Fibrinolytic treatment of ST-elevation myocardial infarction

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Summary

Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion therapy in ST-elevation myocardial infarction (STEMI), as long as it can be delivered within 90–120 minutes from patient’s first medical contact, and is the leading reperfusion strategy in most European countries. However, as PPCI cannot be offered in a timely manner to all patients, fibrinolytic therapy (FT) is the recommended choice in patients with an anticipated delay to PPCI of >90–120 minutes, presenting early after symptom onset and without contra-indications. FT should preferably be started in the pre-hospital setting. Following FT, all patients should be transferred to a PCI-center for rescue PCI or routine coronary angiography with PCI as indicated. Such a pharmaco-invasive strategy, combining FT with invasive treatment, has recently been shown to be non-inferior to PPCI in patients living in areas with long transfer delays to PCI (>60 minutes).

In this overview, we will briefly present the evidence for the benefit of FT in STEMI, and discuss the role of FT in the current era of PPCI as well as the optimal treatment following pharmacologic reperfusion.

Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion therapy in ST-elevation myocardial infarction (STEMI), as long as it can be delivered by an experienced team within 90–120 min from patient’s first medical contact (1–3). The percentage of STEMI-patients treated with PPCI is steadily increasing, and PPCI is the leading reperfusion strategy in Europe (4). In this era of PPCI, one might wonder whether fibrinolytic therapy should remain a part of the therapeutic armamentarium of acute STEMI.

In this overview, we will briefly present the evidence for the still existing benefit of fibrinolytic therapy in STEMI as well as the optimal treatment following fibrinolysis. Furthermore, the role of fibrinolytic therapy and the pharmaco-invasive strategy in the current era will be discussed.

Fibrinolytic therapy (FT)

Benefit and risks

Several large trials carried out in the late 1980s showed that FT reduced mortality and morbidity in patients with STEMI (5, 6).

Compared with placebo, approximately 30 early deaths are prevented per 1000 patients treated within six hours after symptom onset (6).

Streptokinase manufactured from beta-haemolytic streptococci was the first fibrinolytic agent to be used, activating both fibrin-bound as well as circulating plasminogen. Later on, the more fibrin-specific recombinant t-PA (tissue plasminogen activator; alteplase) was increasingly used. Mortality with accelerated infusion of t-PA was reduced when compared with strep-
The earlier the patient is presented and the larger the area at risk at the presenting ECG, the more beneficial FT is and the more contraindications become relative.

Pre-hospital administration of FT shortens time to treatment and yields better clinical outcomes than in-hospital administration (8). Several studies have reported outcome data with pre-hospital FT similar to those of PCI, provided early angiography and PCI were performed in those who appeared to have failed lysis (9, 10).

The most important risk of FT is bleeding complications. Intracerebral haemorrhage (ICH) is seen in about 0.5–1.0% of patients treated with fibrinolysis (2, 6), and is associated with high morbidity and mortality (11). The most important risk factors for the development of ICH following FT (2, 12) are:
- advanced age,
- low body weight (<65 kg),
- female gender,
- prior cerebrovascular disease and
- arterial hypertension on admission.

Administration of streptokinase may be associated with hypotension, but severe allergic reactions are rare. The contraindications of fibrinolytic therapy are listed (Tab. 1).

### Adjunctive antiplatelet and anticoagulant therapies

To increase the efficacy of FT and to minimize the risk of early reocclusion, adjunctive antithrombotic therapy is needed. Convincing evidence of the effectiveness of aspirin was demonstrated by the ISIS-2 trial, in which the benefits of aspirin and streptokinase were additive (2, 5). In the CLEARITY-TIMI 28 and COMMIT trials, clopidogrel on top of aspirin reduced the risk of cardiovascular events in patients ≤75 years of age treated with fibrinolysis (13–14). Accordingly, there is a good case for the routine use of clopidogrel added to aspirin as an adjunct to FT. The new antiplatelet agents prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis and should not be used accordingly.

Parenteral anticoagulation has been used extensively during and after FT, and has been shown to improve coronary patency following fibrinolysis with t-PA. More recent studies have favoured enoxaparin over unfractionated heparin, in spite of an increased risk of major bleeding with this anticoagulant (15–16).

- The low molecular weight pentasaccharide fondaparinux was shown to be beneficial in patients who received streptokinase (17).
- The combination of tenecteplase, aspirin, clopidogrel and enoxaparin comprise the antithrombotic drug regimen that has been most extensively studied in modern fibrinolysis trials (18–20).

It is recommended to reduce the dose of both clopidogrel and enoxaparin in the elderly (>75 years), due to the increased risk of bleeding when these drugs are given in addition to FT (Tab. 2) (2, 11). In the STRATEGIC Reperfusion Early After Myocardial infarction (STREAM) trial, even the dose of tenecteplase was reduced in pa-

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**Table 1**

<table>
<thead>
<tr>
<th>Contraindications to fibrinolytic therapy according to Steg et al. (2)</th>
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<tbody>
<tr>
<td><strong>absolute</strong></td>
</tr>
<tr>
<td>previous intracranial haemorrhage or stroke of unknown origin at any time</td>
</tr>
<tr>
<td>ischaemic stroke in the preceding six months</td>
</tr>
<tr>
<td>central nervous system damage or neoplasms or atrophic cardiac malformation</td>
</tr>
<tr>
<td>recent major trauma / surgery / head injury (within the preceding three weeks)</td>
</tr>
<tr>
<td>gastrointestinal bleeding within the past month</td>
</tr>
<tr>
<td>known bleeding disorder (excluding menses)</td>
</tr>
<tr>
<td>aortic dissection</td>
</tr>
<tr>
<td>non-compressible punctures in the past 24 h (e.g. liver biopsy, lumbar puncture)</td>
</tr>
<tr>
<td><strong>relative</strong></td>
</tr>
<tr>
<td>transient ischaemic attack in the preceding six months</td>
</tr>
<tr>
<td>oral anticoagulant therapy</td>
</tr>
<tr>
<td>pregnancy or within one week post partum</td>
</tr>
<tr>
<td>refractory hypertension:</td>
</tr>
<tr>
<td>systolic blood pressure &gt; 180 mmHg and/or</td>
</tr>
<tr>
<td>diastolic blood pressure &gt; 110 mmHg</td>
</tr>
<tr>
<td>advanced liver disease</td>
</tr>
<tr>
<td>infective endocarditis</td>
</tr>
<tr>
<td>active peptic ulcer</td>
</tr>
<tr>
<td>prolonged or traumatic resuscitation</td>
</tr>
<tr>
<td>major surgery (&gt;3 weeks previously)</td>
</tr>
</tbody>
</table>
Mortality increased with increasing risk factors. In high-risk STEMI patients, a longer delay for performing PPCI increased mortality. The beneficial effect of PPCI was time-dependent: mortality increased with increasing delay from treatment (22–23).

Furthermore, the benefits of PPCI compared with FT as the time delay for performing PPCI increased (24).

From randomized trials it was calculated that a PCI-related delay of 80–120 minutes abandoned the survival benefit of PPCI compared to FT (25–26). Caution is needed when interpreting the results of these post-hoc analyses, because no specifically designed study has addressed this issue.

Registry data has suggested that age, symptom duration and infarct location influence the PCI-related delay where the advantage of PPCI is lost (27). Furthermore, the acceptable PCI-related delay seems to be affected by the patient risk:

- In high-risk STEMI patients, a longer PCI-related delay can be accepted (28–29).
- In patients with cardiogenic shock, PCI is the preferred treatment (30).

This means that to select the optimal reperfusion strategy for STEMI patients, one should consider both patient characteristics and time delays. The ESC Guidelines on Myocardial Revascularization from 2010 conclude that the incremental benefit of PPCI over timely FT is jeopardized when PCI-related delay exceeds 60–120 min, depending on age, duration of symptoms, and infarct location (1).

**FT versus primary percutaneous coronary intervention**

From 1993 to 2003, several studies were performed demonstrating the superiority of mechanical reperfusion over the pharmacological approach (21). Coronary flow was restored in about 90% of STEMI patients with PPCI compared to 40–60% with FT, and even when patients had to be transferred from an initial institution to another, better clinical outcomes were achieved using PPCI. A meta-analysis of 23 trials showed a reduction in mortality from 7% with fibrinolysis to 5% with primary PCI (21).

The beneficial effect of PPCI was time-dependent:

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- Furthermore, the benefits of PPCI compared with FT decreased as the time delay for performing PPCI increased (24).

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### Combination of FT and PCI

Attempts have been done to take advantage of the greater availability of FT as well as the higher degree of reperfusion obtained by PPCI, by combining both pharmacological and mechanical reperfusion strategies.

After failed FT, rescue PCI is the strategy of choice and should be offered as soon as possible (2, 31).

As up to 40% of patients might not react properly to FT, it is suggested that all patients treated with lytic therapy should be transferred to a PCI-capable hospital (2).

After successful FT, a strategy of routine angiography some hours after lysis has been shown to be beneficial (2, 18, 19, 32) (Fig. 1). The optimal time frame for angiography following FT is unknown. Very early angio/PCI might increase the risk of ischemic complications, as suggested by the ASSENT-4 study (33). In contrast, recent studies with angiography as early as 2–3 h after FT have shown improved outcomes with no increased risk of bleeding and no thrombotic complications compared to later angiography (5, 34) (Fig. 2). The more intense antithrombotic co-therapy used in recent fibrinolysis trials as well as increased use of the radial approach have probably contributed to these results. The current ESC STEMI guidelines advocate routine angiography between 3 and 24 h following fibrinolysis (2). Accordingly, optimal “pharmacological reperfusion” seems virtually to be a combination of the pharmacological and the mechanical approach: the “pharmacoinvasive” reperfusion strategy.

The recently published STREAM study evaluated a pharmacoinvasive strategy compared to PPCI in early presenting STEMI patients with long transfer delays to PCI (20). A total of 1892 patients with large STEMs presenting within three hours after symptom onset, who were unable to undergo primary PCI within one hour, were randomized in the ambulance or a non-PCI hospital to either PPCI, or FT with bolus therapy according to guidelines (2).

#### Tab. 2  Recommended doses of fibrinolytic agents as well as antiplatelet and anticoagulant co-therapies

<table>
<thead>
<tr>
<th>drug</th>
<th>dosage</th>
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<tbody>
<tr>
<td>fibrinolytic agent</td>
<td>tenecteplase (TNK–tPA)</td>
</tr>
<tr>
<td></td>
<td>single i. v. bolus:</td>
</tr>
<tr>
<td></td>
<td>- 30 mg if &lt; 60 kg</td>
</tr>
<tr>
<td></td>
<td>- 35 mg if 60 to &lt;70 kg</td>
</tr>
<tr>
<td></td>
<td>- 40 mg if 70 to &lt;80 kg</td>
</tr>
<tr>
<td></td>
<td>- 45 mg if 80 to &lt;90 kg</td>
</tr>
<tr>
<td></td>
<td>- 50 mg if ≥ 90 kg</td>
</tr>
<tr>
<td>reteplase (r-PA)</td>
<td>10 units + 10 units i. v. bolus given 30 min apart</td>
</tr>
<tr>
<td>antiplatelet co-therapies</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>- oral dose of 150–325 mg or</td>
</tr>
<tr>
<td></td>
<td>- i. v. dose of 250 mg if oral ingestion impossible</td>
</tr>
<tr>
<td></td>
<td>- maintenance dose of 75–100 mg/day orally</td>
</tr>
<tr>
<td>clopidogrel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- loading dose of 300 mg if age ≤ 75 years</td>
</tr>
<tr>
<td></td>
<td>- maintenance dose of 75 mg/day</td>
</tr>
<tr>
<td>anticoagulant co-therapies</td>
<td>enoxaparin (with alteplase, reteplase or tenecteplase)</td>
</tr>
<tr>
<td></td>
<td>- patients ≤ 75 years: i. v. bolus of 30 mg followed 15 min later</td>
</tr>
<tr>
<td></td>
<td>- s. c. dose of 1 mg/kg every 12 h until hospital discharge for</td>
</tr>
<tr>
<td></td>
<td>- a maximum of 8 days.</td>
</tr>
<tr>
<td></td>
<td>- the first two doses should not exceed 100 mg.</td>
</tr>
<tr>
<td></td>
<td>- patients &gt; 75 years: no i. v. bolus. Start with first s. c. dose of</td>
</tr>
<tr>
<td></td>
<td>- 0.75 mg/kg with a maximum of 75 mg for the first two s. c. doses.</td>
</tr>
<tr>
<td></td>
<td>- patients with creatinine clearance of &lt; 30 ml/min regardless of</td>
</tr>
<tr>
<td></td>
<td>- age: The s. c. doses are repeated every 24 h.</td>
</tr>
</tbody>
</table>

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Fig. 2 Routine angioplasty after fibrinolysis in ST-elevation myocardial infarction according to Halvorsen and Huber (5): rate of primary end point in six randomized clinical trials evaluating routine early percutaneous coronary intervention (PCI) compared with standard treatment after fibrinolysis in ST-elevation myocardial infarction. SIAM III: Southwest German Interventional Study in Acute Myocardial Infarction; GRACIA-1: Grupo de Análisis de la Cardiopatía Isquémica Aguda-1 trial; CAPITAL-AMI: Combined Angioplasty and Pharmacological Intervention versus Thrombolysis Alone in Acute Myocardial Infarction trial; CARESS-in-AMI: Combined Abciximab Retepase Stent Study in Acute Myocardial Infarction; TRANSFER-AMI: Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction; NORDISTEMI: NORwegian Study on DIstrict treatment of ST-Elevation Myocardial Infarction.
only 60 minutes. In cardiogenic shock, PPCI was the recommended treatment irrespective of time delay. These recommendations and treatment goals were kept more or less unchanged in the 2012 version of the ESC STEMI-guidelines as well as in the recent update of the American College of Cardiology Foundation/American Heart Association guideline for the management of ST-elevation myocardial infarction (2, 3, 42). However, achieving these treatment goals proves impossible in many areas of the world, mainly because of long transfer distances to PCI facilities, and also because STEMI-care is not streamlined enough between different levels and components of the health care system (23, 35–39, 43, 44).

Both the European as well as the North American guidelines recommend that if PPCI cannot be delivered within 120 min from FMC and in the absence of contraindications, FT should be considered, particularly if it can be delivered pre-hospitaly and within the first 2 h from symptom onset (Fig. 1). FT should be followed by rescue PCI in cases of failed fibrinolysis, or by routine angiography after successful FT (Fig. 1).

The ESC STEMI guidelines 2012 recommend monitoring and reporting of actual time delays for treatment, and in an effort to improve time to reperfusion, suggest specific quality targets both for performing PPCI as well as for delivering FT (2). The quality target for performing PPCI (≤90 min) is shorter than the maximal PCI-related delay of 120 min (useful in selecting PPCI over FT), and has been (mis)interpreted as a tool to skew the choice of reperfusion strategies towards FT (42, 45). However, as already mentioned, the ESC 2012 recommendations for choice of reperfusion therapy in relation to anticipated time delays are very similar to the 2008 version, as no new randomised trials challenging these recommendations have been published.

### The role of fibrinolysis in the era of PPCI

Even if the standard reperfusion strategy in Europe is PPCI, one size does not fit all (46). There are parts of the world where distance, climate, and the availability of facilities will result in significant delays in the delivery of PPCI, and the guidelines recognize this by defining a role for FT in specific settings.

Patient characteristics favouring on-site FT vs. transfer for PCI are listed (Tab. 3) (5). Especially in remote, sparsely populated areas with long transfer distances to PCI, FT should be the recommended choice in early presenting STEMI patients without cardiogenic shock and without contra-indications for FT.

But also in urban areas, FT could be considered, at least for patients with large and fresh infarctions (e.g. anterior wall within two hours of onset of pain) and low bleeding risk, if prolonged transfer times to PCI are expected, if between-hospital transfers are necessary, or if catheterisation laboratories are busy and cannot provide immediate mechanical reperfusion (25, 39).

If appropriate facilities exist, with trained medical or paramedical staff able to analyse on-site or to transmit the ECG to the hospital for interpretation, FT should be initiated in the pre-hospital setting (2).

The aim is to start FT within 30 minutes of symptom onset (Fig. 1). FT should be followed by rescue PCI in cases of failed fibrinolysis, or by routine angiography after successful FT (Fig. 1).

### Fig. 3 Results of the STREAM trial: primary percutaneous coronary intervention versus fibrinolysis: Kaplan-Meier curve of the primary end point (p = 0.21 by the log-rank test; reprinted with kind permission from Armstrong P et al. (20))

**Tab. 3**

Selecting reperfusion strategy according to Halvorsen S and Huber K (5)

<table>
<thead>
<tr>
<th>reperfusion strategy</th>
<th>preferred treatment</th>
</tr>
</thead>
</table>
| primary PCI          | - if available within 90–120 min from first medical contact  
                       - in late presenters (> 3 h from symptom onset)  
                       - in patients with contra-indications for fibrinolysis  
                       - in cardiogenic shock  
                       - in patients with increased bleeding risk  
                       - in the elderly (?) |
| fibrinolysis          | - In patients with short time from presentation and without contraindications, when primary PCI cannot be performed within 90–120 min from first medical contact.  
                       - May be considered in very early presenters (< 1 h from symptom onset) with low bleeding risk and large anterior infarctions. |

PCI: percutaneous coronary intervention
arriving at the ambulance. For patients arriving at a non-PCI hospital, a realistic aim is also to initiate FT within 30 minutes (door-to-needle time).

Modern pharmacologic reperfusion therapy is no longer FT alone, but FT should be followed by transfer for rescue PCI or routine coronary angiography with FT if indicated (2, 3, 5).

STEMI systems of care

To deliver optimal reperfusion treatment within the recommended time limits to all STEMI patients, it is recommended to build up and organize systems of care (STEMI networks) for close cooperation (2, 3) of

- emergency medical systems (EMS),
- non-PCI capable hospitals and
- hospitals with PCI facilities.

The recently published STREAM study demonstrated the key role of pre-hospital systems capable of early diagnosis, therapy and triage at the first point of care (20).

In well-organized STEMI networks, it is possible to offer PPCI within the recommended time to the majority of patients, and pre-hospital FT followed by immediate transfer to a PCI centre to patients living in remote areas but also in metropolitans if transfer delay is expected (46–47).

Published results from these regional systems of care have demonstrated that simple strategies and coordination of systems of care make reperfusion therapy of most STEMI patients achievable within recommended time frames and with low mortality (19, 20, 47–54).

Conclusions

In spite of PPCI being the preferred treatment of STEMI, there is still a role for FT, which remains a valuable option for treatment of STEMI in remote regions without PCI-facilities, but may also be considered in urban areas with traffic problems and only a few active catheterisation laboratories. Provided it is administered sufficiently early, and followed by routine angiography/PCI in responders and rescue PCI in non-responders, FT might result in clinical outcomes that are comparable to those obtained with transfer for primary angioplasty.

Therefore, FT should still be considered in STEMI patients presenting early after symptom onset, when the expected time delay to PCI is prolonged.

All patients treated with FT (pre-hospital or in a non-PCI capable hospital) should be transferred to a primary PCI centre for rescue PCI or routine angiography. FT as part of a pharmaco-invasive reperfusion strategy, should still be offered wherever PPCI cannot be guaranteed within the recommended time frame, and should remain an important part of the therapeutic armamentarium of STEMI networks in many regions.

Conflict of interest

The authors declare that they have no conflict of interest.

References


