International Journal of Cardiology 154 (2012) 275–281

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Timing of events in STEMI patients treated with immediate PCI or standard medical therapy: Implications on optimisation of timing of treatment from the CARESS-in-AMI trial

Konstantinos Dimopoulos [a], Dariusz Dudek [b], Federico Piscione [c], Waldemar Mielecki [b], Stefano Savonitto [d], Francesco Borgia [a,c,*], Ernesto Murena [e], Antonio Manari [f], Achille Gaspardone [g], Andrzej Ochala [h], Krzysztof Zmudka [i], Leonardo Bolognese [j], Philippe Gabriel Steg [k], Marcus Flather [a], Carlo Di Mario [a] and on behalf of the CARESS-in-AMI (*C*ombined *A*bciximab *RE*-teplase *S*tent *S*tudy in *A*cute *M*yocardial *I*nfarction) Investigators (All Investigators and Committees are listed in the Appendix)

[a] *Royal Brompton Hospital & Imperial College, London, UK*
[b] *Jagiellonian University Medical Centre, Krakow, Poland*
[c] *Federico II University, Naples, Italy*
[d] *Ospedale Niguarda-Ca' Granda, Milano, Italy*
[e] *Ospedale S. Maria delle Grazie, Pozzuoli, Naples, Italy*
[f] *Arcispedale San Maria Nuova, Reggio Emilia, Italy*
[g] *Ospedale Sant'Eugenio, Roma, Italy*
[h] *Gornoslaskie Centrum Kardiologii, Katowice, Poland*
[i] *Spital Jana Pawla II, Krakow, Poland*
[j] *Ospedale San Donato, Arezzo, Italy*
[k] *Hopital Bichat, Paris, France*

ARTICLE INFO

Article history:
Received 12 June 2010
Accepted 16 September 2010
Available online 20 October 2010

Keywords:
Acute myocardial infarction
Thrombolysis
GpIIb/IIIa inhibitors
Percutaneous coronary intervention

ABSTRACT

Objectives: Early angioplasty after thrombolysis is now recommended for ST-elevation myocardial infarction, but the current guidelines propose a wide time-window ranging between 3 and 24 h after lytic administration. To identify the optimal timing for PCI after thrombolysis, we analyzed frequency and time course of the adverse events in patients randomized in the multicenter CARESS-in-AMI trial.

Methods: 598 high-risk patients with STEMI recruited in the CARESS-in-AMI study, were divided into the Immediate PCI group (IMM, $n=298$), Rescue PCI group (RES, $n=107$) and Standard Treatment Arm without rescue PCI (STA, $n=193$).

Results: RES patients had worse pre-procedural TIMI flow and post-procedural blush grade. At 30 days, there were 23 deaths: 11 (10.3%) in RES, 9 (3%) in IMM and 3 (1.6%) in STA ($p<0.001$). There were 22 episodes of refractory ischemia or re-infarction: 17 (8.8%) in the STA group, 4 (1.6%) in IMM and 1 (0.9%) in RES ($p<0.001$). In the RES group 10/11 (90.9%) deaths occurred before day 5. In the STA group, all deaths and the majority of ischemic events occurred after day 3. A reduction of risk of death was observed if PCI after thrombolysis was performed within 3.35 h from initial hospitalization.

Conclusions: The mortality benefit of immediate referral to PCI after pharmacological treatment for STEMI derives from a reduction in the time to reperfusion of patients with failed thrombolysis in need of rescue PCI. In patients with evidence of successful reperfusion, "elective" PCI within 3 days may be sufficient to reduce the recurrent ischemic events.

1. Introduction

Early elective angioplasty after successful thrombolysis has recently joined rescue angioplasty in the new STEMI guidelines of the ACC/AHA and ESC [1,2]. The wide time-window recommended for elective angioplasty after thrombolysis (in the ESC between 3 and 24 h expressly discouraging earlier PCI) reflects uncertainty on the best time of treatment. Very early treatment allows mechanical recanalization and flow restoration in patients with persistent

Abbreviations: STEMI, ST-elevation myocardial infarction; PCI, Percutaneous coronary intervention; CABG, Coronary Artery Bypass Grafting; TIMI, Thrombolysis In myocardial infarction.

* Corresponding author. Interventional Cardiology Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK. Tel.: +44 20 7351 8616; fax: +44 20 7351 8629.
E-mail addresses: frborgia@unina.it, f.borgia@rbht.nhs.uk (F. Borgia).

0167-5273/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2010.09.042

occlusion or <TIMI 3 flow after lysis, not always identifiable based on symptoms and ECG changes, and prevents early vessel reocclusion. The CARESS-in-AMI trial showed that high-risk STEMI patients treated at a non-interventional centre with half-dose reteplase and abciximab who are immediately transferred for PCI have a lower rate of death and/or recurrence of ischemic events at 30 days from presentation [3]. The benefits of immediate transfer to routine invasive revascularization after fibrinolysis in STEMI patients have been recently reported in a larger randomized trial [4] and confirmed also when STEMI patients were enrolled in a rural area with long transfer distances to PCI and widespread use of pre-hospital thrombolysis [5]. Moreover also the opinion that clinical advantages of early PCI after lysis are paid with an increased risk of major bleedings or strokes definitely fell into oblivion, considering that all trials comparing immediate revascularization after successful thrombolysis and standard ischemic-guided therapy did not show significant differences in intra-hospital [3,4] and 30 days [5] safety outcome between two strategies.

A recurrent criticism to these studies where early PCI has been performed immediately after thrombolysis has been that similar results could be consistently achieved by previous trials just performing PCI in the first 24 h after lytics, with intervals up to 16.7 ± 5.6 h after lytic administration in the largest of them (GRACIA-1) [6]. This delay offers practical advantages, avoiding the challenge of the emergency transport of unstable patients in the middle of the night and the burden of additional STEMI patients to be treated out of hours, allowing centers to concentrate in the goal of reducing door-to-balloon time in primary angioplasty [7–9]. We aimed to investigate the timing of the adverse events in patients randomized to early PCI after successful thrombolysis or standard symptom-guided strategy to assess whether PCI needs to be performed immediately after thrombolysis in all patients with high-risk STEMI.

2. Methods

The CARESS-in-AMI study [3] was conducted in 61 hospitals in 3 countries and involved networks of non-PCI ("spoke") centers ($n=41$) and specialist PCI ("hub") centers ($n=20$). Patents with STEMI who were admitted to a spoke centre within 12 h from onset of pain were included if they had one or more high-risk features: cumulative ST-segment elevation >15 mm, new LBBB, previous myocardial infarction, Killip Class ≥2 or left ventricular ejection fraction ≤35%. Patients with previous CABG or PCI in the territory of the likely culprit vessel, cardiogenic shock, need for concomitant major surgery, severe chronic renal or hepatic impairment, myocardial infarction within the previous 2 weeks or contraindications to thrombolytic therapy, abciximab, aspirin or clopidogrel were excluded. All patients were treated pharmacologically with half-dose reteplase, aspirin, unfractionated heparin and abciximab and then randomized to either immediate transfer to the hub site for PCI (Immediate PCI group) or to continued care at the spoke site with transfer only for rescue PCI due to persistent ST-segment elevation, ongoing chest pain or hemodynamic instability (Standard Care/Rescue PCI group). Clopidogrel (300 mg bolus) was started upon arrival in the angioplasty centre and continued in the first 30 days with the maintenance dose of 75 mg once a day.

For the purpose of the present analysis, patients recruited in the CARESS-in-AMI study, were divided into Immediate PCI group (IMM = 298), Rescue PCI group (RES, $n=107$) and Standard Treatment Arm without rescue PCI (STA, $n=193$). The frequency and time course of adverse events within 30 days from recruitment in the three groups were analyzed.

2.1. Outcome measures

The primary outcome was a composite of all-cause mortality, re-infarction and refractory myocardial ischemia within 30 days from randomization. Re-infarction and refractory myocardial ischemia were defined as previously reported [3]. An independent Core Laboratory reviewed all the baseline and 90 min ECGs to confirm the indications for rescue angioplasty and evaluated the baseline and post-PCI angiogram with complete quantitative angiographic measurements as well as evaluation of the TIMI flow grade, corrected TIMI frame count, and myocardial blush. An independent Critical Events Committee screened and adjudicated all serious adverse events based on the review of the original source documents. Their frequency and time course within 30 days from recruitment in the three groups were analyzed to identify the optimal timing for PCI after thrombolysis.

2.2. Statistical issues

Statistical analysis was preformed using R version 2.7.1 (The R Foundation for Statistical Computing, Vienna, Austria). Intention to treat analysis only was performed. Categorical variables were expressed as frequency (percentage) while continuous variables were expressed as mean ± standard deviation, with the exception of time intervals expressed as median (interquartile range). Comparison between groups was performed using the Wilcoxon, Fisher or Kruskal–Wallis test as appropriate. A two-sided p-value <0.05 was deemed indicative of statistical significance. The Cox proportional hazards regression analysis was used to assess the effect of timing of PCI on the composite primary endpoint and on death. Kaplan–Meier survival curves were also plotted. To explore the functional form of the relationship between time from admission to reperfusion and the risk of death in patients requiring rescue or immediate PCI, smoothing splines were applied in the Cox regression. A two-sided p-value <0.05 was considered indicative of statistical significance.

3. Results

3.1. Clinical characteristics and outcome according to transfer for immediate or rescue PCI

Of the 598 patients recruited in the CARESS-in-AMI trial, 396 were transferred to a PCI centre and 346 underwent PCI within 24 h from admission. In total, 298 patients were allocated to immediate PCI (IMM group), of which 289 (97%) were transferred to the PCI centre and 255(88.2) received PCI. Of the 300 patients allocated to standard treatment, 107 (35.7%) patients were transferred for rescue PCI (RES group), while 193 (64.3%) received standard care without rescue PCI (STA group). The reason for transfer to rescue PCI was persistence of symptoms or ST-elevation >50% after 90 min from first administration of reteplase in 72 (65.4%) of patients and haemodynamic destabilization in the remainder.

Clinical and demographic characteristics of these 3 groups (IMM, RES and STA) are presented in Table 1. The RES group had a higher baseline heart rate (ANOVA $p=0.001$), prevalence of hypercholesterolemia ($p=0.007$), previous stroke ($p=0.01$), and anterior infarct ($p=0.005$). Maximal ST-elevation on admission was also significantly higher in the RES group compared to the STA group ($p=0.007$) and compared to the IMM group ($p=0.04$). Times of events in the three groups of patients are reported in Fig. 1. The interval between onset of pain to angiography was longer in the rescue group (543 min versus 362 min in IMM, $p<0.001$) because of the delay between pharmacological treatment and angiography due to the 90 min of observation required by protocol (211 versus 135 min, $p<0.0001$). Pre-procedural TIMI flow grade was lower ($p=0.001$, Fig. 2a) and maximal diameter stenosis higher ($p=0.003$, Table 2) in the RES group compared to IMM group. There were no differences in pre-procedural lesion length, RVD or the prevalence of thrombus, eccentricity or calcification. In 6.9% of RES patients mechanical thrombectomy was used, compared to 3.5% in the IMM group ($p=0.24$); distal protection devices were used in 1 (1.1%) of RES and 5 (1.9%) of IMM patients ($p=1$). After PCI, there was a comparable acute gain and maximal diameter stenosis in both groups. Residual ST-segment elevation post-PCI was higher in the RES group compared to IMM ($p=0.0002$), while there was no significant difference in post-procedural TIMI flow (TIMI 3 in 89.8% of IMM versus 87.8% in RES), or TIMI frame count (31.7 ± 16.1 frames in IMM versus 33.9 ± 17.1 frames in RES, $p=0.19$). Because of the need of a prolonged acquisition including the vessel periphery, myocardial blush score could be attributed only to 49% of patients in the RES and IMM groups. Myocardial blush score was significantly higher in the IMM group, with 61.8% of patients having a blush score of 3 in IMM versus 39.0 in RES ($p=0.04$, Fig. 2b).

At 30 days, there were 23 deaths: 11 (10.3%) in RES, 9 (3%) in IMM and 3 (1.6%) in STA ($p<0.001$). There were 22 episodes of refractory ischemia or re-infarction: 17 (8.8%) in the STA group, 4 (1.6%) in IMM and 1 (0.9%) in RES ($p<0.001$). The majority of deaths in the RES group (10/11, 90.9%) clustered in the first 4 days after randomization. In the STA group, all deaths and the majority of ischaemic events occurred after day 3 (Fig. 3). When exploring the relationship between time from first hospital admission to reperfusion and the risk of death in patients requiring rescue or immediate PCI, patients

Table 1
Baseline demographic and clinical characteristics.

	Overall	Standard treatment, no PCI	Immediate PCI	Rescue PCI	*p*-value
n (%)	598 (100)	193 (32.3)	298 (49.8)	107 (17.9)	
Age (years)	59.9 ± 10.0	59.0 ± 9.9	60.2 ± 10.2	60.9 ± 9.3	0.23
Male (%)	78.6	80.8	77.9	76.6	0.63
Hypertension (%)	42.8	46.6	38.9	46.7	0.16
Hypercholesterolaemia (%)	26.8	31.1	21.1	34.6	0.007
Diabetes mellitus (%)	14.7	14	14.8	15.9	0.91
Current or previous smoker (%)	57	64.2	53.4	54.2	0.05
Treatment prior to presentation with:					
ASA (%)	19.4	19.7	17.1	25.2	0.19
ACE-inhibitors (%)	23.7	21.8	24.8	24.3	0.73
Statins (%)	11.5	11.4	9.7	16.8	0.14
Beta blockers (%)	15.4	15.5	13.1	21.5	0.12
Prior history of:					
Myocardial infarction (%)	10.7	10.4	11.7	8.4	0.62
Stroke (%)	1.5	0.5	1	4.7	0.01
PCI (%)	2.5	3.1	2.3	1.9	0.78
CABG (%)	0.2	0	0.3	0	0.6
Congestive heart failure (%)	0.8	1	0.7	0.9	0.9
Blood pressure on recruitment					
Systolic (mm Hg)	137.4 ± 23.7	137.8 ± 25.9	137.1 ± 22.3	137.4 ± 24.0	0.94
Diastolic (mm Hg)	84.3 ± 13.6	85.4 ± 14.2	83.4 ± 13.3	84.8 ± 13.4	0.26
Heart rate (bpm)	75.0 ± 16.5	72.5 ± 16.6	74.8 ± 16.2	79.8 ± 16.2	0.001
Infarction site					
Anterior (%)	46.7	37.3	50	54.2	0.005
Inferior (%)	48.2	59.1	44.3	39.3	0.006
Killip classification					
Class 1 (%)	56.4	60.6	55.4	51.4	0.27
Class 2 (%)	42.1	38.3	42.6	47.7	0.29
Class 3 (%)	1.5	1	2	0.9	0.59
Left ventricular ejection fraction (%)	45.9 ± 9.6	47.9 ± 9.2	44.9 ± 9.3	44.3 ± 10.9	0.01
Onset of symptoms to enrollement (min)	193.6 ± 154.7	187.9 ± 134.9	196.9 ± 169.3	194.7 ± 146.1	0.82
Onset of symptoms to angiography (min)	411.3 ± 276.7	–	362.3 ± 200.6	543.6 ± 389.5	<0.001

with greater delay appeared to be at higher risk, with a cut-off at approximately 3.35 h. Despite the trend was clear and consistent (HR 3.81, 95%CI: 0.83–17.4, $p = 0.08$, Fig. 4) this difference did not reach significance due to the low event rate.

There was no significant difference in TIMI major ($p = 0.14$) or minor ($p = 0.29$) bleeding between groups. Patients in the IMM group had a higher incidence of TIMI minimal bleeding (7.7% versus 1.6% in STA and 3.7 in RES, $p = 0.005$). There was no significant difference in the incidence of stroke (1.04% in STA versus 1.0% in IMM versus 2.8% in RES, $p = 0.35$).

4. Discussion

Detailed analysis of events in the two subgroups (RES and STA) of the standard approach arm of the CARESS-in-AMI study demonstrated that patients requiring rescue PCI had the highest mortality risk and accounted for most of the deaths in this population, while those with successful pharmacological reperfusion not requiring rescue PCI have a low mortality risk but are at higher risk of recurrent ischemia. Timing of events in these groups also differs significantly, with most of the deaths occurring within the first days after randomization, concentrated in the RES subgroup (10/11 deaths in this group occurred before day 5), and the vast majority of ischemic events occurring late after randomization, concentrated in the STA group. These observations give opposite indications on the optimal time of PCI after lytics.

The current approach to failed reperfusion after lytics, sending patients to rescue angioplasty only after 60–90 min of inactive observation, appears illogical and ineffective. The most recent AHA/ACC and ESC guidelines give a lukewarm indication to rescue angioplasty (class of recommendation IIa), limited to patients with at least a moderate area of myocardium at risk and symptom onset within 12 h [1,2]. In fact, only two large randomized studies have addressed in the stent era the use of rescue PCI: the Middlebrough Early Revascularization to Limit Infarction (MERLIN) trial [10] which enrolled 307 patients with STEMI treated within 10 h with Streptokinase and the REACT trial [11] randomizing 427 patients with STEMI and failed thrombolysis to repeated thrombolysis ($n = 142$), conservative treatment ($n = 141$), or rescue PCI ($n = 144$). Even with the inclusion of 6 more trials in a recent meta-analysis including 1177 patients [12], rescue PCI only showed a trend towards reduction in all-cause mortality (Relative Risk [RR] 0.69; 95% CI 0.46–1.05). The significant reduction in the risk of heart failure (RR = 0.73 95% CI 0.54–1.00) and re-infarction (RR = 0.58 95% CI 0.35–0.98) after rescue angioplasty was balanced by the increased risk of stroke (RR = 4.98 95% CI 1.10–22.5) and minor bleeding (RR = 4.58 95% CI 2.46–8.55). The favorable results obtained in the group of elective transfer of all patients post-lytics in the CARESS-in-AMI trial (median interval thrombolysis/elective angioplasty 169 min) [3], CAPITAL-AMI (84 min) trial [13], NORDISTEMI (162 min) trial [5] and TRANSFER-AMI (234 min) trial [4] call for a drastic change in the current attitude to wait for response to treatment in patients receiving lytics. Since there is a growing network of 24/7 PCI centers ready for primary angioplasty with a team available at the time of arrival, there is no advantage to delay transfer and risk a dangerous and unnecessary worsening of the myocardial damage if the patient does not respond to lytics. In fact, in this and other studies the bleeding risk after PCI was not associated with the time delay after thrombolysis [3,14] and the excess mortality and recurrent ischemia observed in a previous trial using thrombolysis as a "facilitated" approach was not observed [15]. The higher risk of complications of lytics when performed in the first hours after thrombolysis was probably caused by an insufficient concomitant antiplatelet treatment. If this limitation is addressed by the use of a combined treatment with IIb–IIIa inhibitors widely used alone or in combination with lytics for STEMI patients transferred to PCI [14,16,17] or high loading dose of clopidogrel [18] or prasugrel [19,20], it will be difficult to argue against a policy of early elective angioplasty. Our findings, however, suggest that some flexibility may be allowed for patients with evidence of reperfusion after

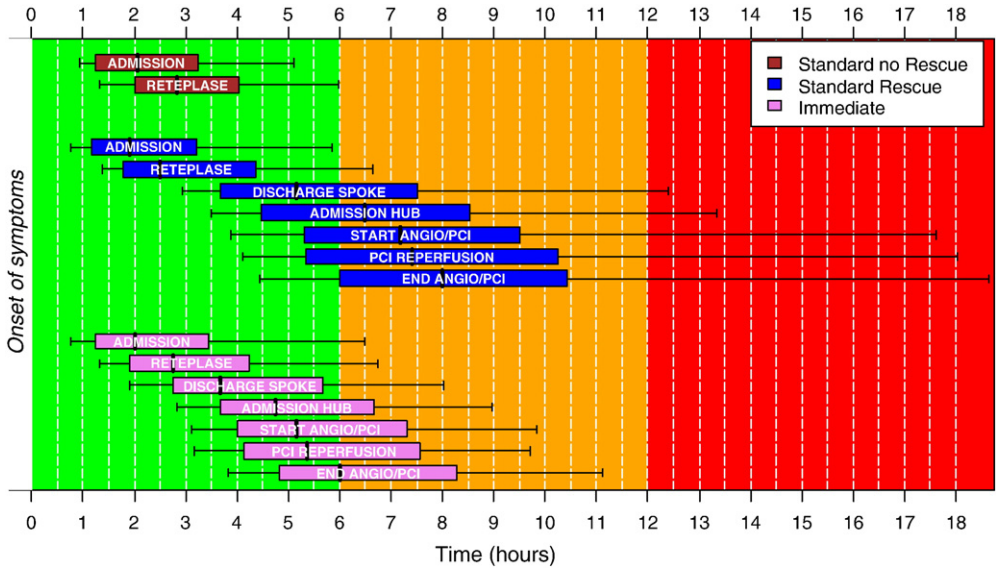

Fig. 1. Timing of events in the three comparison groups.

thrombolysis. In this patient cohort, stringent protocols aiming at minimization of the delay to PCI developed for patients undergoing primary or rescue PCI may not be required. In these patients, "elective" PCI within 1–3 days may be sufficient to reduce the incidence of ischemic events which cluster between day 4 and 20 post-MI. In practice, however, the immediate availability of the angioplasty team and the uncertainty to on whether reperfusion occurred only based on clinical/electrocardiographic parameters [21–23] are likely to translate into immediate angioplasty treatment also for patients with evidence of successful thrombolysis at the time of arrival.

Detailed analysis of the characteristics and outcome of patients undergoing rescue PCI in the CARESS-in-AMI trial provided other interesting observations. Patients requiring rescue PCI had more pronounced ST-elevation on admission compared to those in the STA group, suggesting a higher ischemic burden. After PCI, the higher blush grade and residual ST-elevation in the RES group compared to patients in the IMM group who underwent PCI earlier suggest more severe persistent myocardial injury, which is likely to have contributed to the higher mortality in this group. Stone et al. reported strong correlation between myocardial blush after PCI in STEMI patients and late outcome, with one-year cumulative mortality of 6.8% for Grade 3 myocardial blush, 13.2% for Grade 2 and 18.3% for Grade 0/1 ($p = 0.004$) [24]. In fact, the number of deaths in the RES group alone was by far higher to that in the entire IMM arm of the CARESS-in-AMI trial and accounted for the vast majority of deaths in the Standard care/rescue PCI arm. Early relief of ischemia in this high-risk group, thus, appears paramount in reducing early mortality.

4.1. Limitations

This was a post-hoc analysis and its results should be taken as hypothesis-generating rather than conclusive. The relatively low event rate was a further limitation to the analysis and new larger trials or analytical meta-analyses of early post-thrombolysis PCI trials are required. The combination of half-dose reteplase and abciximab is not a recommended lytic treatment in the current guidelines for the treatment of STEMI [1,2], even though this lytic cocktail has been shown to have similar or greater efficacy than conventional full-dose thrombolysis in large angiographic studies [25,26], with no differences in major adverse events when used in patients <75 years of age in a large comparison with full-dose reteplase [27,28]. The similar results of the TRANSFER-AMI and NORDISTEMI trials [4,5] which used tenecte-

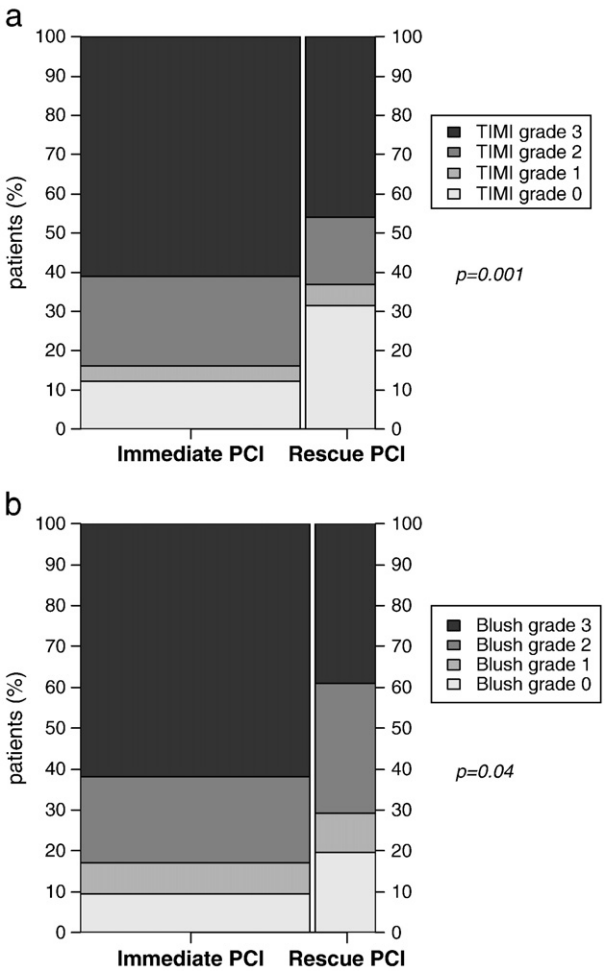

Fig. 2. (a): pre-procedural TIMI flow in the IMM and RES groups. Patients requiring rescue PCI had a significantly worse pre-procedural TIMI flow compared to those undergoing immediate PCI. (b): myocardial blush grade in the IMM and RES groups. Myocardial blush was significantly better in patients undergoing immediate PCI.

Table 2
Angiographic and procedural characteristics.

	Overall	Immediate PCI	Rescue PCI	*p*-value
n(%)	396(100)	289(72.9)	107(27.1)	
Number of diseased vessels				
1 (%)	46.2	45	49.5	0.43
2 (%)	30.8	31.8	28	0.54
3 (%)	19.7	21.1	15.9	0.32
PCI performed (%)	346(87.4)	255(88.2)	91(85)	0.4
Reason for not performing PCI				
TIMI 3 flow (%)	56	64.7	37.5	0.13
No stenoses >50% (%)	26	17.6	43.7	0.03
Unsuitable anatomy (%)	16	20.6	6.2	0.41
Emergency CABG planned (%)	18	17.6	18.8	1
Lesion treated				
Left anterior descending (%)	48.8	49.6	46.1	0.6
Circumflex (%)	8.4	7.8	10.5	0.48
Right coronary artery (%)	36.6	36.9	35.5	0.89
Thrombotic material (%)	50.3	48.3	56.6	0.24
Ulcerated lesion (%)	31	30.8	32	0.87
Eccentric lesion (%)	94.9	95.7	98.2	1
Calcification				
None (%)	83.6	84.2	81.2	0.57
Moderate (%)	16.1	15.4	18.8	0.56
High (%)	0.3	0.4	0	1
Angulation, >45 degrees (%)	5.4	6.2	2	0.32
Bifurcation protected (%)	7.3	8.1	3.9	0.38
Tortuosity				
Mild to moderate (%)	22.2	23.8	16.7	0.24
Severe (%)	1.3	1.3	1.5	1
Length (mm)	12.2 ± 5.9	12.2 ± 5.3	12.2 ± 7.7	0.48
Pre-procedural TIMI grade				
0 (%)	16.9	12.2	31.6	0.0003
1 (%)	4.2	3.8	5.3	0.52
2 (%)	21.4	22.8	17.1	0.34
3 (%)	57.5	61.2	46.1	0.024
Pre-procedural TIMI frame count (sec)	48.4 ± 28.6	44.7 ± 25.9	59.6 ± 33.1	0.001
Pre-procedural reference vessel diameter (mm)	3.02 ± 0.52	3.03 ± 0.52	2.97 ± 0.51	0.4
Pre-procedural minimal lesion diameter (mm)	0.75 ± 0.47	0.81 ± 0.43	0.59 ± 0.53	0.001
Pre-procedural diameter stenosis (%)	75.0 ± 15.3	73.3 ± 14.2	80.3 ± 17.2	0.003
Post-procedural blush grade				
0 (%)	11.6	9.6	19.5	0.10
1 (%)	8.1	7.6	9.8	0.74
2 (%)	23.2	21.0	31.7	0.15
3 (%)	57.1	61.8	39.0	0.01
Post-procedural TIMI grade				
0 (%)	2.3	2.5	1.4	1
1 (%)	1.3	0.8	2.7	0.24
2 (%)	7.1	6.8	8.1	0.8
3 (%)	89.4	89.8	87.8	0.67
Post-procedural TIMI frame count (sec)	32.2 ± 16.4	31.7 ± 16.1	33.9 ± 17.2	0.19
Post-procedural reference vessel diameter (mm)	3.14 ± 0.48	3.16 ± 0.48	3.09 ± 0.47	0.32
Post-procedural minimal lesion diameter (mm)	2.61 ± 0.65	2.64 ± 0.66	2.49 ± 0.61	0.086
Post-procedural diameter stenosis (%)	18.5 ± 0.16	17.6 ± 0.16	19.5 ± 0.15	0.051
Acute gain (mm)	1.86 ± 0.69	1.83 ± 0.68	1.93 ± 0.74	0.37

CORE Lab analysis of QCA data available for 81.9% of IMM versus 71.0% RES patients. Analysis of post-procedural TIMI frame count and blush score was available in 49% of patients.

plase, enoxaparin and loading and maintenance dose of clopidogrel may address criticisms related to the thrombolytic regimen or to the absence of enoxaparin and clopidogrel in the STA group of CARESS-in-AMI trial.

5. Conclusions

In depth analysis of the timing of adverse events in the CARESS-in-AMI trial suggests that all high-risk STEMI patients receiving thrombolysis in a non-PCI centre should be routinely and immediately transferred for PCI. Earlier access to angioplasty in patients with failed reperfusion appears to confer a mortality benefit compared to the traditional current approach of transferring thrombolysed patients for rescue angioplasty after an observation period. In patients who have, upon arrival, evidence of reperfusion the main advantage of early angioplasty is prevention of recurrent ischemia and an elective angioplasty within 1–3 days can be sufficient to achieve this goal.

Conflict of interest statement

Carlo Di Mario, Dariusz Dudek, Stefano Savonitto, Federico Piscione had minor financial revenues from consultancies, speaker's bureau honoraria, and received travel grants from Eli Lilly Italia S.p.A, Eli Lilly UK, Eli Lilly Critical Care Europe and Biotronik GmbH Germany.

Acknowledgement

The CARESS-in-AMI trial was sponsored by the Italian Society of Interventional Cardiology (GISE) and endorsed by the Italian Association of the Hospital Cardiologists (ANMCO).

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [29].

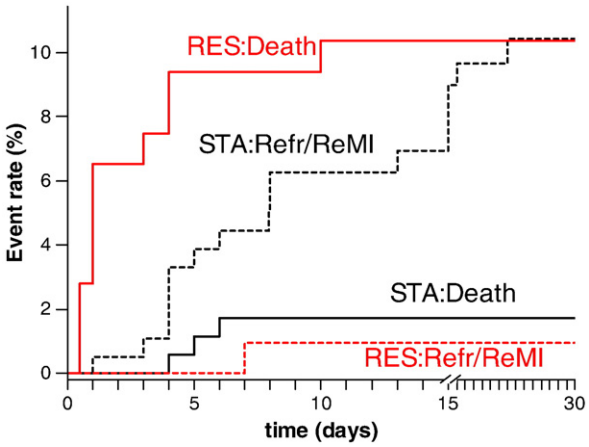

Fig. 3. Kaplan–Meier curves for death and the combined endpoint of refractory ischemia or re-infarction in the STA and RES groups. No deaths occurred during the first 3 days after recruitment in patients demonstrating reperfusion after pharmacological treatment and thus not requiring rescue PCI (STA group). These patients, however, unlike the rescue subgroup had progressive linear increase of refractory ischemia and recurrent MI in the 30 days post lytic administration.

Appendix

Data Safety Advisory Board: M Simoons (Thoraxcenter, Dijkzigt Hospital, Rotterdam, The Netherlands), G Di Pasquale (Ospedale Maggiore, Bologna), E Boersma (Erasmus University, Rotterdam, The Netherlands).

Critical Event Committee: S Savonitto (Cardiology, Ospedale Niguarda-Ca' Granda, Milan, Italy), B Meier (Bern, Switzerland), I Santilli (Stroke Unit, Department of Neurosciences, Ospedale Niguarda-Ca' Granda, Milan, Italy).

Statistics: E Bonizzoni (Institute of Biostatistics, Pavia, Italy), M Roughton, K Dimopoulos (Royal Brompton Hospital and Imperial College London), T Clayton (London School of Hygiene and Tropical Medicine, London, UK).

Co-ordinating Centre: Mediolanum Cardio Research, Milan: R Panzarasa, C Monelli, F Cattaneo, A Formosa.

Data management: Clinical Trials and Evaluation Unit, Royal Brompton Hospital, London M Flather, F Nugara, P Loane.

Core lab for ECG and QCA: CORISIS, St Denis, France: B Glatt.

Investigators

Principal Investigators: C Di Mario (Chairman), D Dudek (Co-PI & National Coordinator, Poland), L Bolognese (Co-PI & National Coordinator, Italy), PG Steg (Co-PI & National Coordinator, France).

Italy (263 patients)

F Piscione, F. Borgia, O Viola (Policlinico Universitario Federico II-Napoli-HUB), E Murena, G Sibilio (Osp.S.M.delle Grazie-Pozzuoli-Spoke/82 pt), S Baldi, P Villani (Osp. M.Scarlato-Scafati-Spoke/5 pt), D Prinzi, P de Rosa (Osp.S.Giuliano-Giugliano-Spoke/3 pt).

A Manari, V Guiducci (Osp.S.M. Nuova-Reggio Emilia-HUB), S Di Stefano, M Conti (Osp. di Guastalla-Guastalla-Spoke/24 pt), G Gambarati, A Reverzani (Osp.Magati-Scandiano-Spoke/21 pt), E Catellani, A Piazza (Osp.Franchini-Montecchio-Spoke/10 pt), L Lusetti, M Donateo (Osp. S.Sebastiano-Correggio-Spoke/4 pt), R Violini, MS Nazzaro (Osp.S.Camillo-Roma-HUB), A Gaspardone, C Citone (Osp.S. Eugenio-Roma-Spoke/26 pt), G Giorgi, G Sarli (Osp.S.Sebastiano Martire-Frascati-Spoke/2 pt), M Child, V Balian (Osp. di Circolo-Busto Arsizio, Varese/HUB), D Nassiacos, S Meloni (Osp. provinciale di Saronno-Saronno-Spoke/11 pt), M Onofri, C Gualtierotti (Osp. Galmarini9-Tradate-Spoke/5 pt), L Niccoli, F Ettori (Spedali Civili-Brescia-HUB), E Renaldini, L Parola (Osp.Civile-Gavardo-Spoke/11 pt), GF Pasini, M Schettino (Osp La Memoria-Gavardo-Spoke/3 pt), L Bolognese, G Falsini, F Liistro (Osp.S.Donato-Arezzo-HUB), G Mantini, T Taddei (Osp.S.Giovanni-Valdarno-Spoke/6 pt), F Cosmi, D Cosmi (Osp.S.Margherita-Cortona-Spoke/5 pt), R Tarducci-Osp. della Valtiberina-Sansepolcro/1 pt), G Baralis, A Dellavalle, G Steffenino (Osp.S. Croce e Carle-Cuneo-HUB), C Bruna, S Goletto (Osp di Mondovì-Mondovì-Spoke/10 pt), B Doronzo, L Correndo (Osp.S.S.Annunziata-Savigliano-Spoke/2 pt), A Benassi (Hesperia Hospital-Modena-HUB), G Patrizi, S Ricci (Osp.Ramazzini-Carpi-Spoke/5 pt), F Melandri, G Gazzotti (Osp.Civile di Sassuolo-Sassuolo-Spoke/2 pt), A Montinaro (Osp. V.Fazzi-Lecce-HUB), A Albanese (Osp.S.Caterina Novella-Galatina-Spoke/1 pt), G De Rinaldis (Osp.S Giuseppe da Copertino-Copertino-Spoke/1 pt), M. Zanchetta, L Pedon (P.O.Cittadella-Cittadella, Padova-HUB), A Daniotti, F Alitto (P.O.Montebelluna-Montebelluna-Spoke/6 pt), A Zampiero, P Contessotto (P.O di Camposampiero-Camposampiero-Spoke/2 pt), G Piovaccari (Ospedale degli Infermi-Rimini-HUB), L Rusconi (Osp.Ceccarini-Riccione-Spoke/5 pt), E Tartagni (Osp.M.Bufalini-Cesena-Spoke/2 pt), Z Olivari, E Franceschini Grisolia (Osp.Cà Foncello-Treviso-HUB), M

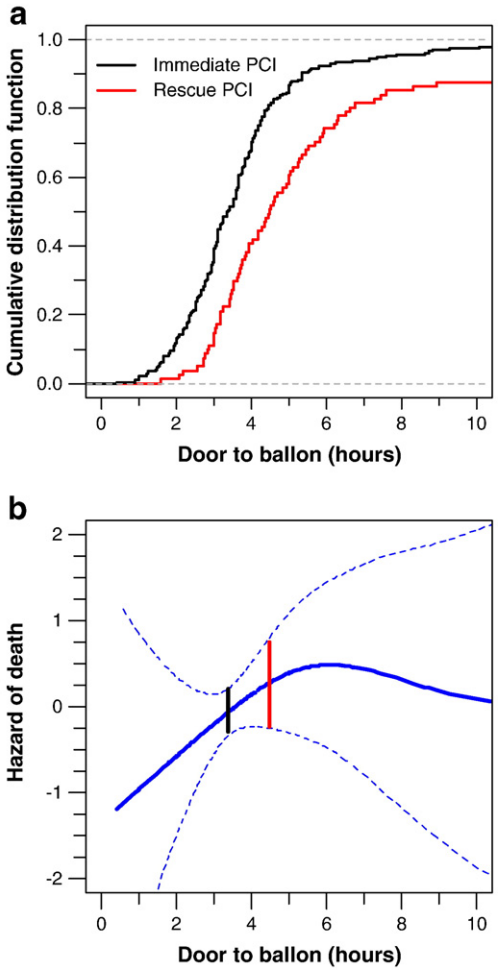

Fig. 4. (a): distribution of the time from admission to mechanical reperfusion in the IMM (black line) and RES (red line) groups. (b): In blue, the functional form (and 95% confidence intervals) of the relation between time from initial hospital admission to PCI and the hazard of death in patients who underwent immediate or rescue PCI (Black and red line indicate the hazard of death at a time corresponding to the median door-to-balloon time for immediate and rescue PCI groups, respectively). The hazard of death tends to increase with time, but the low number of events results in wide confidence intervals.

Guarnerio-G Bilardo (Osp.S.M.del Prato-Feltre-Spoke/3 pt), P Delise, F Caprioglio (P.O Ulss 7-Conegliano Veneto-Spoke/2 pt), A Colombo, F Airoldi (HSR-Milano-HUB), M De Martini (P.O di Desio e Seregno-Desio-Spoke/3 pt).

Poland (301 patients)

D Dudek, W Mielecki (Szpital Uniwersytecki-Krakow/HUB), K Zmudka, B Guzik (Szpital Jana Pawla II-Krakow-HUB), A Radziszewski (Szpital Powiatowy-Dabrowa Tarnowska-Spoke/64 pt), P Chrusciel (Szpital Powiatowy-Nowy Targ-Spoke/61 pt), J Nowak (Szpital Powiatowy-Chrzanow-Spoke/28 pt), M Zalewski, A Szpot (Szpital Powiatowy-Zakopane-Spoke/24 pt), A Blaszkowski (Szpital Powiatowy-Sucha Beskidzka-Spoke/21 pt), T Czopek, I Gluszek, S Kocemba (Szpital Powiatowy-Wadowice-Spoke/21 pt), M Karpinski, J Chodorowski (Szpital Powiatowy-Limanowa-Spoke/19 pt), S Slowinski, E Krupa (Szpital Powiatowy-Tarnow-Spoke/15 pt), S Malinowski, R Wysocka (Szpital Powiatowy-Nowy Szacz-Spoke/11 pt), B Derlaga, D Babiarz (Szpital E.Szczeklika-Tarnow-Spoke/8 pt), G Mach (Szpital Powiatowy-Oswecim-Spoke/4 pt), I Keller Konopka (SP ZOZ-Brzesku-Spoke/1 pt), T Krupnicki, D Domagala (Szpital w Szczyrzu-Szczyrzyc-Spoke/1 pt), A Ochala, A Michalewska (Gornoslaskie Centrum Kardiologii-HUB), M Finik, M Sieron (Szpital Powiatowy-Jaworzno-Spoke/18 pt), P. Wolkowski (Szpital Powiatowy-Dabrowa Gornicza-Spoke/3 pt), Z Bryndal, A Zublewicz (Szpital Miejski-Tychy-Spoke/1 pt), E Kocot M Hamankiewicz, M Pawlowska (Szpital Powiatowy-Bedzin-Spoke/1 pt).

France (36 patients)

G Steg (Hop Bichat-Paris-HUB), A Richard (SMUR Beaujon-Clichy-Spoke/11 pt), A Pansieri (CH-H. Duffaut-Avignon-HUB), M Aboukalil (SAMU CH-H.Duffaut-Avignon-Spoke/7 pt), B Colin (CH Service des Urgences-Carpentras-Spoke/2 pt), M Hamon (Hopital de Caen-Caen-HUB), A Touambilanga (CH L.Pasteur-Cherbourg-Spoke/7 pt), Y Gottwalles (Clinique St.Joseph-Colmar-HUB), J Cabalion (CH 2-Selestat).

References

[1] Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008;51:210–47.

[2] Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29:2909–45.

[3] Di Mario C, Dudek D, Piscione F, Mielecki W, Savonitto S, Murena E, et al. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomized, multicentre trial. Lancet 2008;371:559–68.

[4] Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med Jun 25 2009;360(26):2705–18.

[5] Bøhmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (Norwegian study on district treatment of ST-elevation myocardial infarction). J Am Coll Cardiol Sep 4 2009 [Epub ahead of print].

[6] Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomized controlled trial. Lancet 2004;364:1045–53.

[7] Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J 2006;27:779–88.

[8] Manari A, Ortolani P, Guastaroba P, Casella G, Vignali L, Varani E, et al. Clinical impact of an inter-hospital transfer strategy in patients with ST-elevation myocardial infarction undergoing primary angioplasty: the Emilia-Romagna ST-segment elevation acute myocardial infarction network. Eur Heart J 2008;29:1834–42.

[9] Bassand JP, Danchin N, Filippatos G, Gitt A, Hamm C, Silber S, et al. Implementation of reperfusion therapy in acute myocardial infarction. A policy statement from the European Society of Cardiology. Eur Heart J 2005;26:2733–41.

[10] Sutton AG, Campbell PG, Graham R, Price DJ, Gray JC, Grech ED, et al. A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: the Middlesbrough Early Revascularization to Limit Infarction (MERLIN) trial. J Am Coll Cardiol 2004;44:287–96.

[11] Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med 2005;353:2758–68.

[12] Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, Foody JM, Krumholz HM, Phillips CO, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. J Am Coll Cardiol 2007;49:422–30.

[13] Le May MR, Wells GA, Labinaz M, Davies RF, Turek M, Leddy D, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). J Am Coll Cardiol 2005;46:417–24.

[14] Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205–17.

[15] van der Werf F, Ross A, Armstrong P, Granger C. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomized trial. Lancet 2006;367:569–78.

[16] Marzocchi A, Manari A, Piovaccari G, Marrozzini C, Marra S, Magnavacchi P, et al. Randomized comparison between tirofiban and abciximab to promote complete ST-resolution in primary angioplasty: results of the facilitated angioplasty with tirofiban or abciximab (FATA) in ST-elevation myocardial infarction trial. Eur Heart J 2008;29:2972–80.

[17] Dudek D, Siudak Z, Janzon M, Birkemeyer R, Aldama-Lopez G, Lettieri C, et al. EUROTRANSFER Registry Investigators. European registry on patients with ST-elevation myocardial infarction transferred for mechanical reperfusion with a special focus on early administration of abciximab—EUROTRANSFER Registr. Am Heart J 2008;156(6):1147–54.

[18] Mehilli J, Kastrati A, Schulz S, Frungel S, Nekolla SG, Moshage W, et al. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. Circulation 2009;119:1933–40.

[19] Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in comparison to clopidogrel for inhibition of platelet activation and aggregation-thrombolysis in myocardial infarction 44 trial. Circulation 2007;116:2923–32.

[20] Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723–31.

[21] Klootwijk P, Langer A, Meij S, Green C, Veldkamp RF, Ross AM, et al. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST-segment monitoring in the GUSTO-I trial. Eur Heart J 1996;17:689–98.

[22] Hohnloser SH, Zabel M, Kasper W, Meinertz T, Just H. Assessment of coronary artery patency after thrombolytic therapy: accurate prediction utilizing the combined analysis of three noninvasive markers. J Am Coll Cardiol 1991;18:44–9.

[23] Ophuis AJ, Bar FW, Vermeer F, Janssen W, Doevendans PA, Haest RJ, et al. Angiographic assessment of prospectively determined non-invasive reperfusion indices in acute myocardial infarction. Heart 2000;84:164–70.

[24] Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. J Am Coll Cardiol 2002;39:591–7.

[25] Antman EM, Gibson CM, de Lemos JA, Giugliano RP, McCabe CH, Coussement P, et al. Combination reperfusion therapy with abciximab and reduced dose reteplase: results from TIMI 14. The thrombolysis in myocardial infarction (timi) 14 investigators. Eur Heart J 2000;21:1944–53.

[26] 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.

[27] Topol EJ. 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.

[28] Savonitto S, Armstrong PW, Lincoff AM, Jia G, Sila CA, Booth J, et al. Risk of intracranial haemorrhage with combined fibrinolytic and glycoprotein 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.

[29] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.