Evolution From Fibrinolytic Therapy to a Fibrinolytic Strategy for Patients With ST-Segment–Elevation Myocardial Infarction

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Placebo-controlled trials with fibrinolytic agents first demonstrated important reductions in morbidity and mortality when reperfusion therapy was administered to patients with ST-segment–elevation myocardial infarction (STEMI). Although primary percutaneous coronary intervention (PCI) is a better reperfusion strategy when compared with fibrinolytic therapy in randomized clinical trials, geographic access and logistical delays in time-to-treatment may decrease some of the benefits of primary PCI in clinical practice. Patients in the comparative trials were selected for randomization, delays to primary PCI were short, differences between treatments were magnified by the inclusion of studies with streptokinase, bleeding and intracerebral hemorrhage (ICH) rates with fibrinolysis may have been increased by higher anticoagulation targets than are now used, and reinfarction rates after fibrinolysis may have been higher than in the current era where clopidogrel and enoxaparin have shown benefit. Most importantly, fibrinolytic therapy was tested as monotherapy, with crossover to rescue PCI or the early invasive strategy discouraged by most protocols. In contrast, national registry reports including a broader spectrum of patients, time delays, interventional cardiologists, and hospitals have shown no difference in mortality rates between primary PCI and fibrinolytic therapy coupled with early coronary angiography. Thus, the fibrinolytic strategy that includes timely coronary angiography, and is now recommended by practice guidelines, is different from the fibrinolytic therapy that was tested years ago against placebo or primary PCI.

The best current fibrinolytic strategy may include the combination of bolus tenecteplase, aspirin, clopidogrel, and enoxaparin as initial therapy. Clopidogrel is recommended because prasugrel and ticagrelor have not been tested with fibrinolytic therapy. These agents facilitate prehospital treatment and improve outcomes in patients with STEMI compared with historical in-hospital fibrinolytic therapy. Importantly, included in the fibrinolytic strategy is emergent coronary angiography for reperfusion failure and coronary angiography within 24 hours after successful reperfusion.

This fibrinolytic strategy was recently tested against primary PCI in the Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial that included 1892 patients with STEMI. It is important to note that these patients were a select group that differed from routine reperfusion candidates. They presented within 3 hours of symptom onset (not 6 or 12 hours), were able to undergo primary PCI within 1 hour of first medical contact (not 2 hours), had at least 2 mm of ST-elevation on their qualifying ECG (not 1 mm), and were given prehospital (not in-hospital) tenecteplase. The median time from symptom onset to start of reperfusion therapy was only 100 minutes in the fibrinolytic group versus 178 minutes in the primary PCI group, so more patients in the fibrinolytic group were within the optimal 2-hour myocardial salvage window. The composite primary end point of death, shock, congestive heart failure, or reinfarction (not death or reinfarction) at 30 days was 12.4% in the fibrinolytic group and 14.3% in the primary PCI group (relative risk, 0.86; 95% confidence interval, 0.68–1.09; P=0.21). The earlier administration of fibrinolytic therapy was associated with lower rates of cardiogenic shock and congestive heart failure, more aborted myocardial infarction, and higher patency rates on the initial coronary angiogram, but there were no differences in death or reinfarction rates. Nonintracranial bleeding and ICH after a protocol amendment were higher with fibrinolytic therapy, but not statistically different. The authors suggested that a very early fibrinolytic strategy in patients with potentially large myocardial infarct size was an effective reperfusion strategy that could compete with primary PCI.

This relatively small trial has some limitations when compared with the large randomized trials that have changed clinical practice. It was designed as a proof of concept trial without a primary hypothesis, the electrocardiographic enrollment criteria for inferior STEMI were changed and the dose of tenecteplase in the elderly was halved during the enrollment period, and only ≈5 patients per site were enrolled per year over the ≈4-year enrollment period. The authors suggested that there were challenges with funding and recruitment. Therefore, STREAM was not an all-comers trial and the results do not apply to patients with >3 hours of symptom onset, smaller potential myocardial infarct size, or in-hospital fibrinolytic therapy.

In this issue of Circulation, Sinnaeve et al report the 1-year mortality results from STREAM, a secondary end point with only 119 events. All-cause mortality was insignificantly higher with primary PCI (6.7% versus 5.9%), but there was no difference in
cardiac mortality (4.0% versus 4.1%). Inexplicably, the 1-year composite primary end point and the other secondary end point (shock, heart failure, reinfarction) results are not included in the report. After speculating that the fibrinolytic strategy might offer greater benefit than primary PCI with longer PCI-related delays, better selection of appropriate candidates for subsequent coronary artery bypass graft surgery, and better 5-year survival rates because of a reduction in cardiogenic shock and congestive heart failure events, they appropriately conclude that the fibrinolytic strategy is a “safe and effective alternative reperfusion therapy strategy” for patients in regions across the world where primary PCI is not readily available.

The major complication of fibrinolytic therapy is bleeding, with ICH the most dreaded complication. The risk for ICH is highest in those aged ≥75 years. The clopidogrel 300-mg loading dose recommended with fibrinolytic therapy in younger patients should not be given in this subgroup because it has not been tested for safety. Compared with tenecteplase and unfractionated heparin, tenecteplase and enoxaparin were initially shown to increase the risk of ICH in patients aged >75 years, leading to the recommendation that the 30-mg intravenous bolus injection of enoxaparin be eliminated and the subcutaneous maintenance dose be reduced to 75% of that in younger patients. An important contribution of the STREAM trial is the observation that the initial increased risk of ICH in patients aged ≥75 years with the combination of tenecteplase, clopidogrel, and enoxaparin was corrected by reducing the tenecteplase dose by 50%. There were 3 ICH events in 37 patients in this subgroup before the protocol amendment, but no events in 97 patients after the amendment. Although efficacy has not been proven, safety is paramount in this age group, so fibrinolytic treatment protocols should emphasize these dose reductions for tenecteplase, clopidogrel, and enoxaparin in patients aged ≥75 years. Hopefully, this will encourage the treatment of more elderly patients who have previously been denied the potential benefits of reperfusion therapy because of the real concern about the increased risk for ICH. The risk for ICH after the protocol amendment for all patients (n = 1505) was 0.5% with the fibrinolytic strategy and 0.3% with the primary PCI strategy (P = 0.45), a reassuringly low rate that compares favorably against the reduction of embolic stroke previously documented with reperfusion therapy versus the natural history of STEMI.

Primary PCI is still the preferred reperfusion strategy when time-to-treatment delays are short and the patient can be treated at a properly equipped hospital by an expert interventional cardiologist. It is the treatment of choice despite delays in time-to-treatment for patients who have contraindications for fibrinolytic therapy or hemodynamic instability, and it is used to be the preferred treatment for patients with >3 hours of symptom duration, although that older recommendation was not included in the most recent STEMI guidelines. However, many communities in North America and most communities around the world do not have primary PCI capability or access. The STREAM trial did not prove that a fibrinolytic strategy is equivalent to primary PCI. Even though it was designed to give every possible advantage to the fibrinolytic strategy, it was limited by selection criteria, slow enrollment, and sample size. Nevertheless, it adds more evidence to support the conclusion that a fibrinolytic strategy including early coronary angiography is an excellent therapy for STEMI when primary PCI is not readily available, especially in patients with potentially large myocardial infarct size or when early treatment is possible. The benefit of fibrinolytic therapy versus no reperfusion therapy in STEMI is a major medical advance often forgotten by cardiologists working at hospitals with PCI capability who are enthusiastic about primary PCI.

Unfortunately, there may never be another large randomized trial of fibrinolytic therapy in STEMI. The STREAM investigators deserve major credit for highlighting how the old fibrinolytic therapy has evolved to a new fibrinolytic strategy and for demonstrating how it can safely and efficiently be delivered. For patients with STEMI around the world who do not have access to primary PCI, fibrinolytic therapy should be administered unless contraindicated and followed by timely coronary angiography, if logistically and economically possible.

Disclosures
None.

References


**Key Words:** Editorials ◼ fibrinolysis ◼ myocardial infarction ◼ percutaneous coronary intervention ◼ reperfusion therapy
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_Circulation_. 2014;130:1133-1135; originally published online August 26, 2014;
doi: 10.1161/CIRCULATIONAHA.114.012539

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/130/14/1133

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