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