International Journal of Cardiology xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

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

Time-to-treatment and infarct size in STEMI patients undergoing primary angioplasty

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ARTICLE INFO

Article history:
Received 28 August 2011
Received in revised form 5 March 2012
Accepted 10 April 2012
Available online xxxx

Keywords:
Primary angioplasty
Infarct size
Time-to-treatment

ABSTRACT

Background: Several reports have shown that in patient with ST-segment elevation acute myocardial infarction (STEMI) longer ischemia time is associated with impaired reperfusion and higher mortality. However, there is still some doubts with regards time to reperfusion role in patients treated with primary percutaneous coronary intervention (PCI). Therefore, the aim of the current study was to evaluate the impact of time-to-treatment on infarct size as evaluated by myocardial scintigraphy in a large cohort of STEMI patients undergoing primary PCI.
Methods: Our population is represented by 830 STEMI patients undergoing primary PCI. Infarct size was evaluated at 30 days by technetium-99m-sestamibi.
Results: Time-to-treatment was significantly associated with age and dyslipidemia. Time-to-treatment linearly affected the rate of postprocedural TIMI 3 flow ($p<0.0001$) and scintigraphic infarct size ($p<0.001$). The impact of time-to-treatment on infarct size persisted in the analysis restricted to patients with postpocedural TIMI 3 flow, and after correction for confounding factors such as age, dyslipidemia, postprocedural TIMI 3 flow (OR [95% CI] = 1.26 [1.14–1.39], $p<0.001$).
Conclusions: This study shows in a large population of STEMI patients undergoing primary PCI that time-to-treatment is linearly associated with infarct size.

1. Introduction

Availability of pharmacologic and mechanical reperfusion therapies has significantly reduced cardiac mortality among ST-segment elevation acute myocardial infarction (STEMI) patients [1–11]. However, even though primary angioplasty has been shown to be superior to thrombolysis, mainly due to a larger success in epicardial recanalization, a suboptimal myocardial reperfusion is observed in a still relevant percentage of patients [12,13]. A clear relationship between mortality and time delay from symptom-onset to treatment has been demonstrated in patients with STEMI treated by thrombolysis [14,15]. Some studies have suggested a prognostic impact of time-to-treatment in STEMI patients undergoing primary angioplasty [16–21]. However, few data have been reported in terms of infarct size. Moreover, myocardial perfusion scintigraphy has been widely used to accurately assess infarct size in clinical trials and in current medical practice. Therefore, the aim of the current study was to evaluate the influence of symptom-onset-to-balloon time on infarct size as evaluated by technetium-99m-sestamibi in a large cohort of patients with STEMI treated by primary angioplasty.

2. Materials and methods

Our population is represented by 830 STEMI patients treated by primary angioplasty undergoing evaluation of infarct size at 30 days after the intervention. All patients were admitted within 12 h from symptom onset. All patients received aspirin (500 mg intravenously), heparin (60 IU/kg IV) (both administrated out-of-hospital if patients were transported by an ambulance otherwise at hospital admission after diagnosis) and clopidogrel (at hospital admission after diagnosis). The decision to provide Gp IIb–IIIa inhibitors was left at the discretion of the operator in the cath lab. All patients were on dual oral antiplatelet therapy (aspirin and clopidogrel or ticlopidine) for at least 4 weeks after stent implantation. Ischemia time was defined as the interval between symptoms onset to first balloon inflation. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [49].

2.1. Coronary angiography and mechanical revascularization

Selective coronary angiography was performed in multiple projections before mechanical reperfusion. Immediately after diagnostic angiography, angioplasty with stenting of the infarct-related vessel was performed using standard material. Successful primary percutaneous coronary intervention was defined as Thrombolysis In Myocardial Infarction (TIMI) grade 3 coronary flow in the treated vessel with a residual stenosis <20% [22].

2.2. Infarct size assessment

As previously described [23], gated single-photon emission computed tomography (SPECT) acquisition began 60 min after technetium-99m-sestamibi injection (740 MBq), using a double-head gamma-camera equipped with high-resolution collimators, 180°

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doi:10.1016/j.ijcard.2012.04.078

rotation arc, 32 projections, 60 s/projection, 8 frames/heart cycle and 64×64 matrices. The studies were reconstructed using filtered back-projection without attenuation or scatter correction and realigned along the heart axis. Perfusion defects were quantified as percentage of LV wall, with the defect threshold set at 60% of peak uptake [24].

2.3. Statistical analysis

Statistical analysis was performed with the SPSS 15.0 statistical package. Continuous data were expressed as mean ± SD and categorical data as percentage. The ANOVA test was appropriately used for continuous variables. The chi-square test or the Fisher's exact test was used for categorical variables. Patients were divided according to ischemia time (<2 h, 2–3 h, 3–4 h, 4–5 h, 5–6 h, and ≥6 h). Multiple logistic regression analysis was used to evaluate the impact of ischemia time on infarct size after adjustment for significant ($p<0.05$) confounding baseline characteristics.

3. Results

Patients characteristics are shown in Tables 1 and 2. Time-to-treatment was significantly associated with age ($p<0.001$) and dyslipidemia ($p<0.001$). No differences were observed in terms of other clinical characteristics. Time-to-treatment inversely affected the rate of postprocedural TIMI 3 flow ($p<0.0001$) (Adjusted OR [95% CI] = 0.69 [0.59–0.81], $p<0.001$).

As shown in Fig. 1, time-to-treatment was linearly related to infarct size. Similar results were observed when infarct size was dichotomized according to the median value (OR [95% CI] = 1.25 [1.13–1.37], $p<0.001$) (Fig. 2). These data were confirmed even in the analysis restricted to patients with postprocedural TIMI 3 flow (Figs. 1B and 2B) and after the exclusion of patients with previous MI (n = 34). Fig. 3 shows the impact of ischemia time as continuous function on infarct size ($R^2 = 0.0.14$, beta = 0.015, $p<0.001$). Identical results were found after the exclusion of patients with previous MI ($R^2 = 0.0.14$, beta = 0.015, $p<0.001$). Therefore, infarct size increased by 0.9% per each hour delay to treatment. Subanalyses conducted according to a threshold of ischemia time of 3 h did not show any heterogeneity in any of the analyzed subgroups according to age, sex, diabetes, preprocedural TIMI flow, anterior infarct location and multivessel disease (Fig. 4). By multiple regression analysis, time-to-treatment significantly affected infarct size even after correction for clinical (age and dyslipidemia) and procedural (postprocedural TIMI 3 flow) characteristics (OR [95% CI] = 1.26 [1.14–1.39], $p<0.001$).

4. Discussion

This is one of the largest study conducted so far evaluating the impact of time-to-treatment on scintigraphic infarct size in STEMI patients undergoing primary PCI. We found that time-to-treatment was linearly and independently associated with infarct size.

Primary angioplasty has been shown to provide mortality benefits as compared to thrombolysis. However, despite optimal epicardial recanalization, suboptimal reperfusion and therefore larger infarct size is observed in a relatively large proportion of patients, especially in those at high-risk undergoing mechanical reperfusion [25,26]. Despite the demonstrated prognostic role of time to therapy and its linear association with outcome in patients with STEMI treated by thrombolysis [14,15], there is still doubt with regard to its role in patients treated with primary angioplasty [16–21].

Brodie et al. [16] observed a better outcome among patients undergoing primary angioplasty within 2 h from symptom onset, whereas a relatively stable mortality rate was observed between 2 and 12 h. Consistent with these data, Zijlstra et al. [15], in a recent pooled-analysis of several randomized trials comparing primary angioplasty and thrombolysis, found a direct relationship between time from symptom onset to treatment only in patients treated by thrombolysis, but not by primary angioplasty. Consisting with these data, the Munich group has shown a significant impact of time-to-treatment on infarct size only with thrombolysis but not with primary angioplasty [27]. However, the same group has subsequently observed a significant impact of preprocedural TIMI 3 flow (surrogate marker of ischemic time) on scintigraphic infarct size [28]. In fact, a similar impact of preprocedural TIMI flow was observed also in other studies [29–31].

Conversely, several additional reports have shown the impact if ischemia time on mortality. Cannon et al. [18] in a cohort of 27,080 patients undergoing primary angioplasty found door-to-balloon time to be associated with mortality. These findings were confirmed by Antoniucci et al. [19] in high-risk patients. The Zwolle group analyzed the impact of time-to-treatment as a continuous function in a population of 1791 STEMI patients [20]. After correction for baseline confounding factors, they observed that every 30 min of delay to treatment was associated with 7.5% increase in the relative risk of 1-year mortality. In another analysis confined to patients undergoing transferring for primary angioplasty, De Luca et al. [32] found that interhospital delay was significantly associated with mortality.

In the DANAMI-2 trial, Maeng et al. [33] found that time-to-treatment significantly affected predischarge ejection fraction and 3-year mortality. Data from a recent updated meta-analysis of trials comparing primary angioplasty vs. thrombolysis [34], have shown similar impact of time-to-treatment for both reperfusion strategies. Several additional studies have been conducted to contribute to explain the prognostic role of ischemia time in primary angioplasty. De Luca et al. [35] showed in a population of 1072 STEMI patients that time-to-treatment had a significant impact on myocardial perfusion (as evaluated by myocardial blush and ST-segment resolution), enzymatic infarct size and predischarge ejection fraction. Interestingly, these results were confirmed in the analysis restricted to patients with postprocedural TIMI 3 flow. Thus, even though primary angioplasty is able to restore TIMI 3 flow independently from the time of treatment, this cannot abrogate the deleterious effects of ischemia time on myocardial necrosis and perfusion. More recently, data from the EMERALD trial [36] have shown a clear relationship between time-to-treatment, myocardial perfusion and infarct size analyzed by

Table 1
Baseline demographic and clinical characteristics according to time-to-treatment.

	Ischemia time (hours)						
Variable	<2 (n = 106)	2–3 (n = 228)	3–4 (n = 212)	4–5 (n = 126)	5–6 (n = 72)	>6 (n = 77)	p Value trend
Age (years)	62.4 ± 11.1	62.6 ± 11.2	63.5 ± 12.6	65.6 ± 11.7	65.8 ± 12.5	66.2 ± 13.1	<0.001
Female gender (%)	18.9	18.0	23.6	19.8	25	24.7	0.16
Smoking (%)	52.8	52.6	46.7	37.3	47.2	50.6	0.16
Diabetes (%)	10.4	13.2	14.2	20.6	9.7	13	0.51
Hypertension (%)	53.8	37.7	43.9	46.8	45.8	37.7	0.48
Dyslipidemia (%)	37.7	41.2	35.5	26.2	31.9	19.5	<0.001
Preinfarction angina (%)	7.3	7.1	7.9	2.9	8.8	15.8	0.65
Previous MI (%)	3.8	3.9	5.2	4.8	1.4	2.6	0.51
Previous CABG (%)	0	0.4	1.9	0.8	1.4	0	0.7
Previous PTCA (%)	3.8	5.3	2.8	2.4	0	3.9	0.19
Cardiogenic shock (%)	6.6	1.8	6.6	3.2	2.8	2.6	0.095

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Table 2
Angiographic and procedural characteristics according to time-to-treatment.

	Ischemia time (hours)						
Variable	<2 (n = 106)	2–3 (n = 228)	3–4 (n = 212)	4–5 (n = 126)	5–6 (n = 72)	>6 (n = 77)	p Value trend
Chronic occlusion (%)	3.6	4.3	7.7	5.8	2.9	0	0.795
Collateral circulation							0.22
RENTROP 0 (%)	96.4	88.9	88.7	87.0	85.7	90.0	
RENTROP 1 (%)	1.8	7.7	8.3	8.7	8.6	5.0	
RENTROP 2 (%)	1.8	2.6	2.3	4.3	5.7	0	
RENTROP 3 (%)	0	0.9	0.8	0	0	0	
Pre-procedural TIMI flow							0.31
TIMI 0–1 (%)	80.3	80.5	84.1	77.2	88.0	82.1	
TIMI 2 (%)	12.8	9.8	7.3	13.2	7.2	13.7	
TIMI 3 (%)	6.8	9.8	8.6	9.6	4.8	4.2	
Infarct-related artery							0.92
RCA (%)	41.0	45.2	46.8	47.1	48.2	44.8	
CX (%)	15.7	14.5	11.1	17.6	15.7	11.5	
Graft (%)	0	0	0.4	0	0	0	
LAD (%)	43.6	40.3	41.3	35.3	36.1	43.8	
LM (%)	0	0	0.7	0	0	0	
Multivessel disease (%)	40.0	37.9	43.0	44.1	42.0	41.7	0.428
N. lesions							0.27
1 (%)	76.9	79.8	77.9	72.8	80.7	69.8	
2 (%)	17.1	15	18.7	22.8	14.5	21.9	
3 (%)	5.1	4.0	3.0	3.7	3.6	7.3	
Abciximab (%)	98.3	91.1	87.2	86.8	85.5	94.8	0.13
Stenting (%)	98.2	99.1	99.2	98.5	97.1	100	0.95
Thrombectomy (%)	39.6	43.8	40.5	39.7	47.2	46.7	0.6
IABP (%)	4.3	2.8	5.5	1.5	4.8	7.3	0.21
Post-procedural TIMI 3 flow (%)	95.7	93.9	95.7	86.7	85.5	80.0	<0.001

scintigraphy. Similar finding has been observed in a pooled analysis of 4 trials performed by Stone et al. [37], even though the impact was mostly observed within the first hours. A recent study conducted by Tarantini et al. [38] has evaluated the impact of time-to-treatment on infarct size, estimated by MRI. Supporting data by De Luca et al. [20], they observed a significant increase in infarct size by every 30 min delay to treatment.

In our study, including 830 STEMI patients undergoing primary angioplasty, we found that infarct size, accurately assessed by myocardial perfusion scintigraphy, was linearly related to time-to-treatment. The relationship was observed even when restricted to patients with postprocedural TIMI 3 flow. In fact, the impact of time-to-treatment

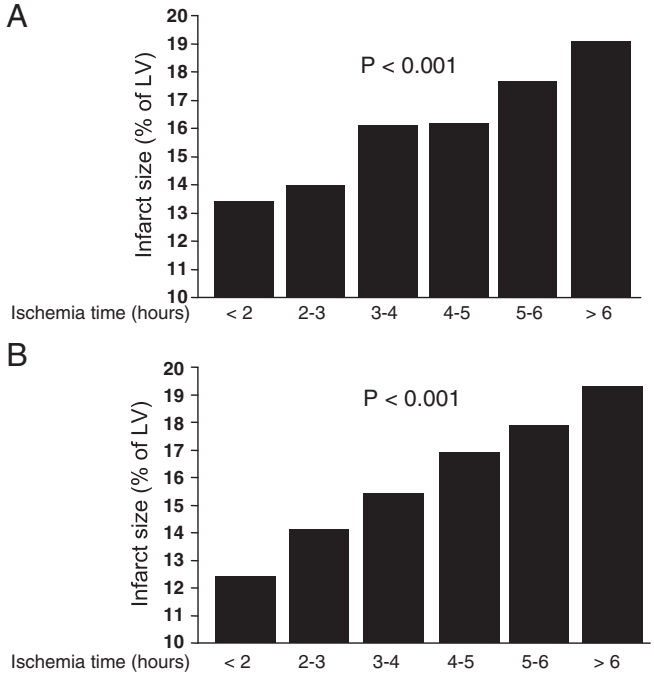

Fig. 1. Bar graph shows the significant relationship between ischemia time and scintigraphic infarct size in all population (A), that was confirmed in the analysis restricted to patients with postprocedural TIMI 3 flow (B).

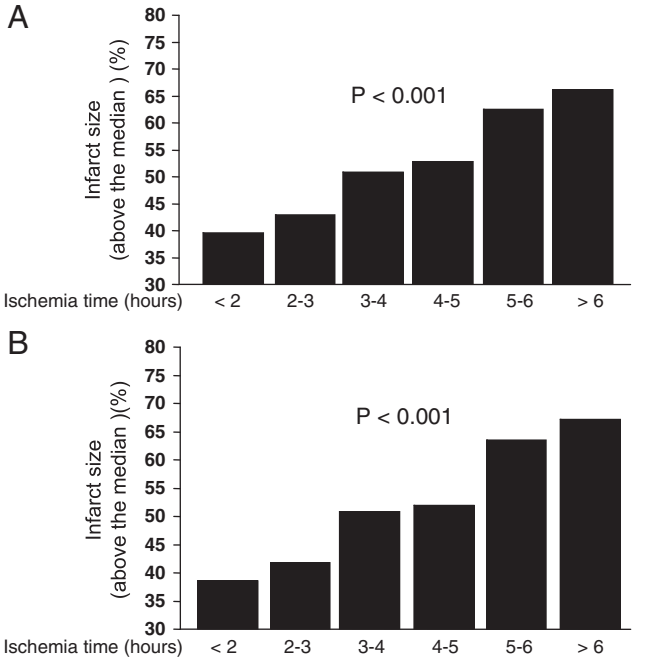

Fig. 2. Bar graph shows the significant relationship between ischemia time and scintigraphic infarct size (as above the median) in all population (A), that was confirmed in the analysis restricted to patients with postprocedural TIMI 3 flow (B).

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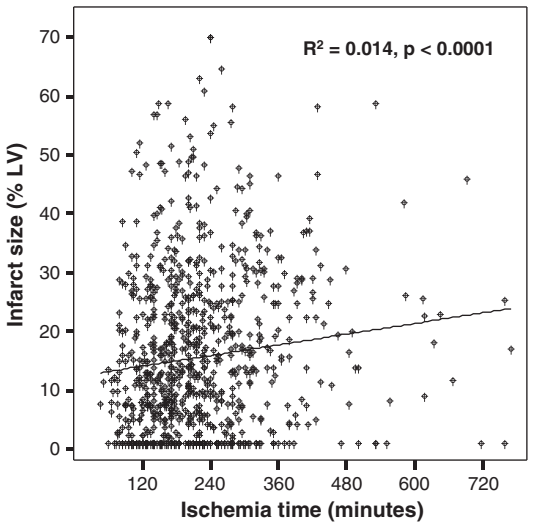

Fig. 3. Impact of ischemia time (in minutes on X-axis) on infarct size (as % of left ventricle (LV) on Y-axis). R^2-values and *P*-values refer to the linear correlations.

on infarct size persisted after correction for confounding factors, such as age, dyslipidemia and postprocedural TIMI 3 flow.

All these data support the need to shorten ischemia time by early diagnosis and direct transportation to the cath lab. The experience in Zwolle showed that interhospital delay was an independent predictor of mortality [32]. Similarly, the Danish experience strongly demonstrated the importance and clinical impact on long-term mortality [39] and occurrence of heart failure [40] of health care organization and system delays. Several trials and meta-analysis have evaluated the role of pharmacological facilitation. Studies on facilitation with lythic therapy showed a significant increase in the risk of major bleeding complications and reinfarction [41,42], and therefore this strategy has been abandoned, whereas great attention has been paid to Gp IIb–IIIa inhibitors. A previous meta-analysis based on individual patients' data [10] showed that early abciximab, but not Eptifibatide and Tirofiban, was associated with significant benefits in mortality. These beneficial effects have been confirmed at long-term follow-up [43]. However, more recently high-dose bolus of tirofiban and double bolus of eptifibatide have been shown to provide more complete and faster inhibition of platelet aggregation and therefore larger benefits would be expected from these new dosages. The on-time-2 trial [44] investigated the benefits from early high-dose tirofiban administration in the ambulance as compared to placebo, with significant benefits in preprocedural recanalization and ST-resolution. When the data were pooled with the pilot phase, there was a significant reduction in mortality. These beneficial effects have been confirmed in large registries [45]. Therefore despite the negative results of the largest randomized trials (FINESSE) [46], based on the demonstrated prognostic role of ischemia time, and the current evidence from randomized and registry data, early administration of Gp IIb–IIIa inhibitors may be considered, especially among high-risk patients.

5. Study limitations

We assessed the infarct size 1 month after the index infarction instead of at hospital discharge, as in the majority of previously published studies. On the other hand, this circumstance should be more effective in preventing interference of myocardial stunning with the extent of perfusion defects [47]. We did not performed routinely in all patients with coronary angiographic control before gated SPECT to allow the exclusion of infarct-related vessel restenosis. A potential bias of later presentation of patients with bigger infarcts seems unlikely, since there was no significant difference between study groups regarding the incidence of cardiogenic shock, anterior infarct location, resuscitation/intubation, and left bundle branch block at presentation. Only a minority of patients were treated with thrombectomy, with similar rates across time intervals. However, confirming the results of the JETSTENT trial [48], the use of thrombectomy did not affect infarct size ($11.9 \pm 10\%$ vs. $13.1 \pm 11\%$, $p = 0.25$). Finally, our data must be interpreted with the concept that ischemia time is just a piece of the puzzle. In fact, final infarct size is certainly influenced by aging, preprocedural TIMI flow, IRA location, and periprocedural factors such as ischemia reperfusion damage, distal atherothrombotic embolization, and no-reflow. Therefore, despite the relatively low *R* square value, we strongly believe that the 0.9% increase in infarct size per each hour of ischemia time (as estimated by our coefficients)

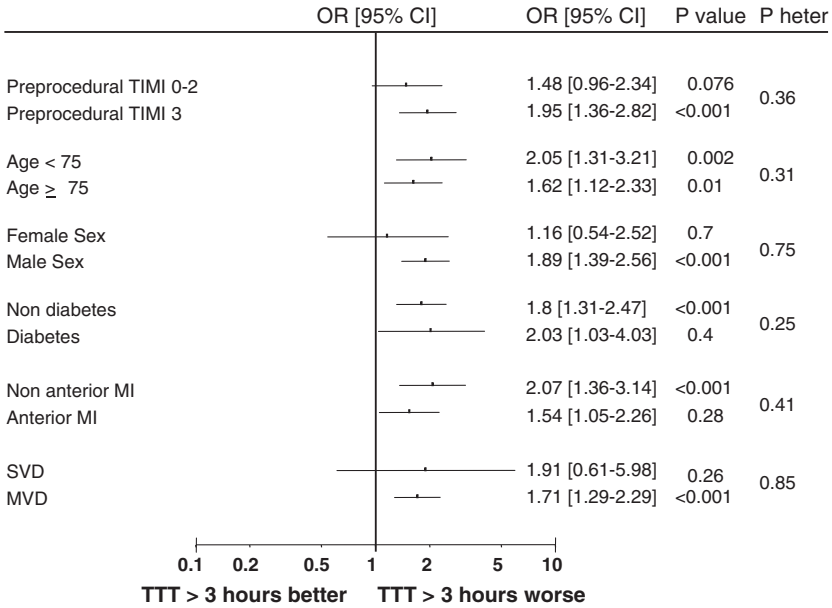

Fig. 4. Impact of ischemia time (≥ or <3 h) on infarct size (as % above the median) in subgroups of patients.OR = odds ratio; MI = myocardial infarction, SVD = single-vessel disease; MVD = multivessel disease.

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is not only statistically ($p<0.0001$) but, in consideration of the above mentioned aspects and the fact that it is a modifiable variable, also clinically significant. In fact, the impact of ischemia time on infarct size is the explanation of the demonstrated effect of ischemia time on survival.

6. Conclusions

This study showed that among STEMI patients undergoing primary angioplasty, time-to-treatment is linearly and independently associated with scintigraphic infarct size. Therefore, all the attempts should be made in order to reduce ischemia time by making aware patients of heart attack symptoms and of prompt emergency system activation, direct transportation to the cath lab and potentially early pharmacological reperfusion.

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Please cite this article as: De Luca G, et al, Time-to-treatment and infarct size in STEMI patients undergoing primary angioplasty, Int J Cardiol (2012), doi:10.1016/j.ijcard.2012.04.078

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