

UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

DOCTORAL SCHOOL



PhD THESIS

**THE PREDICTIVE VALUE OF FREQUENT RISK
FACTORS IN THE OCCURRENCE OF ACUTE
CORONARY EVENTS**

PhD Supervisor

Prof. Univ. Dr. Doina CÂRSTEA

PhD Student

Maria Marilena FRUNZULICĂ

CRAIOVA

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INTRODUCTION

An acute coronary event (ACE) is a term that refers to any group of clinical symptoms that are compatible with acute myocardial ischemia and which cover a clinical spectrum of conditions ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI).

Unstable angina (AI) and non-ST segment elevation myocardial infarction (NSTEMI) are strongly related from the physiopathological point of view, but differ in terms of prognosis and severity.

NSTEMI diagnosis can usually be set only when ischemia becomes severe enough to cause myocardial damage that may lead to the release of one of the biologic markers of myocardial necrosis (specific troponins T or I or creatine kinase muscle-brain fraction [CK-MB]).

Unlike NSTEMI, the patient is deemed to have already experienced an unstable angina UA episode if no such biomarker can be detected in the bloodstream hours after the onset of the ischemic chest pain.

Unstable angina has one or more of the three main types of expression: (1) Angina at rest (usually lasting less than 20 minutes), (2) a new onset of severe angina (less than 2 months before), and (3) an ascending emergence pattern (increase in intensity, duration, frequency, or any combination of these three factors).

In the United States of America, about 1.35 million admission are required for ACE every year (either as primary or secondary diagnosis within the admission), of which nearly 1 million is represented by myocardial infarction (MI), and the rest are represented by UA. Nearly two-thirds of patients with AMI are diagnosed with NSTEMI and the rest with STEMI.

PURPOSE OF THE STUDY

The study aims to investigate the prevalence of acute coronary events in the general population and the risk factors associated to them, as well as the impact of prognostic factors in the evolution of acute coronary events.

Specific objectives of the personal study

- Assessing the frequency of acute coronary events in the general population of Olt County.
- Investigating the risk factors associated with the occurrence of acute coronary events.
- Analysing the prognostic factors involved in the evolution of acute coronary events.

The practical value of the study

The study provides relevant information on the frequency of acute coronary events that shape a local (Slatina Municipality) and regional (Olt County) image useful to health services regarding one of the "hottest" medical issues.

The assessment of risk factors not only allows the identification of their association with the analysed pathology but also ensures the identification of their prevalence in the studied population with implications in their prophylactic measures in order to control and limit the impact upon the general population or upon the population groups.

This study highlights relevant information on long-term mortality in cases of individuals who suffered acute coronary events, being identified prognostic factors whose approach in medical practice provides additional support in the long-term case management.

The personal study involved the formation of two working groups. This approach involved the sizing, different representativeness and the need to ensure optimal statistical significance of the specific objectives derived from the purpose of the study.

The first batch was set up to achieve the study's objective of estimating the prevalence of acute coronary events. In order to ensure the representativeness conditions, a large volume sample had to be approached. The volume of the batch sample was sized to 865 subjects. Subjects were randomly selected from the lists of patients of 2 individual family medicine practices in Slatina Municipality. The batch was sized according to the general structure of the population according to age and gender distribution.

Although the prevalence of cardiovascular diseases in the general population is high, with the main cardiovascular condition that increases the frequency of cardiovascular diseases

being arterial hypertension, the other entities in the cardiovascular disease group are less frequent. Moreover, the lack of a national, regional or local registry of acute coronary events, including acute coronary infarction, stable or unstable angina, greatly limits the sensitivity of their prevalence studies.

The batch has been structured by the random selection of a number of male and female subjects similar to that of the general population. Table no. 1 reflects the representativeness of the study batch made up for batch I compared to the structure per sex of the general population of Olt county, which represented the basis of selection of the subjects included in the study group. Thus, a smaller percentage of male subjects was noticed, representing 43.33% of the population of Olt county, with a similar weight of 44.2% at the level of the batch of male subjects. The sex ratio was also at close values, in the case of the studies batch its value was 0.79, and for the Olt county population the sex ratio was 0.77. The mean age of the studied batch was 44.47 ± 12.93 years of age.

Limits of the study

Estimating the prevalence of acute coronary events could not have a very large sample due to technical reasons, however, the volume of the sample was consistent (N = 865 subjects).

Even the random selection of patients from the lists corresponding to the two family medicine practices in Slatina observes the variability of such samples, the selected subjects being predominantly from the urban environment and insured with the health insurance fund.

All potential bias of selection and response cannot be excluded.

The retrospective and not prospective nature of the study limits the complete identification of the association of risk factors.

RESULTS AND DISCUSSIONS

Of all the 865 subjects enrolled in the study, a number of 52 subjects reported as suffering or having suffered an acute coronary event. The prevalence of acute coronary syndrome was thus detected at a prevalence rate of 6.01%.

The prevalence of acute myocardial infarction was 1.5%, (*Figure no. 1. 2*), which was found in a number of 13 subjects included in this study. However, the prevalence of angina was higher, as it was identified in a number of 39 subjects, outlining a value of 4.97%.

20 cases of acute cardiovascular events were identified in the males, which, in relation to the overall number of male subjects (382 subjects) included in batch I, have led to a 5.24% prevalence calculation.

In female subjects the prevalence of acute coronary events was higher (6.63%), this being obtained by relating the number of women who suffered acute coronary events ($n = 32$) to the overall number female subjects included in batch I. Although the prevalence of acute coronary events was almost 20% higher in females, the relative risk assessment of acute coronary events did not show statistical significance (relative risk - 1.26, IC 95% = 0.73 2, 18, statistical significance - $P = 0.394$).

The comparative analysis of age averages in cases of acute coronary events reported the tendency of their occurrence around the age of 55 in the case of male subjects and relatively later, around the age of 60 in the case of female subjects, the difference in age averages being statistically significant ($p < 0.0385$).

Acute myocardial infarction was most commonly identified in the sixth decade of life, where female prevalence was 8.47%, and in the case of male subjects the prevalence of acute myocardial infarction was 5.88%. Until this age, myocardial infarction tends to be rare, but there has been recorded a higher incidence in men, in which case acute myocardial infarction tends to develop earlier. Thus, in the fifth decade, acute myocardial infarction was identified in 2% of subjects, and in the fourth decade of life in less than 1% (0.85%).

Risk analysis based on the educational level which the subjects had identified a risk for acute coronary events nearly 7 times higher in subjects who only completed primary studies (RR = 6.82; IC95% 2.8652 to 16.2549; $P < 0.0001$) and almost 2 times higher in those who graduated from secondary education (RR = 1.83, IC95% 0.965 to 3.5748, $P = 0.0529$) compared to those who graduated forms of higher education.

The number of subjects reported to drink alcohol was 605 subjects, which increased the prevalence of alcohol consumption among the subjects of the group to 70.71%. This relatively high rate does not count neither the frequency, type nor duration of alcohol consumption, as it is related to the socio-cultural specificity of the southern region of the country, which includes Olt County.

Alcohol consumption was different as proportion among male and female subjects. For men, the alcohol consumption ratio was 85.79%, of the overall 382 male subjects 326

declared to be alcohol consumers. In women less than 60% admitted that they consumed alcohol, only 280 female subjects out of the overall 477 subjects who accepted to answer this question stated they consumed alcohol (58.7%).

Differences in the type, rhythm, and duration of alcohol consumption are likely to be those that substantially change the frequency of acute coronary events in women compared to men.

Acute myocardial infarction was exclusively identified in male subjects consuming alcohol, with an AMI prevalence of 1.84% (6/326). No case of AMI was recorded in male subjects who did not consume alcohol. Although this may suggest a relatively strong link between alcohol consumption in men and the occurrence of MI, this may be also due to the much higher prevalence of alcohol consumption among men (approx. 85%), making it difficult to identify the effect of alcohol consumption as a causal factor. In the case of spirit drinkers there was found one of the highest prevalence of acute cardiovascular events among daily consumers of such drinks. Although only 9 out of the overall subjects declared themselves to be daily consumers of spirits, 3 of them suffered an acute coronary event, accounting for a 33.33% ACE share among daily spirit drinkers.

The lowest frequency of ACE was noted in those who stated that they consumed spirit drinks only 2-3 times per month (1/90), where the prevalence of acute coronary events was 1.11%, as well and in those who said they did not consume any spirit drinks (6/180) in which the ACE prevalence was 3.33%. The risk of acute coronary events in large spirits consumers was nearly 3 times higher than those who consumed spirits at a frequency of no more than once a week, and its appropriate statistical significance was also ensured. (RR = 2.9286, IC95% 1.2047 to 7.1193, P = 0.0177)

Paradoxically, the subjects who declared that they did not drink wine at all, the prevalence of acute coronary events was high, with a value of 12.5%, of the 24 non-consumers of wine 3 subjects suffered acute coronary events.

In subjects with a frequent consumption of wine, this pattern of consumption including those who used to consume wine daily or 2-3 times a week, the prevalence of acute coronary events was 8.74% (9/103) this the value being almost double compared to that recorded in subjects who consumed wine less frequently (4.88%). The risk of acute cardiovascular events in wine consumers with a daily or weekly frequency was twice as high as in those who

consumed wine at least once a week. The relative risk value was 2.07 (IC 95% 1.0441 to 4.2426, P = 0.0403)

In conclusion, consumption of alcoholic beverages, even on a daily basis, affects differently the state of health in general and the occurrence of acute coronary events. At least the type of alcoholic drink strongly modulates the prevalence of acute coronary events.

Thus, spirits are by far the strongest involved in the possibility of being associated with acute events if they are consumed on a daily basis (33.33%). The prevalence of acute coronary events in daily wine consumers (17.24%) was almost 2 times lower than the one found for spirits. Beer consumed even with a daily frequency was associated with the lowest prevalence of acute coronary events (9.52%), more than 3 times lower than the one found for spirits.

Of the overall 263 subjects who declared themselves to be smokers, the number of subjects who were affected by acute coronary events was 24. For subjects who smoked on a daily basis, the prevalence of acute coronary events was 9.13%, meaning nearly 1 in 10 smokers may develop acute coronary events. Unlike other risk factors, smoking does not always confirm the complete reversibility of the risk of developing cardiovascular diseases by quitting smoking, especially if it has spread over a long period of time. In other words, even if smoking cessation brings certain and confirmed benefits in reducing the risk of occurrence or development of cardiovascular diseases, residual risk remains particularly important for long-term smokers.

This phenomenon explains the high prevalence of acute coronary events in former smokers, as noted in this study, where ACE prevalence was 8.81%, close to that noticed with daily smokers. 14 of the 159 subjects who had quit smoking developed acute coronary events.

Another factor contributing to the prevalence of acute coronary events in former smokers is related to the motivation for smoking cessation, which in many cases is due to the very deterioration in health, of which cardiovascular diseases represent the most frequent reasons.

The risk of acute coronary events in smokers, regardless of their frequency or the fact that they quit smoking at the time of study, was more than 2 times higher than in the case of subjects who had never smoked (RR = 2.27; IC95% 1 , 2068 to 4.2604, p = 0.01).

Considering a higher prevalence of AMI in smokers, the risk of acute myocardial infarction was 2.5 times higher in subjects reported as smokers, irrespective of its frequency, compared to non-smokers (RR 2.5; IC95% 0.7036 to 8 , 9065, $p = 0.156$).

The risk calculated for male smokers, regardless of the smoking frequency, was 2.26 times higher compared to non-smoker males, but lacking statistical significance ($P = 0.363$). This may be due to either the higher prevalence of smoking among men, nearly 70%, to the relatively low prevalence of AMI in the general population but especially to the complex interaction and other risk factors.

Prevalence in smoking and non-smoking female subjects led to a risk of acute myocardial infarction in female smokers or who had smoked 5 times higher compared to those who had never smoked (RR = 5.26; IC95% 1.0476 26.4225, $P = 0.0438$).

Moreover, in female subjects, even smoking cessation seems not to be beneficial in reducing the incidence of acute myocardial infarction, because 3.8% of former smokers have developed an acute myocardial infarction.

Compared to female subjects who had never smoked, the risk of acute myocardial infarction was nearly 9 times higher in subjects of the same sex who were former smokers (RR = 9.19; 95% CI 1.0269 to 87, 0968; $P = 0.0441$).

The risk of acute coronary events in subjects with body mass index greater than 25 (overweight or obese subjects) was 2.2 times higher compared to normal weight subjects with a body mass index below 25 (RR = 2.2; IC95% of RR 1,2651 to 3,8357; $p = 0,005$), the relative risk value having a high statistical significance ($p = 0,005$).

An upward trend was identified to the prevalence of acute coronary events in relation to the increase in body mass index values, the prevalence of acute coronary events being highest in subjects whose BMI was in the obesity class (10%) and 7.52% in overweight subjects.

The risk of acute coronary events in female subjects was 4 times greater compared to normal weight cases of the same sex, with the risk showing high statistical significance (RR = 3.96, IC95% 1.5819 to 9.8988, $p = 0.003$).

Obesity is, according to the chart below, one of the most important vectors associated with acute myocardial infarction. In women with obesity, the prevalence of acute myocardial infarction was 8.16%, the value detected being more than 20 times higher than the one

recorded in normal weight subjects (0.36%) and over 6 times higher compared to the prevalence of acute myocardial infarction in overweight women.

The risk of acute myocardial infarction was 22.6 times greater in obese female subjects (RR = 22.612, IC95% 2.581 to 198.082, P = 0.0049), and the cumulative risk of AMI in subjects of the same sex with values of AMI over normal values was 8.18 times higher than in normal weight subjects (RR = 8.19, IC95% 1.0933 to 67.4815, P = 0.0407).

For male subjects, the prevalence of coronary events in subjects with hypercholesterolemia was less than 20% (17.65%) lower than in female subjects with hypercholesterolemia associated with a very high prevalence of acute coronary events (25%). However, men not affected by hypercholesterolemia showed a prevalence of acute coronary events below 3%.

The risk of acute coronary events in male subjects affected by hypercholesterolemia was nearly 7 times higher compared to subjects unaffected by hypercholesterolemia, the risk being highly significant from the statistical point of view (RR = 6.93; IC95% 2.9447-16.2922; P < 0.0001).

Diabetes mellitus is one of the risk factors confirmed by this study as one with a strong association with acute coronary events. In case it exists, the prevalence of acute coronary events exceeded 20%, the exact value being 21.5%.

In the context in which the prevalence of acute myocardial infarction in non-diabetes cases was 1% (1.09%), the risk of acute myocardial infarction in diabetic cases was almost 9 times higher in subjects surveyed than in patients unaffected by diabetes (RR = 8.93; IC95% 2.8702 - 27.7979; P = 0.0002).

Although only 22 subjects confirmed that they suffered from rheumatoid arthritis, its prevalence at the level of the batch being only 2.54%, it was found that 6 cases with rheumatoid arthritis were associated with acute coronary events (27.27%).

The prevalence of acute coronary events in subjects without rheumatoid arthritis was 5.46%, and a risk of acute coronary events in the case of association with rheumatoid arthritis was confirmed as being 5 times higher (RR = 5, IC95% 2.3895-10.4543; P < 0.0001).

Acute myocardial infarction showed a higher discrepancy in terms of prevalence in subjects showing present or past depression: In this category of subjects the prevalence of

myocardial infarction was (7.69%) unlike those without depression, where the prevalence of acute myocardial infarction was only 1.41%.

The risk of death compared to the age group under the age of 50 varied depending on the age group, being minimum in the lower age groups, 2 times higher for the 50-54 years old and 55-59 years old age group, but statistically insignificant ($P = 0.34$, $P = 0.48$).

In contrast, for the age group of 60-64 years old, the risk of death was 4.5 times higher than the risk for subjects with acute coronary events less than 50 years of age ($RR = 4.5$; $IC95\%$ 1.2308 to 16, 4528, $P = 0.023$) and more than 5 times higher in the age group over the age of 64 ($RR = 5.27$, $IC95\%$ 1.4785 to 18.8037, $P = 0.0104$).

The risk of death was also in the case of subjects without coronary events, higher in male subjects, the risk rates in these cases being twice as high as compared to female subjects ($RR = 2.22$; $IC95\%$ 0.3014 to 16.3832, $P = 0.4334$).

The impact of diabetes on mortality has been validated both in cases affected by acute coronary events and in those not affected. In diabetic patients with acute coronary events, mortality was 65%, but it was high also in non-diabetic cases (49%). The absence of acute coronary events marked much lower mortality rates, but these were influenced by the presence of diabetes, with mortality being minimal in those without diabetes (6.9%) and almost double in cases with present diabetes (13.49%).

The risk of death at 4 years was 50% higher in cases with blood glucose levels higher than normal rates ($RR = 1.46$, $IC95\%$ 1.012 - 2.515, $P = 0.0467$), compared to patients who were affected by the presence of acute coronary events in those where the presence of atrial fibrillation was confirmed, the mortality was lower, its value being 15.79%. However, in the case of those with ACE, the presence of atrial fibrillation brings a mortality 2 times higher as compared to cases without atrial fibrillation; however, in their case, the risk of death was not statistically significant ($RR = 2.27$, $IC 95\%$ 0.741 to 6.967, $P = 0.1505$).

CONCLUSIONS

1. The prevalence of acute coronary events was noticed at a rate of 6.01% and 1.5% for acute myocardial infarction, while angina pectoris had a higher prevalence of 4.97%.
2. The mean age of cases with acute coronary events was nearly 15 years of age greater than that of subjects without acute coronary events.

3. The predominant age range for the occurrence of acute coronary events is 60-69 years of age, where almost 20% of subjects had had an acute coronary event, between 50 and 59 years of age, one in 10 subjects had been affected by an acute coronary event (9.4%).
4. Age in acute myocardial infarction was 4 years higher in males (aged 62.17 ± 4.88) compared to women (aged 58.86 ± 8.9).
5. Acute myocardial infarction was the most common coronary event noted in the sixth decade of life, with a 8.47% prevalence in women and 5.88% in men. Until this age, myocardial infarction tends to be rare, but there is a higher incidence in men where acute myocardial infarction tends to prematurely develop. Thus, in the fifth decade of life, acute myocardial infarction was identified in 2% of subjects, and in the fourth decade of life in less than 1% (0.85%).
6. Acute myocardial infarction was exclusively identified in male alcohol users, with an AMI prevalence of 1.84% (6/326). No case of IMA was reported in male subjects who did not consume alcohol. The risk of acute coronary events in large spirits consumers was nearly 3 times higher than those who consumed spirits at a frequency of no more than once a week, even the daily consumption of alcoholic beverages affects differently general health status and the occurrence of acute coronary events.
7. At least the type of alcoholic drink strongly modulates the prevalence of acute coronary events. Thus, spirits are by far the strongest involved in the possibility of associating with acute events if they are consumed on a daily basis (33.33%). The prevalence of acute coronary events in daily wine consumers (17.24%) was almost 2 times lower than the one found for spirits. Beer consumed even with a daily frequency was associated with the lowest prevalence of acute coronary events (9.52%), more than 3 times lower than the one found for spirits.
8. One of the spectacular aspects highlighted in our study is the differential prevalence of acute coronary events depending on the type of alcohol in those who did not consume at all a certain type of alcohol. If for spirits the low prevalence of ACE is natural, the fact that in non-consuming subjects the prevalence of ACE was over 10%; but especially with those who did not drink beer and who had a prevalence of over 15% of acute coronary events; this strongly pleads for the rather protective role of moderate beer or wine consumption.

9. The risk of acute coronary events in smokers, regardless of their frequency or the fact that they quit smoking at the time of study, was more than 2 times higher than in the case of subjects who had never smoked. Considering a higher prevalence of AMI in smokers, the risk of acute myocardial infarction was 2.5 times higher in subjects reported as smokers, irrespective of its frequency compared to non-smokers. The analysis of smoking frequency and its connection to acute myocardial infarction revealed a high rate of acute myocardial infarction in former smokers, namely 4.4%, and in smokers who used to smoke on a daily basis (1.57%).
10. Acute myocardial infarction in non-smoking subjects was present in less than 1% of subjects, and its prevalence among subjects who had never smoked was 0.83%.
11. In fact, the factor that has decisively influenced the prevalence of smoking is the period of exposure to this risk factor, i.e. the number of years the subjects have smoked. Thus, in cases where no acute coronary events were noted, the period during which subjects were exposed to smoking was 16 years (16.02 ± 9.17 years of age, IC95% 15.16-16.87), and for those who experienced acute coronary events, the period was over 20 years, the average duration of smoking was 22.29 ± 11.55 years (IC95% 17.41 - 27.17).
12. A strong relationship was noted between the time when subjects were exposed to smoking and the presence of acute coronary events, and linear regression analysis revealed the strong correlation between smoking duration and the prevalence of acute coronary events ($r^2 = 0.93$).
13. The risk of acute coronary events in subjects with body mass index greater than 25 (overweight or obese subjects) was 2.2 times higher compared to normal weight subjects with a body mass index below 25 (RR = 2.2; IC95% of RR 1,2651 to 3,8357; $p = 0,005$), the relative risk value having a high statistical significance ($p = 0,005$) An upward trend was identified to the prevalence of acute coronary events in relation to the increase in body mass index values, the prevalence of acute coronary events being highest in subjects whose BMI was in the obesity class (10%) and 7.52% in overweight subjects.
14. The educational level significantly influenced the risk for the occurrence of acute coronary events as being nearly 7 times higher in subjects who only completed primary studies (RR = 6.82; IC95% 2.8652 to 16.2549; $P < 0.0001$) and almost 2 times

higher in those who graduated from secondary education (RR = 1.83, IC95% 0.965 to 3.5748, P = 0.0529) compared to those who graduated forms of higher education.

15. Diabetes mellitus is one of the risk factors confirmed by this study as one with a strong association with acute coronary events. Its presence was associated with a 20% prevalence of ACE, 4 times higher than for those without diabetes, the risk being higher for women with diabetes (RR = 5) than for men (RR = 2). The risk of death by more than 50% in diabetic cases confirmed the negative prognostic value of this risk factor, similar data being reported by other researchers, Malmberg within the 2009 OASIS study (76) identified a risk 1.89 times higher and Bernton in the ABC2 study published in 2014 (73) drew attention to the long-term mortality rate of diabetic cases with acute coronary events in the medical past.

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