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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

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Aims This study sought to evaluate the impact of an inter-hospital transfer strategy on treatment times and in-hospital and 1 year cardiac mortality of patients with ST-segment elevation acute myocardial infarction (STEMI) undergoing primary percutaneous intervention (p-PCI) in the Italian region of Emilia-Romagna, where an efficient region-wide system for reperfusion has been established.

Methods and results 3296 patients with STEMI, undergoing on-site p-PCI (2444 patients) (OS group) or p-PCI after inter-hospital transfer (852 patients) (T group) between 1 January 2004 and 30 June 2006 in the Italian region of Emilia-Romagna, were considered. During the study period, the number of patients undergoing p-PCI increased both for patients admitted to interventional centres and for those admitted to peripheral hospitals. At the same time, the proportion of patients with STEMI initially admitted to peripheral hospitals and not transferred and the door-to-balloon time delays of transfer patients decreased. In spite of longer door-to-balloon delay in the transfer group [112 min (86–147) vs. 71 min (46–104)], in-hospital cardiac mortality (OS 7.0 vs. T 5.4%, $P = 0.10$) did not significantly differ between the two groups. After multivariable adjustment, the transfer strategy was not associated with increased risk of in-hospital [odds ratio 0.956; 95% confidence interval (CI) 0.633–1.442] and 1 year (hazard ratio 0.817; 95% CI 0.617–1.085) cardiac mortality.

Conclusion This study, concerning an established STEMI regional network, suggests that a strategy of inter-hospital transfer for p-PCI, when supported by an organized system of care, may be applied with rapid reperfusion times and favourable short- and long-term clinical outcomes.

Keywords Myocardial infarction • Angioplasty • Registry • Network organization

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Introduction

Several fibrinolytic and angioplasty studies have demonstrated that reperfusion delay is an important and independent predictor of survival[1–4] in patients with ST-segment elevation acute myocardial infarction (STEMI). In patients with STEMI, primary percutaneous intervention (p-PCI) is considered the best therapeutic option for reperfusion, when it can be performed in a timely fashion and by an expert team.[5] However, the low number and the non-homogeneous distribution of interventional facilities across the country represent the major limitations for the widespread use of p-PCI in the real world, particularly in patients initially admitted to non-interventional hospitals.[6] In order to offer p-PCI to these patients, a policy of immediate inter-hospital transfer to the hub centres has been advocated.[7–9] Randomized trials comparing on-site fibrinolysis with transfer for p-PCI have shown a better outcome for transferred patients.[10] However, although a very short transfer delay was maintained in these trials, such delay increases significantly in the real world.[11] This can modify the final results because when time to treatment is far from the optimal most of the advantages of p-PCI over thrombolysis could be lost. Therefore, the aim of this study was to evaluate the impact of an inter-hospital transfer strategy on in-hospital and 1 year cardiac mortality of patients with STEMI undergoing p-PCI in the Italian region of Emilia-Romagna, where an efficient region-wide system for reperfusion, as already exists for trauma care, has been established.

Methods

Study population and setting

Patients with STEMI who were treated with p-PCI in our region were eligible for this study. The Italian region of Emilia-Romagna is an industrial, mainly urban area located in the central-northern Italy with almost 4.1 million inhabitants. At present, 28 intensive cardiac care units serve this area but only nine of them, located in the main towns, provide a round-the-clock service for p-PCI. All of them are considered high procedural volume centres ($\geq$650 PCI/year), and since 2004, at least 80 p-PCI per year (range 80–310 p-PCI) have been performed in every hub centre in our region by high-volume senior interventionalists (>180 PCI/year). After the publication of the ACC/AHA guidelines,[5] a quality-improvement project on p-PCI for STEMI (the PRIMA-RER project) was set up by the Health Care Agency of Emilia-Romagna region.[12] According to this project, all patients directly admitted to hospitals with interventional facilities have been offered p-PCI as the preferred reperfusion strategy since 1 January 2004. On the other hand, patients initially admitted to peripheral non-interventional hospitals are treated with thrombolysis or rapidly transferred for p-PCI according to their risk profile and the expected time delay for p-PCI. In particular, the PRIMA-RER project recommends the transfer of all patients with STEMI to a hub centre for mechanical reperfusion unless the expected extra-delay due to p-PCI organization could be longer than 120 min. The transfer is particularly recommended for patients with thrombolysis contraindication, shock, pain-to-admission delay >3 h, ST elevation $\geq$6 EKG leads, or age >75 years. Although the most appropriate system organization could vary from hospital to hospital, an overall set of statements was provided according to the national recommendations on STEMI networks.[13] These recommendations focused on each component of the reperfusion process: the emergency medical system, the emergency department, the catheterization laboratory, and inter-hospital transfer. In particular, several requirements were accomplished: immediate activation of the catheterization laboratory team through a single phone call, immediate activation of transport services provided by ambulance or helicopters equipped with trained nurses and medical staff, acceptance of patients with STEMI at hub centres regardless of bed availability, administration of adjunctive treatment as defined by national recommendations,[13] and fast track to the catheterization laboratory when indicated. Focusing on the transfer policy, in all cases of suspected STEMI, an electrocardiographic evaluation has to be done in <10 min at the emergency department. Afterwards, emergency medicine physicians make the treatment decision according to local protocols and the clinical situation, even without the involvement of a cardiologist, if he is not immediately available. In addition, either the emergency department physician or the cardiologist calls the ambulance dispatcher to arrange immediate transfer and notify the catheterization laboratory of the hub centre of the impending arrival of a patient with STEMI. As shown in *Table 1*, this organization system has been progressively implemented across the region since 2004. The distance between different spoke centres and the nine catheterization laboratories ranged from 12 to 58 km. This referral strategy received prior approval from various hospital Ethics Committees and the study protocol was in accordance with the Declaration of Helsinki.

Study design and eligibility criteria

In the Emilia Romagna region, all data regarding interventional coronary procedures are recorded in a regional web-based database, the REAL registry.[14] In brief, this registry represents an on-going, prospective, observational quality programme study and contains comprehensive clinical and procedural data of all consecutive patients undergoing either elective or emergency coronary angioplasty in Emilia-Romagna. Because the REAL registry was designed to observe and improve current clinical practice, the Ethics Committees of each participating hospital required only ordinary written informed consent for interventional procedure (according to national regulations) and anonymous publication of scientific data was allowed. In addition, protected health information was removed before data collection, and patient data were anonymously stored in a dedicated database located at the regional Health Care Agency of Emilia-Romagna. Clinical data were analysed in accordance with and under the supervision of the regional heath care administrators. From 1 January 2004 to 30 June 2006, 22 871 patients underwent elective or emergency PCI in the Emilia-Romagna region and were recorded in the REAL registry. In the present study, we analysed data from 4069 patients with STEMI (<12 h from symptom onset), who were treated with p-PCI either at the admitting hospital (OS group) or after an inter-hospital transfer (T group), and who were residents in the Emilia-Romagna region. From this population, 170 (4.2%) patients were excluded because they underwent rescue PCI or planned PCI immediately after thrombolysis and 563 (13.8%) patients owing to missing or incomplete data (6.6% in the T group and 7.2% in the OS group, respectively). Our study population therefore consisted of 3296 patients, 2444 patients admitted to hospitals with interventional facilities and 852 patients transferred for p-PCI (*Figure 1*). Mean follow-up was 537 days (median 509 days, range 125–1034 days) and 100% complete.

ST-segment elevation acute myocardial infarction diagnosis and primary percutaneous intervention protocol

STEMI was defined as an ST-segment elevation in at least two adjacent leads $\geq$0.1 mV in leads IIII, aVF, aVL, V4–V6, and $\geq$0.2 mV in leads V1–V3 as recorded in the first ECG obtained on admission.[15] p-PCI was performed according to local standards and stenting was strongly encouraged. No restriction policy based on age, sex, clinical status, or

Table 1 Progressive ST-segment elevation acute myocardial infarction network implementation during the study period

Variables	2004 (year)	2005 (year)	2006 (first semester)
Emilia-Romagna region p-PCI			
On-site p-PCI, *n*	879	985	580
Transfer p-PCI, *n*	281	359	212
Non-transferred STEMI patients admitted to non-PCI centres, %	26.0	19.5	15.5
Age (years), mean ± SD	77 ± 13	78 ± 13	81 ± 12
Charlson index, mean ± SD	1.4 ± 1.7	1.6 ± 1.7	1.7 ± 1.8
Mortality, %	25.5	32.2	31.2
Network door-to-balloon time			
On-site p-PCI, min (median 25th–75th)	73 (50–102)	69 (43–100)	74 (47–115)
Transfer p-PCI, min (median 25th–75th)	114 (90–146)	111 (90–150)	107 (81–140)
IIb/IIIa inhibitor use			
On-site p-PCI, %	89.8	89.6	90.7
Transfer p-PCI, %	90.8	91.1	92.5
In-hospital overall mortality			
On-site p-PCI, %	7.9	7.4	5.8
Transfer p-PCI, %	6.7	6.4	3.8

Data are presented as numbers or percentages for categorical variables, and as mean ± SD or medians (25th–75th percentiles) for continuous variables.

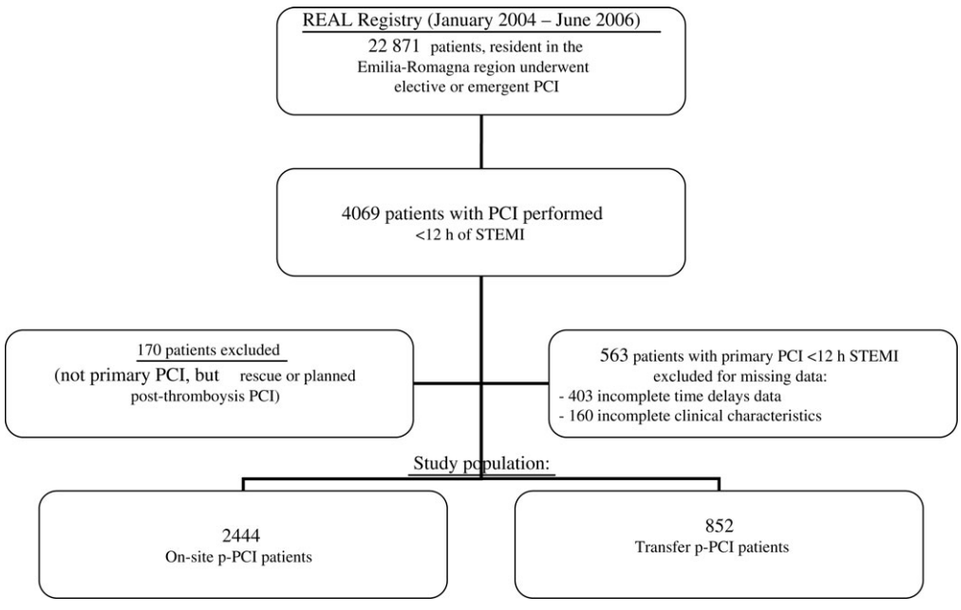

Figure 1 Patient flow diagram of the study.

co-morbidities was applied to any p-PCI protocols at local hospitals. Before p-PCI, all patients received aspirin and intravenous heparin according to standard protocols at different hospitals. The use of glycoprotein (GP) IIb/IIIa inhibitors was strongly encouraged for all eligible patients triaged to p-PCI as soon as possible after the diagnosis of STEMI and was mandatory, unless contraindicated, in several local reperfusion protocols. If a stent was deployed, patients were given a loading dose of 300 mg clopidogrel as soon as possible, followed by a maintenance dose of 75 mg for at least 1 month (6–12 months for drug-eluting stents).

Definitions and follow-up data collection

TIMI flow rate of the infarct-related artery (IRA) was assessed visually by the operator and classified according to the Thrombolysis In Myocardial Infarction (TIMI) grading system. The TIMI flow scale of 0–3[16] was evaluated locally according to standard definitions. Cardiogenic shock was defined as persistent systolic blood pressure $<$90 mmHg, unresponsive to i.v. fluid administration (or the need for vasopressor agents to maintain systolic pressure $\geq$90 mmHg), secondary to left or right ventricular dysfunction.[12]

In all patients undergoing p-PCI, the following time intervals were carefully collected: time of symptom onset, time of arrival at the first hospital, time of ambulance departure from the peripheral hospital, time of arrival at the hub centre, time of the first balloon inflation during p-PCI. To calculate the door-to-balloon delay of transferred patients, time of arrival at the first hospital was considered as the starting time. Main co-morbidities were recorded and a comprehensive risk profile was defined for every single patient according to the Charlson index.[17] Follow-up data were obtained directly and independently from the Emilia-Romagna Regional Health Agency through the analysis of hospital discharge records and municipal civil registries. Specific queries were sent to every single institution to justify/correct discrepancies between administrative data and data derived from the web-based database.

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD and categorical data as percentages. For group comparisons, two-tailed Student's unpaired *t*-test was used for continuous variables, and χ^2 test was used for categorical variables. According to the ACC/AHA Task Force on Performance Measures, indications and median values for time delays (25th–75th) were considered,[18] and the non-parametric Wilcoxon rank-sum test was adopted for time-delay group comparisons (on-site vs. transfer p-PCI). Differences in all-cause and cardiac mortality rates between on-site p-PCI and transfer p-PCI patients during the follow-up period were assessed by the Kaplan–Meier method. The obtained curves were compared using the log-rank test. Multivariable logistic regression analysis was conducted to evaluate the adjusted effect estimates associated with the transfer p-PCI. For this analysis, a multivariable logistic regression model was fit, for which in-hospital cardiac mortality was the dependent variable of interest. The following 15 variables (potential confounders) were included in the multivariable model: age, sex, Charlson index, left main disease, multivessel coronary disease, diabetes, prior PCI, prior coronary artery bypass, prior myocardial infarction, left ventricular ejection fraction $\leq$35%, cardiogenic shock, anterior infarction site, GP IIb/IIIa inhibitor administration, basal TIMI flow 0/1, final TIMI flow 3 (heart rate and systolic pressure were excluded from the model owing to co-linearity with cardiogenic shock). To assess linearity, we categorized continuous variables as intervals and performed the score test for trend of odds on the proportions of death at each interval. The predictive accuracy of the model correlated well with the observed events (*c*-statistics 0.92, Hosmer–Lemeshow goodness-of-fit $P = 0.61$). A multivariable Cox regression analysis was conducted to evaluate the adjusted effect estimates on 1 year cardiac mortality associated with transfer p-PCI. To adjust for potential confounders, the aforementioned 15 variables were included in the model. The proportional hazards assumption was tested on the basis of Schoenfeld residuals. The relationship between door-to-balloon time and in-hospital cardiac mortality was assessed as a continuous function with a univariate logistic regression analysis [in-hospital cardiac mortality was the dependent variable, and door-to-balloon time (minutes) the only independent covariate; odds ratio (OR) 1.003, 95%CI 1.001–1.005, $P = 0.01$]. All statistical tests were two-sided ($P < 0.05$ was considered to be significant). All analyses were performed with the SAS 9.1 system (SAS Institute, Cary, MI, USA). The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Tables 2 and *3* report the baseline demographic, clinical, and procedural characteristics of different groups. Few clinical differences were observed between the two groups. Transferred patients had a significantly higher proportion of anterior myocardial infarction, and the percentage of patients with cardiogenic shock tended to be higher in the non-transferred subjects. OS p-PCI patients had a significantly higher proportion of pre-PCI TIMI 0/1 flow and lower rate of direct stenting. Angiographic success was similar in both groups. Pre-hospital delays did not differ between T and OS patients. On the other hand, as expected, patients undergoing inter-hospital transfer for p-PCI had longer door-to-balloon and pain-to-balloon delays. However, owing to the anticipated mobilization of the catheterization laboratory team, if we consider the door-to-balloon delay at the PCI centres, T patients showed a significantly shorter delay with respect to OS patients [36 min (25–55) vs. 71 min (46–104), $P < 0.0001$]. Interestingly, the median door-to-balloon delay of transferred patients was only 38 min longer than that of non-transferred ones, and 56.7% of T patients and 81% of OS patients had the balloon inflated within 2 h of the first medical contact. Accordingly, the difference between the median of pain-to-balloon delay in the two groups was limited (40 min). As given in *Figure 2*, when analysed as a continuous variable, door-to-balloon delay in the overall population was inversely correlated with in-hospital cardiac mortality (OR 1.003, 95% CI 1.001–1.005, $P = 0.01$). As given in *Table 4*, the unadjusted rates of in-hospital overall and cardiac mortality did not significantly differ between the two groups. At logistic regression analysis (*Table 5*), the transfer strategy had no relevant negative impact on in-hospital cardiac mortality [OR 0.956, 95% confidence interval (CI) 0.633–1.442, $P = 0.82$], whereas increasing age (OR 1.067, 95% CI 1.050–1.085, $P < 0.0001$), shock (OR 8.886, 95% CI 6.051–13.050, $P < 0.0001$), low left ventricular ejection fraction (OR 5.034, 95% CI 3.295–7.691, $P < 0.0001$), basal TIMI 0–1 (OR 2.229, 95% CI 1.400–3.550, $P = 0.0007$), Charlson index (OR 1.416, 95% CI 1.248–1.607, $P < 0.0001$), and multivessel disease (OR 1.869, 95% CI 1.025–3.406, $P = 0.04$) did. Finally, the use of GP IIb/IIIa inhibitors (OR 0.553, 95% CI 0.352–0.869, $P = 0.01$), final TIMI 3 flow (OR 0.327, 95% CI 0.214–0.500, $P < 0.001$), and male gender (OR 0.584, 95% CI 0.407–0.840, $P = 0.004$) were associated with a better outcome; (*C*-statistic 0.92; Hosmer–Lemshow goodness-of-fit, $P = 0.61$). As given in *Table 4*, the unadjusted cardiac mortality rate at 1 year follow-up was 10.2% for on-site p-PCI patients and 7.4% for transferred subjects ($P = 0.02$). However, after multivariable adjustment (*Table 6* and *Figure 3*), long-term cardiac mortality did not significantly differ between the two groups [hazard ratio (HR) 0.817, 95% CI 0.617–1.085, $P = 0.16$]. Interestingly, the

Table 2 Baseline demographic and clinical characteristics of the study population

Characteristic	On-site p-PCI (n = 2444)	Transferred p-PCI (n = 852)	P-value
Age, years	66.9 ± 13.2	66.0 ± 13.2	0.103
Male gender, %	70.8	73.4	0.159
Diabetes mellitus, %	19.1	20.9	0.417
Hypercholesterolaemia, %	49.3	53.1	0.060
Hypertension, %	59.8	62.4	0.183
Smokers, %	33.2	33.2	0.997
Prior myocardial infarction, %	13.3	12.0	0.326
Prior coronary angioplasty, %	9.5	8.2	0.283
Prior coronary bypass surgery, %	2.6	2.8	0.734
Anterior infarction, %	48.1	53.7	0.006
Charlson index	1.5 ± 1.0	1.5 ± 1.0	0.926
Systolic blood pressure, mmHg	124.6 ± 28.8	126.9 ± 27.2	0.100
Heart rate, b.p.m.	77.0 ± 18.2	76.8 ± 17.5	0.834
Shock, %	9.5	7.5	0.087
Poor LVEF (≤0.35), %	15.0	13.2	0.233
Multivessel disease, %	53.3	55.3	0.350
Time delays			
Pain-admission, min (median 25th–75th)	95 (60–168)	100 (60–170)	0.409
Door-to-balloon, min (median 25th–75th)	71 (46–104)	112 (86–147)	<0.0001
Pain-to-balloon, min (median 25th–75th)	178 (125–272)	218 (171–312)	<0.0001

Data are presented as percentages for categorical variables, and as means ± SD or medians (25th–75th percentiles) for continuous variables. LVEF, left ventricular ejection fraction.

Table 3 Angiographic and procedural characteristics of the study population

Characteristic	On-site p-PCI (n = 2444)	Transferred p-PCI (n = 852)	P-value
Left main, %	0.9	0.6	0.439
Left anterior descending, %	47.1	53.3	0.001
Right coronary artery, %	36.8	32.4	0.021
Left circumflex, %	14.2	12.4	0.199
Lesion length, mm	19.5 ± 9.2	20.0 ± 8.6	0.174
Reference diameter[a], mm	3.0 ± 0.5	3.1 ± 0.5	0.043
Multivessel p-PCI, %	8.2	7.0	0.261
Basal TIMI Flow 0/1[a], %	73.2	64.9	0.001
Final TIMI Flow 3[a], %	91.5	91.7	0.810
Stent implantation, %	91.5	91.7	0.810
Direct stenting, %	21.2	26.2	0.002
Pharmacological treatment			
Gp IIb/IIIa inhibitors, %	89.9	91.3	0.415

Data are presented as percentages for categorical variables, and as means ± SD or medians (25th–75th percentiles) for continuous variables.
[a]Visual estimation.

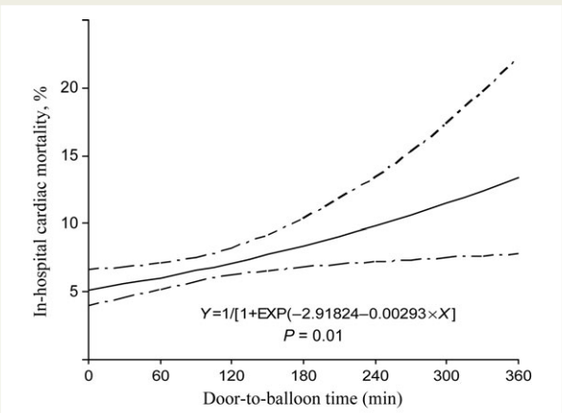

Figure 2 Relationship between door-to-balloon time and in-hospital cardiac mortality, as a continuous function, assessed with a univariate logistic regression model. Dotted lines represent 95% confidence intervals of predicted in-hospital cardiac mortality.

number of patients undergoing p-PCI during the study period increased both at interventional centres and at peripheral hospitals (*Table 1*). On the other hand, the proportion of patients with STEMI initially admitted to peripheral hospitals and not transferred decreased. Notably, the risk profile of these non-transferred patients who were treated at the peripheral hospital increased to such a level that we would expect that most of them would not be eligible for reperfusion. It is worth noting that during the

Table 4 Unadjusted cumulative frequencies of all-cause and cardiac mortality according to the treatment group

	On-site p-PCI (n = 2444), % (95% CI)	Transfer p-PCI (n = 852), % (95% CI)	*P*-value
In-hospital			
All-cause mortality	7.2 (6.2–8.3)	5.9 (4.3–7.5)	0.17
Cardiac mortality	7.0 (6.0–8.0)	5.4 (3.9–6.9)	0.10
One-year			
All-cause mortality	12.5 (11.2–13.9)	9.0 (7.2–11.1)	0.01
Cardiac mortality	10.2 (9.1–11.5)	7.4 (5.8–9.4)	0.02

Values are presented as percentages and 95% CI.

Table 5 Logistic multivariable regression analysis of in-hospital cardiac mortality in the overall study population

Variables	OR	95% CI	*P*-value
Age, year	1.067	1.050–1.085	<0.0001
Male gender	0.584	0.407–0.840	0.004
Charlson index (each incremental unit)	1.416	1.248–1.607	<0.0001
Multivessel disease	1.869	1.025–3.406	0.04
Cardiogenic shock	8.886	6.051–13.050	<0.0001
Left ventricular ejection fraction ≤35%	5.034	3.295–7961	<0.0001
GP IIb/IIIa inhibitor administration	0.553	0.352–0.869	0.01
Pre-p-PCI TIMI flow 0–1	2.229	1.400–3.550	0.0007
Post p-PCI TIMI flow 3	0.327	0.214–0.500	<0.0001
Transfer p-PCI	0.956	0.633–1.442	0.82

Only variables reaching $P < 0.05$ at multivariable analysis and transfer p-PCI are listed in the table.

study period, median door-to-balloon delays of patients transferred to the hub for p-PCI decreased from 114 to 107 min. These favourable effects of the regional network translated into a tendency towards a lower in-hospital mortality in both groups.

Discussion

The results of the REAL registry confirm that when an efficient system for reperfusion is established, inter-hospital transfer for p-PCI can be achieved even in the real-world with very short additional time delays (limited to 38 min, on average) and favourable in-hospital and 1 year outcomes compared with on-site p-PCI.

Table 6 Cox multivariable regression analysis of 1 year cardiac mortality in the overall study population

Variables	HR	95% CI	*P*-value
Age, year	1.063	1.051–1.076	<0.0001
Charlson index (each incremental unit)	1.272	1.176–1.375	<0.0001
Cardiogenic shock	3.973	3.023–5.220	<0.0001
Left ventricular ejection fraction ≤35%	3.179	2.368–4.269	<0.0001
GP IIb/IIIa inhibitor administration	0.589	0.444–0.781	0.0002
Pre-p-PCI TIMI flow 0–1	1.397	1.035–1.884	0.03
Post-p-PCI TIMI flow 3	0.425	0.325–0.556	<0.0001
Transfer p-PCI	0.817	0.617–1.085	0.16

Only variables reaching $P < 0.05$ at multivariable analysis and transfer p-PCI are listed in the table.

A strategy of inter-hospital transfer for p-PCI necessarily increases time to treatment, and delays in reperfusion are common for transferred patients.[11] Of note, fast transportation of patients with STEMI to the most appropriate facility is hampered by several logistic factors, such as transfer distances, lack of standardized guideline-based protocols, or of an efficient organized inter-hospital network. Furthermore, this transfer strategy may hamper the caseload or the reimbursements of the community hospitals; these could negatively affect them when most of their STEMI patients are transferred to the hub for p-PCI. Although the concept that time is muscle is still valuable and current guidelines for STEMI strongly recommend a door-to-balloon time within 90 min,[5] a recent meta-analysis of several randomized trials has extended the superiority of p-PCI over thrombolysis to a broader time interval. Notably, benefits are observed even when the PCI-related delays are up to 120 min[19,20] and data from high-volume institutions with remarkable experience in p-PCI and effective inter-hospital transfer systems demonstrate that the additional delay due to the transfer itself could be modest and its negative prognostic effects minimal.[21,22] Applying a systematic implementation of a pre-defined strategy, as described by Bradley *et al.*,[23] a significant reduction in door-to-balloon time has been demonstrated for patients admitted to non-interventional hospitals. In recent experiences[24,25] in which a regional system of care targeted to quality improvements and timeless optimization of reperfusion for STEMI was implemented, a similar reduction in door-to-balloon delays has been reported. Unfortunately, such results could be different when we deal with a less efficient transport system or with unselected populations, different institutions, and logistical organizations. In a single-centre observational study,[26] the median door-to-balloon time was 179 min in 871 patients transferred from non-interventional hospitals, and in the NRMI 3–4 registry,[11] the median door-to-balloon delay was 180 min, and only 4.2% of patients had a door-to-balloon delay ≤90 min. Based on the Emilia-Romagna regional organization, where hospital networks for reperfusion according to a hub-and-spoke model have been

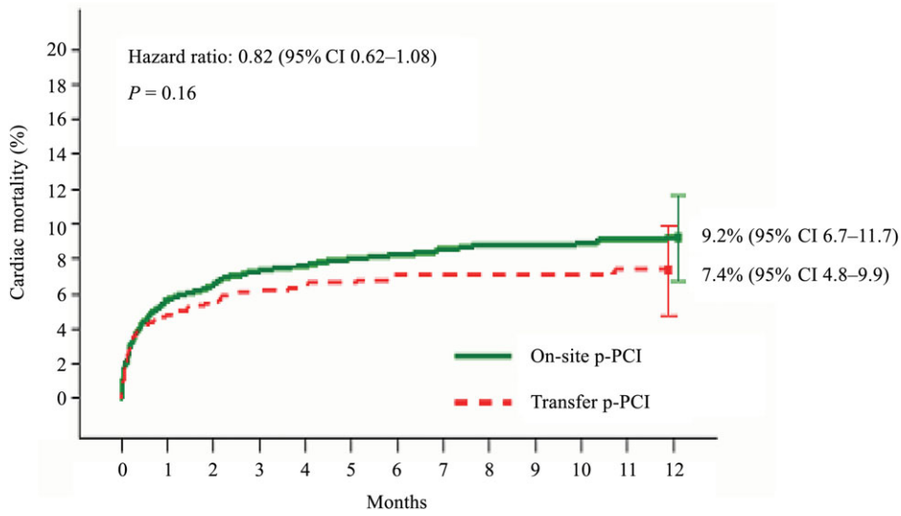

Figure 3 One-year adjusted cardiac mortality in patients treated with primary percutaneous intervention performed on-site or after inter-hospital transfer.

established for several years, a quite short median door-to-balloon delay was achieved. Notably, the median door-to-balloon time in our registry was 112 min for transferred patients. These values are lower than those observed in NRMI 3–4 and close to those reported by a meta-analysis of randomized trials on immediate transfer for p-PCI[10] and also to those reported by two recent experiences from the Minnesota area,[24,25] emphasizing the concept that organization is a key point in achieving acceptable door-to-balloon times. Notably, even in the recent quality-improvement RACE study, the post-intervention door-to-balloon delay was 128 min for transferred patients.[27] The median door-to-balloon delay in our non-transferred patients was rather long (71 min). This value, although far from optimal, is consistent with previous Italian experiences in which a median door-to-balloon delay of 83 min was reported.[28] Furthermore, analysing individual patient data from 22 randomized trials comparing p-PCI and in-hospital fibrinolysis, Boersma *et al.*[20] reported a median door-to-balloon delay of 76 min for patients treated with p-PCI. In addition, contemporary experiences form North American networks report a door-to-balloon delay ranging from 68 to 90 min for non-transferred patients treated with p-PCI.[24,25,27]

The limited difference in door-to-balloon delay between T and OS p-PCI patients that we observed seems mainly due to the short time delays of transferred patients. Probably, short inter-hospital distances, excellent road communications, and the absence of densely populated areas could have reduced these transport times. However, an established regional coordination of this reperfusion system could be the most important issue since it favours an efficient transfer strategy and an optimal utilization of different local networks. This concept has been recently emphasized by the results of the RACE study,[27] where the implementation of optimal processes to improve reperfusion either at peripheral hospitals or at interventional centres has been clearly shown to increase the quality of treatment of STEMI patients. Similar results have been achieved in our network since most of the quality-improvement processes applied in the RACE study have been capitalized. In particular, during the study period, we observed a consistent reduction in the proportion of patients admitted to peripheral hospitals who were not transferred for reperfusion and a progressive reduction in door-to-balloon delay of transferred patients. Despite the encouraging results that we have reported, it is noteworthy to underline that, even in the real world,[12,29] further decrease in reperfusion delays can be reached by systematically implementing the pre-hospital triage. However, we have to keep in mind that this strategy represents a possible option only for patients who call the emergency system at first, whereas for self-presenting patients, an inter-hospital transfer strategy has to be considered.

Study limitations

Our analysis has several limitations and should be interpreted accordingly. First, as an observational matched cohort analysis, we adjusted for observed clinical and angiographic differences between patient cohorts. However, unaccounted differences may have remained and influenced our findings. Secondly, the selection process used may be taken into account. Since we used the catheterization laboratory registry as a starting point, our registry selected only patients who were transferred and reached the catheterization laboratory alive. Therefore, it may not represent all patients eligible for transfer or reperfusion. However, since the network recommendations for thrombolysis were rather selective even at peripheral hospitals, and since transfer for rescue or intended PCI after thrombolysis was encouraged and the clinical profile of non-transferred subjects was rather unfavourable, we expect that a few patients underwent thrombolysis at peripheral hospitals without being transferred to the hub afterwards. In addition, the percentage of non-transferred subjects was reduced from 26 to 15.5% during the study period and their mean age and co-morbidity risk profile

increased substantially; we thus expect that most patients eligible for reperfusion were actually transferred to the hub centres. This hypothesis could be supported by a similar post-intervention proportion (15%) of non-reperfused patients observed in the RACE study. In-hospital mortality of non-transferred patients at peripheral hospital is rather impressive, but their risk profile was equally high. Thus, in-hospital mortality could be expected to be in the range of 30%, as we observed. In addition, since only patients who received p-PCI and who did not die before the procedure were considered in our analysis, we cannot exclude that the low in-hospital mortality of transferred patients could be explained by this selection bias. In fact, in clinical practice, it is reasonable to assume that even the most severe patients admitted to interventional centres are submitted to p-PCI, whereas at peripheral hospitals they might not since they may not be stable enough to allow transportation or they could even die during transport. Unfortunately, deaths or complications that occurred during transfer were not systematically identified in different centres. Although this is a well-known limitation of these studies,[27] several other randomized trials on inter-hospital transfer for p-PCI[26,30,31] documented that this policy is fairly safe, with few complications occurring during transportation and should not have affected outcomes.

This study was a registry study based on a prospectively assembled database, part of a quality-improvement programme. All STEMI patients who underwent p-PCI within 12 h from symptoms onset during the pre-specified study period were included in the analysis. Since the analysis itself was retrospective, a formal power analysis was not performed. For this reason, we cannot exclude that the non-significant difference in terms of short- and long-term outcome could be due to a too small sample size. Of note, the observed 1 year-adjusted cardiac mortality 95% CIs of the two study groups resulted quite wide (6.7–11.7 T group vs. 4.8–9.9 OS group), suggesting that the failure of detecting a significative difference between OS and T patients cannot be taken as a proof of equivalence (a type II error cannot be excluded).

Finally, owing to missing data, 563 patients were excluded from the analysis. The in-hospital mortality associated with excluded patients was higher than that recorded in the overall study population [53/563 (9.4%) vs. 227/3296 (6.9%), $P = 0.04$]. We do not, however, think that this finding could have altered the main study results because comparable in-hospital death rates were observed in the excluded patients both when p-PCI was performed on-site [40/422 patients (9.5%)] or after inter-hospital transfer [13/141patients (9.2%)].

Conclusions

In an established STEMI regional network, a strategy of inter-hospital transfer for p-PCI may be applied with rapid reperfusion times and favourable short- and long-term clinical outcomes when supported by an organized system of care. Strategies that focus on processes within the hospital and that emphasize logistical details and re-engineering of process-of-care systems in order to reduce the inter-hospital delay could make transfer for p-PCI a realistic strategy.

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