

The pharmaco-invasive approach to STEMI: when should fibrinolytic-treated patients go to the "cath lab"?

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ABSTRACT

Although primary percutaneous coronary intervention (PCI) in clinical trials has lower rates of reinfarction, stroke and mortality than fibrinolytic therapy, because of system delays in routine practice, field triage and prehospital administration of fibrinolytic therapy may lead to similar clinical outcomes, especially in those patients who present in the first 2 h after symptom onset. Necessary for these outcomes is the liberal use of both rescue PCI and in-hospital revascularisation. Non-invasive prediction of failed reperfusion may be enhanced by the use of ST recovery, patient characteristics and troponin T levels, measured by point-of-care assays. This review focuses on the timing of, and indications for, an invasive strategy after fibrinolytic therapy, including that for failed pharmacological reperfusion.

The goal of treatment of patients with ST elevation myocardial infarction (STEMI), including those with presumed new-onset left bundle branch block, is to restore oxygenation and the supply of metabolic substrates to myocytes, as persistent thrombotic occlusion of the infarct-related artery (IRA) impairs left ventricular function and reduces survival. Various features on a presenting electrocardiogram (ECG) are of immediate and long-term prognostic significance, including the amount of ST segment elevation, the presence of Q waves and infarct location as well as the extent of ST recovery determined on the postfibrinolytic and prefibrinolytic ECGs.¹⁻⁴

In patients presenting within 12 h of symptom onset with STEMI, mortality is reduced by pharmacological reperfusion with fibrinolytic, antiplatelet and antithrombotic therapies.⁵ Furthermore, primary percutaneous coronary intervention (PCI) reduces the rates of reinfarction, stroke and mortality compared with fibrinolytic therapy,⁶ and therefore many centres have adopted primary PCI as their preferred reperfusion strategy.⁷ However, despite recent suggestions that thrombolysis has "lost its mojo",⁸ for a variety of reasons including system delays predominantly in emergency departments, for the foreseeable future a significant percentage of patients with STEMI, both world wide and in the United Kingdom are likely to be given fibrinolytic therapy.⁷ In this paper we discuss the pharmaco-invasive approach to the treatment of STEMI, focusing predominantly on rescue PCI.

PREHOSPITAL FIBRINOLYSIS

Early administration of fibrinolytic therapy in the ambulance reduces mortality compared with

administration after hospital arrival, making this a potentially attractive reperfusion strategy.^{9, 10} Examining this approach in routine care, the French USIC registry reported that patients treated with prehospital fibrinolysis had better survival rates than those undergoing primary PCI.¹¹ In the clinical trial setting, in Comparison of Angioplasty and Prehospital Thrombolysis In Myocardial infarction (CAPTIM), which randomised patients to receive prehospital fibrinolysis or primary PCI, those patients presenting <2 h after symptom onset had outcomes when randomised to prehospital fibrinolytic therapy as good or perhaps even better (eg, reduced cardiogenic shock) than those patients randomised to undergo primary PCI.¹² In the CAPTIM trial, fibrinolytic treated patients had rescue PCI and in-hospital PCI rates of 26% and 60%, and such rates are probably necessary to achieve outcomes as good as or potentially better than those achieved with primary PCI. Also, about 20% of patients in the ASessment of the Safety and Efficacy of New Treatment strategy-4 trial (ASSENT-4) were randomised in the ambulance to receive either prehospital (full dose) tenecteplase-facilitated PCI or primary PCI, and these patients had similar outcomes to those in the CAPTIM trial; the subgroup of 320 patients receiving prehospital fibrinolysis had a 30-day mortality of 3.1% compared with 3.7% for those randomised in the ambulance to receive primary PCI.¹³ Thus, in patients presenting early (<2-3 h) after symptom onset, prehospital fibrinolysis with a policy of liberal use of rescue PCI can achieve mortality rates of $\leq 4\%$, which are similar to those achieved by contemporary primary PCI.¹⁴ Performance of prehospital ECGs has recently been supported by an American Heart Association scientific statement.^{14a}

RESCUE ANGIOPLASTY

The utility of rescue angioplasty after fibrinolysis for STEMI was debated during the 1990s but received conceptual support from the meta-analysis performed by Ellis and coworkers in 2000,¹⁵ which showed that patients with TIMI 0-1 flow had better outcomes after rescue PCI than with conservative treatment. A more recent meta analysis of rescue PCI compared with conservative treatments,¹⁶ largely reflecting results from two randomised trials conducted in the United Kingdom in conjunction with three small trials, shows improved outcomes, and a trend towards mortality advantage associated with rescue PCI.

The first "large" trial of a rescue PCI strategy, the Middlesbrough Early Revascularisation to

Limit Infarction (MERLIN) trial, randomised 307 patients who failed to achieve 50% ST recovery at 60 min after fibrinolytic therapy (60% streptokinase) to either rescue PCI or conservative treatment (repeat administration of fibrinolytic therapy was discouraged).¹⁷ Overall, there was no difference in the outcomes of mortality or left ventricular function at 30 days, though there was improved event-free survival in the rescue PCI arm, largely owing to a decrease in subsequent revascularisation procedures (6.5% vs 20.1%, $p < 0.01$).

The 427 patient REscue Angioplasty versus Conservative Therapy (REACT) study, which used $< 50\%$ ST recovery at 90 min as an entry criteria, demonstrated a 50% reduction at 6 months in the composite of mortality, stroke, severe heart failure and recurrent myocardial infarction in patients undergoing rescue PCI compared with those randomised to either fibrinolytic readministration or conservative treatment; a reduction which was consistent across all age groups.¹⁸ At Liverpool Hospital (Sydney, Australia), we have found that among consecutive patients undergoing rescue angioplasty, $\sim 90\%$ after tenecteplase and with $> 70\%$ glycoprotein IIb/IIIa antagonist use, there was a 6-month mortality of 4% in those without cardiogenic shock; a similar mortality to that reported for primary PCI.¹⁹

The rates of both rescue PCI to achieve reperfusion when fibrinolytic therapy has failed, and early non-emergent percutaneous or surgical revascularisation after fibrinolytic therapy, have varied markedly in the trials examining strategies of transfer for primary PCI compared with (local) administration of fibrinolysis,²⁰ confounding their applicability to current practice. In these trials the patients came from a variety of clinical settings and healthcare systems, ranging from community hospitals to regional tertiary centres, and they received various pharmacological treatments and interventional techniques. Importantly, for example, the low rate (2.6%) of rescue PCI in DANAMI-2²¹ does not reflect contemporary practice.

The risk of serious bleeding has been an important cause of clinician concern about performance of PCI, including rescue PCI, in the first few hours after full-dose fibrinolytic therapy. Though there was an increased risk of minor bleeding associated with rescue PCI in the meta-analysis of Wijeyesundera *et al*,¹⁶ only REACT has reported major bleeding rates and found no difference in the rescue PCI and conservative arms.¹⁸ Nonetheless a radial artery approach to rescue PCI has been reported to be associated with low rates of transfusion compared with those reported with the femoral approach.^{19 22 22a}

PATIENT SELECTION CRITERIA FOR RESCUE PCI

In making triage decisions for rescue PCI, time is of the essence and the non-invasive evaluation of reperfusion needs to be performed quickly at the bedside. Early studies using intracoronary streptokinase in patients with STEMI described four features associated with recanalisation of the IRA: relief of chest pain, development of reperfusion arrhythmias, resolution of ST elevation (known as ST recovery) on the ECG and rapid release of biochemical markers.^{23 24} The prompt resolution of chest pain should be a goal in all patients, although complete resolution of pain has been shown to occur in only 29% of patients with patent arteries²⁵ and thus has not been a consistent and reliable guide to reperfusion. Also, the presence of accelerated idioventricular rhythm is not sufficiently sensitive to be of value in aiding triage decisions, despite this classic reperfusion arrhythmia being specific for patency of the IRA.²⁶

The degree of ST recovery has been shown to be associated with patency and flow in the IRA, with $> 70\%$ ST recovery

associated with a 90–95% probability of achieving a patent IRA.^{27 28} Single-lead ST-segment measurement has been found to be as good a predictor as multilead measurements,^{2 4} despite being less complex and easier to calculate at the bedside. However, ST recovery is an imperfect discriminator between TIMI grade 2 and TIMI grade 3 flow, with up to 50% of patients with persistent ST elevation having a patent IRA at the time of angiography.²⁹ Thus the lack of ST resolution can indicate failure of perfusion at a myocyte/microvascular level, and in these patients persistent ST elevation is associated with more extensive myocardial damage and a higher long-term mortality rate.²

Continuous ST-segment monitoring is the best method of assessing ST recovery,³⁰ but this has continuity limitations during patient transfer(s), whereas 12-lead ECGs provide “snapshots” of ST recovery. Various time intervals between recordings have been used in different studies. For example, the MERLIN study used 50% ST recovery in the lead with maximal ST elevation at 60 min, whereas the REACT study used 50% ST recovery at 90 min. This 30-min difference may in part provide a mechanistic explanation for the differences in the trial outcomes (ie, REACT was considered “positive” and MERLIN “negative”). Almost 50% in the interventional group in the MERLIN study had reperfused at 84 min (median) after fibrinolysis when angiography was performed, and one might have expected a similar proportion of later spontaneous reperfusion in those not randomised to undergo rescue PCI. Thus, patients in the conservative (or fibrinolysis readministration) arms of the REACT study, who had failed to achieve ST recovery by 90 min, may have been less likely to have subsequently reperfused than those in the “conservative group” in the MERLIN study.

Reperfusion of an occluded IRA is associated with an abrupt rise in cardiac marker levels and the rate of increase in these levels over the first few hours after reperfusion therapy is associated with the IRA TIMI flow grade at 90 min.^{30–33} Although measurement of cardiac marker levels and ST recovery together with clinical characteristics can enhance non-invasive prediction of reperfusion, this has been determined retrospectively in a reperfusion score.³⁴ Laboratory assays to measure cardiac marker levels are of little use in the triage of patients in the time-sensitive manner that is needed for urgent mechanical revascularisation. But, the immediate availability of cardiac troponin levels (and CK-MB and myoglobin) measured by point-of-care assays, can facilitate clinical decisions.

Aside from rescue PCI, a specific indication for immediate angiography with a view to revascularisation is cardiogenic shock. In those patients in the SHOCK trial treated with fibrinolytic agents, intra-aortic balloon counter pulsation was not associated with increased bleeding and the lowest mortality rate was found in those who received this combination; intra-aortic balloon counter pulsation was almost invariably inserted at the time of emergency angiography.³⁵

FACILITATED PCI: EMERGENCY ANGIOGRAPHY AND ANGIOPLASTY AFTER “SUCCESSFUL FIBRINOLYSIS”

The role of fibrinolytic administration followed by routine immediate PCI (facilitated PCI) remains uncertain after the early cessation of ASSENT-4 and slow recruitment to other trials comparing strategies of primary PCI with facilitated PCI. In ASSENT-4, patients were given full-dose tenecteplase before urgent angiography performed at 1–3 h.¹³ The trial was halted early by the data and safety monitoring committee, owing to concerns about the increased mortality in the tenecteplase-facilitated PCI arm of 6% compared with 3.7% in the primary

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PCI. A mortality rate of 6% was similar to that reported from tenecteplase-treated patients in the earlier ASSENT trials. The mortality hazard ratio (HR) for patients allocated to initial tenecteplase was not significant after adjustment for baseline risk (HR = 0.637 (95% CI 0.373 to 1.088)).¹³ Importantly, in ASSENT-4 the patients in PCI centres who received tenecteplase presented later and had a higher mortality than those recruited in the ambulance. There are several potential explanations for these findings, including a possible lack of familiarity in PCI centres with fibrinolytic regimens, lack of any infusion of heparin and the shorter than expected median time period between patients receiving fibrinolytic therapy and PCI. These factors may in part explain the increase in periprocedural thrombotic complications in those patients pretreated with tenecteplase in PCI centres.

In the Facilitated Intervention with Enhanced reperfusion Speed to Stop Events (FINESSE) trial,^{35a} patients presenting with STEMI with an expected delay of 1–4 h before primary PCI did not benefit from treatment with either abciximab alone, or in combination with reteplase, before PCI. The combined abciximab/reteplase strategy was associated with improved TIMI 3 flow before PCI, but there was no difference in TIMI 3 flow after PCI. Additionally, both upstream pharmacological strategies were associated with increased bleeding compared with “in-lab” abciximab. Though the non-inferiority study GRACIA-2, which compared immediate post-lysis PCI with primary PCI, showed improved tissue perfusion with initial fibrinolysis,³⁴ the concept of facilitated PCI is not supported by the currently available clinical outcome data.

TIMING OF NON-EMERGENCY ANGIOGRAPHY AND INTERVENTION

The current European PCI guidelines recommend routine coronary angiography and, if applicable, PCI in all patients after successful thrombolysis.³⁶ In registry studies of fibrinolytic-treated patients from Western Europe, high rates of in-hospital angiography and PCI are reported.¹¹ Also a recent 20-centre Australian survey showed that after STEMI, 87% of patients underwent in-hospital angiography, with 65% having PCI.³⁷ The WEST (Which Early ST elevation myocardial infarction Therapy) trial supports an approach of urgent, but non-immediate, post-fibrinolytic PCI.³⁸ In this study, 304 patients were randomised to one of three groups: (a) tenecteplase and usual care; (b) tenecteplase and mandatory invasive study <24 h, including rescue PCI for failed reperfusion and (c) primary PCI. Although there was a significant difference in the rate of death and reinfarction between A and C (13.0% vs 4.0%, $p = 0.021$), there was no difference between B and C (6.7% vs 4.0%, $p = 0.378$). Importantly, however, in this study patients were excluded if primary PCI was considered to be available within 1 h of diagnosis.

The GRACIA-1 study evaluated the timing of angiography after fibrinolysis. After tissue plasminogen activator therapy, 500 patients were randomised to either angiography and PCI or coronary surgery within 24 h or an ischaemia-guided approach.³⁹ As the primary end point included the need for (further) revascularisation as well as death and reinfarction it was perhaps not surprising that this rate was lower in the group requiring urgent angiography (6.4% vs 11.6%; $p = 0.043$).

In comparison, the Combined Abciximab RE-teplase Stent Study (CARESS) in acute myocardial infarction data appear to support the concept of very early angiography in fibrinolytic-treated patients who present to a non-PCI hospital.^{39a} In this study, patients with high risk STEMI (high risk defined by

>15 mm ST elevation, left bundle branch block, ejection fraction <35%, Killip class ≥ 2 , or prior myocardial infarction) had a lower rate of the composite primary end point of death, reinfarction or refractory ischaemia when taken for immediate revascularisation compared with those treated with a rescue-only strategy. Overall, there was no decrease in death or reinfarction, and the difference in the primary end point was driven mainly by a decrease in refractory ischaemia. There was an increase in bleeding with the immediate revascularisation strategy, but no increase in intracranial haemorrhages or the need for transfusion. Of note, the median times from pharmacological pretreatment to balloon inflation in FINESSE was 90 min, and in CARESS was 136 min. However, in FINESSE those patients randomised outside PCI centres, with a median additional delay of 35 min, did not appear to benefit from upstream treatment.

Finally, regionalisation of an integrated pharmaco-invasive approach to STEMI care from two centres in Minnesota USA and also North Carolina has been reported recently.^{40–42} Taken together, these studies support the use of early fibrinolytic therapy when primary PCI is not immediately available. Interestingly the lowest reported mortality was 3.7% (95% CI 0.1% to 7.1%) in the patients referred to the Mayo clinic (Rochester, Minnesota) who had received early fibrinolysis at a referral centre. In this protocol, patients were given full-dose fibrinolytic therapy if the onset of symptoms was <3 h before presentation, and all patients treated with fibrinolysis were immediately transferred to the PCI centre for evaluation for either rescue PCI or routine elective catheterisation at 24–48 h.⁴¹ Thus the optimal timing of angiography in patients receiving “successful fibrinolysis” is uncertain, as data between regional STEMI care studies and randomised trials are somewhat discordant. Randomisation of such transfer patients after “successful fibrinolysis” based on our reperfusion score,³³ to immediate versus routine angiography, is underway.

CONCLUSION

In-hospital fibrinolysis, especially in hospitals with routine 24-h primary PCI capability and acceptable routine “door to balloon” times, cannot currently be recommended. However, many patients with STEMI are still treated with fibrinolytic therapy for a variety of reasons, particularly in the prehospital setting. The need for rescue PCI should be determined at 60–90 min in all patients after fibrinolytic therapy. Prediction of failed reperfusion, including assessment of ST recovery, and potentially the use of point-of-care assays of markers of myocardial necrosis, could facilitate triage to either emergency angiography and, when appropriate, rescue PCI. Those who are felt to have reperfused pharmacologically should undergo non-emergent angiography and subsequent revascularisation where indicated, but this should be delayed for at least 2 h after the fibrinolysis, though the optimal timing remains uncertain.

Competing interests: None.

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