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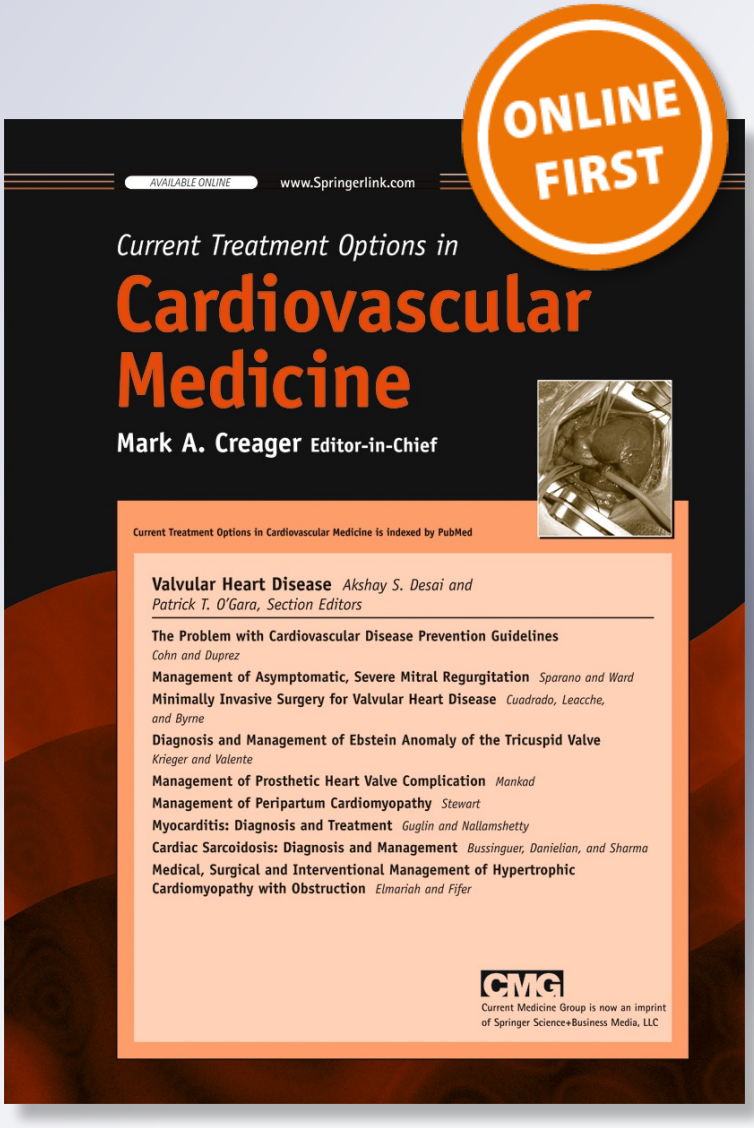
Current Treatment Options in Cardiovascular Medicine

ISSN 1092-8464

Curr Treat Options Cardio Med
DOI 10.1007/s11936-012-0218-1



Springer

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DOI 10.1007/s11936-012-0218-1

Coronary Artery Disease (PG Steg, Section Editor)

Is There Still a Role for Fibrinolysis in ST-Elevation Myocardial Infarction?

C. El Khoury, MD
F. Sibellas, MD
E. Bonnefoy, MD[*]

Address
*Intensive and Coronary Care Unit, Cardio-Vascular University Hospital, 59 Bd Pinel, Hospices Civils de Lyon, Lyon, 69008, France
Email: eric.bonnefoy-cudraz@univ-lyon1.fr

Keywords Acute myocardial infarction · Thrombolysis · Fibrinolysis · Networks · Guidelines · Streptokinase · Tenecteplase · Reteplase · Alteplase · Pharmaco-invasive angioplasty · Rescue angioplasty · Facilitated angioplasty · Reperfusion delays · STEMI

Opinion statement

Fibrinolysis had long been the reference treatment in patients with ST-Elevation Myocardial Infarction (STEMI). It was associated with a large reduction in mortality as compared with delayed or no reperfusion in patients managed early, within the first 2 hours from the onset of symptoms. Fibrinolysis also had well-known potential complications: cerebral haemorrhage, especially in patients beyond 75 years, and reinfarction. Primary percutaneous intervention (PCI) has overcome most of these limitations, but at a price: PCI-related delays that can reduce the expected benefit of primary PCI compared with fibrinolysis. That primary PCI is today the treatment of choice in patients with STEMI is no longer discussed. However, fibrinolysis should still maintain a role in the management of acute myocardial infarction (AMI) for three reasons. First, fibrinolysis is no longer a stand-alone treatment. Modern fibrinolytic strategies combine immediate fibrinolysis, loading dose of thienopyridines, and transfer to a PCI hospital for rescue or early PCI within 24 hours. These strategies capitalize on the hub-and-spoke networks that have, or should have, been built everywhere to implement primary PCI. The overall clinical results of these modern fibrinolytic strategies are now similar to those of primary PCI. Second, a substantial number of patients cannot be managed with primary PCI within the reasonable time thresholds set by the guidelines. In the case of long PCI-related delays, patients will benefit from fibrinolysis before or during transfer to a PCI hospital. Third, modern fibrinolytic strategies—immediate fibrinolysis followed by rescue or early PCI—may even offer the best results of all in a subset of patients. Patients of less than 75 years, managed within the first 2 hours and who cannot have immediate PCI, will fare better with a modern fibrinolytic strategy than with primary PCI. Guidelines advocate regional networks between hospitals with and without PCI capabilities, an efficient ambulance service and standardization of AMI management

Published online: 30 November 2012

through shared protocols. These regional logistics of care are essential to take full advantage of fibrinolysis strategies. In order to check that these strategies are correctly applied, networks need ongoing registries, as well as benchmarking and quality improvement initiatives.

Introduction

The aim of reperfusion therapy in acute myocardial infarction (AMI) is to reduce mortality and morbidity. It is best achieved when complete and sustained patency of the infarct-related coronary artery is obtained as early as possible.

Historically, fibrinolysis as the first reperfusion treatment had revolutionized the management of AMI. Later on, it was challenged and overcome by primary percutaneous intervention (P-PCI).

This evolution was hotly debated, and should be understood in the context of the diffusion of coronary angiography and percutaneous intervention (PCI) in developed countries. The development of P-PCI paralleled the evolution of coronary angiography and PCI as central strategy in the assessment and treatment of most coronary syndromes. This period was associated with a large increase in the number of interventional centres and interventional cardiologists. Implementing primary PCI was among the sound arguments to advocate the opening or extension of an intervention centre.

Things have evolved. The debate has been more constructive, thanks to a better understanding of the limitations of P-PCI and studies that assessed different modalities of combining PCI and fibrinolysis in ST-Elevation Myocardial Infarction (STEMI) patients who do not qualify for immediate P-PCI.

To better understand how there is still an important role for fibrinolysis in STEMI management, this article will address three stages: 1) evolution of fibrinolysis as a reference treatment; 2) how PCI solved the drawbacks of fibrinolysis and imposed itself as the reference treatment; and 3) why the best way to solve PCI-delay limitations is through implementing strategies that combine fibrinolysis and PCI in specific subsets of patients.

STAGE I: fibrinolysis as the reference treatment

Streptokinase and urokinase

- In the 1950s, streptokinase (SK) started to be used in humans to treat vascular thrombosis. From the time it was first evaluated, fibrinolysis was shown to be effective, but with limitations including: reocclusion and bleeding.
- SK is antigenic and can cause formation of antibodies. Fever and hypotension were directly related to the dose. Urokinase (UK) was developed a few years later. A high molecular weight form is isolated from urine and another low molecular weight form is obtained from cell cultures. Unlike SK, UK has no antigenic properties. As SK, it activates plasma plasminogen, as well as the plasminogen that is embedded in thrombus. It leads to systemic degradation of fibrinogen and some coagulation factors. Other forms of UK were developed through recombinant technology, using Escherichia coli and murine hybridoma cell line in the late 1970s. The best known is prourokinase, a urokinase precursor that is inert in plasma and is activated in the thrombus, where it activates fibrin-bound plasminogen. It is therefore much more fibrin-specific than SK and UK [1].

- These early fibrinolytic agents had their dose defined during the 1980s. They were tested in the settings of coronary, cerebral, and peripheral vascular occlusion. During this period, several trials assessed adjuvant antithrombotic and antiplatelet treatments and their optimal dosing [2, 3].

Recombinant tissue plasminogen activator and reteplase

- Tissue plasminogen activator (tPA) is a natural fibrinolytic agent produced by the endothelial cells. It is a fibrin-specific agent that binds strongly to fibrin in the thrombus. It facilitates the conversion of plasminogen to plasmin within the clot.
- A recombinant form of tPA, rtPA, was quickly becoming the reference fibrinolytic agent in STEMI. In the GUSTO-I study published in 1994, ~41,000 patients were randomized to compare SK and rtPA in conjunction with intravenous or sub-cutaneous heparin in AMI [4]. rtPA was associated with a higher coronary patency rate and lower mortality, but a slightly higher rate of intracranial haemorrhage.
- The study also established the heparin regimen associated with rtPA. Therefore, all subsequent fibrinolytic agents had to be compared with rtPA.

Bioengeneering of tPA

- tPA was bioengineered to enforce its fibrin affinity, resistance to plasminogen inactivator and to increase its half-life through reduction of its hepatic clearance. Resulting molecules were reteplase, TNK-tPA and lanoteplase. TNK-tPA was compared to rtPA in the ASSENT-2 trial, an equivalence study [5]. A weight-adjusted single bolus of tPA performed as well as the 90 min rtPA infusion. Like SK or UK, reteplase also had a lower fibrin-binding activity than rtPA, a characteristic that was supposed to decrease the risk of distant clot lysis and haemorrhage. Reteplase was compared to rtPA in the GUSTO III trial, a superiority study [6]. Mortality and disabling stroke were similar with rtPA and reteplase. Lanoteplase was compared to rtPA in the InTIME-II trial [7]. Due to doubled incidence of haemorrhagic stroke (from 0.6 % to 1.1 %), its further development was limited.

Benefits and drawbacks of fibrinolysis

Mortality reduction

- Fibrinolysis in AMI is associated with an important reduction in mortality. Pooling nine trials including 45,000 patients with ST segment elevation, the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group found that fibrinolysis was associated with 3 % absolute mortality reduction (AMR) in patients treated within 6 hours [8].
- They also found that this mortality reduction was higher in patients with high risk features: anterior AMI (AMR 3.7 %), left bundle

branche block on the electrocardiogram (ECG) (AMR 4.9 %), PA< 100 mmHg (AMR 6.2 %).

- They have shown that this mortality reduction was greater when fibrinolytic treatment was administered earlier. Boersma et al. further explored this in a landmark meta-analysis [9]. They found that the relationship between mortality and the time elapsing between the onset of symptoms and fibrinolysis is non-linear. Short treatment delays amplify the survival benefit of fibrinolysis. An exponential mortality reduction was noted when fibrinolytic therapy was initiated within 3 hours of the onset of chest pain. The proportional mortality reduction was 44 % in patients treated within 2 hours, and 20 % in those treated later. It popularized the concept of the "golden hour," that is, the first hour from the onset of symptom where the absolute mortality reduction is 6.5 %.
- To shorten delays in administration of fibrinolysis, prehospital fibrinolysis had been implemented in several countries. Studies that compared prehospital fibrinolysis to inhospital fibrinolysis consistently found that prehospital fibrinolysis was associated with an important reduction of treatment delay and a trend toward reduction in mortality. The European Myocardial Infarction Project Group randomized 2,750 patients to prehospital or inhospital fibrinolysis [10]. The prehospital group received fibrinolysis on average 55 min earlier than those in the hospital. There was a nonsignificant reduction in overall mortality at 30 days in the prehospital group (9.7 % vs. 11.1 %; P=0.08) and a significant cardiovascular mortality reduction (8.3 % vs. 9.8 %; P=0.049). A meta-analysis, indicated that prehospital fibrinolysis was associated with a reduction of 45 min in treatment delay, plus a 2 % absolute and 17 % relative reduction in mortality [11].
- Paramedics may administer fibrinolysis in the ambulance. Ambulance-based prehospital fibrinolysis, with or without ECG transmission, was found to be feasible and safe [12]. Ambulance-based fibrinolysis, had been successfully implemented in Sweden, England, Wales, Canada and some centres in the US [13].
- At best, fibrinolysis results in an aborted infarction. Aborted infarction refers to patients who are known to avoid myocardial necrosis with prompt reperfusion. It is often defined as maximal CK$\leq$2 upper limit of normal, combined with typical evolutionary ECG changes. It differs from masquerading myocardial infarction, where there is neither a rise in enzyme levels nor the evolutionary ECG changes. The frequency of aborted AMI was 13 % in the ASSENT 3 study [14]. There was a strong relationship between frequency of aborted AMI and time from the onset of symptom to treatment: 25 % within the 1st hour, 17 % in 1–2 hours, with a clear drop-off after 3 hours. Around half of aborted AMI also had a<70 % reduction in ST seg-

ment elevation at 60 min after fibrinolysis. Mortality in these patients was 1 % at 1 month.

Reperfusion

- Achievement of early, complete reperfusion is an important mechanism for improved survival with fibrinolytic therapy. Full patency (TIMI 3 flow) is obtained in ∼50–60 % of patients treated with fibrin-specific fibrinolytic agents.
- There is a direct relationship between survival and TIMI 3 flow 90 min after start of fibrinolysis [14]. As compared to TIMI 0–2 flow, early TIMI 3 flow was associated with halved mortality at 1 month with an additional 5 % reduction in mortality from 30 days to 2 years [15].

Haemorrhage and stroke

- A rare but much feared complication of fibrinolysis is an intracranial haemorrhage (ICH). The risk of primary ICH is ∼0.6–0.8 % with fibrin-specific fibrinolytics. The FTT estimated that fibrinolytic therapy was associated with about four extra strokes per 1,000 during days 0–1 [8]. Of these, two were associated with an early death and were already accounted for in the overall mortality reduction, one was moderately or severely disabling, and one was not. tPA and bolus treatments are associated with an increased risk in ICH [16, 17]. The strongest independent risk factor for ICH is old age. Most ICH occurred beyond 75 years in the GUSTO study and in analysis of the NRMI2 registry [18, 19]. In patients <65 years, the risk of ICH is extremely low [20].

Reinfarction

- Reinfarction is another important drawback of fibrinolysis. It is relatively uncommon, occurring in 5–6 % of patients, half of them within 4 days after fibrinolysis and 25 % within the first 2 days [21]. Reinfarction increases mortality two-fold in patients who benefited from revascularisation with PCI, to five-fold in those treated conservatively. Reinfarction was not related to the fibrinolysis, but rather to advanced age, a shorter time to fibrinolysis, anterior AMI, or lower arterial pressure.

Adjuvant therapy

- Efforts to improve patency and reduce reinfarction rate with adjuvant treatment have often been hampered by an increased rate of age-dependant haemorrhage.
- In GUSTO V, combined reteplase and abciximab led to fewer deaths or non-fatal reinfarctions but more non-intracranial bleeding complications [22]. Similarly, in ASSENT-3, the combination of tenecteplase and abciximab was associated with significantly fewer efficacy

endpoints (30 day mortality, inhospital reinfarction, or inhospital refractory ischemia), but a higher rate of haemorrhage, especially in patients over 75 years [23].

- Success came with the carefully designed CLARITY trial [24]. It included patients up to 75 years of age with STEMI who were treated with fibrinolysis and randomised to clopidogrel or placebo. All patients underwent angiography between days 2 and 8. With Clopidogrel, there was a significant 36 % increase in TIMI 3 flow rate and a trend toward reduction in reinfarction rate before angiography, from 3.6 % to 2.5 % (P=0.08).

STAGE II: primary PCI to overcome the limitations of fibrinolysis

Primary PCI addresses most of the limitations of fibrinolysis

- Primary PCI (P-PCI) overcomes the main limitations of fibrinolysis: TIMI 3 flow, reinfarction, and haemorrhagic stroke. This was clearly demonstrated in the early studies comparing P-PCI to fibrinolysis, followed by conservative care. In the GUSTO IIb trial, P-PCI was associated with 33 % reduction in reinfarction and 80 % reduction in disabling stroke. TIMI 3 flow was achieved in 73 % of patients in the P-PCI group [25].
- In DANAMI-2, patients admitted in the community hospitals were randomized to transfer for P-PCI or fibrinolysis in the index hospital with no subsequent PCI [26]. The results were similar to those of GUSTO IIb. There was a 40 % reduction of the composite primary outcome in the P-PCI group. The better outcome after angioplasty was driven primarily by a reduction in the rate of reinfarction (1.6 % in the P-PCI vs. 6.3 % in the inhospital fibrinolysis group; P<0.001). There was also a nonsignificant reduction in stroke (1.1 % vs. 2.0 %; P=0.15), and a trend toward reduction in the rate of death (6.6 % vs. 7.8 %, P=0.35).
- Similar results were observed in the PRAGUE-2 study that also investigated the benefits of transfer for P-PCI versus fibrinolysis and conservative management in the index hospital [27]. There was a trend toward reduction in mortality in the P-PCI arm. However, this benefit was confined to the patients randomized more than 3 hours after the onset of symptoms. For others (< 3 hours), mortality was identical to fibrinolysis.
- Combining the results of all the trials that compared thrombolysis and primary PCI, Keeley, in 2003, found that latter was associated with significant reduction of short-term death (5 % vs. 7 %), nonfatal reinfarction (3 % vs. 7 %), and stroke (1 % vs. 2 %) [28].
- P-PCI may still improve its results with stenting, gpIIb/IIIa antagonists, and thrombo-aspiration. Primary stenting has reduced by almost half the rate of reinfarction at 30 days, at the cost of a nonsignificant 30 % increase in bleeding complications [29]. A similar observation is seen with glycoprotein IIb/IIIa (gpIIb/IIIa)

inhibitors, especially abciximab in combination with PCI [30, 31]. Thrombo-aspiration reduces the risk of cardiac death and reinfarction [32]. Moreover, radial access reduces the risk of bleeding in AMI [33•] and is now a class IIa recommendation [34••].

- P-PCI has been a success, and is the reference reperfusion treatment in patients presenting with an evolving myocardial infarction [35]. However, it is also obvious that these technical improvements in P-PCI will also benefit strategies that combine fibrinolysis and PCI.

The benefit of P-PCI over fibrinolysis is dependent on patient risk and delay to balloon inflation

- In the DANAMI-2 study, at 3 years of follow-up, the benefit of P-PCI over conservative fibrinolysis was restricted to those at high risk (25.3 % for PCI vs. 32.6 % for fibrinolysis; P=0.02), whereas a trend towards higher mortality was seen in the majority of patients at low risk (8 % for PCI vs. 5.6 % for fibrinolysis; P=0.11) [36]. In the community, at least 75 % of patients are not high-risk patients [37].
- Like fibrinolysis, efficacy of P-PCI, and especially myocardial salvage, is dependent on the time to reperfusion from the onset of symptoms [38].
- Working with median time to reperfusion (door to needle and door to balloon) in 645 hospitals participating in the NRMI registry, and data of almost 200,000 patients, Pinto found that mortality advantage of P-PCI over inhospital fibrinolysis declines as the delay between fibrinolysis infusion and balloon inflation increases [39]. Every 30 min increase in this delay was associated with a 10 % increase in the relative risk of inhospital death. P-PCI related delay of 114 min was associated with adjusted odds of death identical to that of immediate fibrinolysis. The survival advantage of P-PCI was lost sooner among younger patients, those who presented earlier or had an anterior AMI. Even for a PCI delay as short as 40 min, the benefit of immediate fibrinolysis over P-PCI was possible in patients younger than 65 years of age, with an anterior infarction and a prehospital delay of less than 2 hours. On the other hand, longer P-PCI–related delays were acceptable among patients who presented late or were older. Different methods were used to assess this relationship, and similar results were given [40].

Even with improved system of care, there will still remain substantial PCI-related delays in many patients

- Most guidelines, American and European, support 90–120 min "first medical contact to balloon" time threshold for P-PCI. The recent European guidelines set the following first medical contact treatment thresholds: "for fibrinolysis ≤30 min; for primary PCI≤90 min (≤ 60 min if the patient presents within 120 min of symptom onset or directly to a PCI-capable hospital)" [34••].

- Observational registries teach us that guideline-recommended thresholds are rarely achieved in the environments that have not been primed to focus on reducing delays. Total "first medical contact to balloon" time for transfer of patients undergoing P-PCI in the United States was on average 180 min, with only 4.2 % of patients being within 90 min [41].
- Reworking the system of care improves results. However, even with an upgraded management and efficient networks, many patients suffer long delays. In the French MICU services, in 2005, still half of the patients had P-PCI more than 100 min after first medical contact [42]. In the Vienna network, the mean time from the first medical contact to balloon was 81±51 min [43]. Implementation of a statewide system in North Carolina allowed a substantial reduction in time and an increase in the number of patients treated within the benchmark [44]. However, 28 % of patients managed in the PCI hospital still had door-to-balloon time of more than 90 min. In patients presenting to a non-PCI hospital, the door-in to door-out time was still a median of 71 min. Adding the door-to-balloon delay will push many of those patients over the recommended threshold. There has been continuous improvement over time, but median door-to-balloon time in non-PCI hospitals was still between 103 min for the nearest hospital and 138 min for the furthest [45].
- That is why the recent European guidelines on the management of AMI put such emphasis on the logistics of prehospital care, with no less than six class I recommendations [34••]. The main points are: "The pre-hospital management of STEMI patients must be based on the regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary PCI available to as many patients as possible. All EMSs, emergency departments, and coronary care units must have a written and updated STEMI management protocol, preferably shared within the geographical networks. Ambulance teams must be trained and equipped to identify STEMI (with use of ECG recorders and telemetry as necessary) and administer initial therapy, including thrombolysis where applicable."

STAGE III: modern fibrinolytic strategies

- Implementation of an efficient network with management protocols clearly benefits fibrinolytic strategies too. In the RACE network, the proportion of patients with door-to-needle time of less than 30 min increased from 35 % to 52 % [44, 45]. In the Vienna network, this delay was a mean of 17±13 min, and ~20 min in the prehospital MICU French system [43].
- Moreover, it opens numerous opportunities in combining fibrinolysis and PCI. Combining fibrinolysis and PCI is an idea as old as fibrinolysis itself [46]. Early results were disappointing because of the

limitations of PCI before stents, thienopiridine, and gpIIb/IIIa antagonists [47].

- In the 2000s, studies brought a much clearer picture of how the combination of PCI and fibrinolysis may improve patient's outcome.

Rescue PCI

- Rescue PCI is the most obvious form of fibrinolysis–PCI combination. Historically, small trials that looked at the benefit of PCI in patients with clinically failed reperfusion after fibrinolysis found no clear benefit of this invasive strategy [48]. With the RESCUE and the MERLIN trials, there was a reduction of revascularisation, but no significant difference in reinfarction [49, 50].
- In the much recent REACT trial, with liberal use of stents and gpIIb/IIIa antagonists, there was a 50 % reduction of cardiovascular events at 6 months and 12 months, and more than a 50 % reduction in mortality at 4 years [51•].
- In most contemporary fibrinolytic studies, rescue PCI is performed in 25–35 % of patients [52–54].

Facilitated PCI

- Facilitated PCI is a systematic PCI that is performed as soon as possible after fibrinolysis. Studies on facilitated PCI led to disappointing results. The ASSENT 4 PCI study compared tenecteplase followed by immediate or as soon as possible PCI with P-PCI [55]. Patients in the facilitated arm were not preloaded with clopidogrel; gpIIb/IIIa antagonists were prohibited, except in bailout situations; and no heparin was administered after the bolus of tenecteplase. As compared with P-PCI, the facilitated strategy was associated with higher rate of reinfarction, repeat target vessel revascularisation, and stroke. There was also a trend toward higher mortality in this group. Similar results were observed in the small LEIPZIG study that showed trends toward higher infarct size and higher event rates with facilitated PCI [56].
- These results were unfortunate, but in accordance with studies on facilitated PCI performed in the early period of fibrinolysis [47]. In the first 2 hours following fibrinolysis, it has been shown that platelet aggregation, procoagulant state and residual thrombus burden were higher [57–59]. Therefore, PCI in these settings is much more challenging.
- The FINESS study seemed the best designed to face this challenge [60]. It randomized patients to P-PCI and in-lab abciximab or PCI with upfront abciximab or PCI with upfront half dose reteplase and full dose abciximab. There were no differences between the three groups for the primary end-points (death, congestive, heart failure, cardiogenic shock, ventricular fibrillation beyond 48 hours) or any of its components. There was a higher rate of non-intracranial haemorrhage in the facilitated strategy.

- Immediate PCI following fibrinolysis is clearly discouraged. With rescue PCI, patients treated with fibrinolysis need to be transferred to a PCI capable hospital as soon as possible to limit delays, in case of failed fibrinolysis [61].

Early PCI

- The best strategy following successful fibrinolysis had been a matter of debate for many years, especially for patients managed in the non-PCI hospitals. This debate had been settled through the results of several European and Canadian studies that recruited patients in non-PCI hospitals and assessed the benefit of their transfer to a PCI capable hospital for early angiography and possibly PCI.
- Of note, in many of these studies, the early PCI group was scheduled to undergo a strategy similar to facilitated PCI. However, due to a relatively long transfer time from the non-PCI hospital to the PCI center, delays between administration of fibrinolysis and PCI were well beyond the first 2 hours post-fibrinolysis. Moreover, the two largest and most recent studies, CARESS-in-AMI and TRANSFER-AMI [62, 63•], either administered gpIIb/IIIa with fibrinolysis (CARESS-in-AMI) or preloaded most patients with clopidogrel (TRANSFER-AMI). This strategy, early—not immediate—PCI after fibrinolysis had been labelled "pharmaco-invasive".
- In CARESS-in-AMI [62], 600 high-risk patients aged 75 years or younger in non-PCI hospitals were treated with half-dose reteplase, abciximab, heparin, and aspirin, and were randomly assigned to either an immediate transfer to the nearest interventional centre for PCI, or to management in the local hospital with a transfer only if rescue PCI was needed. Rescue PCI was done in 30.3 % in the local arm of the study. The transfer strategy reduced the combined end-point of death, reinfarction, or recurrent ischemia from 10.7 % to 4.4 %. TIMI 3 flow was observed before PCI in 61 % of these patients. There was no increase in major or minor haemorrhages.
- TRANSFER-AMI [63•] recruited 1,059 high-risk patients who were receiving aspirin, tenecteplase, heparin, or enoxaparin at non-PCI hospitals. They were randomized to either standard treatment (including rescue PCI if required, or delayed angiography), or a strategy of immediate transfer to another hospital and PCI within 6 hours after fibrinolysis. In the standard management group, 88.7 % underwent cardiac catheterization a median 2.4 days after tenecteplase, and in 34.9 %, urgent catheterization within 12 hours. In the transfer group, the median time from tenecteplase to balloon was 3.9 hours. Baseline TIMI 3 flow was present in 52 % of the patients. The gpIIb/IIIa antagonists were administered in 83 % of the patients. There was 36 % reduction in the primary end-points of death, reinfarction, or recurrent ischemia. Most PCI patents in both groups had stents.
- Several meta-analysis have been performed pooling pharmaco-invasive studies from 2000 to 2009 [52, 64, 65]. They concluded that

there was some evidence for reduction in the risk of total mortality in patients undergoing immediate or early PCI within 24 hours of fibrinolysis. The strategy appeared safe, with no increased risk of major haemorrhage and was associated with reduced recurrence of ischemia and reinfarction.

Fibrinolysis to improve reperfusion strategies based on primary PCI

- One may wonder why we still need fibrinolysis if an improved fibrinolytic strategy relies so much on PCI.
- Firstly, because as discussed above, there is still a substantial number of patients who have long delays to P-PCI. There is strong evidence that a strategy of rapid delivery of fibrinolysis, coupled with rescue or routine early coronary angiography within 24 hours of initial treatment, may bring similar results as P-PCI [42, 54, 66].
- Secondly, data does exist showing the benefit of the combined fibrinolysis-PCI strategies over P-PCI in patients, who are managed very early after the onset of symptoms. In these patients, fibrinolysis followed by the rescue or an early PCI may even deliver the best result of all.
- The CAPTIM study was a multicentre trial of 840 patients managed in the pre-hospital settings by the mobile intensive-care units [53, 67•]. Patients were randomized to pre-hospital fibrinolysis (PH-fibrinolysis) with alteplase or P-PCI. All patients were transferred immediately and directly from the pre-hospital settings to a centre with round-the-clock access to emergency angioplasty. With the PH-strategy, half of the patients received fibrinolysis within the first 2 hours of the onset of symptoms, 26 % had rescue angioplasty, and 85.4 % underwent angiography during the index hospitalization and 70.4 % angioplasty. The rate of the primary endpoint (death, reinfarction, stroke) was 8.2 % and 6.2 % in the PH-fibrinolysis and P-PCI strategies, respectively (P=0.29). Mortality was 3.8 % amongst the patients assigned to PH-fibrinolysis and 4.8 % in those assigned to P-PCI (p=0.61). This difference was exclusively related to a very low mortality in patients managed within 2 hours of the onset of symptom in the PH-fibrinolysis strategy. After follow-up of 5 years, patients included within 2 h in the PH-fibrinolysis strategy had 5.8 % mortality, while the P-PCI group had 11.1 % (P=0.04). Rates were 14.5 % and 14.4 %, respectively, in patients included after 2 h (P= 0.92) [68•].
- Similar results were observed in real life in France, where for historical reasons, the hub-and-spoke care system based on the mobile intensive care units (MICU) and reference hospitals had been implemented long ago. Assessment of prehospital fibrinolysis by the MICU services had been done repeatedly in nationwide registries [69•]. In USIC-2000, inhospital mortality was 3.3 % for PH-fibrinolysis, 8.0 % for inhospital lysis, 6.7 % for the primary percutaneous interventions and one-year survivals were respectively 94 %,

89 % and 89 % [70]. The apparent benefit of PH-fibrinolysis was driven by the very low mortality observed in patients treated within the first 3 hours from the onset of symptoms.

- By setting up similar organization, it is possible in a relatively short period to obtain comparable results [71]. The Vienna STEMI registry group organized a network that consisted of the Viennese Ambulance Systems and five PCI hospitals [43]. Diagnosis and triage of patients with acute STEMI was done in the ambulance. An algorithm was set to use the fastest reperfusion strategy; P-PCI or fibrinolysis in STEMI managed within 2–3 hours from the onset of symptoms. The fibrinolytic strategy was done in 26 % of patients, half of them within the 2 first hours from the onset of symptoms. PCI was performed during the index hospitalization in 91 % of patients who had fibrinolysis with ~50 % proceeding to immediate angioplasty. The lowest inhospital mortality (5.1 %) was observed in the subgroup of patients who received fibrinolysis within 2 hours from the onset of symptoms.
- The Mayo Clinic STEMI Protocol Regional systems of care organized transfer of patients presenting initially in a regional hospital to the PCI hospital. If the onset of symptoms was <3 hours, they received the full-dose fibrinolytic therapy before transfer. Mortality rates at intermediate follow-up was 6.9 % in these patients, while it was 10.5 % for P-PCI in the PCI hospital and 8.8 % in patients transferred for P-PCI [72].
- More information on the modern fibrinolytic strategy will be made available when results of The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study become available in 2013 [73]. The study randomized acute STEMI patients presenting early after symptom onset in who PCI is not feasible within 60 min of first medical contact. Patients are randomized to fibrinolysis combined with enoxaparin, clopidogrel, and aspirin, and cardiac catheterization within 6 to 24 hours or rescue coronary intervention if reperfusion fails within 90 min of fibrinolysis versus PCI performed according to local guidelines.

The main barrier to modern fibrinolytic strategies: on-field organisation

- Modern fibrinolytic strategies are far from the historical image of a stand-alone treatment in a far away hospital. They are sophisticated strategies that capitalize on the hub-and-spoke networks that have or should have been built everywhere to implement primary PCI.
- At the same time, implementing a fibrinolytic strategy along with primary PCI at the scale of a network is much more complex than focusing only on having PCI correctly done.
- If algorithms have to include strict time components, they also have to incorporate quite different adjuvant pharmacological treatments.
- For primary PCI, standard protocols include bivalirudin, aspirin, prasugrel or ticagrelor, and unfractionated heparin. Enoxaparin and

clopidogrel are second-line treatment if the former are unavailable. Fondaparinux is not recommended.

- For fibrinolysis, enoxaparin (or fondaparinux if streptokinase is used) and clopidogrel are recommended. Different doses of clopidogrel and enoxaparin have to be used, depending on the patient age or the presence of a renal dysfunction. Dosages of enoxaparin, unfractionated heparin, and clopidogrel are also different in primary PCI and fibrinolysis. Ticagrelor and prasugrel have not been studied in fibrinolysis strategies, and are not endorsed at the time of fibrinolysis even if a switch from clopidogrel to prasugrel or ticagrelor might be possible after early or rescue angioplasty.
- Bivalirudin has been compared with unfractionated heparin in the HERO-2 trial [74]. There was a trend toward more major bleedings and intracerebral bleeding in the bivalirudin group than in the heparin group.
- As a consequence, a network that will implement a dual strategy of pre-hospital fibrinolysis with transfer to a PCI capable hospital and primary PCI will have to equip ambulances with bivalirudin, enoxaparin, unfractionated heparin, prasugrel or ticagrelor, clopidogrel, tenecteplase and aspirin. It also has to build protocols with three regimens of enoxaparin and clopidogrel, and two regimens of unfractionated heparin.
- It is relatively easy to draw protocols that include most of these requirements. However, their application in the field is complex, especially in pre-hospital settings. Therefore, it does not come as a surprise that a striking decline in fibrinolysis use is observed [69•, 75•].
- Physicians could be comforted by the fact that mortality had consistently declined over the last 10 years with the increased number of patients treated with primary PCI. This viewpoint can be misleading, and should be discussed, because a substantial part in this fall in mortality comes from an overall improvement in AMI management. Analysis of the French registries from 1995 to 2010 gives a good insight into this trend [69•]. From 1995 to 2010, 30-day mortality fell from 13.7 % to 4.4 %. During the same period, primary PCI rate increased from 11.9 % to 60.8 % and fibrinolysis fell from 37.5 % to 13.9 %, whereas the overall rate of hospital PCI increased from 61.4 % to 86.7 %. A more detailed examination of these results gives a more complex figure: mortality decreased from 8.2 % to 2.1 % with fibrinolysis, from 8.7 % to 3.2 % with primary PCI, but also from 18.9 % to 8.7 % without any reperfusion. During the years 1995–2010, there was a major increase in the prescription of ACE inhibitors (from 47.7 % to 64.8 %), beta-blockers (65.2 % to 80.7 %) and statins (from 9.8 % to 89.9 %). A similar trend in mortality, reperfusion therapy and secondary-prevention drugs rates was observed in the MINAP project that has overseen the development of primary PCI in England and Wales over the last 10 years [75•].

- With such interlinked trends, it will be impossible for networks, even those with the best registries, to assess the benefit or the drawback of reducing the rate of modern fibrinolysis strategies.
- However, numerous studies have proved that outcomes are worst in patients who are not treated according to the guidelines [76, 77].
- The three stages outlined in this review are the historical trends of reperfusion treatment in AMI. They are also the paths that most systems have followed to achieve the aim of performing PCI in all patients who need it. Currently, most systems of care in Europe and America have moved relatively easily from stage 1 to stage 2 putting fibrinolysis aside. Moving to stage 3 requires strong organisational capabilities, but is essential to be able to bring the utmost benefit associated with primary PCI in most patients and with fibrinolysis and transfer in the selected subset of patients managed very early or those who have too long transfer or PCI related delays. Guidelines advocate regional networks between hospitals with and without PCI capabilities, an efficient ambulance service, and standardization of AMI management through shared protocols. These regional logistics of care are essential to take full advantage of modern fibrinolysis strategies. To check that these strategies are correctly applied, networks need ongoing registries as well as benchmarking and quality improvement initiatives.

Treatment

Pharmacologic treatment

Doses and contraindication are quoted from the recent (2012) European guidelines for the management of AMI in patients presenting with ST-segment elevation [34••].
All these drugs have common contra-indications:

o Absolute

Previous intracranial haemorrhage or stroke of unknown origin at any time
Ischaemic stroke in the preceding 6 months
Central nervous system damage or neoplasms or atrioventricular malformation
Recent major trauma/surgery/head injury (within the preceding 3 weeks)
Gastrointestinal bleeding within the past month
Known bleeding disorder (excluding menses)
Aortic dissection
Non-compressible punctures in the past 24 h (e.g. liver biopsy, lumbar puncture)

o Relative
Transient ischaemic attack in the preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week postpartum
Refractory hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Prolonged or traumatic resuscitation

Alteplase

Standard dosage	10-mg, 50-mg and 100-mg vials, reconstituted with sterile water to 1 mg/mL 15-mg IV bolus followed by 0.75 mg/kg (up to 50 mg) IV over 30 min and then 0.5 mg/kg (up to 35 mg) IV over 60 min. The maximum total dose is 100 mg for patients weighing more than 67 kg.
Cost/cost-effectiveness	Expensive

Reteplase

Standard dosage	Reconstitute two 10-units vials with sterile water (10 mL) to 1 U/mL. Adult dose of reteplase : Two IV boluses of 10 units each. Normal saline (NS) flush is administered before and after each bolus. • The first 10 units IV bolus is given over 2 min; • The second 10 units IV bolus is given 30 min later over 2 min.
Special points	There is no weight adjustment.
Cost/cost-effectiveness	Expensive

Tenecteplase

Standard dosage	Reconstitute tenecteplase 50-mg vial in 10 mL sterile water (5 mg/mL). Tenecteplase is administered in a 30–50 mg IV bolus over 5 seconds. Adult dose is calculated on the basis of the patient's weight : • <60 kg: 30 mg (6 mL) • 60–69 kg: 35 mg (7 mL) • 70–79 kg: 40 mg (8 mL) • 80–89 kg: 45 mg (9 mL) • ≥90 kg: 50 mg (10 mL)
Cost/cost-effectiveness	Expensive.

Streptokinase

Standard dosage	The adult dose of streptokinase for AMI is 1.5 million units in 50 mL of 5 % dextrose in water (D5W), given IV over 60 min.

Contraindications	Prior SK or anistreplase
Main side effects	Fever and hypotension are common allergic reactions. They often force the termination of infusion before a therapeutic dose can be administered.
Cost/cost-effectiveness	Inexpensive

Other treatments

Aspirin with fibrinolysis

Standard procedure	Aspirin Starting dose 150–500 mg orally or i.v. dose of 250 mg if oral ingestion is not possible.

Clopidogrel with fibrinolysis

Standard procedure	Clopidogrel Loading dose of 300 mg orally if aged ≤75 years, followed by a maintenance dose of 75 mg/day.

Unfractionated heparin with fibrinolysis

Standard procedure	60 U/kg i.v. bolus with a maximum of 4000 U followed by an i.v. infusion of 12 U/kg with a maximum of 1000 U/h for 24–48 h. Target aPTT: 50–70 s, or 1.5 to 2.0 times that of control, to be monitored at 3 h, 6 h, 12 h and 24 h.

Enoxaparin with fibrinolysis

Standard procedure	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 h until hospital discharge for a maximum of 8 days. The first two doses should not exceed 100 mg. In patients >75 years of age: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg for the first two s.c. doses. In patients with creatinine clearance of <30 mL/min, regardless of age, the s.c. doses are given once every 24 h.

Fondaparinux with streptokinase

Standard procedure	2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily, up to 8 days or hospital discharge.

Acknowledgements

The authors are grateful to Dr Mikhail Altman for his help in editing the manuscript.

Disclosures

C. El Khoury: none; F. Sibellas: none; E. Bonnefoy: Payment for development of education presentations and has had travel/accommodation expenses covered by Boehringer Ingelheim

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