

EDITORIAL COMMENT

Beyond the Guidelines Stance

Green Light for Very Early Angiography After Fibrinolysis*



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Fibrinolysis remains a cornerstone for the treatment of ST-segment elevation myocardial infarction (STEMI) when primary percutaneous coronary intervention (PCI) is not readily available. Its administration in a pre-hospital setting increases the proportion of patients undergoing rapid reperfusion with resultant improved outcomes compared with in-hospital administration (1). The logistic difficulties of implementing primary PCI, coupled with the evidence of benefit of (pre-hospital) fibrinolysis administered very early after the onset of symptoms, served as foundation for developing a unified approach, the “pharmacoinvasive strategy,” to the management of STEMI patients. In the last decade, the combination of fibrinolysis with subsequent routine coronary angiography and PCI (if required) has been fully studied and compared in randomized trials with both fibrinolysis alone and/or primary PCI, and it has been shown to be superior in terms of reinfarction and recurrent ischemia when compared with a “watchful waiting” approach, in which angiography is indicated only in patients with spontaneous or induced severe ischemia or left ventricular dysfunction (2). Accordingly, the American College of Cardiology Foundation/American Heart Association guidelines consider the transfer of STEMI patients treated by fibrinolysis to PCI-capable hospitals for angiography and PCI, even when hemodynamically stable and with clinical evidence of successful reperfusion, as a Class IIa (Level of Evidence: B) recommendation (3). Stronger is the endorsement of the pharmacoinvasive strategy provided by the European

Society of Cardiology guidelines (Class I indication, Level of Evidence: A) (4). A central issue remains the optimal delay between fibrinolysis and angiography. On the basis of the 3 most recent trials (NORDISTEMI [NORwegian study on District treatment of ST-Elevation Myocardial Infarction] (5), CARESS-in-AMI [Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction] (6), TRANSFER-AMI [Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction] (7), and WEST [Which Early ST-Elevation Myocardial Infarction Therapy] (8), all of which had a median delay between lysis and angiography of 2 to 3 h, a time window of 3 to 24 h after successful lysis is recommended in both guidelines.

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To further address this matter, in this issue of *JACC: Cardiovascular Interventions*, Madan et al. (9) utilize the largest available pooled clinical database using individual patient-level data of 7 randomized trials, evaluating an early invasive (median time from fibrinolysis to angiography <12 h) versus a “watchful waiting” approach. The median symptom onset to angiography time was 5.3 h. Of 1,238 patients undergoing angiography, 87% underwent PCI (with glycoprotein IIb/IIIa inhibitor in 63% of the cases), <15% received DES, and the majority had a femoral vascular access site. The 30-day and 1-year death or reinfarction rates, as well as in-hospital major bleeding, were not influenced by the different time from fibrinolysis to angiography, but recurrent ischemia increased significantly when time to angiography was longer than 4 h ($p = 0.02$). In contrast, the time from symptom onset to angiography remained a significant predictor of 1-year death or reinfarction and recurrent ischemia.

The major effect of time from symptom onset to angiography on outcome is not surprising,

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considering that 45% of the study patients had ineffective reperfusion (Thrombolysis In Myocardial Infarction flow grade <3) after fibrinolysis. From a pathophysiologic point of view, a longer symptom onset to angiography time corresponds to a longer “true” ischemic time when the occlusion of the infarct related artery persists (10). As such, it is related to a more pronounced myocardial and microvascular injury, larger infarct size, and worse clinical outcome, even when optimal mechanical reperfusion is applied (11-13). Additionally, the adverse effect of prolonged system delay (time from first medical contact to initiation of reperfusion) in terms of mortality and hospital readmission for congestive heart failure is well known (14).

More interesting and novel is the reported neutral effect or potential benefit of the very early (<2 h) pharmacoinvasive strategy in terms of angina reduction. Moving from a trial based to a patient-level meta-analysis permitted the authors to: 1) extrapolate the data of patients treated very early; and 2) dilute the bias of the variable angiography performance according to patient risk in the nonroutine strategy among trials. In this regard, the angiography rate ranged from >95% in TRANSFER-AMI (7) and NORDISTEMI (5) to <35% in CARESS-in-AMI (6) and WEST (8), because these trials restricted to those patients who needed rescue PCI. The interplay among baseline patient risk, time delay from fibrinolysis to angiography, and outcome might be complex. Thus, although high-risk patients presenting earlier might benefit the most from a short lytic to angiography time compared with lower-risk patients or late-comers, a routine early strategy in a real-world setting could harm unstable patients, for whom the risks of long interhospital transfers might be greater than any potential benefit. Notably, in the TRANSFER-AMI trial, despite the fact that the early pharmacoinvasive strategy was associated with a significant reduction of the composite cardiac endpoint and a nonsignificant reduction of death and reinfarction within 30 days, there was a significant inverse interaction between baseline risk according to GRACE (Global Registry of Acute Coronary Events) score and treatment effect (e.g., 16% of higher-risk patients had harm, whereas lower-risk patients had a benefit). Notwithstanding, a patient with a lower GRACE score but with a residual significant stenosis of the infarct-related artery supplying a large territory of viable myocardium might be the one who benefits most from a successful very early PCI. On the contrary, in the older patient with renal dysfunction, diabetes, and patent infarct-related artery with residual moderate lesion, even a successful PCI cannot change the intrinsic high-risk profile according to GRACE score.

Accordingly, by multivariate analysis, Madan et al. (9) found that the prediction model of early and late adverse outcome was almost entirely grounded in clinical variables included in the Thrombolysis In Myocardial Infarction risk score, and that these are generally irreversible risk factors despite successful PCI. Nevertheless, in these high-risk patients, adjunctive PCI to lytic might still provide a benefit in terms of recurrent ischemic events, not necessarily related to the infarct related artery.

A further argument of discussion is whether a very early invasive strategy (<2 h), as proposed by the authors, should be differentiated from facilitated PCI. Besides the lower platelet inhibition in the facilitated PCI studies, a major difference seems to be that trials evaluating facilitated PCI compared it with primary PCI. Exceptions are the STREAM (15) and the GRACIA-2 (Grup de Anàlisis de la Cardiopatia Isquèmica Aguda-1) (16) trials, which indeed had a longer time delay to adjunctive PCI. With the inherent limitations of correlating different trials, if we compare the very early cohort (<2 h) of Madan et al. (9) with the facilitated arms of the ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention) (17) and FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) (18) trials, the former had a lower risk profile (30-day mortality rate: 2.6% compared with 6% and 5.2%, and 1-year mortality rate: 4% compared with 7.8% and 6.3%, respectively). Nevertheless, the early cohort of Madan et al. (5) still carried an increased rate of stroke and major bleeding that was consistently higher than that observed in the primary PCI arms of the aforementioned trials (5.5% vs. 4.4% and 3.6%). In other words, when available, primary PCI always performs better than facilitated PCI.

In conclusion, we are indebted to the authors for providing us with more evidence that a pharmacoinvasive approach without time delay to perform angiography and PCI (if appropriate) might be the way to go. Nevertheless, considering that primary PCI, if available, is better than facilitated PCI, the extra mile is to identify specific barriers to the implementation of guidelines and to define actions to ensure that the majority of STEMI patients have access to the life-saving optimal reperfusion therapy (i.e., primary PCI). This is the mission of the ambitious European initiative of “Stent for Life” (19).

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