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STATE-OF-THE-ART PAPER

Therapy for ST-Segment Elevation Myocardial Infarction Patients Who Present Late or Are Ineligible for Reperfusion Therapy

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Despite the wide contemporary availability of pharmacological and mechanical means of reperfusion, a very significant proportion of ST-segment elevation myocardial infarction (STEMI) patients are still not offered any reperfusion therapy, and some of them are considered "ineligible for reperfusion." Spontaneous reperfusion and contraindications to the use of fibrinolytics and/or mechanical reperfusion methods account only for a small part of these clinical situations. The boundary between "timely" and "late" presentation in STEMI, the appropriateness of percutaneous intervention in patients presenting late after onset of symptoms, and the impact of sex and age on the eligibility and/or choice of reperfusion therapy continue to be challenged by the most recent published data. In the current invasive-driven reperfusion era, if scientific evidence and clinical guidelines are applied diligently, the vast majority of eligible STEMI patients should receive reperfusion therapy. Pharmacological nonlytic therapy of patients with STEMI, regardless of the choice of reperfusion strategy or the absence of it, is clearly defined by the current practice guidelines. Available data suggest that for patients who do not receive any form of reperfusion, anticoagulation therapy with low molecular weight heparin provides a clear additional mortality benefit versus placebo. Fondaparinux as compared with usual care (unfractionated heparin infusion or placebo) significantly reduces the composite of death or myocardial reinfarction without increasing severe bleeding or number of strokes. In the treatment of late-presenting patients with STEMI (beyond the first 12 h after onset of symptoms), clinical evaluation and risk stratification represent the crucial elements helping in decision making between therapeutic interventions. (J Am Coll Cardiol 2010; 55:1895–906) © 2010 by the American College of Cardiology Foundation

The most severe form of acute coronary syndrome (ACS) after sudden cardiac death is ST-segment elevation myocardial infarction (STEMI). According to the NRMI-4 (Fourth National Registry of Myocardial Infarction), 29% of infarction patients experience a STEMI (1), whereas a European survey, the EHS-ACS-II (Second Euro Heart Survey on Acute Coronary Syndromes), reported that 47% of ACS patients present with STEMI (2).

Prompt and complete coronary reperfusion using fibrinolysis or primary percutaneous coronary intervention (PCI) is the goal in STEMI, to reduce infarct size, adverse outcomes, and mortality. Current guidelines advocate attempting reperfusion therapy for all STEMI patients presenting within 12 h of symptom onset (3–5), and a recent analysis from the GRACE (Global Registry of Acute Coronary Events) shows that primary PCI is rapidly becoming the preferred approach (6). However, a significant proportion of STEMI patients are not offered any reperfusion therapy, and a small fraction of STEMI patients are considered "ineligible for reperfusion." In this review, we will describe the burden of "STEMI with no reperfusion therapy" and its causes, and review the data on antithrombotic and nonantithrombotic therapies (work-reducing and others) used in "no-reperfusion therapy" patients.

STEMI With No-Reperfusion Therapy

Magnitude of the Problem

Undertreatment. In the era preceding the widespread use of primary PCI, the German MITRA (Maximal Individual Therapy in Acute Myocardial Infarction) registry reported that no-reperfusion therapy was offered to 42.2% of patients with STEMI presenting within 48 h from symptom onset (7), whereas the French ACS registry from year 2000 reported that only 53% of STEMI patients presenting within 5 h of symptoms received reperfusion (8). In the EHS study, only 56% of STEMI patients received reperfusion therapy (35% with fibrinolytic agents, 21% with primary PCI) (9). Among 8,305 patients with STEMI in the ACOS (Acute Coronary

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Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ACS = acute coronary syndrome
ASA = acetylsalicylic acid
CI = confidence interval
LMWH = low molecular weight heparin
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
RRR = relative risk reduction
SR = spontaneous reperfusion
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
UFH = unfractionated heparin

Syndrome) registry, 28.3% did not receive any form of reperfusion (10). Between 2001 and 2002, in the TETAMI (Treatment With Enoxapam and Tirofiban in Acute Myocardial Infarction) randomized trial and registry, 28% of patients presenting within 12 h from onset of symptoms did not receive reperfusion therapy (11). Unfortunately, in the largest study to date of patients with STEMI (12), only half of the patients presenting within 24 h and not treated with mechanical reperfusion received fibrinolytic drugs. More recently, some progress has been made. In 2006, 33% of the GRACE patients presenting within 12 h of STEMI received no reperfusion (Fig. 1) (6). In the NRMI registry, the proportion of patients with STEMI eligible for but not receiving any form of reperfusion therapy slowly decreased from 1992, but remained as high as 28.1% in 2006 (Fig. 2) (13). A similar pattern was also seen in the more recent OASIS-6 (Sixth Organization to Assess Strategies in Acute Ischemic Syndromes) trial (23.7% of patients not receiving reperfusion) (14).

What are the clinical outcomes of patients encountering "missed opportunities" for reperfusion? Most clinical trials exclude these patients from their analyses. The few studies focusing on this topic demonstrate that the lack of reperfusion therapy translates into worse outcomes. In the TETAMI registry, 30-day mortality was only 4.4% in patients who received reperfusion therapy, but 12% in patients who did not receive it. Similarly, the triple end point of death, myocardial reinfarction, or recurrent angina occurred in only 11% of patients receiving reperfusion compared with 19.1% of patients who did not (Fig. 3). In the ACOS registry, in-hospital mortality was 14% among patients not receiving reperfusion and only 6.3% among patients receiving reperfusion (10).

Variables Associated With No-Reperfusion Therapy

Why do so many patients presenting with STEMI within 12 h from onset of symptoms not receive any reperfusion therapy? Spontaneous reperfusion and contraindications to the use of fibrinolytics and/or mechanical reperfusion account for a part of these clinical situations. In reality, these entities represent only a small fraction of the untreated patients. Another important association with no-reperfusion therapy is represented by patients who present between 12 and 24 h or later after the debut of symptoms. By the time many of these patients present to the hospital, their symptoms have diminished, and many are hemodynamically and electrically stable. The current STEMI guidelines do not recommend attempting mechanical or pharmacological reperfusion in such "late" and stable patients. Figure 4 summarizes the various clinical scenarios that can occur in the setting of STEMI and the available therapeutic options.

Patients presenting <12 h from onset of symptoms.

SPONTANEOUS REPERFUSION. Spontaneous reperfusion (SR) is a well-recognized scenario in STEMI, but its incidence varies widely (4% to 57%) in different reports (15–17). In a study of 710 STEMI patients eligible for reperfusion (15), SR (defined as ≥70% resolution of the cumulative ST-segment elevation compared with the initial electrocardiogram, and >70% reduction in pain) was observed in 155 (22%). The outcomes of patients with SR were better than those of patients without SR. On multivariate analysis, SR was significantly associated with a lower incidence of the composite of 30-day mortality, congestive heart failure, and recurrent ACS. In a pre-specified subgroup analysis of the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial (16), SR defined as angiographic TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 in the culprit vessel before PCI (first contrast injection), occurred in 11.5% of patients, and more commonly in nondiabetic patients. Nondiabetic patients with SR showed significant improvement in 90-day composite outcome of death, shock, or congestive heart failure versus without SR (4.0% vs. 8.9%, $p = 0.001$). A systematic analysis of the occurrence and prognostic implications of SR using electrocardiographic and angiographic assessments was done in a substudy of the ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction-4) PCI trial in 585 patients with STEMI randomized into the primary PCI arm (17). The SR assessed by ≥70% cumulative ST-segment elevation resolution or by TIMI flow grade 3 in the infarct-related artery before PCI as comparable (14.9% vs. 14.7%). However, only electrocardiographic SR was associated with a lower mortality, whereas no such differences were evident in patients with angiographic SR versus no SR. This finding supports the concept that resolution of ST-segment elevation reflects both the recanalization of the culprit epicardial vessel and a better microvascular flow at the cellular level (18).

CONTRAINDICATIONS. Absolute and relative contraindications for fibrinolysis are clearly defined in the current STEMI clinical guidelines and are mostly related to the risk of intracerebral bleeding (3–5). The true incidence of these contraindications is rarely reported in clinical studies, but it is probably very low. In the TETAMI randomized trial, only 1.4% of eligible patients did not receive fibrinolytic therapy because of absolute contraindications, and 2.6% because of relative contraindications (19). Primary PCI rarely has contraindications, except for the fear of bleeding from the adjunctive antithrombotic therapy (20).