THE ROLE OF SPECIFIC RISK FACTORS ON THE PROGNOSISOF ACUTE MYOCARDIAL INFARCTION

PhD Thesis – Short version

Réka Skoda

Theoretical and Translational Medicine Division

Semmelweis University

Supervisor: Dávid Becker, MD, PhD, FESC

Official reviewers: Gergely Szabó, MD, PhD

Péter Kenyeres, MD, PhD

Head of the Complex Examination Committee: István Karádi, MD, D.Sc

Members of the Complex Examination Committee:

Charaf Hassan, MSc, D.Sc

Henriette Farkas, MD, PhD

Budapest

2025

I. INTRODUCTION

In our country, more than 30,000 people suffer myocardial infarction every year. Although invasive haemodynamic care and its national network are now at European standards, cardiovascular death is still one of the leading causes of mortality in Hungary. Hungarian patients suffering acute myocardial infarction have worse short- and long-term prognosis compared to those living in West-European countries with similar cardiovascular care network.

Acute coronary syndrome - prevalence

Acute coronary syndrome is a potentially life-threatening disease that affects many patients. The incidence of acute coronary syndrome increases with age, however incidence rates at younger age, under the age of 45 is constantly increasing. Based on data from Hungarian Myocardial Infarction Registry, in hospital-, 30-day- and 1-year mortality in STEMI were 9,9%, 14,4% and 21,2%; in case of NSTEMI 7,7%, 11,8% and 22,9%.

Acute coronary syndrome – therapy, patient management

In case of STEMI, performing primary percutaneous coronary intervention is crucial. Since 2014, acute interventional care in Hungary has been available to everyone within a one-hour driving distance (Figure 1). In case of STEMI every minute counts, the coronary artery is totally occluded.

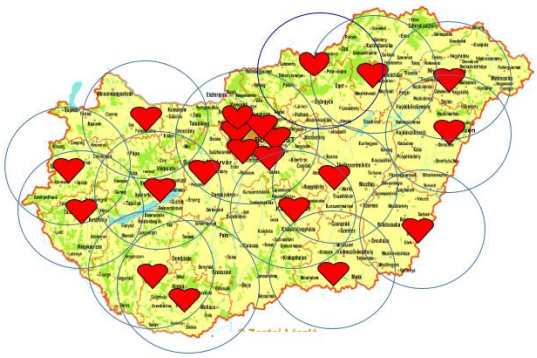


Figure 1: Map of Hospitals with Cath-Lab in Hungary

According to the last ESC Guidelines for the management of acute coronary syndromes, ECG changes and cardiac troponin levels are important in triage and risk stratification, however after the acute management all ACS patients should be treated on a common pathway.

Acute coronary syndrome – risk factors

The health-damaging effect of smoking is known, besides that, sedentary lifestyle, hypertension, high cholesterol, triglyceride levels as well as diabetes mellitus count as conventional risk factors. Diabetes mellitus (DM) is a significant risk factor for cardiovascular disorders, as the abnormal metabolic state increases the risk for atherosclerosis and consecutive vascular occlusive disorders. Due to the lifelong nature of DM, it has been demonstrated to have significant effects on patients' morbidity and mortality. Female gender can appear as a risk factor of ACS mortality. According to some new national and international studies the mortality rates after an acute myocardial infarction are higher than then those men. Differences in age, the less invasive aspect of treatment by women are the possible reasons. Early ventricular fibrillation (EVF) is another risk factor for in-hospital mortality. Early ventricular fibrillation develops within 48-72 hours after the myocardial infarction symptoms' onset, and it is independent from any reoccurring ischaemia or heart failure. Literature regarding the short- and long-term prognosis of patients surviving ST-elevation myocardial infarction complicated by EVF is controversial.

Acute cardiovascular care in Hungary

A recent study, describing characteristics, management and outcomes of hospitalised STEMI patients shows the similarities and differences of acute coronary care in certain European countries (Hungary, Estonia, Sweden and Norway). Despite the fact that Hungary has the second highest number of PCI hospitals and has the highest number of primary PCI centres with 24/7 service, unfortunately Hungary had the highest standardized death rate of all-cause and of ischaemic heart disease among these countries in the studied period (2014-2017). The comparison of the in-hospital management showed that Hungary had the highest number of primary PCI-s, and invasive treatment strategies and rates of recommended medications at discharge were high. In spite of the high level acute cardiovascular care and treatment strategies Hungary had the worst 30-day (15.2%) and 1-year (23.3%) mortality. The Hungarian AMI population had almost the highest rate of modifiable risk factors.

II. OBJECTIVES

The analysis was performed by studying the data of a Hungarian single-center database containing the data of more than 10,000 consecutive patients suffering from acute myocardial infarction. The follow-up period is uniquely taking place over a very long period.

The main goal of our research is:

1. Examination of the country specific factors influencing the prognosis of acute myocardial infarction
2. Reviewing whether early invasive strategy could reduce mortality rates to a Western-European level
3. Investigating whether female sex could have a negative effect on prognosis after suffering acute myocardial infarction due to its not typical presentation or aetiology
4. Evaluation of the impact of diabetes and kidney disease on prognosis before the era of the new diabetes modifying drugs
5. Analysing the importance of early ventricular fibrillation, as one of the most common potentially lethal complication after acute myocardial infarction.

III. METHODS

Patient population: VMAJOR-MI Registry

A total of 12120 patients with acute coronary syndrome have been undergoing percutaneous coronary intervention between 2005 and 2013 at our institution. Follow up time was 4366 days. The first patient was enrolled on the 1st April 2005, and end-point data of all-cause mortality was collected on 15th March 2017. These consecutive patients' data was collected into a retrospective database called the Városmajor Myocardial Infarction Registry (VMAJOR-MI Registry), in which all the available demographic data and clinical data are summarized. Our database comprised patients having Type 1 myocardial infarction, those with Type 2 myocardial infarction were excluded, as well as patients undergoing urgent coronary artery bypass grafting.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved in advance by the locally appointed ethics committee (30088- 2/2014/EKU). The outcome of the study was all-cause mortality. The National Health Care Institute provided the accurate details on the above endpoint with occurrence dates.

Subgroup analysis:

- Impact of sex on the survival of acute myocardial infarction
- Impact of diabetes – before the era of the new disease modifying drugs

From the detailed VMAJOR-MI-registry only patients with conformed diabetic state were enrolled to our diabetes study; patients treated conservatively and undergoing CABG were excluded. Among the enrolled patients 4388 subjects had diabetes.

- The significance of early ventricular fibrillation

EVF was defined as ventricular fibrillation requiring defibrillation in the first 48 h after AMI. Patients in the EVF group included those who suffered VF before or after revascularization as long as it was within 48 h. n our study, the resuscitation data refer to on-site, lay resuscitation. Only patients who received protocol-based care and resuscitation at the clinic were included in the study. Other types of ventricular arrhythmias, such as ventricular tachycardia, were not examined.

- Prognosis of NSTEMI patients complicated by EVF at higher age

From our database we enrolled only patients having NSTEMI. We divided patients into two groups based on whether their myocardial infarction led to EVF. Patients were further grouped based on age (above or below the age of 70 years).

- Prognosis and clinical characteristics of patients with EVF

Two groups were created based on the fact that AMI was complicated by EVF or not. Patient group with EVF was further divided regarding their general condition (good vs. poor). We evaluated the patients' clinical characteristics at discharge. Patients who were released home or to a cardiac rehabilitation facility and did not require further in-patient cardiac care (no heart failure, no recurrent malignant arrhythmia) created the good general condition patient group. To the poor general condition group, we enrolled patients who died at our institution or were transferred to another department on invasive respiratory treatment or needed further in-patient cardiac care because of heart failure, arrhythmias or any other even non-cardiac reasons.

Statistical methods

The results are expressed as mean standard deviation of mean (S.D.) and sample size (n) for each treatment group with normal distribution. The normal distribution of data was checked by applying the Shapiro–Wilk's test. When the non-normally distributed data were analysed, the homogeneity of variances was assessed using a Levene's test. The means were compared using a Student's t-test in case of normal distribution and (ii) a Mann–Whitney-Wilcoxon test was used for datasets that were not normally distributed. A separate analysis of variance (ANOVAs) with a Tukey's correction for multiple comparisons was applied where appropriate. A Pearson chi-square test (c2) or Fisher's exact test was applied in the case of categorical data.

Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazard model. Survival time of the different patient groups was compared using Kaplan- Meier survival analysis. All statistical analysis was two-tailed; the level of significance was $p<0.05$.

IV. RESULTS

Impact of sex on the survival of acute myocardial infarction

There was a significant difference ($p<0.001$) between the mean age of women (70±12.5 years) and men (64±12.8 years). Despite the age difference the incidence of complications after an AMI such as heart failure ($p=0.046$), CPR ($p=0.017$) and ventricular fibrillation ($p=0.008$) were significantly lower among women.

Considering the mean time frame in case of a STEMI (7.9 ±12.7 hours by women; 7.5 ±13.9 hours by men) there was no difference. Although we found that in general women got proper care sooner than men, it is worth to highlight that young women who died within one month reached the hospital significantly later than men below the age of 45 (18.3 hours ± 11.6; 6.1 hours±3.6; $p=0.0025$).

Among women below the age of 45 heart failure (25%) and NSTEMI (61%) was more common than at higher age ($p=0.005$). Besides that, comparing the results of young men and women, we found that NSTEMI is significantly more common by women below the age of 45 (61%, 87/143; 51%, 285/564; $p=0.03$).

The effect of diabetes mellitus and chronic renal failure on the prognosis in the pre-Disease Modifying Drug-era

Diabetic patients are more likely to suffer NSTEMI, and are associated with worse left ventricle and renal function; resulting poorer survival chances.

We compared the prognosis of diabetic and non-diabetic patients based on the type of the myocardial infarction, left ventricle- and renal function. Figure 2 shows the mean survival days of the different patient groups.

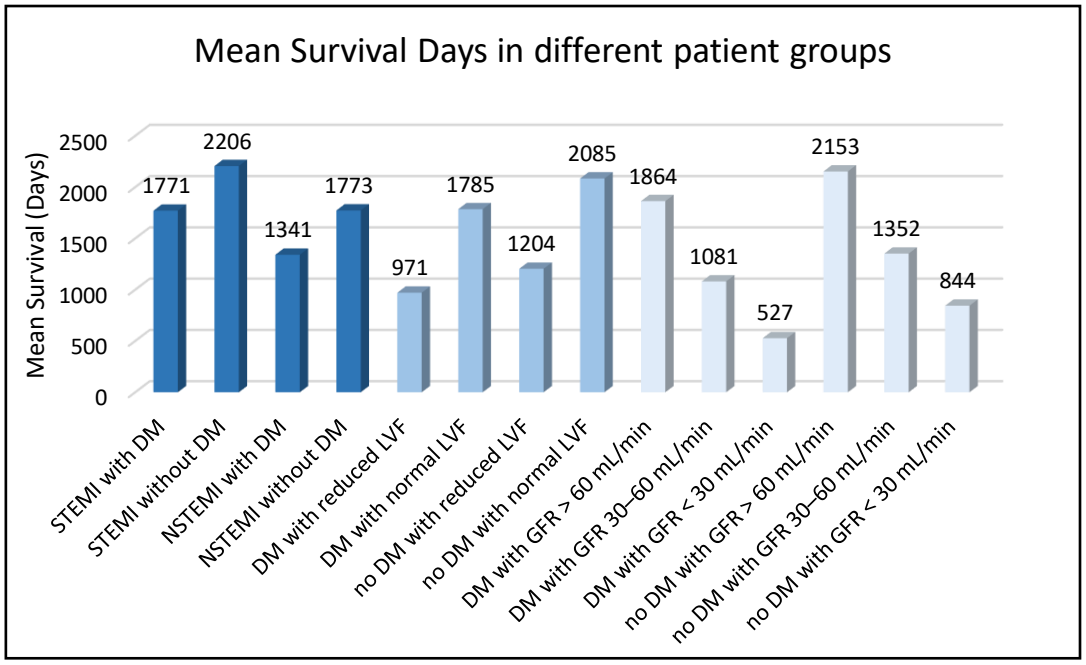


Figure 2.: Survival of patients regarding the presence or absence of diabetes mellitus in patients surviving myocardial infarction, in patients with reduced vs. normal left ventricular function, with reduced vs. normal renal function

We used Kaplan-Meier analysis to predict the most vulnerable patient group regarding the prognosis. In the first analysis we compared 4 patient group based on the type of the myocardial infarction and the diabetic state (Figure 3.1)

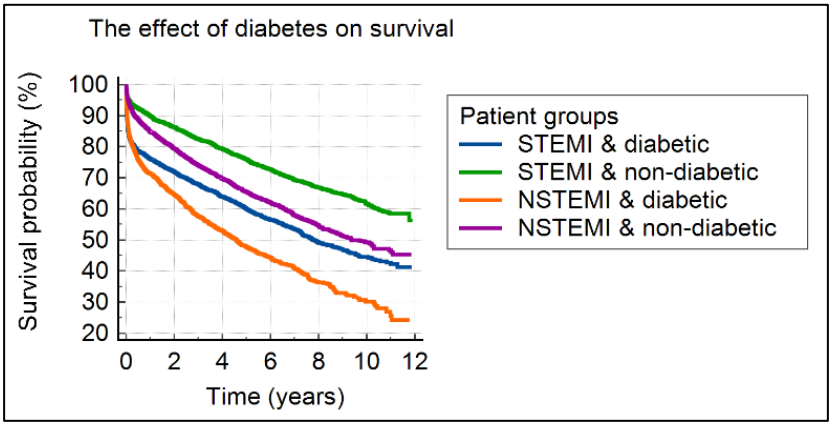


Figure 3.1: Kaplan-Mayer analysis illustrating survival in diabetic versus non-diabetic patients with ST-elevation versus non-ST-elevation myocardial infarction

The second Kaplan-Meier analysis presented that survival is primary affected by the left ventricle function rather than diabetes mellitus Figure 3.2. Similar results occurred reviewing the renal function Figure 3.3.

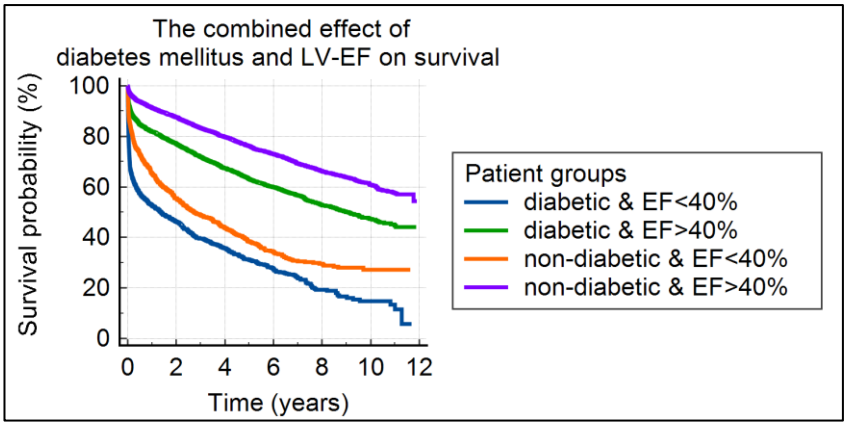


Figure 3.2: Kaplan-Mayer curves illustrating survival in diabetic versus non-diabetic patients with reduced versus normal left ventricular function

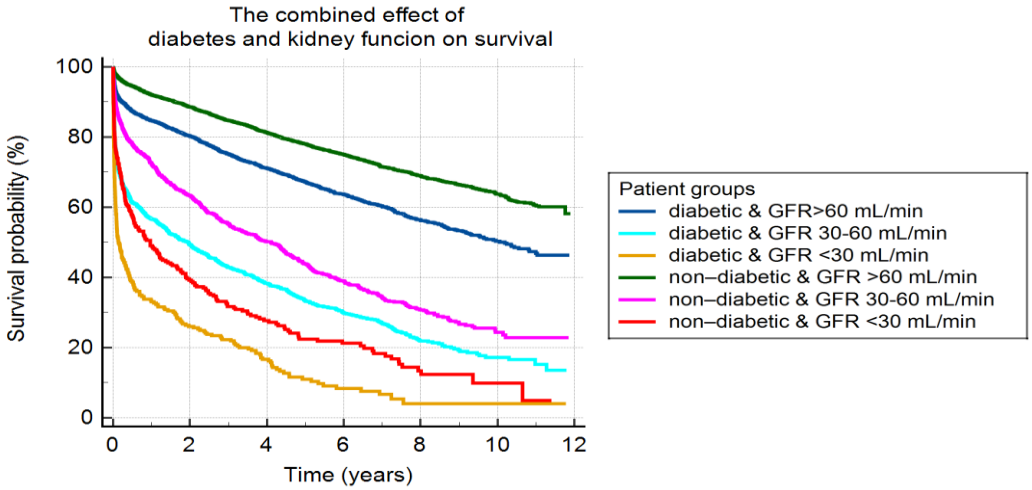


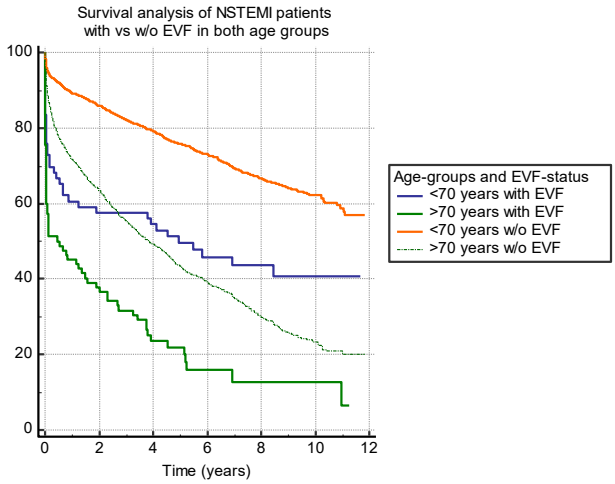
Figure 3.3: Kaplan-Mayer curves illustrating survival in diabetic versus non-diabetic patients with worsening renal function

The significance of early ventricular fibrillation

Prognosis of NSTEMI patients complicated by EVF at higher age

NSTEMI is more common at higher age, however ventricular fibrillation is still the most serious early complication. Examining the significance of the EVF with these conditions is particularly less studied.

NSTEMI patients suffering EVF had the following clinical characteristics: poor left ventricle function, larger infarct size characterized by higher troponin, and higher CKMB, and were more likely to have diabetes. They suffered more severe infarction with more complications such as cardiogenic shock and increased need for invasive respiratory treatment. Given these significant differences, it is not surprising that EVF-positive patients also had higher mortality rates than control patients. 30-day mortality was 24% vs 4.6% and 1-year mortality was 39% vs 10.6% in EVF vs. non-EVF patients.



EVF patients at younger , as well as at older age, >70 years had significantly ($p<0.0001$) lower survival probability compared to non-EVF ones (Figure 4)

Figure 4: Survival analysis of EVF-positive compared to EVF-negative NSTEMI patients in both age groups

Cox regression analysis showed that in patients <70, EVF is an independent risk factor for all mortality (HR:2.38), in addition to other factors such as diabetes mellitus (HR: 2.02), heart failure (HR: 3.66), cardiogenic shock (HR: 8.99), and invasive respiratory treatment (HR: 5.4). Similarly, in patients above the age of 70 years, EVF is also an independent risk factor for mortality (HR: 2.1) as well as diabetes mellitus (HR: 1.5), heart failure (HR: 2.4), cardiogenic shock (HR: 4.85), and invasive respiratory treatment (HR: 3.2). Seeing the significance of the EVF being independent risk factor for mortality in NSTEMI, we found that further evaluation of risk factors for mortality in NSTEMI complicated by EVF is necessary. Factors influencing mortality in NSTEMI patients surviving EVF are presented in Table 1.

Factors influencing mortality in NSTEMI patients surviving EVF below the age of 70				***Factors influencing mortality in NSTEMI patients surviving EVF above the age of 70***			
	HR	**95% CI of HR**	**P**		**HR**	**95% CI of HR**	**P-**
LVEF (%)	0.95	0.92 to 0.98	0.0009	**LVEF (%)**	0.97	0.95 to 0.99	0.011
Diabetes mellitus	1.93	1.29 to 2.88	0.0014	**Diabetes mellitus**	1.47	0.90 to 2.40	0.1262
Cardiogenic shock	6.14	2.96 to 12.76	<0.0001	**Cardiogenic shock**	2.32	1.27 to 4.25	0.0065
Heart failure	2.65	1.34 to 5.22	0.0049	**Heart failure**	1.33	0.82 to 2.18	0.2571
CPR	2.50	1.30 to 4.82	0.006	**CPR**	1.08	0.63 to 1.84	0.7901
2-vessel disease	1.293	0.57 to 2.92	0.5473	**2-vessel disease**	1.13	0.67 to 1.84	0.6330
3-vessel disease	2.13	0.89 to 5.06	0.0872	**3-vessel disease**	1.76	0.91 to 3.41	0.0948

Table 1: Cox regression analysis of factors influencing mortality in NSTEMI patients surviving EVF

EVF developed before revascularization (75%, 51/68) in most subject below the age of 70 years. The timing had no influence on either the short- or long-term mortality. At higher age (>70 years), most EVF also developed before revascularization (74%, 61/82). In contrast to younger patients, in patients >70 years, EVF that occurs after revascularization was associated with a higher risk of 30-day mortality (OR 11.2), however 1-year mortality was not significantly different.

Prognosis and clinical characteristics of patients with EVF in the 6-week guideline offered time period in STEMI and NSTEMI

In order to see whether it is safe to wait 6 weeks before the assessment of implanting an implantable cardioverter defibrillator we divided our patients in low risk and high-risk patient groups. Potentially high-risk patients in poor general condition have been compared to the assumed low-risk good general condition patient group. Patients in poor general condition were older, more likely to have diabetes, reduced left ventricle and kidney function. They had higher cardiac biomarker, peak troponin T levels, higher lactate dehydrogenase (LDH) levels meaning more necrosis, larger infarct size. Inflammatory parameters were elevated as well. The acute event was more severe: higher rate of heart failure events and cardiogenic shock. Three-vessel-disease complicated with poor condition was associated with higher 6-week mortality (93.02%, 40/43; P=0.0043).

25 patients were discharged in good condition however died within 6 weeks. Comparing their clinical data to those who survived, the following factors were found to be significant: mean age (74 vs. 62 years, P=0.0119), diabetes (83.33% vs. 49.70%, P=0.0022), mean troponin T (5,764 vs. 3,137 ng/L, P=0.0161), LVEF <40% (59.09% vs. 21.71%, P=0.0023), more severe acute event—heart failure (52.00% vs. 20.00%, P=0.0073), invasive respiratory treatment (72.00% vs. 28.12%, P=0.0002).

When comparing EVF-negative patients dying within 6 weeks to EVF-positive patients in good general condition dying within 6 weeks no significant difference between the two groups were found besides diabetes.

V. CONCLUSION - OUR NEW FINDINGS:

1. In the aspect of acute coronary syndrome care, early invasive strategy can reduce the higher mortality rates when compared to Western-European countries.

2. Similarly early invasive strategy is beneficial in case of women suffering myocardial infarction. However, traditional risk factors – such as higher cholesterol levels, type of the myocardial infarction, heart failure - do not influence the prognosis in women at younger age.

3. When investigating the role of traditional risk factors like diabetes mellitus, reduced kidney function, we confirmed the negative impact of both risk factors which highlights the importance of the new antidiabetic drugs – SGLT2 inhibitors, GLP-1 agonists.

4. Our results showed that EVF is an independent risk factor for mortality. The first 3 years past the index event is critical in the prognosis of young patients surviving myocardial infarction complicated by EVF.

5. The timing of ICD implantation for secondary prevention is crucial regarding the prognosis of the patients. Our results support that it is safe to wait 6 weeks with the evaluation, but we could select a certain patient population who would benefit from a closer follow up – reduced left-ventricle function, NSTEMI, complicated index event.

VI. PUBLICATIONS

Related to the present Thesis

1. **Skoda, R** ; Nemes, A ; Bárczi, G ; Gajdácsi, J ; Vágó, H ; Ruzsa, Z ; Édes, IF ; Szabó, L ; Czimbalmos, C ; Sydó, N; Dinya, E; Merkely, B; Becker, D Prognosis and clinical characteristics of patients with early ventricular fibrillation in the 6-week guideline-offered time period: is it safe to wait 6 weeks with the assessment? (results from the VMAJOR-MI Registry) QUANTITATIVE IMAGING IN MEDICINE AND SURGERY 11 : 1 pp. 402-409. , 8 p. (2021)
2. **Skoda, R**; Nemes, A; Bárczi, Gy; Vágó, H; Ruzsa, Z; Édes, I F; Oláh, A; Kosztin, A; Dinya, E; Merkely, B; Becker, D Survival of Myocardial Infarction Patients with Diabetes Mellitus at the Invasive Era (Results from the Városmajor Myocardial Infarction Registry) JOURNAL OF CLINICAL MEDICINE 12 : 3 Paper: 917 , 8 p. (2023)
3. **Skoda, R**; Bárczi, Gy; Vágó, H; Nemes, A; Szabó, L; Fülöp, G; Hizoh, I; Domokos, D; Törő, K; Dinya, E, Merkely, B; Becker, D Prognosis of the non-ST elevation myocardial infarction complicated with early ventricular fibrillation at higher age GEROSCIENCE: OFFICIAL JOURNAL OF THE AMERICAN AGING ASSOCIATION (AGE) 43 : 5 pp. 2561-2571. , 11 p. (2021)
4. **Skoda, R** ; Bárczi, Gy ; Vágó, H; Czimbalmos, Cs ; Doan, NK ; Édes, I F; Ruzsa, Z; Dinya, E; Merkely, B; Becker, D Miokardiális infarktusos nők halálozásának epidemiológiai vizsgálata CARDIOLOGIA HUNGARICA 48 : 6 pp. 380-383. , 4 p. (2018)

Other publications

1. Becker, D; Fülöp, GÁ ; Sax, B ; **Skoda, R** ; Merkely, B A kardiológia kihívásai a COVID-19-pandémia idején ORVOSKÉPZÉS 95 : 3 pp. 510-516. , 7 p. (2020)
2. Juhász, V ; Ország, A ; Balla, D ; Szabó, L ; Sydó, N ; Kiss, O ; Csulak, E ; Babity, M ; Dohy, Zs ; **Skoda, R**; Becker, D; Merkely, B; Benczúr, A; Vágó, H Blood Test-Based age Acceleration Is Inversely Associated with High-Volume Sports Activity

MEDICINE AND SCIENCE IN SPORTS AND EXERCISE 56 : 5 pp. 868-875. , 8 p. (2024)

3. Voith, L; Nowotta, F**; Skoda, R**; Merkely, B; Becker, D Koszorúér-angioplasztika súlyos miokardiális infarktusban a légzés és a keringés eszközös támogatásával CARDIOLOGIA HUNGARICA 50 : 2 pp. 106-110. , 5 p. (2020)

4. Voith, L; Édes, I.F. ; **Skoda, R**. ; Szigethi, T. ; Becker, D. ; Merkely, B. Nem ST-elevációs infarktus – az intervenciós szívizommentés mostohagyereke: Egy intézet tapasztalatai ORVOSI HETILAP 164 : 47 pp. 1865-1870. , 6 p. (2023)

5. Voith, L; Édes, I F; Zima, E; Szigethy, T ; **Skoda, R** ; Becker, D; Merkely, B Koronáriaintervenció akut miokardiális infarktusban SARS-COVID-19-járvány alatt CARDIOLOGIA HUNGARICA 53 : 1 pp. 37-41. , 5 p. (2023)

6. Ocsovszky, Zs; Otohal, J; Berényi, B; Juhász, V; **Skoda, R**; Bokor, L; Dohy, Zs; Szabó, L; Nagy, Gy; Becker, D, Merkely. B; Vágó. H The associations of long-COVID symptoms, clinical characteristics and affective psychological constructs in a non-hospitalized cohort PHYSIOLOGY INTERNATIONAL 109 : 2 pp. 230-245. , 16 p. (2022)

7. Voith, L; Édes, I F; Nowotta, F; **Skoda, R**; Bárczi, Gy; Merkely, B; Becker, D Primer coronariaintervenció ST-elevációs infarktusban: Változások öt év alatt ORVOSI HETILAP 162 : 13 pp. 497-503. , 7 p. (2021)

8. Becker, D; **Skoda, R**; Bokor, L; Bárczi, Gy; Vágó, H; Gajdácsi, J ; Belicza, É; Nemes, A; Dinya, E; Törő, K; Merkely, B A hazai szívinfarktus-ellátás eredményét befolyásoló tényezők elemzése LEGE ARTIS MEDICINAE 30 : 8-9 pp. 383-390. , 8 p. (2020)

9. **Skoda, R**; Fulop, G; Csulak, E; Danics, K; Toro, K; Bokor, L; Barczi, Gy; Merkely, B; Becker, D The secondary effect of the first wave of COVID-19 and its consequences on myocardial infarction care in a high volume Hungarian cardiovascular centre COR ET VASA 63 : 3 pp. 345-349. , 5 p. (2021)

10. **Skoda, R** ; Juhász, V ; Dohy, Z ; Pintér, A ; Bokor, L ; Bárczi, G ; Vágó, H ; Merkely, B ; Becker, D The effect of COVID-19 pandemic on myocardial infarction care and on its prognosis - Experience at a high volume Hungarian cardiovascular center. PHYSIOLOGY INTERNATIONAL 109 : 3 pp. 419-426. , 8 p. (2022)

11. Pólos, M; Domokos, D; Şulea, C-M; Benke, K; Csikós, G; Nagy, A; **Skoda, R**; Szabó, A ; Merkel, E; Hartyánszky, I; Szabolcs, Z; Merkely, B; Becker, D Needle in the heart: a rare case of cardiac tamponade caused by a migrated foreign body and mimicking ST segment elevation myocardial infarction BMC CARDIOVASCULAR DISORDERS 21 : 1 Paper: 143 , 6 p. (2021)