



## Trends in Acute Myocardial Infarction Mortality and Morbidity from 1979 to 2001 in the City of Zagreb, Croatia

Inge Heim, Mirjana Jembrek-Gostović, Josipa Kern<sup>1</sup>, Vladimir Jonke, Maja Svetina

*Institute for Cardiovascular Prevention and Rehabilitation; and <sup>1</sup>Andrija Štampar School of Public Health, Zagreb University School of Medicine, Zagreb, Croatia*

<b>Aim</b>	To define trends in age-adjusted acute myocardial infarction mortality and morbidity in women and men in the city of Zagreb, Croatia, in the period 1979-2001.
<b>Methods</b>	Acute myocardial infarctions occurring in both men and women at ages between 25 and 74 years were analyzed by using 1979-2001 data from the Acute Myocardial Infarction Population-based Register for the City of Zagreb, Croatia. The patients with myocardial infarction were identified retrospectively from the hospital discharge reports and death certificates in Zagreb hospitals and the Croatian Statistical Bureau.
<b>Results</b>	Over the period of 23 years, a total of 25,359 cases of acute myocardial infarction were registered in the city of Zagreb (18,345 men and 7,014 women). The age-adjusted attack rate for men was the lowest in 1981 (170 per 100,000 population) and the highest in 1993 (274 per 100,000 population), with a decreasing trend toward 2001. The rate for women was between 49 per 100,000 population in 1979 and 86 per 100,000 population in 1993, with a decreasing trend afterwards. Between 1993 and 2001, the rate for men decreased by 68.6% and for women by 62.8% ( $P=0.370$ ). The age-adjusted mortality rate showed more pronounced changes and was much higher for men than for women. The rates per 100,000 population among men varied between 80 and 140, and among women between 20 and 40. Between 1993 and 2001, the age-adjusted myocardial infarction mortality rates decreased by 56.3% and 52.5% in men and women, respectively ( $P=0.670$ ). The age-adjusted prehospital mortality rate for men was much higher than the hospital mortality rate and had an obvious decreasing trend since 1993. Both rates were much lower for women. Twenty-eight-day case-fatality rate for men ranged from 38.5% to 49.1%, and from 39.0% to 64.0% for women. It did not change much in men during the observed period. Women younger than 45 years had a significantly greater risk of a fatal heart attack, whereas the risk was greater for men in the older age groups (55-74 years).
<b>Conclusion</b>	The age-adjusted attack rates, mortality rates, prehospital death rates, and case-fatality rates showed a definite decline since the early 1990s for both men and women, but the decline was greater for men.

Coronary heart disease, together with cerebrovascular diseases, is the major cause of death in Europe (1). However, its epidemiology varies. In Finland, Sweden, Norway, and Denmark the mortality rates of standardized death rates from coronary heart disease have been declining at all ages over the past decades (2,3). The reasons for this decline are probably healthier lifestyle, reduc-

tion of risk factors, and better treatment. Populations in South European countries, such as France, Spain, and Portugal, have relatively low death rates due to their Mediterranean diet. On the other hand, some countries in Eastern and Central Europe, such as Hungary and Romania (3), continue to have high death rates from acute myocardial infarction, with the highest rates found in the coun-

tries of the former Soviet Union (1). Since a great deal is known about the personal, genetic, biological, and lifestyle factors, which influence the development of coronary heart diseases, it should be possible to prevent or at least postpone death in the populations at increased risk.

Our aim was to evaluate the mortality and morbidity from acute myocardial infarction in the population of Zagreb, Croatia, using the data from the Acute Myocardial Infarction Population-based Register for the City of Zagreb.

### Methods

We retrospectively analyzed the data from the Acute Myocardial Infarction Population-based Register for the City of Zagreb, Croatia, which was started in 1979. All men and women who suffered from acute myocardial infarction and were hospitalized in Zagreb hospitals, whether they survived or not, were included in the Register together with those who died before hospitalization. Although there is no upper age limit in the Register, we analyzed only the patients aged 25-74 years to be able to compare the data with other registers and projects, which use the age of 64 or 74 years as the upper age limit (4-7). The total number of residents and the number of municipalities in Zagreb have changed since 1979. From 1979 to 1995, the City of Zagreb had 14, and for a short time even 15, municipalities. From 1996 onwards, there were only 11 municipalities because 4 out of previous 15 became independent towns (Dugo Selo, Samobor, Velika Gorica, and Zaprešić). To define the morbidity and mortality rates, we used the exact number of the inhabitants of Zagreb in each year.

The diagnosis of myocardial infarction was based on at least two out of the following three criteria: a) typical acute symptoms – chest pain for more than 30 minutes; b) increased enzyme concentrations – creatine kinase and creatine kinase-MB twice the upper normal value within 72 hours after the onset of acute symptoms, and c) electrocardiogram changes with or without ST-segment elevation (8).

We used the diagnosis codes 410 and 412 from the 9th Revision of the International Classification of Diseases (ICD-9; ref. 9), and the diagnosis codes I21 and I22 from the ICD-10 after 1994 (10).

An acute myocardial infarction reoccurring within 28 days was not registered as a new event (the unit of registration). The acute myocardial infarction rates were defined as a sum of definite, recurrent, and possible infarctions. Possible myocardial infarctions mostly included fatal cases where autopsy was not performed and not all the above listed criteria were met.

To determine the occurrence of myocardial infarction, the following indicators were used: attack rate, indicating the number of events occurring in the population; mortality rate, indicating the number of deaths in the population over a period of time; annual case-fatality rate, indicating the proportion of deaths among patients; and cumulative case-fatality rate in patients over a time period of 23 years. Attack and mortality rates were age-adjusted to the European standard population, used to calculate age-standardised rates, and calculated by using the direct method with 5-year age groups to obtain more accurate age-adjustment (11). Attack rate was presented by year and sex. Mortality rate was presented by year and sex and by prehospital and hospital mortality. Annual crude case-fatality rate was presented by sex and age.

### Statistical Analysis

The age differences between men and women, decrease in attack rate, mortality rate, and difference in case-fatality rate were tested by  $\chi^2$  test, with  $P < 0.05$  considered statistically significant. Odds ratio (OR) and 95% confidence intervals (CI) were used in determining the risk of fatal heart attack in women and men. Statistical analysis was performed with Microsoft's Excel for Windows.

### Results

Over the period of 23 years, a total of 25,359 cases of acute myocardial infarction in the 25-74-year age group were registered in the city of Zagreb. There were 18,345 (72.3%) events in men and 7,014 (27.7%) in women. The age distribution of acute myocardial infarction by sex showed that almost half of men who suffered acute myocardial infarction were aged <60, 19.2% were aged 60-64, while only 35.1% of men were aged 65-74 years (Table 1). Among women who had acute myocardial infarction, 24.1% were aged <60 years, 17.8% were in the 60-64 age group, while 58.1% were in the 65-74 age group. The median

**Table 1.** Cumulative number of acute heart attacks in men and women in the city of Zagreb, 1979-2001, by age groups and case fatality

Age group (years)	Acute myocardial infarction (cumulative No.)					
	men			women		
	fatal	non-fatal	total (%)	fatal	non-fatal	total (%)
25-29	13	26	39 (0.2)	4	0	4 (0.1)
30-34	42	86	128 (0.7)	12	8	20 (0.3)
35-39	125	257	382 (2.1)	30	30	60 (0.9)
40-44	269	629	898 (4.9)	41	77	118 (1.7)
45-49	505	1,057	1,562 (8.5)	93	145	238 (3.4)
50-54	890	1,481	2,371 (12.9)	166	305	471 (6.7)
55-59	1,278	1,739	3,017 (16.5)	290	491	781 (11.1)
60-64	1,609	1,905	3,514 (19.2)	542	706	1,248 (17.8)
65-69	1,738	1,661	3,399 (18.5)	863	957	1,820 (26.0)
70-74	1,735	1,300	3,035 (16.5)	1,173	1,081	2,254 (32.1)
Total	8,204	10,141	18,345 (100.0)	3,214	3,800	7,014 (100.0)

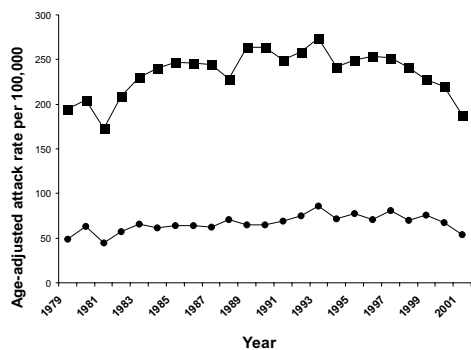
age at the time of the attack was 66 (range, 25-74 years) for women and 61 (range, 25-74 years) for men.

#### Age-adjusted Attack Rate

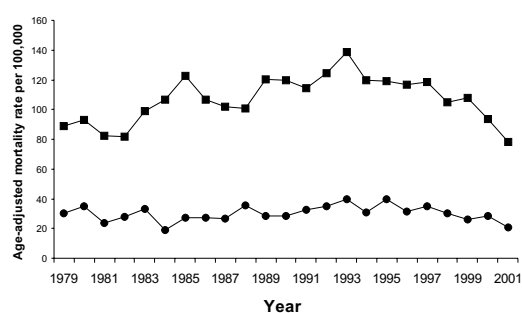
The age-adjusted attack rate of acute myocardial infarction among men was the lowest in 1981 (170 per 100,000 population) and the highest in 1993 (274 per 100,000 population), when it started decreasing. The attack rate among women ranged between 49 per 100,000 population in 1979 and 86 per 100,000 population in 1993, when it started showing the same decreasing trend as in men and returning back to the level of 1979. Fluctuations in the attack rate were more pronounced among men than among women (Fig. 1); the attack rate fell by 68.6% among men and by 62.8% among women between 1993 and 2001 ( $\chi^2_1 = 0.802$ ,  $P = 0.370$ ).

#### Age-adjusted Mortality Rate

Men had more pronounced changes in age-adjusted mortality rate, which was also higher

**Figure 1.** Age-adjusted attack rate for acute myocardial infarction in the population of the City of Zagreb, 1979-2001. Squares – men; circles – women.

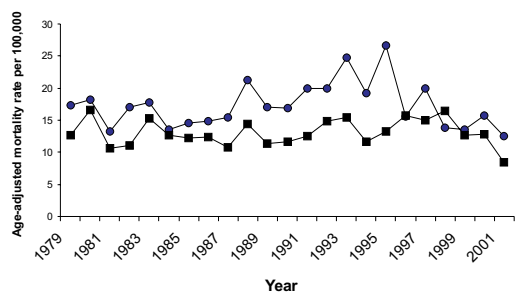
than in women. There was an increase in the age-adjusted mortality rate in men from 80 per 100,000 population in 1982 to 140 per 100,000 population in 1993, when it was the highest and started to decline steadily until 2001. In women, the changes were not so pronounced and the rate varied between 20 and 40 per 100,000 population, showing a clear decreasing trend since 1995 (Fig. 2). Between 1993 and 2001, the age-adjusted myocardial infarction mortality rates decreased by 56.3% and 52.5% among men and women, respectively ( $\chi^2_1 = 0.181$ ,  $P = 0.670$ ).

**Figure 2.** Age-adjusted mortality rate for acute myocardial infarction in the population of the City of Zagreb, 1979-2001. Squares – men; circles – women.

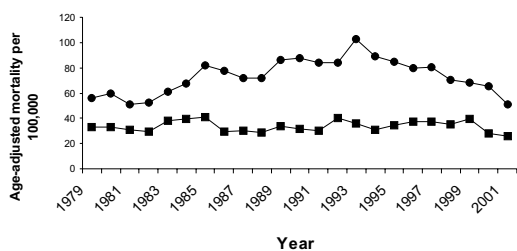
The age-adjusted prehospital mortality rate among men was much higher than the age-adjusted hospital mortality rate, showing an obvious decreasing trend since 1993. Both prehospital and hospital mortality rates among women were much lower, with the prehospital rate being higher than the hospital rate, especially between 1987 and 1995. Both prehospital and hospital mortality rates showed a declining trend, but prehospital mortality declined faster in both men and women. The age-adjusted hospital mortality did not vary much and has shown no tendency to decline among men. Among women, the rate showed more pronounced variations and since 1998 has had a declining trend (Figs. 3 and 4).

#### Case-Fatality Rate

Twenty-eight-day case-fatality rate for men ranged from 38.5% to 49.1% (44.6% on average) and from 39.0% to 64.0% for women (46.4% on average). For both women and men, the case-fatality rate showed a slow but increasing trend towards the older age groups, although in the age groups between 25 and 39 years the rates



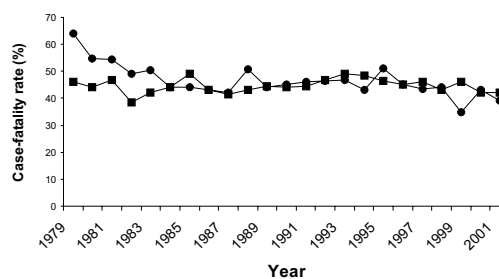
**Figure 3.** Age-adjusted prehospital and hospital mortality rate for acute myocardial infarction in women in the City of Zagreb, 1979-2001. Squares – hospital mortality; circles – prehospital mortality.



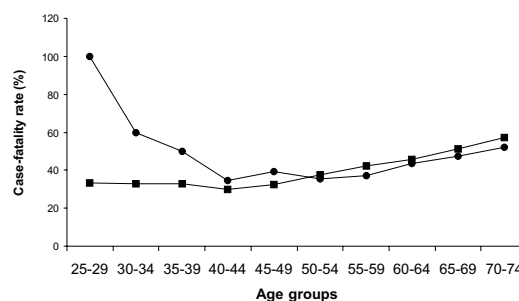
**Figure 4.** Age-adjusted prehospital and hospital mortality rate from acute myocardial infarction in men in the City of Zagreb, 1979-2001. Squares – hospital mortality; circles – prehospital mortality.

among women were very high. Annual case-fatality rate among women was the highest in 1979, when it began to decline until 1984. After 1984, it varied mostly between 40% and 50%, reaching 40% towards 2001. The variations in the annual case-fatality rate among men were not so obvious and there was no noticeable decline. The rate among men varied between 40% and 50% during the study period, reaching 40% in 2001 (Fig. 5). The median case-fatality rate for hospitalized cases among men was 24.9% (range, 15.4-38.4%) and 31.1% (range, 14.6-48.9%) among women ( $\chi^2_1=0.953, P=0.329$ ).

The analyses by age groups and sex showed that case-fatality rate over a 23-year period among men had a horizontal trend in the 25-45 age groups, increasing towards the older age groups. This curve was somewhat different among women. The highest rate was in the younger age groups among women, showing a declining trend towards 40-44 age group and increasing



**Figure 5.** Case-fatality rate for acute myocardial infarction in the population of the City of Zagreb, 1979-2001. Squares – men; circles – women.



**Figure 6.** Case-fatality rate for acute myocardial infarction in the population of the City of Zagreb, 1979-2001, according to age groups. Squares – men; circles – women.

again from 50-55 age group towards older age groups (Fig. 6).

The risk of fatal heart attack was higher among younger women than men, but in older age groups (> 55 years), the risk was greater in men (Table 2).

**Table 2.** Sex-based odds ratio (OR) with 95% confidence intervals (CI) for fatal myocardial infarction by age groups (1979-2001)

Age groups (years)	Risk of fatal myocardial infarction		
	sex	OR (95% CI)	P
25-34	women	4.07 (1.64-10.10)	0.001
35-44	women	1.49 (1.08-2.06)	0.015
45-54	women	1.05 (0.89-1.24)	0.580
55-64	men	1.14 (1.03-1.26)	0.011
65-74	men	1.17 (1.09-1.27)	<0.001

### Discussion

The results of our study showed that the age-adjusted rates for acute myocardial infarction, such as attack rate, mortality rate, and case-fatality

rate, declined after 1993 in the population of Zagreb. Both attack and mortality rates of acute myocardial infarction were strongly related to sex and age. More than half of women who suffered from myocardial infarction were in the 65-74 age group, whereas most men were younger than 65. The difference in mean age between men and women was statistically significant. The same distribution of patients with myocardial infarction with regard to age and sex is present in some other registers, such as those in Sweden (12) and Denmark (13).

There was no significant difference between women and men in the city of Zagreb in the decline of rates. The decline in attack and mortality rates may be largely due to the reduction in risk factors for coronary artery disease (14) in the last decades (antismoking campaigns and promotion of healthy diet and physical activity) and improvements in the treatment of risk factors, for example, a substantial increase in the use of aspirin and statins, although thrombolytic therapy could have been used more often. According to the data from the Register, in the 1990s thrombolytic therapy was used in only 10 to 15% of the cases and percutaneous coronary interventions in the acute phase had not been used on a large scale at that time.

The attack and mortality rates were much higher among men than among women, with a peak in 1993. There was a war in Croatia at that time and many displaced people from all over the country and refugees from Bosnia came to Zagreb. According to the data of the Zagreb Statistical Bureau, their number was the highest in 1993 (119,428 displaced persons and refugees) and then decreased to 20,487 in 1997 (15). However, it was not possible for us to identify them in the Register because registrars and the staff in hospitals did not register them as such. Thus, although they were not permanent residents of the city of Zagreb, we could not exclude them from our analysis and it is possible that the rates in 1993 were actually lower than our data suggested. Furthermore, some non-fatal cases of acute myocardial infarction (silent myocardial infarction) went unrecognized because people did not go to hospital, while the registration of fatal events was probably complete over the whole time period and in accordance with routine mortality statistics in Croatia, although there are always problems with out-of-hospital fatal events. Autopsy, which could help to

establish the cause of death in most cases, was not always performed. The proportion of autopsies declined because of financial constraints, and access to detailed information on out-of-hospital deaths was not always adequate.

The change from ICD-9 to ICD-10 could cause considerable change in the number of deaths reported for a given disease. However, acute myocardial infarction is an acute event that has had a single code in both Revisions (410 or I21), as well as a recurrent event (412 or I22), so the change in the reported deaths from myocardial infarction was not expected.

As we could see, the majority of deaths caused by myocardial infarction occurred out of hospital (4). Almost three-quarters of all deaths occurred in the prehospital phase, probably due to delayed transport of the patients to hospitals (6). The out-of-hospital deaths remain a challenge for preventive measures: organization of quicker transportation to hospital, education of laypeople to recognize the symptoms acute myocardial infarction and perform resuscitation, and other preventive measures.

Out-of-hospital mortality of acute myocardial infarction in Zagreb declined faster than the in-hospital mortality. The Minnesota Heart Survey showed the opposite, ie, the in-hospital mortality declined faster (16). We could assume that preventive measures were successful but we cannot confirm it.

The 28-day case-fatality rate after acute myocardial infarction was the same among women and men, 46% and 45%, respectively. In 29 populations included in the MONICA study (6), the age-adjusted case-fatality rate was calculated and related to age and sex. Median 28-day population case fatality was 49% in men and 51% in women (6), which was higher than in Zagreb. Median 28-day case-fatality rate for hospitalized events was 22% for men and 27% for women (17). This compares to our data for Zagreb population (24% for men and 31% for women), with no significant difference between men and women. In the Glasgow MONICA project, population case-fatality rate was very similar (47%), and even lower (40%) in the Belfast MONICA project (18). The rate for women in Zagreb in the three age groups between 25 and 39 years was very high, probably due to the small absolute numbers of myocardial infarction cases in younger women.

We found that women between 25 and 44 years of age had a significantly greater risk of fatal heart attack, whereas for men, this risk was greater in the 55-74 age groups. Although many studies investigated sex differences in mortality after myocardial infarction (19,20), the reasons for these differences are still not clear (21). Do fewer women receive medical treatment or do they experience more vague symptoms, which may account for delay in hospitalization and underuse of effective therapies, or do they benefit less from certain therapies? Further research is needed to elucidate these questions.

Troponin as a diagnostic marker had not yet been used routinely in our hospitals at the time of our study, so it could not have had the effect on the hospitalization rate as in other countries (22).

Our study has several limitations. First, the reliability and accuracy of the definition of underlying cause of death depends on the certifier of each death and national nosologists who determine the codes and the underlying causes. The incidence of initial and recurrent attacks could not be assessed properly because there was no information on previous myocardial infarction in those who died before hospitalization and, in most cases, an autopsy was not performed. Second, silent myocardial infarction or acute myocardial infarction with atypical symptoms occurs in 5-25% of patients (23-25). However, there are no data for Zagreb. Third, 1-3% of the hospital patient records were missing, so we could not obtain data for these patients. Although computerized information system helps us to obtain at least part of the data, if there is no hard copy, but the problem remains.

Despite improved diagnostics and treatment and increased public awareness of the problem, acute myocardial infarction remains one of the leading causes of death in Croatia. Given the high burden of acute myocardial infarction in our country, more efforts are needed to implement registers in bigger cities in Croatia (26). National and regional registers nowadays serve many useful purposes and have many important functions (27,28). These registers make a valuable contribution by calling our attention to certain issues (29) and provide the best approach to assessing the impact of myocardial infarction in a population (30).

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**Correspondence to:**

Inge Heim

Golubovac 13

10000 Zagreb, Croatia

[inge.heim@zg.htnet.hr](mailto:inge.heim@zg.htnet.hr)