

Specific and Gender Differences between Hospitalized and out of Hospital Mortality due to Myocardial Infarction

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ABSTRACT

In this paper, the authors evaluate gender related differences of myocardial infarction mortality before and after hospital admittance. Myocardial infarction mortality in the Clinical Hospital Split in the seven years period between 2000 and 2006, have been analyzed together with out of hospital sudden death patients with acute myocardial infarction established during autopsy. During the seven year period between 2000 and 2006, 3434 patients were treated for myocardial infarction in the Split Clinical Hospital, 2336 (68%) males and 1098 (32%) females with a 12% total mortality (427 patients). The annual number of hospitalized persons has been increasing during that period (474 in yr. 2000 vs. 547 in yr. 2006), while mortality decreased from 15% in 2000 to 9.6% in 2006. Female patients had significantly higher hospital mortality than male patients, (228 or 21% vs. 202 or 9%, $p < 0.05$). Women also had significantly higher total AMI mortality (23.7% vs. 15.7%, $p < 0.05$). Anterior myocardial infarction with ST elevation in precordial leads had significantly higher mortality (19%) compared to patients with lateral (11%), inferior (10%) myocardial infarction with ST elevation and also NSTEMI (4%) mortality $p < 0.05$. Female patients more frequently die in hospital, 84% (230) than out of hospital 16% (43). From the total number of AMI deaths (388) in male patients, 56% (217) were in hospital and 44% (171) out of hospital ($p < 0.001$). Men had significantly higher prehospital mortality rate than women (81% vs. 19%, $p < 0.05$). Men also more frequently died from ventricular fibrillation (22% vs. 10%, $p < 0.05$), while women died more frequently of heart failure, cardiogenic shock, and myocardial rupture (33% vs. 15% $p < 0.05$). Regarding the total number of deaths from myocardial infarction men had significantly higher prehospital mortality compared to women (178 or 7.3% vs. 43 or 3.7%, $p < 0.05$). Anterior myocardial infarction had a significantly higher rate in patients dying pre-hospital (58%), in contrast to inferior (36%) and lateral myocardial infarction with ST elevation (6%) $p < 0.05$. We have concluded that male patients die more frequently within the first few hours of AMI mostly due to malignant arrhythmias, while female patients died in sub acute stage due to heart failure while being hospitalized. Nevertheless total mortality of AMI remains significantly higher in women.

Key words: myocardial infarction, mortality, gender

Introduction

Death due to coronary disease in Croatia, and in the middle Dalmatian area, has been constantly growing during the last few decades. The number of patients with myocardial infarction (MI) has been on the increase for the last twenty five years. Advanced medical treatment has reduced myocardial infarction hospital mortality, and together with continuous preventive measures has contributed to extend the life expectancy of the inhabit-

ants of Croatia Economic transition and the onset of the Consumer Society have increased the level of stress for the last fifteen years¹⁻⁵. An increased number of patients with hypertension, hypercholesterolemia, and smoking among patients with coronary artery disease, in the middle Dalmatian area and Croatia, with respect to other developed European countries, indicates the insufficient coronary risk factors prevention⁶⁻⁹.

Around 30% of patients died from acute myocardial infarction and more than a half of them before reaching hospital¹⁰. Women had better pre-hospital survival, higher hospital mortality and, roughly, equal mortality after hospital discharge.

Late arrival to the coronary care unit after onset of MI, increases the overall mortality, especially in the pre-hospital segment.

Myocardial infarction mortality depends on the size and localization of infarction, myocardial function, and susceptibility to malignant arrhythmias, sensitivity to pain, and patient age and gender¹².

In respect to the complexity and diversity of influential factors, this research will be focused on pre-hospital and hospital mortality with respect to age, gender and the localization of the myocardial infarction.

Patients and Methods

During the period between January 1, 2000 and December 31, 2006, the total mortality of all acute myocardial infarction patients hospitalized at The Department of Cardiology – Clinical Hospital Split has been analyzed, with respect to the patient’s age and gender, localization of infarct, as well as to the causes of death. Data has been gathered from the case-histories.

Diagnosis of myocardial infarction has been established on the basis of anamnesis data, characteristic changes in the electrocardiogram, and increased levels of the so called »specific cardiac enzymes« (CPK 2x normal, MB-CPK >10% CPK, increased levels of troponin) – the hallmarks of the myocardial necrosis¹⁰. The localization of infarction has been determined according to electrocardiograms. Elevated ST segment 0.1 mV in precordial leads (V1–V4) marked the anterior myocardial infarction (STEMI). The quoted changes in II, III and aVF marked inferior infarction, while the same changes in leads I, aVL; V5–V6 marked the lateral myocardial infarction. Posterior myocardial infarction which counts for 1–2%, has been included in the group of the inferior myocardial infarctions. Patients with ST segment changes (inverted T waves and ST segment depression) in the electrocardiogram have been considered to have non ST elevation myocardial infarction (NSTEMI). In the patients that have died before reaching hospital, fresh thrombi in coronary arteries and histological finding of myocardial necrosis have been established on autopsy, confirming the diagnosis of acute myocardial infarction as the cause of death¹³. Data has been obtained in »Pathology and forensic medicine institute Clinical Hospital Split«.

The results obtained are presented graphically, and statistically processed. Level of significances has been set to $p < 0.05$.

Results

In the period from 1 January 2000 to 31 December 2006 3.434 patients have been hospitalized in the clinical

hospital Split because of acute myocardial infarction, 2.336 (68%) among them men and 1.098 (32%) women. The average age of men was 61.2 ± 9.6 , and that of women 66.5 ± 10.7 . Mortality among men was 9%, and 21% among women.

The number of hospitalized patients shows a constant tendency of increase from 474 in 2000 to 547 in 2006, while hospital mortality tends to decrease, from 15% in 2000 to 9.5% in 2006. $\chi^2 = 14.2$, $p < 0.05$. Fig. 1.

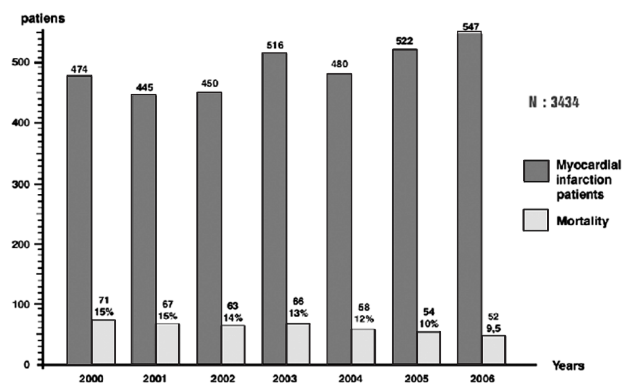


Fig. 1. Annual number of hospitalized myocardial infarction patients and mortality

Myocardial infarction with ST elevation was found in 69% hospitalized patients, with anterior (30%) and inferior (28%) localizations almost equally represented, while the frequency of lateral MI was significantly lower (11%). NSTEMI frequency was 25%. The significantly largest mortality was among the patients with anterior MI localization (18%) in respect to (10%) inferior and lateral localization (11%). $\chi^2 = 29$, $p < 0.001$ NSTEMI possesses the lowest mortality (4%). $\chi^2 = 59$, $p < 0.001$. Fig. 2.

The cause of death analysis in patients with MI with respect to gender has significantly shown a more frequent occurrence of ventricular fibrillation in men than in women (44%, towards 21%) $\chi^2 = 26.6$, $p < 0.01$, while

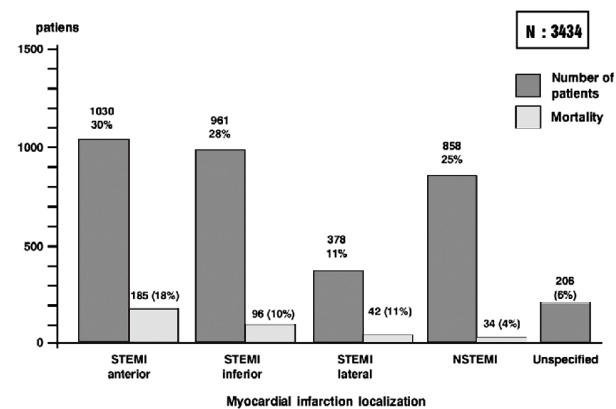


Fig. 2. Myocardial infarction localization; percentage and mortality, University hospital Split 2000–2006.

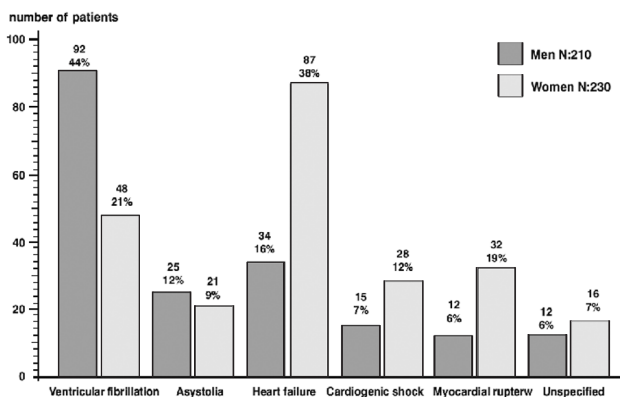


Fig. 3. Myocardial infarction dying mechanism in men and women in University hospital Split 2000–2006.

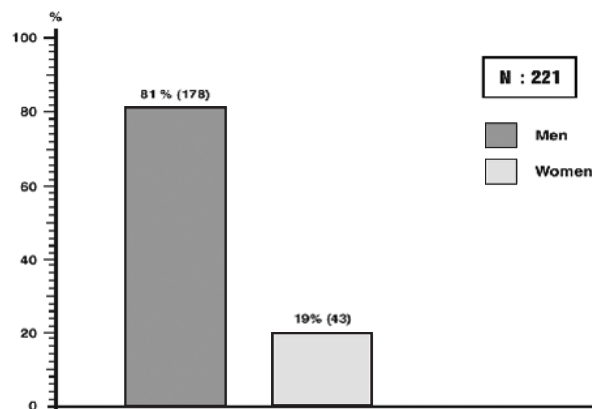


Fig. 4. Mortality before reaching hospital in men and women in Split region.

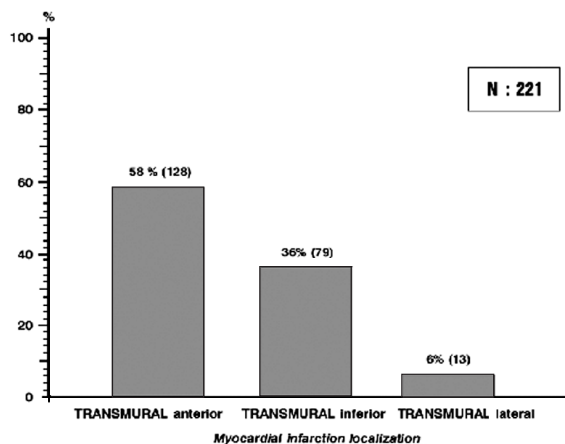


Fig. 5. Myocardial infarction localization in men and women died before reaching hospital.

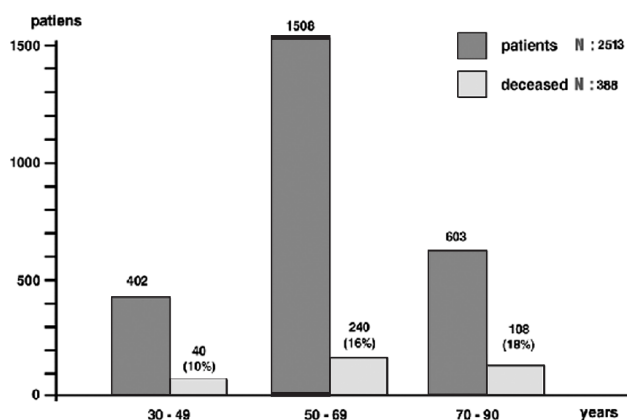


Fig. 6. Number of men died of myocardial infarction according to age groups in Split region 2000–2006.

women more frequently die from heart failure, cardiogenous shock, and myocardial rupture (64% vs. 29%) $\chi^2=53.5$ $p<0.01$. Fig. 3.

According to autopsy finding in patients who died outside of hospital, there are four times more men than women among them. Fig. 4.

The Town of Split region has an out of hospital MI mortality 7/100.000 (95% CI: 4.4–9.6). Men had 11.2/100.000 (95% CI: 6–16.4) MI out of hospital mortality, women had 2,6/100.000 (95% CI 0.2–5)

Among the patients who died before arriving to hospital, anterior myocardial infarct (58%) is significantly mo-

re frequently occurring in respect to inferior (36%) and lateral (6%). Fig. 5.

The total sum of myocardial infarction patient mortality before reaching hospital is significantly larger in men than in women (6.0% towards 3.8%) $p<0.05$. while hospital mortality is significantly larger in women (20% towards 8.4%) $p<0.05$.

The total mortality in women was also significantly higher in respect to the mortality in men (24% towards 15.4%) $p<0.05$. Table 1.

Annual MI morbidity in men was 159/100.000 (95% CI: 139–178), and 69/100.000 (95% CI: 56–81) in women,

TABLE 1
NUMBER OF PATIENTS WITH MYOCARDIAL INFARCTION AND MORTALITY IN SPLIT REGION

	Men	Women	p
Number of patients	2514	1141	
Died out of hospital	178 (6%)	43 (3.8%)	<0.001
Died in hospital	210 (8.4%)	230 (20%)	<0.001
Total	388 (15.4%)	273 (24%)	<0.001

implying that annual MI morbidity was 2.3 times higher in men than in women. Overall MI morbidity was 113/100.000 (95% CI: 101–124).

Age group analysis shows that men mostly died between the ages 50 and 60, while women almost equally died between the ages 50 and 69, and between the ages 70 and 90. Figs. 6 and 7.

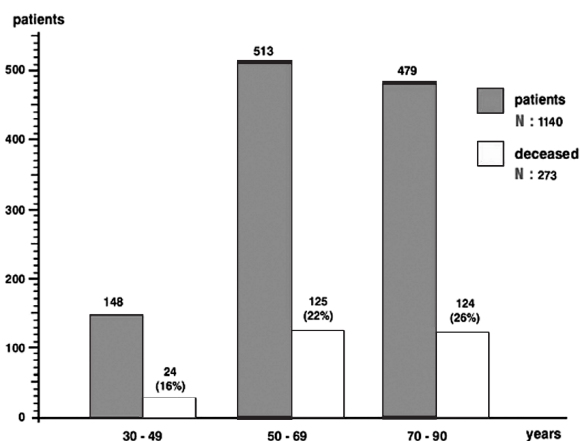


Fig. 7. Number of women died of myocardial infarction according to age groups in Split region 2000–2006.

Significantly, the lower MI mortality in both groups was between the ages of 30 and 49 ($\chi^2=5.6, p<0,05$ and $p<0,01$). MI morbidity was 2–3 higher in men than in women in all age groups. Table 2.

TABLE 2
AVERAGE MYOCARDIAL INFARCTION ANNUAL MORBIDITY (ON 100.000 INHABITANTS, CI 95%) ACCORDING TO GENDER AND AGE GROUPS IN SPLIT REGION 2000.–2006.

Age groups	Men	Women
30–49	86 (60–113)	32 (16–48)
50–69	443 (372–513)	138 (100–175)
70–90	587 (440–734)	268 (193–343)

According to official data compiled in 2001, the Split region had 463,656 inhabitants, 226.131 men, and 237.545 women. There were 66.501 men and 66.373 women between the ages 30 and 49, and 48.657 men and 53.176 women between the ages 50 and 69 and 14.672 men compared to 25.550 women between the ages 70 and 90.

Discussion

The obtained results of this retrospective study for the seven-year period, between 2000 and 2006, demonstrates that the number of hospitalized men with MI in The Clinical Hospital Split was more than twice that of the number of hospitalized women (68% towards 32%).

The number of hospitalized patients with MI has shown an annual growth tendency, while hospital mortality tends to decrease.

In the conducted research women were on average five years older than men (66 towards 61 yr/age).

The twice larger representation of men among MI patients can be attributed to the preventive effect of estrogen on the atherogenesis in women during the fertile period, as well as the significantly larger levels of high density lipoproteins in women¹⁰.

Therefore, the atherosclerotic process on coronary arteries in men is more accelerated, which explains why the male persons with myocardial infarction are, on average, five years younger than women.

A stressful lifestyle induced the appearance and intensity of the risk factors, thus accelerating atherogenesis in coronary arteries¹⁰.

Due to the use of modern drug treatment, and following the introduction of percutaneous coronary interventions in acute MI, mortality significantly decreased between 2000 and 2006, from 15% to 9.5%.

In the developed countries of Europe hospital MI mortality descended to 7%¹. MI Mortality in Clinical Hospital Split was 9.5% in 2006.

According to our study findings the largest mortality was in patients with anteroseptal STEMI (18%), and with lateral (11%) and inferior STEMI (10%). The smallest mortality was in patients with NSTEMI (4%).

That corresponds with statement that mortality from MI is in correlation with the size of the myocardial necrosis and the occluded coronary artery related to the irrigative area. Greater necrotic area considerably damages the left ventricular function which additionally reduces coronary circulation and facilitates conditions for malignant arrhythmias and heart failure¹⁰. Research has shown that the largest number of men die from MI between the ages 50 and 70. Women almost equally die at the ages between 50 and 70, and 70 and 90. American research has shown that men have significantly higher MI morbidity and death rate at the ages from 30 to 75.

Research results indicate that pre-hospital MI mortality in men is almost twice the mortality of women (7.0% vs. 3.7%). However the hospital mortality in women is two-and-a-half times greater than in men (21.2% vs. 8.4%). Therefore, the total mortality in women is significantly higher than mortality in men (25% towards 15.4%). After the age of 75, MI morbidity, and there with the number of the deceased, is larger in women than in men¹⁰. This was explained by faster atherogenesis in women after menopause, and by the fact that the men with increased risk already had MI. Even in highly developed countries acute MI mortality remains about 30%, with prehospital mortality counting for more than half of this number¹⁵.

Results of our study shows that men have a higher pre-hospital mortality, while the hospital mortality in women is significantly higher, and surpasses the men's

pre-hospital mortality, thus the overall MI mortality in women remains higher.

Considering that of the total annual IM mortality, 38% occurs within 2 hours after onset of the disease^{16–18}. Although the hospital mortality in the last two decades has been reduced in most countries, 10–15% of patients die throughout the hospital medical treatment and additional 5–10% in the first year after the MI^{16–18}.

Women MI mortality, according to various studies, is estimated in the range from 9% to 42%. Although some do not recognize gender difference in the severity and complexity of coronary artery lesions, with equal medical treatment in both genders, women mortality remains two to threefold higher than in men^{19–20}. Women have better surviving *ab initio* the infarct to the reception, larger hospital mortality and equal mortality after the dismissal from the hospital.

The lower pre-hospital mortality in women has been accompanied by the larger hospital mortality, whereupon the start advantage fades, and both men and women MI mortality after hospital dismissal equates to the research conducted in Glasgow during 1996¹¹. Principal causes of death in patients with MI are malignant arrhythmias, heart failure and myocardial rupture¹⁰.

In spite of numerous studies, dilemmas about the higher MI mortality in women, and the female gender as independent, MI mortality risk factor remained. In MILS studies (Multicenter Investigation of Infarct Size)²¹, as well as in the study of Greenland et al., hospital mortality in women, even after adjustments according to the age and risk factors, remained twice as many than in men.

On the contrary Dittrich et al.²³, as well as Robinson and coworkers²⁴ had found that after the stratification according to age, initially larger mortality in women equalizes with the mortality in men. Therefore, numerous authors are inclined to claim that the larger women mortality has been induced because of the older age and higher MI risk factor burden, and that the gender is not independent MI mortality predictor^{24–26}.

Fabijanić and coworkers' study in KB Split indicated that the most reliable mortality predictor is systolic pressure value below 100 mm Hg in the acute phase of MI, that was significantly more present in women²⁶. This is so, also, according to Carion and coworkers' research conclusion²⁷. Women tend to develop left ventricular failure in MI more often than men^{19,28}. Fiebach and coworkers pointed out in their research that at admittance women had significantly more often LV failure clinical signs, pulmonary edema and cardiogenic shock even though CPK values difference and anterior myocardial infarction incidence in women and men were statistically indifferent.

The Authors concluded that the higher LV failure incidence in women in MI of the same size, indicates that women have smaller compensatory reserve in noninfarcted myocardium, that is to say lower LV distensibility, whereupon congestions are more frequent in women than in men²⁹. More frequent LV failure in woman can be

explained by gender dependent mechanisms of LV stroke volume enhancement. Men dominantly increase stroke volume by augmentation of ejection fraction, with small or none changes in left ventricular enddiastolic volume.

Women enhance LV stroke volume primarily by elevation of left ventricular end diastolic pressure without changes in EF³⁰. Since even small damage in left ventricular myocardial mass (<8%) leads to impairment of diastolic function, left ventricular failure appears¹⁰. Echocardiographic studies reveal that LV myocardial mass is 30% greater in men than in women, presumably due to androgen activity^{31,33}.

Anterior MI is on average larger, with the larger left ventricular damage, lower EF, with more frequent complications and therewith higher mortality^{10,31}.

In spite of roughly equal incidence of anterior and inferior MI in men and women, larger loss of myocardial mass, accompanied by the LV dysfunction and consequently by more frequent complications and higher mortality is observed in women^{21,22,34}. The most frequent cause of sudden cardiac death is coronary artery occlusion after unstable plaque rupture. More than the half of MI deaths happens out of hospital.

Patients die out of hospital most frequently due to malignant arrhythmias, while hospitalized patients have the heart failure as the most common cause of death¹⁰.

In Glasgow the MONICA study showed a higher MI mortality in men before reaching hospital, and higher mortality in women during hospital treatment, leading to the conclusion that the mechanism of death in MI infarction is different in men and women¹¹.

Studies have shown that men more often die from the heart rhythm disorder, and women from heart failure, cardiogenic shock and myocardial rupture^{11,21,36}. The quoted difference in mechanism of dying between men and women are believed to be due to gender differences and sensitivity to ischemic and reperfusion damages, electrophysiological and autonomous regulation differences^{36–42}.

Autonomous nerve system activity has the significant role in the outcome of acute coronary syndrome³⁸. The hyperactivity of sympathetic stimulates formation of the malignant ventricular arrhythmias, while the vagal activation has the protective effect³⁹. Autonomous system reaction and occurrence of ventricular arrhythmias are influenced by coronary artery stenosis severity, beta adrenergic blockade, and patient's gender. Localization of occlusion in IRA does not influence autonomous system reaction³⁸. First phase of acute occlusions is critical for the clinical outcome in out-patient deaths^{10,16,18}.

Throughout two minute balloon occlusion of coronary artery, women have more frequent vagal activation, followed by bradycardia, fall in arterial pressure and significantly reduced ectopic activity.

The mentioned vagal activation protects women from malignant disorders of heart rhythm³⁹.

Our study shows that men more frequently die from the ventricular fibrillation, and women from heart fail-

ure, cardiogenic shock and myocardial rupture, what explains the mentioned difference in vagal reaction and strength of myocardial muscle.

Cardiogenic shock and heart failure are more frequent hospital causes of death in women which can be explained by larger relative loss of myocardial mass, which was also shown in the results of other researchers^{12,40}. Myocardial rupture, presented with pulseless electrical activity, is more frequent in women, which is explained by the smaller strength of heart muscle, thinner wall and weaker collateralization, due to the accelerated atherosclerosis after menopause^{35,41}.

Besides, women who get ill from MI are, on average, 5 to 10 years older than men, and have more risk factors. In patients older than 45, hypertension, hyperlipidemia and diabetes are more frequently found in women, while within smokers in men^{28,42}.

According to results obtained in our study, myocardial infarction mortality is lower in younger age groups in men and in women, while morbidity remains higher in men throughout all age groups. It could be explained by the influence of age and sex hormones on atherogenesis¹⁰.

The analysis of the cause of sudden death in the five-year period between 2000 and 2004, based on autopsy findings in Split region, has shown that cardiovascular

diseases appear as the cause of death in 70% of cases, half of them being MI, (35%) a third heart failure (23%), and a sixth pulmonary artery embolism (12%). Cerebrovascular and respiration diseases are involved in 8% of cases, and malignant and other illnesses in 14% of cases⁴³. Our research shows that men represent 80% of MI patients who died before reaching hospital.

Conclusion

Men are hospitalized more than twice as frequently with diagnosed MI than women. The number of patients hospitalized with diagnosed MI has been in constant growth during a seven-year period.

MI hospital mortality has constantly decreased, and MI mortality in hospital is significantly higher in women, in fact two and half times higher than in men. Anteroseptal MI has significantly higher mortality than other MI localizations.

Men significantly more often die from MI at the age of 50 to 70, and women almost equally at the age of 50 to 69 and from 70 to 90.

Men significantly more often die from ventricular fibrillation, and women from heart failure. Prehospital mortality is four times higher in men. The total MI mortality is 1.7 times higher in women than in men.

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OSOBITOSTI PREHOSPITALNOG I HOSPITALNOG MORTALITETA OD INFARKTA MIOKARDA U ODNOSU NA SPOL

SAŽETAK

Cilj ovog rada bio je utvrđivanje specifičnosti mortaliteta od infarkta miokarda u odnosu na spol prije dolaska u bolnicu kao i za vrijeme hospitalizacije. Tijekom sedmogodišnjeg razdoblja od 2000. do 2006. godine analiziran je mortalitet od infarkta miokarda svih bolesnika koji su liječeni u KB Split kao i u bolesnika koji su umrli naglom smrću a na obdukciji im je utvrđen akutni infarkt miokarda. U tom periodu u KB Split liječno je zbog infarkta miokarda 3434 bolesnika od čega je 2336 (68%) muškaraca i 1098 (32%) žena. Ukupni mortalitet hospitaliziranih bolesnika je 12,8% (440). Broj hospitaliziranih pokazuje tendenciju rasta, od 474 u 2000. do 547 u 2006. godini, a hospitalni mortalitet trend smanjenja, od 15% u 2000. do 9,5% u 2006. godini. Hospitalni mortalitet je značajno veći u žena nego u muškaraca 21% (228) prema 9% (202), $p < 0,05$. Ukupni mortalitet žena je međutim značajno veći u odnosu na mortalitet muškaraca (23,7% prema 15,7%, $p < 0,05$). Među hospitaliziranim bolesnicima statistički je značajno najveći mortalitet bolesnika sa anteriornim infarktom i eleviranom ST spojnicom (19%) u odnosu na inferiorni (10%) i lateralni infarkt sa ST elevacijom (11%) te infarkt miokarda bez ST elevacije (4%), $p < 0,05$. Muškarci značajno češće umiru od fibrilacije ventrikla (22% prema 10%, $p < 0,05$), dok žene češće umiru od dekomenzacije, kardiogenog šoka i ruptуре miokarda (33% prema 15%, $p < 0,05$). Žene statistički značajno više umiru u bolnici 84% (230), a manje izvan bolnice 16% (43) u odnosu na muškarce kojih u bolnici umire 56% (217), a izvan bolnice 46% (171), $p < 0,001$. U ukupnom broju oboljelih od infarkta miokarda prehospitalni mortalitet značajno je veći u muškaraca 7,3% (178) u odnosu na žene 3,7% (43), $p < 0,05$. Prehospitalno umire značajno više muškaraca nego žena (81% prema 19%, $p < 0,05$). Značajno su učestaliji anteriorni (58%) u odnosu na inferiorne (36%) i lateralne infarkte miokarda sa ST elevacijom (6%) $p < 0,05$ u bolesnika umrlih izvan bolnice. Iz navedenih rezultata zaključujemo da muškarci značajno češće umiru u prvih nekoliko sati prije dolaska u bolnicu od ventrikularne fibrilacije, a žene u subakutnoj fazi infarkta miokarda pod slikom popuštanja srca za vrijeme boravka u bolnici. Međutim i pored toga ukupni mortalitet na broj oboljelih značajno je veći u žena u odnosu na muškarce.