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Results of the Croatian Primary Percutaneous Coronary Intervention Network for Patients with ST Elevation Acute Myocardial Infarction

Vjeran Nikolić Heitzler, PhD^a, Zdravko Babic, MD^a, Davor Milicic, PhD^b, Mijo Bergovec, PhD^c, Miroslav Raguz, MD^c, Jure Mirat, PhD^d, Maja Strozzi, PhD^b, Zeljko Plazonic, MD^e, Lovel Giunio, PhD^f, Robert Steiner, PhD^g, Boris Starcevic, PhD^c, Ivica Vukovic, PhD^f.

Affiliations:

^a Coronary Care Unit (CCU), Cardiovascular Department, Sestre milosrdnice University Hospital (UH), Vinogradska 29, Zagreb, Croatia

^b Cardiovascular Clinic, Clinical Hospital Center Zagreb, Kispaticeva 12, Zagreb, Croatia

^c Cardiovascular Department, Dubrava UH, Gojka Suska 6, Zagreb, Croatia

^d Cardiovascular Department, Sveti Duh General Hospital, Sveti Duh 64, Zagreb, Croatia

^e Cath lab, Cardiovascular Department, Clinical Hospital Center Rijeka, Kresimirova 42, Rijeka, Croatia

^f Cath lab, Cardiovascular Department, Clinical Hospital Center Split, Soltanska 1, Split, Croatia

^g Cardiovascular Department, Osijek UH, J. Huttlera 4, Osijek, Croatia

Corresponding Author: Zdravko Babic, tel: +38513787937, fax: +38513787788, email: zbabic@net.hr

mailing address: Sestre milosrdnice University Hospital, Vinogradska 29, Zagreb, Croatia

Short running head: Croatian Primary PCI Network

Abstract:

The Republic of Croatia, with gross domestic product per capita of 11,554 US \$ in the year 2008, is economically less developed western country. The goal of this investigation is to prove that a well organised primary percutaneous coronary intervention (PCI) network in an economically less developed country equalizes the prospects of all patients with acute ST elevation myocardial infarction (STEMI) at the level comparable to economically more developed countries. The authors prospectively investigated 1190 acute STEMI patients treated with primary PCI in eight centers across Croatia (677 non-transferred, 513 transferred). Postprocedural TIMI flow, in-hospital mortality and major adverse cardiovascular events (MACE) (mortality, pectoral angina, restenosis, reinfarction, coronary artery by-pass graft and cerebrovascular accident rate) in the six-month follow-up were compared between non-transferred and transferred subgroups in general, as well as in subgroups of older patients, female gender and those with cardiogenic shock. In all investigated patients the average door-to-balloon time was 108 minutes and total ischemic time 265 minutes, postprocedural TIMI 3 flow was established in 87.1% of them, while in-hospital mortality was 4.4%. No statistically significant difference in results of treatment was found between transferred and non-transferred patients in general, as well as in subgroups of older than 75 years, female gender and those with cardiogenic shock. In conclusion, Croatian Primary PCI Network ensures results of treatment of acute STEMI comparable to those of randomised studies and registries of economically more developed countries.

Key words:

STEMI; primary PCI; network; Croatia.

INTRODUCTION

In the year 2002, 5,525 Croatians suffered from acute myocardial infarction, and approximately 4,000 had STEMI. Out of them 54% were treated in the county institutions with less than 100 acute myocardial infarctions a year and without interventional capabilities. Among these patients 62% were men, 39% were capable of working actively (22% women and 49% men), and more were affected by arterial hypertension and diabetes compared to other European countries. Such a high percentage of STEMI could be explained by underdiagnosis and underreporting of NSTEMI in that time.¹⁻² In the year 2007, 6,420 Croatians were hospitalised because of acute myocardial infarction, but with decreasing tendency of cardiovascular mortality in general.³

Having recognised the above said problems related with treating acute STEMI in Croatia, and knowing the world trends and recommendations, in the middle of 2005 Croatian Cardiac Society introduced Croatian Primary PCI Network into the health care system of the Republic of Croatia. The main goal was to achieve equal quality treatment of acute STEMI in all parts of Croatia. Currently, 8 high-volume PCI centers all over Croatia are included in this network covering around 75% of population (Figure 1).⁴

The main goals of this investigation are: 1.) To evaluate treatment results of patients with acute STEMI treated with primary PCI in Croatian Primary PCI Network and to compare these results with published randomised studies and registries data; 2.) To prove equality of treatment results in all Croatian Primary PCI Network patients even in those at higher risk (older patients, female gender, patients in cardiogenic shock). The main hypothesis is that a well organised primary PCI network, even in an economically less developed country, equalizes the prospects of all STEMI patients in all parts of the country at a level comparable to that in economically more developed countries.

METHODS

This investigation prospectively studies 1190 consecutive acute STEMI patients treated between September 1, 2005 and March 1, 2007 with primary PCI in eight PCI centres in all parts of Croatia (four with and four without on-site cardiac surgery) included in the Croatian Primary PCI Network. In 677 investigated patients acute STEMI was diagnosed in one of the centers with on-site PCI laboratory (cath-lab), where primary PCI was performed (non-transferred patients). In the remaining 513 patients acute STEMI was diagnosed in the hospitals without on-site cath-lab, so they were urgently transferred with ambulance to already quoted PCI centers for primary PCI (transferred

patients). The diagnosis of STEMI was established and primary PCI performed using the actual criteria of the European Cardiac Society.⁵ In brief, the patients with an episode of chest discomfort within the last 12 hours and ST-elevation in the ECG in at least two consecutive leads were included. Immediately after diagnosis, patients waiting for transfer (transferred) or primary PCI (non-transferred) patients received the loading dose of 300 mg salicylic acid, 600 mg clopidogrel, and intraprocedurally 70-100 IE/kg of unfractionated heparin, and, according to judgment of interventional cardiologist, a GPIIb/IIIa inhibitor.

After primary PCI the patients were hospitalized on average 2 to 3 days in coronary care units in PCI centers with continuous monitoring and treatment. Afterwards they finished their hospital treatment in cardiac departments of those hospitals (non-transferred patients), or they were transferred back to their county hospitals (transferred patients). During their first hospital stay, general information (name, age, gender) and information on the time of the first symptoms, time of arrival in the first hospital and/or PCI center, time of the first balloon insufflation during primary PCI, affected myocardial wall and coronary artery, postprocedural flow, as well as eventually cardiogenic shock and lethal outcome were collected. Six months after discharge, data about major adverse cardiovascular events (MACE) (pectoral angina, restenosis, reinfarction, mortality, coronary artery by-pass graft surgery and cerebrovascular accident rate) were collected for investigated patients during their examination, by checking medical documentation or by telephone contact with patients, patients' family members or home physicians. Including the follow-up, this investigation covers the period between September 1, 2005 and August 3, 2007.

Cardiogenic shock was defined as a clinical state of hypoperfusion characterised by systolic blood pressure <90 mmHg and/or capillary wedge pressure >20 mmHg and/or cardiac index <1.80 l/min m².⁵ Total ischemic time or symptom onset-to-balloon time was calculated as the time between the first symptoms and balloon insufflation during primary PCI, door-to-balloon time as the time between arrival in the first hospital (with or without on-site cath-lab) and balloon insufflation during primary PCI, symptom onset-to-door time as the time between the first symptoms and arrival in the first hospital (with or without on-site cathlab).

Postprocedural flow was classified according to the Thrombolysis in Myocardial Infarction (TIMI) grading system at the scale of 0-3.⁶

Nominal (categorical) variables were analysed using Pearson Chi-Square and Fisher's

Exact Test, and quantitative variables by Mann-Whitney Test. Differences between subgroups with elimination of influence of other variables were analysed using multivariate log-linear analysis. The value of $p < 0.05$ was considered significant for all used tests. The statistical analysis was performed by using Statistica 6.0 program.

The investigation was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and was approved by the appropriate institutional review committees.

RESULTS

The descriptive statistic data and times to reperfusion of all investigated patients, transferred and non-transferred, are shown in Table 1 and the results of their treatment in Table 2. There are no significant differences between transferred and non-transferred patients in the investigated descriptive parameters. Also, a higher percent of cardiogenic shock among non-transferred patients was insignificant. The average distance of transfer in the subgroup of transferred patients was 72 kilometers. The latter group of patients has longer door-to-balloon and symptom onset-to-balloon times, which can be expected because transfer time is included in the two times to reperfusion. In Croatian Primary PCI Network during the investigated period 37% of all investigated patients received primary PCI within recommended 90 minutes after arrival in the first hospital. Among non-transferred patients this percentage was 47%, and among transferred 25%. Transferred patients in this investigation have tendency of better treatment results compared to non-transferred, but without statistical significance at the multivariate level. During primary PCI 93% of patients received stents. Follow-up data rate was 89%.

The descriptive statistical data and times to reperfusion of subgroups of patients older than 75 year, female patients in cardiogenic shock are shown in Table 3, and the results of their treatment in Table 4. In comparison with all investigated patients, those older than 75 years have higher percentage of patients with cardiogenic shock, especially non-transferred, and their times-to-reperfusion are longer. There are no significant differences in the results of treatment between transferred and nontransferred older patients, but the results for both subgroups are worse than those for all investigated patients. In comparison with the results for all investigated patients, female patients are older, with all times-to-reperfusion longer, and somewhat worse treatment results. Patients with cardiogenic shock are on average older with more frequently culprit lesion at the left main level than

all investigated patients. Results of their treatment and their prognosis are more serious than those of patients without this complication.

Authors found no statistically significant differences in investigated results of treatment between subgroups of patients treated in PCI centers with and without cardiosurgical back-up. Also, among door-to-balloon subgroups (<90, 90-180, and >180 minutes) none of results differences was statistically significant. Among onset-to-balloon time subgroups (<90, 90-180, 180-360, and >360 minutes) a statistically significant difference on multivariate level was found only for in-hospital mortality in the subgroup of patients with longest onset-to-balloon time (3.5 vs. 4.5 vs. 2.6 vs. 5.7%, $p=0.04$).

DISCUSSION

Average age, gender distribution, affected myocardial wall, as well as coronary arteries in transferred and non-transferred patients in this investigation correspond to the results of other such investigations at hospital, regional or national level.⁷⁻¹² The percentage of patients with cardiogenic shock in the literature that investigated primary PCI in STEMI is between 2% in PRAGUE-2 study⁹ and 7-12% in other studies^{10,11,13} compared to our 6.7%. Somewhat higher percentage of this complication among non-transferred patients in this study is insignificant, but could be reason for better results of transferred patients. The average transport distance of 72 kilometers also corresponds to such distances in DANAMI⁷ (3-150 kilometers) and PRAGUE-2 study (5-120 kilometers).⁹

Vienna STEMI Registry Group¹², on smaller area in comparison with the Croatian Primary PCI Network, found shorter door-to-balloon time, but because of relatively long symptom onset-to-door time total ischemic times are similar. All times to reperfusion in DANAMI study⁷, as well as in Emilia-Romagna ST-segment elevation acute myocardial infarction network¹¹ are shorter than in this study. On the other hand, the results of these times in investigations outside Europe are worse than in this and in other European studies (for example, average door-to-balloon time of 142 minutes in Canadian transferred patients or 128 minutes in transferred patients in the USA).^{14,15} In comparison with ACTION Registry¹⁶ from the United States, the percentage of transferred patients treated with primary PCI within 90 minutes after arrival in the first hospital is higher in this study (12 vs. 25%), but not in non-transferred patients (80 vs. 47%). Investigating the same percentages, Italian

investigators on regional network level report better results (32% for transferred and 70% for non-transferred). After these results, the leaders of the Croatian Primary PCI Network started with actions for improvement of door-to-balloon time, especially in non-transferred patients.¹⁷ Percents of optimal postprocedural TIMI flow in this study, and other similar studies^{8,9,18} are positioned between 82% reported in DANAMI⁷ and 95% by German authors in 2007.¹³ Italian¹¹ and German¹³ groups also found better postprocedural TIMI flow in transferred patients. Early mortality rates reported in similar studies^{10,19} are between 2.1 and 8.1% and, among other things, depend on definition (in-hospital or 30-day mortality). Reported mortality rates in six months to one year are mostly between 7 and 10%, and also depend on the duration of the follow-up.^{7-9,11,18} Problem with definition of MACE (types of events included, duration of follow-up) was found in their comparison between studies.^{7-9,11-13} Nevertheless, results for mortality and MACE revealed in the Croatian Primary PCI Network investigation and quoted in Table 2 are mostly within the frameworks of such results reported in other primary PCI networks established at city, regional or national level in economically more developed countries compared to Croatia (Table 5).

Relatively higher percentage of female gender among older patients, higher percentage of complex coronary lesions and complications, as well as longer times to reperfusion are reported in the literature.^{5,12,20} Lower percentage of optimal postprocedural TIMI flow, and higher mortality rate among older patients are also known from the literature.^{19,21} All these tendencies are found in our investigation too. The absence of significant differences in the results of treatment between transferred and non-transferred older patients found here proves that the Croatian Primary PCI Network ensures equal treatment for this hazardous subgroup of patients in all parts of the country.

There are reports^{22,23} that find no significant difference between genders in the results of primary PCI in acute STEMI or PCI in general. On the other hand, data from the Austrian acute PCI registry¹² revealed higher age, higher percentage of cardiogenic shock, as well as higher in-hospital mortality in female gender, while another study²⁴ proved worse prognosis of female patients only during follow-up. The latter results (higher age, more cardiogenic shock, and even longer times to reperfusion) are found also in this investigation, as well as less benefit of primary PCI in female compared to male patients. Nevertheless, the authors again find no significant difference between transferred and non-transferred subgroups of female patients.

Older age, female gender, three-vessel disease and disease of proximal parts of coronary arteries, infarction of anterior myocardial wall, as well as longer times to reperfusion, are independent risk factors for cardiogenic shock in acute STEMI.^{25,26} In this investigation, patients in cardiogenic shock are also older with more left-main culprit lesions and tendency of more infarctions of the anterior wall. The introduction of primary PCI in the treatment of acute STEMI complicated with cardiogenic shock reduced mortality from over 80% to 40-50%.^{17,26,27} Postprocedural TIMI flow less than 3 is an independent factor for occurrence and prognosis of cardiogenic shock.^{25,26} Percentage of postprocedural TIMI flow 3 and in-hospital mortality rate found in this investigation (Table 4) are similar to results in quoted studies. The absence of significant differences in the results between transferred and nontransferred subgroups of patients in cardiogenic shock again proved equal treatment for this hazardous subgroup of patients in all parts of Croatia.

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Contributing authors:

Sestre milosrdnice University Hospital (UH), Zagreb: Hrvoje Pintaric, Kresimir Stambuk, Sime Manola, Marin Pavlov, Sime Mihatov

Clinical Hospital Center Zagreb, Zagreb: Aleksander Ernst, Eduard Margetic, Ivan Skorak, Kreso Putarek, Bruno Skoric, Danijel Lovric

Dubrava UH, Zagreb: Miomir Veskovic, Nikola Todorovic, Josica Sikic, Drazen Sebecic, Sveti Duh General Hospital (GH), Zagreb: Edvard Galic, Ilko Vuksanovic

Clinical Hospital Center Rijeka, Rijeka: Rajko Miskulin, Djuro Marinovic, David Gobic, Vjekoslav Tomulic

Clinical Hospital Center Split, Split: Branimir Markovic, Josip Lukenda

Osijek UH, Osijek: Damir Kozmar, Zorin Makarovic, Damir Kirner

Magdalena Special hospital for Cardiovascular surgery and Cardiology, Krapinske Toplice: Mihajlo Sesto, Robert Bernat, Nikola Milicic, Hrvoje Stipic, Tomislav Sipic

Cakovec GH, Cakovec: Rudolf Hranilovic

Bjelovar GH, Bjelovar: Mario Ivanusa

Zabok GH, Zabok: Stjepan Rogan

Varazdin GH, Varazdin: Dubravko Trsinski

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Figure 1. Croatian Primary Percutaneous Coronary Intervention Network

Map of Croatia with PCI centres and 150 km circles of their jurisdiction in acute STEMI



Table 1 Descriptive statistic data and times to reperfusion in Croatian Primary PCI Network

Variable	All pts.	Transferred pts.	Non-transferred pts.	p
Age (median, range)	60 y (24-95)	59 y (29-95)	60 y (24-92)	0.08**
Gender (M/F)	73.3%/26.7%	75.7%/24.5%	71.7%/28.3%	0.15*
Myocardial wall (anterior/inferior)	42.6%/57.4%	39.8%/60.2%	44.8%/55.2%	0.12*
Coronary artery (LAD/Cx/RCA/LM/by-pass)	41.7%/13.8%/43.4% /0.7%/0.5%	40.6%/15.6%/42.7% /0.4%/0.7%	42.5%/12.3%/44.0% /1.0%/0.2%	0.27*
Cardiogenic shock	6.7%	5.5%	7.6%	0.19*
<i>Symptom onset-to-door</i> (median, range)	130 min. (15-1365)	135 min. (15-1230)	130 min. (15-1365)	0.45**
<i>Door-to-balloon</i> (median, range)	108 min. (10-540)	123 min. (35-540)	96 min. (10-465)	<0.01**
<i>Symptom onset -to-balloon</i> (median, range)	265 min. (45-702)	298 min. (84-702)	255 min. (45-695)	<0.01**

LAD – left anterior descending coronary artery

ACx – circumflex coronary artery

RCA – right coronary artery

LM – left main

Symptom onset-to-door – time between first symptoms and arrival in the first hospital (with or without on-site cath-lab)

Door-to-balloon – time between arrival in the first hospital (with or without on-site cath-lab) and balloon insufflation during primary PCI

Symptom onset-to-balloon– time between first symptoms and balloon insufflation during primary PCI

* χ^2 test (transferred vs. non-transferred pts.)

** Mann-Whitney U-test (transferred vs. non-transferred pts.)

Table 2 Results of treatment in Croatian Primary PCI Network

Variable	All pts.	Transferred pts.	Non-transferred pts.	p*	p**
Postprocedural TIMI 3 flow	87.1%	89.9%	85.2%	0.03	0.05
Mortality (in-hospital)	4.4%	2.9%	5.4%	0.04	0.20
Mortality (6 month follow-up)	1.2%	0.5%	1.7%	0.24	0.82
Pectoral angina (6 month follow-up)	12.1%	11.4%	12.6%	0.70	0.13
MACE (other) (6 month follow-up)	6.4%	5.8%	7.1%	0.59	0.08

MACE (other) - major adverse cardiovascular events (restenosis, reinfarction, coronary artery bypass graft and cerebrovascular accident)

* χ^2 test (transferred vs. non-transferred pts.)

** multivariate log-linear analysis (transferred vs. non-transferred pts.)

Table 3 Descriptive statistic data and times to reperfusion in subgroups of patients

Variable	>75 years			Female			Cardiogenic shock		
	T	N-T	p	T	N-T	p	T	N-T	p
Age (median, range)	-	-	-	66(29-92) years	67(24-89) years	0.07 *	65 (52-81) years	70 (40-89) years	0.25 **
Gender (M/F)	66.0% /34.0%	53.0% /47.0%	<0.01 *	-	-	-	75.0% /25.0%	66.7% /33.3%	0.67 *
Myocardial wall (anterior/inferior)	37.2% /62.8%	43.6% /56.4%	0.05 *	35.5% /64.5%	45.4% /54.6%	0.14 *	50.0% /50.0%	40.0% /60.0%	0.60 *
Coronary artery (LAD/Cx/RCA/LM/by-pass)	37.3%/7.7% /51.0%/2.0% /2.0%	45.1%/11.3% /38.0%/ 5.6%/0	0.37 *	38.2%/15.2 %/45.7% /0.9%/0	41.7%/10.6 %/45.9% /1.2%/0.6%	0.47 *	45.8%/16.7 %/33.3% /4.2%/0	27.5%/12.5 %/47.5% /12.5%/0	0.32 *
Cardiogenic shock	15.9%	22.6%	0.40 *	5.8%	8.9%	0.48 *	-	-	-
Symptom onset-to-door (median, range)	171 (30-1230) min.	155 (15-1080) min.	0.27 **	171 (20-1230) min.	150 (30-1080) min.	0.71 **	120 (45-780) min.	180 (25-1080) min.	0.07 **
Door-to-balloon (median, range)	162 (23-540) min.	110 (10-330) min.	0.02 **	130 (28-501) min.	100 (10-355) min.	<0.01 **	125 (40-240) min.	95 (35-285) min.	0.18 **
Symptom onset-to-balloon (median, range)	348 (120-650) min.	283 (45-570) min.	< 0.01 **	318 (84-690) min.	270 (60-660) min.	<0.01 **	230 (145-650) min.	255 (105-510) min.	0.77 **

LAD – left anterior descending coronary artery

ACx – circumflex coronary artery

RCA – right coronary artery

LM – left main

Symptom onset-to-door – time between first symptoms and arrival in the first hospital (with or without on-site cath-lab)

Door-to-balloon – time between arrival in the first hospital (with or without on-site cath-lab) and balloon insufflation during primary PCI

Symptom onset-to-balloon – time between first symptoms and balloon insufflation during primary PCI

* χ^2 test

** Mann-Whitney U-test

Table 4 Results of treatment in subgroups of patients

Variable	>75 years				Female				Cardiogenic shock		
	T	NT	p*	p**	T	NT	p*	p**	T	NT	p*
Postprocedural TIMI 3 flow	81.3 %	73.6 %	0.33	0.26	84.5	81.1	0.58	0.97	38.1	47.4	0.68
Mortality (in-hospital)	9.4 %	15.4 %	0.32	0.74	2.6	4.9	0.51	0.49	45.5	52.4	0.79
Mortality (6 month follow-up)	0 %	5.0 %	0.24	0.69	2.0	4.9	0.65	0.74	0	0	-
Pectoral angina (6 month follow-up)	16.0 %	13.6 %	0.75	0.54	19.2	11.7	0.38	0.84	0	3.5	0.66
MACE (other) (6 month follow-up)	3.3 %	3.6 %	0.96	-	7.4	9.1	0.98	0.28	6.3	3.7	0.61

MACE (other) - major adverse cardiovascular events (restenosis, reinfarction, coronary artery by-pass graft and cerebrovascular accident)

* χ^2 test

** multivariate log-linear analysis

Table 5 Gross domestic product per capita – list of countries (year 2008)²⁸

COUNTRY	GROSS DOMESTIC PRODUCT PER CAPITA (US \$)	RANK IN WORLD
DENMARK	56427	6
UNITED STATES OF AMERICA	45790	10
AUSTRIA	45343	11
FRANCE	41523	14
CANADA	40222	15
GERMANY	40079	16
ITALY	35494	18
SLOVENIA	22523	26
CZECH REPUBLIC	16271	30
CROATIA	11554	38