ORIGINAL RESEARCH

Outcomes of Patients Presenting With Clinical Indices of Spontaneous Reperfusion in ST-Elevation Acute Coronary Syndrome Undergoing Deferred Angiography

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***Background*—**Few data are available regarding the optimal management of ST-elevation myocardial infarction patients with clinically defined spontaneous reperfusion (SR). We report on the characteristics and outcomes of patients with SR in the primary percutaneous coronary intervention era, and assess whether immediate reperfusion can be deferred.

***Methods and Results*—**Data were drawn from a prospective nationwide survey, ACSIS (Acute Coronary Syndrome Israeli Survey). Definition of SR was predefined as both (1) ≥70% reduction in ST-segment elevation on consecutive ECGs and (2) ≥70% resolution of pain. Of 2361 consecutive ST-elevation–acute coronary syndrome patients in Killip class 1, 405 (17%) were not treated with primary reperfusion therapy because of SR. Intervention in SR patients was performed a median of 26 hours after admission. These patients were compared with the 1956 ST-elevation myocardial infarction patients who underwent primary reperfusion with a median door-to-balloon of 66 minutes (interquartile range 38–106). Baseline characteristics were similar except for slightly higher incidence of renal dysfunction and prior angina pectoris in SR patients. Time from symptom onset to medical contact was significantly greater in SR patients. Patients with SR had significantly less in-hospital heart failure (4% versus 11%) and cardiogenic shock (0% versus 2%) ($P<0.01$ for all). No significant differences were found in in-hospital mortality (1% versus 2%), 30-day major cardiac events (4% versus 4%), and mortality at 30 days (1% versus 2%) and 1 year (4% versus 4%).

***Conclusions*—**Patients with clinically defined SR have a favorable prognosis. Deferring immediate intervention seems to be safe in patients with clinical indices of spontaneous reperfusion. **(*J Am Heart Assoc*. 2017;6:e004552. DOI: 10.1161/JAHA.116.004552.)**

Key Words: outcome • spontaneous reperfusion • ST-elevation myocardial infarction

Spontaneous reperfusion (SR) in the setting of ST-elevation acute coronary syndrome (STE-ACS) is reported in up to 30% of patients,[1–5] and was defined in most of these studies as a patent infarct-related artery on initial angiography. There are very few data regarding clinically defined SR in STE-ACS patients.[6,7] While the most recent European and American practice guidelines[8,9] include patients with clinically defined SR within the context of non-STE-ACS, few specific recommendations are made for these patients. Specifically, the timing of intervention in patients with SR remains unclear. The purpose of this study is to report on the characteristics and outcomes of a large cohort of consecutive patients with clinical evidence of SR in the primary percutaneous coronary intervention (PCI) era, and to assess whether immediate reperfusion can be deferred.

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An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/6/7/e004552/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In this large real-world clinical series of ST-elevation myocardial infarction patients, we found that clinical outcomes were equivalent between patients demonstrating spontaneous reperfusion who were treated with deferred percutaneous coronary intervention compared with ST-elevation myocardial infarction patients without signs of reperfusion who underwent immediate intervention.

What Are the Clinical Implications?

- Deferring immediate intervention may be safe in patients presenting with clinical indices of spontaneous reperfusion.

Methods

Study Population

Patients were drawn from the ACSIS (Acute Coronary Syndrome Israeli Survey), a prospective nationwide survey conducted over a period of 2 months every 2 to 3 years since 1992. Data are collected prospectively from all patients discharged with any diagnosis corresponding to the ACS spectrum in each of the 25 coronary care units and cardiology wards operating in Israel. Institutional review board approval was obtained at all participating centers and all patients provided informed signed consent to participate in the survey. Demographic and clinical data are recorded on prespecified forms. The discharge diagnoses are recorded as determined by the attending physicians based on clinical, electrocardiographic, and biochemical criteria. In-hospital, 30-day, and 1-year outcome data are ascertained by hospital chart review, telephone contact, and clinical follow-up data. Patient management is at the discretion of the attending physicians. Mortality data during hospitalization and at 30 days and 1-year posthospitalization are determined for all patients from hospital charts and by Register. All parameters captured by the registry are defined by the protocol.

The population of the current study comprised consecutive STE-ACS patients eligible for primary reperfusion therapy and included in ACSIS 2006, 2008, 2010, and 2013. Patients who were not eligible for reperfusion or who presented in Killip class ≥2 and therefore had a guideline-based indication for early intervention[8,9] regardless of whether they had persistent ST-elevation or not, were excluded from the analysis. Of 7486 consecutive ACS patients admitted during the study periods, 2361 patients were admitted with a diagnosis of STE-ACS, were eligible for reperfusion therapy, and were included in the study group. Of these, 405 (17%) were not treated with primary reperfusion therapy (either primary PCI or thrombolysis) because of a diagnosis of SR. These patients were compared with the 1956 STEMI patients who underwent primary reperfusion. During the study periods, there were no specific national guidelines regarding patients with clinical signs of SR, and all decisions regarding these patients were made at the discretion of the treating physician. The study flow is shown in Figure 1.

Diagnosis of STE-ACS was based on the presence of both ST-segment elevation (≥1 mm in ≥2 contiguous leads) and typical anginal-type discomfort. Diagnosis of STEMI was based on the presence of an increase in serum troponin above the 99th percentile in patients with a diagnosis of STE-ACS. Diagnosis of SR was made according to a predefined definition of both (1) ≥70% reduction in sum ST-segment elevation on consecutive ECGs before administration of definitive reperfusion therapy, and (2) ≥70% resolution in pain assessed using a visual analog score of 0 to 10 (0 denotes no pain, 10 denotes maximal experienced pain). The primary outcome measure was 1-year mortality. The secondary outcome measures were in-hospital death, congestive heart failure, cardiogenic shock, stroke, peak creatine kinase level, and left ventricular ejection fraction, 30-day death, rehospitalization for congestive heart failure, and 30-day major adverse cardiac event including death, recurrent myocardial infarction, and stroke.

Outcomes were uniformly defined: Congestive heart failure denoted patients who developed any heart failure during their hospitalization including any pulmonary congestion, third heart sound, pulmonary edema, or cardiogenic shock; cardiogenic shock was defined as persistent hypotension (systolic blood pressure <90 mm Hg) unresponsive to volume expansion and accompanied by signs of tissue hypoperfusion; stroke was defined as persistent new neurological deficits lasting more than 24 hours and accompanied by corresponding findings on brain computed tomography; transient ischemic attack was defined as transient (<24 hours) neurological deficits without evidence of infarct on brain computed tomography; peak creatine kinase level was the highest level of creatine kinase measured on serial measurements following admission; left ventricular ejection fraction was defined echocardiographically during hospitalization; rehospitalization for congestive heart failure was defined as hospital readmission with a primary diagnosis of heart failure.

Statistical Analysis

Data preparation was done using SAS (SAS® 9.4; SAS Institute, Cary NC) and the statistical analysis was carried out using R.[10] Characteristic of study participants were compared using χ^2 test for categorical variables and Student *t* test or Wilcoxon rank tests, as appropriate for continuous variables. The Kruskal–Wallis test was used for comparison of non-normally distributed continuous variables.

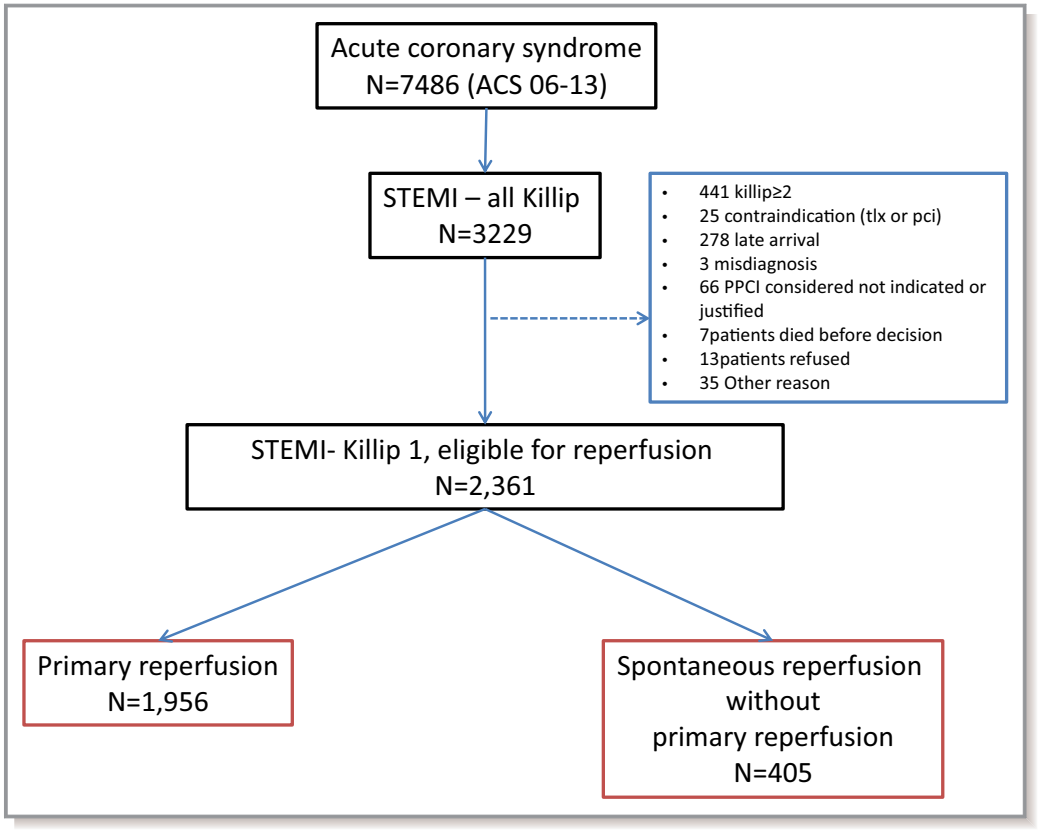

Figure 1. Study flow. PPCI indicates ; STEMI, ST-elevation myocardial infarction.

Multivariate logistic regression analysis was performed to determine association between baseline variables and occurrence of SR. All variables listed in Table 1 were considered to be included in the model. The final model selection was based on (1) prespecified covariates considered by the authors to have clinical relevance; (2) univariant analysis of factors with a $P<0.10$; and (3) selection of factors based on model fit statistics AIC and −2 log likelihood. Based on this methodology, the final model included the following covariates: age, sex, prior MI, prior angina, prior therapy with aspirin, prior coronary revascularization (PCI or coronary artery bypass graft), diabetes mellitus, hypertension, current smoker, chronic renal failure, and prior stroke.

Propensity score matching was done using Matching Package.[11] Variables selected for propensity score were those selected in the logistic model, and are included in Table 2. The model fit C-Statistics was C=0.76. Matching was performed using a ratio of 1:4 (SR:primary reperfusion). Function Match (®) from R package Matching was used with Caliper=NULL and the distance.tolerance=1e-05 indicating a small distance is permitted, which is practically the exact method. No patients were excluded because they could not be matched.

Cox proportional hazards model was performed for 30-day and 1-year outcome. The following prespecified covariates (considered by the authors to be of clinical relevance) were included in the 30-day and 1-year outcome models: age, sex, symptoms onset to first medical contact, diabetes mellitus, hypertension, prior MI, and prior revascularization (PCI or coronary artery bypass graft). The proportional hazard model was tested by the interaction SR×time, which was found to be not significant.

The probability of all-cause 1-year mortality was graphically displayed using the Kaplan–Meier method.

Results

The baseline characteristics of SR and primary reperfusion patients are shown in Table 1. Notably, there were no significant differences between groups with respect to age, sex, anthropomorphic characteristics, prior PCI or bypass surgery, prior antiplatelet medication or statin use, or anticoagulant or antiplatelet medication administered before arrival at the hospital. Patients with SR had a slightly but significantly higher incidence of renal dysfunction and prior angina pectoris. Time from symptom onset to first medical contact was significantly longer in patients with SR. In a logistic regression model, presence of prior angina pectoris and renal insufficiency remained independently associated with SR (Table 2).

Table 1. Baseline Characteristics

	Primary Reperfusion (N=1956)	Spontaneous Reperfusion (N=405)	*P* Value
Age (y)	59.6±12.1	59.6±12.4	0.98
Male	1647 (84)	333 (82)	0.32
Diabetes mellitus	516 (26)	94 (23)	0.18
Hypertension	945 (48)	189 (47)	0.53
Dyslipidemia	1240 (64)	273 (67)	0.16
Chronic renal failure	77 (4)	25 (6)	0.04
Smoker	994 (51)	207 (51)	0.88
Body mass index	28.3±16.6	27.8±5	0.42
Waist circumference	99±14	99±15	0.16
Prior myocardial infarct	378 (19)	75 (19)	0.71
Prior coronary bypass grafting	50 (3)	14 (3)	0.31
Prior percutaneous coronary intervention	397 (20)	79 (20)	0.73
Prior angina pectoris	405 (21)	109 (27)	0.006
Prior heart failure	31 (2)	10 (2)	0.21
Prior chronic lung disease	43 (4)	5 (4)	0.76
Peripheral vascular disease	98 (5)	23 (6)	0.59
Prior cerebrovascular accident	91 (5)	12 (3)	0.13
Time from symptom onset to first medical contact, min	184±457	297±677	0.006
Prior aspirin	653 (33)	131 (32)	0.67
Prior clopidogrel	85 (4)	16 (4)	0.72
Prior statin	672 (34)	142 (35)	0.80
Prehospital aspirin administration	1643 (84)	348 (86)	0.36
Prehospital clopidogrel administration	375 (19)	77 (19)	1.0
Prehospital heparin administration	1257 (64)	255 (63)	0.64

All data are presented as N (%).

Of 1956 patients referred for primary reperfusion, 1753 (89%) underwent urgent angiography, of whom 1686 (96%) underwent primary PCI with a median door-to-balloon of 66 minutes (interquartile range 38–106), 203 (8.6%) underwent thrombolytic therapy, 11 (0.6%) were referred for coronary artery bypass graft, and 56 (3.2%) underwent no revascularization. Of the 405 patients not referred for primary reperfusion because of SR, 366 (90%) underwent coronary angiography at a median of 26 hours after admission (interquartile range 13–46 hours). PCI was performed in 281 (77%), 19 (5%) were referred for coronary artery bypass graft, and 66 (18%) underwent no revascularization.

Table 2. Multivariate Predictors of SR

Effect	Odds Ratio	95% Wald Confidence Limits
Age (age >58 vs age ≤58) (y)	1.04	0.83 to 1.3
Female	1.17	0.87 to 1.57
No prior diabetes mellitus	1.28	0.99 to 1.66
Chronic renal failure	1.72	1.06 to 2.78
Prior angina pectoris	1.38	1.08 to 1.78
No past stroke or transient ischemic attack	1.77	0.95 to 3.3
Time from symptom onset to first medical contact	1.34	1.07 to 1.69

SR indicates spontaneous reperfusion.

Multivessel disease was equally prevalent between patients undergoing primary reperfusion (1080, 56%) and SR (202, 54%) (*P*=0.41).

In-hospital and 30-day outcomes, as well as 1-year mortality are shown in Table 3. As shown, patients with SR had significantly fewer major adverse outcomes during their hospital course including lower incidence of heart failure and cardiogenic shock, and had a shorter coronary care unit stay (4.4±3 versus 3.9±2.1, *P*<0.001). Patients with SR had less myocardial damage as assessed by significantly lower peak creatine kinase levels and higher left ventricular ejection fraction (Table 3). At 30-day follow-up, they had less heart

Table 3. In-Hospital and 30-Day Outcomes and 1-Y Mortality

	Primary Reperfusion (N=1956)	Spontaneous Reperfusion (N=405)	*P* Value
In-hospital outcomes			
Congestive heart failure	208 (11)	18 (4)	<0.001
Cardiogenic shock	47 (2)	0 (0)	0.001
Stroke/transient ischemic attack	18 (1)	1 (0)	0.17
Peak creatine kinase level	1525±2313	579±722	<0.001
Left ventricular ejection fraction, %	46±10	49±10	<0.001
In-hospital death	36 (2)	5 (1)	0.4
30-d outcomes and 1-y mortality			
Rehospitalization for CHF	31 (2)	3 (1)	0.11
30-d MACE (death/ recurrent myocardial infarction/stroke)	80 (4)	16 (4)	0.9
30-d cardiac death	29 (2)	5 (1)	0.66
1-y death	80 (4)	15 (4)	0.72

All data are presented as N (%). CHF indicates congestive heart failure; MACE, major adverse cardiac event.

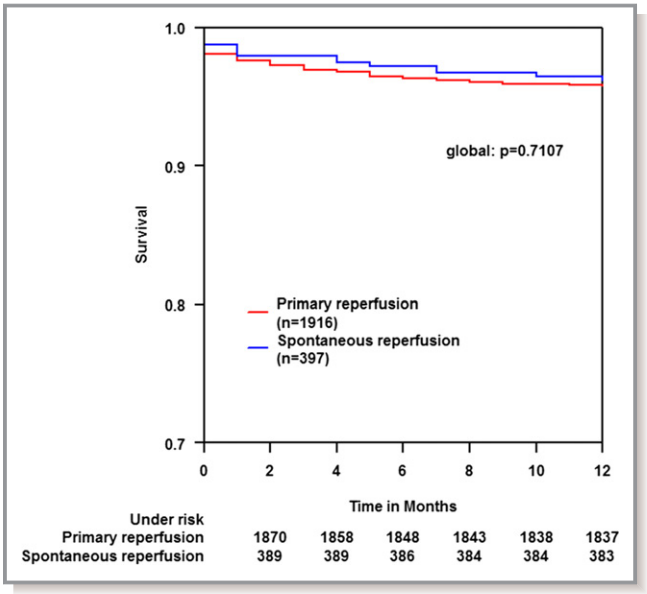

Figure 2. Kaplan–Meier graphs for 1-year mortality.

failure. Thirty-day and 1-year major adverse cardiac events and mortality were equivalent between groups (Table 3, Figure 2). Propensity matching was performed to account for selection bias. The 405 patients with SR were compared with 1620 propensity-matched patients who underwent primary reperfusion. The results of this analysis are shown in Table 4 and are almost identical to the nonmatched results.

Table 4. In-Hospital and 30-Day Outcomes and 1-Y Mortality: Propensity-Matched Populations

	Primary Reperfusion (N=1620)	Spontaneous Reperfusion (N=405)	*P* Value
In-hospital outcomes			
Congestive heart failure	177 (11)	18 (4)	<0.001
Cardiogenic shock	41 (2.5)	0 (0)	0.002
Stroke/transient ischemic attack	18 (1)	1 (0)	0.18
Peak creatine kinase level	1525±2313	579±722	<0.001
Left ventricular ejection fraction, %	46±10	49±10	<0.001
In-hospital death	34 (2)	5 (1)	0.35
30-d outcomes and 1-y mortality			
Rehospitalization for CHF	25 (2)	3 (1)	0.18
30-d MACE (death/ recurrent myocardial infarction/stroke)	73 (4.5)	16 (4)	0.7
30-d cardiac death	29 (2)	5 (1)	0.52
1-y death	71 (4)	15 (4)	0.79

All data are presented as N (%). CHF indicates congestive heart failure; MACE, major adverse cardiac event.

Median time to catheterization in patients with SR was 26 hours after admission (interquartile range 13–46 hours). Kaplan–Meier analysis of 1-year mortality shows no difference between patients undergoing catheterization within or beyond the median of 26 hours after admission (Figure 3).

Catheterization was performed beyond 24 hours after hospitalization in 179 patients (52%) and beyond 48 hours after hospitalization in 76 patients (22%). Similarly, no significant differences in outcomes including 30-day recurrent ischemia, 30-day heart failure, 30-day stent thrombosis, 30-day death, and 1-year death were noted for patients undergoing coronary angiography beyond 24 hours or beyond 48 hours when compared with those undergoing coronary angiography within 24 hours after admission (Tables 5 and 6).

Discussion

In this large-scale national study, 2361 consecutive STE-ACS patients who were eligible for primary reperfusion were recruited. Of these, 405 (17%) did not receive primary reperfusion therapy because of a clinical diagnosis of SR. The clinical diagnosis of SR was stringent and included both ≥70% pain resolution and ≥70% electrocardiographic ST-resolution. To the best of our knowledge, this is the largest

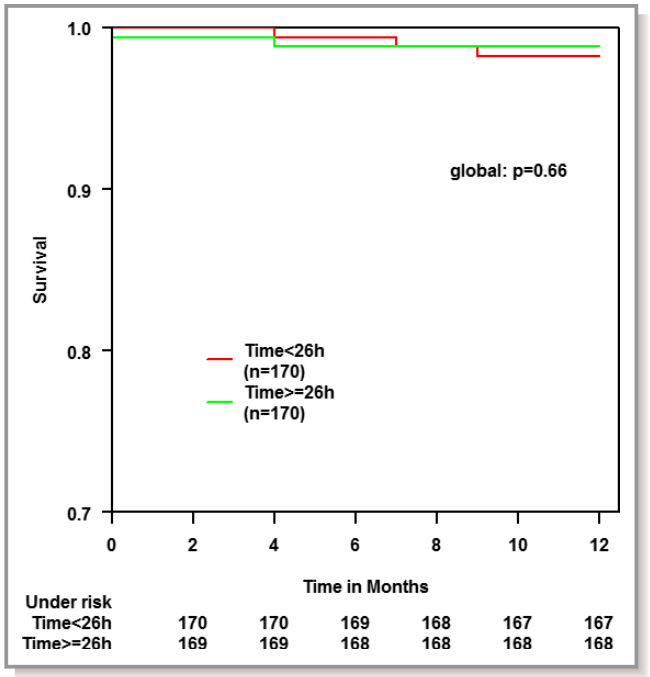

Figure 3. Kaplan–Meier graphs for 1-year mortality in patients with spontaneous reperfusion stratified according to time from presentation to performance of angiogram. Red line: patients undergoing angiography within the median of 26 hours after admission. Green line: patients undergoing angiography beyond the median of 26 hours after admission.

Table 5. Outcomes of Patients With SR Undergoing Coronary Angiography Within 24 H and Beyond 24 H After Admission

	Angiography Within 24 H (N=187)	Angiography Beyond 24 H (N=179)	*P* Value
30-d heart failure	6 (4.3)	7 (4.3)	0.99
30-d recurrent ACS	2 (1.3)	6 (3.6)	0.2
30-d stent thrombosis	2 (1.3)	1 (0.6)	0.52
30-d death	0	1 (0.6)	0.34

ACS indicates acute coronary syndrome; SR, spontaneous reperfusion.

and most comprehensive report of patients presenting with clinically defined SR, constituting ≈20% of all patients presenting with STE-ACS in the era of widespread use of primary PCI. The major finding of our study is that patients with STE-ACS presenting with clinical evidence of reperfusion have favorable outcomes despite not undergoing immediate reperfusion. Despite similar baseline characteristics, SR patients had significantly better in-hospital outcomes than STE-ACS patients undergoing immediate reperfusion. They had lower risk of heart failure, cardiogenic shock, arrhythmias, heart blocks, and had shorter coronary care unit stay. Mortality and major adverse cardiac event rates were similar between groups at 30 days as was 1-year mortality.

The proportion of SR in our study was similar to that found in a previous prospective angiographic study of SR[5] and consistent with other studies.[2,4] Terkelsen et al, using continuous ST monitoring, found spontaneous ST-resolution in 22 of 92 patients (24%) with STE-ACS before primary PCI.[12] Most studies assessed only angiographic markers of SR and demonstrated that in patients undergoing mechanical reperfusion, a patent infarct-related artery on the initial angiogram is associated with better outcomes.[3,6,13] Bainey et al examined coronary artery patency and ST-resolution in a large prospective study of patients undergoing angiography within 60 minutes after the defining ECG. Both angiographic and electrocardiographic SR occurred in ≈15% of patients. Clinical outcomes were better aligned with electrocardiographic ST-resolution than with angiographic infarct-related artery patency.[6] The authors concluded that the ECG was a more reliable measure of improved clinical outcomes and hypothesized that this difference may be attributable to improved myocardial reperfusion and less microvascular injury in patients with ST-resolution, both of which are poorly predicted by angiographic infarct-related artery patency.[14]

Table 6. Outcomes of Patients With SR Undergoing Coronary Angiography Within 24 H and Beyond 48 H After Admission

	Angiography Within 24 H (N=187)	Angiography Beyond 48 H (N=76)	*P* Value
30-d heart failure	6 (4.3)	2 (2.8)	0.59
30-d recurrent ACS	2 (1.3)	0	0.33
30-d stent thrombosis	2 (1.3)	0	0.33
30-d death	0	0	NA

ACS indicates acute coronary syndrome; SR, spontaneous reperfusion; NA, .

Since one of the aims of our study was to assess the safety of deferring immediate angiography in patients with SR, we excluded from the comparison group patients presenting in Killip class 2 or more as these patients have a class I indication for urgent angiography regardless of whether or not there were signs of ST-resolution on ECG. Ultimately, the majority of patients in our study underwent angiography and 69% underwent PCI at a median of 26 hours after admission. Outcomes of patients undergoing deferred angiography (more than 24/48 hours after admission) were equivalent to those undergoing early angiography (<24 hours after admission).

In current American and European practice guidelines,[8,9] management of patients presenting with clinical SR appears within the context of non-STE-ACS; however, no specific comment is made regarding the management of these patients. The current study constitutes the largest report of patients presenting with clinically defined SR and as such adds significant data on the outcomes of SR patients. The favorable outcomes noted in SR patients undergoing deferred angiography probably reflect the selection of patients with myocardial reperfusion. Primary reperfusion therapy can effectively restore epicardial flow; however, it is not universally successful in restoring myocardial perfusion. Failure to attain effective myocardial reperfusion (as assessed by ECG or myocardial imaging) is associated with worse outcomes in patients undergoing primary reperfusion. Thus, myocardial reperfusion is the ultimate goal of reperfusion therapy. Since patients with clinical SR have a high probability of myocardial reperfusion, the main rationale to perform angiography is the identification of lesions with a high likelihood of causing re-ischemia or reinfarction. In this respect, it is important to note the absolute low and equivalent rate of reinfarction among SR and primary reperfusion patients. Our findings regarding the timing of reperfusion among patients presenting with clinical signs of SR are supported by a previous angiographic by Steg et al.[1] In this study, 47 consecutive patients with STE-ACS in whom spontaneous Thrombolysis in Myocardial Infarction III flow was found in the infarct-related artery before any intervention were managed conservatively, without emergent PCI. Of these 47 patients, only 6 developed recurrent ischemia requiring emergency PCI and none of the patients had reinfarction. Furthermore, of 39 patients who underwent scheduled predischarge repeat angiography, 11 (constituting approximately one fourth of the entire cohort) had residual stenosis <50% and did not require PCI.

This study adds significant data to our previously published study on this topic,[7] both in its much larger sample size and in its inclusion of contemporary STE-ACS patients treated predominantly with primary PCI. The exclusion in our current study of patients presenting in Killip class >1 is significant in that it examines exclusively a group of patients for whom no clear guideline recommendation exists regarding the timing of intervention.

While this study constitutes the largest cohort of patients in the literature with clinically defined SR, there are a number of significant limitations: Because of the nonrandomized nature of our study, we cannot exclude the possible benefit of primary intervention in patients with clinical SR; however, the results of the propensity-matched populations do support the veracity of these results. Another significant limitation is the lack of detailed angiographic data, which prevent us from comparing coronary anatomical differences between the groups.

In conclusion, patients with clinically defined SR have a favorable prognosis. The outcomes of patients with clinically defined SR undergoing deferred intervention seem similar to corresponding patients undergoing primary reperfusion for STE-MI.

Disclosures

None.

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Supplemental Material

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