Prehospital Fibrinolysis As an Alternative to Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction When Resources Are Limited

Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med 2013;368:1379–87.

Study Overview

Objective. To determine whether prehospital fibrinolysis coupled with routine early coronary angiography provides comparable clinical outcomes with primary percutaneous coronary intervention (PCI) for patients with acute ST-segment elevation myocardial infarction (STEMI).

Design. A phase 3, open-label, parallel-group, randomized controlled trial (the STREAM trial).

Setting and participants. This multicenter study was conducted at 99 sites in 15 countries and enrolled 1915 patients from March 2008 to July 2012. Patients with an acute STEMI presenting within 3 hours of symptom onset who could not undergo primary PCI within 1 hour after the first medical contact were enrolled and randomized to either the intervention or control group.

Intervention. The intervention group received a weight-based fibrinolytic (tenecteplase) combined with low-molecular-weight enoxaparin, and the control group received primary PCI. Urgent PCI in the fibronolysis group was permitted at any time in the presence of hemodynamic or electrical instability, worsening ischemia, or progressive or sustained ST-segment elevation at the discretion of the investigators. For patients aged ≥ 75 years, the initial treatment protocol reduced the dose of enoxaparin and omitted the antiplatelet therapy clopidogrel. After 21% of the final patient population enrollment, the treatment protocol was amended (on 24 August 2009) to reduce the dose of tenecteplase by 50% for patients aged ≥ 75 years due to an excess of intracranial hemorrhage in that age-group.

Main outcome measure. The primary outcome was a composite of all-cause mortality, shock, congestive heart failure, or reinfarction at 30 days. Other outcomes examined included the 4 individual components of the primary end point, ischemic stroke, intracranial hemorrhage, nonintracranial bleed, and other serious clinical events.

Main results. In both the intervention and control group, mean age was 60 years, with similar Killip class, heart rate, systolic blood pressure, infarct location and body weight. Both groups had more male participants (79.4%

in fibrinolysis and 78.1% in primary PCI). The primary PCI group had a higher proportion of patients with a history of previous congestive heart failure compared with the fibrinolysis group (1.7% vs. 0.3%, respectively). Otherwise, there were no statistical differences in the rate of previous PCI, myocardial infarction, bypass grafting, hypertension, and diabetes history between the 2 groups.

As expected, the fibrinolysis group had a longer median time delay from randomization to angiography—2.2 hours for the 36% who required rescue or urgent intervention and 17 hours for the remaining 64% of patients, as compared with 1.1 hours for the primary PCI group. In regard to the median time delay from symptom onset to start of reperfusion treatment, it was lower for the fibrinolysis group with tenecteplase at 1.7 hours as compared with the primary PCI group with arterial sheath insertion at 3.0 hours.

No differences in the primary end point were found between patients receiving fibrinolysis, comprising 116 of the 939 participants (12.4%), and those who underwent primary PCI in the fibrinolysis group, 135 of the 943 participants (14.3%). The adjusted relative risk for the primary endpoint was 0.86 (95% confidence interval [CI], 0.68–1.09). No differences were found between the 2 groups for the individual components of the primary end point.

The overall rate of stroke was higher in the fibrinolysis group than in the primary PCI group (1.6% vs. 0.5%, $P = 0.03$). After protocol amendment to reduce the dose of tenecteplase by 50% among patients aged ≥ 75 years, intracranial hemorrhage was comparable between the 2 groups (0.5% in the fibrinolysis group vs. 0.3% in the primary PCI group, $P = 0.45$).

Conclusion. Prehospital fibrinolysis coupled with routine early coronary angiography provides comparable clinical outcomes with PCI for patients with acute STEMI.

Commentary

Timely reestablishment of coronary blood flow is the treatment objective in patients with STEMI [1]. In previous studies, primary PCI is recognized as a superior reperfusion strategy to fibrinolysis when it is performed in a timely fashion, preferably within 90 minutes of first medical contact or, for patients requiring transfer from a non-PCI capable hospital, within 2 hours [2,3]. Successful primary PCI reperfusion per the ACC Foundation/AHA guidelines relies on a combination of factors including patient's utility of pre-hospital emergency medical service (EMS), EMS training, prehospital catheterization laboratory activation protocols, non-PCI facility transfer protocol, and an expert 24/7 PCI facility. Despite efforts directed towards improving the system delay, a substantial portion of STEMI patients do not receive primary PCI within the recommended time frame [4,5].

This study attempted to address the challenges of providing care for STEMI patients in geographically remote areas or in health care systems in which primary PCI within 2 hours is not possible. When an optimal fibrinolysis strategy was used, short-term outcomes were comparable. However, previous studies have shown that patients treated with fibrinolysis strategies performed worse than those who underwent primary PCI for both short and long-term outcomes [1,6]. The current study lacks information on outcomes beyond 30 days and should be interpreted with caution.

Another important finding from this study is the need for reduction in fibrinolysis in patients aged ≥ 75 years due to increased bleeding risk in this subgroup. Prior to protocol amendment, intracranial hemorrhage occurred in 9 of the 939 subjects (1.0%) in the fibrinolysis group and 2 of the 948 subjects (0.2%) in the primary PCI group. After protocol amendment, intracranial hemorrhage occurred in 4 of the 747 subjects (0.5%) in the fibrinolysis subgroup and 2 of the 758 subjects (0.3%) in the primary PCI group. The higher rate of intracranial bleeding, together with the non-inferiority design of the study, led an editorialist for the *New England Journal of Medicine* to make the interesting conclusion to favor efforts to design health systems that allow patients to receive rapid PCI uniformly instead of the published fibrinolysis protocol [3].

The study has several limitations. While studies conducted in multiple countries usually improve generalizability of the results, in the case of STEMI diagnosis, the wide variation in experience and training of prehospital care/emergency department personnel became a limiting factor. Finally, the fibrinolytic manufacturer Boehringer Ingelheim sponsored this study. The results of this study may increase the use of fibrinolysis in STEMI when primary PCI is not available.

Applications for Clinical Practice

The results of the study by Armstrong et al indicate that prehospital fibrinolysis coupled with routine early coronary angiography provides comparable clinical outcomes

with primary PCI for patients with acute STEMI. In geographically remote areas or in health care systems in which primary PCI within 2 hours is not possible, a regional guideline for reperfusion strategy by fibrinolysis en route to a PCI center may become an option. In addition, a change in dosing of fibrinolysis in patients aged ≥ 75 years may be needed in light of the increased bleeding risk in this subgroup.

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References

1. Keeley EC, Grines CL. Primary coronary intervention for acute myocardial infarction. JAMA 2004;291:736–9.
2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362-425.
3. Bhatt DL. Timely PCI for STEMI--still the treatment of choice. N Engl J Med 2013;368:1446–7.
4. Parikh SV, Jacobi JA, Chu E, et al. Treatment delay in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a key process analysis of patient and program factors. Am Heart J 2008;155:290–7.
5. Terkelsen CJ, Sorensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA 2010;304:763–71.
6. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.