

Recommendations for an efficient and safe use of fibrinolytic agents



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ST-segment myocardial infarction (STEMI) is caused by thrombotic occlusion of a major coronary artery. Rapid restoration of coronary blood flow is essential in preventing myocardial necrosis. Early reperfusion of the infarct-related artery limits infarct size and improves outcome. Achieving the shortest possible delay between symptom onset and reperfusion is therefore one of the most critical factors in the management of STEMI.

Reperfusion can be achieved mechanically, using primary percutaneous coronary intervention (PCI), or pharmacologically, using fibrinolytic agents.¹⁻⁴ Only a minority of hospitals worldwide provide a 24/7 hours primary PCI service by an experienced team. Fibrinolysis, in contrast, is universally available and does not require advanced logistics. Lytic therapy therefore is a valuable alternative, and is still used for the treatment of acute myocardial infarction in the majority of centers worldwide.

Fibrinolytic therapy & fibrinolytic agents

Clot lysis can be attained by activating the endogenous fibrinolytic system, using plasminogen-activating agents. These agents convert plasminogen to plasmin, which then degrades fibrin, a major constituent of clots (Figure 1).

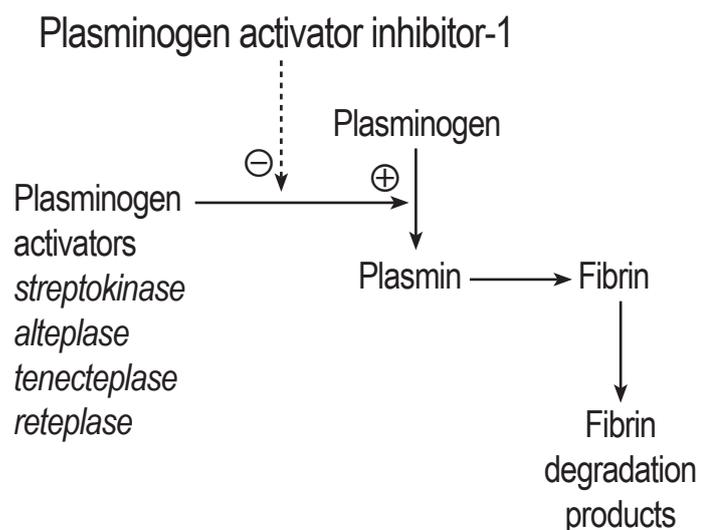


Figure 1: Mechanisms of clot lysis.

Fibrinolytic agents are generally divided in fibrin-specific agents and non-fibrin-specific agents. Fibrin-specific drugs, such as alteplase, tenecteplase or reteplase, are more efficient in dissolving thrombi and do not deplete systemic coagulation factors, in contrast with non-fibrin-specific agents, such as streptokinase (Table 1).

First-generation fibrinolytic regimens, including streptokinase and alteplase required continuous intravenous infusion. Contemporary fibrinolytic strategies, however, consist of intravenous bolus administration of second and third generation fibrinolytics. Using bolus fibrinolytic agents decreases the risk of dosing errors and facilitates pre-hospital initiation of reperfusion therapy.⁵

Fibrinolysis unfortunately has several limitations. Fibrinolytics need 30 to 45 minutes on average to recanalize the infarct-related artery, and complete patency is only achieved in 50 to 60 % of patients. Bleeding complications, especially intracranial hemorrhages, also continue to be a concern: up to 1% of patients experience an intracranial hemorrhage. Risk factors for developing intracranial hemorrhage include advancing age, female gender and a history of hypertension.⁶

On the other hand, reocclusion due to pro-thrombotic side effects is also common; occurring in 5 to 15% of previously recanalized arteries.⁷ This results in further worsening of left ventricular function and a steep increase of in-hospital mortality. Reocclusion is mediated by the interaction of vasospasm, aggregating platelets,

clot-bound thrombin, the thrombogenicity of partially lysed clot and ruptured atheroma, or the persistence of a flow-limiting stenosis in the absence of a percutaneous intervention. Fibrin-specific drugs might also promote reocclusion due to paradoxical pro-coagulant and platelet-activating side effects. As a consequence, one or more additional antithrombotic agents are required when a fibrin-specific agent is given. In addition, this also implies that avoiding reocclusion whilst simultaneously minimizing the risk of bleeding complications, might be difficult.

Streptokinase

Streptokinase is a non-fibrin-specific fibrinolytic agent that indirectly activates plasminogen. Because of its lack of fibrin specificity, streptokinase depletes systemic coagulation factors, inducing a lytic state. Although newer fibrin-specific fibrinolytics have theoretical and clinical advantages, streptokinase remains widely used because of its low cost. Unfortunately, preexisting anti-streptokinase antibodies may impede reperfusion after treatment with streptokinase.⁸ In addition; administration of streptokinase also invariably induces anti-streptokinase antibodies, precluding safe re-administration.

The first large trial to show a significant reduction in mortality with a fibrinolytic agent was the landmark GISSI-1 trial.⁹ In this study, 11,806 patients with an acute myocardial infarction presenting within 12 hours

Table 1: Antithrombotic co-therapies with fibrin-specific fibrinolytics.

Therapy	Drug	Dosage
<i>Antiplatelet co-therapy</i>	Aspirin	150-325 mg orally or 250 mg IV if ingestion is not possible.
	Clopidogrel	Loading dose 300 mg (75 mg if age > 75 years)
<i>Anticoagulant co-therapy</i>	Unfractionated heparin	IV bolus of 60 U/kg (max 4,000 U) Infusion of 12 U/kg (max 1,000/hr) for 24 - 48 hours Target aPTT: 50-70 sec; first monitoring after 3 hours
	Enoxaparin	< 75 years
		> 75 years
Fondaparinux	IV bolus of 2.5 mg. SC 2.5 mg QD until discharge	

of symptom onset were randomized to either reperfusion therapy with streptokinase or standard non-fibrinolytic therapy. In-hospital mortality was 10.7% in patients treated with intravenous streptokinase versus 13.1% in controls, resulting in 23 lives saved per 1,000 patients treated. This benefit in mortality was even preserved at ten-year follow-up.¹⁰ A second 17,187-patient landmark trial, ISIS-2, corroborated these results.¹¹

Alteplase

Recombinant tissue-type plasminogen activator (rt-PA or alteplase) is a single-chain tissue-type plasminogen activator molecule. It has considerably greater fibrin-specificity than streptokinase, but induces nevertheless mild systemic fibrinogen depletion. Because of its short half-life, alteplase requires a continuous infusion.

In two large mortality trials, ISIS-3 and GISSI-2, alteplase, given as a 3-hour continuous infusion, was not found to be superior to streptokinase.^{12,13} The question which of the two fibrinolytic drugs is the most effective in terms of mortality reduction was answered in the first GUSTO trial.¹⁴ In this large trial, a 'front-loaded' 90-min dosing regimen of alteplase was used (Table 2), which had earlier been shown to achieve higher patency rates than the previously used 3-hour scheme. 30-day mortality was significantly lower in patients receiving alteplase compared to those treated with streptokinase (6.3% vs. 7.4%). The 1% lower mortality rate at 30 days with front-loaded alteplase corresponds with a significantly higher epicardial patency rate at 90 minutes: 54% versus only 32% with streptokinase.¹⁵

Retepase

Retepase, a second-generation fibrinolytic agent, was a first attempt to improve on the shortcomings of alteplase. It is a mutant of alteplase in which the finger,

the kringle-1 domain and epidermal growth factor domains are removed. This causes decreased plasma clearance, allowing double-bolus administration. The removal of the finger domain somewhat diminishes fibrin specificity, although inactivation by plasminogen activator inhibitor (PAI-1) remains similar with alteplase. Compared to alteplase, reteplase achieved higher patency rates in two pilot studies.^{16,17}

In the GUSTO-III trial, 15,059 patients were randomized to double-bolus reteplase, given 30 min apart, or front-loaded alteplase.¹⁸ Mortality at 30 days was similar in both treatment arms (7.47% vs. 7.24%, respectively), as was the incidence of hemorrhagic stroke or other major bleeding complications. Similar mortality rates were maintained for both treatment groups at one-year follow-up.¹⁹ In other words, higher TIMI-3 rates at 90 min with reteplase, as seen in the two pilot studies, did not translate into lower short-term or long-term mortality rates. The reason for this incongruity remains unclear, but might be explained in part by increased platelet activation and surface receptor expression with reteplase compared to alteplase.

Tenecteplase

Tenecteplase (TNK-t-PA) is also derived from alteplase, after mutations at three places (T103, N117, KHRR296-299). These changes enhance fibrin binding and specificity, plasma half-life, and resistance to PAI-1. Its slower clearance allows convenient single-bolus administration. Tenecteplase leads to faster recanalization compared to alteplase, and also has higher fibrinolytic potency on platelet-rich clots than its parent molecule. In two pilot trials (TIMI 10A and 10B), patency rates after 30 or 40 mg tenecteplase were comparable to those achieved with front-loaded alteplase.^{20,21} A 50-mg dose of tenecteplase, however, was discontinued early because of an excessive subsequent incidence of

Table 2: Characteristics and dosing regimens of fibrinolytic agents.

Characteristic	Streptokinase	Alteplase	Retepase	Tenecteplase
Fibrin-specificity	No	++	+	+++
Half-life (min)	18 - 23	3 - 4	18	20
Antigenicity	+++	No	No	No
Administration	1-hour infusion	Bolus & 90-min infusion	Double bolus	Single bolus
Dose	1.5 MU	15-mg bolus 0.75 mg/kg i.v. (max 50) over 30 min 0.5 mg/kg over 60 min	10 U + 10 U 30 min apart	Weight-adjusted: <60 kg: 30 mg 60-69.9 kg: 35 mg 70-79.9 kg: 40 mg 80-89.9 kg: 45 mg ≥90 kg: 50 mg

intracranial hemorrhages.

In the double-blind ASSENT-2 trial, 16,949 patients were randomized to weight-adjusted single-bolus tenecteplase or standard front-loaded alteplase.²² Specifically designed as an equivalency trial, this study showed that tenecteplase and alteplase had equivalent 30-day mortality rates (6.18% vs. 6.15%). Mortality rates remained similar at one-year follow-up.²³ Although the rates of intracranial hemorrhage were low, and similar for tenecteplase (0.93%) versus alteplase (0.94%), female patients, elderly >75 years and patients weighing less than 67 kg tended to have lower rates of intracranial hemorrhage after treatment with tenecteplase.⁶ Non-cerebral bleeding complications occurred less frequently in the tenecteplase group, and as a consequence, there was also less need for blood transfusion after tenecteplase, especially in high-risk patients.

Indications and contra-indications for fibrinolytic therapy

Indications

Patients younger than 76 years with typical chest pain of up to 12 hours duration presenting with electrocardiographic ST-segment elevations or new bundle-branch block are eligible for fibrinolytic therapy.³ The usual electrocardiographic criterion for administration of fibrinolytic therapy is at least 0.1 mV of ST-segment elevation in two or more contiguous leads. Since mortality is significantly higher in patients with complete left bundle-branch block, administration of a fibrinolytic agent is also recommended in this population.²⁴ Indeed, fibrinolysis in patients presenting with a new bundle-branch block, obscuring ST-segment elevation, reduces mortality by 25%.

Contraindications

Contraindications to fibrinolysis are, in essence, precautions to avoid excessive hemorrhage in patients with co-morbidities that increase the risk of bleeding complications (Table 3).

In these patients, especially those with a previous history of stroke or recent major surgery, primary PCI should be considered. Since arterial hypertension increases the risk for intracranial hemorrhage, patients presenting with persisting high blood pressure are usually also not eligible for lytic therapy, although a history of systemic hypertension in itself does not predispose to intracranial hemorrhage with lytic therapy. It is less clear whether fibrinolytic agents can be safely administered, after successful treatment of high blood pressure at initial presentation. Nevertheless, because there is a substantial mortality benefit with fibrinolytic agents, even in patients presenting with hypertension, fibrinolysis should still be considered in patients with high blood pressure on admission, after successful initiation of antihypertensive treatment, when primary PCI is not available.

Adjunctive antithrombotic therapy with lytics

Antiplatelet therapy

• Aspirin

Low-dose aspirin remains the cornerstone of anti-thrombotic therapy in STEMI patients. In ISIS-2, low-dose aspirin was associated with improved outcome in STEMI patients, irrespective of receiving fibrinolysis or placebo.¹¹ Aspirin also significantly reduced nonfatal re-infarction (1.0% vs. 2.0%) and was not associated with any significant increase in intracranial hemorrhages. In the most recent meta-analysis of the Antithrombotic Trialists' Collaboration including 19,288 patients from 15 STEMI trials, aspirin use was associated with a significant reduction in cardiovascular death (23 lives saved per 1,000 patients treated) and non-fatal reinfarction (13 events prevented per 1,000 patients treated).²⁵ Overall, a small increase of intracranial hemorrhages (1 to 2/1,000) was seen in patients taking low-dose to aspirin.

Two small trials suggest that the benefit of aspirin in the setting of fibrinolytic therapy might be time-dependent. Patients who received aspirin before fibrinolysis had a lower 7-day mortality than patients who

Table 3: Contraindications for fibrinolysis.

Absolute contraindications	Relative contraindications
<ul style="list-style-type: none"> - Previous hemorrhagic stroke or stroke of unknown origin at any time - Non-hemorrhagic stroke in preceding 6 months - Known bleeding diathesis - Suspected aortic dissection - Intracranial neoplasm - Central nervous system trauma - Non-compressible punctures 	<ul style="list-style-type: none"> - Surgery or trauma within past 2-4 weeks - Uncontrolled hypertension on presentation (>180/100 mmHg) - Prolonged resuscitation - Oral anticoagulant use with INR >2.3 - Recent (internal) bleeding - Active peptic ulcer - Previous use of streptokinase

received the first dose of aspirin after administration of the fibrinolytic agent.²⁶ Similarly, patients with a STEMI had a better survival rate at 30 days when they received aspirin before hospital admission compared to in-hospital initiation.²⁷

• Clopidogrel

Despite systematic use of aspirin in lytic-treated patients, reocclusion and reinfarction after successful pharmacological reperfusion continues to be a problem. The CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) trial examined whether the addition of a second oral antiplatelet agent on top of aspirin, the ADP receptor inhibitor clopidogrel (300 mg bolus followed by 75 mg daily), was associated with higher rates of infarct-related artery patency in patients treated with a fibrinolytic agent.²⁸ At angiographic follow-up at least two days after fibrinolytic therapy, patients treated with clopidogrel had significantly lower TIMI flow grade 0 or 1 rates. Clopidogrel appeared to improve patency rates by preventing reocclusion rather than through facilitating early reperfusion.²⁹ No increased risk of bleeding complications with clopidogrel was observed. Since no patients over 75 years of age were included, however, it remains uncertain whether dual antiplatelet therapy is safe in the elderly treated with lytic therapy. Clopidogrel also improved outcome after PCI in CLARITY, regardless of the duration of pretreatment or whether patients received additional glycoprotein IIb/IIIa inhibitors.³⁰ These results suggest that starting clopidogrel at the time of fibrinolysis could obviate the need for additional glycoprotein IIb/IIIa inhibitors when a rescue PCI would be necessary.

• Glycoprotein IIb/IIIa inhibitors

The addition of glycoprotein (GP) IIb/IIIa inhibitors such as abciximab, eptifibatid or tirofiban to fibrinolytic agents reduces the risk of recurrent ischemia and reocclusion due to the prothrombotic side effects of fibrinolysis. Several trials indeed indicate that abciximab with half-dose fibrinolytic not only modestly enhances recanalization of the culprit vessel but also improves tissue reperfusion.³¹ The effect of improved epicardial patency rates on outcome with combination therapy using abciximab in addition to half-dose fibrinolytic therapy, was tested in the GUSTO-V (reteplase) and ASSENT-3 (tenecteplase) trials.^{32,33} In both trials, mortality rates were similar, but half-dose fibrinolytic plus abciximab was associated with a reduction in non-fatal ischemic complications. Although intracranial hemorrhage rates were comparable between treatment arms, major bleeding complications and transfusion rates were more frequent in the half-dose fibrinolytic plus abciximab arm. Patients older than 75 years experienced significantly more bleeding complications. The combination of half-dose lytic and abciximab

was also tested as a facilitation of primary PCI in the FINESSE trial.³⁴ In this trial, 2,452 patients planned to undergo primary PCI were randomized to half-dose reteplase plus abciximab, upfront abciximab or abciximab only just before the PCI. Although significantly more patients had early ST-segment resolution with the combination treatment, outcomes were not different between the treatment strategies. Taken together, combination therapy with half-dose fibrinolysis and abciximab results in a significant reduction in ischemic complications after acute myocardial infarction, but this benefit is offset by an increased risk of bleeding complications, particularly in the elderly.

Anticoagulant therapy

• Unfractionated heparin and low molecular weight heparin

The use of unfractionated heparin (UFH) is generally not recommended with non-fibrin-specific fibrinolytics. In contrast, UFH has been standard adjunctive anti-thrombotic therapy with fibrin-specific fibrinolytics since GUSTO-I, although other studies were unconvincing. Several fibrinolytic trials have studied the use of low-molecular weight heparin (LMWH), which does not require monitoring of its anticoagulant effect and can be given subcutaneously. In ASSENT-3, a significant improvement in the primary combined efficacy and safety end point was seen with tenecteplase and enoxaparin when compared to tenecteplase and UFH.^{32,35} Unfortunately, a significant increase in intracranial hemorrhages was seen in the ASSENT-3 PLUS trial, using the same combination.³⁶ The excess of intracranial bleeding complications was predominantly observed in elderly patients. Using an age-adjusted dose, however, enoxaparin did not increase the risk of intracranial hemorrhage after fibrinolytic therapy while still reducing the risk of ischemic complications in the ExTRACT-TIMI 25 study.³⁷ Another LMWH, reviparin, was tested in the CREATE study. 15,570 patients with a STEMI, of which over 70% received lytic therapy, were randomized to either placebo or reviparin.³⁸ Reviparin significantly reduced 30-day mortality and reinfarction, but bleeding complications were more frequent with reviparin, especially in patients receiving reperfusion therapy. Meta-analyses of trials comparing LMWH to UFH confirm that LMWH reduce the risk of death and reinfarction, but are associated with a higher risk of bleeding complications.^{39,40}

• Fondaparinux

Fondaparinux, a synthetic pentasaccharide, is a selective factor Xa inhibitor. As with LMWH, fondaparinux does not need monitoring of its anticoagulant effect. In the OASIS-6 trial, fondaparinux was compared with UFH or placebo in 12,092 patients with ST-elevation

myocardial infarction.⁴¹ Lytic therapy was given to 45% of patients (n = 5,436), most of them receiving a non-fibrin-specific agent. In these patients, fondaparinux was associated with a significant 21% lower risk of death or myocardial infarction when compared to standard heparin or placebo.⁴² Nevertheless, the risk of bleeding, including intracranial hemorrhage, was considerably lower with fondaparinux, irrespective of the type of fibrinolytic agent. The latest European guidelines recommend fondaparinux as adjunctive therapy to streptokinase (class IIa B) but not to fibrin-specific agents because of paucity of +outcome data with this combination.³

• Bivalirudin

In contrast with UFH, which only inhibits fluid-phase thrombin, bivalirudin is a direct thrombin-specific anti-coagulant that inhibits both fibrin-bound and fluid-phase thrombin. Because inadequately inactivated thrombin at the site of thrombus is in part responsible for the pro-coagulant side effect of thrombolysis, direct inhibition of thrombin might thus reduce the occurrence of ischemic complications after reperfusion.

In the HERO-2 trial, 17,073 patients were randomized to streptokinase and UFH or streptokinase and bivalirudin.⁴³ Mortality at 30 days was not different for both regimens, but re-infarction rate was significantly lower in the bivalirudin group (1.6% vs. 2.3% for UFH), suggesting that early and more efficient inhibition of thrombin can inhibit reocclusion. Mild to moderate bleeding complications were higher in the bivalirudin group, possibly due to higher aPTT values observed in the bivalirudin group. Bivalirudin has not been studied as an adjunctive antithrombin with fibrin-specific agents.

Fibrinolysis in the elderly

Registries have suggested an excessive mortality in fibrinolysis-treated patients over 75 years of age, possibly due to an excess of major bleeding complications.^{44, 45} This excessive mortality might also be explained in part by negative selection, as fitter elderly patients might have been more likely amenable for primary PCI. Mortality rates in observational studies, however, are in contrast with findings from large randomized trials. In the unpublished SENIOR PAMI trial, primary PCI was not found to be superior to primary PCI in 481 elderly patients (≥ 70 years of age). Furthermore, data from the Fibrinolytic Therapy Trialists (FTT) group in 3,300 STEMI patients over the age of 75 showed a significant absolute mortality reduction by fibrinolytic therapy that was even greater than in younger patients (34 versus 16 patients per 1,000 randomized).⁴⁶ A larger absolute benefit of fibrinolysis in elderly patients, might in part be explained by their higher baseline risk.⁴⁷ Lower ICH rates with tenecteplase as compared to alteplase in older

patients in the ASSENT-2 study indicate that the timely use of a more fibrin-specific agent might be preferable in older patients without contraindications for fibrinolytic therapy.⁶

Fibrinolysis in diabetics

Diabetic patients are less likely to be treated with fibrinolysis than non-diabetic patients.^{6, 25} This probably reflects the more frequent atypical or late presentations of these patients. Because fibrinolysis is thought to be most effective in the first hours after symptom onset, late presentation in patients with diabetes may be in part responsible for the reduced use of pharmacological reperfusion. It may also be related to concerns over an increased risk of intracranial or retinal hemorrhage. These concerns, however, are unsubstantiated: patients with diabetes are not likely to experience increased retinal or major bleeding complications after fibrinolysis.^{8, 26} In any case, individuals with diabetes do present later than those without diabetes. In addition, small mechanistic studies have suggested that fibrinolytic therapy may be less effective in individuals who have diabetes, irrespective of the delay between symptom onset and first medical contact. Such findings contrast with results from large clinical trials, however, which show that patients with diabetes benefit equally, if not more, than patients who do not have diabetes.²⁸ Thus, as in non-diabetic patients, fibrinolysis should be considered in lytic-eligible STEMI patients with diabetes and should be initiated as soon as possible if primary PCI is not an option.

Fibrinolysis and time-to-treatment

The advantages of fibrinolytic therapy are time-dependent. Although administering fibrinolytics up to 12 hours after the onset of symptoms may be beneficial in terms of outcome, every minute that reperfusion is postponed will unavoidably result in more extensive necrosis and worse outcome. In a meta-analysis, the mortality reduction following fibrinolytic therapy was calculated to be 44% in patients treated within 2 hours versus 20% in those treated later.⁴⁸ Early in the course of STEMI, the thrombus may be smaller and easier to lyse, which might in part explain the more prominent benefit of lytics in the first hours after symptom onset.

Pre-hospital therapy

Initiation of lytic therapy at the time of first medical contact, e.g. in the pre-hospital setting, speeds up reperfusion and might hence improve outcome. Several trials and registries have compared pre-hospital fibrinolysis with in-hospital fibrinolysis. A meta-analysis of six trials including 6,434 patients clearly demonstrates that the time gained with pre-hospital treatment resulted in a significant 17% mortality reduction compared with

fibrinolysis initiated in the emergency department.⁴⁹ In a more recent cohort study, time to fibrinolysis was almost 1 hour shorter with pre-hospital diagnosis and lytics administered by trained paramedics in the ambulances, when compared with regular in-hospital lytic therapy.⁵⁰ The significant amount of time gained by administering fibrinolytics in the pre-hospital setting resulted in a reduction of adjusted 1-year mortality by almost 30%. In the French USIC registry, the risk of death at one year was even more than 50% lower after pre-hospital fibrinolysis, compared to other treatment strategies.⁵¹ In patients treated prehospitally within 3.5 hours of symptom onset, 1-year survival was close to 99% in this study.

Studies comparing on-site fibrinolysis with transport for primary PCI in low-risk patients suggest that, even with transport-related time delays up to 90 minutes, primary PCI is superior to fibrinolysis. Nevertheless, time gained with pre-hospital administration might challenge this difference in outcome. In the CAPTIM trial, patients were randomized to either pre-hospital fibrinolysis with accelerated alteplase or primary PCI after transport to a center with interventional facilities.⁵² In essence, CAPTIM compared two reperfusion strategies, because more than 30% of patient in the pre-hospital lytic arm underwent urgent (rescue) angiography. Results from CAPTIM suggest that outcome after pre-hospital fibrinolysis is at least comparable to that with primary PCI, especially in patients presenting very early after symptom onset.^{52, 53}

Fibrinolysis or referral for primary PCI?

In hospitals without interventional facilities, patients presenting with STEMI can either be treated with fibrinolysis on-site or referred to another hospital for primary PCI. Current guidelines explicitly recommend primary PCI in patients presenting with STEMI.^{54, 55} On aggregate, they require that an experienced team starts the intervention within 90-120 minutes after initial presentation. In non-interventional hospitals, patients need to be transported to the nearest PCI center, requiring established communication and transportation routines between the referring and receiving hospitals. In a real-world setting, however, door-to-balloon times are unfortunately often much longer than 90 minutes, with only a minority of patients effectively treated within these targets.^{4, 56} Uncertainties about delays associated with communicating with the receiving catheterization laboratory, arranging patient transfer and mobilizing an interventional team within a 90-to-120-min interval often confuse physicians who refer patients for primary PCI. Results from studies comparing on-site fibrinolysis to primary PCI have even raised the impression that the superiority of primary PCI justifies long treatment delays caused by transportation. Different meta-analyses pooling these studies, however, suggest that the mortality benefit of primary PCI over fibrinolysis disappears with PCI-related delays exceeding one to two hours.^{57, 58} An analysis of the NRM databases sheds more light on how to triage patients to fibrinolysis or transport for primary PCI⁵⁹ (Figure 2).

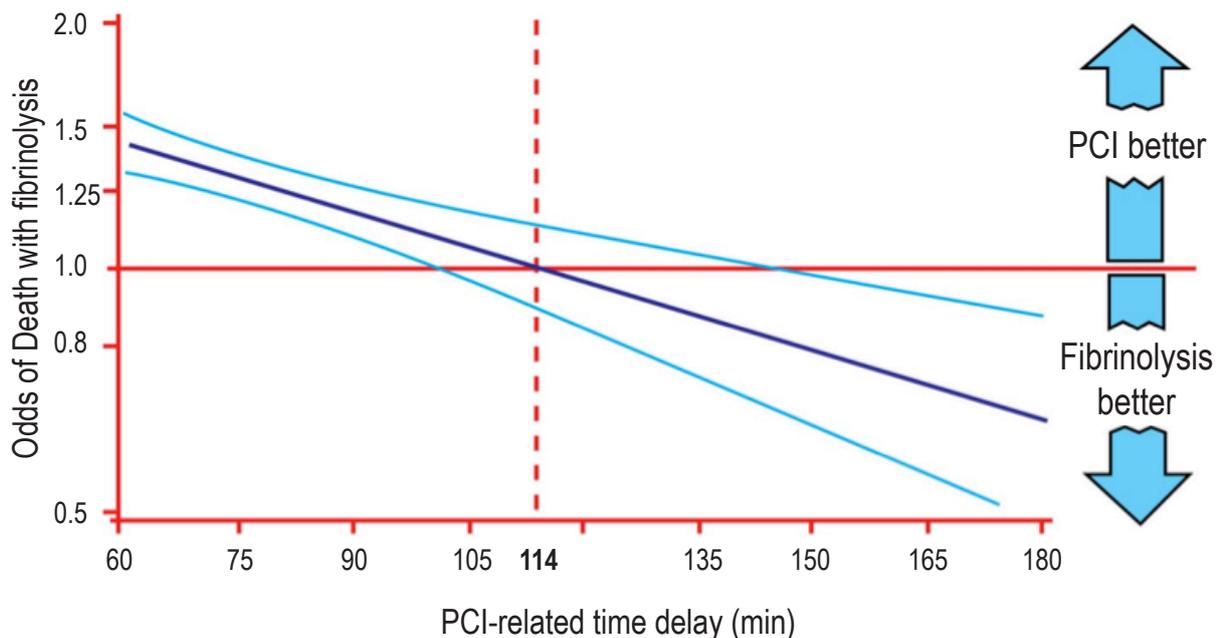


Figure 2: Decision in selecting reperfusion strategies, based on NRM databases analysis. (License No:2800051106031)⁵⁹

Increasing delays between door-to-needle times, versus door-to-balloon time was found to impair outcome: a 10% increased risk of in-hospital mortality for every 30 minutes delay that is lost with transferring the patient versus on-site fibrinolysis. When the PCI-related delay reaches 114 minutes, the benefit of primary PCI over fibrinolysis disappears in the overall population. The advantage of primary PCI over fibrinolysis in terms of outcome is lost even at much shorter PCI-related delays in younger patients (< 65 years) presenting with an anterior infarction within 2 hours of symptom onset. The benefit of lytic therapy might indeed be more pronounced in fresh occlusive clots jeopardizing a large myocardial area at risk, while younger patients are less at risk for bleeding complications. On aggregate, when primary PCI is not available within 90 (AHA/ACC) to 120 (ESC) minutes or when in doubt about transportation delays, STEMI patients should receive lytic therapy in the absence of contra-indications.^{3,54} In the latest ESC guidelines, the anticipated PCI-related treatment delay should even be shorter in patients presenting within 3 hours of symptom onset and with a large amount of ischemic myocardium at risk.³ Likewise, current AHA/ACC guidelines indeed imply that there is no strong preference of PCI over fibrinolysis in patients presenting within three hours of symptom onset.⁵⁴

Angiography and PCI after fibrinolysis

Unsuccessful or suboptimal epicardial reperfusion of the infarct-related artery occurs in 20 to 40% of fibrinolytic-treated patients, and is associated with poor functional recovery of the left ventricle and increased mortality. Failure of fibrinolysis to recanalize the occluded artery is generally suspected when chest pain or ST-segment elevation persists at 60 to 90 minutes after treatment initiation. Results from the recent REACT study clearly indicate that immediate rescue PCI is preferred over repeated fibrinolysis or a conservative approach when fibrinolysis is unsuccessful.⁶⁰ In contrast with earlier studies that failed to show a benefit with rescue PCI, almost half of rescue PCI patients received additional abciximab, indicating that additional antiplatelet therapy might be necessary to prevent early (re)thrombosis.

It is less clear whether a systematic approach of early planned PCI after fibrinolysis, often referred to as '*facilitated PCI*', is beneficial. Earlier small studies

showed that this strategy was both effective and safe.^{61,62} Results from the large ASSENT-4 PCI outcome trial, however, suggest that a planned PCI within the first two hours after fibrinolysis might even be harmful. In this trial, STEMI patients were randomized to full-dose tenecteplase followed by early planned PCI or primary PCI alone.⁶³ Unfortunately, the study was halted prematurely because of excess mortality and early reinfarction in the facilitated arm. This might have been caused by a lytic-induced prothrombotic state, unopposed by potent antiplatelet agents early after PCI, as neither up-front clopidogrel nor abciximab were given to lytic-treated patients. In any case, the combination of reduced-dose reteplase with the glycoprotein IIb/IIIa inhibitor abciximab also failed to improve outcome compared to primary PCI plus abciximab alone in the FINESSE trial.³⁴

A meta-analysis of studies comparing PCI within 24 hours after fibrinolysis versus a more conservative approach, suggests that routine early stenting might improve outcome.⁶⁴ In these studies however, rescue PCI was only rarely used in the conservative arm. Moreover, PCI was only performed very late after fibrinolysis, precluding potential myocardial salvage. The question as to whether lytic-treated patients should be immediately transferred to an interventional facility versus being transferred only when rescue PCI is indicated was directly addressed in the recent CARESS study. In this study, 600 high-risk STEMI patients in non-interventional hospitals were treated with half-dose reteplase plus abciximab and randomized to either immediate transfer to a PCI facility or local care with transfer only in case of persistent ST-segment elevation or clinical deterioration.⁶⁵ Median time between fibrinolysis and PCI was only 135 minutes in the routine referral group. Immediate transfer was found to be clearly associated with a lower risk of death, reinfarction or refractory ischemia at 30 days. The recent TRANSFER-MI and NORDISTEMI studies confirm a benefit of an invasive treatment after lytic therapy.^{66,67} All these results suggest that all high-risk STEMI patients who are treated with fibrinolysis should be systematically and if possible immediately transferred to a PCI-capable center. However, to avoid reocclusion during early PCI, due to prothrombotic side effects of the lytic agent and spontaneous reocclusion later, the ESC guidelines recommend performing a diagnostic angiography and PCI within 3 to 24 hours after successful fibrinolysis, in order to decide on the final treatment (PCI, CABG or medical management).³

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