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

PhD Thesis

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LIST OF ABBREVIATIONS

ACS – Acute Coronary Syndrome

AMI – Acute Myocardial Infarction

BMI – Body Mass Index

CABG – Coronary Artery Bypass Grafting

CAD – Coronary Artery Disease

CI – Confidence Interval

CK – Creatine Kinase

CK-MB – Creatine Kinase - MB

CPR – Cardiopulmonary Resuscitation

CRP – C-Reactive Protein

CRT – Cardiac Resynchronization Therapy

DM – Diabetes Mellitus

DMD – Disease Modifying Drug

ECG - Electrocardiography

ESC – European Society of Cardiology

EVF – Early Ventricular Fibrillation

GFR - Glomerular Filtration Rate

GLP-1 – Glucagon-like Peptide 1

GRACE – Global Registry of Acute Coronary Events

HR – Hazard Ratio

ICD – Implantable Cardioverter Defibrillator

LV – Left Ventricle

LVEF – Left Ventricle Ejection Fraction

MI – Myocardial Infarction

NSTE-ACS – Non.ST-elevation Acute Coronary Syndrome

NSTEMI – Non ST-elevation Myocardial Infarction

OR – Odds Ratio

PCI – Percutaneous Coronary Intervention

SGLT-2 – Sodium-Glucose Transport Protein 2

ST.D. – Standard Deviation

STEMI – ST-elevation Myocardial Infarction

VF – Ventricular Fibrillation

VT – Ventricular Tachycardia

WBC- White Blood Cell

I. INTRODUCTION

In our country, more than 30,000 people suffer myocardial infarction every year (1). 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.

The topic of this PhD thesis is the examination of the data of more than 12,000 patients who underwent percutaneous coronary intervention due to acute myocardial infarction between 2005 and 2014 at the Heart and Vascular Center of Semmelweis University. Retrospective analysis of risk factors leading to myocardial infarction and factors influencing short- and long-term survival. We would focus on investigating risk factors which can cause the gap in mortality rates when comparing European and Hungarian statistics.

Acute coronary syndrome

Prevalence

Acute coronary syndrome is a potentially life-threatening disease that affects a large number of patients. In Europe, the average incidence of myocardial infarction is 100-500/100,000 inhabitants/year, although there are some geographical differences. In the Mediterranean countries this number is 100-200, in Western Europe 200-300, in Hungary 400-500. Lifetime prevalence is 30% in men and 15% in women. The incidence of acute coronary syndrome increases with age, however incidence rates at younger age, under the age of 45 is constantly increasing (2). 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% (1). Based on the latest Eurostat data from 2021 Hungary had one of the highest mortality rate regarding acute myocardial infarction (~6000 death/9.6 million inhabitants), as well as regarding all cardiovascular mortality (~ 21000 death/9.6 million inhabitants).* Figures below show Hungary's status amongst the European countries in acute myocardial infarction - (Figure 1a) and all cardiovascular mortality (Figure 1b)

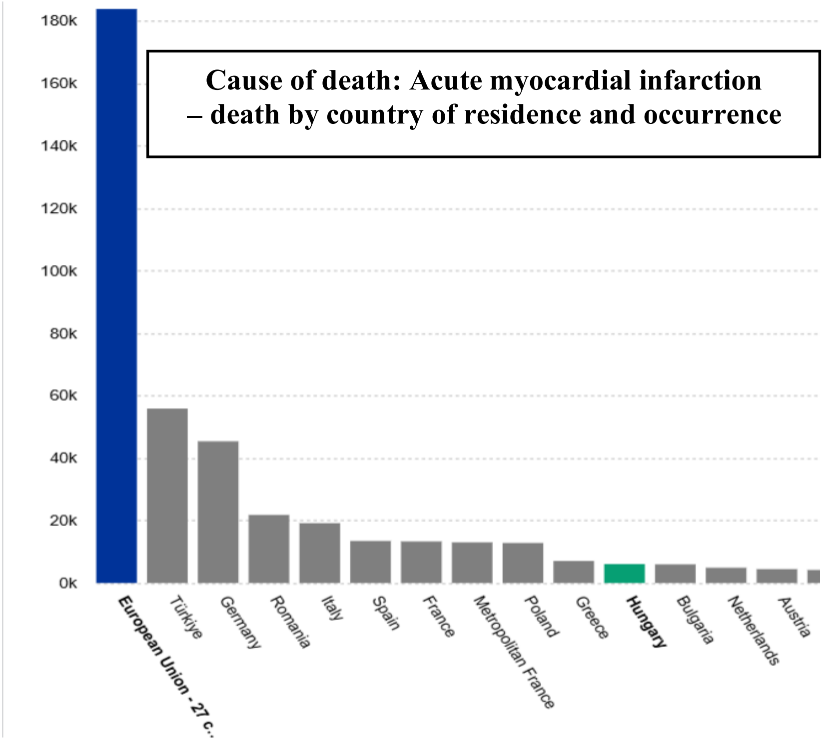

Figure 1a: Acute myocardial infarction – mortality in European countries

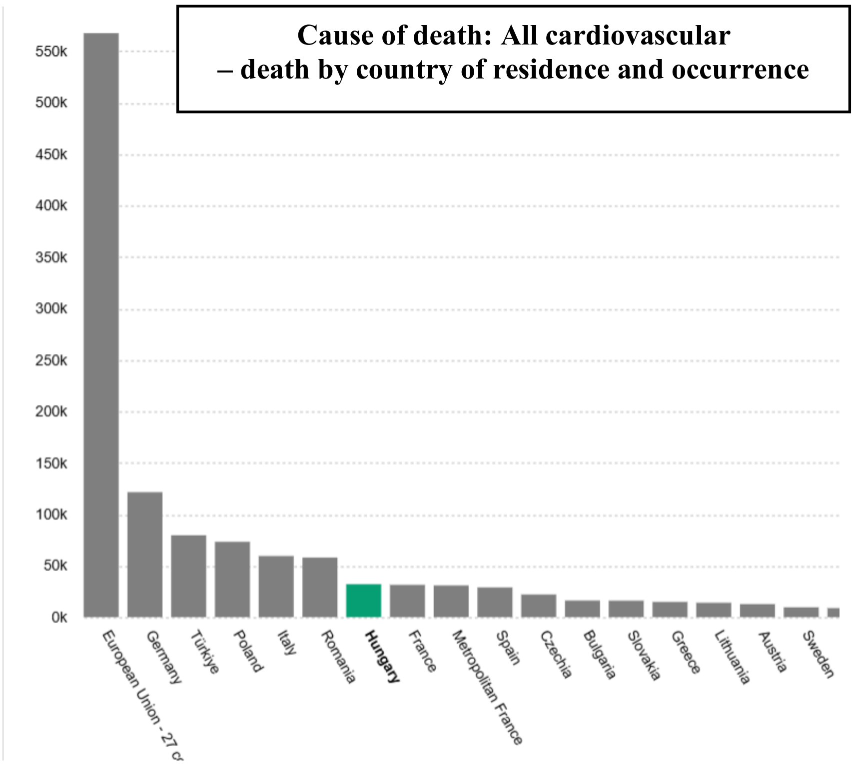

Figure 1b: Cardiovascular mortality in European countries*

*https://ec.europa.eu/eurostat/databrowser/explore/all/all_themes?lang=en&display=list&sort=category

Definition

Acute coronary syndrome includes all medical conditions characterized by acute insufficiency of blood and oxygen supply to a part of the heart muscle. The clinical manifestations of ACS are ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina (Figure 2). The diagnosis is based on the electrocardiogram (ECG) and the biomarker levels. If in addition to typical chest pain ST-segment elevation, left or right bundle branch block is shown on the ECG, the diagnosis is ST-elevation myocardial infarction (STEMI). If, in addition to typical chest pain and biomarker positivity, other ECG abnormalities appear, such as ST-depression (>1mm) in the two connected leads, T-wave changes, turning negative (>1mm) or no visible ECG abnormalities at all, then the diagnosis is myocardial infarction without ST-elevation (NSTEMI). If, in addition to typical symptoms of ischemia, we do not experience an increase in biomarker levels, we are talking about unstable angina. Acute coronary syndrome is usually due to a dynamic change occurring in an unstable, vulnerable plaque - ulceration, rupture, haemorrhage - which might lead to thrombosis and vasospasm. Partial, subendocardial lumen obstruction is usually characteristic of NSTEMI, while complete, transmural, subepicardial obstruction is characteristic of STEMI.

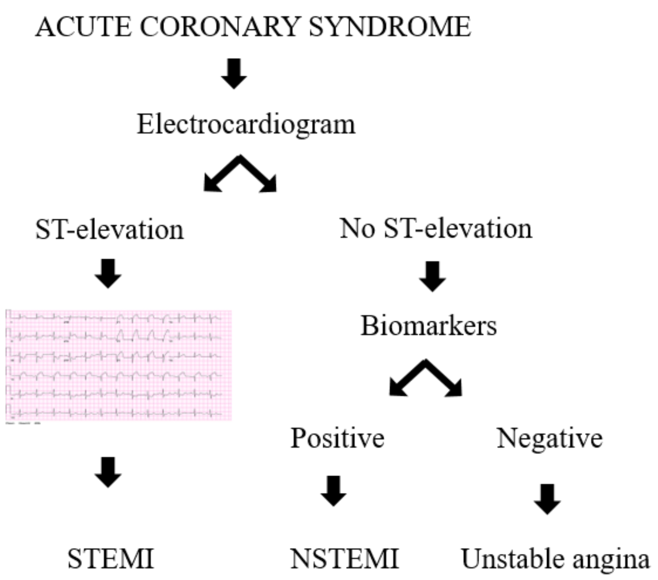

Figure 2: The clinical manifestations of acute coronary syndrome

The Fourth Universal Definition of Myocardial Infarction differentiates myocardial injury from myocardial infarction. “The term myocardial injury should be used when there is evidence of elevated cardiac troponin values.” Acute myocardial infarction means acute myocardial injury with clinical evidence of myocardial ischaemia with changing troponin levels and one of the following: symptoms of myocardial ischaemia or new ischaemic ECG changes or development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of a coronary thrombus by angiography. The Universal Definition of Myocardial Infarction classifies acute myocardial infarction (AMI) into 5 different groups based on the pathomechanism and characteristics of its development. In Type 1, the intraluminal thrombus develops on the basis of atherosclerotic plaque rupture, ulceration, fissure or dissection. In Type 2, the oxygen demand of the myocardium and the oxygen supply is unbalanced, which can be traced back to anaemia, coronary spasm or arrhythmia. Type 3 includes sudden cardiac death, often confirmed during autopsy. Infarction experienced during percutaneous coronary intervention belongs to group 4a, while stent thrombosis proven in connection with angiography or autopsy belongs to group 4b. Finally, Type 5 is classified as a myocardial infarction caused during a coronary bypass (CABG) procedure. The higher mortality observed at a younger age can be explained by the different pathomechanism, small vessel disease, spontaneous coronary dissection, and plaque erosion are more common. An atypical, smaller infarction is associated with less heart muscle death, so a low biomarker level further complicates the diagnosis(3).

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 3). In case of STEMI every minute counts, the coronary artery is totally occluded. Each 30-minute delay increases mortality by approximately 7.5% (4-6).

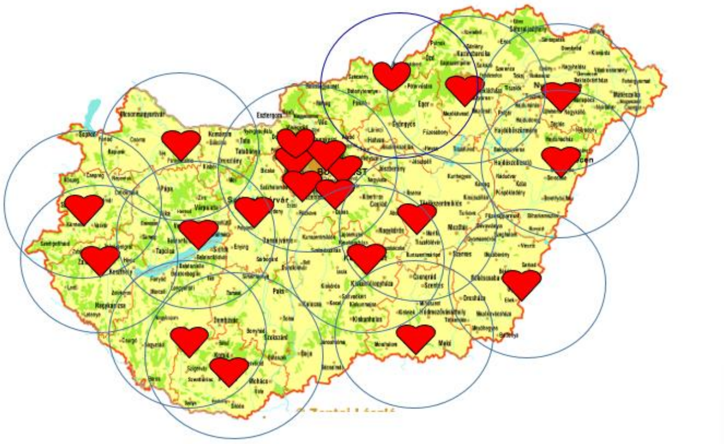

Figure 3: Map of Hospitals with Cath-Lab in Hungary

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(7). For patients presenting with persistent ST-segment elevation immediate primary percutaneous coronary intervention is crucial, within 2 hours of the diagnosis based on ECG. Even 24 hours after the first symptoms, the primary PCI strategy is justified if symptoms of ischemia still exist, in case of hemodynamic instability or life-threatening cardiac arrhythmias.

Risk stratification plays an important role in the management and treatment of acute coronary syndrome without ST-segment elevation. Immediate invasive strategy (<2h) is necessary in very high risk NSTEMI patients. This means hemodynamic instability, cardiogenic shock, recurrent/refractory chest pain despite medical treatment, life-threatening arrhythmias, mechanical complications of MI, acute heart failure clearly related to NSTE-ACS, ST-segment depression > 1mm/ 6 leads plus ST-segment elevation aVR and/or V1. An early invasive strategy is defined as coronary angiography performed within 24 h of hospital admission. It is recommended in high risk patients: established

NSTEMI diagnosis, dynamic new or presumably new contiguous ST/T-segment changes, GRACE-score>140.

Risk factors, prevention

The health-damaging effect of smoking is known, there is a significant correlation between developing heart diseases and smoking. Besides smoking, sedentary lifestyle, hypertension, high cholesterol, triglyceride levels as well as diabetes mellitus count as conventional risk factors(8-10). The attention of researchers is increasingly directed toward non-conventional risk factors. Lately, the role of genetic factors, the effect of systemic inflammation, elevated homocysteine- and lipoprotein A levels are highly investigated. Lipoprotein A's role on atherosclerosis, and its target as a treatment option is highly investigated(11, 12). Primary prevention, minimizing the development of the main risk factors, contributes the most to reducing cardiovascular mortality, however it is important to highlight the importance of secondary prevention, treatment protocols defines by the guidelines.

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(13). Due to the lifelong nature of DM, it has been demonstrated to have significant effects on patients' morbidity and mortality(14). In diabetic patients the control of cardiovascular risk factors leads to substantial reductions in cardiovascular events. Studies have shown that newer antidiabetic drugs (SGLT-2 inhibitors, GLP1 agonists) have favourable cardio metabolic effect besides their traditional glucose lowering effect (15).

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 (16). Differences in age, the less invasive aspect of treatment by women are the possible reasons (17). There are sex differences in pathophysiology, clinical presentation and prevention of coronary heart disease (18). Differences in pathophysiology may suggest different therapeutic approach, in some cases less invasive management. The clinical presentation of a myocardial infarction in women often differs from the typical chest pain or chest discomfort. They can present with atypical chest pain, dyspnea, weakness or fatigue. These differences can affect the appropriate identification of ischemic symptoms which can result in delayed revascularization, more complications after AMI and higher mortality rates (19). The current guidelines do not offer a diagnostic perspective that takes the differences in both sexes into consideration

Complications and prognosis

There are different score systems to determine the outcome of acute coronary syndrome, which can be used to figure out the probability of death in the hospital, in 30-days, in 6 months, in 1 year. The GRACE Score, recommended by the European Society of Cardiology, is an internationally validated score system with data from more than 100,000 patients, which can be used to individually calculate the probability of survival for each patient. In order to calculate the survival probability 8 variables are needed: age, pulse rate, systolic blood pressure, Killip-class, creatinine level, biomarker levels, cardiac arrest at admission, ST-segment deviation (20).

In the United States the TIMI risk assessment system is more used, needing less variables: blood pressure and pulse rate, age (21). The Reynold Risk Score predicts the 10-year probability of suffering acute myocardial infarction or stroke. This risk score is based on age, blood pressure, cholesterol levels, smoking, inflammation (CRP-level) and genetic effects (acute myocardial infarction by parents before the age of 60 years (22). These risk scores can help in objective, individual risk stratification, in order to choose high-risk patients who will benefit from an early invasive care or need closer follow-up at discharge.

Complications of acute coronary syndrome and their severity depend on the extent, time and location of the occlusion. Cardiogenic shock is one of the main cause of mortality after myocardial infarction, in-hospital death probability is 50% (23). Cardiogenic shock can occur in STEMI as well as in NSTEMI, and have similarly high mortality. In STEMI the severe necrosis and myocardial damage caused by the acute occlusion might lead to cardiogenic shock. In NSTEMI the acute hypoxia, electrical inhomogeneity is the cause. Myocardial ischaemia, the arrhythmogenic scar tissue and increased sympathetic tone can lead to ventricular tachyarrhythmias. According to the GISSI-2 trial early ventricular fibrillation (EVF) is an independent risk factor for in-hospital mortality (24). 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. Implantable cardioverter defibrillator (ICD) implantation as primary prevention is recommended for patients who have heart failure with reduced left ventricular function despite optimal medical treatment six weeks after the acute event. In the early period (within 40 days), ICD implantation or the use of a portable defibrillator vest is recommended for incomplete revascularization, previous reduced systole left ventricular function or in the case of malignant ventricular arrhythmia more than 48 hours after the infarction (7).

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) (25).

Table 1: Background information for Estonia, Hungary, Norway, and Sweden for 2014-207*

Acute coronary care baseline information (Hungary, Estonia, Norway, Sweden)				
	HUNGARY	ESTIONIA	NORWAY	SWEDEN
Population (million)	9.84	1.32	5.23	9.93
Average life expectancy at birth (years)				
Men	72.4	73	80.5	80.9
Women	79.4	81.9	84.2	83.9
All-cause mortality[1]	1473.2	1263.5	943.3	926.2
Death rate of ischaemic heart disease[1]	384.3	272.5	93	124.1
Number of PCI hospitals	20	5	7	29
Number of primary PCI centres with 24/7 service	19	2	6	12

[1] standardized, per 100 000 population

*Based on the Table 1 from Eur Heart J Qual Care Clin Outcomes. 2022 May 5;8(3):307-314

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 time period (2014-2017) (Table 1). The comparison of the in-hospital management showed that Hungary had the highest number of primary PCI-s, and invasive treatment strategies (Table 2) 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 (Table 3). The Hungarian AMI population had almost the highest rate of modifiable risk factors (Table 4).

Table 2: Comparison of in-hospital management in Estonia, Hungary, Norway and Sweden*

In hospital management				
	HUNGARY n=23685	ESTIONIA n=4584	NORWAY n=12414	SWEDEN n=23342
Reperfusion, % (95% CI)	82 (81.3-82.3)	75.7 (74.4-76.9)	79.4 (78.7-80.1)	84 (83.5-84.4)
Thrombolysis, % (95% CI)	0.5 (0.4-0.5)	12.4 (11.5-13.4)	13.2 (12.6-13.8)	3.2 (3-3.4)
Primary PCI, % (95% CI)	80.6 (80.1-81.1)	63.4 (62-64.8)	66.2 (65.4-67)	77.3 (76.8-77.9)
Coronary angiography, % (95% CI)	83.1 (82.6-83.5)	80.4 (79.2-81.5)	84.6 (83.9-85.2)	93 (92.7-93.4)
PCI, % (95% CI)	81.3 (80.8-81.8)	72.8 (71.5-74.1)	77.8 (77.1-78.6)	89.1 (88.7-89.5)

*Based on the Table 3 from. Eur Heart J Qual Care Clin Outcomes. 2022 May 5;8(3):307-314

Table 3: Age standardized 30-day and 1-year death rate in Estonia, Hungary, Norway and Sweden*

Age standardized mortality rates				
	HUNGARY	ESTIONIA	NORWAY	SWEDEN
30 days, % (95% CI)	15.02 (14.6-15.7)	11.8 (10.9-12.9)	12 (11.4-12.6)	8.8 (8.4-9.2)
1 year, % (95% CI)	23.3 (22.7-24)	18.7 (17.5-19.9)	15.5 (14.8-16.2)	13.1 (12.5-13.6)

*Based on the Table 6 from Eur Heart J Qual Care Clin Outcomes. 2022 May 5;8(3):307-314

Table 4. Modifiable Risk factors in Estonia, Hungary, Norway and Sweden*

Modifiable risk factors				
	HUNGARY	ESTIONIA	NORWAY	SWEDEN
BMI, median	27	28	26	26
Current smoker, % (95% CI)	32.0 (30.3–33.2)	34.5 (33.1–35.9)	38.0 (37.1–38.8)	25.1 (24.6–25.7)
Hypertension, % (95% CI)	73.9 (73.3–74.5)	78.6 (77.4–79.8)	39.2 (38.3–40.0)	49.4 (48.7–40.0)
Diabetes mellitus, % (95% CI)	28.3 (27.7–28.9)	20.6 (19.5–21.8)	13.9 (13.3–14.5)	13.9 (13.3–14.5)
Hyperlipidaemia, % (95% CI)	28.7 (28.1–29.4)	66.1 (64.7–67.5)	22.5 (21.8–23.3)	23.2 (22.7–23.8)

*Based on Table 2 from Eur Heart J Qual Care Clin Outcomes. 2022 May 5;8(3):307-314

In order to identify the cardiovascular risk factors of the Hungarian population we previously compared our data to the GRACE (Global Registry of Acute Coronary Events) Registry patients. Table 5 shows that our patients' cardiovascular risk profile at admission is worse than the European- American average. Our patient population was significantly older, more likely to have hypertension and diabetes, and had worse Killip classification profile indicating worse cardiovascular outcome.

Table 5: Comparison of the risk factors of the Hungarian and GRACE Registry population

	Hungarian cohort n=1400	**GRACE cohort n=15007**	**p-values**
Age, years (mean)	67.7	65	<0.0001
Prior MI, %	41.4	32.0	<0.0001
Prior PCI, %	23.6	15.3	<0.0001
Prior CABG, %	9.9	13.4	<0.0001
Hypertension, %	64.6	58.2	<0.0001
Diabetes mellitus, %	34.4	23.5	<0.0001
Chronic heart failure, %	11	10.1	0.1434
Pulse rate at admission, beat/min (mean)	75	79	<0.0001
Systolic blood pressure, Hgmm (mean)	130	143	<0.0001
Cardiac biomarker positivity, %	71.9	33.6	<0.0001
Killip-class I, %	77.6	84.2	<0.0001
Killip-class II, %	14.9	12.7	0.0188
Killip-class III, %	5.1	2.7	<0.0001
Killip-class IV, %	2.4	0.4	<0.0001
Cardiac arrest, %	2.4	1.2	0.0002

During our analysis, we compared the expected and actual mortality of our NSTEMI patients at 6 months using the GRACE risk calculator. Based on the classification at the time of admission, the expected and actual mortality of patients in medium (3-8%) and high risk (>8%) groups is shown is Figure 4. The expected mortality without PCI calculated on the basis of the GRACE-score is higher than the mortality of the GRACE population. The long-term life expectancy of NSTEMI patients treated with PCI is much better compared to the non-PCI treated group. PCI improves the originally expected poor outcome of our patients to a European level.

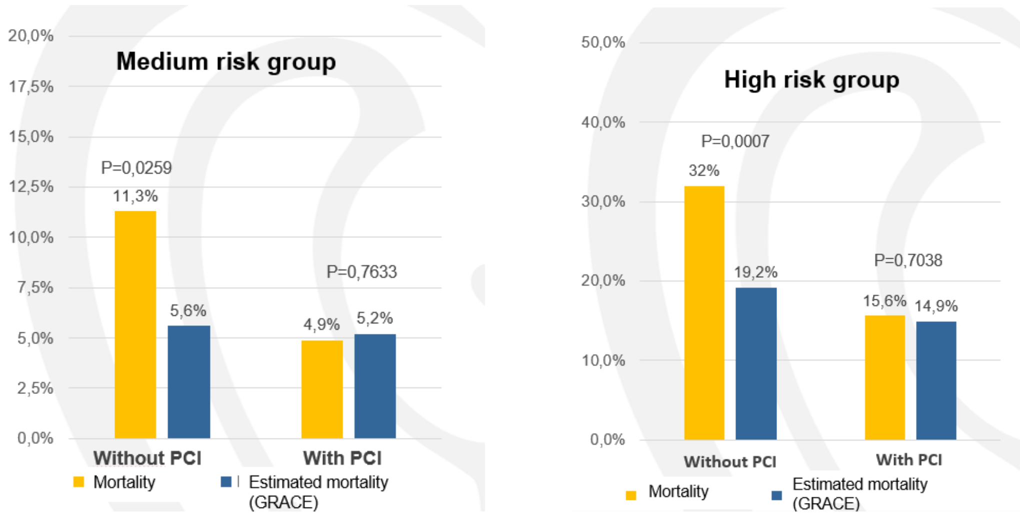

Figure 4: Comparison of mortality rates (real and estimated) with and without coronary intervention

II. OBJECTIVES

The main goal of our research is:

1. Examination of the factors influencing the prognosis of acute myocardial infarction, the importance and role of these factors is not clear according to the current literature
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.

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 of time.

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. Demographic data include gender, date of birth, date of admission, and date of death. Clinical patient data include laboratory findings at admission (troponin T, CK-MB, creatinine, glucose, cholesterol, LDL-cholesterol), type of infarction (STEMI, NSTEMI), results from echocardiography, left ventricle ejection fraction (LV-EF), and coronary angiography. The initiating acute event has been characterized by the following factors: complicated by EVF, cardiogenic shock, on-site resuscitation, heart failure, invasive respiratory treatment. Table 6 shows the general characteristics of our patient population.

Table 6: General clinical characteristics of VMAJOR-MI Registry patient population

General characteristics of VMAJOR-MI Registry patient population	
Mean Age (years±SD)	66.5 ±12.9
Male (%)	62.3
Mean BMI (kg/m^2±SD)	27.8 ±5.2
Mortality characteristics of VMAJOR-MI Registry patient population	
Mean survival (days±S.D)	1771 ±1203
30-days mortality (%)	8.7%
1-year mortality (%)	18.4%
Characteristics of the acute event	
STEMI (%)	46.6%
EF (%±SD)	48.7 ±12.4
Cardiogenic shock (%)	5.4%
Ventricular fibrillation (%)	4.5%
Need for respiratory treatment (%)	9.6%
Heart failure after MI (%)	18.1%

For the diagnosis of STEMI, a clinical presentation typical of ongoing myocardial ischaemia, ST-segment elevation in at least 2 consecutive leads on the 12-lead electrocardiogram (ECG), and subsequent confirmation by elevation of necrosis markers were required. For the diagnosis of NSTEMI, only necrosis marker elevation with typical symptoms, such as chest discomfort, upper extremity discomfort, dyspnoea, fatigue, were required. Coronary stenosis was evaluated from multiplane projections and a luminal diameter reduction of >50% was considered significant. The extent of the coronary artery disease was evaluated based on the number of coronary arteries with significant stenosis. Left Main (LM) artery stenosis was considered as a separate entity.

The definition of cardiogenic shock was based on clinical criteria, such as systolic blood pressure <90 mm Hg with adequate volume and clinical or laboratory signs of hypoperfusion. Clinical signs of hypoperfusion are cold extremities, oliguria, mental confusion, narrow pulse pressure. Laboratory findings are metabolic acidosis, elevated serum lactate and creatinine(26).

The diagnosis of heart failure was made by the existing clinical symptoms like breathlessness, ankle swelling, elevated jugular venous pressure, pulmonary crackles, peripheral oedema(26).

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.

Impact of sex on the survival of acute myocardial infarction

We performed a retrospective analysis on the data of 12120 consecutive patients (4573/12120, 38% women; 7547/12120, 62% men) suffering acute myocardial infarction. Parameters examined included age, the type of the myocardial infarction (STEMI or NSTEMI), troponin levels, the time frame in case of a STEMI. Short term, 30 day and long term, 1-year survival data was calculated in the patients.

Diabetes study – before the era of the new diabetes 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, while 7018 patients were non-diabetic. The primary outcome of the study was all-cause mortality. The National Health Care Institute provided accurate details on the above endpoint with occurrence dates. 30-day and 1-year mortality as well as long term survival was examined in different patient groups based on diabetic state, type of myocardial infarction, systolic heart performance and kidney function.

The definition of DM was based on the American Diabetes Association (27), meaning higher than normal blood glucose level. Diabetic patients defined as patients having higher blood sugar levels than normal (>= 7,8 mmol/L). HgA1c levels were not available.

Transthoracic echocardiography was performed in all the cases in accordance with applicable guidelines. The LV function was represented by LV-EF. The laboratory examinations included the evaluation of renal function using GFR in all the subjects. The severity of renal dysfunction was established according to recent guidelines (28).

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 and clinical characteristics of patients with EVF

From this epidemiological sub-study only patients managed conservatively or treated with CABG were excluded. 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.

Prognosis of NSTEMI patients complicated by EVF at higher age

From our database we enrolled only patients having NSTEMI. Patients with ST-segment elevation, those treated conservatively or underwent CABG were excluded. We divided patients into two groups based on whether or not their myocardial infarction led to EVF. Data from EVF-positive patients was supplemented by information on laboratory parameters such as potassium levels, white blood cell (WBC) count, and C-reactive protein (CRP) levels, as well as by information on detailed coronary status such as the number of vessels affected, and the number of vessels treated by PCI. Patients were further grouped based on age (above or below the age of 70 years).

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.

The Kaplan–Meier product-limit method of survival analysis was used to summarize the follow-up. The differences in survival rates between groups were tested using a long-rank test. The analysis was two-sided, with a level of significance of 0.05. All the statistical analyses were performed using the SAS 9.4 (SAS Institute Inc., Cary, NC, USA) software package. For offline data analysis and graph creation, a commercial software package was used (Microsoft Excel 2016).

Cox proportional hazard model was used to identify whether EVF was an independent risk factor for mortality. The model included the general risk factors such as age, gender, diabetes mellitus, left ventricle function, severity of acute event—heart failure, cardiogenic shock, invasive respiratory treatment—and EVF. Cox regression analysis was performed in order to identify clinical characteristics associated with mortality. The model included all available risk factors of acute coronary syndromes and ventricular fibrillation such as gender, age, body mass index (BMI), diabetes mellitus, LV-EF, complications of the acute event (on-site CPR, cardiogenic shock, heart failure), coronary angiographic results (coronary status—vessels affected, PCI results— stent implantation on how many vessels), and the time of the VF (before, during, or after the revascularization but within 48 h). 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 (Table 7.1.).

Table 7.1.: The incidence of complications after acute myocardial infarction in

Comparison of the incidence of complications after acute myocardial infarction between women and men			
	WOMEN	MEN	p
Ventricular Fibrillation	3.8% (173/4517)	4.9% (362/7468)	**0.0083**
CPR	2.1% (96/4517)	2.8% (211/7468)	**0.0173**
Heart failure	17.3% (779/4517)	18.7% (1396/7468)	**0.0458**
Need for respiratory therapy	9.3% (419/4517)	9.7% (723/7468)	0.4633
Cardiogenic shock	5.2% (235/4517)	5.6% (415/7468)	0.4051

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 in the time frame. Comparing the mortality rates of men and women in case of early (performed within 6 hours) and late (performed after 12 hours) STEMIs the one month/ one-year mortality rates were higher. The difference showed a tendency but it was not significant (Table 7.2.).

Table 7.2: 30-days and 1-year mortality rates based on the timeframe in case of STEMI

The 30-days and one-year mortality rates of women and men based on the timeframe in case of STEMI						
	Early- 30 days mortality			**Late- one-year mortality**		
TIME-FRAME	**WOMEN**	**MEN**	**p**	**WOMEN**	**MEN**	**p**
<6 h	7.6% (75/987)	6.9% (119/1723)	0.4281	16.2 (160/987)	15.2% (261/1723)	0.3854
6-12 h	7.7% (24/312)	10.% (51/509)	0.3728	15.7% (49/312)	18.9% (96/509)	0.3195
>12 h	10.3% (24/234)	6.8% (27/400)	0.3260	21.4% (50/234)	16.5% (66/400)	0.2522

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). Women below the age of 45 who died within one month had significantly higher STEMI rates (75%, 6/8; 37%, 52/139; p=0.0383) and mean triglyceride levels (mmol/L) (2.24±1.61; 1.38±0.94; p=0.0277) compared to all young women. There was no significant difference in case of one-year mortality between these two groups. 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). We examined the risk factors affecting the prognosis by all patients as well as at younger age (Table 7.3.). Higher cholesterol levels, the presence of cardiogenic shock and heart failure worsens the survival. Patients with NSTEMI have worse outcome compared to those with STEMI.

Table 7.3.: The risk factors influencing the prognosis at all age and below 45 years

The risk factors influencing the prognosis among all patients and at younger age						
		Parameter Estimate	P value	Hazard Ratio (HR)	95% HR Lower CL	95% HR Upper CL
All patients	**STEMI**	-0.0779	**<0.0001**	0.86	0.79	0.92
	Cardiogenic shock	0.0810	**0.0361**	1.17	1.01	1.37
	Heart failure	0.0702	**0.0028**	1.15	1.05	1.26
	Cholesterol	0.0330	**0.0153**	1.03	1.01	1.06
Women	**Cholesterol**	0.0478	**0.0358**	1.05	1.00	1.09
	STEMI	-0.0863	**0.0045**	0.84	0.75	0.95
<45 years all patients	STEMI	-0.0998	0.185	0.82	0.61	1.10
	Cardiogenic shock	0.1520	0.3812	1.35	0.68	2.68
	Heart failure	0.0913	0.2924	1.20	0.85	1.68
	Cholesterol	0.0813	0.1702	1.08	0.96	1.22
<45 years women	Heart failure	-0.0044	0.9828	0.99	0.44	2.21
	STEMI	0.0213	0.9062	1.04	0.51	2.12
	Cholesterol	0.0611	0.6447	1.06	0.82	1.38
	Cardiogenic shock	0.7802	**0.0102**	4.76	1.45	15.64
	Need for respiratory therapy	0.4808	**0.0283**	2.61	1.11	6.18

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

Our analysis showed significant differences in demographic and clinical data in patients with vs without diagnosed diabetes mellitus. The detailed analysis is shown in Table 8.1.

Table 8.1.: Demographical and clinical characteristics of our patient population

Demographic and clinical data of our patients			
	Patients with DM	**Patients without DM**	***p***
mean age (years)	68.0 ± 12.7	65.0 ± 13.3	<0.0001
male (%)	57.7 (2533/4388)	65.3 (4585/7018)	<0.0001
mean BMI (kg/m^2)	28.6 ± 5.4	27.4 ± 5.4	<0.0001
mean survival (days)	1560 ± 1201	1971 ± 1180	<0.0001
30-day mortality (%)	13.5 (586/4330)	4.3 (299/6987)	<0.0001
1-year mortality (%)	25.7 (1111/4330)	12.4 (869/6987)	<0.0001
NSTEMI (%)	45.7 (1916/4195)	55.6 (3701/6662)	<0.0001
STEMI (%)	54.3 (2279/4195)	44.5 (2961/6662)	<0.0001
ventricular fibrillation (%)	6.9 (300/4334)	3.2 (221/6940)	0.0600
cardiogenic shock (%)	10.2 (442/4334)	2.6 (179/6942)	0.0020
heart failure (%)	26.8 (1162/4334)	12.9 (892/6942)	<0.0001
mean LV-EF (%)	46.0 ± 13.8	50.2 ± 11.3	<0.0001
mean cholesterol (mmol/L)	4.6 ± 1.4	4.7 ± 1.34	0.0429
mean LDL-cholesterol (mmol/L)	2.98 ± 1.31	3.0 ± 1.3	0.0899
mean triglyceride (mmol/L)	1.6 ± 1.4	1.4 ± 1.1	<0.0001
mean eGFR (mL/min)	72.9 ± 30.3	83.7 ± 31.1	<0.0001
mean creatinine (um/L)	104 ± 69.3	92.5 ± 66.9	<0.0001
mean peak Troponin (ng/L)	2478 ± 4560	1613 ± 3010	<0.0001

Diabetic patients are more likely to suffer NSTEMI, and are associated with worse left ventricle and renal function. Diabetic patients have poor survival chances. Table 8.2 shows the mean survival days in our patient groups based on left ventricle and renal function.

Table 8.2: Mean survival days in diabetic and non-diabetic patients based on left ventricle- and renal function

Mean survival (days) of patients with versus without diabetes mellitus			
	Patients with DM	**Patients without DM**	***p***
STEMI (n)	1770	2206	<0.0001
NSTEMI (n)	1341	1773	<0.0001
LV-EF < 40%	970	1203	<0.0001
LV-EF > 40%	1784	2085	<0.0001
GFR > 60 mL/min	1863	2152	<0.0001
GFR 30-60 mL/min	1080	1351	<0.0001
GFR < 30 mL/min	527	843	<0.0001

We compared the prognosis of diabetic and non-diabetic patients based on the type of the myocardial infarction, left ventricle- and renal function. Figure 5 shows the mean survival days of the different patient groups.

In both myocardial infarction types diabetic patients had worse 30-day- and 1-year mortality rates compared to non-diabetic ones. In case of STEMI 30-day- as well as 1-year mortality was higher in diabetic patients (13.6% vs 4 % p=0.0022; 22.7% vs 9. 5%

p<0.001). We detected the same significant differences in NSTEMI patients as well (12,6% vs 4,5% p=0,0029; 28,1% vs 14,7% p<0,0001).

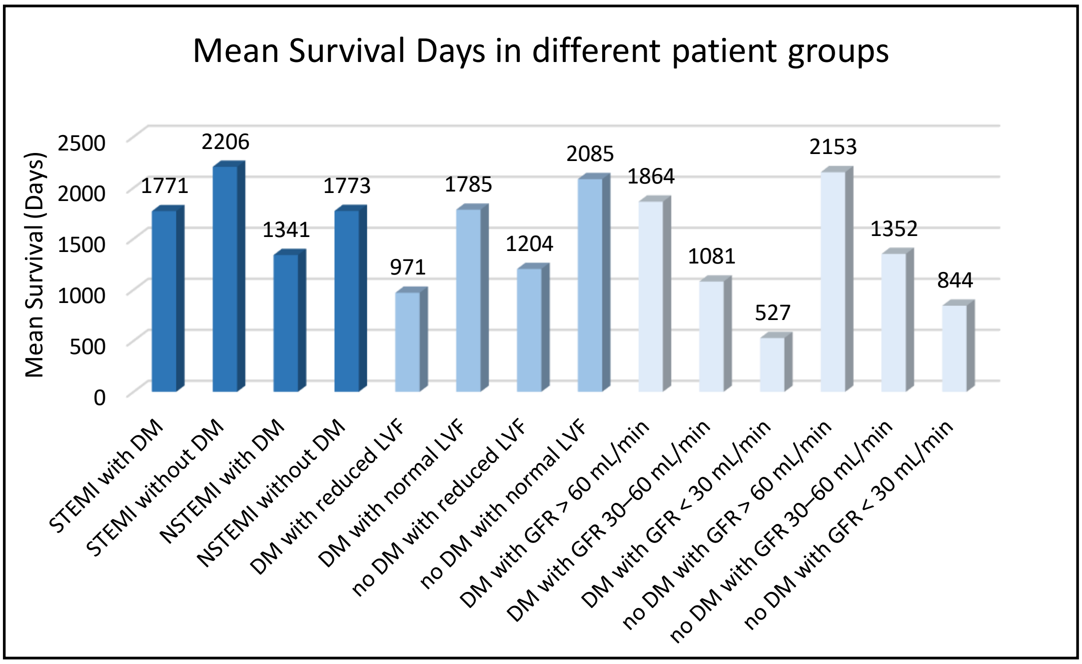

Figure 5.: Survival of patients regarding the presence or absence of diabetes mellitus in patients surviving myocardial infarction, in patients with reduced vs. normal left ventricular function, with reduced vs. normal renal function

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 6.1 shows that diabetic patients have worse prognosis.

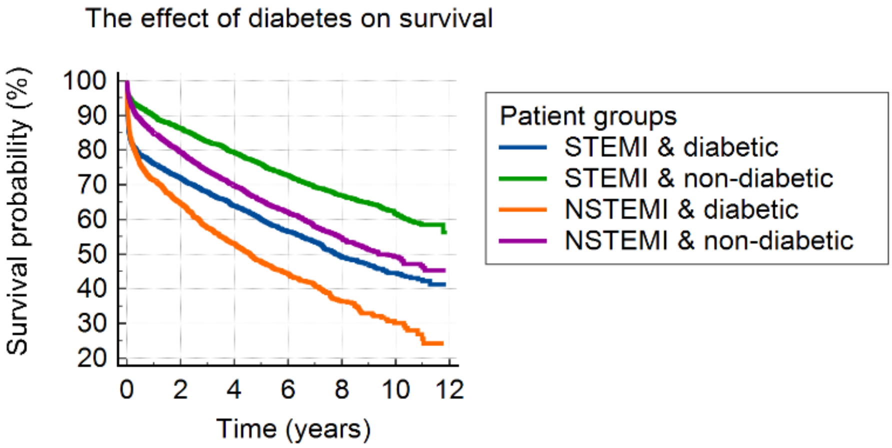

Figure 6.1: Kaplan-Mayer analysis illustrating survival in diabetic versus non-diabetic patients with ST-elevation versus non-ST-elevation myocardial infarction

The second Kaplan-Meier analysis presented that survival is primary affected by the left ventricle function rather than diabetes mellitus Figure 6.2. Similar results occurred reviewing the renal function Figure 6.3.

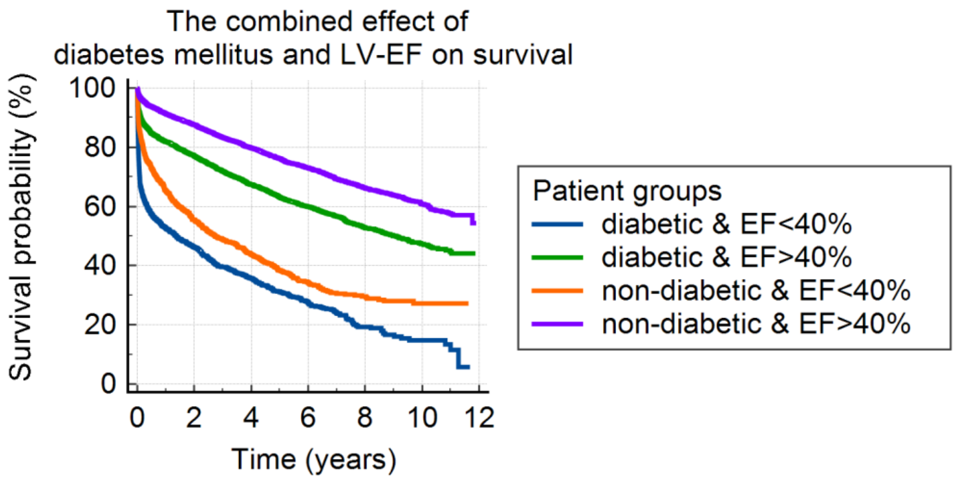

Figure 6.2: Kaplan-Mayer curves illustrating survival in diabetic versus non-diabetic patients with reduced versus normal left ventricular function

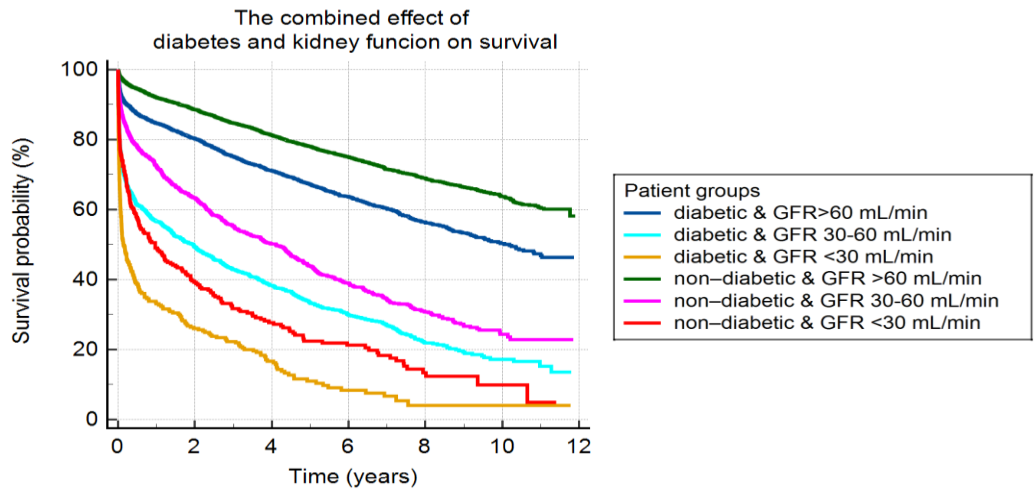

Figure 6.3: Kaplan-Mayer curves illustrating survival in diabetic versus non-diabetic patients with worsening renal function

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.

In order to analyse the significance of EVF we compared first the clinical characteristics of patients below the age of 70 years having NSTEMI with and without EVF. 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 <70, respectively. However, additional mortality (mortality between 30 days and 1 year) did not differ significantly. (Table 9.1)

Table 9.1: Clinical characteristics of NSTEMI patients, differences between EVF-positive and EVF-negative patients

Characteristics of patients < 70 years			
	with EVF	**w/o EVF**	**p**
Gender, male (%)	66.7% (44/66)	68.6% (2108/3074)	0.7871
Mean BMI (kg/m^2)	29.2±6.4	28.8±5.5	0.564
LV-EF<40% (%)	**39.2% (20/51)**	**15% (367/2455)**	**0.0041**
Serum Creatinine>100 umol/L (%)	**39.7% (25/63)**	**20.6% (588/2860)**	**0.0223**
Mean Troponin T (ng/L)	**2073.9±3219.1**	**902.3±1992.2**	**0.0006**
Mean CK-MB (U/L)	**158.7±195.2**	**74.8±94.3**	**<0.0001**
DM (%)	**55.6% (35/63)**	**30.3% (850/2802)**	**0.0016**
Mean cholesterol (mmol/L)	4.7±1.5	4.8±1.4	0.4649
Mean LDL-cholesterol (mmol/L)	2.9±1.3	3.05±1.3	0.3811
Heart failure (%)	27.3% (18/66)	14.4% (442/3074)	0.132
Cardiogenic shock (%)	**18.2% (12/66)**	**2.2% (66/3074)**	**0.0149**
Reanimation (%)	**31.8% (21/66)**	**0.9% (28/3074)**	**0.0021**
Invasive respiratory treatment (%)	**43.9% (29/66)**	**5.6% (172/3074)**	**<0.0001**
Mean survival (days)	**1587.9±1465.7**	**1924.5±1079.8**	**0.013**
30-days mortality (%)	**24.2% (16/66)**	**4.6% (141/3074)**	**0.0027**
1-year mortality (%)	**39.4% (26/66)**	**10.6% (326/3074)**	**<0.0001**
Mortality between 30 days and 1 year (%)	15.2% (10/66)	6.0% (185/3074)	0.2536

*p-value: difference between EVF-positive and EVF-negative NSTEMI patients. Statistical significant differences highlighted bold.

Similar analyses were performed on the patient population above the age of 70. (Table 9.2). Similar findings were found as seen in the younger patient group. Patients with EVF were more likely to have reduced left ventricle ejection fraction (44.4% vs 22.8%) and diabetes (53% vs 37%). They also had more severe complications after the acute event including cardiogenic shock (18% vs 4%) and the need for invasive respiratory treatment (56% vs 9%). Similarly, to the younger patient group, NSTEMI patients above 70 years had higher30-day and 1-year mortality in the EVF group vs non- EVF group (40% vs 10% for 30 days and 55% vs 28% for 1 year).

Table 9.2: Clinical characteristics of NSTEMI patients above the age of 70 years, differences between EVF-positive and EVF-negative patients

Characteristics of patients > 70 years			
	with EVF	**w/o EVF**	**p**
Gender, male (%)	64.6% (53/82)	53,0% (1548/2923)	0.094
Mean BMI (kg/m^2)	26.6±4.4	27.1±4.8	0.4132
LV-EF<40% (%)	**44.4% (32/72)**	**22.8% (529/2323)**	**0.0053**
Serum Creatinine>100 umol/L (%)	58.2% (46/79)	44.0% (1205/2736)	0.0574
Mean Troponin T (ng/L)	1235.7±1695.8	841.1±1638.1	0.1232
Mean CK-MB (U/L)	**103.5±94.8**	**77.3±94**	**0.0311**
DM (%)	**53.2% (42/79)**	**37.0% (989/2672)**	**0.0344**
Mean Cholesterol (mmol/L)	**3.9±1.4**	**4.3±1,3**	**0.0167**
Mean LDL-cholesterol (mmol/L)	2.3±1.3	2.6±1.2	0.0666
Heart failure (%)	40.2% (33/82)	26.3% (768/2923)	0.0762
Cardiogenic shock (%)	**18.3% (15/82)**	**4.4% (128/2923)**	**0.0297**
Reanimation (%)	**29.3% (24/82)**	**0.7% (20/2923)**	**0.0105**
Invasive respiratory treatment (%)	**56.1% (46/82)**	**8.9% (261/2923)**	**<0.0001**
Mean survival (days)	**747.3±1026.9**	**1255.8±1032.3**	**<0.0001**
30-days mortality (%)	**40.2% (33/82)**	**10.2% (298/2923)**	**<0.0001**
1-year mortality (%)	**54.9% (45/82)**	**28.3% (826/2923)**	**0.0001**
Mortality between 30 days and 1 year (%)	14.6% (12/82)	18.1% (528/2923)	0.7597

p-value: difference between EVF-positive and EVF-negative NSTEMI patients. Statistical significant differences highlighted bold.

Abbreviations: BMI=Body Mass Index, LV-EF= Left Ventricle Ejection Fraction, DM=Diabetes mellitus

Comparing mortality rates for NSTEMI patients surviving EVF in patients below 70 years vs above 70 years, no significant difference has been found in 30-day mortality (24% vs 40% p=0.2709), in 1-year mortality (39% vs 55% p=0.2085), or in mortality between 30 days and 1 year (15% vs 14.6% p=0.9728). EVF patients at younger (Figure 7.1), as well as at older age, >70 years (Figure 7.2), had significantly ($p<0.0001$) lower survival probability compared to non-EVF ones.

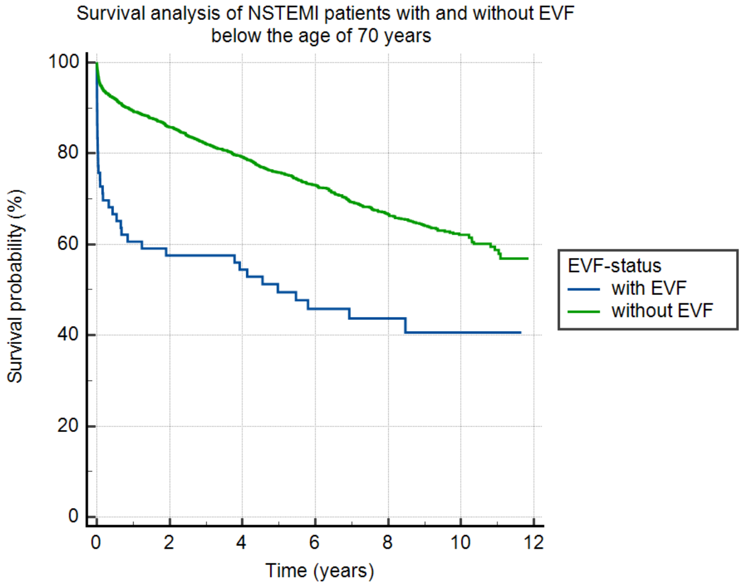

Figure 7.1: Survival analysis of EVF-positive compared to EVF-negative NSTEMI patients below the age of 70 years

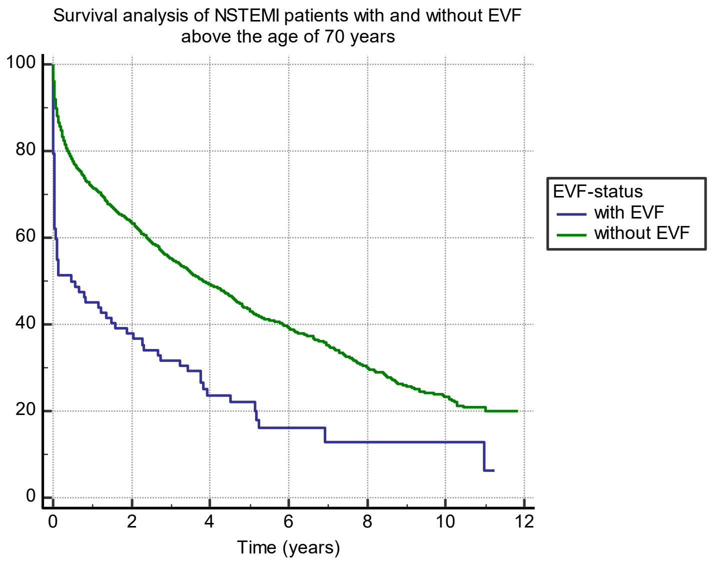

Figure 7.2: Survival analysis of EVF-positive compared to EVF-negative NSTEMI patients above the age of 70 years

Figure 7.3 displays survival probability in the 4 patient groups (based on age and EVF).

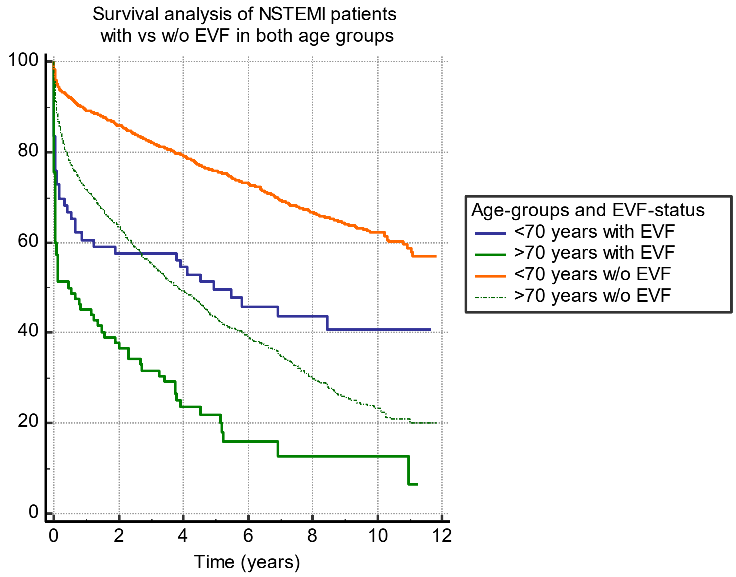

Figure 7.3: Survival analysis of EVF-positive compared to EVF-negative NSTEMI patients in both age groups

Cox regression analysis showed that in patients <70, EVF is an independent risk factor for all mortality (HR:2.38) (Table 9.3), 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) (Table 9.4).

Table 9.3: Cox regression analysis of factors influencing mortality in NSTEMI patients below the age of 70 years

Factors influencing mortality in NSTEMI patients below the age of 70 years			
	HR	**95% CI of HR**	**P**
LVEF (%)	0.9549	0.9505 to 0.9593	<0.0001
Diabetes mellitus	2.0263	1.7685 to 2.3216	<0.0001
Cardiogenic shock	8.9915	6.9951 to 11.5577	<0.0001
Invasive respiratory treatment	5.4124	4.5299 to 6.4668	<0.0001
Heart failure	3.6573	3.1696 to 4.2201	<0.0001
Early ventricular fibrillation	2.3813	1.7133 to 3.3097	<0.0001

Table 9.4: Cox regression analysis of factors influencing mortality in NSTEMI patients above the age of 70 years

Factors influencing mortality in NSTEMI patients above the age of 70 years			
	HR	**95% CI of HR**	**P**
BMI	0.9804	0.9693 to 0.9917	0.0007
LVEF (%)	0.967	0.9633 to 0.9706	<0.0001
Diabetes mellitus	1.5217	1.3822 to 1.6754	<0.0001
Cardiogenic shock	4.8505	4.0652 to 5.7875	<0.0001
Invasive respiratory treatment	3.244	2.8442 to 3.7001	<0.0001
Heart failure	2.3965	2.1761 to 2.6392	<0.0001
Early ventricular fibrillation	2.1383	1.6780 to 2.7249	<0.0001

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 9.5. In patients below the age of 70 years, these factors include diabetes mellitus (HR: 1.9), cardiogenic shock (HR:6.1), heart failure (HR: 2.65), and CPR (HR: 2.5). However, at higher age (above 70 years), the only factor influencing mortality was cardiogenic shock (HR: 2.3). The extent of the coronary artery disease did not affect mortality in either age group.

Table 9.5: Cox regression analysis of factors influencing mortality in NSTEMI patients surviving EVF

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

In order to find out whether the timing of EVF, with respect to the timing of the coronary revascularization, had an effect on prognosis, we explicated whether mortality was different in patients who experienced EVF either before or after PCI. 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 (Table 9.6). 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 (Table 9.7).

Table 9.6: The effect of the EVF's occurrence on the 30-days- and 1-year mortality in all NSTEMI patients

30-days mortality in patients below the age of 70						
	Total	*Dead*	*%*	*p*	*OR*	*OR 95% CI*
*VF during rev.**	12	1	8.33	x		
*VF before rev.**	51	13	25.49	0.1984	0.2657	0.0312-2.2626
VF after rev. <48 hours*	5	2	40	0.1186	7.3	0.4836-111.19
1-year mortality in patients below the age of 70						
	Total	*Dead*	*%*	*p*	*OR*	*OR 95% CI*
*VF during rev.**	12	2	16.67	x		
*VF before rev.**	51	22	43.14	0.0893	0.2636	0.0524-1.327
*VF after rev. <48 hours**	5	2	40	0.3014	3.33	0.319-34.83

*revascularisation

Table 9.7: The effect of the EVF's occurrence on the 30-days- and 1-year mortality in NSTEMI patients above 70 years

30-days mortality above the age of 70						
	Total	*Dead*	*%*	*p*	*OR*	*OR 95% CI*
*VF during rev.**	9	1	11.11%	x		
*VF before rev.**	61	25	40.98%	0.0834	0.18	0.021-1.53
VF after rev.* <48 hours	**12**	**7**	**58.33%**	**0.027**	**11.2**	**1.04-120.4**
1-year mortality above the age of 70						
	Total	*Dead*	*%*	*p*	*OR*	*OR 95% CI*
*VF during rev.**	9	4	44.44%	x		
*VF before rev.**	61	32	52.46%	0.653	0.725	0.177-2.962
*VF after rev. <48 hours**	12	9	75%	0.153	3.75	0.587-23.94

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. The clinical characteristics of our patients are presented in Table 10.1. Potentially high-risk patients in poor general condition has been compared to the assumed low-risk good general condition patient group. Poor condition meant patients who died at our institution or were transferred to another department on invasive respiratory treatment or needed further in-patient cardiac care. 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.

Table 10.1: Differences in clinical parameters according to the general condition of patients with early ventricular fibrillation

Differences in clinical parameters according to the patients' general condition			
	Poor general condition*	**Good general condition****	**P**
Mean age (years)	67.00±11.99	63.00±13.12	0.0004
Male gender (%)	69.7% (124/178)	66.2% (245/370)	0.2528
Mean body mass index (kg/m2)	27.50±4.92	28.10±5.20	0.1336
Mean peak troponin (ng/L)	4299.00±5040.43	3290.00±4830.04	0.0465
Mean CK (UI/L)	4070.00±7191.80	1879.00±2142.77	<0.0001
Mean lactate dehydrogenase (U/L)	2665.00±3533.94	1264.00±1061.65	<0.0001
Mean creatinine (µmol/L)	134.00±82.37	89.00±32.60	<0.0001
Mean cholesterol (mmol/L)	4.00±1.45	4.60±1.39	<0.0001
Mean LDL (mmol/L)	2.47±1.26	2.90±1.43	0.0018
Mean potassium (mmol/L)	4.20±0.74	4.0±0.60	0.0006
Mean white blood cell (mmol/L)	16.60±6.57	13.30±5.16	<0.0001
Mean C-reactive protein (mg/L)	40.20±59.10	21.30±41.31	<0.0001
Mean LVEF	37.000±11.850	46.000±10.997	<0.0001
LVEF <40%	52.1% (74/142)	23.3% (77/331)	<0.0001
Diabetes mellitus	69.3% (115/166)	52.0% (185/356)	0.0015
STEMI	64.0% (105/164)	73.8% (262/355)	0.0308
Heart failure	39.3% (70/178)	22.2% (82/370)	0.0106
Cardiogenic shock	40.5% (72/178)	7.3% (27/370)	0.0008
Cardiopulmonary resuscitation	56.2% (100/178)	26.8% (99/370)	<0.0001
Invasive respiratory treatment	82.6% (147/178)	31.1% (115/370)	<0.0001
VF before revascularization	85.4% (152/178)	71.6% (265/370)	0.0007
VF during revascularization	3.4% (6/178)	20.8% (77/370)	0.1502
VF after revascularization <48 h	11.2% (20/178)	7.6% (28/370)	<0.0001
Mean survival time (days)	260.00±728.86	2146.40±1310.50	<0.0001
30-day mortality	74.7% (133/178)	5.7% (21/370)	<0.0001
1-year mortality	86.5% (154/178)	14.3% (53/370)	<0.0001

*patients who died at our institution or were transferred to another department on invasive respiratory treatment or needed further in-patient cardiac care; **, patients who were released home or to a cardiac rehabilitation facility and did not require further in-patient cardiac care.

Table 10.2 presents the analyses regarding the impact of the extent of the disease and its invasive treatment on 6-week mortality based on the general condition of the patients. Three-vessel-disease complicated with poor condition was associated with higher 6-week mortality (93.02%, 40/43; P=0.0043). The extent of the coronary artery disease (CAD) had no impact on mortality in patients with good condition.

Table 10.2: The impact of the extent of disease and its invasive treatment on 6-week mortality based on the general condition of patients with early ventricular fibrillation

The impact of the extent of disease and its invasive treatment on 6-week mortality based on the patients' condition				
Poor general condition*				
Extent of the disease				
	Total	Dead	%	P
1-vessel disease	69	49	71.01	–
2-vessel disease	45	35	77.78	0.2432
3-vessel disease	43	40	93.02	0.0043
LM included	20	15	75.00	0.3817
Invasive treatment				
	Total	Dead	%	P
On 1 vessel	111	83	74.77	–
On 2 vessels	35	30	85.71	0.1087
On 3 vessels	8	7	87.50	0.2252
Not performed	24	20	83.33	0.2091
Good general condition**				
Extent of the disease				
	Total	Dead	%	P
1-vessel disease	193	8	4.15	–
2-vessel disease	105	6	5.71	0.4464
3-vessel disease	55	9	16.36	0.2073
LM included	15	2	13.33	0.3122
Invasive treatment				
	Total	Dead	%	P
On 1 vessel	302	15	4.97	–
On 2 vessels	34	5	14.71	0.2357
On 3 vessels	6	0	0	–
Not performed	27	5	18.52	0.1715

*, patients who died at our institution or were transferred to another department on invasive respiratory treatment or needed further in-patient cardiac care; **, patients who were released home or to a cardiac rehabilitation facility and did not require further in-patient cardiac care.

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 (Table 10.3): 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).

Table 10.3: Differences in clinical parameters of patients leaving institution in good general shape but dying within six weeks vs. survivors

Differences in clinical parameters of patients in good general condition*			
	Dying within 6 weeks	**Surviving after 6 weeks**	**P**
Mean age (years)	74.00±9.86	62.00±12.94	0.0119
Male gender	68.0% (17/25)	66.1% (228/345)	0.4333
Mean body mass index (kg/m2)	26.46±3.30	28.20±5.31	0.0752
Diabetes mellitus	83.3% (20/24)	49.7% (165/332)	0.0022
Mean peak troponin (ng/L)	5764.55±9246.67	3137.00±4418.00	0.0161
Mean creatinine (µg/L)	108.13±34.90	88.00±32.06	0.0017
Mean glucose (mmol/L)	11.02±4.00	8.99±4.56	0.0173
Mean cholesterol (mmol/L)	3.60±1.14	4.67±1.38	0.0004
Mean LDL (mmol/L)	2.06±1.18	3.00±1.43	0.0030
Mean potassium (mmol/L)	4.03±0.88	4.00±0.58	0.4072
Mean white blood cell (mmol/L)	13.90±4.62	13.30±5.20	0.2915
Mean C-reactive protein (mg/L)	50.60±66.80	19.07±37.95	0.0003
LVEF <40% (%)	59.1% (13/22)	20.7% (64/309)	0.0023
STEMI	56.5% (13/23)	75.0% (249/332)	0.0689
Heart failure	52.0% (13/25)	20.0% (69/345)	0.0073
Cardiogenic shock	20.0% (5/25)	6.4% (22/345)	0.1672
On-site CPR	40.0% (10/25)	25.8% (89/345)	0.1694
Respiratory treatment	72.0% (18/25)	28.1% (97/345)	0.0002
VF before revascularisation	76.0% (19/25)	71.3% (246/345)	0.3307
VF during revascularisation	12.0% (3/25)	21.5% (74/345)	0.3470
VF after revascularisation, <48 h	12.0% (3/25)	7.3% (25/345)	0.3857
Mean survival (days)	18.70±11.83	2.300.00±1220.42	<0.0001

*patients who were released home or to a cardiac rehabilitation facility and did not require further in-patient cardiac care

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. The full analysis is shown in Table 10.4.

Table 10.4: Clinical characteristics of patients dying within 6 weeks. Comparison of patients' data having early ventricular fibrillation and leaving the hospital in good general condition and patients not having early ventricular fibrillation

Clinical characteristics of patients dying within 6 weeks			
	Good general condition and VF+	**VF−**	**P**
All cases	6.8% (25/370)	7.9% (902/11,440)	0.4143
Mean age (years)	74.77±9.80	74.62±10.38	0.3430
Male gender	68.0% (17/25)	53.9% (486/902)	0.1253
NSTEMI	43.5% (10/23)	54.5% (469/860)	0.2438
LVEF <40%	59.1% (13/22)	50.5% (372/736)	0.2722
DM	83.3% (20/24)	63.8% (535/838)	0.0368
Creatinine <100 (µmol/L)	50.0% (12/24)	60.0% (513/855)	0.2425
Cardiogenic shock	20.0% (5/25)	29.8% (269/902)	0.3169
On site CPR	40.0% (10/25)	6.0% (54/902)	0.0009
Heart failure	52.0% (13/25)	47.8% (431/902)	0.3821

V. DISCUSSION

Although the diagnosis and treatment of acute coronary syndromes has been developing, cardiovascular disease are still the leading cause of death and loss of disability adjusted life years globally(29-31). In the Europe and Central Asia region 30% of all death were due to coronary artery disease. According to the global burden of disease study, in 2019 ischaemic heart disease and stroke were the leading causes of disability adjusted life years (DALYs)(32).

Similar to international data, most death in Hungary are caused by cardiovascular disease. In most cases the main cause of death is acute coronary syndrome, its early or late complications. In Hungary, more than 6000 people suffer heart attacks every year, about 1/3 of them is lethal (33).

That is why it is important to evaluate and highlight the risk factors influencing the prognosis after myocardial infarction. With the developing drug and device treatment options it is essential to screen those risk populations who would benefit from closer follow up, latest treatment options.

Impact of gender on survival of acute myocardial infarction

Female gender can occur as a risk factor in the prognosis of surviving myocardial infarction. As mentioned before, the differences in clinical presentation can lead to delayed revascularisation, more complications and higher mortality rates. Because of the atypical presentation, less diagnostic catheterizations are performed by women but the rates of revascularization after the angiography are equal to those in men(34). The higher mortality rates at younger age are to explain with the different patomechanism, disease of coronary microvasculature, coronary dissection and plaque erosion. The prevalence of cardiovascular risk factors as diabetes, hypertonia, hypercholesterinemia is higher in younger women than those in younger men(2).

The routinely used risk prediction models such as GRACE and TIMI scores were developed in patient populations that were two thirds male that’s why the proper risk stratification is even more harder(19). According to international studies not only the mean age but also the rate of complications –such as bleeding, heart failure, cardiogenic shock- after an AMI is higher among women. The risk of having any ventricular arrhythmia is the same in both sexes (19) Although the mean age of women in our study is also higher, the incidence of heart failure and CPR is significantly lower. The early revascularization lowers the risk of cardiogenic shock and other complications after an AMI. Usually women with NSTE-ACS are treated less aggressively than men. As a consequence, women had higher rate of in hospital mortality and heart failure (35). According to the CURE trial for women suffering from NSTE-ACS the outcomes are much worse when the intervention is not performed (36). However, women undergoing primary coronary intervention are usually at higher age and suffer from several comorbidities, their long term survival is better than those in men. It is necessary to point out that because of their baseline characteristics, higher rate of diabetes, hypertension and other comorbidities, their periprocedural risk is somewhat higher (37). Women can get proper care in the same time frame as men if the atypical symptoms are recognized early. As seen in our patient population women got invasive treatment in the same time-frame as men, comparing to some international results reporting delays in the invasive management of female acute coronary syndrome patients (19). Comprehensive diagnostic tests, early angiography and revascularization contributes to reduce women's early- one month- and late – one year- mortality rates to the same level as men's. There is a different disease mechanism causing myocardial infarction among young women. This is supported by the fact that the risk factors influencing the survival in the whole study-population (cholesterol levels, type of the myocardial infarction, heart failure) do not play part at younger age. But the severity of the acute event has a hazard ratio of 3-5. Acute myocardial infarction complicated by cardiogenic shock elevates the mortality risk by 4.7 fold. If the patient requires respiratory treatment at the ICU the mortality risk is elevated by 2.6 times. The higher rate of NSTEMI's, heart failures and worse mortality rates experienced below the age of 45 confirm the importance of analyzing the clinical appearance and risk factors of AMI of the young.

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

Hyperglycaemia and diabetes mellitus count as a traditional risk factor for developing cardiovascular diseases due to their effects on micro-and macrovasculature. Diabetic patients are more likely to develop have atherosclerosis, three-vessel disease, having complications after myocardial infarction resulting in impaired left ventricular function.(38, 39) Diabetic nephropathy and neuropathy are known manifestations of the developed disease. Patients suffering from chronic heart failure have worse 5-year survival and have higher risk of hospitalization if they have diabetes mellitus as well(40). It was known that diabetes mellitus and hyperglycaemia at admission (41) is an independent risk factor for cardiac adverse events. The HORIZONS-AMI trial showed that both newly diagnosed and known diabetic patients have worse 3-year mortality and both diabetic patient groups have higher major cardiac event rates in 3 years compared to non-diabetic ones(42). In our study we aimed to assess the effect of diabetes mellitus on mortality after myocardial infarction. We intended to compare the impact of diabetes on survival in different subgroups, such as type of myocardial infarction, based on left ventricle- and kidney function. Diabetic patients had higher mortality rates compared to non-diabetic subjects regardless of the type of MI. Our results imply based on Kaplan-Meier curves that the presence of diabetes has more impact on mortality than the type of myocardial infarction. Similar analysis showed that reduced LV function affects more the prognosis rather than diabetes. Same conclusion was met when investigating the role of renal function and diabetes, survival was mainly affected by renal function. Our results highlighted the since then known fact that using novel diabetic drugs – like sodium glucose cotransporter-2 (SGLT-2) inhibitors, glucagone-like peptid 1 (GLP-1) receptor agonist – improve survival rates of not just diabetic, but also of patients suffering from chronic heart failure or impaired kidney function. Several trials, such as DAPA-HF (43), DAPA-CKD (44), DELIVER (45), EMPEROR –REDUCED, EMPEROR-PREVERVED the risk modifying benefits and impact on improving survival of SGLT-2 inhibitors in heart failure, chronic kidney disease, cardiovascular disease regardless of diabetic state (46, 47).

The significance of early ventricular fibrillation

Ventricular tachyarrhythmia is the most common cause of sudden cardiac death in case of myocardial infarction. Early ventricular fibrillation occurs within 48-72 hours of the symptoms onset, and has no connection to recurring ischaemia or heart failure.

FAST-MI program declared that mortality in STEMI patients is declining. However despite novel drug therapy and invasive patient management, NSTEMI mortality is stable(48). The incidence of ventricular arrhythmias is higher in STEMI than in NSTEMI (10.0% vs 2.1%) (49), however the reason behind the higher mortality could be the less studied effect of ventricular arrhythmias and the aged NSTEMI population. In our

NSTEMI patient population 2,4% (151/6179) experienced EVF regardless of age, which is consistent with literature data (50). The necessity of invasive management –coronary angiography - of patients after VT/VF is proven by literature data, as survival rates have risen in all acute myocardial infarction patients (47% to 60%), in STEMI (59% to 74%) as well as in NSTEMI (43% to 57%) (51). Despite the fact that at our high volume institute most NSTEMI patients are treated invasively NSTEMI patients surviving EVF have higher short- and long-term mortality regardless of age. Our Kaplan-Meier analysis based on the effect of EVF and age on survival (Figure 6.3) showed that in the first 3 years, younger patients surviving EVF have worse survival chances compared to older age group without EVF. At this 3 year turning point age becomes more important regarding survival than the EVF complication. The impact of EVF on survival is proven by the results of our Cox-regression analysis, such as EVF is an independent risk factor for mortality regardless of age. Our results are consistent with previous studies which state that EVF patients are more likely to have reduced LV-EF, and extent coronary artery disease causing higher mortality rates (50). In our study the extent of the coronary artery disease had no effect on prognosis at any age group. However, at higher age besides EVF the only factor influencing mortality was cardiogenic shock. In the <70 years' age group the presence of diabetes mellitus, reduced LV-EF, heart failure, cardiogenic shock or on-site resuscitation affected mortality. When analysing the impact of the timing of EVF (to the timing of the intervention), at higher age it had prognostic value but not in younger patients. This is a new finding compared to former studies stating no difference in mortality in STEMI (52).

There is an increased risk of suffering sudden cardiac death after AMI, especially in high-risk patient groups, for patients with impaired LV systolic function (EF<40%). It is a highly studied question: when is the optimal timing of risk stratification for implanting an ICD. ICD implantation for primary and secondary prevention reduces all-cause mortality, DINAMIT and IRIS trials stated that ICD implantation within 40days past the AMI does not reduce mortality in high risk patients. Based on the guideline's recommendation the optimal timing of the decision making is at 6 weeks. But is it safe to wait that long since we know that EVF is a significant predictor for 30-day and 1-year mortality(53). Moreover, Masuda et al. found that EVF is associated with higher in-hospital and increased 5 –year mortality (54). On the other hand, the GISSI-2 trial declared that EVF is an independent risk factor for in hospital mortality but had no effect on post discharge to 6 month prognosis (24). Seeing these inconsistent results in our study we tried to find those patient groups who are at higher risk and we should follow up closely to prevent any life threatening arrhythmias. We sorted our patients into two groups based on their general condition at discharge. We found that the extent of the CAD, so the myocardium at risk had an effect on the 6-week prognosis but only in patients with the poor general condition. In the good general condition patient group, we could select those patient who have low risk in the critical 6 weeks' time period. However, despite the good condition higher age, diabetes, NSTEMI, impaired LVEF, reduced kidney function, larger infarct size, so higher troponin levels elevated the risk of mortality within 6 weeks. An interesting finding was that there was no significant difference in 6 weeks' mortality in EVF- vs EVF+ patients in good general condition.

VI. CONCLUSIONS:

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.

LIMIATATIONS

Our results are based on a single-center, retrospective database. The National Health Care Institute could only provide all-cause mortality data; cardiovascular mortality data was not available. Because of its retrospective kind, specific angiography results were not available, for example coronary dissections in case of young women. The National Health Insurance Fung could not provide data for further major cardiac events.

VII. SUMMARY

On the basis of examining more than 10 000 patients it is predictable that with an invasive aspect of care higher mortality rates seen in the literature can be avoided.
Early invasive strategy contributes to decrease mortality rates in women. We found that traditional risk factors - higher cholesterol levels, type of the infarction, heart failure - do not play part at younger age. It pays attention to the need for studying the clinical appearance and risk factors of acute myocardial infarction of the young.
Our results confirmed the negative prognostic impact of diabetes on survival. Diabetes has more prognostic value than the type of the myocardial infarction but still left ventricle - and renal function are the leading survival modifying factors. Our study was conducted prior to the disease modifying drug-era. At that time, we called attention to the potential beneficial effect of the new diabetes drugs (SGLT-2 inhibitors, GLP-1 antagonists). Since than their morbidity and mortality modifying effect is proven.
Despite the invasive strategy patients surviving early ventricular fibrillation (EVF) have worse prognosis. We have proven that EVF is an independent risk factor for mortality regardless of age. In the first 3 years past the index event, younger patients surviving EVF have worse survival chances compared to older ones without EVF. At this 3-year turning point age becomes more important regarding survival than the EVF. Our other new finding was that the prognosis had no correlation with the extent of the coronary artery disease either at lower or at higher age in non-ST-segment elevation myocardial infarction (NSTEMI). Studying the time of EVF (with respect to the timing of intervention), it impacted the prognosis in older but not in younger patients.
We have proven that generally it is safe to wait 6 weeks as offered in the guidelines with the decision of a possible ICD implantation. We could select those patients who would benefit from a closer follow up - patents with poor general condition at discharge, those with in good condition but having reduced LV function, NSTEMI. Practically, it is safe to wait at patients in good general condition, but patients with the mentioned risk factors benefit from a close follow up and might need an earlier device implantation.

It refers to the confirmation of our results, that the ESC 2023 Acute Coronary Syndrome Guideline recommends an early CRT/ICD implantation in special patient groups (7).

VIII. REFERENCES

1. Jánosi A. A szívinfarktus miatt kezelt betegek ellátásának és prognózisának fontosabb adatai. Nemzeti Szívinfarktus Regiszter 2020. CARDIOLOGIA HUNGARICA. 2021;51(4):6.
2. Dreyer RP, Sciria C, Spatz ES, Safdar B, D'Onofrio G, Krumholz HM. Young Women With Acute Myocardial Infarction: Current Perspectives. Circ Cardiovasc Qual Outcomes. 2017;10(2).
3. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-64.
4. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109(10):1223-5.
5. Khot UN, Johnson ML, Ramsey C, Khot MB, Todd R, Shaikh SR, et al. Emergency department physician activation of the catheterization laboratory and immediate transfer to an immediately available catheterization laboratory reduce door-to-balloon time in ST-elevation myocardial infarction. Circulation. 2007;116(1):67-76.
6. Williams DO. Treatment delayed is treatment denied. Circulation. 2004;109(15):1806-8.
7. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023;44(38):3720-826.
8. Jousilahti P, Laatikainen T, Peltonen M, Borodulin K, Männistö S, Jula A, et al. Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years: population based observational study. Bmj. 2016;352:i721.

9. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.
10. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083-96.
11. Di Fusco SA, Arca M, Scicchitano P, Alonzo A, Perone F, Gulizia MM, et al. Lipoprotein(a): a risk factor for atherosclerosis and an emerging therapeutic target. Heart. 2022;109(1):18-25.
12. Duarte Lau F, Giugliano RP. Lipoprotein(a) and its Significance in Cardiovascular Disease: A Review. JAMA Cardiol. 2022;7(7):760-9.
13. Arun D, Munir W, Schmitt LV, Vyas R, Ravindran JI, Bashir M, et al. Exploring the Correlation and Protective Role of Diabetes Mellitus in Aortic Aneurysm Disease. Front Cardiovasc Med. 2021;8:769343.
14. Afanasiev SA, Garganeeva AA, Kuzheleva EA, Andriyanova AV, Kondratieva DS, Popov SV. The Impact of Type 2 Diabetes Mellitus on Long-Term Prognosis in Patients of Different Ages with Myocardial Infarction. J Diabetes Res. 2018;2018:1780683.
15. Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL, Chyun DA, et al. Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association. Circulation. 2022;145(9):e722-e59.
16. Kawamoto KR, Davis MB, Duvernoy CS. Acute Coronary Syndromes: Differences in Men and Women. Curr Atheroscler Rep. 2016;18(12):73.
17. Araújo C, Laszczyńska O, Viana M, Dias P, Maciel MJ, Moreira I, et al. Quality of Care and 30-day Mortality of Women and Men With Acute Myocardial Infarction. Rev Esp Cardiol (Engl Ed). 2019;72(7):543-52.
18. Sarma A, Scott NS. Assessing and Modifying Coronary Artery Disease Risk in Women. Curr Treat Options Cardiovasc Med. 2017;19(7):51.
19. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation. 2016;133(9):916-47.

20. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). Bmj. 2006;333(7578):1091.
21. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. Jama. 2000;284(7):835-42.
22. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. Jama. 2007;297(6):611-9.
23. Vahdatpour C, Collins D, Goldberg S. Cardiogenic Shock. J Am Heart Assoc. 2019;8(8):e011991.
24. Volpi A, Cavalli A, Santoro L, Negri E. Incidence and prognosis of early primary ventricular fibrillation in acute myocardial infarction--results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) database. Am J Cardiol. 1998;82(3):265-71.
25. Blöndal M, Ainla T, Eha J, Lõiveke P, Marandi T, Saar A, et al. Comparison of management and outcomes of ST-segment elevation myocardial infarction patients in Estonia, Hungary, Norway, and Sweden according to national ongoing registries. Eur Heart J Qual Care Clin Outcomes. 2022;8(3):307-14.
26. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;24(1):4-131.
27. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. J Clin Endocrinol Metab. 2013;98(5):1845-59.
28. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825-30.

29. Dagenais GR, Leong DP, Rangarajan S, Lanas F, Lopez-Jaramillo P, Gupta R, et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. Lancet. 2020;395(10226):785-94.

30. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation. 2022;145(8):e153-e639.

31. Ralapanawa U, Sivakanesan R. Epidemiology and the Magnitude of Coronary Artery Disease and Acute Coronary Syndrome: A Narrative Review. J Epidemiol Glob Health. 2021;11(2):169-77.

32. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.

33. Jánosi A. A szívinfarktus miatt kezelt betegek ellátásának és prognózisának fontosabb adatai. Nemzeti Szívinfarltus Regiszter 2019. Cardiologica Hungarica. 2020;50:5.

34. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. N Engl J Med. 2000;343(1):8-15.

35. Hansen KW, Soerensen R, Madsen M, Madsen JK, Jensen JS, von Kappelgaard LM, et al. Developments in the invasive diagnostic-therapeutic cascade of women and men with acute coronary syndromes from 2005 to 2011: a nationwide cohort study. BMJ Open. 2015;5(6):e007785.

36. Anand SS, Xie CC, Mehta S, Franzosi MG, Joyner C, Chrolavicius S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. J Am Coll Cardiol. 2005;46(10):1845-51.

37. Anderson ML, Peterson ED, Brennan JM, Rao SV, Dai D, Anstrom KJ, et al. Short- and long-term outcomes of coronary stenting in women versus men: results from the National Cardiovascular Data Registry Centers for Medicare & Medicaid services cohort. Circulation. 2012;126(18):2190-9.

38. Srinivasan MP, Kamath PK, Bhat NM, Pai ND, Bhat RU, Shah TD, et al. Severity of coronary artery disease in type 2 diabetes mellitus: Does the timing matter? Indian Heart J. 2016;68(2):158-63.

39. Tomizawa N, Nojo T, Inoh S, Nakamura S. Difference of coronary artery disease severity, extent and plaque characteristics between patients with hypertension, diabetes mellitus or dyslipidemia. Int J Cardiovasc Imaging. 2015;31(1):205-12.

40. Dauriz M, Mantovani A, Bonapace S, Verlato G, Zoppini G, Bonora E, et al. Prognostic Impact of Diabetes on Long-term Survival Outcomes in Patients With Heart Failure: A Meta-analysis. Diabetes Care. 2017;40(11):1597-605.

41. Cui CY, Zhou MG, Cheng LC, Ye T, Zhang YM, Zhu F, et al. Admission hyperglycemia as an independent predictor of long-term prognosis in acute myocardial infarction patients without diabetes: A retrospective study. J Diabetes Investig. 2021;12(7):1244-51.

42. Ertelt K, Brener SJ, Mehran R, Ben-Yehuda O, McAndrew T, Stone GW. Comparison of Outcomes and Prognosis of Patients With Versus Without Newly Diagnosed Diabetes Mellitus After Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction (the HORIZONS-AMI Study). Am J Cardiol. 2017;119(12):1917-23.

43. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008.

44. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-46.

45. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022;387(12):1089-98.

46. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022;400(10365):1788-801.

47. Patel PA, Cubbon RM, Sapsford RJ, Gillott RG, Grant PJ, Witte KK, et al. An evaluation of 20 year survival in patients with diabetes mellitus and acute myocardial infarction. Int J Cardiol. 2016;203:141-4.
48. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al. Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. Circulation. 2017;136(20):1908-19.
49. Al-Khatib SM, Granger CB, Huang Y, Lee KL, Califf RM, Simoons ML, et al. Sustained ventricular arrhythmias among patients with acute coronary syndromes with no ST-segment elevation: incidence, predictors, and outcomes. Circulation. 2002;106(3):309-12.
50. Piccini JP, White JA, Mehta RH, Lokhnygina Y, Al-Khatib SM, Tricoci P, et al. Sustained ventricular tachycardia and ventricular fibrillation complicating non-ST-segment-elevation acute coronary syndromes. Circulation. 2012;126(1):41-9.
51. Patel N, Patel NJ, Macon CJ, Thakkar B, Desai M, Rengifo-Moreno P, et al. Trends and Outcomes of Coronary Angiography and Percutaneous Coronary Intervention After Out-of-Hospital Cardiac Arrest Associated With Ventricular Fibrillation or Pulseless Ventricular Tachycardia. JAMA Cardiol. 2016;1(8):890-9.
52. Jabbari R, Risgaard B, Fosbøl EL, Scheike T, Philbert BT, Winkel BG, et al. Factors Associated With and Outcomes After Ventricular Fibrillation Before and During Primary Angioplasty in Patients With ST-Segment Elevation Myocardial Infarction. Am J Cardiol. 2015;116(5):678-85.
53. García-García C, Oliveras T, Rueda F, Pérez-Fernández S, Ferrer M, Serra J, et al. Primary Ventricular Fibrillation in the Primary Percutaneous Coronary Intervention ST-Segment Elevation Myocardial Infarction Era (from the "Codi IAM" Multicenter Registry). Am J Cardiol. 2018;122(4):529-36.
54. Masuda M, Nakatani D, Hikoso S, Suna S, Usami M, Matsumoto S, et al. Clinical Impact of Ventricular Tachycardia and/or Fibrillation During the Acute Phase of Acute Myocardial Infarction on In-Hospital and 5-Year Mortality Rates in the Percutaneous Coronary Intervention Era. Circ J. 2016;80(7):1539-47.

IX. BIBLIOGRAPHY

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)

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