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EDITORIAL

Pharmaco-Invasive Strategy: The Answer to Improving ST-Elevation–Myocardial Infarction Care

Amgad Mentias, MD; Saket Girotra, MD, SM

ST-segment–elevation myocardial infarction (STEMI) is a leading cause of death worldwide,[1] and immediate reperfusion can be life-saving.[2] Although primary percutaneous coronary intervention (PCI) is the most effective modality for achieving reperfusion in STEMI,[2,3] the benefit of primary PCI over thrombolytics on survival is time-dependent. Prior studies have showed that the survival benefit of primary PCI over thrombolytics may be negated if PCI-related delay exceeds by >60 minutes.[4] Accordingly, national quality improvement initiatives during the past decade have focused on reducing delays in primary PCI, especially in patients who present directly to a PCI-capable hospital.[5]

See Article by Fazel et al.

However, availability of primary PCI for STEMI patients remains uneven. In the United States, only one third of acute care hospitals have 24×7 PCI capability and nearly 20% of the population lives >60 minutes from a PCI capable facility.[6] Among all STEMI patients, ≈30% initially present to a non-PCI capable hospital.[7] Access to primary PCI is substantially worse in low- to middle-income countries where cardiac catheterization services are largely confined to big cities leaving vast swaths of the population out of the coverage area. For example, in India, 70% of the 1.3 billion population lives in rural areas and the nearest cardiac catheterization laboratory may be hundreds of miles away.[8] Even in major cities, access to a PCI-capable hospital is often limited by long transport times and lack of efficient transfer protocols.[8]

Given the challenges in providing timely access to primary PCI to STEMI, alternative reperfusion options for patients who initially present to non-PCI capable hospitals are important. These approaches include use of thrombolytics alone, or a hybrid approach—use of thrombolytics up front followed by invasive angiography either immediately (facilitated PCI), or after a waiting period of 3 to 24 hours (pharmaco-invasive approach). Given that thrombolytics alone fail to achieve reperfusion in ≈30% of patients and another 30% may experience recurrence of ischemia and ST elevation following initial reperfusion,[9,10] a hybrid approach is attractive because it combines the immediate availability of thrombolytic therapy, with the higher success rate of mechanical reperfusion upon transfer to PCI-capable centers. While, numerous randomized controlled trials over the past 2 decades have compared individual strategies for STEMI management, head-to-head trials comparing pharmaco-invasive strategy with facilitated PCI have been lacking.

To address this gap in knowledge, Fazel et al, in this issue of the *Journal of the American Heart Association (JAHA)*, report the results of a network meta-analysis of 31 randomized controlled trials comparing primary PCI, thrombolytics alone,

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Correspondence to: Saket Girotra, MD, SM, Division of Cardiovascular Diseases, University of Iowa Carver College of Medicine, Iowa City, IA 52242. E-mail: saket-girotra@uiowa.edu

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pharmaco-invasive, and facilitated PCI.[11] Among the 4 reperfusion modalities, they found that primary PCI was the best modality with the lowest odds for mortality (odds ratio [OR], 0.73; 95% CI, 0.61–0.89), nonfatal reinfarction (OR 0.38; 95% CI, 0.29–0.50) and stroke (OR, 0.38; 95% CI, 0.24–0.60), and thrombolytics was the worst. Using Bayesian analysis, the probability that pharmaco-invasive strategy had the highest mortality was 6% compared with 24.2% for facilitated PCI; and the probability that pharmaco-invasive strategy had the highest rate of major bleeding was 19.8%, compared with 77.4% for facilitated PCI. These findings were consistent across a range of sensitivity analyses.

These findings highlight that when primary PCI is not available in a timely manner, a hybrid approach should be preferred over using thrombolytics alone. Furthermore, among the hybrid approaches, a pharmaco-invasive approach is superior to facilitated PCI. Even though facilitated PCI has been shown to achieve a higher pre-PCI patency rate when compared with primary PCI, the potential benefit of immediate mechanical reperfusion following thrombolytics may be counterbalanced by a higher risk of bleeding.[12–14] In addition, data also suggest transient platelet activation immediately following thrombolytics which may contribute to the risk of re-occlusion and thrombosis.[15] Delaying invasive angiography by a few hours following thrombolysis likely avoids the above complications, and strikes the right balance between pharmacological and mechanical reperfusion. Accordingly, in the current American College of Cardiology/American Heart Association guidelines, pharmaco-invasive strategy carries a class IIa recommendation with the recommendation for performing coronary angiography and PCI within 3 to 24 hours after thrombolytic therapy, and recommendation against performing PCI in the first 3 hours.[2]

However, some questions remain unanswered. First, because of lack of patient-level data, the authors were unable to determine the threshold at which delay in primary PCI would negate its benefit over a pharmaco-invasive approach. However, in prior studies that compared primary PCI with thrombolytics, a delay of up to 60 minutes was found acceptable.[4] Given that pharmaco-invasive strategy is superior to thrombolytics, and delays in patients transferred for primary PCI after often longer than 60 minutes in contemporary practice, it stands to reason that a pharmaco-invasive approach would be an appropriate option when access to primary PCI is delayed. Second, to what extent does time from symptom onset impact the relative rankings of individual reperfusion therapies? Most trials that compared pharmaco-invasive strategy to primary PCI included patients within 3 to 6 hours of symptoms onset.[16,17] It remains unclear whether the relative rankings of different reperfusion strategies differs in patients with longer time from symptom onset to clinical presentation.

Despite the above limitations, the findings of the study from Fazel et al have important implications for improving STEMI care in the United States and abroad. Their findings serve as an important reminder that a pharmaco-invasive approach is an appropriate alternative when timely access to primary PCI is not available among patients eligible for thrombolysis. Despite these data, a pharmaco-invasive strategy remains under-used in 30% of the STEMI patients who present to a non-PCI capable hospital in the United States. A study using 2008 to 2012 data from the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry found that among such STEMI patients at a non-PCI capable hospital who were also eligible for thrombolytics, >70% were transferred for primary PCI, to a hospital that, on average was 58 minutes away.[7] The door-to-balloon time was >2 hours in nearly 50% of such patients, which likely negated any survival benefit of primary PCI. These data highlight that there is a tremendous opportunity to optimize reperfusion strategies for STEMI who present to non-PCI capable hospitals especially in settings when timely access to primary PCI is not available.

The promise of pharmaco-invasive strategy maybe further magnified in low-to-middle income countries, where access to primary PCI is out of the reach for most of the population and a vast majority of STEMI patients are treated with thrombolysis alone.[8,18] A pharmaco-invasive strategy has the potential to expand the therapeutic time window for reperfusion when the nearest cardiac catheterization may be several hours away. However, high levels of poverty, lack of health insurance, and scarcity of resources such as ambulances and large geographic distances can make developing STEMI systems of care in resource poor settings a daunting task. Therefore, the Tamil Nadu STEMI program is a shining example in which the above challenges were overcome through the adoption of a pharmaco-invasive approach. The program included 4 tertiary medical centers (hub hospitals) located in Tamil Nadu, a state in Southern India that established a regional network with 35 primary care clinics and small hospitals (spoke) across the state and optimized reperfusion strategies for patients, especially greater use of a pharmaco-invasive strategy for patients presenting at spoke locations. Care was coordinated through the real time transmission of electrocardiography and other clinical data between the hub and spoke sites using technology and collaboration with government and non-government agencies. The implementation of the program was a resounding success.[19] Although the overall use of reperfusion remained unchanged at ≈75%, the post-implementation phase was associated

with a 33% reduction in use of thrombolytics in favor of a 2-fold increase in use of a pharmaco-invasive strategy or primary PCI. Increase in use of invasive strategy was especially prominent in patients who initially presented to spoke locations, in whom use of primary PCI or pharmaco-invasive strategy increased from 3.5% in the pre-implementation phase to 31.3% during the post-implementation phase ($P<0.0001$). One-year mortality was also lower during the post-implementation phase (adjusted OR, 0.76; 95% CI, 0.58–0.98; $P=0.04$).[19] Similar initiatives that integrate primary PCI with pharmaco-invasive approach within regional systems of care are being implemented in other developing countries.[20]

In conclusion, the work by Fazel et al highlights that a pharmaco-invasive approach for reperfusion in STEMI is safe and effective and has the potential to enhance care for the vast majority of patients across the world who are treated in settings where timely access to primary PCI is not readily available.

ARTICLE INFORMATION

Affiliations

From the University of Iowa Carver College of Medicine, Iowa City, IA (A.M., S.G.) and Center for Access and Delivery Research and Evaluation, Iowa City Veterans Affairs Medical Center, Iowa City, IA (S.G.).

Disclosures

None.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596.
2. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, 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–e425.
3. 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.
4. Nallamothu BK, Antman EM, Bates ER. Primary percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: does the choice of fibrinolytic agent impact on the importance of time-to-treatment? *Am J Cardiol*. 2004;94:772–774.
5. Krumholz HM, Herrin J, Miller LE, Drye EE, Ling SM, Han LF, Rapp MT, Bradley EH, Nallamothu BK, Nsa W, et al. Improvements in door-to-balloon time in the United States, 2005 to 2010. *Circulation*. 2011;124:1038–1045.
6. Concannon TW, Nelson J, Goetz J, Griffith JL. A percutaneous coronary intervention lab in every hospital? *Circ Cardiovasc Qual Outcomes*. 2012;5:14–20.
7. Vora AN, Holmes DN, Rokos I, Roe MT, Granger CB, French WJ, Antman E, Henry TD, Thomas L, Bates ER, et al. Fibrinolysis use among patients requiring interhospital transfer for ST-segment elevation myocardial infarction care: a report from the US National Cardiovascular Data Registry. *JAMA Intern Med*. 2015;175:207–215.
8. Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D, Reddy KS, Gupta R, Joshi P, Kerkar P, Thanikachalam S, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. *Lancet*. 2008;371:1435–1442.
9. Langer A, Krucoff MW, Klootwijk P, Simoons ML, Granger CB, Barr A, Califf RM, Armstrong PW. Prognostic significance of ST segment shift early after resolution of ST elevation in patients with myocardial infarction treated with thrombolytic therapy: the GUSTO-I ST segment monitoring substudy. *J Am Coll Cardiol*. 1998;31:783–789.
10. Ohman EM, Califf RM, Topol EJ, Candela R, Abbottsmith C, Ellis S, Sigmon KN, Kereiakes D, George B, Stack R. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. TAMI Study Group. *Circulation*. 1990;82:781–791.
11. 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.
12. Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. *Eur Heart J*. 2000;21:823–831.
13. Assessment of the S, Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention i. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet*. 2006;367:569–578.
14. Berkowitz SD, Granger CB, Pieper KS, Lee KL, Gore JM, Simoons M, Armstrong PW, Topol EJ, Califf RM. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. The global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) I investigators. *Circulation*. 1997;95:2508–2516.
15. Moser M, Nordt T, Peter K, Ruef J, Kohler B, Schmittner M, Smalling R, Kubler W, Bode C. Platelet function during and after thrombolytic therapy for acute myocardial infarction with reteplase, alteplase, or streptokinase. *Circulation*. 1999;100:1858–1864.
16. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368:1379–1387.
17. Kastrati A, Mehilli J, Schlotterbeck K, Dotzer F, Dirschinger J, Schmitt C, Nekolla SG, Seyfarth M, Martinoff S, Markwardt C, et al. Early administration of reteplase plus abciximab vs abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2004;291:947–954.
18. Kimeu R, Kariuki C. Assessment of the management of acute myocardial infarction patients and their outcomes at the Nairobi Hospital from January 2007 to June 2009. *Cardiovasc J Afr*. 2016;27:218–221.
19. 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.
20. Kaifoszova Z, Kala P, Alexander T, Zhang Y, Huo Y, Snyders A, Delport R, Alcocer-Gamba MA, Gavidia LM. Stent for life initiative: leading example in building STEMI systems of care in emerging countries. *EuroIntervention*. 2014;10(suppl T):T87–T95.