Circulation

ON MY MIND

The Future of Pharmacoinvasive Therapy for ST-Segment–Elevation Myocardial Infarction Reperfusion in the Post-STREAM Era

Thomas Alexander, MD, DM; Dharam J. Kumbhani, MD, SM; Ajit Mullasari Sankardas, MD, DM

Coming on the heels of the STREAM trial (STREAM-Strategic Reperfusion [With Tenecteplase and Antithrombotic Treatment] Early After Myocardial Infarction),[1] the recently concluded STREAM-2 trial (Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction)[2] has provided additional data in pharmacoinvasive (PI) reperfusion as a reperfusion strategy in ST-segment–elevation myocardial infarction (STEMI) when time delays are expected. To summarize the findings of these 2 trials, patients with STEMI within 3 hours of chest pain and with expected delays of >1 hour to primary percutaneous coronary intervention (PCI) were randomly assigned to PI versus primary PCI. STREAM was conducted with full-dose tenecteplase in the PI arm, which was amended after one-fifth of expected randomization to half-dose tenecteplase in patients >75 years of age due to an increased risk of intracranial bleeding. STREAM-2, on the other hand, randomly assigned patients >60 years of age (mean age, 71 years) and used half-dose tenecteplase in the PI group from the outset. Both studies showed similar results for PI versus primary PCI for the primary composite end point of death, shock, reinfarction, and heart failure at 30 days (STREAM-1: 12.4% versus 14.3%; relative risk, 0.86 [95% CI, 0.68–1.09]; STREAM-2: 12.8% versus 13.3%; relative risk, 0.96 [95% CI, 0.62–1.48]).

However, there are 2 areas of concern. The first is the issue of intracranial hemorrhage. In STREAM, more intracranial hemorrhages occurred in the fibrinolysis group than in the primary PCI group (1.0% versus 0.2%, P=0.04). The rates of nonintracranial bleeding were similar in the 2 groups. In STREAM-2, despite the use of half-dose tenecteplase, intracranial hemorrhage was numerically higher in the PI arm (1.5% [6 events] versus 0%). This could be a real finding because it is concordant with the STREAM data, although it could also be due to a protocol violation, for instance, use of additional heparin during the PCI. The second area of concern is the issue of failed reperfusion with tenecteplase and the need for emergent rescue PCI, 36% in STREAM and 34% in STREAM-2.

So, to summarize, the Achilles heel of a PI strategy is failed reperfusion and increased intracranial bleeding. The best strategy to deal with failed reperfusion is to institute fibrinolysis within the golden first hour where reperfusion results can be similar to primary PCI.[3] There is also an added advantage of increased percentage of aborted myocardial infarction if fibrinolysis is initiated early; however, this may only be feasible in a small minority of patients, because most patients with STEMI present >1 hour from the onset of ischemic symptoms. The issue of increased bleeding risk, however, will require different strategies and studies. Ischemic times in the PI arms of both STREAM trials were similar and fairly short (100–110 minutes). In this setting, pre-PCI baseline TIMI II/III flow rates in the PI arms were fairly similar (74.1% in STREAM-1, 71.6% in STREAM-2) despite the use of half-dose tenecteplase in the latter. Could half-dose tenecteplase in younger patients or even lower doses in the elderly patients produce similar reperfusion rates without increased bleeding rates? Could avoiding the standard strategy of coadministration of heparin reduce bleeding rates? These strategies need to be studied in future PI trials.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Thomas Alexander, MD, DM, Kovai Medical Center and Hospital, No. 99, Avanashi Rd, Coimbatore, India 641014. Email tomalex41@gmail.com

For Sources of Funding and Disclosures, see page 733.

Circulation is available at www.ahajournals.org/journal/circ

The findings of STREAM and STREAM-2 are relevant globally. Delays to access in primary PCI even in countries with mature STEMI networks are well known. Reliable availability of 24/7 primary PCI centers, distance from a reperfusion center, especially for rural communities, and index presentation to non-PCI centers are all barriers and can lead to significant delays in primary PCI. These deficiencies are even more stark in low- and middle-income countries where PCI centers are even more scarce and access is more problematic, even as the number of eligible patients continues to increase. In many of these countries the largest percentage of patients either gets no reperfusion or, at best, standalone fibrinolysis.

A recent meta-analysis[4] of different reperfusion strategies in STEMI has shown that the PI strategy is superior to standalone fibrinolysis and compares well with primary PCI in terms of mortality, reinfarction, and stroke, but with a small increase in bleeding complications. A PI-centered strategy may be more viable from a public health and policy perspective in resource-poor settings. We ran the TN STEMI study (Tamil Nadu–ST-Segment Elevation Myocardial Infarction Program)[5] as a "hub and spoke" model in Southern India. At baseline, 11.5% of all enrolled patients with STEMI (19.4% of patients presenting to spoke hospitals) received no reperfusion and 53.6% of all patients (77.1% of patients presenting to spoke hospitals) received standalone fibrinolytic reperfusion. Once a PI strategy was implemented, the use of standalone fibrinolytic reperfusion decreased to 29.4% (46.3% at spoke hospitals), and the combined primary PCI and PI treatment numbers increased from 35% to 60.8%. This resulted in a 1-year adjusted mortality reduction of 22% compared with preimplementation. This strategy (STEMI India model) is now being implemented in different states in India and other low- and middle-income countries.

Timely primary PCI has been shown to be the most effective and safe reperfusion strategy. The totality of data, including STREAM-2, supports the utility of PI reperfusion as an effective strategy when there are time delays in accessing primary PCI, albeit with significant lingering concerns of intracranial hemorrhage and failed reperfusion. This strategy will be more relevant in low- and middle-income countries as they transition from no-reperfusion to standalone fibrinolysis to the PI strategy of reperfusion, and ultimately to primary PCI-based STEMI networks.

ARTICLE INFORMATION

Affiliations

Department of Cardiology, Kovai Medical Center and Hospital, Coimbatore, India (T.A.). Division of Cardiology, UT Southwestern Medical Center, Dallas, TX (D.J.K.). The Madras Medical Mission, Mogappair, Chennai, India (A.M.S.).

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, et al; STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368:1379–1387. doi: 10.1056/NEJMoa1301092
2. Van de Werf F, Ristić AD, Averkov OV, Arias-Mendoza A, Lambert Y, Kerr Saraiva JF, Sepulveda P, Rosell-Ortiz F, French JK, Musić LB, et al. Half-dose tenecteplase or primary percutaneous coronary intervention in older patients with ST-segment–elevation myocardial infarction in STREAM-2: a randomized, open-label trial. *Circulation*. 2023;148:753–764. doi: 10.1161/circulationaha.123.064521
3. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute J-M, et al; Comparison of Angioplasty and Prehospital Thromboysis in Acute Myocardial Infarction study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet*. 2002;360:825–829. doi: 10.1016/S0140-6736(02)09963-4
4. Fazel R, Joseph TI, Sankardas MA, Pinto DS, Yeh RW, Kumbhani DJ, Nallamothu BK. Comparison of reperfusion strategies for ST-segment–elevation myocardial infarction: a multivariate network meta-analysis. *J Am Heart Assoc*. 2020;9:e015186. doi: 10.1161/JAHA.119.015186
5. Alexander T, Mullasari AS, Joseph G, Kannan K, Veerasekar G, Victor SM, Ayers C, Thomson VS, Subban V, Gnanaraj JP, et al. A system of care for patients with ST-segment elevation myocardial infarction in India: the Tamil Nadu–ST-Segment Elevation Myocardial Infarction Program. *JAMA Cardiol*. 2017;2:498–505. doi: 10.1001/jamacardio.2016.5977