Primary angioplasty: Preprocedural pharmacological therapy

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Primary coronary angioplasty has been shown to be an effective reperfusion therapy for patients with acute myocardial infarction, not only for those who present to PTCA centres but also for patients who present to hospitals without angioplasty facilities. With the increasing use of primary angioplasty more patients will be transferred to a (tertiary) PTCA centre. An increase in treatment delay is associated with a worse clinical outcome. The importance of an open infarct-related vessel at acute angiography is becoming clear. Pharmacological pretreatment of patients during transportation to a PTCA centre with the aim to open the infarct-related vessel in advance might be beneficial. Glycoprotein IIb/IIIa receptor blockers seem to be the agents of choice for facilitated PTCA. The safety and (cost) effectiveness of this pretreatment of patients transported to undergo primary angioplasty remain to be evaluated. (*Neth Heart J* 2006;14:55-61.)

Keywords: PTCA, transportation, myocardial infarction

Primary coronary angioplasty in patients with acute myocardial infarction (MI) has been shown to be an effective reperfusion therapy both at short- and long-term follow-up. In 1993 the first randomised trials comparing immediate coronary angioplasty with thrombolytic therapy in acute myocardial infarction reported a better clinical outcome with immediate coronary angioplasty.[1,2] This was also confirmed at long-term follow-up.[3] The use of stents may further improve outcome after primary angioplasty.[4,5] These studies were all performed in centres with PTCA facilities. However, even when transfer to an angioplasty centre is necessary, primary angioplasty remains superior to immediate thrombolytic therapy.[6] Results can be further improved by pharmacological pretreatment during transportation with the aim to improve patency of the infarct-related vessel before primary angioplasty.

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Effect of treatment delay on outcome

Recent European (2003) and American guidelines (2004) for treatment of acute MI report that patients in cardiogenic shock and patients with contraindications for thrombolytic therapy have a class I indication for transportation to a PTCA centre to undergo primary angioplasty.[7,8] In addition, primary angioplasty is the treatment of choice in high-risk patients (large MI, Killip class III) whenever the procedure can be performed within 90 minutes after diagnosis. Transportation of patients with acute MI is safe and feasible but may lead to an increase in treatment delay. Zijlstra et al. reported in 1997 that the influence of transportation on total ischaemic time was limited and that there was no difference in clinical outcome at six months between the transferred (high-risk) patients and the nontransferred patients.[9] However, an increase in treatment delay of 45 minutes in patients in the early phase of acute anterior myocardial infarction is associated with a larger infarct size and a worse left ventricular ejection fraction.[10] De Luca et al. showed that every minute of delay counts, so that all efforts should be made to shorten the total ischaemic time for patients treated with primary angioplasty.[11] Also data from the NRMI-2 registry of more than 27,000 patients from 661 hospitals in the United States elegantly showed the relationship between increased mortality and delay in door-to-balloon time, especially when door-to-balloon time is greater than 120

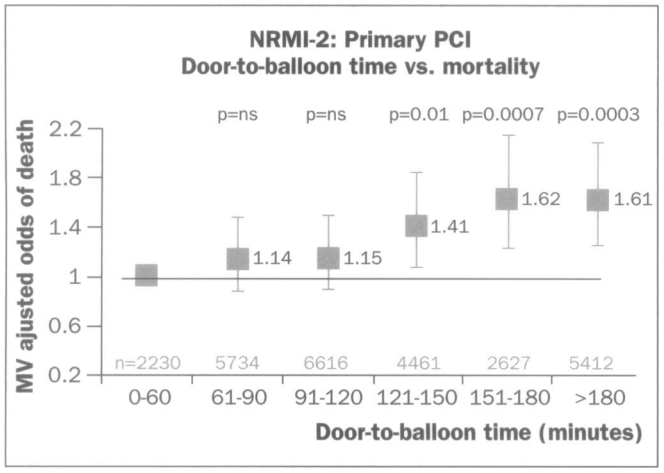

Figure 1. Door-to-balloon time vs. mortality (multivariate adjusted odds). Reprinted with permission from the author.[12]

minutes (figure 1).[12] Door-to-balloon time was more than two hours in nearly 50% of patients in this cohort.

Reduction of treatment delay using prehospital infarct diagnosis and triage

It is possible to achieve a further reduction in time to treatment by infarct diagnosis and risk stratification in the ambulance. The PHIAT (PreHospital Infarction Angioplasty Triage) registry performed in the Zwolle region included more than 200 patients in two years time.[13] When patients were identified as having a large acute MI (i.e. fulfilling electrocardiographic criteria with respect to cumulative ST-segment deviation), immediate transfer to a PTCA centre and preparation of cath lab and personnel were initiated. This was associated with a reduction in total ischaemic time of 45 to 60 minutes compared with patients seen primarily in the emergency room or referred from one of the surrounding non-PTCA centres.[14] The median times from onset of symptoms to admission and from admission to first balloon inflation were 122 and 38 minutes, respectively. It is safe, feasible and effective to identify patients with a large myocardial infarction in this way in order to transport them directly to a PTCA centre, thereby preventing the unnecessary visit to a non-PTCA centre.

Importance of an open vessel at acute angiography

In a study by Brodie and colleagues, a 13-year follow-up of 1490 consecutive patients is reported, all of whom had acute myocardial infarction treated with aspirin and heparin followed by primary angioplasty.[15] TIMI 2 to 3 flow was present at initial angiography in 18.3% of patients, with TIMI 0 to 1 flow in the remainder. Baseline characteristics were similar between the two groups, but those patients with an initial open infarct-related vessel less often presented in cardiogenic shock (1.7 vs. 9.4%, p<0.0001). Patients with initial TIMI 2 to 3 flow had lower peak enzyme values (1328±1529 vs. 2790±2730; p<0.0001), higher acute (54.3±13.4% vs. 51.6±12.8%; p=0.05) and late (59.2±14.2% vs. 54.9±13.1%; p=0.004) ejection fraction and lower 30-day mortality (4.8 vs. 8.9%; p=0.02). Procedural outcomes (i.e. achievement of <50% residual narrowing in the infarct-related artery at the PTCA site with TIMI 2 to 3 flow) were also better in this group (97.4 vs. 93.8%; p=0.02). Lee et al. and Stone et al. published comparable results.[16,17] It was found that patients with 'spontaneous' recanalisation' (after aspirin and heparin in the emergency room) of the infarct-related vessel had a smaller infarct size and a better left ventricular function, and Stone showed that an open (TIMI 3 flow) infarct-related vessel before intervention was an independent predictor of survival and clinical outcome compared with patients without TIMI 2-3 flow at initial angiography. De Luca et al. recently showed that preprocedural TIMI flow is an independent predictor of one-year mortality in high-risk patients (i.e. TIMI risk score ≥4).[18]

In conclusion, these data show that if restoration of antegrade flow occurs before primary angioplasty, clinical outcomes are better, especially in patients at high risk of adverse events.

Situation in the Netherlands

In the Netherlands, the chance of being admitted to a hospital with PTCA facilities is low as only 18 hospitals out of a total of 109 hospitals (17%) have such facilities. Despite that, an increasing percentage of patients with acute MI have undergone primary or rescue angioplasty in recent years [personal communication]. This is due to an increase in referring patients, often with large acute myocardial infarctions, to a centre with PTCA facilities. After PTCA most patients return to their local hospitals after a short period of observation and stabilisation. The mean delay due to transportation and preparation of the cath-lab in transferred patients in the Zwolle area is reported to be 60 to 70 minutes. This might be longer in highly urbanised areas and in hospitals with less experience with primary angioplasty. Therefore, pharmacological pretreatment during transportation aimed at restoration of TIMI 3 flow before angioplasty and facilitating the PTCA procedure might be beneficial, even in small countries like the Netherlands.

Ambulance service structure

In the Netherlands there are 31 ambulance regions with more than 600 ambulances, all staffed with a specialised nurse and a driver. After successful experiments with prehospital infarct diagnosis (+ therapy) in five ambulance regions in the country, all ambulances are equipped with 12-lead ECG computers using an algorithm capable of diagnosing large acute myocardial infarction. Combined with the fact that administration of thrombolytic therapy is part of the continuing education programme of the ambulance personnel, it

is possible to start the pharmacological pretreatment (lytic, IIb/IIIa blocker or combination) shortly after having made the diagnosis in the ambulance.

Facilitated PTCA: which agent?

Aspirin

The beneficial effects of aspirin in patients with acute myocardial infarction were established in the ISIS-2 (International Study of Infarct Survival).[19] Whether this beneficial effect may, in part, be due to a higher initial patency rate has not been studied; however, a retrospective study showed that patients who received aspirin and heparin before transportation had a higher initial patency compared with patients who did not receive these drugs.[20] The prehospital administration of aspirin is a simple, inexpensive and widely applicable treatment option in patients with suspected or confirmed acute myocardial infarction.

Heparin

High-dose intravenous bolus heparin (300 U/kg) together with aspirin (160 mg chewed) before primary angioplasty showed full coronary reperfusion in a considerable number of patients with acute myocardial infarction, especially in those who were treated early.[21] TIMI flow grade 3 was seen in 31% of the patients and TIMI flow grade 2 was seen in 20% of the patients. It was suggested that pretreatment with high-dose heparin might lead to a higher patency rate at initial angiography. However, in a much larger randomised trial in which patients with acute myocardial infarction were randomised to pretreatment with either high-dose bolus heparin (300 U/kg) or low-dose (0 or 5000 U), this was not confirmed.[22] There was no difference in patency at initial angiography and clinical endpoints were similar. Within the high-dose heparin group no benefits were seen with increasing time between administration of heparin and angiography. Therefore, based on these data there is no evidence for pretreatment with high-dose bolus heparin in patients undergoing primary angioplasty.

Thrombolysis

The PACT (Plasminogen-activator Angioplasty Compatibility Trial) showed that a 50-mg bolus of recombinant tissue-type plasminogen activator (rt-PA) resulted in a significantly higher patency rate compared with placebo, when it was given as pretreatment at a mean of 32 minutes ahead of the angiography procedure.[23] However, the primary endpoint of the study (death, re-MI, stroke) was not different and left ventricular function was similar in both treatment groups. It is still unclear whether pretreatment with thrombolytic agents is beneficial in patients who are being transported to a PTCA centre. Two small-sized European

Table 1. Results of the PRAGUE trial.

Outcome 30 days	On-site SK	SK+PTCA	PTCA	P value
Death (%)	14	12	7	
Re-MI (%)	10	7	1	p<0.03
Stroke (%)	1	3	0	
Death/stroke/re-MI combined (%)	23	15	8	p<0.02
Bleeding (%)	0	8	0	
(Re)-PTCA	11	5	4	
CABG (%)	3	2	3	

No deaths or major complications during transportation.
SK=streptokinase, PTCA=percutaneous transluminal coronary angioplasty, MI=myocardial infarction, CABG=coronary artery bypass graft.
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Table 2. Results of the LIMI trial at 42 days follow-up.

	On-site rt-PA (n=75)	rt-PA+PTCA (n=74)	PTCA (n=75)	P value
Death (n)	5	6	5	ns
Stroke	2	3	2	
Re-MI	7	4	1	ns
Death/stroke/re-MI combined	14	13	8	ns
Minor bleeding (%)	11	21	11	

No deaths or major complications during transportation; no severe bleeding complications.
rt-PA=alteplase; PTCA=percutaneous transluminal coronary angioplasty; MI=myocardial infarction.
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Table 3. Primary endpoint of ASSENT 4 at 90 days follow-up.

	TNK + PCI (n= 828)	PCI alone (n=838)	P value
Death/congestive HF, cardiogenic shock	18.8%	13.7%	0.0055

TNK=tenecteplase, PCI=percutaneous coronary intervention, HF=heart failure.
From Van de Werf F, Ross A. American Heart Association Scientific Sessions 2005; Nov 13-16, 2005; Dallas, TX, US.

studies showed that pretreatment with streptokinase or t-PA was associated with a worse outcome compared with transportation without thrombolytic pretreatment despite the fact that the percentage of patients with an open infarct-related vessel was higher in the pretreated group (tables 1 and 2).[24,25] This was mainly due to a higher rate of bleeding and reinfarction in the patients who were treated with thrombolytic therapy.

Recently the Assessment of the Safety and Efficacy of the New Thrombolytic Regimen (ASSENT 4) study was stopped prematurely due to a higher incidence of adverse events in the facilitated PCI arm (table 3).[26] Although the 30-day preliminary results showed that major bleeding and intracranial haemorrhages occurred more frequently in the combined treatment (i.e. facilitated PTCA) group, this cannot fully explain the difference in mortality. More detailed information showed that pretreatment with full-dose tenecteplase (TNK) was associated with a higher incidence of subacute thrombosis and reinfarction, suggesting a prothrombotic effect of thrombolysis. Recently the primary endpoint of the study was presented at the American Heart Association meeting in Dallas and showed a significantly worse outcome in the patients pretreated with thrombolysis. Only the patients who received the full dose of TNK prehospitally in the ambulance showed a trend towards better outcome, however, the results of these subanalyses should be interpreted with caution.

Glycoprotein IIb/IIIa receptor blockers

Abciximab

In 1997 it was shown for the first time that abciximab has lytic potential when given to patients with acute MI.[27] The GRAPE (Glycoprotein Receptor Antagonist Patency Evaluation) study was a small-sized pilot trial which showed that pretreatment with abciximab (250 µg/kg bolus followed by a 12-hour infusion of 10 µg/min) given in the emergency room to patients awaiting primary angioplasty at a median time of 45 minutes before angioplasty was associated with TIMI 3 flow in about 20% and TIMI 2 or 3 flow in about 40% of the patients at angiography. There was no difference in percentage of TIMI 2 or 3 flow between patients who received abciximab early after onset of symptoms or later (>2.5 hours).[28] The ADMIRAL (Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up) study was a randomised, placebo-controlled study, in which a subanalysis showed that abciximab, when given early in the ambulance or the emergency room, was associated with a higher patency rate, a better left ventricular function and a lower rate of death and MI compared with placebo.[29] However, patients who received the active agent only shortly before intervention (in the cath-lab) did not have any benefit. This is in agreement with the results from the larger CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) and RAPPORT (Reopro in Acute myocardial infarction and Primary PTCA Organisation Randomised Trial) trials which showed no long-term benefit in patients who received abciximab during or shortly before the angioplasty procedure.[5,30] In conclusion, abciximab seems useful for facilitation of primary angioplasty, especially when it is administered early.

Eptifibatide

So far, only very few data are known about the effect of pretreatment with eptifibatide alone in patients undergoing angioplasty for acute myocardial infarction. In a small, nonrandomised study early administration of eptifibatide before primary angioplasty resulted in a significantly higher incidence of partial or complete reperfusion of the infarct-related vessel at baseline angiography as well as improvement of several procedural variables, suggesting a decrease in overall procedure complexity.[31]

Tirofiban

Several small trials have shown that this agent can be safely given in patients with acute MI, especially in combination with low-molecular-weight heparin. The TIGER-PA (Tirofiban Given in the Emergency Room Primary Angioplasty) study showed that, when given in the emergency room, tirofiban (bolus of 10 µg/kg followed by 0.15 µg/kg/min maintenance) resulted in a better initial flow of the infarct-related vessel with a lower TIMI frame count, compared with patients who received the agent 34 minutes later in the cath-lab, only shortly before angioplasty.[32] The recently published On-TIME trial showed that the administration of tirofiban, given at a median of one hour before primary angioplasty and started either in the ambulance or in

the referring hospital, did not significantly improve TIMI 3 flow of the infarct-related vessel at initial angiography. Despite an improved patency (i.e. TIMI 2 or TIMI 3 flow), a lower prevalence of thrombus or fresh occlusion, and a better myocardial perfusion in the infarct-related region before primary angioplasty, no beneficial effect on angiographic or clinical outcome after primary angioplasty was found, as compared with initiation of tirofiban in the catheterisation laboratory, a few minutes before primary angioplasty.[33]

In a recently published meta-analysis of six randomised trials (three trials with tirofiban and three trials with abciximab) it was shown that early administration of glycoprotein IIb/IIIa receptor blockers in patients with acute myocardial infarction appeared to improve patency of the infarct-related vessel before primary angioplasty with favourable trends for clinical outcome.[34] TIMI flow grade 2 or 3 (41.7 vs. 29.8%) as well as TIMI flow grade 3 (20.3 vs. 12.2%) were significantly more frequent in the early group compared with the late group: odds ratio 1.69, 95% confidence interval (CI) 1.28 to 2.22 ($p<0.001$) and odds ratio 1.85, 95% CI 1.26 to 2.71 ($p<0.001$), respectively. The early administration of glycoprotein IIb/IIIa receptor blockers was associated with a 28% reduction in mortality from 4.7 to 3.4%, which was not significant but consistent with similar trends for reinfarction and the composite ischaemic endpoint.

Combination of (low-dose) thrombolytic therapy and IIb/IIIa blockade

The SPEED (Strategies for Patency Enhancement in the Emergency Department) trial was a dose-finding study investigating the effect of pretreatment with full-dose abciximab (bolus 0.25 mg/kg, maintenance infusion 0.125 mg/kg/min during 12 hours) and different doses of reteplase and heparin in patients with acute MI.[35] It was shown that the combination of full-dose abciximab, low-dose reteplase (two 5U boluses administered 30 minutes apart) and heparin (60 U/kg, maximum of 4000 U) resulted in the same patency rates compared with normal-dose reteplase, and major bleeding occurred more frequently with reteplase and abciximab combined compared with reteplase alone (9.8 vs. 3.7%). However, when the extent of ST-segment elevation resolution was taken as the endpoint instead of patency, the combination of abciximab and low-dose alteplase was associated with faster and better resolution of ST-segment elevation compared with pretreatment with thrombolytic therapy alone and a reduction in angiographically evident thrombus and residual stenosis.[36,37] The administration of abciximab with alteplase did not increase the incidence of major bleeding compared with alteplase alone.[38] In the ASSENT-3 and GUSTO-V studies, it was shown that the combination of low-molecular-weight heparin or abciximab reduced ischaemic complications but did not reduce short-term mortality.[39,40] In the ASSENT-3 trial the rate of bleeding episodes and the need for transfusion were significantly increased with combined therapy. In the GUSTO-5 trial the rates of intracranial haemorrhage and nonfatal strokes were overall the same for patients treated with half-dose reteplase with abciximab as for patients treated with standard dose reteplase. However, combination therapy was associated with a significant increase in intracranial haemorrhage among patients over the age of 75 (2.1 vs. 1.1%) and with increases in the risk of other bleeding events and the need for transfusion. The risk of intracranial bleeding was age-dependent.[41] In a registry from Dudek et al. it was also shown that the combination of (reduced-dose) alteplase and abciximab caused major bleeding complications in 3% of patients.[42] The recently presented BRAVE (Bavarian Reperfusion Alternatives Evaluation) study showed that no improvement in angiographic outcome post primary angioplasty could be observed, despite a significantly higher initial patency rate.[43] Larger scale studies are planned to evaluate whether pretreatment with the combination of lytic and glycoprotein IIb/IIIa blockade, especially with respect to dosage schemes, is superior to pretreatment with glycoprotein IIb/IIIa blockade alone in infarct patients undergoing angioplasty.[44,45] These clinical trials should be done to evaluate the safety of such combination therapies before they can be applied widely in routine clinical practice.

Conclusion

With the increasing use of primary angioplasty as treatment modality for patients with acute MI, also for patients who primarily present to hospitals without angioplasty facilities, it is to be expected that more patients will be transferred to a tertiary centre in the acute phase of myocardial infarction. As an increase in treatment delay is associated with a worse clinical outcome, the importance of an open infarct-related vessel at acute angiography becomes clear. Pharmacological pretreatment with the aim to open the infarct-related vessel during transportation might be beneficial. From several randomised trials, it becomes evident that a glycoprotein IIb/IIIa receptor blocker is the agent of choice for facilitated PTCA when it is administered early, as initial patency and bleeding complication rates as well as clinical outcomes seem more favourable compared with other agents. Glycoprotein IIb/IIIa receptor blocker therapy should be combined with administration of 250 to 500 mg aspirin intravenously and low-dose heparin (i.e. 5000 IU) intravenously. Whether this is safe and (cost-)effective as pretreatment for patients transported to undergo angioplasty remains to be evaluated in large clinical trials. ■

References

1 Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;**328**:680-4.

2 Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993;**328**:673-9.

3 Zijlstra F, Hoorntje JCA, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;**341**:1413-9.

4 Zhu MM, Feit A, Chadow H, Alam M, Kwan T, Clark LT. Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomised clinical trials. *Am J Cardiol* 2001;**88**:297-301.

5 Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002; **346**:957-66.

6 Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction. A meta-analysis. *Circulation* 2003;**108**:1809-14.

7 Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KAA, Julian D, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. ESC Guidelines. *Eur Heart J* 2003;**24**:28-66.

8 Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. American College of Cardiology, American Heart Association, Canadian Cardiovascular Society: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004;**44**:671-719.

9 Zijlstra F, van 't Hof AWJ, Liem AL, Hoorntje JCA, Suryapranata H, de Boer MJ. Transferring patients for primary angioplasty: a retrospective analysis of 104 selected high risk patients with acute myocardial infarction. *Heart* 1997;**78**:333-6.

10 Liem AL, van 't Hof AWJ, Hoorntje JCA, de Boer MJ, Suryapranata H, Zijlstra F. Influence of treatment delay on infarct size and clinical outcome in patients with acute myocardial infarction treated with primary angioplasty. *J Am Coll Cardiol* 1998;**32**:629-33.

11 De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction. Every minute of delay counts. *Circulation* 2004;**109**:1223-5.

12 Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000;**283**: 2941-7.

13 Ernst NMSKJ, de Boer MJ, van 't Hof AWJ, Hollak F, van de Wetering H, Dambrink JHE, et al. Prehospital triage for angiography-guided therapy for acute myocardial infarction. *Neth Heart J* 2004;**12**:151-6.

14 Zijlstra F. Long-term benefit of primary angioplasty compared with thrombolytic therapy for acute myocardial infarction. *Eur Heart J* 2000;**21**:1487-9.

15 Brodie BR, Stuckey TD, Hansen C, Muncy D. Benefit of coronary reperfusion before intervention on outcomes after primary angioplasty for acute myocardial infarction. *Am J Cardiol* 2000;**85**:13-8.

16 Lee CW, Hong MK, Lee JH. Determinants and prognostic significance of spontaneous coronary recanalization in acute myocardial infarction. *Am J Cardiol* 2001;**87**:951-4.

17 Stone GW, Cox D, Garcia E, Brodie BR, Morice MC, Griffin J, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction. Analysis from the Primary Angioplasty in Myocardial Infarction Trials. Circulation 2001;**104**:636-41.

18 De Luca G, Ernst N, Zijlstra F, van 't Hof AWJ, Hoorntje JCA, Dambrink JHE, et al. Preprocedural TIMI flow and mortality in patients with acute myocardial infarction treated with primary angioplasty. *J Am Coll Cardiol* 2004;**43**:1363-7.

19 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among. 17,187 cases of suspected acute myocardial infarction. *Lancet* 1988;**2**:349-60.

20 Zijlstra F, Ernst N, de Boer MJ, Nibbering E, Suryapranata H, Hoorntje JCA, et al. Influence of prehospital administration of aspirin and heparin on initial patency of the infarct related artery in patients with acute ST elevation myocardial infarction. *J Am Coll Cardiol* 2002;**39**:1733-7.

21 Verheugt FW, Liem AL, Zijlstra F, Marsh RC, Veen G, Bronzwaer JG. High dose bolus heparin as initial therapy before primary angioplasty for acute myocardial infarction: results of the Heparin in Early Patency (HEAP) pilot study. *J Am Coll Cardiol* 1998;**31**: 289-93.

22 Liem AL, Zijlstra F, Ottervanger JP, Hoorntje JCA, Suryapranata H, de Boer MJ, et al. High dose heparin as pretreatment for primary angioplasty in acute myocardial infarction: the Heparin in Early Patency (HEAP) randomized trial. *J Am Coll Cardiol* 2000;**35**:600-4.

23 Ross AM, Coyne KS, Reiner JS, Greenhouse SW, Fink C, Frey A, et al. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. PACT investigators. Plasminogen-activator Angioplasty Compatibility Trial. *J Am Coll Cardiol* 1999;**34**:1954-62.

24 Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicenter randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE-1 study. *Eur Heart J* 2000;**21**:823-31.

25 Vermeer F, Oude Ophuis AJ, van de Berg EJ, Brunninkhuis LG, Werter CJ, Boehmer AG, et al. Prospective randomised comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. *Heart* 1999;**82**:426-31.

26 Van der Werf F. Congress European Society of Cardiology, Hotline Session 3, Stockholm, 2005, and Late Breaking Clinical Trial presentation AHA meeting Dallas 2005.

27 Gold HK, Garabedian HD, Dinsmore RE, Guerrero LJ, Cigarroa JE, Palacios IF, et al. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without exogenous plasminogen activators. Observations in animals and humans. *Circulation* 1997;**95**:1755-9.

28 Van den Merkhof LF, Zijlstra F, Olsson H, Grip L, Veen G, Bar FW, et al. Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty. Results of the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot study. *J Am Coll Cardiol* 1999;**33**:1528-32.

29 Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, et al, for the ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up) Investigators: Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;**344**:1895-903.

30 Brener SJ, Barr LA, Burchenal JE, Katz S, George BS, Jones AA, et al. A randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro And Primary PTCA Organization and Randomized Trial. *Circulation* 1998;**98**:734-41.

31 Cutlip DE, Cove CJ, Irons D, Kalaria V, Le M, Cronmiller H, et al. Emergency room administration of eptifibatide before primary angioplasty for ST elevation acute myocardial infarction and its effect on baseline coronary flow and procedure outcomes. *Am J Cardiol* 2001;**88**:62-4.

32 Lee DP, Huston M, Herity NA. Interim results of the Tirofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) pilot study [abstract]. *J Am Coll Cardiol* 2000;**35**:371A.

33 Van 't Hof AWJ, Ernst N, de Boer MJ, de Winter R, Boersma E, Bunt T, et al. Facilitation of primary coronary angioplasty by early start of a glycoprotein 2b/3a inhibitor: results of the ongoing tirofiban in myocardial infarction evaluation (On-TIME) trial. *Eur Heart J* 2004;**25**:837-46.

34 Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early versus late administration of glycoprotein IIb/IIIa inihibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2004;**292**: 362-6.

35 The SPEED Investigators. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group. *Circulation* 2000;**101**:2788-94.
36 De Lemos JA, Antman EM, Gibson CM, McCabe CH, Giugliano RP, Murphy SA, et al. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction. Observations from the TIMI 14 Trial. *Circulation* 2000;**101**: 239-43.
37 Gibson CM, de Lemos JA, Murphy SA, Marble SJ, McCabe CH, Cannon CP, et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation* 2001;**103**:2550-4.
38 Antman EM, Giugliano RP, Gibson MC, McCabe CH, Coussement P, Kleiman NS, et al, for the TIMI 14 Investigators: Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis In Myocardial Infarction (TIMI) 14 trial. *Circulation* 1999;**99**:2720-32.
39 The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001;**358**:605-13.
40 The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 2001;**357**:1905-14.
41 Savonitto S, Armstrong PW, Lincoff AM, Jia G, Sila CA, Booth J, et al. Risk of intracranial haemorrhage with combined fibrinolytic and glycopr otein IIb/IIIa inhibitor therapy in acute myocardial infarction. Dichotomous response as a function of age in the GUSTO V trial. *Eur Heart J* 2003;**24**:1807-14.
42 Dudek D, Zmudka K, Kaluza GL, Kuta M, Pieniazek P, Przewlocki T, et al. Facilitated percutaneous coronary intervention in patients with acute myocardial infarction transferred from remote hospitals. *Am J Cardiol* 2003;**91**:227-9.
43 Kastrati A, Mehilli J, Schlotterbeck K, Dotzer F, Dirschinger J, Schmitt C, et al. Bavarian Reperfusion Alternatives Evaluation (BRAVE) Study Investigators. Early administration of reteplase plus abciximab versus abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomised trial. *JAMA* 2004;**291**:947-54.
44 Ellis SG, Armstrong P, Betriu A, Brodie B, Herrmann H, Montalescot G, et al. Facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention: design and rationale of the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial [abstract]. *Am Heart J* 2004;**147**:E16.
45 Di Mario C, Bolognese L, Maillard L, Dudek D, Gambarati G, Manarfi A, et al. Combined Abciximab Reteplase Stent Study in acute myocardial infarction (CARESS in AMI). *Am Heart J* 2004;**148**:378-85.