Fibrinolysis and primary PCI for ST-elevation myocardial infarction: call for a more refined perspective

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The latest meta-analysis comparing fibrinolysis with primary percutaneous intervention (PCI) has fuelled the discussion regarding the best reperfusion therapy for acute ST-elevation myocardial infarction.[1] As far as patients presenting to centres with intervention facilities are concerned, the superiority of primary PCI has been unequivocally demonstrated.[2] However, only a small proportion of patients with ST-elevation myocardial infarction primarily present to an intervention centre, the majority go to a hospital without these facilities. The optimal reperfusion strategy for patients presenting to a nonintervention centre or for patients presenting in the prehospital setting has been studied less extensively and the question remains as to whether all these patients should be transferred to an intervention centre to undergo primary PCI.

The available data to date on interhospital transport for primary PCI do show a mortality benefit for primary PCI.[3] Yet, as far as inferences to clinical practice are concerned, it remains to be seen whether these studies are truly representative: almost half of patients in the transportation trials received streptokinase, they were treated relatively late, and the subsequent revascularisation strategy was rather conservative.

The impact of primary PCI as compared with prehospital fibrinolysis in patients presenting in the prehospital setting has so far only been addressed in the randomised CAPTIM trial, without significant differences in outcome.[4] Additional studies are warranted, with early treatment as primary focus. For patients presenting to nonintervention centres or prehospitally, the impact of triage, and of combined pharmaco-invasive reperfusion strategies are promising fields of further exploration. *(Neth Heart J* **2004;12:343-6.)**

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ST-elevation myocardial infarction in an intervention centre

Ever since the first comparisons of primary PCI and fibrinolysis early in the 1990s, the attention for primary PCI has increased accordingly. A primary PCI results in higher epicardial reperfusion rates (TIMI-3 flow of 70 to 95% versus 50 to 60% at 90 minutes after fibrinolysis) and has the advantage of the potential early triage of patients with left main and/or multivessel disease.[2]

A recently published quantitative review of 23 randomised trials showed a significant 30-day mortality reduction from 7 to 5% in favour of primary PCI.[1] Yet, this meta-analysis also included patients presenting to hospitals without intervention facilities.

As early as in 1997 the randomised evidence already proved to be in favour of primary PCI for patients presenting to an intervention centre (table 1).[2] In a quantitative analysis of about 2600 patients, the mortality benefit attained with an intervention is 21 lives saved per 1000 treated patients. Over the years, several additional trials were performed in which accelerated tPA was used in the control arm.[5-7] Irrespective of the use of the type of agent, primary PCI is to be preferred, although the magnitude of benefit differs according to

Table 1. Pooled data from randomised trials in ST-elevation myocardial infarction: primary PCI versus fibrinolysis.

Presentation to intervention centre
21 per 1000 lives saved with primary PCI

	Primary PCI	Fibrinolysis	p value
Mortality*	4.4% 57/1290	6.5% 86/1316	0.02

* JAMA 1997;278:2093-8, 30 days to 6 weeks.

Presentation to nonintervention centre
28 per 1000 lives saved with primary PCI

	Primary PCI	Fibrinolysis	p value
Mortality**	6.8% 84/1242	9.6% 117/1224	0.01

** Eur Heart J 2003;24:21-3, 30 days to 6 weeks.

the pharmacological reperfusion strategy used, varying from 10 per 1000 with accelerated tPA to 50 per 1000 with streptokinase.

With respect to inferences to clinical practice, it should be noted that the trial data stem from highly specialised, high-volume intervention centres, with a lot of experience. The impact of these aspects is illustrated by the outcome of the GUSTO-IIb trial, in which no difference in one-year outcome was observed between fibrinolysis with rt-PA and a primary PCI.[8] Yet, when data were broken down by the experience of the operators, outcome in high-volume centres was significantly better than after fibrinolysis. Registry data corroborate with these findings, underscoring the importance of short door-to-balloon times and good operator experience.[9] Guidelines from the American College of Cardiology and the European Society of Cardiology prescribe that a primary PCI is to be preferred, provided the above-mentioned conditions are met, and the procedure can be performed within 90 minutes after first medical contact. The importance of time delays in primary PCI was recently underlined in an overview of 23 randomised trials, which demonstrated that the benefit of primary PCI on mortality and the combined endpoint of death, reinfarction and stroke may be lost if door-to-balloon times were delayed by more than 62 and 93 minutes, respectively, as compared with the door-to-needle time with fibrinolysis.[10]

The observed mortality benefit with primary PCI has fuelled the call for an increase in the number of intervention centres, but may pose logistic problems. Aspects of early triage, pretreatment, and the need for on-site surgery should therefore be studied more thoroughly. Whether or not all intervention centres need on-site cardiac surgery remains a matter of debate, although at present the number of intervention centres without on-site cardiac surgery but with surgical backup is growing. The C-PORT has shown safety and clinical superiority of primary PCI without on-site cardiac surgery compared with fibrinolysis.[7] Regarding the implementation in daily clinical practice, it is important to be aware of the logistic aspects involved and of the fact that preservation of the currently high standard of interventional experience in the Netherlands should be the cornerstone in the further implementation of the plans.

ST-elevation myocardial infarction in a nonintervention centre

Of all hospitals in the Netherlands, ~19 have facilities for primary PCI. Consequently, a significant proportion of patients with a myocardial infarction present to nonintervention centres. Observational studies have shown the feasibility and safety of interhospital transportation. To date, a mere 2466 patients have been randomised to either fibrinolysis in the nonintervention centre or to referral for a primary PCI.[3] The results suggest that transport for an intervention is more effective than fibrinolysis on the spot (table 1).

Interestingly, the benefit of a primary PCI seems even more outspoken, despite the potential delay associated with transportation. Yet, transfer time only accounted for an average of 39 minutes, with a median randomisation-to-balloon time of about 100 minutes. Critical appraisal as to how representative these trials are of the current clinical situation is, however, warranted. The fact that about 40% of patients in the control arms of the trials received the moderately effective streptokinase may have overestimated the benefit in the pooled analysis of referral for primary PCI.[11,12] Whereas the relative risk reduction in these trials was 24%, it was 14% when compared with rt-PA. Moreover, the DANAMI-2, using rt-PA, had a design that created a disadvantage for fibrinolytic therapy by including patients with prior stroke and advocating re-fibrinolysis instead of angioplasty for an impending reinfarction.[13] A second aspect that may have contributed to an overestimation of the clinical benefit of primary angioplasty in the transportation trials is the fact that one of the transportation trials was limited to high-risk patients, in whom the most pronounced benefit can be obtained.[14] Including these data (relative risk reduction 40%), the benefit for primary PCI in the overall population is probably overestimated. These examples demonstrate that the trials in the meta-analysis are only partly representative of the current clinical situation and that the observed differences can not simply be translated into daily clinical practice in the Netherlands. In addition to the previously mentioned aspects, the reported small additional time delays associated with interhospital transport in the randomised trials may not reflect daily clinical practice. Besides a combined pharmaco-invasive strategy to bridge potential time delays associated with interhospital transport, early treatment by means of

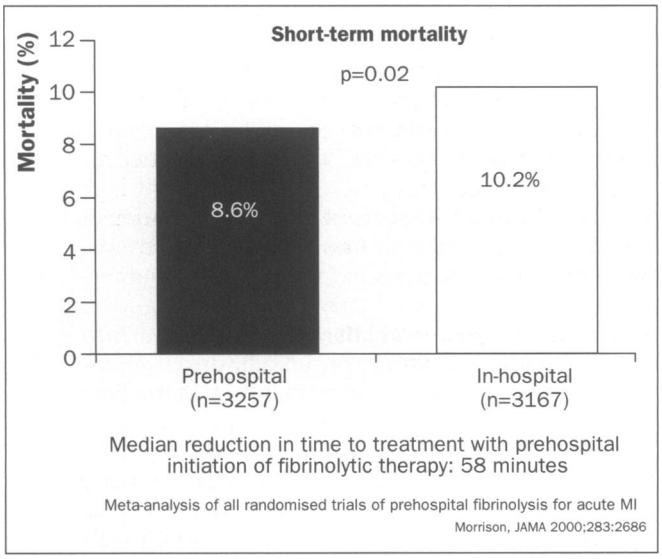

Figure 1. Randomised results of prehospital fibrinolysis vs. in-hospital fibrinolysis.

prehospital triage or prehospital fibrinolysis with or without an additional intervention could be an attractive alternative treatment strategy which deserves further investigation.

ST-elevation myocardial infarction in the prehospital setting

Prehospital fibrinolysis is often underappreciated. The clinical impact of pharmacological reperfusion is highest in patients treated early, and with prehospital initiation of fibrinolytic therapy about one hour is gained as compared with in-hospital initiation in ST-elevation myocardial infarction. Meta-analysis of all randomised prehospital fibrinolysis trials reveals a benefit of 16 to 18 lives saved per 1000 patients treated, a relative reduction of 17% (figure 1).[15] This benefit is of the same order of magnitude as the difference achieved by primary PCI observed in the randomised trials in intervention centres when compared with in-hospital fibrinolysis. The CAPTIM trial is the first multicentre trial in which primary PCI was compared with fibrinolysis in a prehospital setting.[4] A primary PCI after prehospital diagnosis, thus allowing the cath-lab to get ready (median door-to-balloon time: 40 minutes), was compared with prehospital fibrinolytic therapy with a liberal rescue angioplasty policy (26%). All patients were transported to intervention centres. Mortality at 30 days was astonishingly low: 3.8 versus 4.8% for prehospital fibrinolysis and primary PCI, respectively. The combined primary endpoint of death, reinfarction and stroke was not significantly different between groups, although it should be noted that the trial was stopped prematurely due to slow inclusion and lack of finances rendering the study underpowered. An interesting substudy of the CAPTIM showed that in patients treated within two hours of symptom onset a marked one-year mortality benefit was observed in favour of prehospital fibrinolysis (2.2 vs. 5.7%, p=0.058).[16]

The HIS (Holland Infarct Study) was designed to compare rather similar strategies for the situation in the Netherlands: patients with a large ST-elevation myocardial infarction presenting in the ambulance or to a nonintervention centre were randomised to either a primary PCI with abciximab pretreatment or early (preferably prehospitally) initiated fibrinolysis, with a protocol-driven, liberal policy of rescue angioplasty. Unfortunately, the HIS was stopped prematurely due to logistic problems and a lower than anticipated recruitment rate. However, the scientific questions and the design of the study are still up to date and very

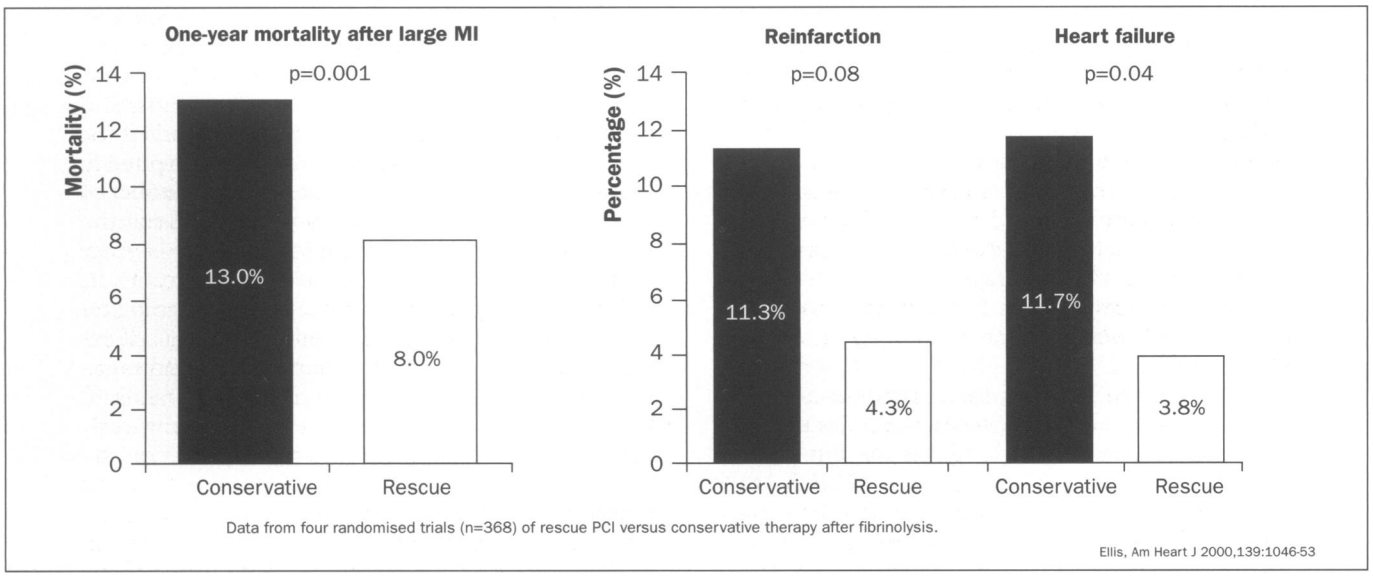

Figure 2. Randomised results of rescue PCI.

relevant. With the promising CAPTIM data, additional prehospital studies are warranted, especially in view of the fact that 50 to 60% of the patients are treated within two hours of symptom onset with prehospital fibrinolysis and the time gain associated with early cath-lab preparation for primary PCI.[17-19]

Future directions

Although the additional benefit of prehospital fibrinolysis compared with in-hospital fibrinolysis is undisputed, TIMI-3 flow will not be realised in a substantial number of patients. A meta-analysis of rescue angioplasty with angiographically documented failed reperfusion in patients with large infarctions demonstrated a significant relative one-year mortality reduction of 38%, equal to 50 lives saved per 1000 patients treated as compared with a conservative strategy (figure 2). In addition, reductions in re-infarction and heart failure are impressive, with events saved per 1000 treated patients of 70 and 80, respectively.[20]

Randomised data from the Maastricht area have shown that a systematic strategy of early angiography with/without 'rescue' angioplasty may result in similar TIMI-3 flow rates as achieved by primary PCI.[21] In spite of this, the potential benefit of rescue angioplasty is often questioned, although the (limited number) of randomised trials suggest a clinically relevant benefit. Of importance though, the CAPTIM used noninvasive clinical grounds to perform rescue angioplasty, whereas in rescue angioplasty trials systematic angiography was performed to assess infarct-related artery patency. In the regions in the Netherlands adopting a policy of rescue angioplasty, a similar noninvasive approach is followed to triage patients.

When a primary PCI is the preferred reperfusion strategy, pretreatment with a glycoprotein IIb/IIIa receptor blocker or fibrinolysis could enhance preprocedural TIMI-3 flow and possibly improve clinical outcome.[22] From either perspective, different combinations of pharmaco-invasive reperfusion strategies should become the subject of further study, preferably in a prehospital setting.

To reduce the bleeding risk associated with full-dose fibrinolysis, half-dose rt-PA pretreatment before rescue angioplasty was tested in the placebo-controlled PACT trial, achieving about 30% TIMI-3 flow in the treatment arm at angiography at a median of 49 minutes after lysis.[23] Primary angioplasty trials using tirofiban or abciximab as pretreatment showed preprocedural TIMI-3 rates of 19 to 30%, sometimes superior and sometimes similar to aspirin and heparin alone.[24,25] None of these trials were designed to demonstrate clinical effect. Given the known 60-minute patency rate of TNK-tPA (60% TIMI-3 flow), pretreatment with this agent before primary angioplasty might be expected to give the most pronounced benefit. This strategy will be compared with a standard primary angioplasty in the clinical ASSENT-4 trial. Studies such as the FINESSE (cath-lab initiated abciximab + primary PCI vs. abciximab pretreatment + PCI vs. 1/2 rPA + abciximab pretreatment + PCI), ADVANCE (eptifibatide + PCI vs. 1/2 TNK + eptifibatide + PCI) and CARESS (1/2 r-PA + routine PCI vs. 1/2 r-PA + rescue PCI) will test other reperfusion strategies.

These trials will give insight into the magnitude of additional clinical benefit from more intensive antithrombotic pretreatment and whether this counterbalances the expected increase in bleeding risk. Moreover, CARESS might provide insight into whether routine angioplasty or clinically driven angioplasty should be opted for after a half-dose fibrinolytic pretreatment.

In conclusion, the obtained overall benefit of primary PCI in an intervention centre is 21 lives saved per 1000 treated patients and ranges from 10 per 1000 with second-and third-generation fibrinolytics to 50 per 1000 with streptokinase. Critical re-appraisal is warranted with respect to how representative the trials involving interhospital transport for primary PCI are for the clinical situation in the Netherlands. On the one hand, data with respect to the mortality benefit for patients presenting to an intervention centre have been thoroughly tested and proven reproducible. Notably, primary PCI should preferably be performed within 90 minutes of presentation. Moreover, the clinical outcome of a primary PCI has been shown to largely depend on the infrastructure of the intervention centre and operator experience. With the increasing number of intervention centres, it is of paramount importance to guarantee the prerequisites with respect to logistics and operator experience, if the currently high standard of care is to be maintained.

On the other hand, further research is warranted to address the issue of patients presenting to a non-intervention centre or prehospitally. With respect to transportation trials, almost half of the control arm data reflect outcome using first-generation, less potent, fibrinolytics and the subsequent revascularisation strategy was rather conservative. Prehospital fibrinolysis, as well as prehospital diagnosis and triage for a primary PCI have been implemented in a growing number of regions in the Netherlands, but trials addressing the influence on outcome of these strategies are lacking. Future trials should therefore focus on early treatment, prehospital triage and the impact on pharmacological pretreatment, whereas in daily clinical practice all efforts should be made to improve our logistics and infrastructure, not only at the level of the hospital itself, but also at a regional level to further improve the treatment of acute ST-elevation myocardial infarction. ■

References

The references of this article can be found on the website (cardiologie.nl), section 'Netherlands Heart Journal'.