Reperfusion Therapy for ST-Segment Elevation Myocardial Infarction Trials, Registries, and Guidelines

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Reperfusion therapy represents an important step forward in the management of patients with ST-segment elevation myocardial infarction (STEMI). Few medicinal treatments have been evaluated so well. In numerous randomized controlled trials, reperfusion therapy proved to reduce infarct size and improve early and long-term clinical outcome when compared with control treatment. The cornerstones of reperfusion therapy include both early complete recanalisation of the infarct-related artery and maintained patency over the long term.

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Nearly half a century ago, the first experience with reperfusion therapy for STEMI using fibrinolytic agents was reported, but most studies were small and had no strict electrocardiography criteria. In the late 1970s, the first randomized trial of intravenous streptokinase infusion in patients with acute (<12 hour) STEMI showed a large early mortality reduction of 50%, but this trial was too small to be conclusive. In the same time period, Rentrop performed the first percutaneous coronary recanalisation procedure in STEMI using a guide wire to dislodge occlusive coronary thrombus, which resulted in coronary reperfusion. The concept of an occluded coronary artery by atherothrombosis was convincingly proven by Dewood in 1980, where in most cases of STEMI an abrupt coronary closure was observed. In the 1980s, many randomized trials comparing intracoronary and later intravenous thrombolytic therapy with placebo/control showed an unequivocal benefit in early mortality with an acceptable bleeding risk. The reduction in mortality was based on the reduction of infarct size and proved to be maintained over a long-term follow-up.

In the early 1980s, a study of percutaneous coronary angioplasty of an occluded coronary artery in STEMI without the use of a thrombolytic was published for the first time. This approach has been compared to intravenous fibrinolysis (first streptokinase and later fibrin-specific lytics) and showed a reduction of infarct size and early mortality to the same extent as fibrinolysis without reperfusion therapy. The major advantages of an interventional approach to reperfusion are 2-fold: a more complete recanalisation and a lower risk of bleeding and reinfarction. Although none of these randomized trials resulted in a mortality benefit for angioplasty by itself, a meta-analysis of 23 randomized trials showed a convincing result of a 30% reduction of early mortality over fibrinolysis. Also, a long-term mortality benefit has been observed. Although primary coronary intervention is the preferred therapy for STEMI, it has severe logistical restraints: Treatment is delayed by transport, emergency department delay, and preparation of the catheterization laboratory. Furthermore, a skilled intervention team must be available 24 hours a day. Therefore, the guidelines emphasize a need to minimize the delay to implementation of an interventional approach with immediate fibrinolysis to 120 minutes and require an experienced angioplasty team to perform the procedure. In many parts of the world, including the West, these requirements are not met. In many percutaneous coronary intervention centers, the number of procedures is low. Time lost to treatment compared with fibrinolysis easily exceeds 40 minutes, the maximal time window in which a mortality benefit of percutaneous coronary intervention in anterior infarction patients younger than age 65 has been observed. The question arises whether the unequivocally favorable results of the trials on primary angioplasty against fibrinolysis with even relatively long transport times can be reproduced in the real world. Several registries showed positive results, but others gave negative answers to this question.

In today’s issue of Circulation an updated meta-analysis on the comparison of primary percutaneous intervention versus fibrinolysis for STEMI is published. This article contains a Bayesian meta-analysis of the large numbers of published randomized trials, as well as a Bayesian meta-analysis of reported observational studies. The randomized trials show a consistent mortality benefit in both the short and long term whereas in the meta-analysis of the observational studies, a benefit in the early term was seen but not in the long term. This publication is not only an update of the more recently published randomized trials of primary angioplasty versus fibrinolysis but also the first meta-analysis of observational rather than randomized studies on reperfusion therapy for STEMI for both the early and long-term outcomes. Mortality is used as an end point, and reinfarction and stroke are explored, but these items are clearly weaker end points, especially in observational studies of the long term. By
design, the trials and registries are open, which confounds the adjudication of both chest pain episodes and cerebral events. Yet reinfarction and stroke both result in considerable early and late mortality. The observational studies show heterogeneous late mortality results. Thus, they clearly cast doubt on the long-term benefit of primary angioplasty in the real world.

Randomized controlled trials have selection bias whereas registries have the inherent flaw due to confounding bias (Table 1). Both evaluations of medical procedures are of the utmost importance. However, clinical trialists despise observational studies because of the confounding factors but should admit that they represent the real world provided that all incident STEMI cases have been entered into the registries. For that purpose, only prospective registries are acceptable for therapy evaluation. In the current issue, only prospective studies of a variable, but some studies of considerable size, have been introduced in the meta-analysis.

Yet the consistent homogeneity of early and long-term mortality effects of primary percutaneous coronary intervention versus fibrinolysis in the randomized trials in the current study confirms the benefit of primary intervention in STEMI. This finding was also seen in the observational studies with regard to the early mortality benefit. However, the heterogeneity of late mortality observed in the meta-analysis of the registrations is also striking, especially where larger registries have been used: the Swedish Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (n = 26,205) and the 4-times larger American National Registry of Myocardial Infarction-3/4 registries (n = 102,086). The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions reported early outcomes that are different from the American registries. Unfortunately, long-term National Registry of Myocardial Infarction-3/4 data are not available. In the first release of the results on prehospital fibrinolysis in the Swedish registry, 1-year mortality was only 7.2% in 1690 patients14 whereas in a later publication this figure was 10.3% in 3087 patients, which is clearly inferior to primary coronary intervention.15 This odd finding underscores the potential shortcomings of observational data. But a sensitivity analysis of the current Bayesian meta-analysis shows that, even without the Swedish registry, the long-term benefit of angioplasty in the observation studies is statistically lacking. Is this finding a true effect or a chance finding?

Many trials and observational studies in the analysis were initiated in the 20th century whereas angioplasty and fibrinolytic strategies have dramatically changed in the early 21st century (Table 2). Rescue angioplasty and follow-up angiography after fibrinolysis are now recommended in the guidelines.10 Finally, clopidogrel is now part of STEMI protocols regardless of whether angioplasty, fibrinolysis, or no reperfusion has been applied. Moreover, the randomized trials have been performed by dedicated interventionalists in high-volume centers whereas in the registries all-comers with STEMI were brought into percutaneous coronary intervention centers with high or low volumes. Furthermore, the axiom of a short time to treatment in angioplasty has been widespread. The same National Registry of Myocardial Infarction-3/4 showed that time lost by angioplasty should be minimized for patients with large (anterior) infarctions whereas in the elderly with smaller infarcts the time delay is less stringent.12 In the future, the results of primary angioplasty may further improve with the use of anticoagulants with a predictable effect.16 However, the outcome of fibrinolysis may get better when triage for STEMI is up front in the ambulance rather than in the emergency room.17

Finally, long-term secondary prevention also has been considerably improved in general. Statins and angiotensin-converting enzyme inhibitors are now mandatory agents in most STEMI patients. In a large Medicare study, long-term mortality after myocardial infarction in the elderly was reduced over time by drug therapy rather than by increased use of angioplasty.18

For a long time, meta-analyses have been used to evaluate treatment effects of certain medical strategies in a broader perspective. However, meta-analyses suffer from potential publication bias and, therefore, may overestimate a treatment effect; they also often show considerable heterogeneity. Unfortunately, many guidelines appreciate meta-analyses as a level of evidence similar to that of individual randomized controlled trials (Table 1). Given the previous findings, this approach must be discouraged. At best, meta-analyses should be used to generate hypotheses rather than underscore the weight of a cluster of individual randomized trials. Even in the absence of properly randomized studies with enough power, meta-analyses should be removed from guidelines when it comes to weighing evidence level.

In conclusion, the Bayesian meta-analysis presented in this issue shows a clear early mortality benefit of primary angio-
plasty over fibrinolysis in STEMI. However, less convincing evidence exists that primary angioplasty in the real world is associated with a better long-term outcome. Factors involved remain largely unidentified, but secondary prevention may be more beneficial today. Regardless of how interesting meta-analyses may be, they are inferior to individual randomized controlled trials even with their inherent flaw of selection bias. Physicians should always be aware that current STEMI guidelines are primarily based on randomized trials rather than on hypotheses, registries, or meta-analyses.

Disclosures
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References

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