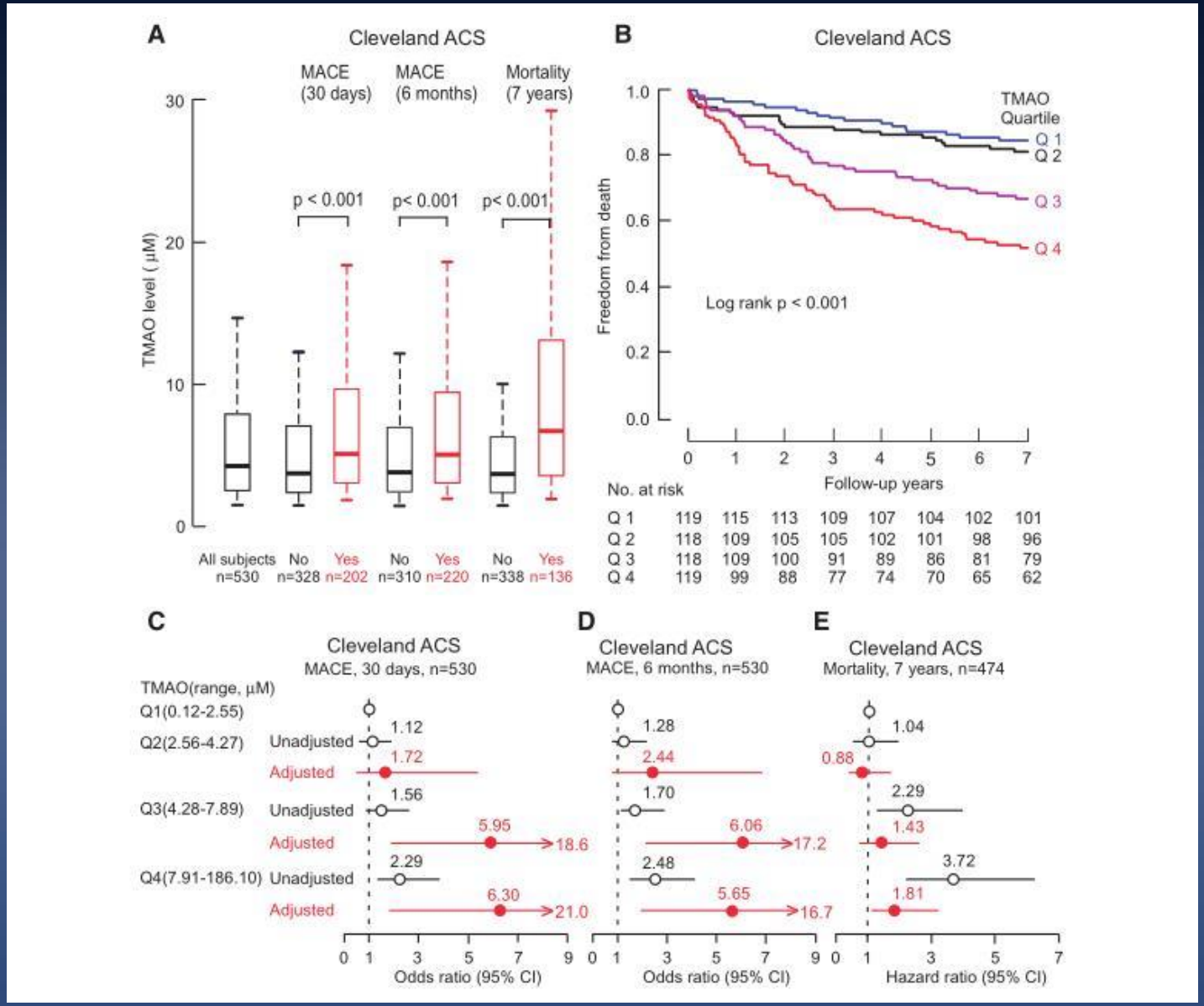
Figure 2. Kaplan–Meier Estimates of Major Adverse Cardiovascular Events, According to the Quartile of TMAO Level.

Data are shown for 4007 participants in the clinical-outcomes study. The P value is for all comparisons.

Tang WH,et al.N Engl J Med,2013,368(17):1575-1584

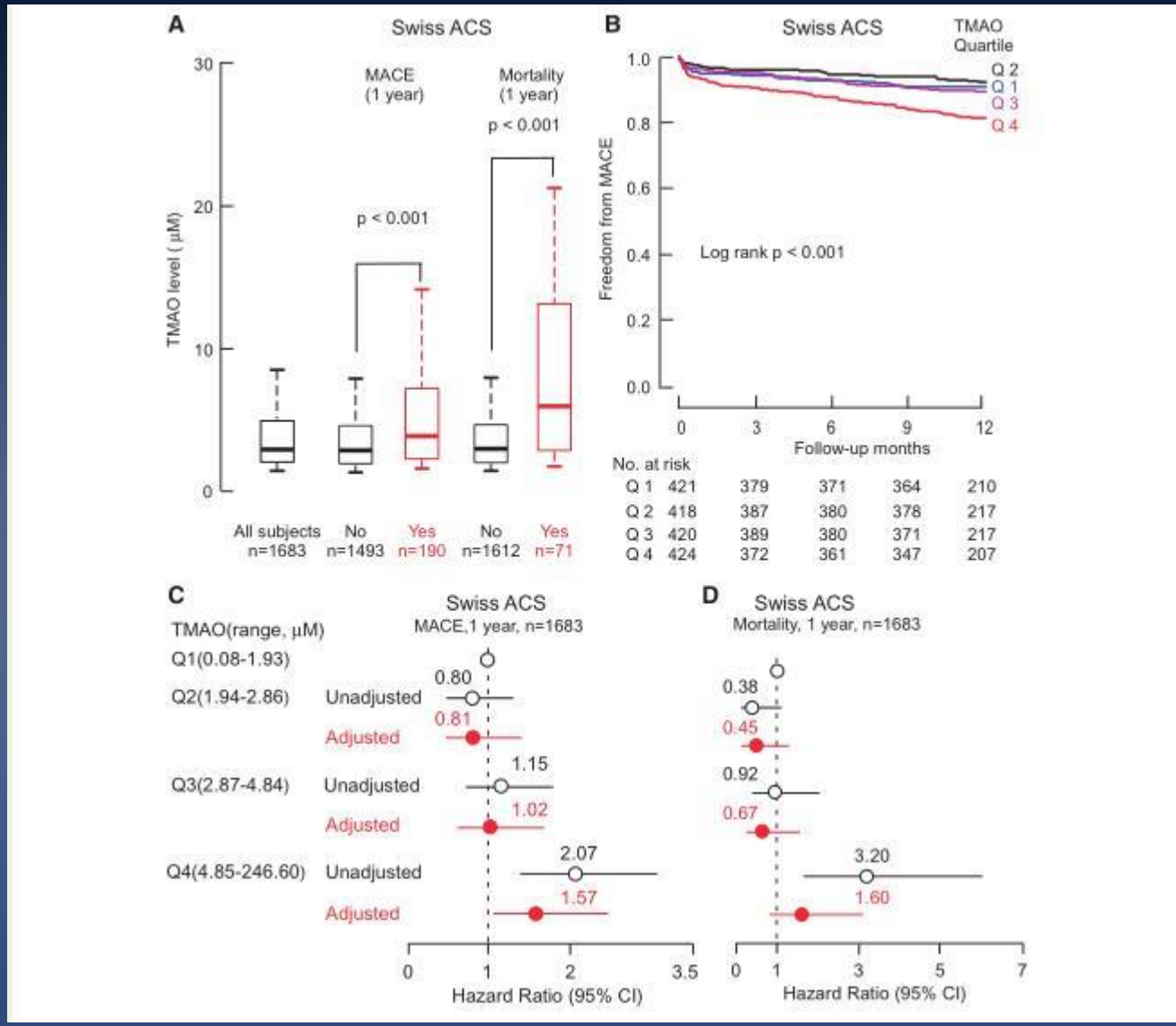
Cleveland Cohort

Gut microbiota–dependent TAMO in acute coronary syndromes: a prognostic marker for incident cardio–vascular events beyond traditional risk factors



Li XS,etal.European Heart Journal (2017) 0, 1–11

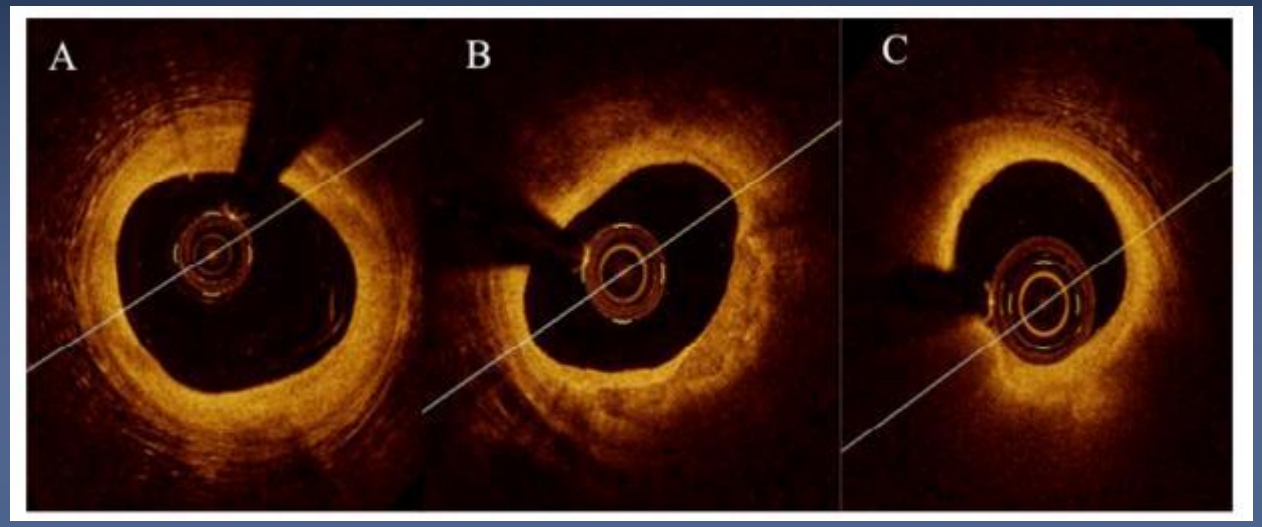
Swiss ACS Cohort

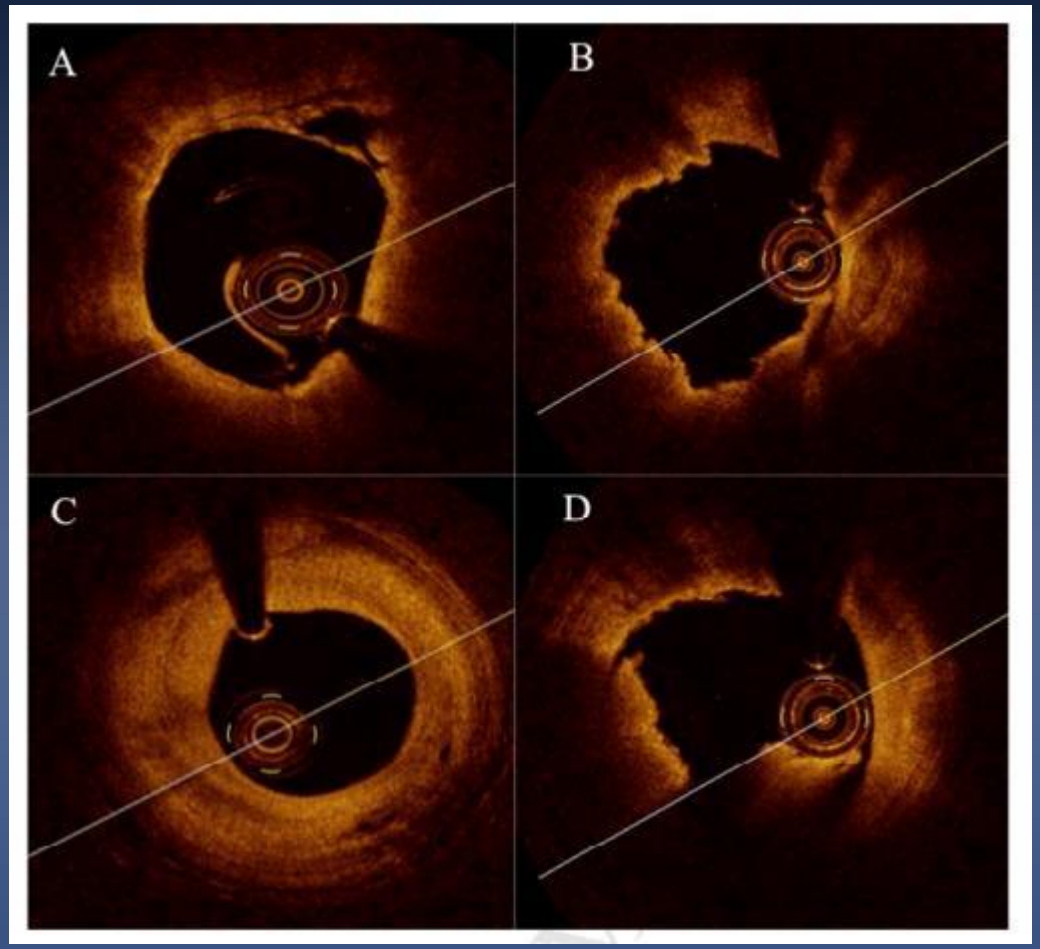


European Heart Journal (2017) 0, 1–11

TMAO and coronary plaque

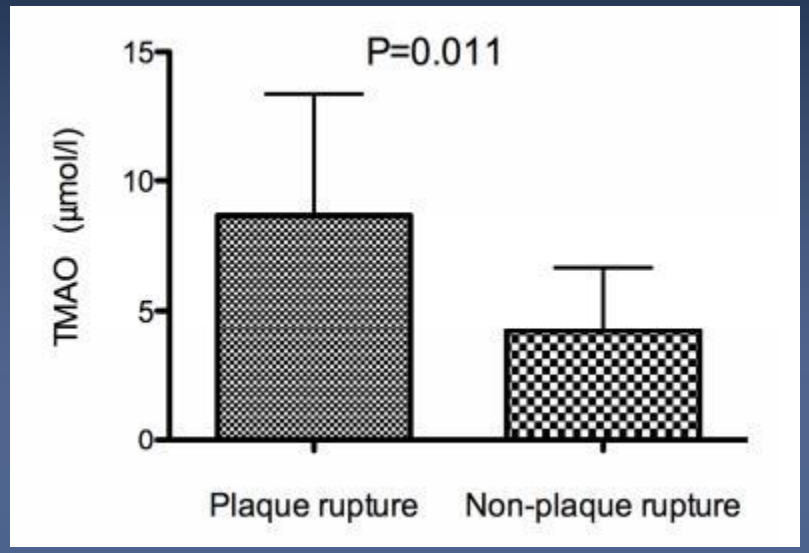
TMAO and vulnerable plaque evaluated by OCT

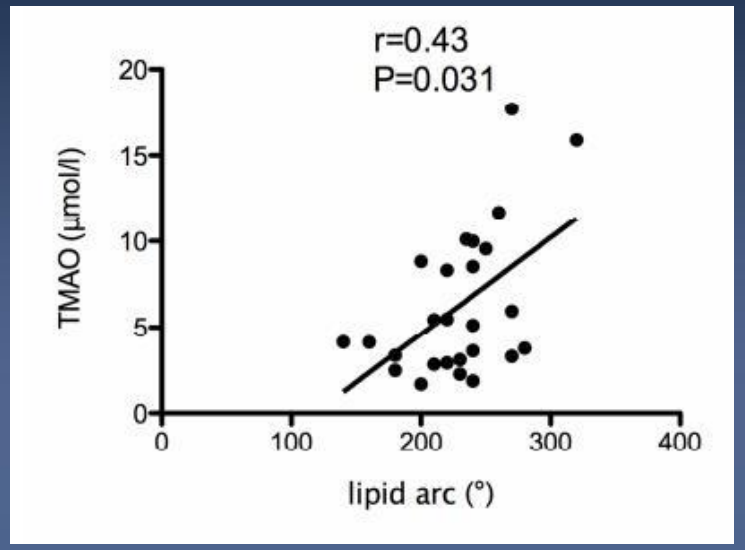


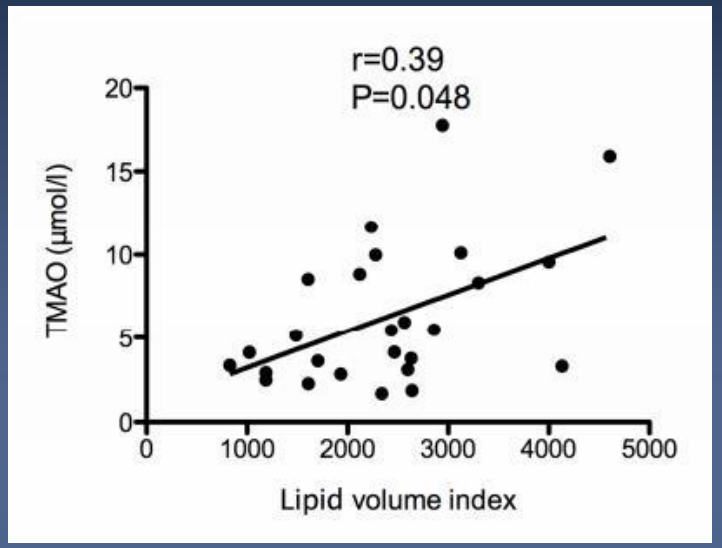


Fu Q,et al. Am J Cardiol,2016,118(9):1311-1315.

TMAO and vulnerable plaque evaluated by OCT



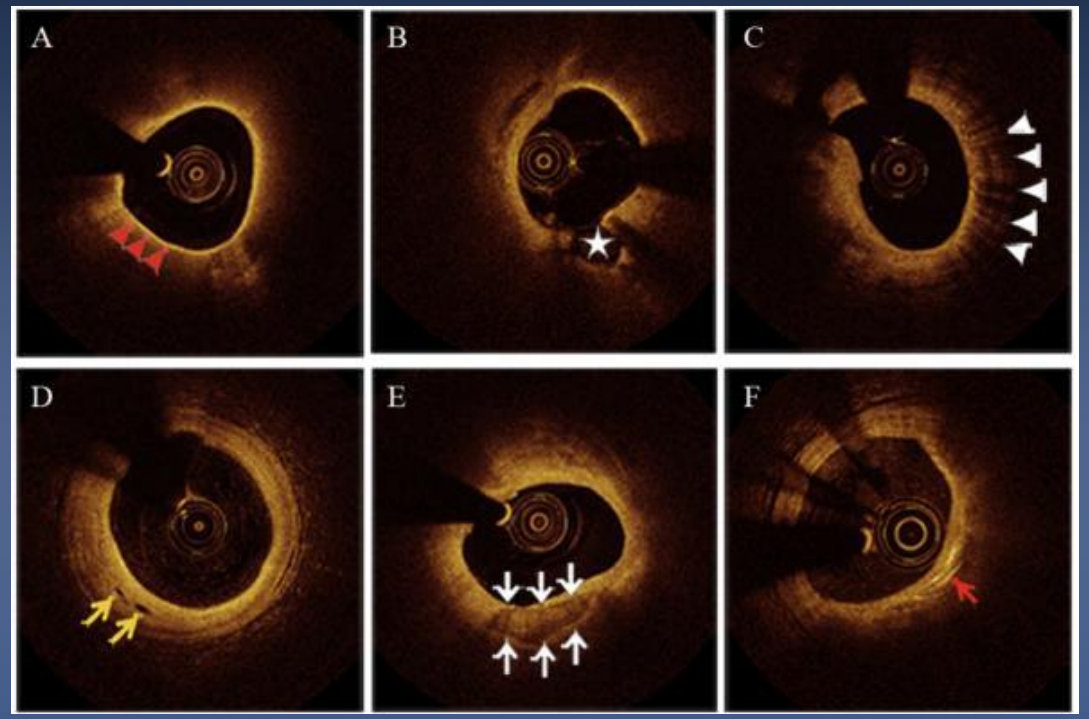


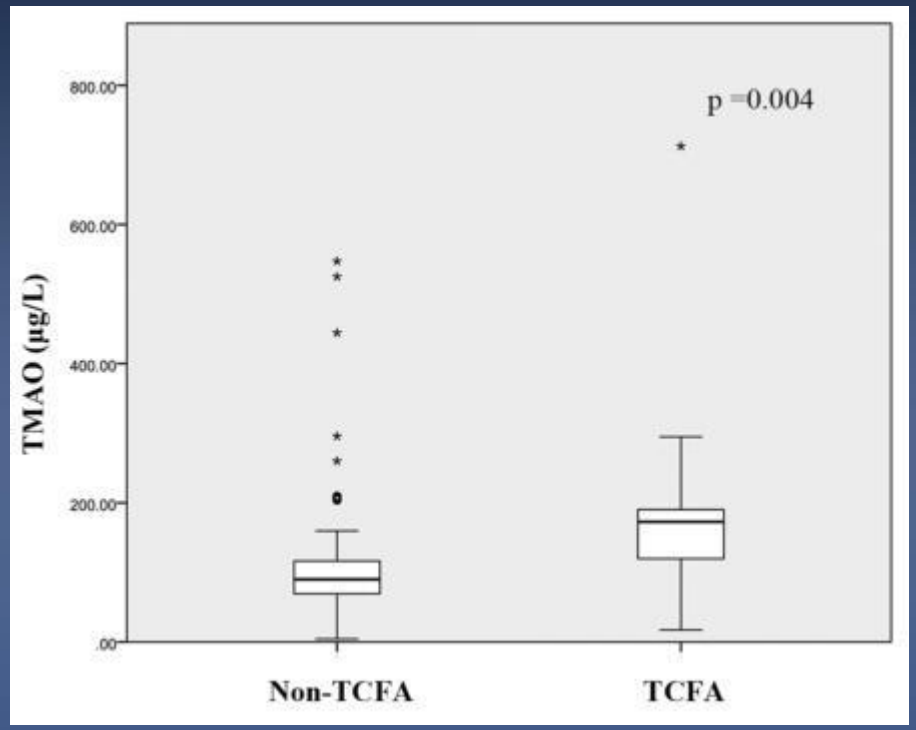


TMAO level may reflect coronary plaque vulnerability and progression.

Fu Q,et al. Am J Cardiol,2016,118(9):1311-1315.

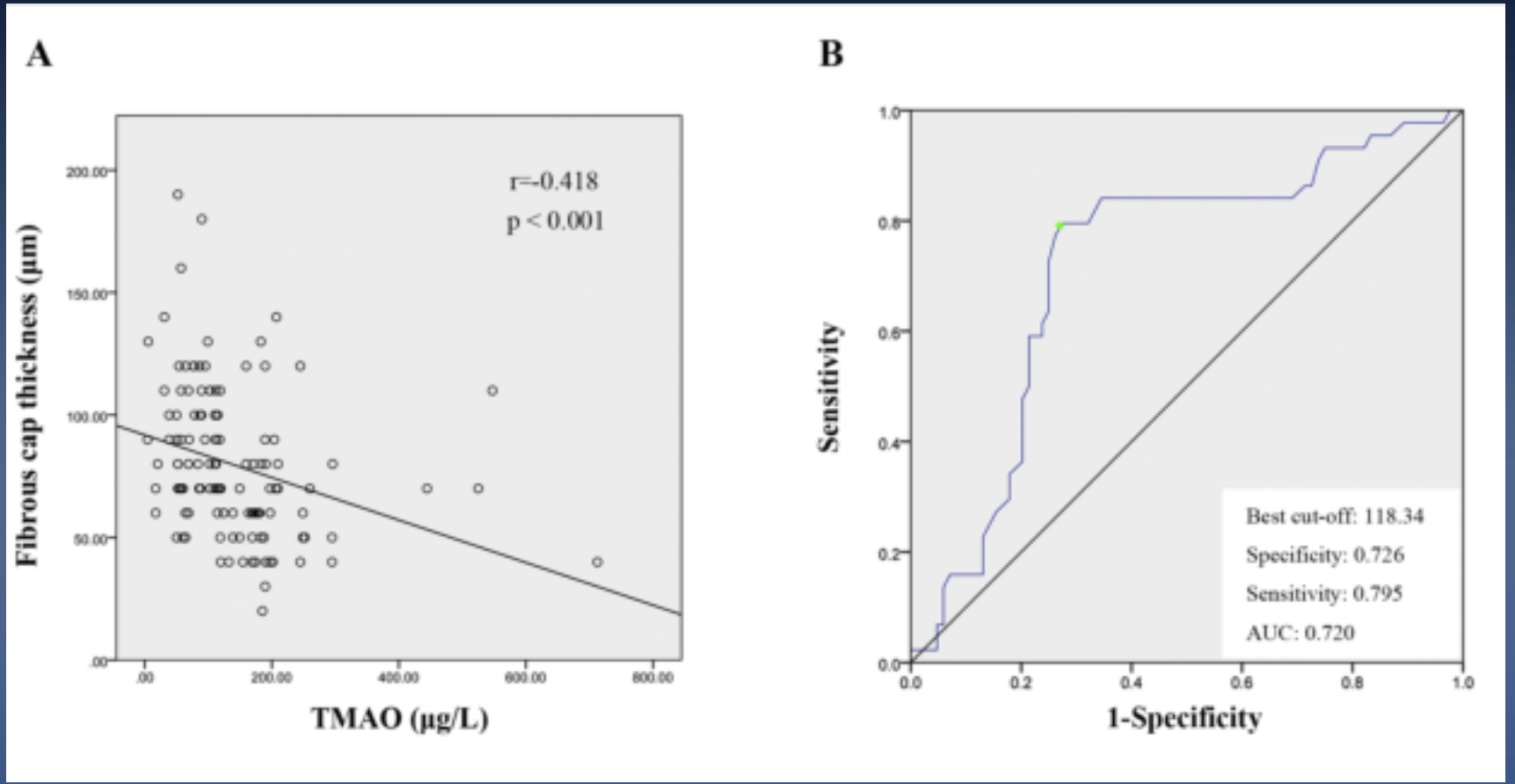
TAMO and vulnerable plaque :OCT findings





Liu XX,et al.doi:10.1016/j.ijcard.2018.04.126

TAMO and vulnerable plaque :OCT findings



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TAMO and vulnerable plaque :OCT findings

Parameters	Total	TMAO level		*P*-value
		Low (n=45)	High (n=45)	
Total plaque number	180	91	89	
Angiographic findings				
Location				0.220
RCA, %	68	40 (44.0%)	28 (31.5%)	
LAD, %	67	30 (33.0%)	37 (41.6%)	
LCX, %	45	21 (23.1%)	24 (27.0%)	
QCA analysis				
MLD, mm	2.11 ± 0.58	2.07 ± 0.56	2.16 ± 0.61	0.301
RVD, mm	3.30 ± 0.54	3.29 ± 0.53	3.31 ± 0.54	0.814
DS, %	64.03 ± 14.51	63.18 ± 14.83	64.90 ± 14.22	0.427
Lesion length, mm	21.88 ± 13.96	22.96 ± 14.79	20.78 ± 13.04	0.295
OCT findings				
Per patient				
Patients with lipid plaque, %	77	38 (84.4%)	39 (86.7%)	0.764
Patients with TCFA, %	34	7 (18.4%)	27 (69.2%)	< 0.001
Patients with Microvessel, %	48	14 (31.1%)	34 (75.6%)	< 0.001
Patients with cholesterol crystal, %	15	6 (13.3%)	9 (20.0%)	0.396
Patients with macrophage, %	49	24 (53.3%)	25 (55.6%)	0.832
Patients with Calcification, %	52	24 (53.3%)	28 (62.2%)	0.393
Patients with Rupture, %	13	7 (15.6%)	6 (13.3%)	0.764
Patients with Thrombus, %	15	8 (17.8%)	7 (15.6%)	0.777
Per plaque				
Lipid plaque, %	128	66 (72.5%)	62 (69.7%)	0.672
TCFA, %	44	9 (13.6%)	35 (56.5%)	< 0.001
FCT, μm	79.92 ± 30.26	93.03 ± 28.28	65.97 ± 25.89	< 0.001
Maximum lipid arc, °	250.17 ± 71.04	240.76 ± 72.82	260.18 ± 68.25	0.123
Microvessel, %	62	18 (19.8%)	44 (49.4%)	< 0.001
Cholesterol crystal, %	16	7 (7.7%)	9 (10.1%)	0.568
Macrophage, %	64	32 (35.2%)	32 (36.0%)	0.912
Calcification, %	84	43 (47.3%)	41 (46.1%)	0.873
Rupture, %	14	8 (8.8%)	6 (6.7%)	0.608
Thrombus, %	17	9 (9.9%)	8 (9.0%)	0.836

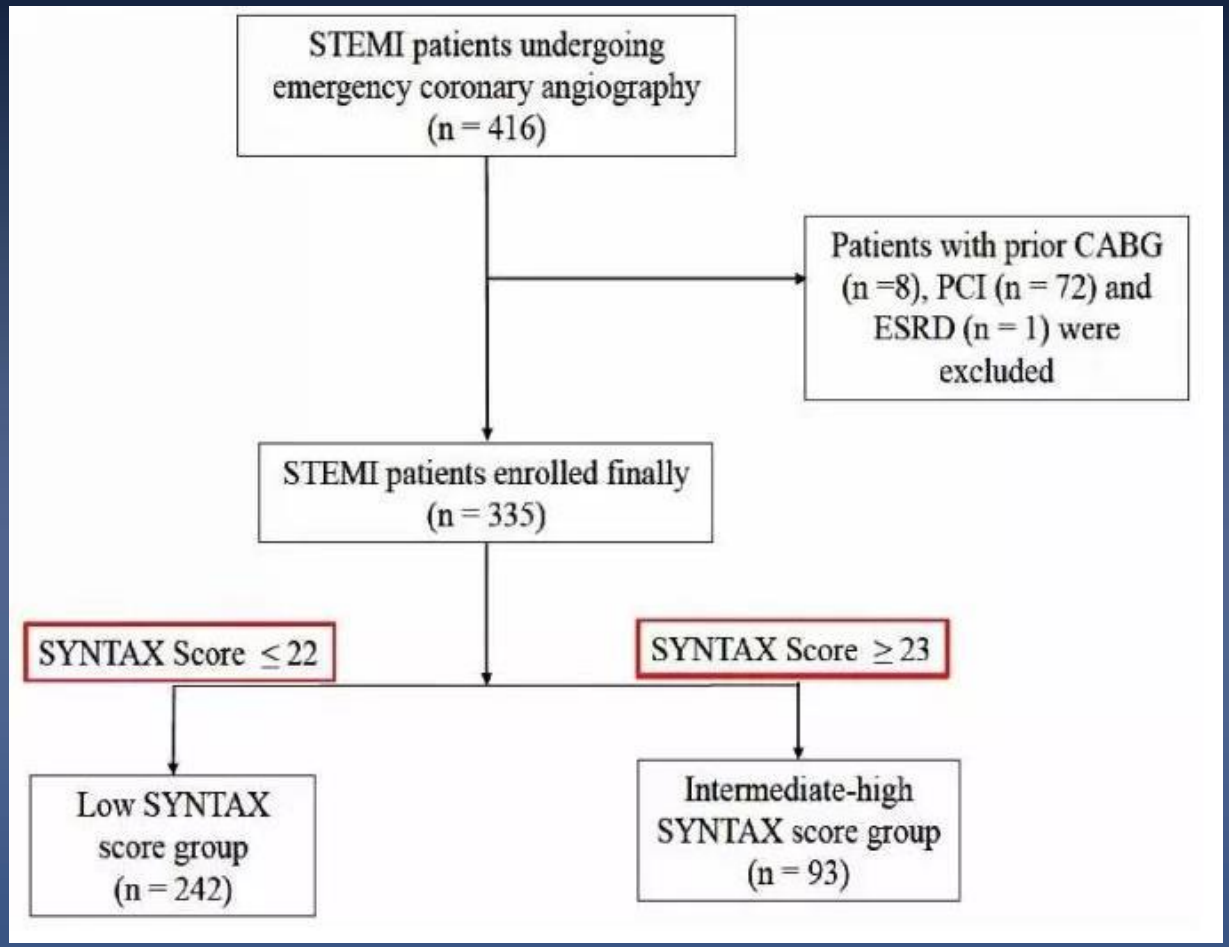
Liu XX,et al.doi:10.1016/j.ijcard.2018.04.126

TAMO and vulnerable plaque :OCT findings

Variables	Univariate		Multivariate	
	OR (95%CI)	*P* Value	OR (95%CI)	*P* Value
Age	1.926(0.919-4.037)	0.083		
Gender (male)	0.605(0.262-1.399)	0.240		
Diabetes mellitus	0.721(0.334-1.559)	0.406		
Hypertension	1.190(0.560-2.527)	0.651		
Current smoking	0.839(0.380-1.849)	0.663		
Prior MI	1.329(0.622-2.843)	0.463		
TC	2.707(1.267-5.784)	0.010	0.828(0.257-2.663)	0.751
TG	1.377(0.659-2.880)	0.395		
HDL-C	1.385(0.666-2.879)	0.384		
LDL-C	2.456(1.151-5.239)	0.020	2.039(0.629-6.602)	0.235
EGFR	0.629(0.301-1.316)	0.219		
TMAO	8.210(3.461-19.476)	< 0.001	7.455(2.753-20.189)	< 0.001
hs CRP (>1mg/L)	2.708(1.207-6.078)	0.016	1.198(0.459-3.126)	0.711
ACS	1.467(0.671-3.211)	0.337	1.941(0.754-4.998)	0.169
Location of the lesion	1.359(0.857-2.155)	0.193	1.130(0.653-1.958)	0.662

Liu XX,et al.doi:10.1016/j.ijcard.2018.04.126

TMAO and coronary atherosclerotic burden in pts with STEMI



Zhao XS,et. Am J Cardiol 2019;123:894-898

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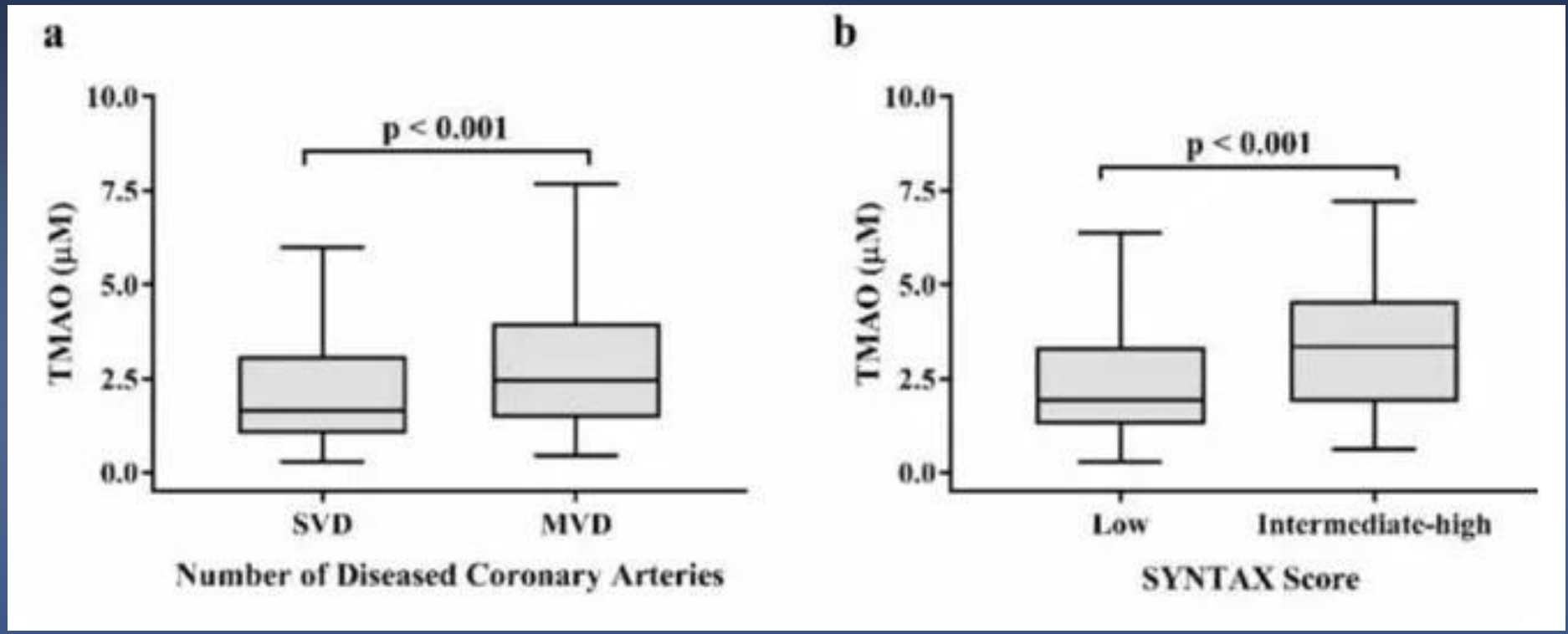
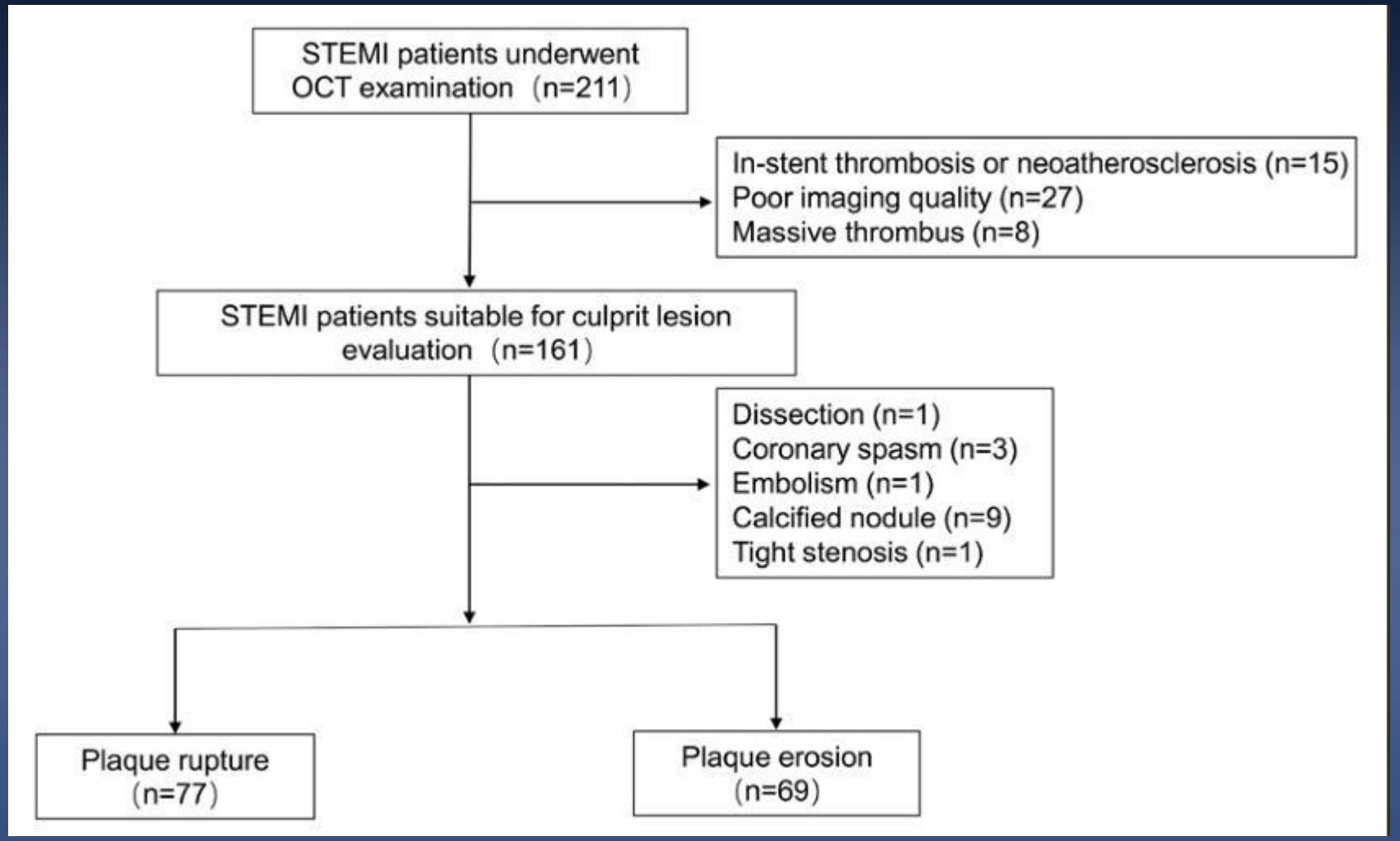


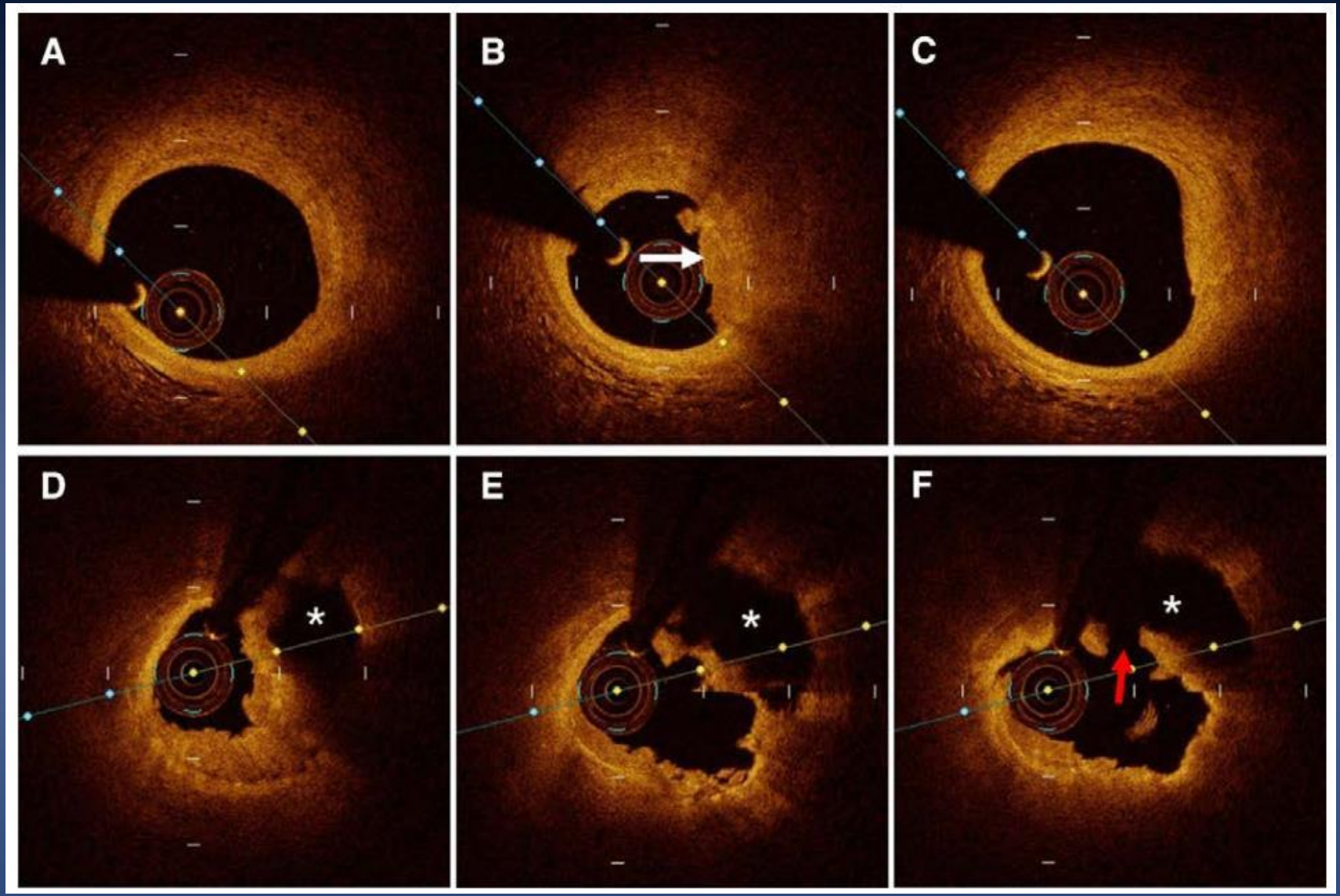
Zhao XS,et. Am J Cardiol 2019;123:894-898

TMAO and plaque rupture



Tan Y,et al.Circ Cardiovasc Interv. 2019;12:e007281.

TMAO and plaque rupture



Tan Y,et al.Circ Cardiovasc Interv. 2019;12:e007281.

TMAO and plaque rupture

Variable	All Subjects (n=146)	Plaque Rupture (n=77)	Plaque Erosion (n=69)	*P* Value
Age, y	57.0±11.0	59.2±10.5	54.5±11.0	0.008
Men, %	82.2	80.5	84.1	0.577
Smoker, %	74.0	70.1	78.3	0.264
Hypertension, %	55.5	58.4	52.2	0.447
Diabetes mellitus, %	28.8	36.4	20.3	0.032
CAD, %	17.1	20.8	13.0	0.215
hs-CRP, mg/L	4.5 (2.2–9.2)	4.4 (2.1–8.5)	5.3 (2.5–9.9)	0.456
LDL-C, mg/dL	114.1±34.0	112.0±32.9	116.4±35.3	0.441
HDL-C, mg/dL	41.2±8.7	40.4±8.2	42.1±9.1	0.223
Triglyceride, mg/dL	127.0 (83.4–173.7)	124.8 (78.3–166.4)	134.5 (92.5–176.6)	0.344
eGFR, mL/min per 1.73 m^2)	98.7 (85.4–109.6)	93.4 (79.0–104.0)	105.3 (93.7–113.1)	<0.001
TMAO, μM	2.28 (1.17–3.70)	3.33 (2.48–4.57)	1.21 (0.86–1.91)	<0.001

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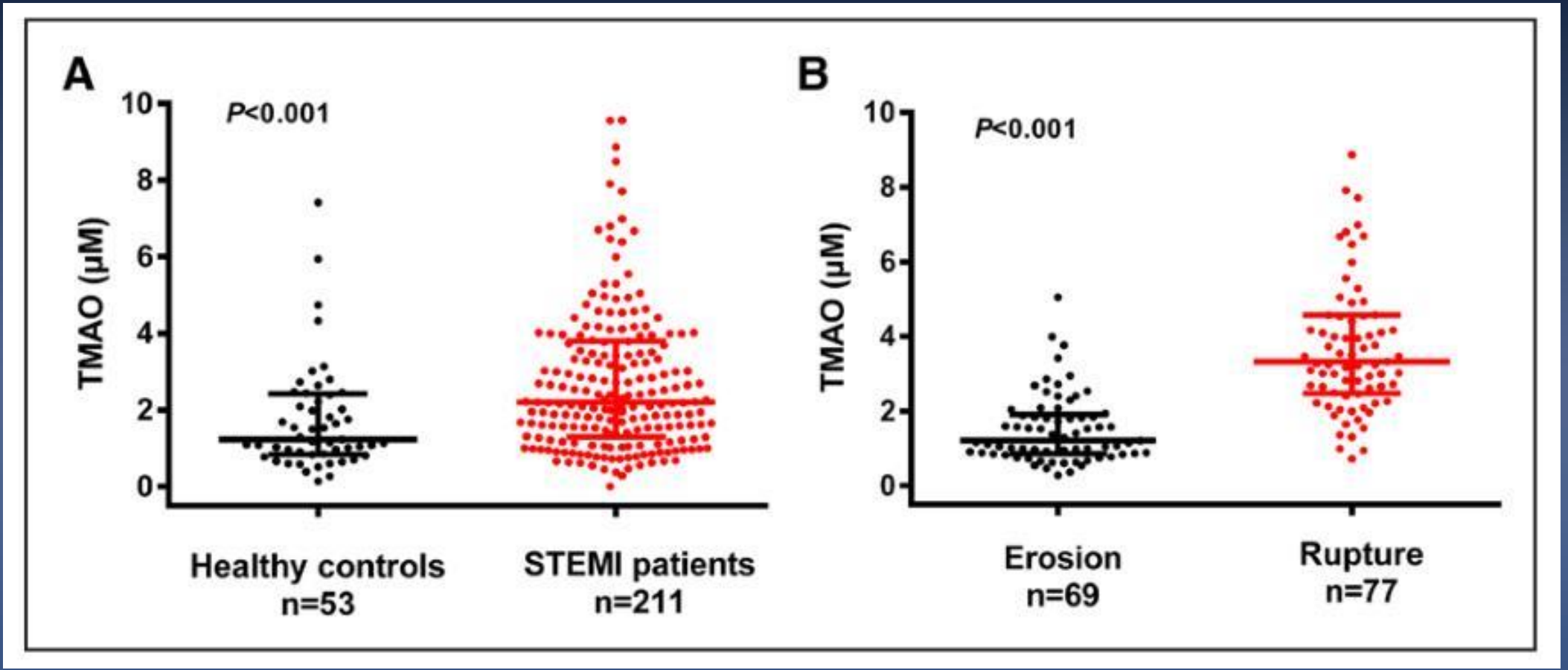
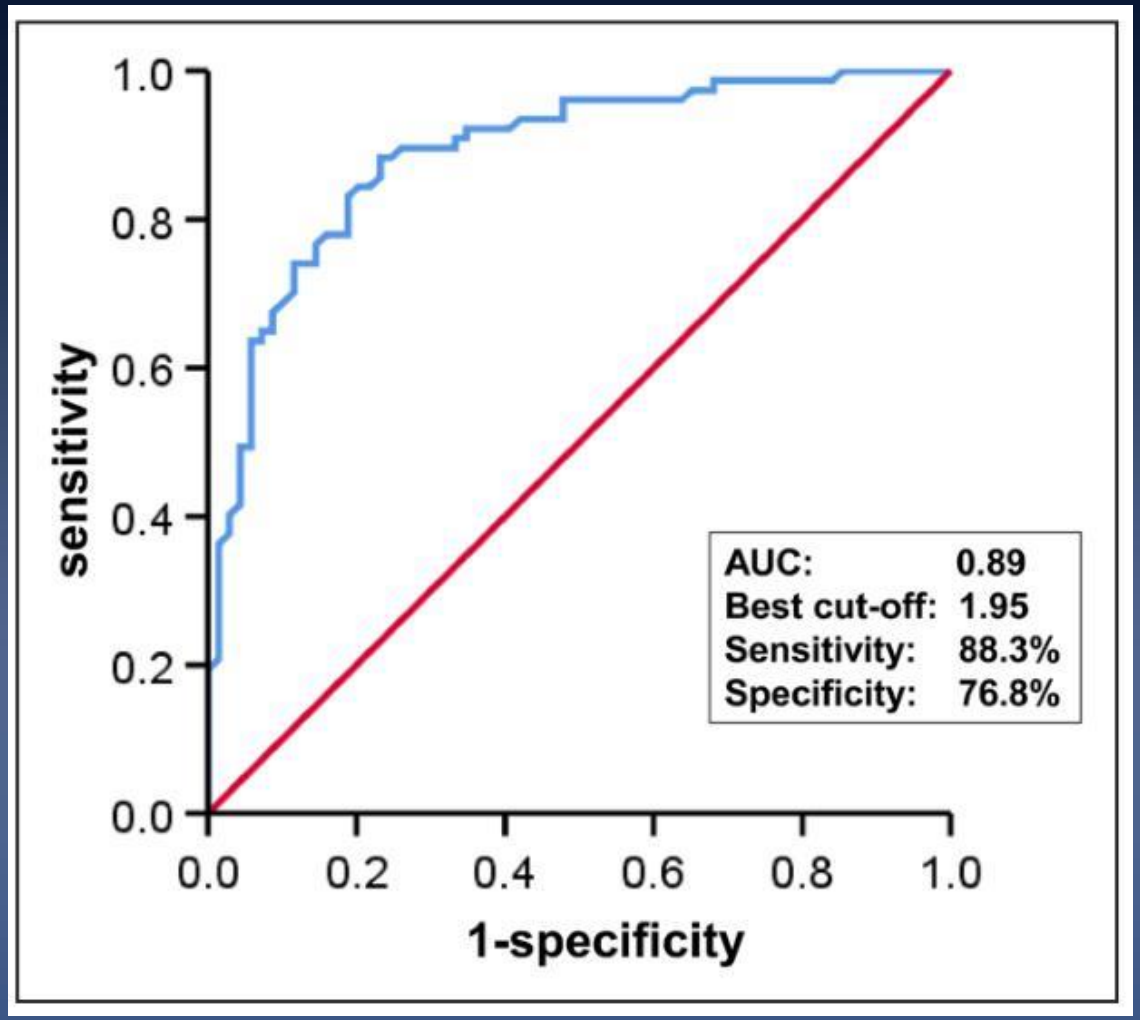
TMAO，plaque rupture and erosion



Tan Y,et al.Circ Cardiovasc Interv. 2019;12:e007281.

TMAO for predicting plaque rupture



TMAO may be used to predict plaque rupture and future cardiac events.

Tan Y,et al.Circ Cardiovasc Interv. 2019;12:e007281.

conclusions

1. Different pathophysiological types may be useful to understand the mechanisms of AMI ,and help to determine the therapeutic decision making.

2. A multibiomarker approach can potentially enhance the diagnostic accuracy and provide more information for the early risk stratification of AMI.

谢谢!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