

Doctoral School of Health Sciences

University of Pécs Faculty of Health Sciences

Head of the Doctoral School Prof. Dr. István Kiss



QUALITY OF LIFE IN PATIENTS WITH ACUTE CORONARY SYNDROME
UNDERGOING PRIMARY CORONARY INTERVENTION

Ph.D. Thesis booklet

Mercedes Anna Ahmann

PR-2. Cardiovascular health science

Programme leader:

Prof. Dr. Zsófia Verzár

Supervisor:

Prof. Dr. Zsófia Verzár, Doctoral School of Health Sciences

University of Pécs Faculty of Health Sciences

Pécs, 2023

1. Introduction

Cardiovascular (CV) disease is the leading cause of death worldwide. According to World Health Organization data published in 2021, cardiovascular disease is the leading cause of death worldwide. In the same year, an estimated 17.5 million people died from CVD, accounting for 31% of all deaths.

There is a wealth of research on cardiovascular disease mortality, yet it is shocking to learn that there are around 32 million data-supported CV events each year, but this is actually estimated to be in the billions, based on hypertension, diabetes, dyslipidemia, smoking and physical inactivity. Smoking is responsible for 6% of global mortality and hypertension for 5.8%. Among the Hungarian population, depending on geography and health care, the proportion of hypertensive patients over 65 years of age reaches 50% in some populations. It is important to know that 25% of patients with vascular disease die suddenly or suffer a heart attack or stroke without having previously developed warning clinical signs.

In addition to comorbidities, a significant proportion of cardiovascular deaths are due to coronary atherosclerosis, one of the most common and severe manifestations of which is acute coronary syndrome (ACS), which is an obstruction of blood flow within the coronary artery. ACS is not a single clinical entity and can be divided into ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) based on the ECG.

2. Scientific objective

Acute coronary syndrome is a very frequently researched area. Despite invasive cardiology, modernisation of drug therapy and digitalisation, mortality rates have not changed significantly. Therefore, we considered it important to explore some new perspectives on the underlying causes of morbidity and mortality in ACS. Our investigation was conducted in four planes.

2.1 The first study was a comparative analysis comparing a Hungarian and an Iraqi population of ACS patients and observing baseline disease parameters, therapeutic

differences and outcome. We were curious to discover whether comparing two populations with such different diets, health status, lifestyles and health care would reveal differences that would move morbidity and mortality data in a positive direction. The study concluded with a quality of life questionnaire completed by both populations.

2.2 The second study was to investigate the serum phenylalanine and tyrosine isomer levels in myocardial infarction patients with and without ST elevation, compared with the lifestyle of the patients. Our scientific objective was to draw these conclusions using such an innovative technique as measured oxidative stress factors compared to patients' quality of life. We were assisted in this by a quality of life questionnaire. We wondered whether ACS could be predicted by tyrosine and phenylalanine levels. What are the risk factors that influence tyrosine levels, making them stand out from other risk factors?

2.3 The third study investigated the first and most common presentation of ACS, sudden cardiac death. We wondered what morbidity rates could be expected based on the initial rhythm. We also considered it important to investigate mortality rates associated with the initial rhythm in the University of Pécs.

2.4 The fourth study built on the data from the population under comparative analysis, which was used to investigate the drug adherence of patients with ACS. We were curious about patients' adherence to therapy and the impact of this phenomenon on morbidity and mortality data

3. Material and method

3.1.A prospective study was conducted between May 2018 and May 2019 in parallel at the Pécs Heart Clinic and the Al-Nasiriyah Heart Centre in Iraq. The inclusion criteria were patients diagnosed with acute coronary syndrome according to the guidelines. Exclusion criteria included unstable angina and incomplete documentation. The study included 164 ACS patients, 64 Hungarian and 100 Iraqi. Data collection methods were document analysis and questionnaire analysis.

3.2.A prospective study was conducted at the University of Pécs University Hospital of Cardiology between January 2017 and March 2017. Inclusion criteria included the basic criteria for the diagnosis of ACS, such as T-troponin positivity, ECG abnormalities

demonstrating AMI with or without ST elevation. 44 patients with ACS were included in the study.

3.3 Our retrospective study was based on data recorded by the Emergency Department of the University of Pécs, Hungary. We conducted our research among patients admitted to the Emergency Department from 6 April 2018 to 31 December 2019 who were likely to have cardiac death of cardiological origin. We selected 192 patients for our study and then followed up 181 patients according to our exclusion criteria. We excluded patients in whom we found incomplete documentation and those in whom the classification of the incipient rhythm was not clearly established.

3.4 Data from a previously studied population were reprocessed. A prospective study was conducted in parallel between May 2018 and May 2019 at the Pécs Heart Clinic and the Al-Nasiriyah Heart Centre in Iraq. We worked with database-recorded data of patients admitted by the two invasive cardiology institutions during this period. Inclusion criteria were patients diagnosed with acute coronary syndrome according to the guidelines. 164 ACS patients, 64 Hungarian and 100 Iraqi, participated in the study. The method of data collection was documentary analysis.

4. Results

4.1 Patients were younger in Iraq (61 vs. 68 years, $p=0.001$) and had a more frequent family history of CAD (9.4% vs. 24.0%, $p=0.018$) than in Hungary. In contrast, Hungarian patients were more likely to have hypertension (89.1% vs. 68.0%, $p=0.002$), dyslipidemia (64.1% vs. 42.0%, $p=0.006$), previous MI (98.4% vs. 24.0%, $p=0.000$), previous PCI (92.2% vs. 23.0%, $p=0.000$) and previous CABG (21.9% vs. 1.0%, $p=0.000$) than Iraqi patients. In terms of diagnoses at hospital admission, Iraqi patients were more frequently diagnosed with STEMI (64.0% vs. 26.6%). In contrast, Hungarian patients were more frequently diagnosed with NSTEMI (73.4% vs. 36.0%). In terms of care protocol, PCI was more frequently performed in Hungary (92.2% vs. 70.0%, $p=0.001$) than in Iraq. And CABG was only performed in Hungary (10.9% vs. 0.0%, $p=0.001$), compared to Iraq (Table 3). For patients diagnosed with STEMI, reperfusion therapy, primary PCI, was performed more frequently in Hungary (94.1% vs. 71.9%, $p=0.048$) than in Iraq (Table 3).

In Hungary, 11.8% of patients undergoing PCI for NSTEMI had a negative coronary angiogram, compared with less than 4% of patients with STEMI. In Iraq, 18% of patients with NSTEMI had a negative coronary angiogram, compared with 5% of patients with STEMI, despite the much lower number of PCI procedures.

There was no significant difference between Hungary and Iraq in terms of mortality rate (6.3% vs. 3.0%), cardiogenic shock (7.8% vs. 5.0%), stroke (0.0% vs. 2.0%) and MACE (14.1% vs. 11.0%) during hospital admission. However, Iraqi patients had a higher rate of hospital reinfarction (14.1% vs. 4.0%, $p=0.020$) than Hungarian patients

4.2 The mean age of the 44 ACS patients was 68.1 years. 75% of the patients were female and 25% male. In terms of BMI, the whole population was classified as obese grade I. In terms of risk factors, hypertension stood out as it was present in a very high percentage (79.5%) of the study population. The distribution of STEMI and NSTEMI was 52.3% vs 47.7%, which is in line with the literature. We investigated the severity of coronary artery disease in both STEMI and NSTEMI groups and found that the extent of vascular disease (single-vessel, double-vessel) in the STEMI patient group was similar in men and women. (3.1% vs 4.8%) In the NSTEMI group, severe coronary artery disease was more common in men (3.2% vs 5.2%). Patients completed an SF-36 quality of life questionnaire after the infarction and then the responses of the two populations were compared based on the total score of all 5 question groups. A significant difference was found in favour of the NSTEMI group for daily activity ($p=0.004$). A significant difference was found in favour of the STEMI population for patient-rated physical health ($p<0.001$). In terms of mental health, we found no difference ($p=0.032$) in the NSTEMI patients' judgments of mental health ($p<0.001$). There was a significant difference between the two groups in the judgments of general health ($p=0.003$).

4.3 %. There were no differences between the two groups in terms of demographic data. The mean age of the non-shock group (63.4; $SD=8.7$) was higher than that of the shock group (55.2; $SD=6.8$), which was in line with the data reported in the literature. The proportion of people aged 60 years and over was thus 70% in the non-shock group and 58% in the shock group, significantly higher in both groups ($p=0.002$) ($p=0.004$) In terms of gender distribution, men were predominantly more numerous in both groups. The proportion was 75/37 in the shock group and 41/28 in the non-shock group. We compared the two groups in terms of risk factors and found significant differences in several areas, such as hospital discharge in the hypertension group ($p=0.001$) and one month survival in

the diabetes group ($p=0.001$). We also examined diabetes test and lipid values, where the abnormal blood glucose value showed a significant difference in favour of the group to be shocked. We also looked at obesity and left ventricular hypertrophy as risk factors, but found no significant difference between the two groups for either. We were curious about some other aspects beyond the study objectives that might be informative in estimating survival. We looked at the association between time to first care and survival and there was no significant difference in resuscitation times between the two groups in either case, although return to spontaneous circulation was higher in patients with non-shockable rhythms. The main endpoint of our study was to examine short- and medium-term survival. Our results showed that even in-hospital survival was significantly higher in the shockable rhythm group than in the non-shockable group (62% vs. 38%, $p=0.002$). Similar results were obtained for 1-month survival (54% vs. 16%, $p=0.004$). We further subdivided the survival data beyond the two basic groups into subgroups based on risk factors and compared the shockable and non-shockable groups. Similar to survival, we found a significant difference in this night for hypertension and diabetes. Obesity and left ventricular hypertrophy showed a significant difference in favour of the non-shock group. We were unable to examine 3-month survival because only 1 person remained in the non-shock group, so the results were statistically insignificant, but the numbers are still informative.

4.4 The proportion of males was higher in both the STEMI and NSTEMI groups, while for comorbidities it was higher in the NSTEMI group and these patients were older.

PCI was used in 67% of patients treated for acute myocardial infarction. This was 88% in the STEMI group and 52% in the NSTEMI group.

During the follow-up period, 32% of patients had a primary endpoint event, such as another heart attack or death. In multivariate analysis, here excluding drug adherence, all comorbidities were found to be significant for prognosis.

A very high percentage of patients (80-90%) received the drug therapy prescribed by the guideline at hospital discharge, and we then looked at adherence after one year. We found good adherence ($>80\%$) with clopidogrel, statin, beta blocker, aspirin in 64.9%, 54.4%, 36.5%, 31.7% of patients.

We have examined some aspects as determinants of adherence, such as the presence of PCI, age, previous infarction. Patients undergoing PCI had higher adherence. Clopidogrel OR=2.05 (95% CI 1.87-2.25 $p<0.0001$), statin OR= 1.25 (95% CI 1.15-1.37 $p<0.0001$),

aspirin OR=1.36 (95% CI 1.25-1.50 p<0.0001. For beta blockers the association was not confirmed OR=1.03 (95% CI 0.94-1.18 p=0.434).

5. Discussion

5.1 The results show that Iraqi patients were more frequently diagnosed with STEMI. In Iraq, the rates of PCI and CABG were significantly lower than in Hungary. Regarding reperfusion therapy in patients diagnosed with STEMI, primary PCI was more common in Hungary than in Iraq. This finding was in line with data recorded in the Hungarian Infarction Registry, where primary percutaneous coronary intervention (PPCI) was performed in 91.1% of patients with STEMI. This may be due to the shortage of facilities in Iraq that can perform PCI, despite the large number of patients. This study therefore confirmed the findings of previous clinical trials that there is a wide variation in care practice between countries in the treatment of patients with ACS. We found that there are differences between guidelines and clinical practice.

In both countries, mortality data were similar at hospital admission, with differences at 30 days and one-year follow-up. In Hungary, complications were more frequent during hospital admission. This may be due to higher prevalence of risk factors such as older age, hypertension, dyslipidemia, previous MI and previous PCI in Hungary than in Iraq. And the 30-day and 1-year mortality rates were more favourable in the Hungarian population than in the Iraqi population, which may be due to the higher incidence of primary PCI in Hungary, which is directly proportional to the more favourable mortality outcomes. An additional important finding was that patients with STEMI had a higher risk of major adverse cardiovascular events (MACE) both in hospital and 30 days after discharge than patients with NSTEMI.

It would be interesting to further investigate the long-term prognosis of the group of patients we studied. What would be the results in 10 years' time in the two countries?

It is interesting to note that only physical health and mental well-being differ between the two populations in terms of their subjective health status, as the two groups have similar overall health status.

5.2 Our previous research has served as a basis for our new research. We found that changes in serum levels of different tyrosine isomers can mediate the effects of oxidative stress on

the myocardium and thus lead to the development of myocardial infarction. This study has helped to confirm the association that phenylalanin and tyrosine isomers act via oxidative stress to induce myocardial infarction.

The clinical significance of the present study lies in the fact that it provides an epidemiological perspective on the effects of chronic inflammatory factors, including the development and progression of ACS.

Our main findings were the associations of hypertension and smoking with tyrosine isomers, from which we concluded that these two factors are the two most important influences on oxidative stress factors and that there are measurable differences in the levels of both phenylalanine and tyrosine isomers. In our analysis of risk factors, we found significant associations between SePhe and hypertension and smoking, Se pTyr and hypertension, and Se mTyr and smoking in STEMI. And in NSTEMI, all our studied parameters showed significance with diabetes and Se Phe with smoking. Further significance was found between Se pTyr, Se mTyr, Se oTyr and hypertension.

When comparing quality of life, the picture was very mixed, with NSTEMI patients rating their activity and mental wellbeing as better, while STEMI patients rated their physical health and general health as better.

The shortcoming of the research and the conclusions drawn from it is that we worked with low numbers of elements, but we obtained very striking results that provide a good basis for further studies.

5.3 As with all research, our main objective was to see how we could benefit from the results. We concluded that the survival rate of sudden cardiac death has improved with advances in medicine, but not significantly. However, an examination of risk factors revealed that many factors adversely affect the outcome of sudden cardiac death. Our results suggest that pathological factors involved in left ventricular wall thickening, such as obesity, may indirectly be important pathogenetic factors for survival. We would like to draw attention to the importance of prevention and to the fact that in many cases sudden cardiac death could be prevented if the population were to undergo appropriate screening and eat more healthily and consciously, as diabetes has a very significant impact on the outcome of heart disease. Around the 5 components of metabolic syndrome, high blood glucose levels have the worst physiological effects on the heart.

A further long-term plan for our study was to ensure that lay assistance in the event of sudden death is provided as early and as competently as possible. In 2017, a study among primary school children found that, although the ability to perform CPR depends on the physical development of the child, a high percentage of them are able to perform CPR successfully.

Based on data reported in the European Resuscitation Council (ERC) 2021 recommendation, the survival of IHCA in Europe at 30-day follow-up ranges from 15% to 34%.(88,89) Important factors influencing survival are the initial rhythm, the site of collapse and, most importantly, the proper performance of cardiopulmonary resuscitation (CPR), which highlights the importance of proper resuscitation education in all areas of healthcare.

5.4. The issue of drug adherence is a very practical aspect of patient care. Inadequate adherence is of great importance in terms of patient recovery and deterioration. In our study, we focused on the importance of secondary prevention, with a particular emphasis on drug adherence in patients with indiscriminate infarction. We found good adherence to clopidogrel, statin, beta blocker, aspirin and RAAS inhibitor drugs in patients who underwent PCI for infarction treatment, with higher adherence to therapy demonstrated for all drugs except beta blockers. In multivariate analysis, the greatest benefit was obtained for statin therapy and aspirin therapy.

6. New findings

6.1. COMPARATIVE ANALYSIS OF PATIENTS WITH ACUTE CORONARY SYNDROME

We compared the care and mortality rates of acute coronary syndrome in two countries with different epidemiology, culture and health financing and found that patients who follow the European guideline (ECG within 10 minutes, PCI within 90 minutes) have better mortality rates.

6.2. COMPARATIVE ANALYSIS OF RISK FACTORS FOR TYROSINES AND ACUTE CORONARY SYNDROME

Our main findings were the associations of hypertension and smoking with tyrosine isomers, from which we concluded that these two factors are the two most important influences on oxidative stress factors and that there are measurable differences in the levels of both phenylalanine and tyrosine isomers. In our analysis of risk factors, we found significant associations between SePhe and hypertension and smoking, Se pTyr and hypertension, and Se mTyr and smoking in STEMI. And in NSTEMI, all our studied parameters showed significance with diabetes and Se Phe with smoking. Further significance was found between Se pTyr, Se mTyr, Se oTyr and hypertension.

6.3. SUDDEN CARDIAC DEATH

Survival rates for sudden cardiac death have improved with medical advances, but not significantly. However, an examination of risk factors has shown that many factors have an adverse effect on the outcome of sudden cardiac death. Our results suggest that pathological factors involved in left ventricular wall thickening, such as obesity, may indirectly be important pathogenetic factors for survival.

6.4. DRUG ADHERENCE IN PATIENTS WITH ACUTE CORONARY SYNDROME

The mortality of patients was compared with the adherence to the respective drugs and the result for statins was that a 25% increase in adherence was associated with a 10% reduction in risk. The final highest rate of risk reduction was for aspirin at 15.8%. We found no association between beta blocker and clopidogrel.

7. Acknowledgements

I would like to thank my supervisor, Professor Zsófia Verzár, for enabling my clinical and research work at the Department of Emergency Medicine and the Department of Cardiology of the University of Pécs, and for providing me with the necessary conditions. Her continuous guidance and support, and the shaping of my clinical and research approach have contributed greatly to the results of my scientific activities.

I would like to thank Dr. Attila Kónyi, Associate Professor, who helped me with his expertise.

I would like to thank Professor István Wittmann for allowing me to participate in several research groups, which contributed greatly to my research work.

I would like to thank Dr. Annamária Pakai Karamánné, Associate Professor for her selfless contribution, and I am grateful for her guidance and comments, which helped me a lot in my publication activities.

I would like to thank Dr. Péter Kanizsai, Associate Professor for his help during my publication.

I would like to thank Tímea Csákvári Molnárné for her help during my publication.

Last but not least, I owe my sincere gratitude to my Family and Friends. Their selfless support and constant encouragement were essential to the success of my research.