The role of fibrinolysis in the era of primary percutaneous coronary intervention

Sigrun Halvorsen1; Kurt Huber2
1Department of Cardiology, Oslo University Hospital, Oslo, Norway; 23rd Department of Medicine, Cardiology and Emergency Medicine, Wilhelminenhospital, Vienna, Austria

Introduction

Most cases of acute myocardial infarction are caused by disruption of an atherosclerotic plaque followed by coronary thrombosis (1). In ST-elevation myocardial infarction (STEMI), the thrombus occludes a major epicardial coronary artery. Such an occlusion is an emergency situation, and flow in the occluded vessel should be restored as fast as possible. Various strategies for reperfusion are available, namely pharmacological reperfusion by fibrinolytic therapy or mechanical reperfusion by primary percutaneous coronary intervention (PCI). Primary PCI has been established as the preferred reperfusion strategy today (2). The percentage of STEMI-patients treated with primary PCI is steadily increasing, and in most European countries, primary PCI is the leading reperfusion strategy (3). In this era of primary PCI, 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 benefit of fibrinolytic therapy in STEMI and discuss the role of fibrinolysis in this era of primary PCI.

Benefit of fibrinolytic therapy

Several large trials carried out in the late 1980s showed that fibrinolytic treatment reduced mortality and morbidity in STEMI, and this advent revolutionised the care of these patients (4–5). 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 (6–7). Mortality with accelerated infusion of t-PA was reduced when compared with streptokinase, and offered the advantage of not being immunogenic. Several mutants of t-PA have been studied. Double-bolus r-PA (reteplase) does not offer any advantage over accelerated t-PA except for easier administration (7). TNK-tPA (tenecteplase) can be given as a single bolus facilitating more rapid treatment in and out of hospital. Tenecteplase was shown to be equivalent to accelerated t-PA for 30-day mortality (6%), and also associated with a significantly lower rate of non-cerebral bleedings (8). In the search for an ideal fibrinolytic agent, several new fibrinolytic drugs have been studied (9), but none has been developed commercially in Western countries.

The most important risk of fibrinolytic therapy is bleeding complications. Intracerebral haemorrhage is seen in about 0.5–1.0% of patients treated with fibrinolysis (7–8, 10) and is associated with high morbidity and mortality (11). Risk factors for the development of cerebral bleeding following fibrinolytic therapy are low body weight (<65 kg), female gender, prior cerebrovascular disease and arterial hypertension on admission (12).

Fibrinolytic treatment is more beneficial in patients presenting early after symptom onset. In a meta-analysis of 22 trials, a substantially larger mortality reduction was found in patients treated with fibrinolysis within the first 2 hours (h) from symptom onset than in those treated later (13). The earlier the patient is presented and the larger the area at risk at the presenting electrocardiogram (ECG), the more beneficial fibrinolytic therapy is and the more contra-indications are relative.

Adjunctive anti-thrombotic medication

To increase the efficacy of fibrinolysis and to minimise the risk of early re-occlusion, adjunctive antithrombotic therapy is indicated (14–15). Convincing evidence of the effectiveness of aspirin was demonstrated by the ISIS-2 trial (5), in which the benefits of aspirin and streptokinase were additive. In the CLARITY-TIMI 28 and COMMIT trials, the effect of clopidogrel on top of aspirin reduced the risk of cardiovascular events in STEMI patients treated with fibrinolysis (16–17). Accordingly, use of clopidogrel on top of aspirin is recommended as an adjunct to lytic therapy (2). Heparin has been extensively used during and after fibrinolysis, and has been shown to improve coronary patency following fibrinolysis with t-PA. In more recent studies comparing heparin with low-molecular-weight enoxaparin, the net clinical benefit have favoured enoxaparin, in spite of an increased risk of major bleeding with this anticoagulant (18–20). Current ESC STEMI guidelines recommend enoxaparin as anti-thrombin co-therapy with alteplase, reteplase and tenecteplase (2). It is important to be aware of the risk of serious bleeding complications when clopidogrel and enoxaparin are given in addition to lytic therapy, and reduced doses for both antithrombotic agents are recommended above the age of 75 (2, 11). The low-molecular-weight pen-
tasaccharide fondaparinux has been shown to be superior to placebo or heparin in preventing death and re-infarction, especially in patients who received streptokinase (21).

Fibrinolysis versus primary PCI

Many studies have demonstrated the superiority of mechanical reperfusion over the pharmacological approach (22). Coronary flow was restored in about 90% of STEMI patients with primary PCI compared to 40–60% with lysis, and better clinical outcome was achieved using coronary angioplasty, even when patients had to be transferred from an initial institution to another (23–24). A meta-analysis of 23 trials showed a reduction in mortality from 7% with fibrinolysis to 5% with primary PCI (22). The major drawback of primary angioplasty is its limited availability and the treatment delay (25). When patients have to be transferred over long distances or from a non-PCI capable hospital to a hospital with facilities for primary angioplasty, the delay can be considerable (26).

The current ESC STEMI guidelines have established primary PCI as the preferred method of reperfusion in STEMI, as long as it can be delivered within 90–120 minutes (min) from patient’s first medical contact (2) (Fig. 1). However, achieving this goal 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 (25–26).

Impact of time delay and patient risk

As the beneficial effect of fibrinolytic therapy is substantially higher in patients presenting early after symptom onset (13), the effect of fibrinolysis compared to primary PCI is dependent on the time delay from symptom onset to treatment. In several trials and registries comparing primary PCI with lytic therapy, mortality were comparable between the two reperfusion strategies when treatment was initiated within 2–3 h from symptom onset (23, 27). However, in a meta-analysis of 22 randomised trials, treatment with primary PCI was associated with lower mortality relative to inhospital fibrinolysis regardless of the presentation delay (28).

Pre-hospital administration of lytic therapy shortens time to treatment and yields better clinical outcomes than in-hospital administration (29). Only one randomised trial, the Comparison of Angioplasty and Prehospital Fibrinolysis in acute Myocardial infarction (CAPTIM), compared primary PCI with pre-hospital fibrinolysis (30–31). This study, as well as data from French registries, have reported outcome data for pre-hospital fibrinolysis comparable to those of primary PCI (30–32). The beneficial effects of early fibrinolysis could also be preserved after follow-up periods from one to five years (32–33). In addition, for patients treated within 2 h of symptom onset, there was a trend towards lower mortality with pre-hospital lysis (31, 33). It is important to notice that in the CAPTIM study, patients were transported to an interventional facility following pre-hospital lysis, for emergent PCI if needed.

The beneficial effects of primary PCI are also time-dependent; mortality increases with increasing ischaemic time (34–35). Furthermore, although primary PCI is commonly more effective than fibrinolytic therapy, the benefits of primary PCI compared with fibrinolysis decrease as the time delay for performing PCI increases. From randomised trials it has been calculated that a PCI-related delay of 80–120 min abandon the survival benefit of primary PCI compared to fibrinolysis (28, 36–38). Evaluation of registry data has shown that the acceptable primary PCI-related delay also depends upon the risk of the patient (39). Both patient age, duration of symptoms and infarct location influence the PCI-related delay where the advantage of primary PCI over fibrinolysis is lost, and to select the optimal reperfusion strategy for STEMI patients, one should consider both patient characteristics and time delays for delivering reperfusion therapy (39). The recent ESC Guidelines on myocardial revascularisation conclude that the incremental benefit of primary PCI over timely fibrinolysis is jeopardized when PCI-related delay exceeds 60–120 min, depending on age, duration of symptoms, and infarct location (40).

Combination of lysis and PCI

Attempts have been done to take advantage of the greater availability of lytic therapy as well as the higher degree of reperfusion obtained by primary PCI, by combining both reperfusion strategies. The results of trials with facilitated PCI, defined as pharmacological reperfusion treatment delivered prior to a planned PCI, have been disappointing (41–42), and facilitated PCI cannot be recommended (2).

After failed fibrinolysis, rescue PCI is the strategy of choice and should be offered as soon as possible (2, 43). Accordingly, it is supposed that patients treated with lytic therapy should be immediately transferred to a PCI-capable hospital (2).

After successful fibrinolysis, a strategy of routine angiography some hours after lysis (a pharmaco-invasive strategy) has been shown to be beneficial (44–50) (Fig. 2). However, the optimal time frame for angiography following fibrinolysis is not yet settled. Very early angiography might increase the risk of ischaemic complications, as suggested by the ASSENT-4 study (41). However, recent studies with angiography as early as 2–3 h after fibrinolysis have shown improved outcomes with no increased risk of bleeding and no thrombotic complications compared to later angiography (47–48, 50). The more intense anti-thrombotic 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 “pharmac-o-invasive reperfusion strategy”).

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Thrombosis and Haemostasis 105.3/2011
Figure 1: Options for reperfusion strategy. The thick arrow indicates the preferred strategy. Reproduced with permission from Van de Werf F, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Reprinted with permission from "Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology". Eur Heart J 2008 (2). PCI = percutaneous coronary intervention.

Figure 2: Routine early PCI after fibrinolysis in ST-elevation myocardial infarction (STEMI). Rate of primary end point in six randomised clinical trials evaluating routine early percutaneous coronary intervention (PCI) compared with standard treatment after fibrinolysis in STEMI. The six trials are the Southwest German Interventional Study in Acute Myocardial Infarction (SIAM III) (45), the Grupo de Análisis de la Cardiopatía Isquémica Aguda-1 (GRACIA-1)(46) trial, the Combined Angioplasty and Pharmacological Intervention versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL AMI)(47) trial, the Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) (48), the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) (49) and the NORwegian Study on DIstrict treatment of ST-Elevation Myocardial Infarction (NORDISTEMI) (50).
The role of fibrinolysis in the era of primary PCI

The ESC STEMI guidelines clearly state that primary PCI is the preferred reperfusion strategy in STEMI if performed by an experienced team within 2 h after first medical contact (i.e. ECG-proven STEMI by a physician or trained paramedic) (2) (Fig. 1). In patients presenting early with large amount of myocardium at risk and low bleeding risk, time delay must be shorter than 90 min. If primary PCI cannot be delivered within these recommended times, and in the absence of contraindications, fibrinolytic therapy should be initiated, preferably in the pre-hospital setting. In cardiogenic shock, primary PCI is the recommended treatment irrespective of time delay.

Since these ESC STEMI-guidelines were launched end of 2008, no new randomised trials comparing primary PCI with fibrinolysis have been published, and in our opinion we should proceed on these guidelines. The new ESC Guidelines on myocardial revascularisation also recommend the same strategy (40). In addition to duration of symptoms and transfer time to PCI, patient’s characteristics are important factors when deciding reperfusion therapy for the individual patient. One treatment strategy does not suit all.

There is still a role for lytic therapy. Especially in remote, sparsely populated areas with long transfer distances to PCI it is impossible to deliver PCI within the recommended time limits, and fibrinolysis should be the recommended choice in early presenting STEMI patients without cardiogenic shock and without contra-indications to fibrinolysis (Table 1). But also in metropolitan areas, lytic therapy should be available, at least for those with large and fresh infarctions (e.g. anterior wall within 2–3 h 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 (39,51). Fibrinolysis should be followed by transfer for routine early angiography (48–50,52).

An ongoing study, Strategic Reperfusion Early After Myocardial Infarction (STREAM), evaluates a strategy of primary PCI compared to pre-hospital lysis followed by invasive evaluation in early presenting STEMI patients with long (>60 min) transfer delays to PCI (53). This trial will add valuable information on the optimal treatment strategy for STEMI-patients living in remote areas without PCI facilities.

The importance of 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 organise systems of care (STEMI networks) in which emergency medical systems (EMS), non-PCI capable hospitals and hospitals with PCI facilities cooperate closely. In well-organised STEMI networks, it is possible to offer primary PCI within the recommended time to the majority of patients, and pre-hospital fibrinolysis followed by immediate transfer to a PCI centre to patients living in remote areas (54). 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 (51,54). The appropriate and timely use of some reperfusion therapy seems to be more important than the choice of therapy (55).

Conclusions

In spite of the increasing use of primary PCI for the treatment of STEMI, there is still a role for fibrinolysis. Lytic therapy remains a valuable option for treatment of STEMI in remote regions without PCI-facilities, but also in overcrowded 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, fibrinolysis might result in clinical outcomes that are comparable to those obtained with primary angioplasty. This applies not only for the early phase after pharmacological reperfusion (i.e. in-hospital or 30-days outcome), but also for long-term mortality. Therefore, lytic therapy should still be considered in STEMI patients presenting early after symptom onset, particularly when the expected time delay to PCI is long. All patients treated with fibrinolysis (pre-hospital or in a non-PCI capable hospital) should be transferred immediately to a primary PCI centre. Based on this knowledge, fibrinolytic therapy has to stay or even be installed wherever primary PCI cannot be guaranteed within the recommended time frame, and will stay an important part of the armamentarium of STEMI networks in many regions for many upcoming years.

Table 1: Selecting reperfusion strategy.

<table>
<thead>
<tr>
<th>When Primary PCI has a role</th>
<th>When Fibrinolysis has a role</th>
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<tbody>
<tr>
<td>● Preferred treatment when available within 90–120 min from first medical contact.</td>
<td>● In patients with short time from presentation and without contraindications, when primary PCI cannot be performed within 90–120 min from first medical contact.</td>
</tr>
<tr>
<td>● In late presenters (&gt; 3 h from symptom onset).</td>
<td>● May be considered in very early presenters (&lt;1 h from symptom onset) with low bleeding risk and large anterior infarctions.</td>
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<tr>
<td>● In patients with contra-indications for fibrinolysis.</td>
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<td>● In cardiogenic shock.</td>
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<td>● In patients with increased bleeding risk.</td>
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<td>● In the elderly (?)</td>
<td>PCI = percutaneous coronary intervention.</td>
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