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Patients with no significant lesions in coronary arteries and ST-segment elevation myocardial infarction have worse outcome than patients with non-ST-segment elevation myocardial infarction: analysis from PL-ACS Registry*

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Abstract

Background: Acute myocardial infarction (MI) in patients with chronic coronary artery disease is usually associated with a rupture of atherosclerotic plaque with subsequent thrombus formation and reduction or block of blood flow what leads to necrosis of myocardium supplied by occluded artery. In some patients with MI, there are no significant lesions in coronary arteries.

Aim: The comparative analysis of ST-segment elevation MI (STEMI) *vs* non-ST-segment elevation MI (NSTEMI) patients without significant angiographic lesions in short and long-term observation as well as identification of predictors of adverse long-term prognosis.

Methods: We analysed all subsequent patients hospitalised due to STEMI and NSTEMI, included in the Polish Registry of Acute Coronary Syndromes in years 2003–2006. Only patients without significant lesions in coronary arteries (stenosis ≤ 50%) were included. Patients were divided into two groups: STEMI and NSTEMI. In these groups we analysed in-hospital parameters, the frequency of cardiac adverse events during hospitalisation and mortality at 30 days, 6 months and 1 year.

Results: Patients with MI and no angiographically significant lesions in coronary arteries comprised 2.9% (n = 972) of all patients hospitalised due to MI (n = 32,959). Risk factors of coronary disease were observed more often in patients with NSTEMI. Mortality during hospitalisation, as well as after 30 days, 6 months, and 1 year was significantly higher in STEMI *vs* NSTEMI patients (3.5% *vs* 0.8%, 5.4% *vs* 0.8%, 8.15% *vs* 3.3%, 9.2% *vs* 4.6%).

Conclusions: 1. In-hospital and long-term prognosis was worse in STEMI *vs* NSTEMI patients. 2. The independent predictors of adverse long-term prognosis during 1 year observation are: older age, risk factors of coronary disease like diabetes mellitus and obesity, depressed left ventricular systolic function, cardiogenic shock and STEMI.

Key words: myocardial infarction, coronary arteries without significant lesions

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INTRODUCTION

Myocardial infarction (MI) in patients with coronary artery disease is most frequently related to unstable atherosclerotic plaque rupture with secondary thrombus formation. This results in flow reduction or cessation and leads to necrosis of the myocardium supplied by the occluded vessel. According to current definition, MI denotes any necrosis related to ischemia and elevation of troponin or cardiac isoenzyme of creatine kinase (CKMB) is a fundamental diagnostic criterion [1, 2]. In a proportion of patients with clinical, electrocardiographic and laboratory features of MI, coronary arteries do not show any significant lesions. This can be observed in 1–12% of the patients with referring diagnosis of MI [3–5]. The cause of MI in these patients has not been precisely clarified. Among potential mechanisms that can be responsible for such events, arterial spasm, spontaneously fibrinolysed coronary thrombus, coagulation disturbances, endothelial dysfunction and cardiomyocyte injury with subsequent necrosis resulting from inflammation have been proposed [6]. Differential diagnosis should include other diseases that can mimic MI, such as myocarditis, tako-tsubo syndrome or pulmonary embolism.

To date, few studies have been published concerning MI without significant changes in the coronaries and long-term prognosis of these patients. Published data include comparisons of such MI patients with typical MI patients undergoing primary coronary intervention. To date, there were no studies comparing ST-segment elevation MI (STEMI) with non-ST-segment elevation MI (NSTEMI) in patients without significant atherosclerotic lesions in the coronaries. The aim of the study was to compare in-hospital and late outcomes in these two patient groups.

METHODS

Study group

Consecutive STEMI and NSTEMI patients hospitalised between October 2003 and August 2006, included in Polish National Registry of Acute Coronary Syndromes (PL-ACS), were analysed. The PL-ACS is a prospective registy of patients with acute coronary syndromes, hospitalised in Polish hospitals. Recruitment commenced in 2003 and continues.

The analysis was carried out in a group of patients in whom no angiographically significant lesions were found in coronary arteries (≤ 50% of lumen narrowing). Myocardial infarction criteria included: chest pain > 30 min, elevated cardiac markers (troponin or CKMB) and the presence of electrocardiographic features of MI (in STEMI patients). Based on electrocardiographic features these patients were divided into two groups. In the first (STEMI) group, patients with electrocardiographic features of STEMI (i.e. ST elevation ≥ 0.1 mV in two or more consecutive limb leads and V4–V6 or ≥ 0.2 mV in V1–V3 precordial leads or new left bundle branch block [LBBB]) were included. In the second (NSTEMI) group, patients without ST elevation were included.

Studied parameters

Cardiovascular (CV) risk factors such as age, sex, arterial hypertension (AH), diabetes mellitus (DM), hypercholesterolaemia and smoking status were compared in the study groups. In-hospital data including adverse CV events were also analysed. One-, 6- and 12-month mortality rates were evaluated. Data concerning survival *vs* death in the long-term follow-up were collected from National Health Fund database. Additionally, factors adversely influencing prognosis were identified.

Definitions

The following definitions were used in the study, according to PL-ACS Registry protocol: AH was defined as diagnosed prior to index admission or as in-hospital blood pressure values of 140/90 or more; obesity was defined as body mass index (BMI) exceeding 30 kg/m^2; DM was defined as diagnosed prior to index admission or as in-hospital fasting glucose level of ≥ 126 mg/dL (twice) or ≥ 200 mg/dL at 2 hours of the oral glucose tolerance test; hypercholesterolaemia was defined as total cholesterol of ≥ 5.2 mmol/L (200 mg/dL), diagnosed either prior to index admission or during index hospitalisation; cardiogenic shock was defined as joint occurrence of the following criteria: (1) clinical (signs of shock, peripheral hypoperfusion), (2) haemodynamic (systemic systolic blood pressure < 90 mm Hg or 90–110 mm Hg while on intraaortic balloon pumping or inotropic drugs). Death (both in-hospital or late) was defined as all cause death.

Statistical analysis

Continuous variables with normal distribution are presented as means and standard deviations. The significance of differences between mean values of continuous variables presenting normal distribution was tested by Student t-test. Categorical variables are presented as numbers and percentages and were compared by χ^2 test (or, in case of small numbers, Yates correction was applied). Analysis of the long-term data was carried out with Kaplan-Meier method and by the log rank test. Factors influencing 12-month mortality were identified by multivariable regression analysis using Cox proportional hazard method, and the results are presented as relative risks and 95% confidence intervals. A two-tailed p value of < 0.05 was considered statistically significant. Statistical calculations were carried out with use of Statistica 7.1 package (StatSoft Inc., USA).

RESULTS

Out of 32,959 patients included in the PL-ACS Registry within the study period from October 2003 to August 2006, admitted for STEMI or NSTEMI, in whom coronary angiography was performed, 972 (2.9%) patients were selected according to predefined angiographic criteria and divided into two groups, depending on ECG findings. In the first group, 368 (37.9%) patients with STEMI were included. Group 2 consisted of 604 (62.1%) NSTEMI patients.

Table 1. Demographic and clinical characteristics of STEMI and NSTEMI patients

	NSTEMI (n = 604)	STEMI (n = 368)	P
Age [years]	60.5 ± 13.0	55.7 ± 15.6	< 0.0001
Female	289 (47.85%)	147 (39.95%)	0.016
Chest pain duration [h]:*			
< 12 h	347 (68.4%)	282 (83.2%)	< 0.0001
> 12 h	160 (31.6%)	57 (16.8%)	< 0.0001
Arterial hypertension	409 (67.7%)	198 (53.8%)	< 0.0001
Type 2 diabetes	85 (14.1%)	36 (9.8%)	NS
Hyperlipidaemia	258 (42.7%)	139 (37.8%)	NS
Obesity	98 (16.2%)	42 (11.4%)	0.038
Smoking	169 (27.98%)	137 (37.2%)	0.003
History of MI	78 (12.9%)	29 (7.9%)	0.015
History of CABG	31 (5.1%)	11 (2.99%)	NS
History of PCI	8 (1.3%)	5 (1.4%)	NS

*Data available for 507 NSTEMI and 339 STEMI patients; STEMI — ST-elevation myocardial infarction; NSTEMI —non-ST-elevation myocardial infarction; MI — myocardial infarction; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention

Table 2. Basic in-hospital clinical parameters in patients with STEMI and NSTEMI without angiographically signifcant changes in the coronaries

	NSTEMI (n = 604)	STEMI (n = 368)	P
Anterior infarction	–	135 (36.7%)	–
Aborted SCD prior to admission	12 (2.05%)	14 (4.1%)	NS
Pulmonary oedema on admission	14 (2.3%)	8 (2.2%)	NS
Cardiogenic shock on admission	4 (0.7%)	13 (3.5%)	0.001
Thrombolysis	3 (0.5%)	11 (2.99%)	0.002
Intraaortic balloon pumping	1 (0.2%)	3 (0.8%)	NS
Ejection fraction (mean):	52.2 ± 11.36	51.8 ± 11.30	NS
≥ 45%	100 (22.7%)	74 (28.35%)	NS
≤ 35%	49 (11.1%)	24 (9.2%)	NS
CK-MB [ng/mL], median (interquartile range)	28.5 (16–48)	46.0 (23–107)	< 0.0001
In-hospital cardiac arrest	6 (1.0%)	11 (3.25%)	0.015
IIb/IIIa inhibitors	4 (0.7%)	0 (0.0%)	NS
Duration of stay [days], median (interquartile range)	4 (3–7)	5 (3–7)	NS
In-hospital course			
Stroke	1 (0.2%)	5 (1.4%)	NS
Reinfarction	11 (1.8%)	8 (2.2%)	NS
Death	5 (0.8%)	13 (3.5%)	0.002
Death, reinfarction or stroke	17 (2.8%)	25 (6.8%)	0.003

CKMB — cardiac isoenzyme of creatine kinase; SCD — sudden cardiac death

Demographic and clinical characteristics of the study groups can be found in Table 1. The NSTEMI patients were older than patients with STEMI. More NSTEMI patients were female. In the NSTEMI group, the coronary risk factors were more prevalent, including AH, type 2 DM and obesity; moreover, history of MI was noted more frequently in this group. On the other hand, more STEMI patients were smokers.

In Table 2 basic in-hospital clinical parameters are presented. Fibrinolysis was more frequently administered in STEMI patients. The frequency of pulmonary oedema was similar in both groups, but STEMI patients more often developed cardiogenic shock. During in-hospital period more cases of cardiac arrest occurred in STEMI as compared to NSTEMI patients. Mean left ventricular ejection fraction

Table 3. Long-term mortality of STEMI and NSTEMI patients without angiographically significant coronary lesions

Mortality	NSTEMI (n = 604)	STEMI (n = 368)	P
1-month	5 (0.8%)	20 (5.4%)	< 0.0001
6-month	20 (3.3%)	30 (8.15%)	0.0009
12-month	28 (4.6%)	34 (9.2%)	0.0037

Abbreviations as in Table 1

(LVEF) during in-hospital period was similar in both study groups. A significantly higher median CKMB values were found in STEMI group.

In-hospital rates of complications such as stroke and reinfarction were comparable in the two groups. Between-group differences were noted regarding in-hospital mortality and combined endpoint including death, reinfarction and stroke. These adverse events occurred significantly more frequently in STEMI patients.

During the long-term follow-up, 1-, 6- and 12-month mortality rates were calculated, as shown in Table 3. At each of these timepoints, mortality rates were significantly higher in STEMI than in NSTEMI patients. The Kaplan-Meier 12-month survival curves are shown in Figure 1.

Additionally, a comparative analysis of STEMI and NSTEMI patients with or without cardiogenic shock was performed. The results were similar in the subgroups with cardiogenic shock whereas in the subgroups without cardiogenic shock, the mortality during long-term observation was significantly higher in STEMI patients (Table 4).

Multivariate analysis demonstrated that independent factors increasing 12-month mortality included age, type 2 DM, obesity, impaired LV systolic function, cardiogenic shock and STEMI (Fig. 2).

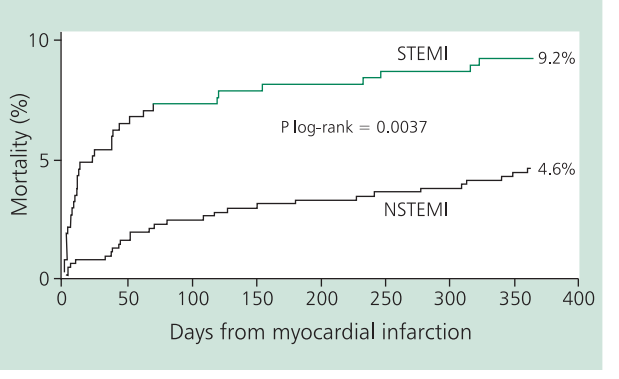

Figure 1. Kaplan-Meier 12-month survival curves in patients with STEMI and NSTEMI

DISCUSSION

We demonstrated that in the group of patients with angiographically nonsignificant changes in the coronary arteries, STEMI patients have worse long-term prognosis than those with NSTEMI. There is a lack of data concerning this issue in literature.

Clinical characteristics of MI patients without significant changes in the coronaries in our study are similar to clinical data from numerous studies comparing STEMI and NSTEMI patients treated by primary angioplasty. In these studies, NSTEMI patients are usually older, have more coronary risk factors and more comorbidities [7–10]. However, it is the age of MI patients without significant changes in the coronaries that draws attention. In the studied population the average age of STEMI patients was 55 years while in the NSTEMI group it was 60 years. Authors of studies concerning this issue point

Table 4. Prognosis in patients with STEMI and NSTEMI with or without cardiogenic shock

	Cardiogenic shock			Without cardiogenic shock		
	NSTEMI	STEMI	P	NSTEMI	STEMI	P
Patients no.	4	13		600	355	
In-hospital reinfarction	0 (0%)	1 (8%)	NS	11 (1.8%)	7 (2.0%)	NS
Stroke	0 (0%)	1 (8%)	NS	1 (0.2%)	4 (1.1%)	NS
Death	1 (25%)	5 (39%)	NS	4 (0.7%)	8 (2.3%)	NS
1-month mortality	1 (25%)	6 (46%)	NS	4 (0.7%)	14 (3.9%)	0.0003
6-month mortality	2 (50%)	6 (46%)	NS	18 (3.0%)	24 (6.8%)	0.0062
12-month mortality	2 (50%)	6 (46%)	NS	26 (4.3%)	28 (7.9%)	0.022

Abbreviations as in Table 1

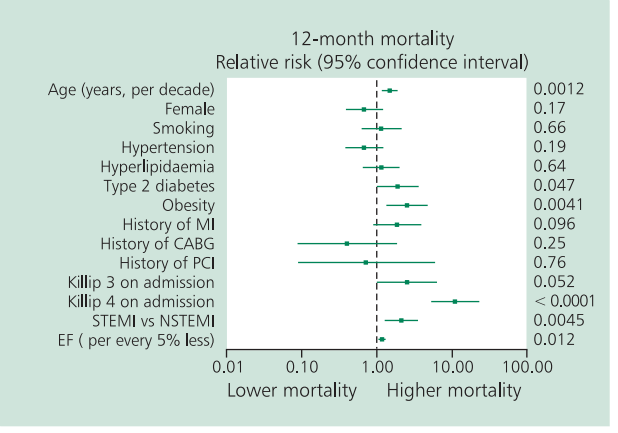

Figure 2. Multivariable analysis of parameters influencing 12-month mortality; abbreviations as in Table 1

out that MI with normal coronary angiogram occurs mainly in patients younger than 50 years, which is on average 10–15 years lower than the age of patients undergoing typical MI caused by unstable plaque rupture. This in turn can be related to less severe disease and better prognosis in this patient group [5, 11–13].

In our study, in-hospital mortality, as well as the composite endpoint consisting of death, reinfarction or stroke, were significantly higher in STEMI patients than in NSTEMI patients. Also, higher 1-, 6- and 12-month mortality rates in the STEMI group as compared to NSTEMI group were observed. Separate analysis that was carried out for STEMI *vs* NSTEMI patients when cases of cardiogenic shock were excluded showed a similar trend. This may be related to greater area of myocardial injury, as markers of myocardial necrosis were higher in this group than in NSTEMI patients. In studies in which typical MI patients were analysed, lower long-term mortality was observed in STEMI as compared to NSTEMI patients [9]. Also Montalescot et al. [7] point out to worse prognosis in NSTEMI *vs* STEMI patients. Similar observation was made by Poloński et al. [14]. The authors pointed out, however, that STEMI patients, after inclusion of age, sex, comorbidities and treatment method in the multifactorial analysis, had worse prognosis as compared to the NSTEMI group.

Studies published during the eighties and the nineties of the 20th century pointed to a very good long-term prognosis in MI patients without changes in the coronary arteries [4, 5, 15, 16]. Betriu et al. [16], Fournier et al. [15] and Ammann et al. [4] demonstrated 100% long-term survival in this patient group.

Larsen et al. [11] presented a different point of view and showed that 12-month mortality rate in the group of patients with normal coronary angiogram was 5.8% and was comparable with mortality of patients with ≤ 50% changes in the coronaries (2.9%) and with single- or two-vessel disease (3.3%). In a study by Bugiardini et al. [17], death or MI during 12-month follow-up occurred in 2.1% of NSTEMI patients without angiographically significant lesions in the coronaries.

Due to the lack of reports in the literature comparing STEMI and NSTEMI patients without significant lesions in coronary arteries our results cannot be put in the context of the results of other authors. However, the reason why no significant lesions are found in MI patients merits attention. One of them could be a spontaneously fibrinolysed thrombus that forms within the coronary tree. In the study groups, nearly 3% of the STEMI patients and 0.5% of the NSTEMI patients received thrombolysis ($p = 0.002$) This is a decidedly smaller percentage compared to other studies. For example, in the studies by Golzio et al. [5] or Ammann et al. [4] thrombolytic agents were administered in nearly 50% of MI patients, in a study by Ahmar et al. [18] — in 30% and in Germing et al. [12] analysis — in 8%.

In patients with suspected MI, in whom coronary angiography reveals no angiographically significant changes in the coronary arteries, there is a high probability of the presence of an inflammatory process in the myocardium and in the coronary arteries. Hakeem et al. [19] described a case of a 24-year old male who presented to hospital with symptoms suggestive of MI. The activity of CKMB and troponin I were elevated, LV systolic function was impaired. As no abnormalities were found in coronary angiography, the patient underwent magnetic resonance imaging scan, what resulted in the diagnosis of myocarditis and initiation of appropriate treatment.

A prerequisite for the diagnosis of MI according to its current definition is elevation of the markers of myocardial necrosis. One should be aware, however, that in many conditions, often with symptoms mimicking MI, cardiac troponin release occurs. Hence, it is possible that in a proportion of the studied population, particularly with NSTEMI, the presence of some other diseases was masked by the signs of MI.

Limitations of the study

There was no further stratification of the patients according to the presence of non-significant lesions of < 50% or lack of lesions (i.e. normal coronary arteries). Moreover, other potential causes of MI without changes in the coronaries were not known. This was related to the range of data and definitions used by the PL-ACS Registry.

CONCLUSIONS

Based on the comparative analysis of MI patients without significant changes in the coronaries in the STEMI and NSTEMI group, it was demonstrated that NSTEMI patients were older and that typical coronary risk factors were more frequently

seen in this group. In-hospital and long-term prognosis was worse in the STEMI group as compared to NSTEMI patients. In MI patients without significant lesions in the coronary angiogram, independent factors adversely influencing 12-month prognosis include older age, the presence of coronary risk factors such as type 2 DM and obesity, impaired LV systolic function, cardiogenic shock and STEMI. This points to necessity of applying adequate and detailed diagnostic strategy in MI (especially STEMI) patients without significant lesions in the coronary arteries, the need for scrutinising the pathogenesis of this phenomenon and administration of adequate treatment.

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Zawał serca z uniesieniem odcinka ST rokuje gorzej niż zawał serca bez uniesienia odcinka ST u chorych bez istotnych zwężeń w tętnicach wieńcowych: analiza z Rejestru PL-ACS*

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Streszczenie

Wstęp: Zawał serca (MI) u osób z chorobą wieńcową jest najczęściej związany z pęknięciem niestabilnej blaszki miażdżycowej z wtórnym tworzeniem się zakrzepu, co skutkuje zmniejszeniem bądź przerwaniem przepływu, prowadzącym do martwicy obszaru mięśnia sercowego zaopatrywanego przez zamknięte naczynie. U części chorych z klinicznymi, elektrokardiograficznymi i laboratoryjnymi cechami MI tętnice wieńcowe nie wykazują istotnych zmian angiograficznych. Dokładna przyczyna tego zjawiska nie została do końca wyjaśniona.

Cel: Celem pracy była analiza porównawcza chorych z MI z uniesieniem odcinka ST (STEMI) i MI bez uniesienia odcinka ST (NSTEMI) bez istotnych zwężeń w tętnicach wieńcowych w obserwacji wewnątrzszpitalnej i odległej oraz ustalenie czynników wpływających niekorzystnie na rokowanie odległe.

Metody: Analizie poddano kolejnych chorych hospitalizowanych z powodu STEMI i NSTEMI w latach 2003–2006 włączonych do Ogólnopolskiego Rejestru Ostrych Zespołów Wieńcowych. Właściwą analizę ograniczono do grupy osób bez istotnych angiograficznie zmian w tętnicach wieńcowych (zmiany ≤ 50%) w koronarografii. W zależności od obrazu elektrokardiograficznego chorych tych podzielono na dwie grupy: STEMI i NSTEMI. Grupy porównywano pod względem częstości występowania czynników ryzyka choroby wieńcowej. Analizie poddano również parametry okresu wewnątrzszpitalnego i występowanie niekorzystnych zdarzeń sercowo-naczyniowych w trakcie hospitalizacji. W poszczególnych grupach oceniano śmiertelność 1-, 6- i 12-miesięczną.

Wyniki: Chorzy z MI bez istotnych zwężeń w tętnicach wieńcowych stanowili 2,9% osób leczonych w analizowanym okresie z powodu MI. U pacjentów z NSTEMI częściej występowały czynniki ryzyka choroby wieńcowej. Zarówno śmiertelność wewnątrzszpitalna, jak i 1-, 6- i 12-miesięczna były istotnie wyższe w grupie chorych z STEMI niż NSTEMI (odpowiednio 3,5% *v*. 0,8%; 5,4% *v*. 0,8%; 8,15% *v*. 3,3%; 9,2% *v*. 4,6%).

Wnioski: Rokowanie w obserwacji wewnątrzszpitalnej i odległej było gorsze w grupie chorych z STEMI w porównaniu z grupą z NSTEMI. U chorych z MI bez istotnych zmian w tętnicach wieńcowych niezależnymi czynnikami pogarszającymi rokowanie w obserwacji 12-miesięcznej są starszy wiek, obecność czynników ryzyka choroby wieńcowej, takich jak cukrzyca typu 2 i otyłość, obniżona funkcja skurczowa lewej komory, wstrząs kardiogenny oraz STEMI.

Słowa kluczowe: zawał serca, tętnice wieńcowe bez istotnych zwężeń, rokowanie 12-miesięczne

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