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5-Year Prognostic Value of No-Reflow Phenomenon After Percutaneous Coronary Intervention in Patients With Acute Myocardial Infarction

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Objectives The objective of this study was to investigate the impact of no-reflow phenomenon on 5-year mortality among patients with acute ST-segment elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI). This impact was also assessed in relation to infarct size.

Background The impact of no-reflow on long-term mortality in patients with STEMI has been insufficiently studied.

Methods This study included 1,406 patients with STEMI treated by primary PCI. No-reflow was diagnosed using angiographic criteria. Infarct size was measured with single-photon emission computed tomography imaging 7 to 14 days after the acute event. The primary outcome was 5-year mortality.

Results The no-reflow phenomenon was diagnosed in 410 patients (29%). Infarct size was 15.0% (6.0% to 29.0%) of the left ventricle in the no-reflow group versus 8.0% (2.0% to 21.0%) of the left ventricle in the reflow group ($p < 0.001$). There were 132 deaths during follow-up. Of them, 59 deaths occurred among patients with no-reflow and 73 deaths occurred among patients with reflow (Kaplan-Meier estimates of 5-year mortality 18.2% and 9.5%, respectively; odds ratio: 2.02; 95% confidence interval: 1.44 to 2.82; $p < 0.001$). The Cox proportional hazards model adjusting for infarct size among other variables identified the no-reflow phenomenon as an independent correlate of 5-year mortality (hazard ratio: 1.66; 95% confidence interval: 1.17 to 2.36; $p = 0.004$).

Conclusions In patients with STEMI treated by primary PCI, no-reflow phenomenon is a strong predictor of 5-year mortality. No-reflow phenomenon after PCI provides prognostic information that is independent of and beyond that provided by infarct size. (J Am Coll Cardiol 2010;55:2383–9) © 2010 by the American College of Cardiology Foundation

No-reflow phenomenon affects a considerable number of patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary reperfusion therapy (1,2). With the ever-increasing use of primary percutaneous coronary intervention (PCI), a better recognition of the no-reflow phenomenon and its treatment is increasingly coming into the spotlight and is expected to become the main focus of research to further improve the efficacy of reperfusion therapy for patients with STEMI. Studies on the impact of no-reflow on mortality have reported short-term mortality, used various methods with differences in sensitivity to detect the no-reflow, and importantly, have included limited numbers of patients (3–7). Few studies with small sample sizes have reported long-term prognosis in patients with no-reflow phenomenon (8,9). Experimental and clinical studies have demonstrated that no-reflow phenomenon is associated with large myocardial necrosis (10–12), known to be an important predictor of mortality (13,14). Although hypotheses have been raised that no-reflow may offer prognostic information beyond that mediated by infarct size (3), no studies have proven these hypotheses in clinical setting.

The objectives of the current study were, first, to investigate the impact of no-reflow phenomenon on 5-year mortality in patients with STEMI treated with primary PCI, and second, to explore whether no-reflow phenomenon offers prognostic information independent of and beyond that provided by infarct size.

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Abbreviations and Acronyms

CI = confidence interval

OR = odds ratio

PCI = percutaneous coronary intervention

SPECT = single-photon emission computed tomography

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

TMPG = Thrombolysis In Myocardial Infarction myocardial perfusion grade

Methods

Patients. Between January 2002 and December 2007, 1,861 patients with STEMI presenting within the first 24 h from the symptom onset were admitted to the Deutsches Herzzentrum and 1. Medizinische Klinik Rechts der Isar in Munich, Germany. Patients undergoing conservative therapy (n = 112), thrombolysis (n = 35), or coronary artery bypass surgery as primary reperfusion strategy (n = 18), and patients with missing scintigraphic examination (n = 173), mechanical failures to open the occluded coronary arteries (n = 31), and angiograms of inadequate quality (n = 86) were excluded. Thus, the current study included 1,406 patients with STEMI who underwent primary PCI and had scintigraphic infarct size measurement obtained 7 to 14 days after intervention. The diagnosis of STEMI was established in the presence of chest pain lasting >20 min associated with electrocardiographic changes (ST-segment elevation ≥1 mm in at least 2 extremity electrocardiographic leads or ≥2 mm in at least 2 contiguous precordial leads or left bundle branch block of new onset). The diagnosis was confirmed by coronary angiography in all patients. Glomerular filtration rate was calculated using the Cockroft-Gault formula. Severity of heart failure was assessed according to Killip classification (15). The study was approved by the institutional ethics committee.

Angiographic analysis and definition of no-reflow. Coronary angiography was performed according to standard criteria. Offline analysis of digital angiograms was performed in the core laboratory using an automated edge detection system (CMS, Medis Medical Imaging Systems, Neuen, the Netherlands) by personnel blinded to the clinical diagnosis. Primary PCI (mostly with stent implantation) and periprocedural care were performed according to the standard criteria. Bare-metal stents were mostly used. Antiplatelet therapy consisted of clopidogrel (600 mg as a loading dose followed by 75 mg/day for at least 4 weeks to 6 months) and aspirin (200 mg/day continued indefinitely). Epicardial blood flow in the infarct-related artery and myocardial perfusion grade were graded according to the TIMI (Thrombolysis In Myocardial Infarction) group definitions (16).

The diagnosis of no-reflow required the following criteria: 1) angiographic evidence of reopening of occluded coronary artery and successful stent placement with no evidence of flow-limiting residual stenosis (<50%), dissection, spasm, or apparent thrombus; 2) angiographic documentation of a TIMI flow grade ≤2, or a TIMI flow grade 3 with a TIMI

Table 1 Demographic and Clinical Characteristics in Patients With No-Reflow and Reflow

Characteristic	No-Reflow (n = 410)	Reflow (n = 996)	p Value
Age, yrs	65.3 [55.0; 73.2]	61.3 [51.6; 71.4]	<0.001
Women	101 (24.6)	244 (25.5)	0.957
Body mass index, kg/m^2	26.3 [24.3; 28.7]	26.2 [24.1; 28.7]	0.601
Diabetes mellitus	85 (20.7)	190 (19.1)	0.477
Arterial hypertension	281 (68.5)	702 (70.5)	0.470
Current smoker	140 (34.1)	454 (45.6)	<0.001
Hypercholesterolemia, ≥240 mg/dl	224 (54.6)	517 (51.9)	0.352
Prior myocardial infarction	50 (12.2)	121 (12.1)	0.981
Prior coronary artery bypass surgery	22 (5.4)	25 (2.5)	0.007
Peak troponin, μg/l	4.9 [2.3; 8.9]	3.5 [1.6; 6.6]	<0.001
Peak creatine kinase-MB, U/l	157.5 [80.5; 291.7]	123.5 [59.0; 252.7]	<0.001
C-reactive protein, mg/l	5.0 [0.0; 12.0]	3.3 [0.0; 10.0]	0.003
Glomerular filtration rate, ml/min	80.3 [56.3; 100.3]	85.7 [64.5; 107.7]	0.005
Infarct location			0.339
Anterior	177 (43.2)	436 (43.8)	
Inferior	180 (43.9)	400 (40.1)	
Lateral	53 (12.9)	160 (16.1)	
Systolic blood pressure, mm Hg	130.0 [110.0; 145.0]	130.0 [115.0; 145.0]	0.999
Diastolic blood pressure, mm Hg	70.0 [62.0; 80.0]	70.0 [64.0; 80.0]	0.468
Killip class			0.026
I	270 (65.8)	733 (73.6)	
II	97 (23.7)	179 (18.0)	
III	20 (4.9)	33 (3.3)	
IV	23 (5.6)	51(5.1)	
Time-to-admission interval, h	5.0 [2.5; 11.2]	4.0 [2.0; 9.0]	<0.001

Data are median [25th; 75th percentiles] or n (%).

myocardial perfusion grade (TMPG) 0 or 1, at least 10 min after the end of PCI procedure. A TMPG 0 was defined when contrast failed to enter the vasculature; TMPG 1, when contrast slowly entered but failed to exit the vasculature (16).

Scintigraphic study. The ^{99m}Tc-sestamibi single-photon emission computed tomography (SPECT) was performed 7 to 14 days after PCI. Patients received an intravenous injection of 27 mCi (1,000 MBq) of ^{99m}Tc-sestamibi, and SPECT was performed 6 to 8 h after injection of radioactive agent. A multihead camera system, equipped with low energy and high resolution collimators, was used for myocardial imaging. Images were acquired in a 64 × 64 matrix by an acquisition time of 40 s per image. With dedicated software (ICON version 6.0.2, Siemens Medical Systems, Inc., Hoffman Estates, Illinois), transaxial slices were reconstructed. A volumetric sampling tool was applied to create polar maps of relative distribution throughout the entire left ventricle. Each polar map was normalized to its individual maximum. The defect size was defined as the <50% uptake area. All measurements were performed in the scintigraphic core laboratory by investigators unaware of clinical or angiographic data.

End points and follow-up. The primary outcome of this analysis was 5-year mortality. The follow-up information was obtained by a telephone call at 30 days, a visit at 6 months, a telephone call at 1 year, and annual telephone calls thereafter. Patients who had cardiac complaints underwent a complete clinical, electrocardiographic, and laboratory evaluation. Information about death was obtained from hospital records, death certificates, or telephone contact with relatives of the patient or referring physician. The follow-up information was obtained by personnel blinded to the clinical characteristics of the patients.

Statistical analysis. Data are presented as median (with 25th and 75th percentiles) or counts and proportions (percentages). The distribution of the data was analyzed with the 1-sample Kolmogorov-Smirnov test. Categorical data were compared with the chi-square test. Continuous data were compared with the Wilcoxon rank-sum test. Five-year mortality was estimated by applying the Kaplan-Meier method and log-rank test, which allowed the calculation of odds ratios [ORs] (with 95% confidence intervals [CIs] and respective p values) associated with no-reflow or reflow after

Table 2 Angiographic Characteristics in Patients With No-Reflow and Reflow

Characteristic	No-Reflow (n = 410)	Reflow (n = 996)	p Value
Left ventricular ejection fraction, %*	48.0 [39.9; 54.0]	50.0 [43.0; 57.0]	<0.001
Number of narrowed coronary arteries			0.109
1	127 (31.0)	364 (36.5)	
2	129 (31.5)	303 (30.4)	
3	154 (37.5)	329 (33.1)	
Multivessel disease	283 (69.0)	632 (63.5)	0.046
Lesion location			<0.001
Left main coronary artery	2 (0.5)	3 (0.3)	
Left anterior descending coronary artery	176 (42.9)	453 (45.5)	
Left circumflex coronary artery	59 (14.4)	177 (17.8)	
Right coronary artery	157 (38.3)	355 (35.6)	
Venous bypass graft	16 (3.9)	8 (0.8)	
Vessel size, mm	2.92 [2.55; 3.31]	2.89 [2.57; 3.25]	0.325
Pre-interventional TIMI flow grade			<0.001
0	240 (58.5)	426 (42.8)	
1	61 (14.9)	101 (10.1)	
2	82 (20.0)	241 (24.2)	
3	27 (6.6)	228 (22.9)	
Post-interventional TIMI flow grade			<0.001
0	23 (5.6)	0 (0.0)	
1	37 (9.0)	0 (0.0)	
2	133 (32.4)	0 (0.0)	
3	217 (52.9)	996 (100)	
TIMI myocardial perfusion grade			<0.001
0	283 (69.0)	0 (0.0)	
1	108 (26.3)	0 (0.0)	
2	19 (4.7)	195 (19.6)	
3	0 (0.0)	801 (80.4)	
Type of intervention			0.514
Stenting	355 (86.6)	875 (87.9)	
Balloon angioplasty	55 (13.4)	121 (12.1)	

Data are median [25th; 75th percentiles] or n (%). *Available in 1,322 patients.
TIMI = Thrombolysis In Myocardial Infarction.

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primary PCI. Univariable and multivariable Cox proportional hazards models were used to assess the association between no-reflow and mortality. All variables of Tables 1 and 2 plus no-reflow and infarct size were entered into the univariable model with 5-year mortality as the dependent variable; variables that resulted significant ($p < 0.05$) from univariable Cox proportional hazards model were entered into the multivariable Cox proportional hazards model using the backward variable selection method. We compared the discriminatory power of multivariable models regarding 5-year mortality with and without the variable no-reflow by calculating the integrated discrimination improvement, according to Pencina et al. (17).

All analyses were performed using the S-PLUS statistical package (Insightful Corp., Seattle, Washington). A $p < 0.05$ was considered to indicate statistical significance.

Results

The study sample included 1,406 patients with STEMI who underwent primary PCI and had infarct size measurement by ^{99m}Tc-sestamibi SPECT imaging 7 to 14 days after intervention. The group with no-reflow included 410 patients (193 patients with TIMI flow grade ≤2 and 217 patients with TIMI flow grade 3 and TMPG <2). The group with reflow included 996 patients. None of the patients with TIMI flow grade ≤2 had a TMPG of 3.

Baseline characteristics. Baseline characteristics of the patients are shown in Table 1. Patients with no-reflow were of older age, had a higher proportion of patients with prior coronary artery bypass surgery, and higher values of peak troponin, peak creatine kinase-myocardial band, and C-reactive protein; and lower values of glomerular filtration rate compared with patients with reflow. Furthermore, patients with no-reflow were less often smokers and had a longer time interval from symptom onset to hospital admission than patients with reflow. Patients with no-reflow had a tendency for being less often in Killip class I than were patients with reflow. Angiographic data are shown in Table 2. Multivessel disease was more often encountered among patients with no-reflow than among patients with reflow. The group with no-reflow had lower left ventricular ejection fraction and higher proportion of patients with baseline TIMI flow grades 0 and 1 compared with patients with reflow (Table 2). Bare-metal stents were used in 274 patients with no-reflow and in 630 patients with reflow (66.8% vs. 66.3%; $p = 0.20$).

No-reflow and scintigraphic infarct size. In the whole study patients, infarct size median (25th to 75th percentiles) in the 7 to 14 days SPECT imaging was 10.0% (2.0% to 24.0%) of the left ventricle. The tertiles of infarct size were as follows: first tertile, 0% to 5.0% of the left ventricle; second tertile, >5.0% to 18.1% of the left ventricle; third tertile >18.1% of the left ventricle. Infarct size in the 7 to 14 days SPECT imaging was 15.0% (6.0% to 29.0%) of the left ventricle in patients with no-reflow versus 8.0% (2.0% to 21.0%) of the left ventricle in patients with reflow ($p < 0.001$) (Fig. 1).

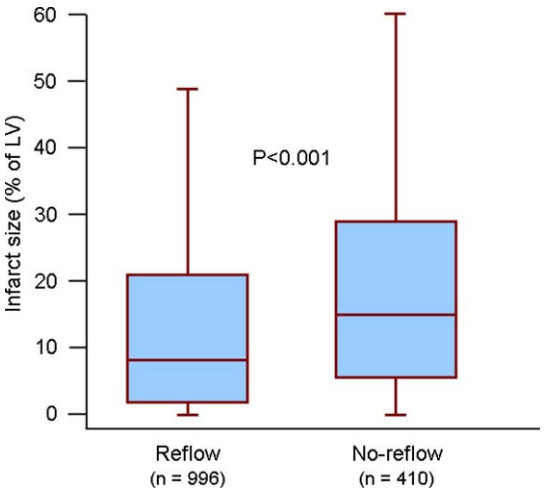

Figure 1 Infarct Size in the 7 to 14 Days Scintigraphy in Groups With Reflow and No-Reflow

Data are medians with 25th to 75th and 5th to 95th percentiles. LV = left ventricle.

No-reflow and 5-year mortality. There were 132 deaths during the follow-up: 59 deaths occurred among patients with no-reflow and 73 deaths occurred among patients with reflow (Kaplan-Meier estimates of 5-year mortality 18.2% and 9.5%, respectively; OR: 2.02, 95% CI: 1.44 to 2.82; $p < 0.001$) (Fig. 2).

Deaths were of cardiovascular origin in 90 patients (68.2%). Of them, 42 deaths occurred in patients with no-reflow and 48 deaths occurred in patients with reflow (estimates of 5-year mortality 12.4% and 6.3%, respectively; OR: 2.18, 95% CI: 1.46 to 3.27; $p < 0.001$).

No-reflow, infarct size, and 5-year mortality. Five-year mortality associated with no-reflow was analyzed according to tertiles of infarct size in the 7 to 14 days SPECT imaging. The data show that with the increase in infarct size, the frequency of no-reflow phenomenon increased significantly (p for trend <0.001). In each of the infarct size tertiles, the presence of no-reflow was associated with an increased risk of 5-year mortality (Table 3).

The univariable correlates ($p < 0.05$) of 5-year mortality were no-reflow, age, sex, body mass index, diabetes mellitus, arterial hypertension, previous myocardial infarction, previous coronary artery bypass surgery, anterior infarct location, Killip class, glomerular filtration rate, C-reactive protein, left ventricular ejection fraction, multivessel disease, infarct-related artery, and scintigraphic infarct size. After application of backward variable selection method in the multivariable Cox model, 7 variables (no-reflow, age, diabetes, Killip class, baseline C-reactive protein, multivessel disease, and infarct size) remained as independent correlates of 5-year mortality (Table 4). The inclusion of the no-reflow

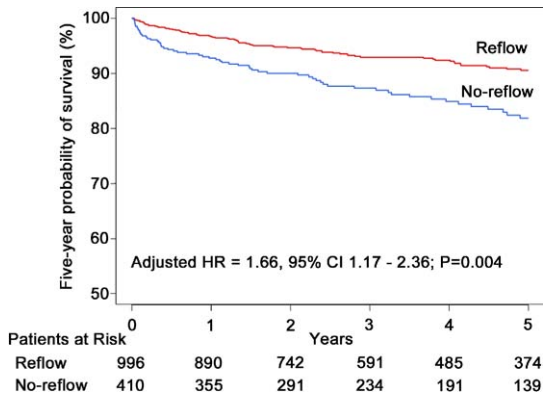

Figure 2 Kaplan-Meier Curves of 5-Year Mortality

Red line = reflow group; **blue line** = no-reflow group.
CI = confidence interval; HR = hazard ratio.

in the multivariable model was associated with an improved discriminatory power of the model regarding the prediction of the 5-year mortality (absolute integrated discrimination improvement = 0.0108, relative integrated discrimination improvement = 7.0%; p = 0.028).

Discussion

The present study represents the largest series of patients with STEMI treated with primary PCI in whom the long-term impact of no-reflow on mortality has been reported. The no-reflow and infarct size were estimated using the angiographic and scintigraphic criteria that are considered as gold standard techniques for diagnosis of no-reflow (2) and infarct size measurement (18) in the clinical setting. The main findings of this study can be summarized as follows: 1) in patients with STEMI, the development of no-reflow phenomenon after primary PCI predicts an increased risk of death up to 5 years after the acute event; and 2) the no-reflow phenomenon provides prognostic information that is independent of and beyond that provided by other relevant clinical factors including the infarct size.

Our group has recently examined the impact of no-reflow on 1-year mortality among patients undergoing PCI for STEMI (12). The current study significantly expands the findings of our prior study by the following means: 1) we used a more sensitive definition of no-reflow in the current study so that no-reflow comprises nearly 30% (as opposed to 10%) of the study group now; 2) we have extended follow-up to true long term (5 years) to assess the impact of this complication; and 3) unlike the prior study, we are able to identify the independent importance of no-reflow even when controlling for infarct size. Thus, our study confirms and extends the findings of our own group as well as those of other groups with important insight into the prevalence and outcomes of this condition, and furthermore, is the first study to suggest that the importance of no-reflow may not be mechanistically related only to infarct size.

The question whether no-reflow impacts the long-term prognosis seems particularly relevant considering that no-reflow is a transient phenomenon that resolves over time in nearly 50% of patients (19). Few prior studies with inadequate sample sizes have investigated the long-term prognosis of patients with no-reflow phenomenon after primary PCI (8,9). Morishima et al. (8) studied 120 patients with a first acute myocardial infarction treated by PCI and found that angiographically defined no-reflow was an independent predictor of cardiac death over a mean follow-up of 5.8 years. In a study by Bolognese et al. (9) that included 124 patients with acute myocardial infarction, microvascular obstruction diagnosed by myocardial contrast echocardiography was the only independent predictor of cardiac death over a mean follow-up of 46 months. By including >1,400 patients with STEMI treated by primary PCI and by using the most accurate criteria for the diagnosis of no-reflow, our

Table 4 Correlates of 5-Year Mortality and Hazard Ratios Calculated by Cox Proportional Hazards Model

Variable	Adjusted Hazard Ratio (95% CI)	p Value
No-reflow phenomenon	1.66 (1.17–2.36)	0.004
Age, for 10-yr increase	1.75 (1.50–2.05)	<0.001
Diabetes mellitus	1.46 (1.01–2.11)	0.040
Killip class, for 1-class increase	1.46 (1.23–1.73)	<0.001
Baseline C-reactive protein, for 1-mg/l increase	1.02 (1.01–1.04)	0.012
Multivessel disease, versus single vessel	1.83 (1.14–2.93)	0.013
Infarct size, for 5% of the left ventricle increase*	1.09 (1.05–1.14)	<0.001

*Measured in the 7 to 14 days single-photon emission computed tomography imaging.
CI = confidence interval.

Table 3 Frequency of No-Reflow and 5-Year Mortality in Patients With No-Reflow and Reflow in Each Infarct Size Tertile

Infarct Size Tertiles	No-Reflow	5-Year Mortality		
		No-Reflow Group	Reflow Group	Odds Ratio (95% CI)*
1 (n = 452)	83 (18.3)	9 (14.2)	19 (7.2)	2.01 (0.93–4.38)
2 (n = 474)	146 (30.8)	17 (14.9)	21 (8.4)	1.90 (1.02–3.57)
3 (n = 480)	181 (37.7)	33 (22.8)	33 (13.4)	1.73 (1.07–2.79)

Data are counts, proportions (no-reflow data), or Kaplan-Meier estimates of 5-year mortality. *The risk of 5-year mortality in patients with no-reflow versus patients with reflow.
CI = confidence interval.

study provides the strongest confirmation of the long-term prognostic impact of no-reflow phenomenon.

Previous studies have convincingly demonstrated a strong association between no-reflow and infarct size (10–12). Several clinical studies have shown that infarct size is an important predictor of mortality (13,14). In a recent study, we have demonstrated that the extent of initial area at risk in patients with STEMI is an independent correlate of no-reflow, and that no-reflow per se independently predicts the infarct size 7 to 14 days after the acute event (12). This inherent relationship between no-reflow and infarct size offers evidence that at least a part of the impact of no-reflow on the prognosis is mediated through the infarct size. However, the present study provides evidence that no-reflow offers additional prognostic information beyond that mediated by the infarct size. First, in each of the tertiles of infarct size, the presence of no-reflow was associated with an increased risk of long-term mortality. Second, the multivariable analysis showed that no-reflow phenomenon predicted the long-term mortality independent of infarct size among other potential confounders. Thus, additional mechanisms are needed to explain the strong impact of no-reflow phenomenon on the long-term mortality of patients with STEMI.

Evidence available suggests that microvascular obstruction—the morphological basis of the no-reflow phenomenon—is a major determinant of the subsequent left ventricular remodeling after primary PCI (3,12,20–22). A recent study by Ørn et al. (20) has demonstrated that persistence of microvascular obstruction 1 week after an acute event was associated with attenuated infarct healing, increased volumes, and reduced left ventricular function at long-term follow-up, possibly reflecting a more severe myocardial damage. A recent study with magnetic resonance imaging showed that persistence of microvascular obstruction was a more powerful predictor of global and regional functional recovery than was transmural extension of infarction (22). An earlier study by Wu et al. (3) demonstrated that microvascular obstruction predicts subsequent ventricular remodeling (increased left ventricular volumes and wall thinning at 6 months) and cardiovascular adverse events (a composite of death, reinfarction, congestive heart failure or stroke) even after being controlled for infarct size. In patients with no-reflow after primary PCI, the persistence of suboptimal blood flow 6 months after acute event was associated with a significant deterioration of the left ventricular function compared with patients who showed resolution of the no-reflow in the 6-month angiography (12). The increased incidence of malignant ventricular arrhythmias, congestive heart failure, and cardiac death among patients with no-reflow has also been demonstrated (8). Since left ventricular remodeling is a predictor of long-term prognosis (23), these findings strongly suggest that no-reflow may impact prognosis through its impact on subsequent ventricular remodeling predisposing for cardiovascular adverse events and increased mortality.

Study limitations. The present study focused primarily on the long-term mortality of patients with no-reflow after primary PCI. We accept as a limitation that we could not provide information on the time-course of no-reflow phenomenon and the evolution of TIMI flow grade after intervention. Although pharmacological agents were occasionally used to treat no-reflow phenomenon after primary PCI, these agents were not systematically used, and thus their therapeutic effects can not be tested in the setting of present study. Data on angiographic thrombotic burden in the infarct-related artery were not available. However, missing thrombotic burden data do not weaken our main analysis of the association between no-reflow and long-term mortality.

Conclusions

The no-reflow phenomenon after primary PCI was a strong predictor of 5-year mortality in patients with STEMI. No-reflow after PCI provides prognostic information independent of and beyond that provided by infarct size. The findings of the current study raise the awareness of the harmful effects of the no-reflow phenomenon, call attention to better diagnosis and treatment, and re-emphasize the need for continuation of research to better understand and treat the no-reflow phenomenon in patients with STEMI after primary PCI.

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