

Gender-related benefit of transport to primary angioplasty: Is it equal?

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Abstract

Background. *Infarct size is correlated with duration of coronary artery occlusion. Evidence suggests that transport for primary angioplasty improves outcomes, but there is no agreement regarding differences in prognosis between men and women. We compared outcomes in men and women with ST-segment elevation myocardial infarction (STEMI) transferred from another hospital against those who had been transported directly to an invasive treatment center.*

Methods. *Data was collected between June 2005 and May 2006 from a registry of 26,035 patients with STEMI and in whom primary angioplasty had been performed.*

Results. *A total of 10,708 patients underwent primary angioplasty. Of these, 3,359 men and 1,469 women were transported directly, while 4,135 men and 1,745 women were transferred from another site. In-hospital mortality and at one month, six months and 12 months after hospital discharge was significantly higher in women than in men. The prognosis of women transported directly was similar to that of women transferred from another site. However, there was a tendency, albeit insignificant, towards higher mortality at six and 12 months in women transported from another hospital.*

Conclusions. *To reduce mortality in STEMI, an immediate reperfusion must not be delayed. This conclusion is valid particularly for women who are at greater risk of death. (Cardiol J 2011; 18, 3: 254–260)*

Key words: ST-segment elevation myocardial infarction, time to reperfusion, transfer, gender

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Introduction

In ST-segment elevation myocardial infarction (STEMI), infarct size is correlated with duration of coronary artery occlusion. De Luca et al. [1] demonstrated that every 30 min delay to revasculariza-

tion will increase annual mortality by 7.5%. Nonetheless, the available evidence suggests that transport for primary angioplasty improves short- and long-term outcomes better than immediate thrombolysis [2, 3]. However, the DANAMI-2 [4] study demonstrated no such benefit in diabetic patients. The same may apply to other patients with STEMI. There is controversy regarding differences in the clinical course of myocardial infarction (MI) and

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prognosis between men and women. Some investigators ascribe higher mortality among women to a worse risk profile and less aggressive treatment strategy [5–7]. Others believe that female gender is an independent predictor of adverse outcome [8, 9]. It is well-known that women are more prone to complications related to invasive procedures [10]. The purpose of the present study was to compare outcomes in men and women with STEMI transferred to a cath lab from another hospital against outcomes in those transported directly to an invasive treatment center.

Methods

The data is based on the Polish Registry of Acute Coronary Syndromes (PL-ACS) [11]. The present data was collected between June 2005 and May 2006. The Registry includes data on patients from 456 sites across Poland. Mortality data after hospital discharge was obtained from the National Health Fund database for all included subjects. All consecutive patients presenting with STEMI diagnosed according to the available guidelines were enrolled in the Registry. Of these, patients who underwent primary angioplasty within 12 hours from symptom onset were analyzed in our study. Demographic features such as age and gender, concomitant diseases, coronary risk factors, previous MI and revascularization, were analyzed. The time from symptom onset to percutaneous coronary intervention (PCI), time from admission to PCI, TIMI flow before and after revascularization, left ventricular ejection fraction (LVEF), cardiovascular, neurological and hemorrhagic complications were recorded. The primary end point was death during hospitalization, at one month, six months and 12 months after hospital discharge.

Statistical analysis

Continuous variables, depending on the data distribution, are expressed as mean \pm SD or median and interquartile range. The significance of differences between groups was determined by use of Student's t-test or the Mann-Whitney U test for those variables which did not conform to a normal distribution. The type of parametric test depended on the homogeneity of variances which was tested using the F-test. Qualitative variables were tested using the χ^2 test. Mortality at 12 months was analyzed using Kaplan-Meier survival curves with log rank test. A multivariate Cox proportional hazard model regression was performed to adjust the influ-

ence of the transfer of patients on 12-month mortality as well as to identify predictors of 12-month mortality in women and men. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A p value ≤ 0.05 (two-tailed) was considered significant.

Results

Basic characteristics

Within the study period, the PL-ACS Registry included data on 26,035 patients with STEMI. Of these, 10,708 (41.1%) patients i.e. 7,494 men and 3,214 women (70% vs 30%; $p < 0.0001$) underwent primary angioplasty. In this population, 4,827 (45%) patients (3,358 [69.6%] men and 1,469 [30.4%] women) were transported directly to a hemodynamic laboratory, while 5,880 (55%) patients i.e. 4,135 (70.3%) men and 1,745 (29.7%) women were transferred from another site. As compared to those taken from home, both men and women who were transferred from another site were slightly younger, but women more often had diabetes mellitus, hypercholesterolemia and obesity, while men had previous MI. In both groups, women were older than men, more frequently had arterial hypertension, diabetes mellitus and obesity, but less often smoked and less frequently had previous MI and coronary artery bypass grafting (CABG) (Table 1).

Time to PCI

In both groups, PCI within three hours of symptom onset was performed more frequently in men than in women (55% vs 51.5%, $p = 0.033$; 39.9% vs 35.3%, $p = 0.001$, respectively). The mean time from symptom onset to PCI was significantly longer both for female and male patients transferred from another site, and additionally longer for women in both groups. By contrast, time from admission to PCI was shorter for patients transferred from another site and comparable in men and women (Table 2).

PCI success

In both groups and both genders, the percentage of infarct-related artery stenting was similar and exceeded 90%. GP IIb/IIIa receptor antagonists were administered in roughly one third of all patients; significantly more frequently in patients transported directly from home, and significantly less often in women. The rate of TIMI 0 flow prior to treatment was similar in men and women in both groups. TIMI 3 flow after PCI was achieved significantly less frequently in women than in men (Table 2).

Table 1. Basic clinical characteristics.

	Direct transport (n = 4,827)		P	Transferred from another hospital (n = 5,880)		P	Significance between groups (p)	
	Females (n = 1,469, 30.4%)	Males (n = 3,358, 69.6%)		Females (n = 1,745, 29.7%)	Males (n = 4,135, 70.3%)		Females	Males
Age (mean ±SD)	71.0 ± 11.8	62.9 ± 12.3	< 0.0001	66.8 ± 11.4	60.4 ± 11.4	< 0.0001	< 0.0001	< 0.0001
Age ≥ 65	873 (59.4%)	1199 (35.7%)	< 0.0001	1018 (58.3%)	1486 (35.9%)	< 0.0001	0.53	0.84
Age < 65	596 (40.6%)	2159 (64.3%)	< 0.0001	727 (41.7%)	2649 (64.1%)	< 0.0001	0.53	0.84
Hypertension	973 (66.2%)	1850 (55.1%)	< 0.0001	1152 (66%)	2352 (56.9%)	< 0.0001	0.90	0.12
Diabetes	342 (23.3%)	458 (13.6%)	< 0.0001	459 (26.3%)	613 (14.8%)	< 0.0001	0.048	0.14
↑ Cholesterol	594 (40.4%)	1454 (43.3%)	0.064	802 (46%)	1830 (44.3%)	0.23	0.0017	0.41
Smoking	445 (30.3%)	1712 (51%)	< 0.0001	526 (30.1%)	2185 (52.8%)	< 0.0001	0.93	0.11
BMI > 30 kg/m ²	300 (20.4%)	418 (12.4%)	< 0.0001	447 (25.6%)	501 (12.1%)	< 0.0001	0.0005	0.66
Previous MI	140 (9.5%)	376 (11.2%)	0.085	164 (9.4%)	528 (12.8%)	0.0003	0.90	0.038
Previous PCI	11 (0.7%)	44 (1.3%)	0.091	14 (0.8%)	49 (1.2%)	0.19	0.86	0.63
Previous CABG	39 (2.7%)	158 (4.7%)	0.0009	45 (2.6%)	187 (4.5%)	0.0005	0.89	0.71

BMI — body mass index; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery by-pass grafting

Table 2. Time to reperfusion, adjunctive treatment and angiographic outcome of primary percutaneous coronary intervention (PCI).

	Direct transport		P	Transferred from another hospital		P	Significance between groups (p)	
	Females	Males		Females	Males		Females	Males
Onset-to-balloon: 0–3 h	699 (51.5%)	1724 (55%)	0.033	582 (35.3%)	1571 (39.9%)	0.0010	< 0.0001	< 0.0001
Onset-to-balloon: 3–12 h	658 (48.5%)	1413 (45%)	0.033	1069 (64.7%)	2362 (60.1%)	0.0010	< 0.0001	< 0.0001
Onset-to-balloon [min]	231 (160–350)	220 (150–330)	0.0081	272 (195–395)	260 (180–380)	0.0009	< 0.0001	< 0.0001
Door-to-balloon [min]	50 (33–80)	49 (30–75)	0.078	40 (28–60)	40 (26–60)	0.21	< 0.0001	< 0.0001
GP IIb/IIIa infusion	406 (27.6%)	1032 (30.7%)	0.031	411 (23.6%)	1126 (27.2%)	0.0034	0.0081	0.0009
Culprit lesion stenting	1345 (91.6%)	3118 (92.9%)	0.12	1609 (92.2%)	3871 (93.6%)	0.050	0.50	0.19
Pre-procedural TIMI flow:								
0	989 (67.5%)	2313 (69%)	0.29	1133 (65.2%)	2615 (63.3%)	0.16	0.18	< 0.0001
1	208 (14.2%)	421 (12.6%)	0.12	185 (10.6%)	488 (11.8%)	0.20	0.0023	0.32
2	159 (10.8%)	355 (10.6%)	0.79	233 (13.4%)	568 (13.7%)	0.73	0.028	< 0.0001
3	110 (7.5%)	264 (7.9%)	0.66	187 (10.8%)	463 (11.2%)	0.62	0.0016	< 0.0001
TIMI flow following PCI:								
0	40 (2.7%)	64 (1.9%)	0.072	50 (2.9%)	70 (1.7%)	0.0037	0.81	0.49
1	37 (2.5%)	46 (1.4%)	0.0047	36 (2.1%)	44 (1.1%)	0.0025	0.39	0.23
2	72 (4.9%)	166 (4.9%)	0.95	103 (5.9%)	215 (5.2%)	0.28	0.21	0.62
3	1320 (89.9%)	3082 (91.8%)	0.030	1556 (89.2%)	3806 (92%)	0.0004	0.53	0.68

Table 3. Left ventricular ejection fraction and in-hospital complications.

	Direct transport			Transferred from another hospital			Significance between groups (p)	
	Females	Males	P	Females	Males	P	Females	Males
LVEF:								
> 50%	582 (54.6%)	1353 (52.2%)	0.17	573 (46.6%)	1326 (45.6%)	0.53	0.0001	< 0.0001
30–50%	447 (42%)	1135 (43.8%)	0.32	597 (48.6%)	1451 (49.8%)	0.46	0.0015	< 0.0001
< 30%	36 (3.4%)	105 (4%)	0.34	59 (4.8%)	134 (4.6%)	0.78	0.087	0.31
Complications:								
STEMI	35 (2.4%)	66 (2%)	0.35	34 (1.9%)	60 (1.5%)	0.16	0.40	0.085
NSTEMI/UA	10 (0.7%)	21 (0.6%)	0.82	12 (0.7%)	23 (0.6%)	0.55	0.98	0.70
Stroke	7 (0.5%)	9 (0.3%)	0.37	15 (0.9%)	6 (0.1%)	< 0.0001	0.19	0.24
Bleeding	17 (1.2%)	21 (0.6%)	0.054	27 (1.5%)	17 (0.4%)	< 0.0001	0.34	0.19
re-PCI (TLR)	11 (0.7%)	39 (1.2%)	0.19	19 (1.1%)	44 (1.1%)	0.93	0.32	0.69

LVEF — left ventricular ejection fraction; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; UA — unstable angina; PCI — percutaneous coronary intervention; TLR — target lesion revascularization

Table 4. In-hospital, 30-day, six-month and one year mortality.

	Direct transport			Transferred from another hospital			Significance between groups (p)	
	Females	Males	P	Females	Males	P	Females	Males
In-hospital	88 (6%)	137 (4.1%)	0.0038	111 (6.4%)	139 (3.4%)	< 0.0001	0.66	0.10
30-day	102 (6.9%)	156 (4.6%)	0.0011	129 (7.4%)	196 (4.7%)	< 0.0001	0.62	0.85
12-month	152 (10.3%)	278 (8.3%)	0.020	215 (12.3%)	336 (8.1%)	< 0.0001	0.080	0.81

In-hospital course

The rate of in-hospital complications in patients with STEMI undergoing primary angioplasty was low. Reinfarction (STEMI or NSTEMI), stroke and non-coronary death were equally frequent in all study groups. Bleeding complications were most frequent among women transferred from another site. LVEF prior to discharge was comparable in men and women. Among patients transported directly from home, LVEF more frequently exceeded 50%, while among those transferred from another site, LVEF tended to range from 30 to 50% (Table 3).

Prognosis

Mortality at all time points was significantly higher in women than in men. The prognosis of women transported directly from home was similar to that of women transferred from another site. However, there was a tendency, albeit insignificant, toward higher mortality at six and 12 months in women transported from another hospital (Table 4). Figure 1 depicts Kaplan-Meier mortality curves in all study groups.

When analyzing mortality depending on total ischemic time measured by onset-to-balloon time

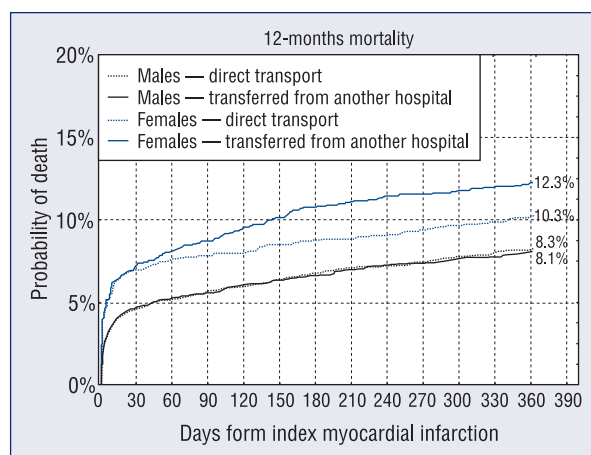


Figure 1. Kaplan-Meier curves for one year mortality in all study groups.

(regardless of whether a patient was transported directly or not) there is a clear significant tendency that the longer the time to recanalization of the infarct-related artery, the higher the mortality. Moreover, mortality in women is higher at all time delays (Table 5).

Table 5. In-hospital and 12-month mortality depending on onset-to-balloon time in patients transported directly and transferred from another hospital.

Time delay	Direct transport			Transferred		
	Females	Males	P	Females	Males	P
In hospital: 0–3 h	5.6%	4.8%	0.53	6.5%	2.9%	0.0018
3–12 h	6.3%	3.4%	0.0004	6.3%	3.4%	< 0.0001
12-month: 0–3 h	9.0%	8.1%	0.58	11.7%	7.1%	0.007
3–12 h	11.2%	8.0%	0.0056	12.3%	8.3%	< 0.0001

Table 6. Multivariate analysis of 12-month mortality, all patients.

	HR (95% CI)	P
Age (for each 10 years more)	1.68 (1.58–1.79)	< 0.0001
Female sex	1.00 (0.87–1.14)	0.95
Hypertension	0.95 (0.83–1.09)	0.45
Diabetes	1.48 (1.28–1.71)	< 0.0001
Hypercholesterolemia	0.81 (0.71–0.92)	0.0018
Smoking	1.01 (0.88–1.18)	0.85
Obesity	1.04 (0.88–1.24)	0.64
Prior MI	1.33 (1.11–1.60)	0.0024
Prior PCI or CABG	1.21 (0.90–1.62)	0.20
CA before admission	1.74 (1.39–2.17)	< 0.0001
Anterior MI	1.55 (1.37–1.76)	< 0.0001
Killip class 3 or 4	6.67 (5.77–7.71)	< 0.0001
Transfer from another hospital	1.01 (0.89–1.15)	0.88

HR — hazard ratio; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; CA — cardiac arrest

Multivariate analysis

In multivariate analysis for all patients, age, cardiac arrest, anterior MI and Killip class 3 or 4 significantly influenced 12-month mortality. No significant impact of transfer from another hospital was observed. In women, the most important factors increasing mortality were Killip class 3 or 4 (HR 4.21, 95% CI 3.27–5.43, $p < 0.0001$) and less than TIMI 3 grade flow following primary PCI (HR 3.25, 95% CI 2.58–4.08, $p < 0.0001$). Similar findings were obtained in men (Tables 6, 7).

Discussion

‘Time is muscle’ is a well-known concept regarding patients with STEMI [1]. In an effort to reduce delay from pain onset to recanalization of the infarct-related artery, physicians in hospitals with-

out invasive cardiac facilities frequently face a dilemma as to whether to transfer a patient to a cath lab or to provide treatment on site.

The DANAMI-2 [12] and PRAGUE-2 [13] trials demonstrated a positive effect of transport to primary angioplasty as compared to fibrinolysis on site regarding 30-day survival in women. The available literature includes no comparison that takes into account sex differences in patients with STEMI without transport and who are transferred to another site to undergo primary PCI. In our study, 30-day mortality did not differ between women transferred to primary angioplasty and those admitted directly to a cath lab. Unlike men, there is a tendency toward higher mortality at one year among transported women, while the 12-month prognosis of men is similar in both groups (Kaplan-Meier survival curves are superimposed) despite the significant prolongation of onset-to-balloon time in the transported group. The delay related to transfer from another site was about 40 min in patients of both genders. Thus we presume that worse long-term prognosis in transferred women is related not only to delayed reperfusion, but also to worse baseline characteristics including more frequent diabetes that has been reported to diminish long-term benefits from transport to primary PCI [4].

An incomplete reading of the present study might lead to the false conclusion that time to revascularization is not associated with mortality, something which obviously conflicts with previous reports and guidelines. In our study, transfer from another hospital has no significant influence on mortality in multivariate analysis.

To clarify this, we performed an additional analysis of mortality depending on onset-to-balloon time. It can clearly be seen that mortality, both in-hospital and long-term, depends on total ischemic time regardless of mode of transport, as the two stage transport does not have to be *a priori* too long. The second important finding is that women have

Table 7. Multivariate analysis of 12-month mortality for both genders.

	Females		Males	
	HR (95% CI)	P	HR (95% CI)	P
Age (for each 10 years more)	1.48 (1.32–1.66)	< 0.0001	1.56 (1.45–1.68)	< 0.0001
Hypertension	1.04 (0.83–1.31)	0.72	0.96 (0.81–1.13)	0.62
Diabetes	1.17 (0.93–1.47)	0.19	1.45 (1.2–1.76)	0.0001
Hypercholesterolemia	0.79 (0.64–0.99)	0.042	0.81 (0.68–0.97)	0.018
Smoking	0.86 (0.63–1.18)	0.36	1.04 (0.88–1.23)	0.61
Obesity	1.11 (0.87–1.42)	0.42	0.92 (0.72–1.18)	0.52
Prior MI	1.52 (1.13–2.04)	0.0051	0.94 (0.74–1.2)	0.63
Prior PCI or CABG	1.05 (0.60–1.84)	0.85	1.32 (0.93–1.86)	0.12
CA before admission	2.07 (1.36–3.14)	0.0006	1.71 (1.31–2.24)	0.0001
Anterior MI	1.36 (1.10–1.69)	0.0052	1.29 (1.09–1.52)	0.0025
Killip class 3 or 4	4.21 (3.27–5.43)	< 0.0001	5.03 (4.14–6.1)	< 0.0001
Onset-to-balloon 0–3 h	1.02 (0.80–1.32)	0.85	1.01 (0.84–1.22)	0.89
TIMI < 3 after PCI	3.25 (2.58–4.08)	< 0.0001	2.73 (2.26–3.3)	< 0.0001
Multivessel disease	1.77 (1.40–2.23)	< 0.0001	1.43 (1.2–1.7)	< 0.0001
LVEF (per 5% less)	1.18 (1.11–1.24)	< 0.0001	1.19 (1.14–1.24)	< 0.0001

HR — hazard ratio; CI — confidence interval; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; CA — cardiac arrest; LVEF — left ventricular ejection fraction

higher mortality than their male counterparts, especially when primary PCI is performed more than three hours after symptom onset.

At first, it was believed that door-to-balloon time was the most important factor related to prognosis [14]. Later, Antoniucci et al. [15] and De Luca et al. [1] demonstrated that onset-to-balloon time (i.e. total ischemic time) is equally significant. In the present study it is shorter (220 min in men and 231 min in women) than in the PRAGUE-2 study [2] (about 277 min for transferred patients), but longer than in the DANAMI-2 trial [12] (188 min for on-site treatment patients and 224 min for those transferred from another site) and in the study by Le May et al. [16] (158 min and 230 min, respectively). The shorter delay recorded in those studies was probably due to the fact that they were randomized controlled studies incorporating many fewer patients and in a smaller area. Also, awareness of participating in a study could have exerted a positive influence on transport organization, thus shortening the delay. The US National Registry of Myocardial Infarction (NRM) includes data on time from first medical contact to reperfusion [17]. In 1999–2002, it was 180 min on average (including transport to PCI 120 min on average). According to the National Cardiovascular Data Registry [15], it improved to 153 min (including transport to PCI 109 min) in 2005–2006. Moreover, a standardized protocol and integrated regional system of transfer for STEMI patients allow further time savings [18].

In contrast to the US data [17], the patients in the present study who were transferred from another site had shorter PCI hospital door-to-balloon time than those who were transported directly from home. This difference was probably related to earlier notification of the hemodynamic team and direct patient transport to the cath lab. It is important to note that although time from symptom onset to PCI was on average 11–12 min longer in women, time from hospital admission to PCI was comparable in patients of both genders.

Recently, gender differences in the course and prognosis of STEMI have been studied extensively [5–9]. Similarly to the present study, women with STEMI have been found to be older and to have more concomitant diseases than men. This undoubtedly increases mortality rates in women with STEMI, and, according to some investigators, if we adjust for these factors, the risk will equalize for men and women [5–7].

Other factors like younger age, pretreatment with aspirin, clopidogrel and heparin, and more frequent pre-procedural TIMI grade 2 and 3 flow in the transferred group may affect both short- and long-term prognosis.

Another reason for worse prognosis in women may be the less frequent use of an invasive approach [5–7]. In our study, all women underwent primary angioplasty, but nevertheless their mortality rates were higher than in men. This could be a result of

the worse baseline clinical profile, longer delay from symptom onset to PCI, suboptimal revascularization and more frequent bleeding complications.

Limitations of the study

This is a large multicenter registry with all the limitations of such a study, but it has the advantage of consisting of a 'real life' population. However, a major limitation is the fact that gender is not the only difference between the two groups, and differences in baseline characteristics all indicate a worse risk profile in women. Finally, a history of coronary events was significantly more frequent in men, and it is conceivable that patients with past MI or revascularization were already taking drugs that could beneficially impact on the acute event. Another important issue is that the slightly higher mortality in women dispatched to interventional facility may reflect a bias related to the initial decision made.

Conclusions

To reduce mortality in STEMI, a decision as to immediate reperfusion must not be delayed and all patients without contraindications to PCI should be referred for invasive treatment. Our main conclusion is that after the initial diagnosis of STEMI, all activities of medical staff should be guided by the concept that 'time is muscle' and no further delay in reperfusion should be allowed, even if transport to another facility is required. This conclusion is valid particularly for women who are at greater risk of death.

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