Supplemental Material

Data S1. SUPPLEMENTAL METHODS

Data collection

From January 1, 2017, to September 4, 2018, conventional cardiac troponin I (cTnI) was measured using the Beckman Coulter Access AccuTnI+3 assay, with a 99th percentile upper reference limit (URL) of 40 ng/L for both men and women. Starting from September 5, 2018, high-sensitivity cardiac troponin I (hs-cTnI) measurements were performed using the Access hsTnI assay (Beckman Coulter), with sex-specific 99th percentile URLs of 19.8 ng/L for men and 11.6 ng/L for women.[45] All analyses were conducted using troponin values expressed as a multiple of the respective URL, taking into account the differences between conventional and high-sensitivity assays, as well as sex-specific thresholds.

The glomerular filtration rate (GFR) was estimated using the CKD-EPI equation. Chronic kidney disease was defined as evidence of kidney damage or a GFR <60 $mL/min/1.73\ m^2$ persisting for at least 3 months, regardless of the underlying cause.

Known cardiovascular disease was adjudicated if at least one of the following was present in the past medical history of the patient:

- Previous myocardial infarction (MI)
- Previous percutaneous coronary intervention (PCI)
- Previous coronary artery bypass graft (CABG)
- Previous transient ischemic attack/stroke
- Peripheral artery disease (PAD)

Complete revascularization was defined as PCI performed on all vessels suitable for successful treatment with PCI, with a diameter of at least 2.5 mm, and showing at least 70% diameter stenosis by visual estimation (or 50–69% diameter stenosis with an FFR $\leq$ 0.80 by visual estimation) in the absence of grafts.[46]

Criteria for precipitating factors in type 2 myocardial infarction

1) Sepsis:

- Clinical presentation compatible with infectious event plus at least one within:
    - fever (defined as body temperature ≥ 38° C)
    - leukocytosis (defined as white blood cells (WBC) > upper reference limit (URL))
    - leucopenia (defined as WBC < lower reference limit (LRL))
    - C-reactive Protein (PCR) > URL

2) Anemia:

- Hemoglobin < 8 g/dL and/or
- Thrombolysis in Myocardial Infarction (TIMI) bleeding major or minor

Major

- Any intracranial bleeding [excluding microhemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging (MRI)]
- Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit
- Fatal bleeding (bleeding that directly results in death within 7 days)

Minor

- Clinically overt (including imaging) blood loss, resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in hematocrit
- No observed blood loss: ≥4 g/dL decrease in the hemoglobin concentration or ≥12% decrease in hematocrit
- Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above:

a) Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)

b) Leading to or prolonging hospitalization

c) Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

3) Tachyarrhythmia: evidence of narrow QRS rhythm (max 120 ms, or > 120 ms in case of bundle branch block) with heart rate ≥ 140 bpm, lasting at least 20 minutes

4) Bradyarrhythmia: heart rate < 40 bpm, lasting at least 20 minutes

5) Respiratory failure: SpO2 < 90%, or SpO2 < 88% if known chronic obstructive pulmonary disease (COPD)

6) Hypertension: systemic systolic arterial pressure > 180 mmHg and/or diastolic arterial pressure > 110 mmHg

7) Hypotension: systemic systolic arterial pressure < 90 mmHg and/or diastolic arterial pressure < 60 mmHg

8) Recent non-cardiac surgery: non-cardiac surgery within 48 hours from index event, requiring regional o general anesthesia

9) Acute kidney injury:

- Creatinine rise ≥ 0.3 mg/dL within 48 hours in comparison to baseline with a value > URL, and/or
- Creatinine rise ≥ 1.5 x in comparison to baseline, and/or
- Urinary output < 0.5 mL/kg/h for at least 6 hours

10) Non-atherosclerotic coronary artery lesions:
    - Spontaneous coronary artery dissection
    - Coronary embolism
    - Coronary vasospasm
    - Myocardial bridging

11) Other: patients who meet the definition of type 2 myocardial infarction (T2MI) but whose causative factors are not included in the criteria listed above

Definition of outcomes

Major adverse cardiovascular events (MACE) was defined as the occurrence of the first among the following events:

- All-cause mortality was defined as death from any cause occurring during the follow-up period.
- Reinfarction was diagnosed if there was documentation of an acute myocardial injury associated with clinical evidence of acute myocardial ischemia occurring during the follow-up. This was determined by the detection of a rise and/or fall in cardiac troponin (cTn) values, with at least 1 value above the 99th percentile URL and at least 1 of the following criteria:
    - Symptoms of myocardial ischemia
    - New ischemic 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 ischemic etiology
  - Identification of a coronary thrombus by angiography or autopsy.

- Unplanned revascularization was defined as revascularization by either PCI or CABG that was not anticipated at the index procedure.
- Stroke was defined as an ischemic cerebral infarction caused by embolic or thrombotic occlusion of a major intracranial artery resulting in a new focal neurologic deficit with signs or symptoms lasting more than 24 hours.
- Hospitalization for heart failure (HF) was defined as an event that meets the following criteria:
  a. Hospitalization, defined as admission to an inpatient unit or a visit to an emergency department resulting in at least 6 hours of hospitalization

     AND

  b. Clinical symptoms of HF, including at least one of the following: new or worsening:
     - Dyspnea
     - Orthopnea
     - Paroxysmal nocturnal dyspnea
     - Increasing fatigue/worsening exercise tolerance

     AND

  c. Physical signs of HF, including at least two of the following:
     - Peripheral edema
     - Pulmonary rales
     - Jugular venous distension
     - Tachypnea (respiratory rate > 20 breaths/minute)
     - Rapid weight gain
     - S3 gallop
     - Increasing abdominal distension or ascites

    - Hepatojugular reflux
    - Radiological evidence of worsening heart failure
    - A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) $\geq$ 18 mm Hg and/or a cardiac output < 2.2 L/min/m^2.

Other outcomes:

- Type 2 reinfarction was defined as reinfarction (as stated above) fulfilling the definition of type 2 myocardial infarction of the 4th universal definition of myocardial infarction[2]
- Cardiovascular death was defined as all death except those in which the exclusive primary and underlying cause was non-cardiovascular

SUPPLEMENTAL TABLES

Table S1. Latent Class Analysis results for various class models.

Model	Model fit criteria	Diagnostic criteria		
	BIC	Smallest class count (n)	Smallest class size (%)	ALCPP
1-class	7184	774	100%	-
2-class	6872	244	31.5%	0.908
3-class	6826	239	30.9%	0.863

Abbreviations: BIC = Bayesian information criterion; ALCPP = average latent class posterior probability.

Table S2. Precipitating factors of T2MI across clinical phenotypes.

	Total N = 774	P1 T2MI N = 244	P2 T2MI N = 530	*P value*
Sepsis, n (%)	78 (10.1)	14 (5.7)	64 (12.1)	*0.007*
Anemia, n (%)	28 (3.6)	1 (0.4)	27 (5.1)	*0.001*
Tachyarrhythmia, n (%)	179 (23.1)	48 (19.7)	131 (24.7)	*0.122*
Bradyarrhythmia, n (%)	12 (1.6)	2 (0.8)	10 (1.9)	*0.264*
Respiratory failure, n (%)	102 (13.2)	16 (6.6)	86 (16.2)	*<0.001*
Hypertension, n (%)	148 (19.1)	45 (18.4)	103 (19.4)	*0.745*
Hypotension, n (%)	28 (3.6)	11 (4.5)	17 (3.2)	*0.368*
Recent non-cardiac surgery, n (%)	22 (2.8)	8 (3.3)	14 (2.6)	*0.620*
Acute kidney injury, n (%)	21 (2.7)	2 (0.8)	19 (3.6)	*0.028*
Non-atherosclerotic coronary artery lesions, n (%)	50 (6.5)	39 (16.0)	11 (2.1)	*<0.001*
Other cause, n (%)	71 (9.1)	16 (6.6)	55 (10.4)	*0.087*
Acute Heart Failure, n (%)	15 (1.9)	1 (0.4)	14 (2.6)	*0.036*
Multiple causes (at least 2 triggers), n (%)	113 (14.6)	26 (10.7)	87 (16.4)	*0.035*
No apparent cause, n (%)	126 (16.3)	64 (26.2)	62 (11.7)	*<0.001*

Abbreviations: T2MI = type 2 myocardial infarction ; P1 = phenotype 1 ; P2 = phenotype 2.

Table S3. Medical therapy at admission and discharge in the non-obstructive CAD cohort stratified by clinical phenotype.

	Total N = 348	P1 T2MI N = 146	P2 T2MI N = 202	*P value*
Medical therapy at admission				
Aspirin, n (%)	103 (29.6)	21 (14.4)	82 (40.6)	*<0.001*
P2Y12-inhibitors, n (%)	23 (6.6)	4 (2.7)	19 (9.4)	*0.014*
Statins, n (%)	100 (28.7)	18 (12.3)	82 (40.6)	*<0.001*
Beta-blockers, n (%)	127 (36.5)	25 (17.1)	102 (50.5)	*<0.001*
ACE-I/ARBs, n (%)	146 (42.0)	27 (18.5)	119 (58.9)	*<0.001*
Oral anticoagulant, n (%)	48 (13.8)	4 (2.7)	44 (21.8)	*<0.001*
Medical therapy at discharge*				
DAPT, n (%)	131 (37.9)	70 (47.9)	61 (30.5)	*<0.001*
Aspirin alone, n (%)	114 (32.9)	35 (24.7)	79 (39.5)	*0.005*
P2Y12-inhibitors alone, n (%)	24 (6.9)	8 (5.5)	16 (8.0)	*0.362*
Statins, n (%)	245 (70.8)	101 (69.2)	144 (72.0)	*0.569*
Beta-blockers, n (%)	256 (74.0)	104 (71.2)	152 (76.0)	*0.318*
ACE-I/ARBs, n (%)	231 (66.8)	70 (47.9)	161 (80.5)	*<0.001*
Oral anticoagulant, n (%)	73 (21.1)	9 (6.2)	64 (32.0)	*<0.001*

Abbreviations: P1 = phenotype 1; P2 = phenotype 2; T2MI = type 2 myocardial infarction; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; ACE-I = angiotensin converting enzyme – inhibitors; ARB = angiotensin receptor blockers.

* Data from patients discharged alive only

Table S4. Medical therapy at admission and discharge and revascularization rate in the obstructive CAD cohort stratified by clinical phenotype.

	Total N = 426	P1 T2MI N = 98	P2 T2MI N = 328	*P value*
Medical therapy at admission				
Aspirin, n (%)	208 (48.8)	25 (25.5)	183 (55.8)	*<0.001*
P2Y12-inhibitors, n (%)	50 (11.7)	5 (5.1)	45 (13.7)	*0.020*
Statins, n (%)	168 (39.4)	20 (20.4)	148 (45.1)	*<0.001*
Beta-blockers, n (%)	221 (51.9)	27 (27.6)	194 (59.1)	*<0.001*
ACE-I/ARBs, n (%)	250 (58.7)	20 (20.4)	230 (70.1)	*<0.001*
Oral anticoagulant, n (%)	54 (12.7)	3 (3.1)	51 (15.5)	*<0.001*
Medical therapy at discharge*				
DAPT, n (%)	328 (78.1)	88 (89.8)	240 (74.5)	*0.001*
Aspirin alone, n (%)	58 (13.8)	6 (6.1)	52 (16.1)	*0.012*
P2Y12-inhibitors alone, n (%)	14 (3.3)	3 (3.1)	11 (3.4)	*0.864*
Statins, n (%)	371 (88.3)	91 (92.9)	280 (87.0)	*0.111*
Beta-blockers, n (%)	375 (89.3)	91 (92.9)	284 (88.2)	*0.192*
ACE-I/ARBs, n (%)	337 (80.2)	78 (79.6)	259 (80.4)	*0.854*
Oral anticoagulant, n (%)	90 (21.4)	8 (8.2)	82 (25.5)	*<0.001*
Myocardial revascularization				
Yes, n (%)	275 (64.6)	76 (77.6)	199 (60.7)	*0.002*
Complete revascularization†, n (%)	157 (57.1)	48 (63.2)	109 (54.8)	*0.209*

Abbreviations: P1 = phenotype 1; P2 = phenotype 2; T2MI = type 2 myocardial infarction; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; ACE-I = angiotensin converting enzyme – inhibitors; ARB = angiotensin receptor blockers.

* Data from patients discharged alive only

† Data from revascularized patients only

Table S5. 30-day outcomes in the overall cohort study and by clinical phenotype.

	Total N = 774	P1 T2MI N = 244	P2 T2MI N = 530	*P value*
MACE, n (%)	25 (3.2)	5 (2.0)	20 (3.8)	*0.207*
All-cause mortality, n (%)	13 (1.7)	0 (0.0)	13 (2.5)	*0.014*
Reinfarction, n (%)	7 (0.9)	2 (0.8)	5 (0.9)	*0.866*
Unplanned revascularization, n (%)	4 (0.5)	1 (0.4)	3 (0.6)	*0.778*
Ischemic stroke, n (%)	2 (0.3)	2 (0.8)	0 (0.0)	*0.037*
HF hospitalization, n (%)	4 (0.5)	1 (0.4)	3 (0.6)	*0.778*
Type 2 reinfarction, n (%)	4 (0.5)	0 (0.0)	4 (0.8)	*0.174*
Cardiovascular death, n (%)	11 (1.4)	0 (0.0)	11 (2.1)	*0.023*

Abbreviations: P1 = phenotype 1; P2 = phenotype 2; T2MI = type 2 myocardial infarction; MACE = major adverse cardiovascular events; HF = heart failure.

Table S6. Sensitivity analysis of long-term outcomes in the two clinical phenotypes after exclusion of patients with coronary artery spasm, embolism, or dissection.

	Total **N = 730**	**P1 T2MI** **N = 210**	**P2 T2MI** **N = 520**	***P value***
MACE, n (%)	369 (50.5)	48 (22.9)	321 (61.7)	*<0.001*
All-cause mortality, n (%)	197 (27.0)	13 (6.2)	184 (35.4)	*<0.001*
Reinfarction, n (%)	88 (12.1)	15 (7.1)	73 (14.0)	*0.010*
Unplanned revascularization, n (%)	40 (5.5)	9 (4.3)	31 (6.0)	*0.368*
Ischemic stroke, n (%)	26 (3.6)	3 (1.4)	23 (4.4)	*0.048*
HF hospitalization, n (%)	107 (14.7)	11 (5.2)	96 (18.5)	*<0.001*
Type 2 reinfarction, n (%)	53 (7.3)	8 (3.8)	45 (8.7)	*0.022*
Cardiovascular death, n (%)	121 (16.6)	4 (1.9)	117 (22.5)	*<0.001*

Abbreviations: P1 = phenotype 1; P2 = phenotype 2; T2MI = type 2 myocardial infarction; MACE = major adverse cardiovascular events; HF = heart failure.

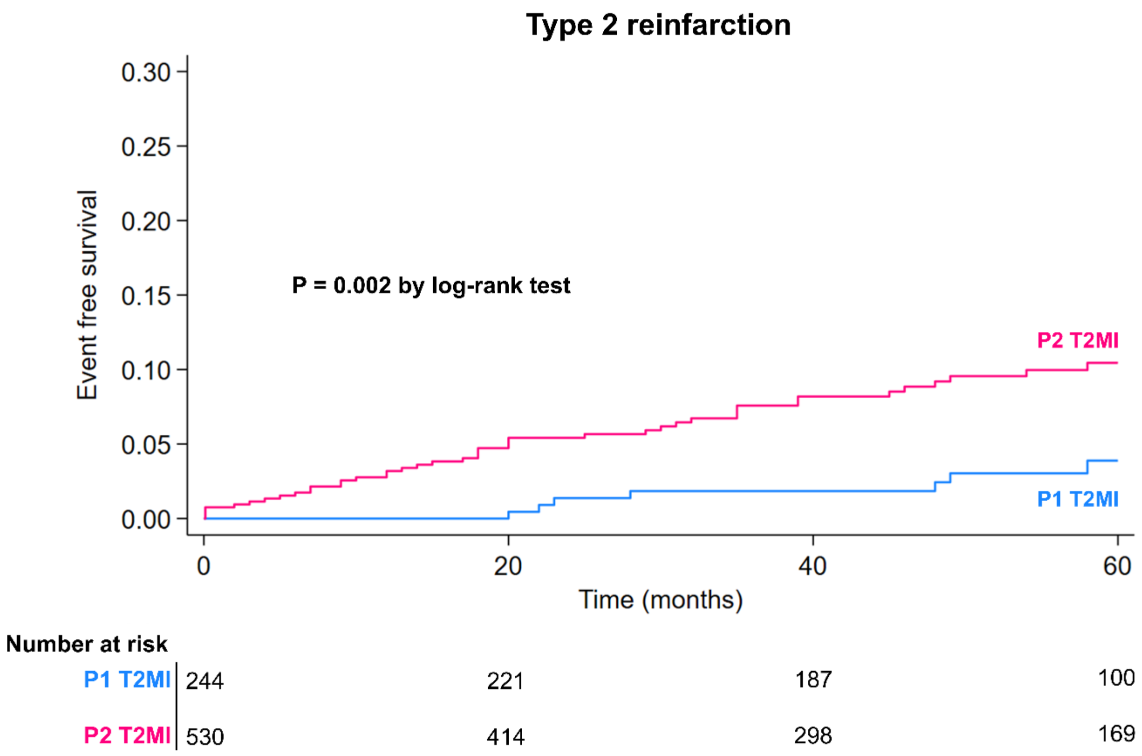
Table S7. Proportional hazards assumption test (Schoenfeld residuals).

	P1 T2MI				P2 T2MI			
Covariate	**rho**	**chi²**	**df**	***P value***	**rho**	**chi²**	**df**	***P value***
Age, years					-0.04994	0.97	1	*0.325*
Gender, female					-0.07351	1.72	1	*0.189*
Dyslipidemia					-0.04286	0.56	1	*0.453*
Diabetes	0.05452	0.15	1	*0.701*				
Known cardiovascular disease					0.05650	0.97	1	*0.324*
COPD					-0.02345	0.17	1	*0.678*
eGFR, mL/min/1.73 m2					-0.01536	0.08	1	*0.773*
Hemoglobin, g/dL					0.03150	0.32	1	*0.569*
LVEF, %	0.17519	3.05	1	*0.081*	-0.03564	0.41	1	*0.524*
Peak cTnI, X URL	0.14889	1.54	1	*0.214*	0.00068	0.00	1	*0.989*
ACE-I/ARBs					0.10422	3.37	1	*0.066*
Gensini score	-0.11968	0.63	1	*0.427*	-0.05299	0.95	1	*0.330*
Global test		**4.26**	**4**	***0.371***		**9.93**	**11**	***0.537***

Abbreviations: P1 = phenotype 1; P2 = phenotype 2; T2MI = type 2 myocardial infarction; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction evaluated by transthoracic echocardiogram; cTnI = cardiac troponin I; URL = upper reference limit; ACE-I = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers.

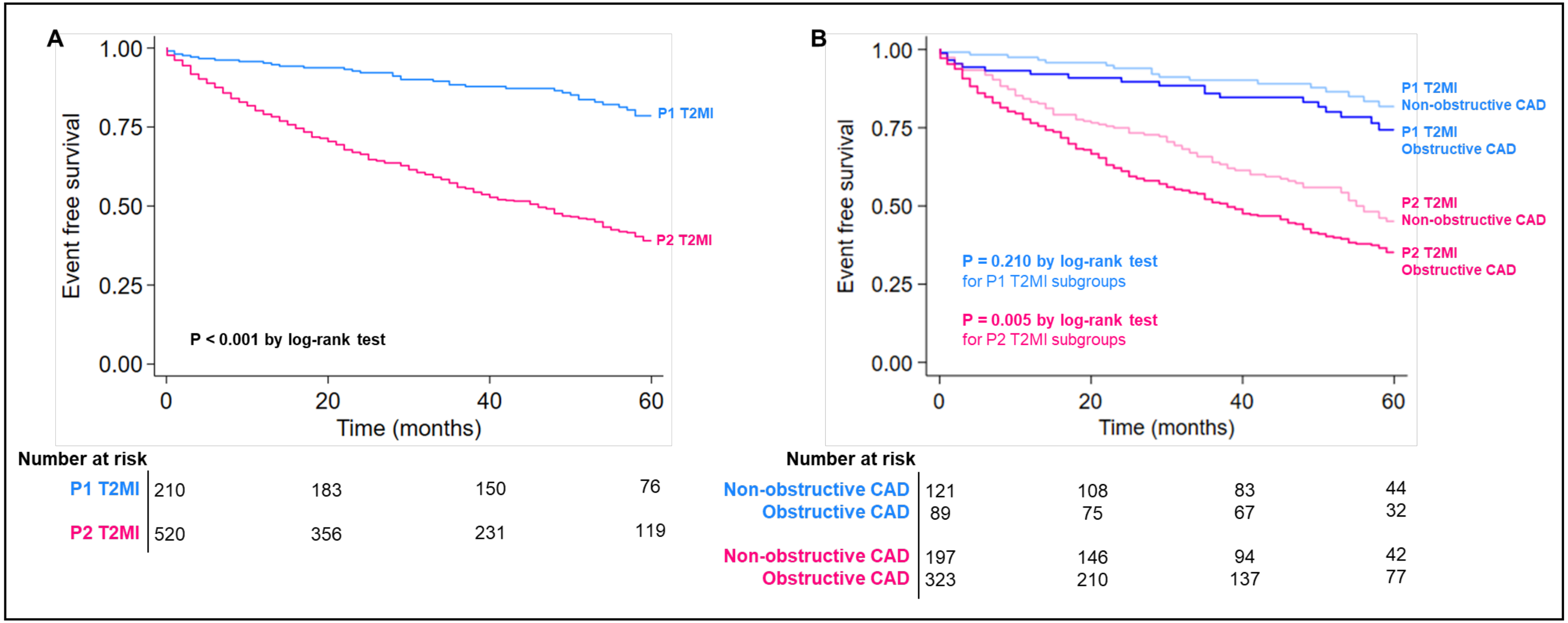
SUPPLEMENTAL FIGURES

Figure S1. Kaplan–Meier estimates of freedom from type 2 reinfarction in the two clinical phenotypes.



Abbreviations: P1 = phenotype 1 ; P2 = phenotype 2; T2MI = type 2 myocardial infarction.

Figure S2. Kaplan–Meier curves for MACE in the sensitivity analysis excluding patients with coronary artery spasm, embolism, or dissection.

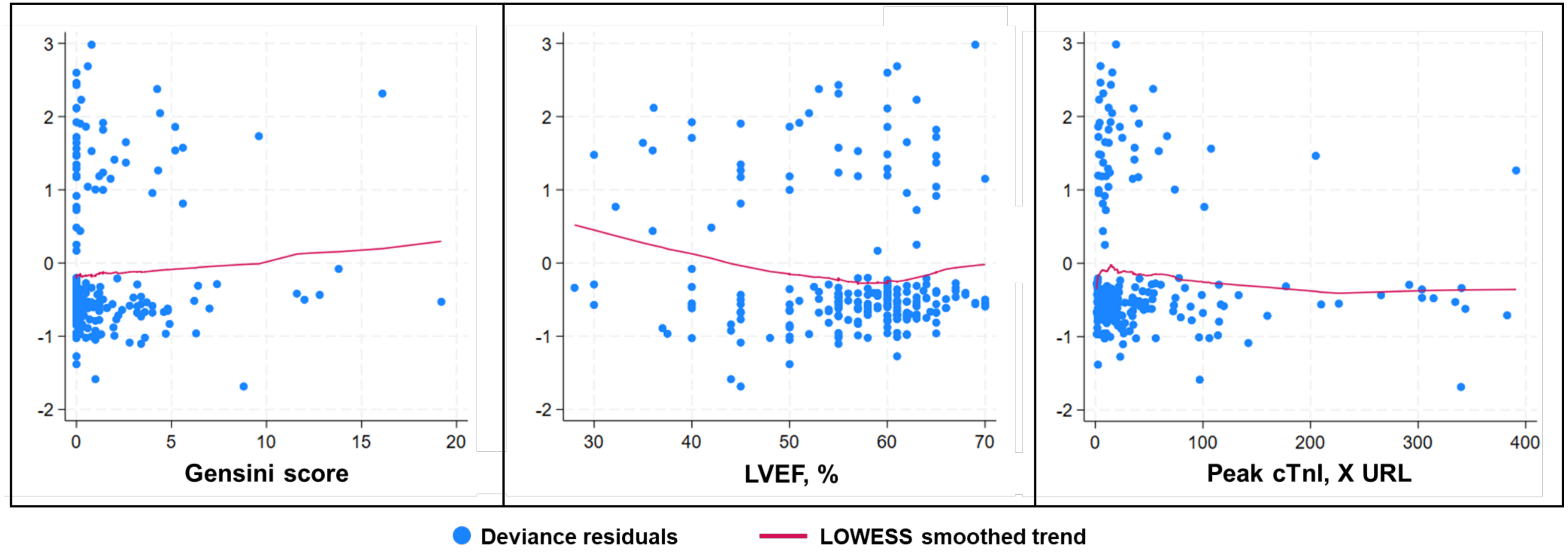


Panel **A** shows survival from MACE in the two clinical phenotypes; Panel **B** shows survival stratified by the presence of obstructive CAD within each phenotype.

In Panel B, the Bonferroni-adjusted significance threshold was set at $p < 0.025$ to account for multiple comparisons.

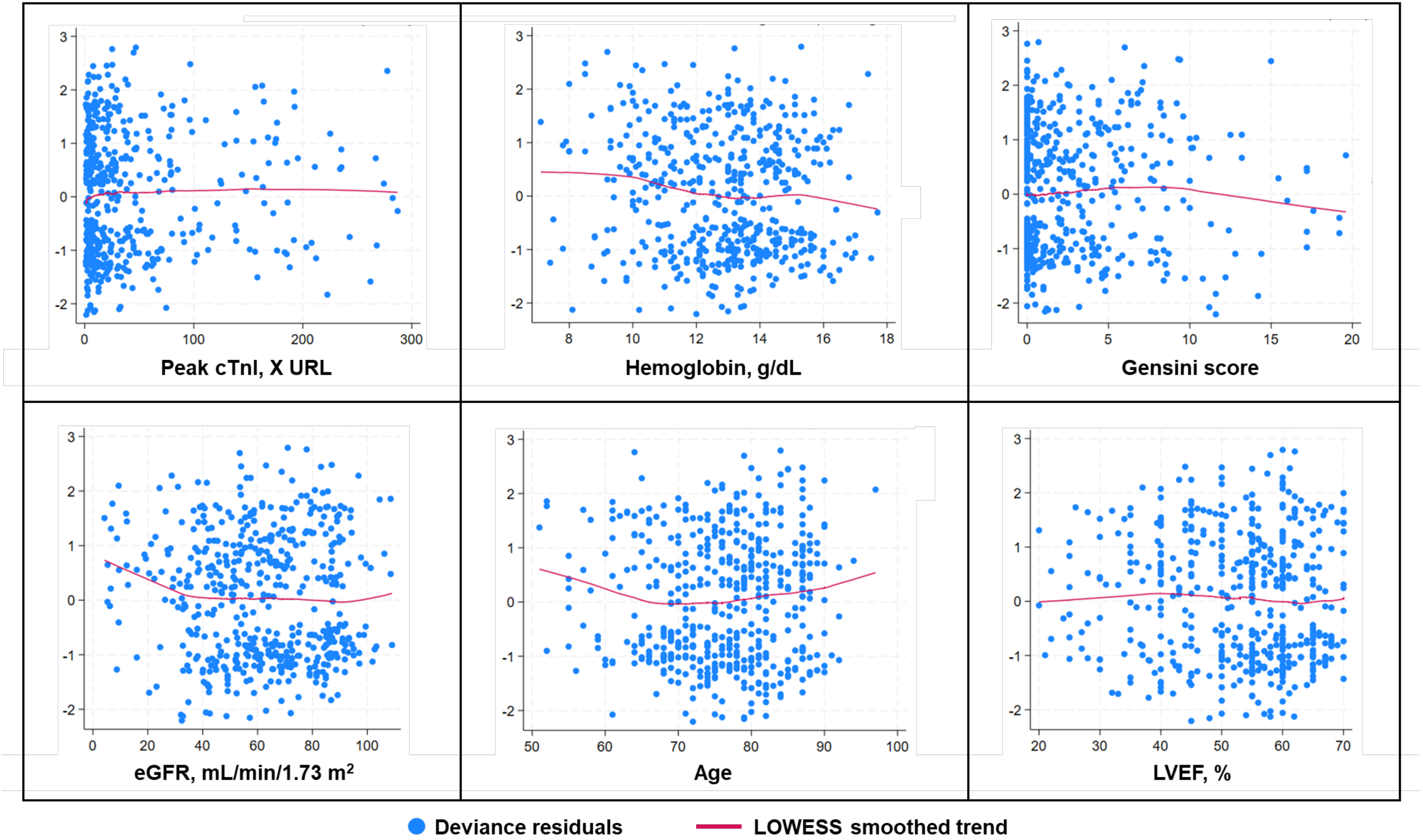
Abbreviations: MACE = major adverse cardiovascular events; CAD = coronary artery disease; P1 = phenotype 1; P2 = phenotype 2; T2MI = type 2 myocardial infarction.

Figure S3. Assessment of linearity in the relationship between continuous covariates and the log hazard in patients with P1 T2MI using deviance residuals.



Abbreviations: P1 = phenotype 1; T2MI = type 2 myocardial infarction; ; LVEF = left ventricular ejection fraction evaluated by transthoracic echocardiogram; cTnI = cardiac troponin I; URL = upper reference limit; LOWESS = Locally Weighted Scatterplot Smoothing.

Figure S4. Assessment of linearity in the relationship between continuous covariates and the log hazard in patients with P2 T2MI using deviance residuals.



Abbreviations: P2 = phenotype 2; T2MI = type 2 myocardial infarction; cTnI = cardiac troponin I; URL = upper reference limit; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction evaluated by transthoracic echocardiogram; LOWESS = Locally Weighted Scatterplot Smoothing.