SUPPLEMENTARY DATA

METHODS OF THE SUPPLEMENTARY DATA

Data collection

Baseline patient characteristics and procedural details, including medical therapy on admission and discharge medications, were prospectively recorded. Upon hospital admission, blood samples were collected for routine laboratory analyses, including complete blood count, electrolytes, creatinine, lipid profile, glucose levels, and cardiac troponin I (cTnI) values. The glomerular filtration rate (GFR) was calculated using the CKD-EPI formula. Chronic kidney disease was defined as kidney damage or GFR < 60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause.[1]

From January 1, 2017 to September 4, 2018, conventional cTnI levels were measured using a chemiluminescent immunoassay for antigen detection (Beckman Coulter Access AccuTnI+3 assay), with a 99th percentile upper reference limit (URL) of 40 ng/L for both men and women. Beginning September 5, 2018, high-sensitivity cardiac troponin I (hs-cTnI) was measured using the Access hsTnI assay (Beckman Coulter), which has a URL of 19.8 ng/L for men and 11.6 ng/L for women.

cTnI levels were measured at hospital admission (0 hours), every 3 hours until the peak level was identified, and within 1 hour prior to coronary angiography. Following percutaneous coronary intervention (PCI), at least 3 cTnI measurements were obtained: immediately after the procedure, and at 3 and 6 hours post-PCI. If post-PCI cTnI levels increased or if clinically indicated (eg, new ischemic symptoms or ECG changes), additional measurements were performed every 3 hours to monitor peak post-PCI levels within the first 48 hours.[2]

All patients underwent a standard 12-lead ECG at multiple time points: at initial medical contact, upon arrival at the cardiac intensive care unit, before PCI, within one hour after PCI

(upon return to the cardiac intensive care unit), and every morning until hospital discharge. In addition, each patient underwent at least one 2-dimensional transthoracic echocardiography (TTE) at the time of NSTEMI diagnosis and another within 48 hours following PCI.[2] Additional ECG and TTE assessments were performed based on clinical indication.

For echocardiographic assessment, at least 3 consecutive cardiac cycles were recorded for each standard view, with all images archived for offline analysis. Left ventricular ejection fraction (LVEF) was measured using the Simpson biplane method, and regional wall motion abnormalities were defined as the presence of at least 2 hypokinetic or akinetic segments, in accordance with the guidelines of the European Association of Cardiovascular Imaging.[3]

Coronary angiography and PCI were performed by expert interventional cardiologists. Anticoagulation regimens, including the management of oral anticoagulation, were administered in accordance with European guidelines.[4-6] Once a diagnosis of NSTEMI was confirmed, all patients received a 250 mg intravenous bolus of aspirin. Procedural anticoagulation was achieved with heparin, aiming for an activated clotting time > 250 seconds. The use of glycoprotein IIb/IIIa inhibitors and cangrelor during the procedure was at the discretion of the operator.

Complex PCI was defined by the presence of at least 1 of the following criteria: multivessel stenting, implantation of 3 or more stents, treatment of 3 or more lesions, bifurcation stenting with 2 stents, total stent length > 60 mm, or PCI involving a chronic total occlusion.[7-9]

Complete revascularization was considered achieved when PCI was performed in all lesions suitable for successful intervention, located in vessels ≥ 2.5 mm in diameter, with visually assessed diameter stenosis ≥ 70%, or 50% to 69% stenosis with a fractional flow reserve ≤ 0.80, in the absence of coronary artery bypass grafts. When complete revascularization was achieved through staged PCI, the additional procedures were performed during the index hospitalization, prior to discharge.[10]

Bleeding Academic Research Consortium (BARC) classification

BARC type 2 includes any overt, actionable sign of bleeding that requires medical intervention (such as prolonged manual or device-assisted compression), requires an increased level of care, or leads to further diagnostic evaluation, but does not meet the criteria for more severe types. BARC type 3 encompasses more significant bleeding and is subdivided into 3 categories: type 3a refers to overt bleeding associated with a hemoglobin drop of 3 to < 5 g/dL or requiring transfusion of 2 to 3 units of blood; type 3b includes bleeding events associated with a hemoglobin drop of 5 g/dL or more, transfusion of 4 or more units, cardiac tamponade, or bleeding requiring surgical intervention; and type 3c comprises intracranial hemorrhage or intraocular bleeding with associated visual loss. Finally, BARC type 5 defines fatal bleeding, with type 5a referring to probable fatal bleeding (when death is likely due to bleeding but not directly observed), and type 5b indicating definite fatal bleeding, confirmed by autopsy or clinical observation.[11]

Secondary endpoints definitions

The definitions of each individual component of the secondary endpoints are listed below:

- **All-cause mortality:** refers to death from any cause occurring during the follow-up period.
- **Reinfarction (type 1, 2, and 4):** defined as acute myocardial injury with clinical evidence of acute myocardial ischemia, occurring more than 48 hours after PCI during follow-up. This definition applies specifically to type 1 and type 2 myocardial infarction (MI). Diagnosis requires a rise and/or fall in cTn levels, with at least 1 value above the 99th percentile URL, accompanied by at least 1 of the following:
    - Symptoms indicative of myocardial ischemia

- New ischemic changes on ECG
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality consistent with ischemia
- Detection of a coronary thrombus via angiography or autopsy (only for type 1 MI)[12]

For the definition of type 4 MI, refer to the Methods section of the main manuscript.

- **Unplanned revascularization:** refers to unexpected revascularization via PCI or coronary artery bypass grafting that was not scheduled during the initial procedure.[13]
- **Stroke:** Defined as an ischemic cerebral infarction resulting from embolic or thrombotic occlusion of a major intracranial artery, leading to a new focal neurological deficit lasting longer than 24 hours.[14]
- **Hospitalization for heart failure (HF):** defined as an event meeting the following criteria:
  - **Hospital admission:** admission to an inpatient unit or emergency department stay lasting at least 6 hours
  - **Clinical symptoms of HF:** At least 1 new or worsening symptom, such as:
    - Dyspnea
    - Orthopnea
    - Paroxysmal nocturnal dyspnea
    - Increased fatigue or reduced exercise tolerance
  - **Physical signs of HF:** At least 2 of the following:
    - Peripheral edema
    - Pulmonary rales
    - Jugular venous distension

- Tachypnea (respiratory rate >20 breaths/min)
- Rapid weight gain
- S3 gallop
- Increasing abdominal distension or ascites
- Hepatojugular reflux
- Radiographic evidence of worsening heart failure
- Right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure ≥18 mm Hg and/or cardiac output < 2.2 L/min/m^2 [15]

- **BARC 2, 3, and 5**

Cardiovascular Mortality: encompasses deaths resulting from acute myocardial infarction, sudden cardiac death, HF, stroke, or other cardiovascular causes.[14]

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Table S1. Angiographic findings underlying type 4a myocardial infarction

Underlying causes	Overall N = 191	Pretreatment n = 118	No pretreatment n = 73
Side-branch occlusion	77 (40.3)	50 (42.4)	27 (37.0)
Any slow flow or no reflow	28 (14.7)	15 (12.7)	13 (17.8)
Dissection	22 (11.5)	14 (11.9)	8 (11.0)
Distal embolization	15 (7.9)	10 (8.5)	5 (6.8)
Thrombus	7 (3.7)	3 (2.5)	4 (5.5)
Others	3 (1.6)	1 (0.8)	2 (2.7)
Nonidentifiable mechanical causes	39 (20.4)	25 (21.2)	14 (19.2)

The data are expressed as No. (%).

Table S2. Predictors of the primary efficacy endpoint on univariate and multivariable logistic regression

	Unadjusted OR (95%CI)	*P*	Adjusted OR (95%CI)	*P*
Age	1.02 (1.01-1.03)	< .001	1.01 (1.00-1.03)	.119
Female sex	1.18 (0.89-1.55)	.247	-	-
Diabetes	1.05 (0.80-1.38)	.705	-	-
Hypertension	1.24 (0.92-1.71)	.169	-	-
Dyslipidemia	0.96 (0.74-1.26)	.760	-	-
Smoking history	1.00 (0.77-1.30)	.760	-	-
Prior MI	1.23 (0.93-1.62)	.147	-	-
Prior PCI	1.13 (0.85-1.50)	.383	-	-
History of cerebrovascular disease	1.01 (0.59-1.64)	.984	-	-
History of peripheral arterial disease	1.38 (0.92-2.03)	.112	-	-
Chronic obstructive pulmonary disease	1.26 (0.86-1.79)	.217	-	-
Chronic kidney disease	1.53 (1.127-1.98)	.002	1.11 (0.75-1.63)	.595
GRACE score > 140	1.34 (1.04-1.73)	.024	0.87 (0.58-1.32)	.521
Complex PCI	2.11 (1.64-2.74)	< .001	2.18 (1.58-3.02)	< .001
Complete revascularization	0.69 (0.54-0.90)	.006	0.80 (0.57-1.13)	.199
Radial access	0.54 (0.40-0.74)	< .001	0.66 (0.44-1.01)	.051
Hemoglobin at admission	0.89 (0.84-0.95)	.001	0.97 (0.89-1.06)	.448
Pretreatment	1.15 (0.84-1.58)	.398	1.08 (0.78-1.51)	.638

OR, odds ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Variables associated with the primary efficacy endpoint in univariate analysis (P < .1) were included in the multivariable logistic regression model.

Table S3. Predictors of the primary safety endpoint on univariate and multivariable logistic regression

	Unadjusted OR (95%CI)	*P*	Adjusted OR (95%CI)	*P*
Age	1.04 (1.02-1.06)	< .001	0.99 (0.96-1.02)	.473
Female sex	2.25 (1.40-3.59)	.001	2.22 (1.31-3.77)	.003
Diabetes	1.39 (0.85-2.23)	.180	-	-
Hypertension	1.12 (0.66-1.97)	.692	-	-
Dyslipidemia	1.00 (0.62-1.64)	.991	-	-
Smoking history	0.83 (0.52-1.32)	.420	-	-
Prior MI	1.22 (0.73-2.00)	.435	-	-
Prior PCI	1.05 (0.61-1.75)	.858	-	-
History of cerebrovascular disease	2.16 (0.73-2.00)	.435	-	-
History of peripheral arterial disease	1.35 (0.61-2.65)	.415	-	-
Chronic obstructive pulmonary disease	1.81 (0.97-3.18)	.050	1.32 (0.67-2.45)	.406
Chronic kidney disease	2.19 (1.37-3.48)	.001	1.16 (0.67-1-33)	.377
GRACE score > 140	3.79 (2.27-6.61)	< .001	3.35 (1.68-6.97)	.001
Complex PCI	1.27 (0.80-2.02)	.303	-	-
Complete revascularization	0.65 (0.41-1.03)	.065	0.80 (0.48-1.33)	.377
Radial access	0.24 (0.15-0.40)	< .001	0.30 (0.18-0.52)	< .001
Hemoglobin at admission	0.84 (0.75-0.95)	.004	1.00 (0.87-1.14)	.960
Pretreatment	2.06 (1.24-3.56)	.007	2.17 (1.28-3.82)	.005

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; OR, odds ratio.

Variables associated with the primary safety endpoint on univariate analysis ($P < .1$) were included in the multivariable logistic regression model.

Table S4. Primary safety endpoint: unadjusted and adjusted odds ratios in the pretreated group according to escalation status

	Escalation n = 87	No escalation n = 653	Unadjusted OR (95%CI)	*P*	Adjusted OR (95%CI)	*P*
BARC type 2, 3, and 5	6 (6.9)	51 (7.8)	0.87 (0.33-1.95)	*.764*	1.09 (0.40-2.58)	*.850*
BARC type 2	5 (5.7)	28 (4.3)	1.36 (0.45-3.34)	*.537*	1.51 (0.49-3.93)	*.426*
BARC type 3	1 (1.1)	23 (3.5)	0.32 (0.02-1.54)	*.266*	0.45 (0.02-2.41)	*.453*
BARC type 5	0 (0)	0 (0)	/	/	/	/

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; OR, odds ratio.

Multivariable logistic regression models were adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking history, prior myocardial infarction, prior percutaneous coronary intervention (PCI), history of cerebrovascular disease, history of peripheral arterial disease, chronic obstructive pulmonary disease, chronic kidney disease, GRACE score, complex PCI, complete revascularization, arterial access site, and hemoglobin at admission.

Table S5. Sensitivity analysis: unadjusted and adjusted odds ratios for patients undergoing early invasive strategy (< 24 hours)

	Pretreatment n = 344	No pretreatment n = 247	Unadjusted OR (95%CI)	*P*	Adjusted OR (95%CI)	*P*
Type 4a MI	54 (15.7)	36 (14.6)	1.09 (0.69-1.74)	*.708*	1.12 (0.70-1.79)	*.642*
BARC type 2, 3, and 5	27 (7.8)	9 (3.6)	2.25 (1.08-5.16)	*.039*	2.87 (1.32-6.85)	*.011*
BARC type 2	14 (4.1)	5 (2.0)	2.05 (0.77-6.42)	*.173*	2.31 (0.85-7.42)	*.122*
BARC type 3	13 (3.8)	4 (1.6)	2.39 (0.83-8.55)	*.132*	3.44 (1.12-13.23)	*.004*
BARC type 5	0 (0)	0 (0)	/	/	/	/

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; OR, odds ratio.

Multivariable logistic regression models were adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking history, prior myocardial infarction, prior percutaneous coronary intervention (PCI), history of cerebrovascular disease, history of peripheral arterial disease, chronic obstructive pulmonary disease, chronic kidney disease, GRACE score, complex PCI, complete revascularization, arterial access site, and hemoglobin at admission.

Table S6. Sensitivity analysis: unadjusted and adjusted odds ratios for patients undergoing delayed invasive strategy (≥ 24 hours)

	Pretreatment n = 396	No pretreatment n = 267	Unadjusted OR (95%CI)	*P*	Adjusted OR (95%CI)	*P*
Type 4a MI	64 (16.2)	37 (13.9)	1.20 (0.78-1.87)	*.419*	1.14 (0.72-1.81)	*.588*
BARC type 2, 3, and 5	30 (7.6)	11 (4.1)	1.91 (0.97-4.04)	*.074*	2.22 (1.09-4.88)	*.035*
BARC type 2	19 (4.8)	6 (2.2)	2.19 (0.91-6.09)	*.099*	2.60 (1.04-7.48)	*.045*
BARC type 3	11 (2.8)	5 (1.9)	1.50 (0.54-4.80)	*.459*	1.62 (0.56-5.37)	*.390*
BARC type 5	0 (0)	0 (0)	/	/	/	/

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; OR, odds ratio.

Multivariable logistic regression models were adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking history, prior myocardial infarction, prior percutaneous coronary intervention (PCI), history of cerebrovascular disease, history of peripheral arterial disease, chronic obstructive pulmonary disease, chronic kidney disease, GRACE score, complex PCI, complete revascularization, arterial access site, and hemoglobin at admission.