

## SEVEN-YEAR TRENDS IN THE CROATIAN PRIMARY PERCUTANEOUS CORONARY INTERVENTION NETWORK

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**SUMMARY** – The authors investigated trends in the Croatian primary Percutaneous Coronary Intervention (pPCI) Network results among three consecutive time intervals (2005–2007, first phase; 2008–2009, second phase; and 2010–2011, third phase). Data on 5650 patients with acute myocardial infarction with ST-elevation (STEMI) transferred or directly admitted and treated with pPCI in 11 Croatian PCI centers during the study period were collected and analyzed. The number of patients with acute STEMI treated with pPCI *per year* rose continuously during the study period (581 *vs.* 1272 *vs.* 1949 patients/year). The patient risk profile worsened during the study period: age (60 *vs.* 61 *vs.* 63 years;  $p < 0.01$ ), anterior myocardial wall involvement (43% *vs.* 44% *vs.* 51%;  $p < 0.01$ ), shock rate (7% *vs.* 9% *vs.* 11%;  $p < 0.05$ ), and percentage of transferred patients (42% *vs.* 36% *vs.* 46%;  $p < 0.01$ ). While the door-to-balloon time shortened (108 *vs.* 98 *vs.* 75 min;  $p < 0.01$ ), the symptom onset-to-door time increased (130 *vs.* 175 *vs.* 195 min;  $p < 0.01$ ), but without statistically significant influence on the total ischemic time. Multivariate log-linear analysis eliminated influence of a higher risk profile on the results of treatment and yielded no statistically significant changes in final TIMI 3 flow (Thrombolysis In Myocardial Infarction 3), in-hospital mortality, and six-month mortality rate, but revealed a significant increase in the rate of angina pectoris (12 *vs.* 22 *vs.* 36%;  $p < 0.01$ ) and other major adverse cardiovascular events (MACE; 6 *vs.* 23 *vs.* 14%;  $p < 0.01$ ) during follow up. In conclusion, the Croatian pPCI Network continuously ensures very good results of STEMI treatment in this economically less developed European country despite worsening of the risk profile in treated patients and opening of new, less experienced PCI centers. The higher percentage of MACE over time could be explained by changes in the pPCI strategy introduced over time (the culprit lesion only) and higher availability of PCI centers for additional PCI after acute STEMI. However, there is room for improvement, especially in reducing prehospital delay.

**Key words:** *Myocardial infarction – therapy; Coronary disease – therapy; Percutaneous coronary intervention; Croatia*

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## Introduction

Acute myocardial infarction (AMI) and its consequences (death, chronic ischemic cardiac disease and heart failure) are the leading cause of death and cardiovascular diseases in developed world. In this context, patients with acute ST-elevation myocardial infarction (STEMI) are at the highest risk. The first-line management of STEMI patients often determines whether the outcome will be survival or death<sup>1</sup>. An integrated network for the management of STEMI allows for early diagnosis and facilitates use of the best strategy to provide the most effective reperfusion therapy<sup>2</sup>. In acute coronary syndromes, timely PCI is a life-saving procedure with favorable long-term prognosis, especially in the setting of STEMI<sup>3,4</sup>. Adherence to evidence based guidelines, assessed by measuring key indicators, allows detecting, evaluating and improving the quality of care<sup>5</sup>.

The incidence and mortality rates of AMI (STEMI in particular) are in decline or have remained stable in western world in the last ten years, probably owing to a combination of lifestyle changes, particularly smoking cessation, and improved pharmacological and interventional treatment. However, different results come from developing countries, where there is still up to 20% increase in STEMI hospitalization every year<sup>5-11</sup>. Furthermore, Glickman *et al.*<sup>12</sup> from the USA claim that initiation of a statewide STEMI collaborative care model was associated with a reduction in mortality rates, but these changes were similar to those seen nationally, and that further studies are needed to evaluate the influence of such systems on the population-based STEMI outcomes.

The Croatian Primary PCI (pPCI) Network was introduced in the mid-2005. The main goal was to achieve equal quality of treatment for acute STEMI in all parts of Croatia. The principles of the Network are as follows: 1) step-by-step implementation principle (presentation of the problem to the authorities, media campaign, extension of primary PCI up to 150 km away from the largest cities of Zagreb and Rijeka in the first year, and after that extension of the Network to the entire Croatia, incorporation in the healthcare system of the Republic of Croatia); 2) proportional allocation of PCI centers in all parts of Croatia; and 3) continuous mutual communication among all participants (meetings, educational courses, evaluation).

After its establishment, first results of this Network were internationally recognized as an example of well-organized PCI network in an economically less developed country<sup>14-17</sup>.

Studies that evaluate trends in the results of such network development over a longer period of time are lacking in the literature. That is why the main goal of this investigation was to evaluate trends in the Croatian pPCI Network results achieved during seven years of its development. The main hypothesis was that over time, the pPCI Network would enable very good results of acute STEMI treatment for clinically and geographically wider groups of patients.

## Patients and Methods

The study included data on 5650 acute STEMI patients treated with primary PCI within the Croatian pPCI Network. Because of discontinuous retrograde register that exists in Croatia, the study period was divided into three intervals: first phase from September 1, 2005 to August 31, 2007; second phase from January 1, 2008 to December 31, 2009; and third phase from November 1, 2010 to November 1, 2011. Study patients were treated at eight PCI centers in the first phase, two new centers were introduced in the second phase, and one center in the third phase, so there were 11 PCI centers in all parts of Croatia (five with and six without on-site cardiac surgery) at the end of the study. In the first, second and third phase of investigation, 1161, 2543 and 1946 STEMI patients were studied, respectively.

In all study patients, acute STEMI was diagnosed in one of the centers with on-site PCI laboratory (catheterization laboratory, cath-lab), where primary PCI was performed (non-transferred patients), or in hospitals without on-site cath-lab, so they were urgently transferred to PCI centers for pPCI (transferred patients). The diagnosis of STEMI was established and primary PCI performed using the then actual criteria of the European Cardiac Society<sup>18-21</sup>. In brief, patients with an episode of chest discomfort within the last 12 hours and ST-elevation on ECG in at least two contiguous leads were included. The patients received the loading dose of 300 mg salicylic acid, 600 mg clopidogrel, intraprocedurally 70-100 IE/kg of unfractionated heparin, and, according to judgment of the interventional cardiologist, a GPIIb/IIIa inhibitor.

After pPCI, patients were hospitalized for 2 to 3 days on average in coronary care units at PCI centers with continuous monitoring and treatment. After that, they finished their hospital treatment at 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 and gender) and information on the time of the first symptoms, time of arrival to the first hospital and/or PCI center, time of the first balloon insufflation during pPCI, affected myocardial wall and coronary artery, postprocedural flow, as well as on cardiogenic shock and lethal outcome were collected. Six months after discharge, data on major adverse cardiovascular events (MACE) (angina pectoris, restenosis, reinfarction, re-PCI, mortality, coronary artery bypass graft and cerebrovascular accident rate) were collected for investigated patients during their examination, by checking medical documentation, or by telephone contact with the patient, patient family members, or home physicians. The investigation was performed between September 1, 2005 and November 1, 2011.

Cardiogenic shock was defined as a clinical state of hypoperfusion characterized by systolic blood pressure <90 mm Hg and/or capillary wedge pressure >20 mm Hg and/or cardiac index <1.80 L/min m<sup>2</sup><sup>[19-21]</sup>. Total ischemic time or symptom onset-to-balloon time was calculated as the time between the first symptoms and balloon insufflations during primary PCI; door-to-balloon time, time between arrival to the first hospital (with or without on-site cath-lab) and balloon insufflations during primary PCI; and symptom onset-to-door time as the time between the first symptoms and arrival in the first hospital (with or without on-site cath-lab). Postprocedural flow was classified according to the Thrombolysis in Myocardial Infarction (TIMI) grading system on the 0-3 scale<sup>22</sup>.

According to the 2011 census, the population of Croatia was 4 284 889, meaning that in the last phase (2010/2011) the Croatian pPCI Network reached a rate of 454.9 pPCI/million inhabitants/year. The gross domestic product (GDP) in 2011 in Croatia was US\$ 13 999<sup>23</sup>.

### **Ethics**

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.

### **Statistics**

Nominal (categorical) variables were analyzed using Pearson  $\chi^2$ -test and Fisher exact test, and quantitative variables by Mann-Whitney test. Differences between subgroups with elimination of influence of other variables were analyzed using multivariate log-linear analysis. The value of  $p < 0.05$  was considered significant in all tests used. Statistical analysis was performed by using the Statistica 6.0 program.

### **Results**

During the three study intervals, the number of patients with acute STEMI treated with pPCI *per year* was on a continuous increase (581 *vs.* 1272 *vs.* 1949 patients/year). Descriptive statistics data and times to reperfusion in study patients in the three time intervals are shown in Table 1. The patient risk profile worsened during the study period, which was statistically significant for advancing age (60 *vs.* 61 *vs.* 63 years;  $p < 0.01$ ), anterior myocardial wall involvement (43% *vs.* 44% *vs.* 51%;  $p < 0.01$ ) and shock rate (7% *vs.* 9% *vs.* 11%;  $p < 0.05$ ), as well as for the percentage of transferred patients (42% *vs.* 36% *vs.* 46 %;  $p < 0.01$ ). During the study period, the door-to-balloon time was statistically significantly shortened (108 *vs.* 98 *vs.* 75 min;  $p < 0.01$ ), whereas the symptom onset-to-door time was statistically significantly prolonged (130 *vs.* 175 *vs.* 195 min;  $p < 0.01$ ). However, the authors found no statistically significant influence of the latter two changes on the total ischemic time.

Patient treatment results accomplished in the three time intervals are shown in Table 2. Univariate analysis showed worsening of final TIMI 3 flow (87% *vs.* 82% *vs.* 85%;  $p < 0.01$ ), in-hospital mortality rate (4% *vs.* 5% *vs.* 8%;  $p < 0.01$ ), angina pectoris (12% *vs.* 22% *vs.* 36%;  $p < 0.01$ ) and other MACE in six-month follow up (6% *vs.* 23% *vs.* 14%;  $p < 0.01$ ) during the study period. However, multivariate log-linear analysis used for elimination of the influence of higher risk profile on the results yielded significant differences only for

Table 1. Descriptive statistics data and times to reperfusion in the Croatian Primary Percutaneous Coronary Intervention Network during the study period (three intervals)

Variable	2005-2007	2008-2009	2010-2011	p
Age (yrs, median, range)	60 (24-95)	61 (21-95)	63 (26-92)	<0.01**
Gender (M/F)	73.3%/26.7%	74.5%/25.5%	72.3%/27.7%	0.39*
Myocardial wall (anterior/inferior)	42.6%/57.4%	44.4%/55.6%	50.7%/48.3%	<0.01*
Coronary artery (LAD/Cx/RCA/LM/by-pass)	41.7%/13.8%/43.4% /0.7%/0.5%	42.3%/13.7%/42.3% /1.4%/0.3%	44.1%/15.5%/38.8% /1.1%/0.5%	0.29*
Non-transferred/transferred	57.8%/42.2%	64.4%/35.6%	53.6%/46.4%	<0.01*
Cardiogenic shock	6.7%	8.8%	10.7%	0.01*
Symptom onset-to-door (median, range)	130 min (15-1365)	175 min (4-960)	195 min (10-1300)	<0.01**
Door-to-balloon (median, range)	108 min (10-540)	90 min (0-288)	75 min (4-432)	<0.01**
Symptom onset-to-balloon (median, range)	265 min (45-702)	277 min (36-1102)	270 min (80-1595)	0.24**

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 to the first hospital (with or without on-site cath-lab); door-to-balloon = time between arrival to the first hospital (with or without on-site cath-lab) and balloon insufflations during primary PCI; symptom onset-to-balloon = time between first symptoms and balloon insufflations during primary PCI; \* $\chi^2$ -test; \*\*Kruskal-Wallis ANOVA by ranks

angina pectoris ( $p < 0.01$ ) and other MACE during follow up ( $p < 0.01$ ).

## Discussion

According to the experience from countries with successful nationwide implementation of PCI in STEMI, there are three realistic goals for pPCI networks at the national level: 1) pPCI should be used for >70% of all STEMI patients; 2) pPCI rates should reach >600 *per* million inhabitants *per* year; and 3) the existing PCI centers should treat all their STEMI patients by pPCI, i.e. should offer a 24/7 service<sup>3</sup>. The

TARGET study<sup>24</sup>, a multicenter, observational study that aimed to evaluate the epidemiological characteristics, management pattern and outcome of acute coronary syndrome patients in Greece, revealed that invasive management was performed in only 40.2% of patients during index hospitalization, concluding that there remains considerable room for improvement in expanding the implementation of invasive management in real world clinical practice. Comparing the treatment of STEMI patients between 2003 and 2009, the Polish Registry<sup>10</sup> showed that pPCI was performed in 51% and 78% of those patients, respectively. Investigating temporal trends in the treatment

Table 2. Results of treatment in the Croatian Primary Percutaneous Coronary Intervention Network

Variable	2005-2007	2008-2009	2010-2011	p*	p**
Postprocedural TIMI 3 flow	87.1%	82.1%	84.5%	<0.01	0.85
Mortality (in-hospital)	4.4%	4.9%	7.6%	<0.01	0.37
Mortality (6-month follow up)	1.2%	1.9%	2.3%	0.41	0.76
Angina pectoris (6-month follow up)	12.1%	21.6%	36.0%	<0.01	<0.01
MACE (other) (6-month follow up)	6.4%	23.2%	14.0%	<0.01	<0.01

MACE (other) = major adverse cardiovascular events (restenosis, reinfarction, re-PCI, coronary artery by-pass graft and cerebrovascular accident); \* $\chi^2$ -test; \*\*multivariate log-linear analysis

of acute STEMI, the authors from the USA<sup>25</sup> revealed an increase in pPCI and decrease in thrombolysis and coronary artery bypass grafting. The same trends between 2000 and 2007 have also been reported from Australia and New Zealand<sup>26</sup> for STEMI patients, reaching an increase in emergency revascularization with pPCI (from 11% to 27%) and in-hospital coronary angiography (from 61% to 76%). Despite the fact that the Croatian GDP is lower in comparison with the most developed countries, an increasing trend and a relatively high rate of STEMI patients treated with pPCI were found in this investigation. It is the consequence of the enthusiastic work of Croatian cardiologists to make the problem recognized among health authorities and other stakeholders. Also, it has enabled the Croatian pPCI Network results to approach the goals set at the beginning of this article.

The increasing age and percentage of female gender among STEMI patients over time, identified in the present study, have also been reported in other studies from different parts of the world<sup>7,10,12</sup>. These groups of patients have a higher risk of developing serious mortality predictors, i.e. cardiogenic shock and heart failure<sup>27</sup>. The increasing trend in the percentage of transferred patients, also recorded in our study, may have unfavorable effect on treatment results, but not according to all authors<sup>28-30</sup>.

Delay to reperfusion in STEMI patients is associated with a higher risk of mortality<sup>31,32</sup>. In the Polish Registry<sup>10</sup>, delay to reperfusion tended to reduce over time, which is probably one of the reasons for decrease in the proportion of patients presenting with pulmonary edema or cardiogenic shock in this registry. On the other hand, the longer symptom onset-to-door time in the Croatian pPCI Network over time could be one of the reasons for a different trend of increase in the proportion of STEMI patients treated with pPCI in cardiogenic shock. The reperfusion times recorded in this study, the door-to-balloon time in particular, were within the limits reported by most of other authors<sup>1,10,29,34</sup>. However, the trend of the door-to-balloon time shortening found here was not enough to lower the mortality rate in STEMI, as reported from several studies<sup>29,30,33-35</sup>. The lack of shortening of the more important total ischemic time because of extended prehospital delay in Croatian patients should stimulate additional actions (media campaign, educa-

tion of out-of-hospital medical staff, continuous quality control, etc.) at the local and national level. Ladwig *et al.*<sup>36</sup>, who report a constantly high prehospital delay in STEMI patients from the Augsburg Myocardial Infarction Registry over a 20-year observation period, emphasize a subgroup of elderly women as a target for improvement of this parameter. Finally, results from the MITRAplus and OPTAMI registry proved that prehospital delay could be an independent predictor of a longer door-to-balloon time<sup>33</sup>.

As in the first phase investigation of the Croatian pPCI Network<sup>14,15</sup>, the postprocedural TIMI 3 flow and in-hospital mortality rate, as well as the mortality and other MACE rate during six-month follow up recorded in this study are comparable with recent results from other pPCI networks<sup>10,13,26,29,37,38</sup>. Most of the latest studies report on decreasing trends in mortality and other complication rates. On the other hand, there are studies reporting results that remained stable over time<sup>11,35,39</sup>. It should be noted that these results depend very much on the risk profile of study patients. In the present investigation, worsening of the patient risk profile during the study period was the main reason why the final TIMI 3 flow, in-hospital mortality, and six-month mortality rate did not change significantly. Also, according to the literature<sup>3,18,19</sup>, less experienced low volume PCI centers could have worse results in the interventional STEMI treatment in comparison with high-volume centers. However, a higher patient risk profile and new PCI centers in the Croatian pPCI Network ensure treatment of acute STEMI for clinically and geographically wider groups of patients, which should be understood as a positive trend. Some of the reasons for the trend of significant increase in the rate of angina pectoris and other MACE during follow up could be found in changes in the strategy of pPCI during the study period (pPCI of the culprit lesion only) and higher availability of PCI centers for additional PCI during follow up after acute STEMI.

In conclusion, the Croatian pPCI Network continuously ensures very good results of treatment for ever greater number of STEMI patients despite worsening of their risk profile and opening of new, less experienced PCI centers. This study has confirmed that there is room for improvement, especially in shortening prehospital delay.

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#### Sažetak

### SEDMOGODIŠNJI TREND OVI U REZULTATIMA HRVATSKE MREŽE PRIMARNE PERKUTANE KORONARNE INTERVENCIJE

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Autori su istražili trendove u rezultatima Hrvatske mreže primarne perkutane koronarne intervencije (*primary percutaneous coronary intervention*, pPCI) između tri razdoblja (2005.-2007. (prva faza), 2008.-2009. (druga faza), 2010.-2011. (treća faza)). Prikupljeni su i izračunati podaci o 5650 bolesnika s akutnim infarktoma sa ST-elevacijom (STEMI) transportiranih ili izravno zaprimljenih i liječenih pomoću pPCI u 11 hrvatskih PCI centara tijekom toga vremena. Godišnji broj bolesnika s akutnim STEMI liječenih pomoću pPCI kontinuirano je rastao tijekom istraživanog vremena (581 prema 1272 prema 1949 bolesnika/godina). Rizični profil bolesnika se pogoršao kroz istraživano vrijeme: dob (60 prema 61 prema 63 godine;  $p < 0,01$ ), zahvaćanje prednje miokardijalne stijenke (43% prema 44% prema 51%;  $p < 0,01$ ), udio šoka (7% prema 9% prema 11%;  $p < 0,05$ ), postotak transportiranih bolesnika (42% prema 36% prema 46%;  $p < 0,01$ ). Dok se vrijeme od dolaska u bolnicu do uvođenja balona skraćivalo (108 prema 98 prema 75 min;  $p < 0,01$ ), vrijeme od nastupa simptoma do dolaska u bolnicu se produžavalo (130 prema 175 prema 195 min;  $p < 0,01$ ), ali bez statistički značajnog utjecaja na ukupno vrijeme ishemijske. Multivarijatna log-linearna analiza, eliminirajući utjecaj višeg rizičnog profila na rezultate liječenja, nije pronašla statistički značajne promjene u završnom protoku TIMI 3 (*Thrombolysis In Myocardial Infarction 3*), bolničkom pobolu i smrtnosti tijekom šest mjeseci, ali je pokazala značajan porast učestalosti pektoralne angine (12% prema 22% prema 36%;  $p < 0,01$ ) i drugih velikih nepovoljnih kardiovaskularnih događaja (*major adverse cardiovascular events*, MACE) (6% prema 23% prema 14%;  $p < 0,01$ ) za vrijeme praćenja. Zaključno, Hrvatska mreža pPCI kontinuirano osigurava vrlo dobre rezultate liječenja STEMI u ovoj slabije razvijenoj zapadnoj zemlji unatoč pogoršanju rizičnog profila liječenih bolesnika, kao i otvaranju novih i manje iskusnih PCI centara. Povećanje postotka MACE može se objasniti promjenama u strategiji pPCI tijekom vremena (pPCI samo za ciljne lezije) i većom dostupnošću PCI centara za dodatnu PCI tijekom praćenja nakon akutnog STEMI. Ipak ima prostora za poboljšanje, osobito u skraćivanju predbolničkog kašnjenja.

Ključne riječi: *Srčani infarkt – terapija; Koronarna bolest – terapija; Perkutana koronarna intervencija; Hrvatska*