Gender Differences in Acute Coronary Syndrome in Serbia before Organized Primary PCI Network Service

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ORIGINAL PAPER SUMMARY
Introduction. Numerous studies were focused on coronary artery disease, most of them in the male population and it seems that data on gender differences in CAD were extrapolated from these studies. Goal. The multi-center prospective study was designed to analyze gender differences in features, clinical presentation, and early in-hospital mortality in patients with acute coronary syndrome (ACS) admitted to coronary units in 50 hospitals in Serbia, during a 12 month-period. Methods. The data were collected from the central register of ACS, admitted to coronary units and intensive care units during a 12-month period. The study protocol included all consecutive patients with diagnosis of ACS. In the study 12,094 patients were analyzed, 7,639 men and 4,455 women. Women were significantly older than men in all ACS manifestations (p<0.001). Results. Incidence of myocardial infarction (MI) in women was the highest between the 7th and 8th life decade, while in men the highest incidence is observed between their sixties and seventies. Equalization in the incidences of MI in men and women is observed between the sixth and seventh life decades. There were significant differences in the incidence of fibrinolytic therapy and heart failure (p<0.001) in favor of women. Women with unstable angina and NSTEMI had higher in-hospital mortality (2.4% vs. 1.7% and 9.0% vs. 7.1%, respectively), without statistical significance, while in STEMI the difference was highly statistically significant (16.1% compared to men 10.1%), p<0.001. Discussion. The mean age of the greatest frequency of occurrence of MI has been shifted five years earlier in the population of women, different from other studies related to the analysis of MI by gender differences. Conclusion. Female mortality was significantly higher compared to men, and the highest mortality was found in women over 75. Precisely this female age subgroup, aged 75 and over, has the highest mortality. Risk factors are the same for men and women, but according to the Framingham study, CAD begins 10-20 ys before in men compared to women and myocardial infarction even 20 years earlier in men than in women (5, 6).

The aim of the study was to analyze gender differences in features and clinical presentation in 12,598 patients with acute coronary syndrome admitted to coronary units in 50 hospitals in Serbia, during a 12 month-period of 2005, before the organized primary PCI network service.

2. METHODS
Data were collected from the central register of acute coronary syndrome from 50 coronary units in Serbia during a 12-month period. The study was designed as a multi-center prospective observational study. The study protocol included all consecutive patients with diagnosis of acute coronary syndrome (ACS).

The data were collected using questionnaire designed by the National Working Group on ACS. The questionnaire was addressed to all subjects with symptoms of ACS, admitted to coronary units and intensive care units during the analyzed time. The questionnaire was filled out based on the principles...
of choosing predefined variables. At the end of a month, all the collected questionnaires were sent to the central registry at the National Health Institute of Serbia. Among the 12,598 patients admitted to hospital coronary and intensive care units with diagnosed acute coronary syndrome during a 12-month period, 12,094 were analyzed. Five hundred and four (4%) patients were lost from the follow-up due to incomplete data source. The data were analyzed with respect to gender differences.

- Parameters of the analysis
- Unstable angina pectoris
- Myocardial infarction

Acute coronary syndrome was defined as unstable angina pectoris and acute myocardial infarction (STEMI and non-STEMI), according to the anamnesis and laboratory findings (CK, CK-MB and troponin level).

According to ECG changes, myocardial infarction was classified as STEMI, non-STEMI infarction.

The localization of myocardial infarction was defined by standard ECG changes. Anteroseptal, anterolateral, expanded anterior, and apical myocardial infarction were regarded as anterior localization of myocardial infarction. Myocardial infarction of posterior, inferior, inferoposterior localization, and inferior localization with myocardial infarction of the right ventricle were regarded as inferoposterior localization of myocardial infarction.

### 2.1. Time between beginning of the chest pain and admittance to hospital

The time between the beginning of the chest pain and admittance to hospital was calculated for each patient. Admission to hospital of patients in the period up to 6 h was considered as the time within the limits of tolerance, whilst the time up to 1 h was considered as optimal. Time intervals were defined as up to 1 h, between 1 hour to 6 h, and over 6 hours.

### 2.2. The mode of arrival to the coronary unit

There were several options for the mode of arrival to the hospital: transportation by its own facilities and the first contact with a doctor at the hospital, patient sent by a primary care doctor, patients sent from other in-hospital departments, sent from other hospitals, and patients transported by city emergency facility.

### 2.3. Risk factors

Behavioral risk factors registered in study were: smoking, obesity, sedentary lifestyle, and stress, while clinical risk factors registered in study were: hypertension, diabetes (type I and II) and hyperlipoproteinemia.

Hypertension was defined by history, previous medical documentation or hospital measurements of systolic blood tension of over 140 mmHg and diastolic blood tension of over 90 mmHg.

Hyperlipoproteinemia was defined by history and medical documentation as well as by hospital measurements of triglycerides of over 1.8 mmol/l, total cholesterol exceeding 5 mmol/l, HDL below 1.0 mmol/l in men and 1.3 mmol/l in women, LDL exceeding 3.4 mmol/l.

Diabetes was defined by previous medical history and documentation as well as by hospital measurements of glycaemia of over 6.1 mmol/l or pathological OGTT.

Smokers were defined by previous history of smoking more than 5 cigarettes per day during the previous year or for several years.

Obesity was defined according to body mass index, exceeding 25.8 kg/m² for women and 26.4 kg/m² for men. Sedentary lifestyle was defined according to history of cumulative daily amount of physical activity (strolling, fast walking, working in the garden, swimming, cycling) less than 30 minutes per day.

Stress was measured by functional stress classification scale – SSFC (Subjective Stress Functional Classification): class I- without stress, class II – not more than usually, class III – more intensive stress than usually having negative influence on daily activities, class IV– the most intensive stress in life.

Heart failure: Heart failure was classified according to NYHA classification.

Therapy: Fibrin therapy administration in patients with STEMI

In-hospital mortality: Age subgroups were defined using 10-ys intervals.

### 2.4. Statistical analysis

The study was reviewed and approved by The Institutional Review Board. All procedures were explained to the parents and participants before obtaining written consent.

The continuous data are expressed as mean ± SD, with 5th and 95th centile ranges to facilitate comparison with the data belonging to controls. For statistical analysis, we used descriptive analysis, testing of the hypotheses and correlation analysis. Statistical analysis was carried out by unpaired t-tests and chi-test between groups. The statistical significance was defined as p<0.05. Statistical computer package SPSS 15 was used.

### 3. RESULTS

Among the 12,598 patients admitted to hospital coronary and intensive care units with diagnosed acute coronary syndrome during a 12-month period, 12,094 were analyzed, 7,639 men and 4,455 women. Five hundred and four (4%) patients were lost from the follow-up due to incomplete data source.

Women were significantly older than men in all acute coronary manifestations. Average age of the men with acute coronary syndrome was 61.46±11.38 ys (18-94 ys range), and of the women 66.42 ±10.73 (19-94 ys range).

Average age of the men with STEMI was 61.19±11.27 ys and for women 66.76 ± 10.85 ys (p=0.001). Women with NSTEMI were also significantly older than men (6.33 ± 10.45 ys vs. 62.65±11.27 respectively) (p = 0.001). Similarly, the women with unstable angina pectoris were also significantly older than men (61.15±11.11 ys vs. 65.36±10.63 ys, respectively) (p<0.01).

Incidence of myocardial infarction in women is the highest between the 7th and 8th life decades, but in men the highest incidence is observed between their sixties and seventies. Equalization in the incidences of myocardial infarction in men and women is observed between the sixth and seventh life decades. STEMI was diagnosed in 6,135 pa-
patients (50.7%), non-ST myocardial infarction was diagnosed in 2,632 patients (19.6%), and unstable angina pectoris in 3,597 (29.7%) patients.

All the manifestations of ACS were more frequently observed in the male population (p<0.001).

Only 19% of the men and significantly lower proportion (14.2%) of the women with STEMI were admitted to the hospital during the first hour after the anginal pain had started (p<0.001). There is also a significant difference in the proportion of men (65.1%) and women (57.2%) admitted to the hospital due to anginal pain during 1-6-hour period, again in favor of the male population (p<0.01).

There was no gender difference in localization of myocardial infarction: in both groups inferoposterior localization was more frequent.

There was a significant gender difference in the incidence of fibrinolytic therapy (p<0.001). Only 6,135 patients (36.2%) with STEMI received fibrinolytic therapy – streptokinase, 1,583 men (36.2%) with STEMI received fibrinolytic therapy (p<0.001). Only 6,135 patients (36.2%) with STEMI received fibrinolytic therapy (p<0.001).

Risk factors, with the exception of stress and smoking, are more frequent in women vs. men. There was no gender difference in the incidence of hyperlipoproteinemia.

Heart failure was observed more frequently in women. Heart failure was present in 2,496 (29.4%) patients with myocardial infarction, in 1,043 women (34.5%) and in 1,453 men (26.5%), p<0.001. Early in-hospital mortality in patients with ACS was 8.3%.

The highest mortality was in the patients with STEMI (12.2%), followed by the patients with non-STEMI (7.8%) and unstable angina pectoris (2.0%).

The women with unstable angina pectoris had higher early in-hospital mortality (2.4%) compared to men (1.7%) and with non-STEMI (9.0% vs. 7.1%), but without statistical difference. On the other hand, the women with STEMI had statistically higher mortality (16.1%) compared to men (10.1%), p<0.001.

4. DISCUSSION

There was a smaller proportion of women in the analyzed group, similar to other reported studies. Women were older than men. The greatest number of female patients was at the age of 70-79 (36.7%). In the younger age subgroups, male to female ratio was 3:1 until the middle of the sixties while they are gradually equalized in the older age subgroups. Higher incidence of myocardial infarction in male patients in the similar age period is also reported by other investigators. The results of the study related to the age of our female and male patients with acute myocardial infarction should be emphasized. The mean age of our female patients with acute myocardial has not been shifted by ten years compared to men as reported in other studies but only by five years. This implicates that myocardial infarction appeared earlier in the observed group of women and equated with the frequency of infarction in the observed population of men five years earlier than reported in other studies. In other studies, similar relationship was shown, but in a much older population of 70-79 years of age (7,8).

All the risk factors, with the exception of stress and smoking, were more frequent in women, while the incidence of hyperlipoproteinemia was similar in men and women. The highest incidence of risk factors was in patients aged above 65. The greatest number of patients had three or more risk factors (35%), 28% of patients had two risk factors, 24% of patients had only one risk factor, and 14% had none of them. Women had three or more risk factors. Sedentary lifestyle is more frequent in the female population, related to their older age, similar to the reported results (8,9).

Diabetes mellitus is the risk factor highly related to coronary artery disease and cardiovascular complications, being an equivalent of CAD (10,11). It is a very important risk factor in the male population in all age subgroups. Diabetes mellitus was more frequently observed in the female population, similar to other investigations (12, 13). As many as 29% of female patients with myocardial infarction aged 45 to 65, who died of cardiovascular complications, had diabetes.

Smoking was significantly less frequently observed in females, especially in older subgroups. Similarly, sedentary lifestyle was more frequent in older women subgroups, reported also in previous studies (3,4).

In the group of patients with acute coronary syndrome hypertension was present in as many as 50% of patients, but significantly more frequently in the female population (65.3%).

Anteroseptal localization of myocardial infarction was less frequently observed in both groups. There was no difference in the incidence of STEMI and NSTEMI in the male and female populations.

The time between the beginning of anginal pain and hospital admittance was longer in the female population. This difference was seen both in the 1st, and 1-6th hour after the beginning of the anginal pain. Women have come later to the hospital compared to men, most often 6 h after the beginning of the pain. Consequently, this has led to a smaller incidence of thrombolytic therapy. This is probably due to atypical symptoms and pain neglecting in the female population, leading to a delay in the diagnosis and hospitalization, similar to other reported data (15,16,17).

Heart failure was more frequently observed in women. Mortality in myocardial infarction was statistically higher in the female population (16.1%) compared to the male population (10.1%) in all age subgroups, as was reported by other authors (18-20). The explanation could be found in the larger number of risk factors in the female population compared to men, although female mortality is higher even in the gender groups with the same

<table>
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<tr>
<th>Outcome</th>
<th>male n</th>
<th>%</th>
<th>female n</th>
<th>%</th>
<th>Total n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived</td>
<td>7093</td>
<td>92.9%</td>
<td>3996</td>
<td>89.7%</td>
<td>11089</td>
<td>91.7%</td>
</tr>
<tr>
<td>Lethal outcome</td>
<td>546</td>
<td>7.1%</td>
<td>459</td>
<td>10.3%</td>
<td>1005</td>
<td>8.3%</td>
</tr>
<tr>
<td>Total</td>
<td>7639</td>
<td>100.0%</td>
<td>4455</td>
<td>100.0%</td>
<td>12094</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

TABLE 2. Outcome in patients with acute coronary syndrome by gender
number of risk factors (21, 22). Women have come to the hospital later than men and, even if they come on time, the symptoms are often unrecognized, which consequently leads to a delay in the diagnosis of ACS. Having been admitted to the hospital later than men, the incidence of thrombolytic therapy administration was lower, leading to its poor efficacy (23–25).

The results of this study have shown that there is a significantly smaller proportion of the female population in patients with all forms of acute coronary syndrome. The mean age of the greatest frequency of occurrence of myocardial infarction has been shifted five years earlier in the population of women compared to the population of men, which is different from other studies related to the analysis of myocardial infarction by gender differences. Women were older and with a higher number of risk factors than men. Female mortality was significantly higher compared to the male population.

Considering the above results, it is necessary to act and improve health programs and organization of the primary and secondary healthcare for patients that are not eligible or cannot be sent for primary PCI. Higher attention should be paid to the female population, since they are at risk in acute coronary syndrome. Primary and secondary prevention should be more effective, promoting healthy lifestyle and avoiding behavior at risk. Continuous educational programs dedicated to women but also to doctors should be organized on a regular basis, emphasizing atypical chest pain presentation in the female population. Although women are older in myocardial infarction, more aggressive therapy in myocardial infarction should be considered in the female population, since studies have shown that early PCI and stent implantation in myocardial infarction can reduce early mortality in the female population.

REFERENCES

1. WHO. The World Health Report 2008—primary Health Care