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Acute Cardiovascular Care: The STREAM Trial*

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Although prompt delivery of primary PCI is the preferred strategy to treat patients with acute STEMI, delays in performing PCI are common when patients present to emergency medical services or hospitals without a cath lab. The delay in reperfusion that results from long transfer to a hospital for primary PCI increases the rates of morbidity and mortality.

In STREAM, 1892 patients with STEMI (≥ 2 mm ST elevation in 2 contiguous leads) who presented within 3 hours of symptom onset and who could not undergo primary PCI within 1 hour of first medical contact were randomized to 1 of 2 strategies: 1) early fibrinolysis followed by coronary angiography in 6 to 24 hours or rescue PCI, if needed, or 2) standard primary PCI.

Patients from 99 sites in 15 countries were included in this trial. The primary endpoint was a composite of death from any cause, shock, congestive heart failure, or reinfarction at 30 days.

In the early fibrinolysis group ($n = 944$), patients received a weight-based bolus of tenecteplase along with aspirin, clopidogrel, and enoxaparin in the ambulance or emergency room. Rescue intervention was performed if there was $< 50\%$ ST-segment resolution in the single lead of an electrocardiogram or clinical evidence of failed reperfusion within 90 minutes after bolus. In the primary PCI group ($n = 948$), patients received antiplatelet and antithrombin treatment according to local standards, and underwent standard primary PCI.

After 20% of the planned recruitment into the study, the bolus dose of tenecteplase was halved in patients aged ≥ 75 years to reduce the risk of intracranial bleeding.

The median time from symptom onset to the start of reperfusion therapy was 100 minutes in patients randomized to the early fibrinolysis group versus 178 minutes in the primary PCI group (Fig. 1).

The early fibrinolysis strategy circumvented an urgent procedure in 64% of the patients. The median time from random-

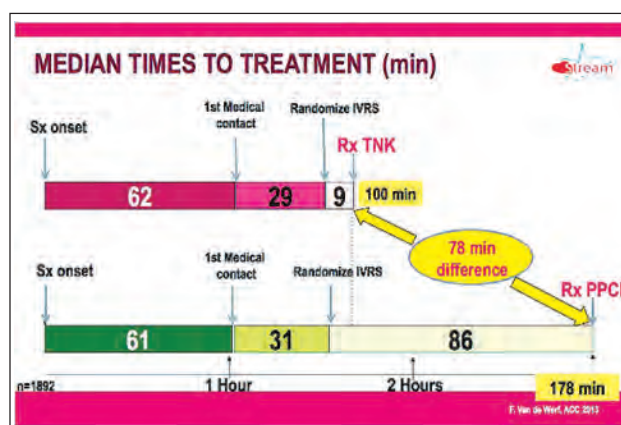


Figure 1: Median Time to Treatment: Early Fibrinolysis Versus Primary PCI. IVRS: interactive voice response system; PPCI: primary percutaneous coronary intervention; TNK: tenecteplase.

ization to angiography was longer in the pharmaco-invasive arm versus the primary PCI group. In the 36% of the patients who required rescue or urgent PCI the procedure was performed after a median delay of 2.2 hours following bolus tenecteplase. In the remaining 64% a non-urgent angiography was performed after a median delay of 17 hours.

Patients assigned to early fibrinolysis were more likely to have TIMI-3 blood flow compared with the primary PCI group (58.5% vs 20.7%, respectively) and less likely to have complete occlusion of an artery (16.0% vs 59.3%, respectively). Coronary artery bypass graft surgery was performed about twice as often in the early fibrinolysis versus the primary PCI group (4.7% vs 2.1%, respectively; $p = 0.002$).

The primary composite endpoint occurred in 12.4% of patients in the early fibrinolysis versus 14.3% patients in the primary PCI group (RR, 0.86; 95% CI, 0.68 to 1.09; $p = 0.24$). This 95% CI excludes a relative excess of 9% in the early fibrinolysis group compared with the primary PCI group, which is within the generally accepted boundaries for non-inferiority. The primary endpoint result was consistent across all prespecified subgroups. There were no significant differences between groups in cardiac-specific mortality or cardiac rehospitalization.

The overall intracranial hemorrhage rate was significantly higher in the early fibrinolysis versus the primary PCI group

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(0.96% vs 0.21%, respectively; $p = 0.04$) but was not significantly different after the trial protocol was amended to reduce the dose of tenecteplase in patients aged ≥ 75 years (0.54% vs 0.26%, respectively; $p = 0.45$). After amendment 3 fatal strokes were observed in the pharmaco-invasive group vs 4 in the primary PCI group.

STREAM showed that a strategy involving early fibrinolysis with bonus tenecteplase and contemporary antithrombotic therapy offers similar efficacy as primary PCI in patients with STEMI who present within 3 hours of symptom onset and who could not undergo primary PCI within 1 hour of first medical contact. An important implication of STREAM is the key role of prehospital systems capable of early diagnosis, therapy and triage at the first point of care.

The study was published online in the NEJM, March 10, 2013.

Comment by Giuseppe Tarantini, MD, PhD, Padua, Italy & Bernard J. Gersh, MB, ChB, DPhil, FRCP, Minnesota, USA

In the 20 years since the GISSI-1 and the ISIS-2 trials of thrombolytic therapy were published, reperfusion therapy for ST-elevation myocardial infarction (STEMI) has continuously evolved [1]. Several meta-analyses, including randomized trials, have demonstrated that primary percutaneous coronary angioplasty (PPCI) is superior to in-hospital fibrinolysis for the treatment of patients with STEMI, even among patients admitted to hospitals without interventional facilities, in which interhospital transfer is necessary [2, 3]. It is generally well accepted that PPCI is the preferred reperfusion therapy for all when it can be performed within 90 minutes of first medical contact by an experienced team. However, many hospitals lack PCI facilities and few provide around the clock staffing for these procedures. As compared to PPCI, fibrinolytic treatment is a therapy that is immediately available and requires much less technical effort and equipment although it does entail the risk of intracranial hemorrhage, lower rates of TIMI 3 flow and a high rate of re-occlusion.

The major remaining area of controversy relates to how much delay can be considered acceptable when transferring a patient for PPCI as opposed to the immediate administration of a fibrinolytic drug. Crucial to this decision is the overall risk of the patient and the duration of ischemia at the time of presentation since the window of opportunity [1, 4]. It has been documented that the impact of treatment delays is greatest within the first 2–3 hours of symptoms as opposed to later on the “flat” part of the curve which relates time of reperfusion and duration of ischemia to the magnitude of the mortality reduction and salvage [5]. In this context, it is noteworthy that when a fibrinolytic agent is administered in pre-hospital setting, it extends the mortality benefit over that achieved with in-hospital administration [6]. This approach to fibrinolysis has proven feasible in various countries and is effective in increasing the proportion of patients treated earlier in their course with resultant improved outcomes [7, 8]. Furthermore, the combination of fibrinolysis with subsequent early (but not immediate) routine coronary angiography, the so-called pharmacoinvasive strategy [9], has been shown to be an effective

strategy and superior to that of lytics alone combined with a “watchful waiting” approach [10–13], although the risk of intracranial hemorrhage remains.

In many parts of the world where access to PCI-capable centers 7 days a week and 24 hours a day is available, the preferred approach is for ambulances to bypass a non-PCI capable hospital and directly transport patients to a PPCI facility [14]. Nonetheless, “one size does not fit all” and the preferred reperfusion strategy will depend to a large extent on geographical and logistical constraints such as distance and weather and regional resources [15].

Two randomized studies, GRACIA-2 [10] and WEST [16], reported comparable efficacy and safety of the pharmacoinvasive strategy versus primary PCI, but these findings could not be considered as being conclusive since the total number of patients randomized in both studies was very low ($n = 416$) and as such these trials were underpowered for clinical endpoints.

The Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial [17] is the first, large, prospective, randomized, multicenter, international study (15 countries) comparing pre-hospital fibrinolysis with PPCI in early presenting patients. A total of 1892 patients with STEMI who had an onset of symptoms within 3 hours before medical contact and who could not undergo PPCI within 1 hour were randomly assigned to receive either PPCI or fibrinolysis (emergency medical personnel or community hospital after amendment) and then transported to a PCI-capable hospital. There were no significant between-group difference in the primary endpoint of death from any cause, shock, congestive heart failure, or re-infarction up to 30 days although the trend favored the pharmacoinvasive group, particularly when the analysis was confined to the majority of patients who were enrolled after an amendment specifying a lower dose of fibrinolytic in patients over the age of 75 years.

The authors concluded that pre-hospital fibrinolysis followed by routine angiography within 6 to 24 hours in stable patients or immediate “rescue PCI” in the remainder is a reasonable alternative to PPCI when delayed by more than 1 hour. Although this study was carefully performed, several issues deserve clarification so that the reader can better put the results in perspective.

First, this is a moderate-sized study that has no primary hypothesis in the statistical assumption and thus should be considered exploratory and limited to STEMI patients receiving fibrinolytic therapy within 3 hours from symptom onset when expected PPCI-related delay was longer than 1 hour, which is, however, the subset of patients supposed to benefit more than any other from expedite fibrinolysis.

Secondly, more than one third of the patients were enrolled in France, where the system of primary care for emergencies is based the *Système d'Aide Médicale d'Urgence* (SAMU) that has been one of the first to promote the use of pre-hospital fibrinolysis through mobile intensive care units with a physician on board and systematic urgent PCI. This extensive experience in terms of patient triage in the setting of prolonged

chest pain may not be directly applicable to other systems delivering pre-hospital fibrinolysis [7].

Third, in the selected population of STREAM trial, the overall rate of intracranial hemorrhage in the fibrinolysis group was five times that in the primary PCI group (1.0% vs. 0.2%; $p = 0.04$). Notably, before thrombolytic dosage amendment 3 of 37 patients (8.1%) 75 years of age or older had intracranial hemorrhage, while in the same age group there were no cases of intracranial hemorrhage (0 of 97 patients, 0%) and differences in intracranial hemorrhage were not significant after dosage amendment ($p = 0.45$). However, the rate of major non-intracranial bleeding was not statistically different between groups. Moreover, the net adverse cardiovascular events rate (composite of primary end-point, ischemic stroke, intracranial and major non intracranial bleeding), was also similar between groups both before (20.5% fibrinolysis versus 19.6% PPCI, RR 1.04; 95% CI 0.87–1.24; $p = 0.6$) and after thrombolytic dosage was reduced by amendment in elderly (19.9% fibrinolysis versus 19.6% PPCI, RR 1.01; 95% CI 0.84–1.22; $p = 0.8$). The evidence from STREAM trial seems thus to confirm the feasibility of a guidelines-supported pharmacoinvasive strategy when timely PPCI cannot be timely albeit at the price of a non statistically significant increase in bleeding and non statistically significant reduction in non-bleeding adverse events.

Fourth, in the PPCI arm of STREAM trial the median delay from symptom onset to arrival to catheterization laboratory was considerably short (i. e. 170 min), and the study was not designed to address the issue whether a pharmacoinvasive approach would be preferable to PPCI in the case of longer door-to-balloon delays. Based on the above mentioned statistically non significant trend of the STREAM trial favoring a pharmacoinvasive approach in terms of the ischemic end-point, further studies should address whether the pharmacoinvasive approach would be superior to PPCI in the substantial subset of patients whom in the community experience much longer PPCI-related delays. Nonetheless we need to be mindful of the caveats and such trials that are determined by specific time-related constraints are difficult to perform and may not see the light of the day. In this context STREAM does demonstrate the feasibility, efficacy and relative safety of the pharmacoinvasive strategy.

Fifth, the hypothetical impact of individual risk on preferred reperfusion strategy is a question that remains unanswered after STREAM trial. Actually, it has to be considered that patients enrolled in STREAM trial were at low risk with a 30-day mortality of 4.4%, for which risk an equivalent early mortality between PPCI of fibrinolysis has been observed by previous risk-benefit analyses [4]. On the contrary, a well-documented incremental survival benefit of PPCI over fibrinolysis has been observed in higher risk STEMI patients for PPCI related delay longer than 90 minutes [4, 18].

Sixth, 36.3% of patients in the thrombolysis arm required urgent coronary angiography. This observation a substantial rate of non-responders to fibrinolytic therapy strongly supports an approach of expedite transfer to a PCI-capable facility for every patient undergoing fibrinolysis after STEMI.

The latest ESC [19] and ACC/AHA guidelines [20] recommend an early routine coronary angiogram with a view to revascularization 3–24 h after successful thrombolysis with a level of recommendation I (Level of Evidence: A) and II (Level of Evidence: B) respectively. This quite demanding recommendation is now further supported also by the results of STREAM trial. The ongoing GRACIA-4 trial will provide further data comparing the clinical efficacy of primary PCI with immediate stent implantation and protective bivalirudin versus a combined strategy of immediate thrombolysis with tenecteplase, aspirin, clopidogrel, and enoxaparin followed by cardiac catheterization. Cardiac catheterization and PCI will be performed immediately if ST segment elevation has not resolved at 90 min or next morning if reperfusion is successful. While we await for additional data, the pivotal question relates to the application in a clinical setting the evidence currently available. The preferred approach remains that of timely PPCI in a PCI-capable center, but we also have a substantial body of evidence to support the pharmacoinvasive strategy as a valuable alternative in many regions of the world where limitations to timely PPCI due to geographical, weather-related and resource constraints persist despite the development of networks. However, it should be also emphasized that even within the confines of well-organized networks there remains considerable room for improvement [21, 22]. Accordingly, in Europe “The Stent for Life” Initiative is supporting implementation of local STEMI treatment guidelines, and helps identify specific barriers to implementation of guidelines and defines actions to make sure that majority of STEMI patients have access to the optimal reperfusion strategy i.e. PPCI. In regions with optimal STEMI networks, but with low density of PCI-capable hospitals, STREAM trial supports the guidelines-recommended option of a pharmacoinvasive approach for early presenters, with administration of thrombolytics followed by expedite interhospital transfer.

On the contrary, avoidance of thrombolysis and rapid transfer to a PCI facility remains advisable for patients presenting later [23].

References:

1. Tarantini G, Van de Werf F, Bilato C, Gersh B. Primary percutaneous coronary intervention for acute myocardial infarction: Is it worth the wait? The risk-time relationship and the need to quantify the impact of delay. *Am Heart J* 2011; 161: 247–53.
2. 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.
3. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation* 2003; 108: 1809–14.
4. Tarantini G, Razzolini R, Napodano M, et al. Acceptable reperfusion delay to prefer primary angioplasty over fibrin-specific thrombolytic therapy is affected (mainly) by the patient's mortality risk: 1 h does not fit all. *Eur Heart J* 2010; 31: 676–83.
5. Gersh BJ, Stone GW, White HD, Holmes DR J. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? *JAMA*. 2005; 293: 979–86.
6. Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *JAMA* 2000; 283: 2686–92.
7. Danchin N, Blanchard D, Steg PG, et al; USIC 2000 Investigators. Impact of prehospital thrombolysis for acute myocardial infarction on 1-year outcome: results from the French Nationwide USIC 2000 Registry. *Circulation* 2004; 110: 1909–15.
8. Kalla K, Christ G, Karnik R, et al; Vienna STEMI Registry Group. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). *Circulation* 2006; 113: 2398–405.
9. Dauerman HL, Sobel BE. Synergistic treatment of ST-segment elevation myocardial infarction with pharmacoinvasive recanalization. *J Am Coll Cardiol* 2003; 42: 646–51.
10. Fernández-Avilés F, Alonso JJ, Peña G, et al; GRACIA-2 (Grupo de Análisis de Cardiopatía Isquémica Aguda) Investigators. Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction

with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial. *Eur Heart J* 2007; 28: 949–60.

11. Le May MR, Wells GA, Labinaz M, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). *J Am Coll Cardiol* 2005; 46: 417–24.

12. Cantor WJ, Fitchett D, Borgundvaag B, for the TRANSFER-AMI Investigators et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009; 360: 2705–18.

13. Ting HH, Rihal CS, Gersh BJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI Protocol. *Circulation* 2007; 116: 729–36.

14. Fosbol EL, Granger CB, Jollis JG, et al. The impact of a statewide pre-hospital STEMI strategy to bypass hospitals without percutaneous coronary intervention capability on treatment times. *Circulation* 2013; 127: 604–12.

15. Nallamothu BK. A race for the base: ST-segment-elevation myocardial infarction sys-

tems of care in low- and middle-income countries. *Circ Cardiovasc Qual Outcomes* 2013; 6: 5–6.

16. Armstrong PW, WEST Steering Committee. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. *Eur Heart J* 2006; 27: 1530–8.

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

18. Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation* 2006; 114: 2019–25.

19. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, et al. D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-seg-

ment elevation. *Eur Heart J* 2012; 33: 2569–619.

20. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, 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. *J Am Coll Cardiol* 2013; 61: e78–140.

21. Wang TY, Nallamothu BK, Krumholz HM, et al. Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous

coronary intervention. *JAMA* 2011; 305: 2540–7.

22. Huber K, Goldstein P, Danchin N, et al. Enhancing the efficacy of delivering reperfusion therapy: A European and North American experience with ST-segment elevation myocardial infarction networks. *Am Heart J* 2013; 165: 123–32.

23. Jollis JG, Al-Khalidi HR, Monk L, et al; Regional Approach to Cardiovascular Emergencies (RACE) Investigators. Expansion of a regional ST-segment-elevation myocardial infarction system to an entire state. *Circulation* 2012; 126: 189–95.

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