European Heart Journal (2007) **28**, 2438–2448
doi:10.1093/eurheartj/ehm369

Transfer with GP IIb/IIIa inhibitor tirofiban for primary percutaneous coronary intervention vs. on-site thrombolysis in patients with ST-elevation myocardial infarction (STEMI): a randomized open-label study for patients admitted to community hospitals

Slawomir Dobrzycki[1], Pawel Kralisz[1]*, Konrad Nowak[1], Przemysław Prokopczuk[1], Waclaw Kochman[1], Janusz Korecki[2], Boguslaw Poniatowski[2], Jerzy Zuk[1], Ewa Sitniewska[1], Hanna Bachorzewska-Gajewska[1], Jerzy Sienkiewicz[3], and Wlodzimierz J Musial[2]

[1]*Department of Invasive Cardiology, State Teaching Hospital, Medical University of Bialystok, Sklodowskiej 24a, 15-276 Bialystok, Poland;* [2]*Department of Cardiology, State Teaching Hospital, Medical University of Bialystok, Poland; and* [3]*Department of Statistics and Medical Informatics, Medical University of Bialystok, Poland*

Received 27 November 2006; revised 25 July 2007; accepted 3 August 2007; online publish-ahead-of-print 20 September 2007

KEYWORDS
ST-elevation myocardial infarction;
Primary PCI;
Thrombolysis;
Transfer;
Platelet GP IIb/IIIa;
Tirofiban

Aims Our study aimed to compare two reperfusion strategies in patients with ST-elevation myocardial infarction (STEMI) admitted initially to a community hospital without catheterization facilities.
Methods and results Four hundred and one patients with STEMI admitted to community hospital (13 hospitals, radius 20–150 km from cath-lab) were randomized to on-site thrombolysis or to transport with tirofiban (10 μg/kg bolus i.v. + i.v. infusion 0.1 μg/kg/min) for primary PCI in single invasive centre. Primary endpoints were total mortality, recurrent MI (re-AMI), and stroke during 1 year follow-up. Delay to reperfusion defined as interval between admission and start of fibrinolysis or primary PCI was 35 and 145 min ($P < 0.0001$). Mean time of tirofiban administration to PCI in transfer group was: 122.3 $\pm$ 35.7 min. Mortality was not different during hospitalization and at 30th-day, with trend towards lower mortality at 1 year in transport group (12.5 vs. 7.0%, $P = 0.061$). There were no differences in the rate of re-AMI and stroke, with trend towards lower incidence of re-AMI in transfer group at 1 year (7.5 vs. 3.5%, $P = 0.073$). Composite of death/re-AMI/stroke was higher in on-site group during follow-up (15.5 vs. 8.0%, $P = 0.019$; 21.5 vs. 11.4%, $P = 0.006$, respectively, at 30th-day and 1 year).
Conclusion Outcomes at 1 year follow-up suggest that transportation with adjunctive therapy with GP IIb/IIIa inhibitor tirofiban for primary PCI is superior to on-site thrombolysis for patient with STEMI presenting to hospital without catheterization facilities.

Introduction

Primary percutaneous coronary intervention (PCI) is currently the preferred reperfusion treatment in ST-elevation myocardial infarction (STEMI).[1] However, the majority of patients present initially to hospitals without catheterization facilities. In this situation, there are two treatment options: rapid transfer to a tertiary centre for primary PCI or on-site fibrinolytic therapy. It has been demonstrated that primary PCI is superior to on-site thrombolysis even when transport to an angioplasty centre is necessary.[2] Present guidelines underline that the time delay from symptom onset to treatment and the volume of procedures performed in PCI centre are essential in making a decision as to which strategy is to be applied.[3,4]

The delay of onset of primary angioplasty and prolonged ischaemia leading to necrosis caused by transportation may diminish the benefits of this strategy over thrombolysis.[5] It seems to be the issue especially when the expected transfer time is long. Early restoration of infarct-related blood flow before primary PCI is associated with improved outcome.[6] Treatment with GP IIb/IIIa inhibitors for transportation for primary PCI, with the potential to improve baseline blood flow in infarct-related artery (IRA), may be the option to hold the advantage of primary PCI in AMI treatment.[7]

The current study is a multi-centre prospective, randomized, open-label study to evaluate the impact of two reperfusion strategies on early and long-term outcomes in patients with STEMI admitted to a community hospital.

* Corresponding author. Tel: +48 857468496; fax +48 85 7468828.
E-mail address: paqral@yahoo.com

Methods

Patients

Patients with STEMI, presented initially to a participating community hospital without primary PCI capabilities, were randomly assigned to on-site thrombolytic therapy or to transportation for primary PCI with adjunctive therapy with tirofiban. Thirteen participating hospitals are located in a radius of 20–150 km from the cath-lab. All primary PCI were conducted in the coordinating invasive centre in Białystok.

Inclusion criteria

Inclusion criteria were patients with STEMI (typical chest pain >30 min, ST-elevation of Pardee wave type of ≥ 0.1 mV in at least two contiguous ECG leads and/or ≥ 0.2 mV in precordial leads) presented within 12 h of the onset of symptoms, age <80 years.

Exclusion criteria

Exclusion criteria were inability to give written informed consent, contraindications to fibrinolytic therapy, severe renal or hepatic failure, previous CABG, left bundle branch block in ECG recording.

Patients in cardiogenic shock were not randomized and were obligatorily transferred and treated with primary angioplasty.

Study protocol

Evaluation of eligibility for the study was performed by a physician in the hospital of admittance who subsequently contacted the coordinating centre by telephone. The consecutively enrolled patients were randomized to treatment groups in accordance with our database computer randomization programme. It took into account sex, age, and MI localization in ECG recording. Qualified patients (fulfilled criteria according to protocol) were described as male or female, <50 years or 50–65 years or 65–75 years or >75 years, with anterior or other infarct. Each patient included in the study and characterized by pre-specified features was automatically coupled by the same consecutive patient in the other group, thus quickly providing an optimal balance between the two groups.

Patients assigned to transfer for primary PCI received heparin (fixed dose bolus i.v. 5.000 IU) and tirofiban (bolus i.v. of 10 μg/kg followed by i.v. infusion at a dose of 0.1 μg/kg/min) as soon as the randomization had been completed, tirofiban was continued during transportation, during PCI and after the procedure. There was no additional heparin for transport until the cath-lab, where, after ACT measurement before PCI, heparin was given (if needed) to keep the ACT at least at 300–350 s.[8] Heparin was restarted in i.v. maintaining infusion after repeated measurement on average 4 h after procedure. It was maintained during tirofiban administration with APTT target value 70 s verified every 6–12 h. It was recommended to administer tirofiban at least 8 h after PCI procedure. We did not utilize LMWH during tirofiban administration. PCI was performed via the femoral artery with standard 6F catheters. PCI was performed even if the patient had clinical resolution of ischaemia and TIMI grade 3 flow on initial angiography with significant stenosis in IRA.

Stent implantation was encouraged and recommended. Ticlopidin or clopidogrel was given in case the stent was implanted. The arterial sheath was removed when APTT was <45 s after procedure and then heparin was restarted during tirofiban administration.

Patients assigned to fibrinolysis received a lytic drug in the hospital of admission. The study protocol did not define which drug had to be administered: the fibrinolytic was part of the admitting hospital's standard of care. It was advised to administer LMWH (fraxiparine) if streptokinase was utilized or unfractionated heparin (UFH) if together with fibrin-specific lytic. Fibrinolytic treatment was initiated at the emergency room (ER) or the intensive cardiac care unit.

All patients in both groups received 325 mg of aspirin orally. Additional treatment was administered at the discretion of the physician. Rescue angioplasty was recommended if there was no resolution of ST-elevation and/or no pain resolution 2 h after lytic administration. Recurrent ischaemia in on-site group during hospitalization was treated invasively in the coordinating centre. However, in either case, the final decision on transfer to PCI centre was at the discretion of the physician in the admitting hospital.

The study was aimed to evaluate the reperfusion treatment in all hospitals in our region, so as to select and adopt the best strategy to a given clinical situation. Therefore, there was a second separate simultaneous randomization: for patients from Białystok municipal hospitals (in a radius of less than 20 km). In this arm, all patients with STEMI were treated with primary angioplasty and were randomized to groups with and without tirofiban during PCI. In the first group, tirofiban was given according to the modified design: bolus i.v. of 10 μg/kg+infusion 0.4 μg/kg for the first 30 min+ infusion at a dose of 0.1 μg/kg/min. The analysis of this part of our programme will be the subject of separate publication. Study design is shown in *Figure 1*.

The protocol of the study was approved by the local Bioethical Committee. Before randomization, written informed consents were obtained for all patients by a physician in the hospital of admittance.

Monitoring and follow-up

The exact times of presentation, evaluation, interhospital transportation, delay to treatment, and detailed timing of PCI were noted.

Major and minor bleeding was classified according to TIMI criteria.[9]

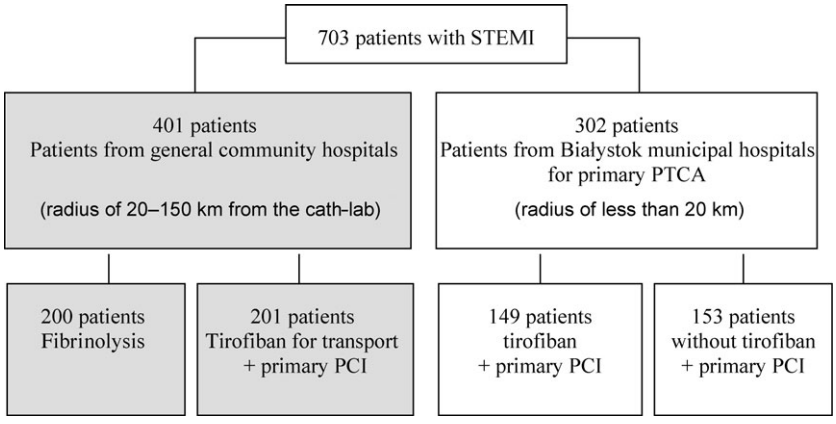

Figure 1 Design of the entire study. Grey bars correspond to the presented data.

Recurrent MI was defined as a new increase in creatinine kinase of at least 50% of the prior value or of more than two times the upper limit of the normal value, accompanied by new ECG changes and/or chest pain recurrence. Stroke was defined as any new neurologic deficit lasting >24 h, and computed tomography was mandatory for stroke confirmation during index hospitalization.

Follow-up clinical examinations were performed in the outpatient clinic of the PCI coordinating centre at discharge, on the 30th day, and finally after 1 year.

Endpoints

The primary endpoints were total mortality, recurrent MI, and stroke during 1 year follow-up. The secondary endpoints were composite of death/re-AMI, death/re-AMI/stroke, and length of hospital stay (LOS).

Statistical analysis

The study was performed in accordance with an intention to treat (ITT) principle which is based on the initial treatment intent, not on the treatment eventually administered. Thereby assigned treatment was considered to have been received if thrombolytic therapy was initiated in patients assigned to thrombolytic therapy and if tirofiban and transfer was initiated with or without successive PCI in patients assigned to transfer for PCI. Based on assumed incidence of the primary endpoint (mortality) of 10% in on-site group and 5% in transfer group, sample size was estimated of 435 patients in each group to achieve 80% power to detect a difference between the group proportions of 0.05. The test statistic used is the two-sided Z test with pooled variance. The endpoint data were available in all randomized patients. Results are expressed as mean $\pm$ SD for normally distributed variables. Time intervals were reported as medians (lower Q1 and upper Q3 quartiles). The independent and the paired-samples two-sided *t*-tests were used to compare normally distributed continuous variables and Mann–Whitney *U* and the Wilcoxon signed-rank two-sided tests were used for not normally distributed. Differences in proportions were evaluated with χ^2 or Fisher's exact test. For mortality and composite endpoint, we presented Kaplan–Meier curves and results of log-rank tests. Results were considered to be statistically significant if $P < 0.05$. Analyses were done with SPSS (version 13.0). Thirty days and 1 year relative risk with two-sided asymptotic 95% CIs on proportions for primary and composite endpoints was calculated. Analyses were done with Review Manager 4.2.10.

Results

Baseline characteristics of the patients

During the study, from 1 February 2002 to 11 November 2003, a total of 476 STEMI patients were assessed for inclusion into the study. Four hundred and one patients were randomly assigned to either fibrynolytic treatment (on-site group, $n = 200$) or transfer for PCI with adjunctive therapy with tirofiban (transfer group, $n = 201$). A baseline clinical characteristic of both groups is presented in *Table 1*.

Table 1 Baseline characteristics of the patients

	On-site group, $n = 200$	Transfer group, $n = 201$	*P-value*
Age	64.1 $\pm$ 10.9	62.9 $\pm$ 12.1	0.5
Male (%)	144 (72%)	152 (75.6%)	0.42
Anterior MI	85 (42.5%)	83 (41.3%)	0.84
Killip's class >1	83 (41.5%)	86 (42.8%)	0.81
Systolic blood pressure (mmHg)	132.8	134.7	0.52
Diastolic blood pressure (mmHg)	81.9	82.8	0.28
Heart rate (bpm)	75.1	75.1	0.54
Hypertension	106 (53%)	106 (52.7%)	0.96
Dyslipidaemia	60 (30%)	68 (33.8%)	0.45
Diabetes	34 (17%)	30 (14.9%)	0.58
Smokers	98 (49%)	76 (37.8%)	0.027
Previous MI	8 (4.0%)	24 (11.9%)	0.005
Family history of CAD	38 (19%)	40 (19.9%)	0.9
BMI	27.8	27.5	0.62

Treatment

In 10 patients (four in on-site group and six in transfer group), the diagnosis of STEMI was false positive. All patients in on-site group received thrombolytic therapy—in all cases it was streptokinase. All patients in transfer group received tirofiban. Catheterization for primary PCI was not performed in one patient who died in the cath-lab of the invasive centre and in one patient who withdrew his consent in the invasive centre, after transfer, due to temporary resolution of ischaemic symptoms. PCI was not performed in 10 patients out of 199 who underwent catheterization. Of these three patients had MI confirmed by typical increase in necrotic enzymes and no significant stenosis in coronary arteries, and one patient received intracoronary thrombolysis (alteplase) due to thrombus in left main and left anterior descendent artery with TIMI 3 flow (*Figure 2*).

The baseline flow in the IRA according to TIMI classification in transfer group is presented in *Figure 3*. Stent was implanted in 75.7% coronary interventions in transfer group. The procedural success (defined as TIMI flow 3 and residual stenosis <50%) was reached in 95.2% (180/189 coronary interventions).

The pharmacological treatment at discharge differed with regard to ACEI assignment (*Table 2*).

Time intervals

Majority of the patients in both groups were admitted within 3 h from MI onset (<2 h 48 vs. 55.7%, $P = 0.12$; <3 h 69.5 vs. 76.1%, $P = 0.14$; <4 h 81.5 vs. 85.6%, $P = 0.27$; in on-site and transfer groups, respectively). Delay to reperfusion was defined as interval between admission and the start of fibrinolysis or primary PCI after transport. All relevant time intervals are presented in *Table 3*. Forty-nine patients (24.4%) in transfer group had time between first medical contact and PCI below 90 min. Total time of tirofiban administration was 21.4 $\pm$ 7.9 h. The decision to prematurely stop the infusion was made on generally accepted indications (predominantly bleeding complications) or in those patients with false positive MI diagnosis with no significant stenosis.

Study endpoints

Early, 30 days and 1 year follow-up was completed for all patients (*Table 4*). In 7 patients in on-site group and 4 patients in transfer group, the information on 1 year follow-up was obtained by telephone. During hospitalization 17 (8.5%) patients died in on-site group vs. 9 patients (4.5%) in transfer group ($P = 0.075$). Mortality was not different between the two groups at 30th-day follow-up (9.0 vs. 5.0%, $P = 0.113$)

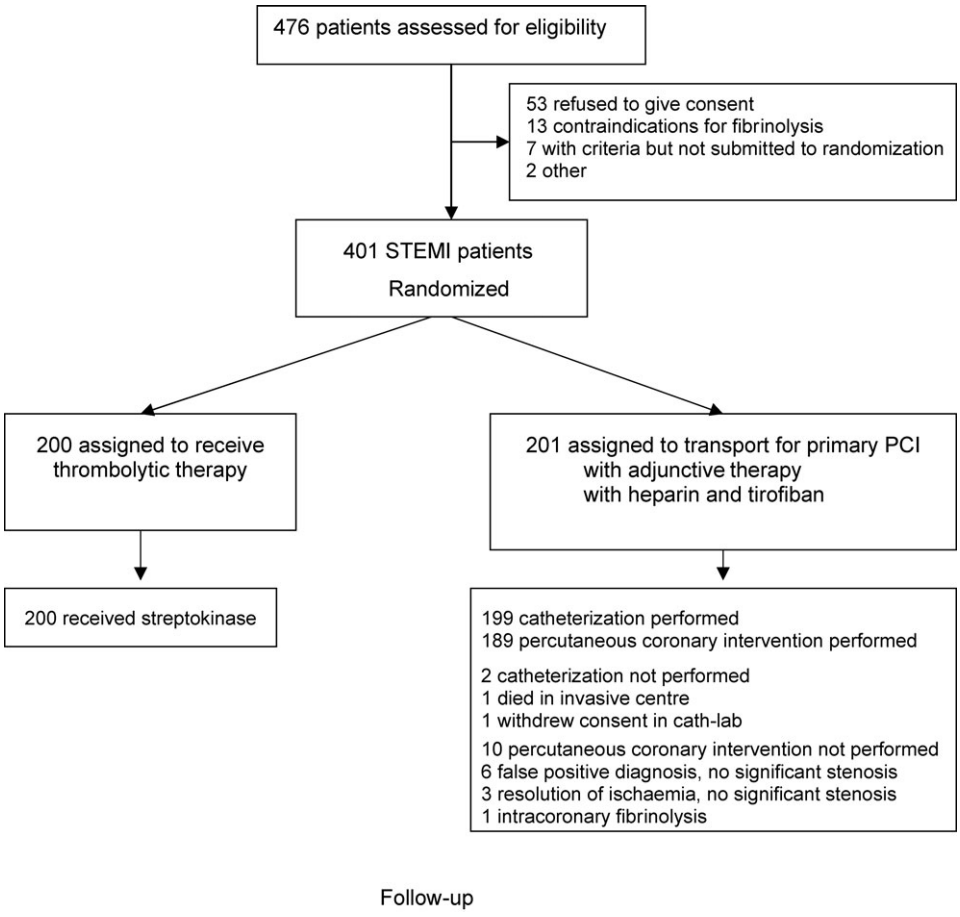

Figure 2 Flow of community hospital patients through the trial.

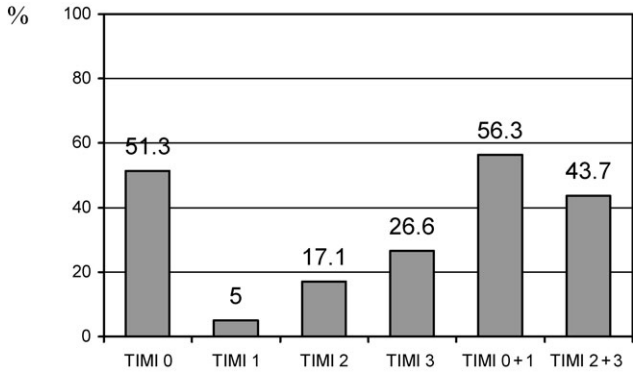

Figure 3 Flow in the infarct related artery according to TIMI classification in the transfer group ($n = 199$).

with the trend towards lower mortality at 1 year follow-up in transfer group (12.5 vs. 7.0%, $P = 0.061$). There were no significant differences in the rate of re-AMI and stroke between the groups during the study, although there was a trend towards lower incidence of re-AMI in transfer group at 1 year follow-up (7.5 vs. 3.5%, $P = 0.073$). The composite of death/re-AMI/stroke was significantly higher in on-site group throughout the follow-up (15.5 vs. 8.0%, $P = 0.019$; 21.5 vs. 11.4%, $P = 0.006$, respectively, for on-site group and transfer group at 30th-day and 1 year follow-up). Patients randomized to transfer had a reduced hospital stay: 9.7 ± 4.3 days vs. 14.1 ± 5.5 days, $P < 0.0001$. *Figure 4* shows 30-day mortality in transfer subgroups created with time delay from admission to start of reperfusion as a cut-off value. *Figures 5* and *6* show results of pre-specified subgroup analyses of mortality and composite endpoint during 30-day and 1 year follow-up. *Figure 7* shows the Kaplan–Meier curves for the mortality and event free survival.

Table 2 Medications at hospital discharge

	On-site group	Transfer group	*P-value*
Aspirin	171 (94.5%)	184 (95.8%)	NS
Beta-blocker	165 (91.2%)	183 (95.3%)	NS
ACEI	152 (84%)	180 (93.8%)	0.003
Statin	158 (87.3%)	163 (84.9%)	NS

Complications during transfer

All patients randomized to transport were transferred to PCI centre. There was one ventricular fibrillation in emergency ambulance during transportation and two ventricular fibrillations in the ER of PCI centre. All these events were successfully treated with defibrillation. There was one death (mechanical dissociation of the heart) in cath-lab before the start of catheterization. There were two bleeding complications that required cessation of tirofiban; they were analysed as bleeding complications during hospitalization in transfer group.

Table 3 Time intervals in study patients

	On-site group, $n = 200$	Transfer group, $n = 201$	*P-value*
Onset of symptoms to admission	120 (60, 200)	105 (50, 180)	0.056
Admission to start of reperfusion	35 (25, 50)	145 (120, 178)	0.0001
Onset of symptoms to start of reperfusion	165 (105, 250)	257 (200, 345)	0.0001
Admission to start of interhospital transportation	–	45 (30, 65)	–
Interhospital transportation	–	60 (45, 75)	–
Arrival to invasive center to baseline TIMI	–	25 (20, 35)	–

All intervals in minutes, median (Q1, Q3).

Table 4 Clinical outcome during hospitalization and at follow-up

	On-site group, $n = 200$	Transfer group, $n = 201$	*P-value*
Hospitalization			
Death	17 (8.5%)	9 (4.5%)	0.075
Re-AMI	6 (3.0%)	5 (2.5%)	0.497
Stroke	3 (1.5%)	0	0.123
Death/re-AMI	23 (11.5%)	14 (7.0%)	0.11
Death/re-AMI/ stroke	25 (12.5%)	14 (7.0%)	0.061
30-day			
Death	18 (9.0%)	10 (5.0%)	0.113
Re-AMI	11 (5.5%)	5 (2.5%)	0.123
Stroke	3 (1.5%)	1 (0.5%)	0.3
Death/re-AMI	28 (14.0%)	15 (7.5%)	0.034
Death/re-AMI/ stroke	31 (15.5%)	16 (8.0%)	0.019
1 year			
Death	25 (12.5%)	14 (7.0%)	0.061
Re-AMI	15 (7.5%)	7 (3.5%)	0.073
Stroke	5 (2.5%)	2 (1.0%)	0.222
Death/ re-AMI	38 (19%)	21 (10.4%)	0.016
Death/ re-AMI/ stroke	43 (21.5%)	23 (11.4%)	0.006

Bleeding

Major bleeding during hospitalization occurred in 4 (2%) patients in on-site group and in 4 (2%) patients in transfer group (relative risk 1.01; 95% CI 0.25–4.08). In on-site group, three patients experienced a stroke due to intracranial hemorrhage (including one fatal stroke), one patient required blood transfusion due to gastrointestinal bleeding. In transfer group, there was one fatal tamponade and three blood transfusions due to gastrointestinal bleeding (one patient), and puncture site bleeding (two patients). Minor bleedings in on-site vs. transfer group were 13 (6.5%) vs. 8 (4.0%) (relative risk 1.63; 95% CI 0.69–3.85).

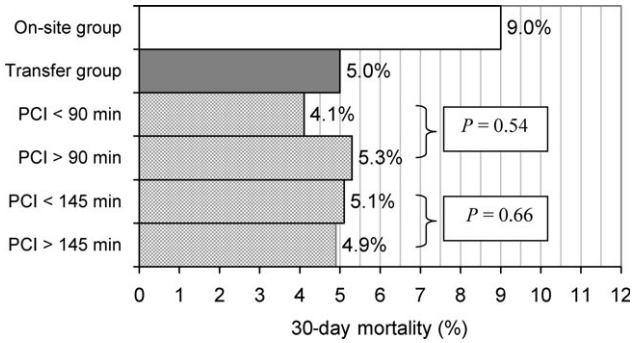

Figure 4 Thirty-day mortality in transfer subgroups created with time delay from admission to start of reperfusion as a cut-off value. PCI < 90 min, PCI >90 min, PCI < 145 min and PCI >145 min indicate transfer subgroups with 90 min (delay in accordance with the guidelines) and 145 min (median delay in transfer group) from admission to start of invasive reperfusion in transfer group, respectively.

Non-protocol cardiac procedures

During index hospitalization, non-protocol catheterization was performed in 22 patients in on-site group and in 9 patients in transfer group ($P = 0.015$). The indications for catheterization were: (i) in on-site group, recurrence of ischaemia with ECG changes (13 patients), failure of thrombolysis (6 patients), recurrent MI (2 patients), other (1 patient); (ii) in transfer group, recurrent MI (5 patients; of these 4 patients due to acute stent thrombosis and 1 patient who initially withdrew consent for catheterization), recurrence of ischaemia with ECG changes (3 patients), other (1 patient). Non-protocol PCI was performed in 14 patients in on-site group compared with 6 patients in transfer group ($P = 0.065$). At 30-day follow-up, unscheduled catheterization was performed in 33 patients (16.5%) in thrombolytic group and in 10 patients (4.97%) in transfer group ($P = 0.0002$).

At 1 year, catheterization was performed in 86 (43%) vs. 27 (13.4%) patients ($P < 0.0001$), PCI procedures in 57 (28.5%) vs. 22 (11%) patients ($P < 0.0001$), coronary artery bypass surgery in 12 (6%) vs. 6 (3%) patients in on-site group vs. transfer group, respectively ($P = 0.145$).

Discussion

The purpose of our study was to evaluate the reperfusion therapy in our region. Thus, we intended to rationalize and justify the routine referral of all patients with STEMI for invasive treatment. In our centre, we started 24 h/7-day invasive treatment of STEMI patients in 1999. At the beginning, patients were referred from hospitals of Białystok. In the next stage, we expanded the area of transfer to community hospitals located in the whole region (up to a radius of 150 km from the invasive centre). Based on retrospective data, we realized that transfer delays were disturbingly long and pre-treatment with potential to compensate for treatment delay was mandatory in these patients. In 1999–2001, we performed a pilot study with GP IIb/IIIa inhibitor tirofiban and we concluded that tirofiban was associated with improvement in coronary blood flow in IRA.[10] Furthermore, there was some evidence that the effect of tirofiban before invasive treatment was dependent on the length of the time of drug administration.[11]

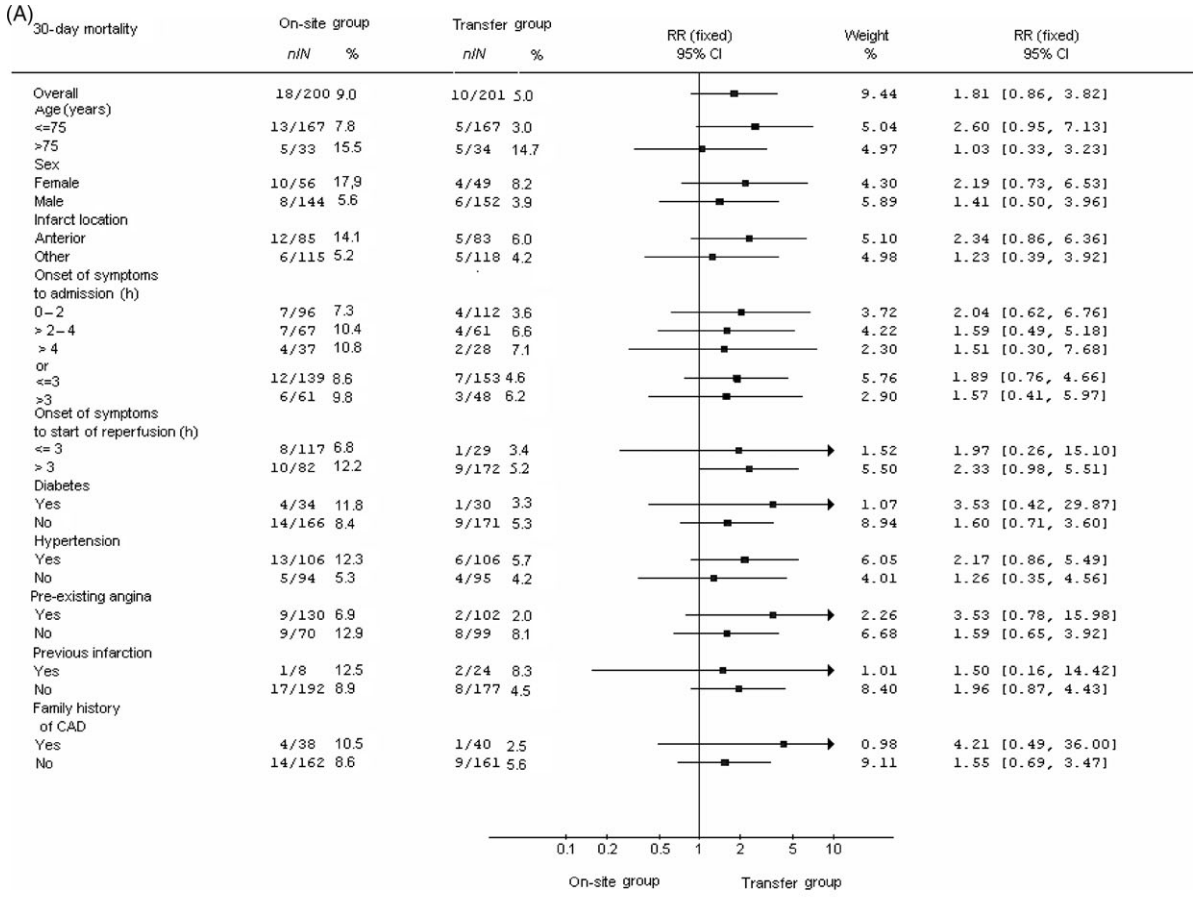

Figure 5 Relative risk (95% coronary intervention) for (*A*) mortality and (*B*) composite endpoint during 30-day follow-up.

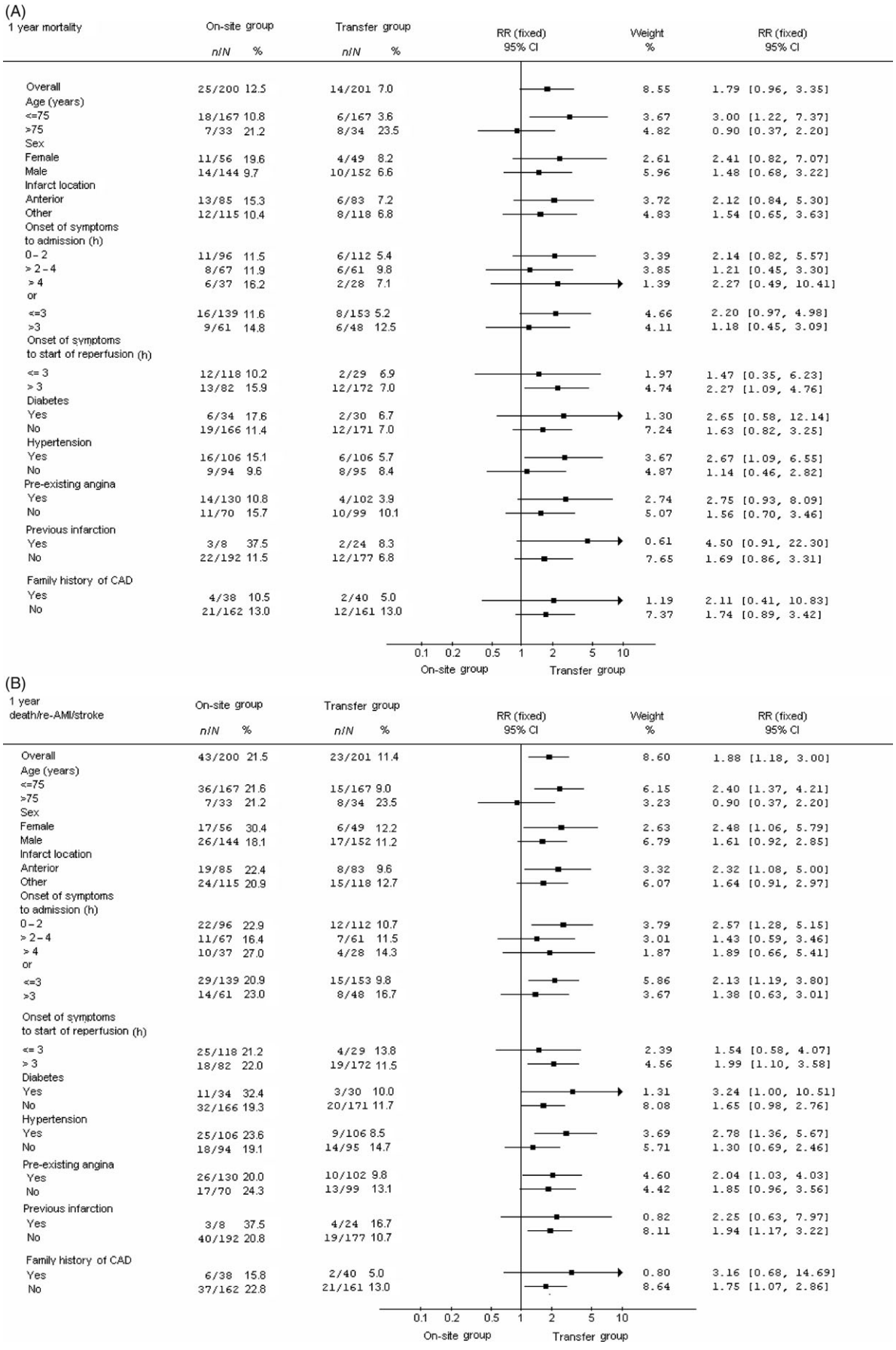

Figure 6 Relative risk (95% coronary intervention) for (*A*) mortality and (*B*) composite endpoint during 1 year follow-up.

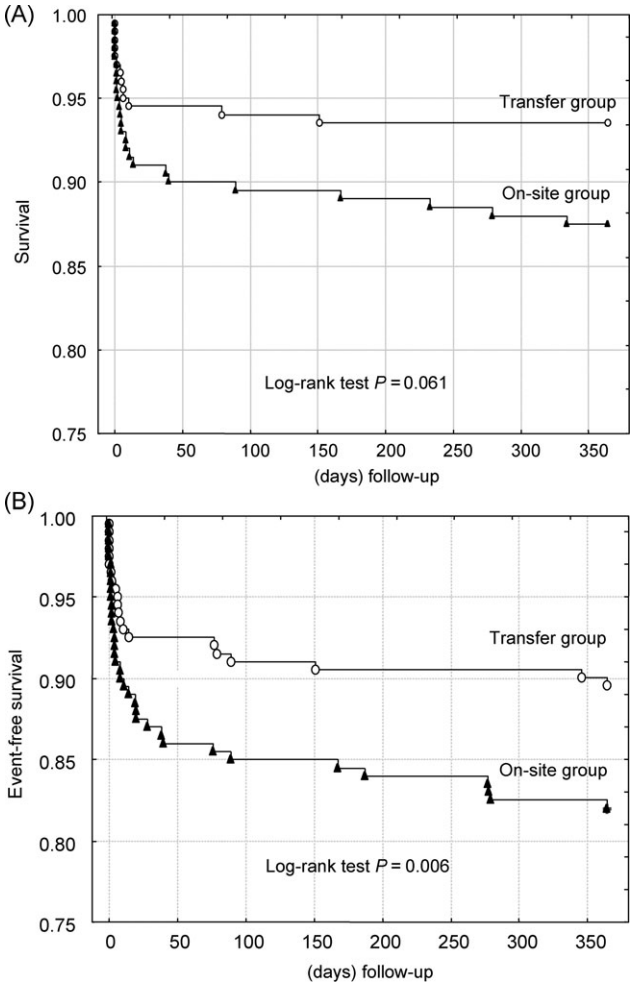

Figure 7 Kaplan–Meier estimates in on-site and transfer groups for (*A*) survival and (*B*) event-free survival (freedom from death, re-MI, stroke).

Therefore, we chose tirofiban as an adjunctive treatment for transferred patients in the design of the present study. Tirofiban had also an important advantage for its significantly lower cost compared with, for example, abciximab.

Meanwhile, the On-TIME trial, performed in 2001–2002 and published in 2004, found that early pre-treatment with tirofiban, despite improved patency (TIMI 2 or 3) and a better myocardial perfusion pre-PCI, had no beneficial effect on post-PCI angiographic or clinical outcome, when compared with late tirofiban administration.[12] The On-TIME evaluated the hypothesis, which was first pointed out in ADMIRAL trial,[13] that clinical benefit of IIb/IIIa platelet inhibitor prior to primary PCI may be dependent on time-period of drug infusion. Nevertheless, the later published pooled data of randomized trials of early (prior to transfer to the cath-lab) vs. late (at the time of PCI) administration of GP IIb/IIIa inhibitor showed significant improvement in normal coronary flow (TIMI 3) with favourable trend in mortality reduction.[14]

The authors hypothesized that limited efficacy of tirofiban in On-TIME trial may be explained by inadequate dosing to achieve the desired level of platelet inhibition. The hypothesis originates from the GOLD study which revealed that the extent of platelet aggregation inhibition is an independent predictor of major adverse cardiac events after PCI (MACE—death/MI/TVR). The highest risk of MACE was found in patients with suboptimal platelet inhibition measured within 10 min and 8 h after the initiation of treatment.[15] In this regard, early tirofiban dosing (related to 10 μg/kg bolus) seemed to be vulnerable and remained under debate. Standard bolus of tirofiban 10 μg/kg, used in GOLD study as well as in On-Time and present study, was proved for insufficient platelet inhibition and was considered as being responsible for worse clinical outcome compared with other GP IIb/IIIa inhibitors.[16] Subsequently, tirofiban with increased bolus to high-dose 25 μg/kg was found to be the most effective drug in achieving optimal early platelet inhibition,[17,18] showing comparable angiographic and clinical outcome to abciximab with good safety profile.[19] Nevertheless, despite favourable data, limited sample size of the studies with high-dose tirofiban performed so far do not allow for established clinical application in STEMI patients. At the same time, in accordance with GOLD study findings, maintaining infusions of tirofiban 0.15 mg/kg/min as in RESTORE trial[20] or 0.1 mg/kg as in PRISM-Plus trial[21] were related to comparable sufficient platelet inhibition. Therefore, in our study, we utilized maintaining infusion i.v. 0.1 mg/kg.

Abciximab trials showed enhancement in TIMI 3 in IRA along with longer time of administration (GRAPE—45 min infusion—TIMI 3 18%; SPEED—60 min infusion—TIMI 3 23%; TIMI 14–90 min infusion—TIMI 3 32%).[22–24] Tirofiban trials, with smaller sample size, suggest the same rule.[12,25] Total pre-treatment time with tirofiban was 79 min in the early group in On-TIME trial compared with 122 min in our study (transfer group). The rate of no-flow (TIMI 0 + 1), patent IRA (TIMI 2 + 3), was surprisingly comparable (57 vs. 56.3%; 43 vs. 43.7%, respectively, for the early group in On-TIME and the present study), and normal flow (TIMI 3) was slightly better in our study (19 vs. 26.6%). Bearing in mind the limitation of such comparison, one could suppose that evidently longer total time of tirofiban administration in our study, as compared with On-TIME study, might be responsible for the trend towards better TIMI 3 flow.

PRAGUE-2 study (streptokinase in hospital of admittance vs. immediate transport for primary PCI) reported the overall 30-day mortality as 10.0% in the thrombolytic group vs. 6.8% in the PCI group, and among 'early presenters' (<3 h from pain onset to admittance) 7.4 vs. 7.3%, respectively.[26] Based on these results, the authors advanced a thesis, further confirmed in guidelines, that thrombolysis should be reserved for patients presenting within <3 h from symptom onset, with long, timely access to primary PCI. In our study, the overall 30-day mortality was slightly lower in both corresponding groups when compared with PRAGUE-2, and the difference, yet not statistically significant, was preserved among 'early presenters' (<3 h from pain onset to admittance)—8.6% in on-site group and 4.6% (relative risk 1.89; 95% CI 0.76–4.66) in transfer group. The total delay to treatment in our study (onset of symptoms to reperfusion therapy) was the same as in PRAGUE-2 study. But there were important differences that could possibly influence the outcome. First, it was the delay between administration of fibrinolytic and mechanical reperfusion with PCI. The benefit of primary PCI is lost once the delay between administration of fibrinolytic and balloon inflation during primary PCI exceeds 1 h.[27] In PRAGUE-2, the difference between two

treatments was 75 min and in our study it was 110 min. Therefore, one could expect the worse outcome in transfer group in our study, especially in 'early presenters'. The important issue is that no patient received GP IIb/IIIa blocker before the intervention in PRAGUE-2 study. And if we look at TIMI-flow before PCI in transported groups, the rate of no-flow (TIMI 0+1), patent IRA (TIMI 2 + 3), and normal flow (TIMI 3) was in favour of patients in our study, transported with adjunctive tirofiban (69 vs. 56.3%; 31 vs. 43.7%, and 17 vs. 26.6%, respectively, for PRAGUE-2 study and present study). If we assume that tirofiban was responsible for the improvement in coronary blood flow, the results of the present study remain in line with previous findings that when reperfusion occurs before primary PCI, the outcomes are better.

On the other hand, ASSENT-4 trial revised the importance of open IRA before PCI as a major determinant of prognosis in STEMI. Full-dose tenecteplase, despite achieving increase in pre-procedural TIMI 3 flow in IRA (43% after median time 104 min), resulted in an increase in mortality, rates of re-infarction, TVR, and bleeding complications compared with PCI alone group.[28] Also previous studies of facilitated PCI with thrombolytic therapy have not proved that significantly higher TIMI flow in IRA before PCI translates to a clear improvement in clinical outcome.[23,29,30] The worse outcome in ASSENT-4 trial was attributed to the excess of thrombotic events, presumably induced by thrombolysis itself and/or not sufficiently prevented. Thus, ASSENT-4 trial underlined the importance of adjunctive antithrombotic treatment in periprocedural period. The occlusion of IRA due to thrombus formation is mediated primarily by platelets and specifically antiplatelet agents appear to be most important in the prevention of ischaemic events. Aspirin and clopidogrel are a must in primary PCI, and GP IIb/IIIa inhibitors, along with preventing both platelet aggregation and tissue-factor-induced thrombin generation might yield additional benefit. Although facilitated regimens of GP IIb/IIIa inhibitors alone have not shown this benefit so far, GP IIb/IIIa inhibitors seem to remain the only reasoned option for pharmacological facilitation of PCI in STEMI.[31] However, the optimal dosing and timing of these drugs warrant further studies.

The rate of bleeding complications in transfer group was low and comparable with the previous studies with tirofiban.[12,25] We did not utilize weight adjusted bolus of UFH; we chose the fixed dose to simplify transferring procedures. Our approach with medium dose bolus and additional UFH was supported by data by Chew *et al.*[8] showing lower incidence of ischaemic events among patients with higher ACT values. However, this relationship has been questioned and it was shown that higher dose of UFH tends to cause more bleeding.[32] If GP IIb/IIIa inhibitors are administered during PCI, both heparin dose reduction and heparin discontinuing after PCI can limit bleeding complications concurrently preserving effective antithrombotic activity.[33,34]

The LOS in our study was longer than usually reported in both groups. Randomized trials report mean LOS from 4.5 to 8 days in primary PCI patients and from 6 to 10 days in fibrinolytic patients.[35–37] Registries, providing better insight into real life practice, show mean LOS of about 9 days.[38] It must be remembered that all participating admitting hospitals in our study (with on-site group) were low volume, public, and non-profit—these are major features that contribute to lengthening the LOS. Furthermore, public funding and administrative factors in Poland, with no underlying economic pressure so far, do not favour the shortening of LOS in community hospitals.

Limitations

Our study has several limitations. First is the lytic drug used—streptokinase. Randomized trials proved t-PA-based fibrinolytics to be the most effective thus setting the standard in thrombolytic treatment. Nevertheless, streptokinase remains an alternative for many patients. In Poland, streptokinase is the prevailing fibrinolytic, mostly due to the fact that while preserving acceptable efficacy, it has incomparable lower costs. Another limitation, in view of studies published after completion of our study, is the lack of pre-treatment with clopidogrel both before fibrinolytic therapy[39] and PCI.[40] Furthermore, all transported patients were treated in a single invasive centre which, considering the relationship between centre characteristic and outcome, might have impact on results. Both groups differed regarding smoking status, previous AMI, and ACEI utilization and these differences were not taken into account in analysis. Finally, an important limitation is the small number of patients included in the study. We initialized the programme supported with a governmental grant and tirofiban was partly delivered free of charge by MSD, Poland. Further funding was intended to be secured by local authorities, but due to budget cuts it could not be maintained.

Conclusion

Our study should be viewed as an endeavour to put the guidelines-recommended treatment into practice. Randomized trials proved undeniably the advantage of primary PCI over thrombolysis. Nevertheless, everyday practice yields challenges that may render this advantage impossible to reproduce. It can be overcome by adjusting available treatment as close to guidelines as possible. In our study, we proposed adjunctive treatment for transport with tirofiban and we reported that this strategy can be effective even when time of transfer is long. Outcomes at 1 year follow-up suggest that transportation with adjunctive therapy with GP IIb/IIIa inhibitor tirofiban for invasive treatment is superior to on-site thrombolysis for patients with STEMI presenting to hospital without catheterization facilities.

Acknowledgements

The study was performed in the Department of Invasive Cardiology as co-ordinating centre; State Teaching Hospital, Medical University of Bialystok, Poland and in the Department of Cardiology, State Teaching Hospital, Medical University of Bialystok, Poland. Cooperating community hospitals were Voivod Hospital in Łomża, Voivod Hospital in Suwałki, community hospitals in Augustów, Dąbrowa Białostocka, Grajewo, Hajnówka, Knyszyn, Mońki, Siemiatycze, Sejny, Sokółka, Wysokie Mazowieckie, Zambrów—all in the Podlasie region, Poland. The study drug tirofiban was partly delivered free of charge by MSD, Poland. We would like to extend our gratitude to physicians of community hospitals and ambulance teams for their contribution to the study.

Conflict of interest: none declared.

Funding

The study was supported with an educational grant no. PCZ-012-22 CO-24/P05/2001 from The State Committee for Scientific Research of the Ministry of Science and Higher Education, Warsaw, Poland.

References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20.
2. 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**:1809–1814.
3. Silber S, Albertsson P, Fernandez-Avilès F, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug J-E, Ruzyllo W, Urban P, Stone GW, Wijns W. Guidelines for Percutaneous Coronary Interventions. The Task Force for Percutaneous Coronary Interventions of the European society of Cardiology. *Eur Heart J* 2005;**26**:804–847.
4. American College of Cardiology, American Heart Association Task Force on Practice Guidelines, 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). *Circulation* 2004;**110**: 588–636.
5. 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**: 1223–1225.
6. Stone GW, Cox D, Garcia E, Brodie BR, Morice MC, Griffin J, Mattos L, Lansky AJ, O'Neill WW, Grines CL. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction. *Circulation* 2001;**104**:636–641.
7. Topol EJ, Neumann FJ, Montalescot G. A preferred reperfusion strategy for acute myocardial infarction. Editorial comment. *JACC* 2003;**42**: 1886–1889.
8. Chew DP, Bhatt DL, Lincoff AM, Moliterno DJ, Brener SJ, Wolski KE, Topol EJ. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation* 2001;**103**:961–966.
9. Bovill EG, Terrin ML, Stump DC, Berke AD, Frederick M, Collen D, Feit F, Gore JM, Hillis LD, Lambrew CT, Leiboff R, Mann KG, Markis JE, Pratt CM, Sharkey SW, Sopko G, Tracy RP, and Chesebro JH for the TIMI Investigators: Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Ann Intern Med* 1991;**115**:256–265.
10. Kochman W, Dobrzycki S, Nowak KS, Chlopicki S, Kralisz P, Prokopczuk P, Bachorzewska-Gajewska H, Gugala K, Niewada M, Mezynski G, Poniatowski B, Korecki J, Musial WJ. Safety and feasibility of a novel dosing regimen of tirofiban administered in patients with acute myocardial infarction with ST elevation before primary coronary angioplasty: a pilot study. *J Thromb Thrombolysis* 2004;**17**:127–131.
11. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E, TACTICS (Treat Angina with Aggrastat Determine Cost of Therapy with an Invasive or Conservative Strategy)–Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**: 1879–1887.
12. van't Hof AW, Ernst N, de Boer MJ, de Winter R, Boersma E, Bunt T, Petronio S, Marcel Gosselink AT, Jap W, Hollak F, Hoorntje JC, Suryapranata H, Dambrink JH, Zijlstra F, On-TIME study group. 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**:837–846.
13. Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, Boulenc JM, Morice MC, Maillard L, Pansieri M, Choussat R, Pinton P, ADMIRAL Investigators. Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;**344**:1895–1903.
14. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs. late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2004;**292**:362–366.
15. Steinhubl SR, Talley JD, Braden GA, Tcheng JE, Casterella PJ, Moliterno DJ, Navetta FI, Berger PB, Popma JJ, Dangas G, Gallo R, Sane DC, Saucedo JF, Jia G, Lincoff AM, Theroux P, Holmes DR, Teirstein PS, Kereiakes DJ. Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention. Results of the GOLD (AU-Assessing Ultegra) multicenter study. *Circulation* 2001;**103**:2572–2578.
16. Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann FJ, Stone GW, DiBattiste PM, Demopoulos L, TARGET Investigators. Do Tirofiban and ReoPro Give Similar Efficacy Trial. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;**344**:1888–1894.
17. Schneider DJ, Herrmann HC, Lakkis N, Aguirre F, Lo MW, Yin KC, Aggarwal A, Kabbani SS, DiBattiste PM. Increased concentrations of tirofiban in blood and their correlation with inhibition of platelet aggregation after greater bolus doses of tirofiban. *Am J Cardiol* 2003;**91**:334–336.
18. Danzi GB, Capuano C, Sesana M, Mauri L, Sozzi FB. Variability in extent of platelet function inhibition after administration of optimal dose of glycoprotein IIb/IIIa receptor blockers in patients undergoing a high-risk percutaneous coronary intervention. *Am J Cardiol* 2006;**97**:489–493.
19. Ernst NM, Suryapranata H, Miedema K, Slingerland RJ, Ottervanger JP, Hoorntje JC, Gosselink AT, Dambrink JH, de Boer MJ, Zijlstra F, van't Hof AW. Achieved platelet aggregation inhibition after different antiplatelet regimens during percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004;**44**:1187–1193.
20. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;**96**:1445–1453.
21. The PRISM-Plus Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q wave myocardial infarction. *N Engl J Med* 1998;**338**:1488–1497.
22. Merkhof LF, Zijlstra F, Olsson H, Grip L, Veen G, Bar FW, van den Brand MJ, Simoons ML, Verheugt FW. 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**: 1528–1532.
23. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group Trial of Abciximab With Without Low-Dose Reteplase for Acute Myocardial Infarction. *Circulation* 2000;**101**:2788–2794.
24. de Lemos JA, Antman EM, Gibson CM, McCabe CH, Giugliano RP, Murphy SA, Coulter SA, Anderson K, Scherer J, Frey MJ, Van Der Wieken R, Van De Werf F, Braunwald E. Abciximab improves both epicardial flow and myocardial perfusion in ST-elevation myocardial infarction. Observations from the TIMI 14 trial. *Circulation* 2000;**101**:239–243.
25. Lee DP, Herity NA, Hiatt BL, Fearon WF, Rezaee M, Carter AJ, Huston M, Schreiber D, DiBattiste PM, Yeung AC, TIrofiban Given in the Emergency Room before Primary Angioplasty. Adjunctive platelet glycoprotein IIb/IIIa receptor inhibition with tirofiban before primary angioplasty improves angiographic outcomes: results of the TIrofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) pilot trial. *Circulation* 2003;**107**:1497–1501.
26. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, Branny M, St'asek J, Formanek P, 'PRAGUE' Study Group Investigators. Long distance transport for primary angioplasty versus immediate thrombolysis in acute myocardial infarction. *Eur Heart J* 2003;**24**: 94–104.
27. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol* 2003;**92**:824–826.
28. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;**367**:569–578.
29. Ross AM, Coyne KS, Reiner JS, Greenhouse SW, Fink C, Frey A, Moreyra E, Traboulsi M, Racine N, Riba AL, Thompson MA, Rohrbeck S, Lundergan CF.

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**:1954–1962.
30. Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre 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 study. *Eur Heart J* 2000;**21**: 823–831.
31. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomized trials. *Lancet* 2006;**367**: 579–588.
32. Brener SJ, Moliterno DJ, Lincoff AM, Steinhubl SR, Wolski KE, Topol EJ. Relationship between activated clotting time and ischemic or hemorrhagic complications: analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. *Circulation* 2004;**110**:994–998.
33. Denardo SJ, Davis KE, Reid PR, Tcheng JE. Efficacy and safety of minimal dose (< or =1,000 units) unfractionated heparin with abciximab in percutaneous coronary intervention. *Am J Cardiol* 2003;**91**:1–5.
34. Karvouni E, Katritsis DG, Ioannidis JP. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions. *J Am Coll Cardiol* 2003;**41**:26–32.
35. Aversano T, Aversano LT, Passamani E, Knatterud GL, Terrin ML, Williams DO, Forman SA, Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT). Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. *JAMA* 2002;**287**:1943–1951.
36. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC *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**:673–679.
37. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;**336**:1621–1628.
38. Lin HC, Chen CS, Lee HC, Liu TC. Physician and hospital characteristics related to length of stay for acute myocardial infarction patients: a 3-year population-based analysis. *Circ J* 2006;**70**:679–685.
39. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E, CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;**352**:1179–1189.
40. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Lewis BS, Murphy SA, McCabe CH, Braunwald E, Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 2005;**294**:1224–1232.

Clinical vignette

doi:10.1093/eurheartj/ehm190
Online publish-ahead-of-print 3 June 2007

A prominent coronary Thebesian system

Kyung Woo Park, Yong-Jin Kim, and Hyo-Soo Kim*

Cardiovascular Center and Department of Internal Medicine, Seoul National University Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Republic of Korea

* Corresponding author. *E-mail address:* hyosoo@snu.ac.kr

A 46-year-old male patient with hypertension and diabetes mellitus presented with chest pain and dyspnoea. He had previously received percutaneous coronary intervention for a proximal left anterior descending coronary artery lesion. However, even after stent implantation, he had recurrent effort angina with dyspnoea. Coronary angiography showed a widely patent stent in the mid-left anterior descending coronary artery and an incidental finding of multiple fistulas between the left coronary artery and the left ventricle (Panels A–D). Note the appearance of multiple minute inter-trabecular vessels after injection of contrast agent into the coronary artery that drain into the left ventricle resulting in the appearance of a left ventriculogram. This is a rare form of coronary fistula where multiple fistulas exist between coronary arteries and the left ventricle. Such arterioventricular fistula is presumed to be due to a prominent coronary Thebesian system and was first reported in 1974. Although the Thebesian system is not familiar to cardiologists, cardiothoracic surgeons recognize the Thebesian system as a route where significant amounts of retrograde cardioplegia can be shunted to the ventricles. It has been well documented in canine hearts, yet the clinical significance of its existence in humans is not clear.

Panels A–D. Right anterior oblique caudal projection of the left coronary artery. After injection of contrast agent into the left coronary artery (Panel A), note the appearance of multiple minute inter-trabecular vessels at the apex of the left ventricle (Panel B) that drain into the left ventricle resulting in the appearance of a left ventriculogram (at diastole: Panel C and at systole: Panel D).