Impact of the postoperative corneal density on the shape of the cornea after corneal cross linking procedure

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Gender and clinical parameters in the first year follow up of treatment outcomes in patients with acute coronary syndrome

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Mentor: Prof. Davor Miličić, MD, PhD, FESC, FAAC

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List of abbreviations:

ACS	Acute Coronary Syndrome
AM	Acute marginal artery
ASMR	Age-standardized mortality rates
CAC	Coronary artery calcium
CAD	Coronary artery disease
CCS	Chronic coronary syndrome
CEE	Central and Eastern Europe
CI	Confidence intervals
CKD	Chronic kidney disease
CVD	Cardiovascular diseases
ESC	European Society of Cardiology
EU	European Union
FFR	Fractional flow reserve
GFR	Glomerular filtration rate
IRA	Infarction related artery
ISACS-TC	International Survey of Acute Coronary Syndromes in the Transitional
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LBBB	Left bundle branch block
LCx	Left circular artery
LMCA	Left main coronary artery
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MVD	Multivessel disease
NACE	Net adverse clinical events
NSTEMI	Non-ST-Elevation Myocardial Infarction
OCT	Optical coherence tomography
OMT	Optimal medical therapy
OR	Odd ratio
PCI	Percutaneous coronary intervention
PD	Posterior descending artery
RBBB	Right bundle branch block
RCA	Right coronary artery
RR	Risk ratios
STEMI	ST-elevation myocardial infarction
UA	Unstable angina

1. Introduction and background for the proposed research

1.1. Anatomy of the Heart and Coronary Arteries

Heart, or *cor* in Latin, is a cone-shaped, hollow, muscular structure approximately the size of a human fist, situated at the center of the chest. It consists of the atrial muscle, ventricular muscle, and specialized muscle fibers. Heart interior is partitioned by a muscular barrier known as the septum, which separates the organ into the left and the right sections. Each side contains two chambers of varying dimensions - the larger chamber is the ventricle, and the smaller chamber is the atrium. The heart valve, positioned between the atrium and ventricle, regulates blood flow from the atrium to the ventricle and prevents blood from flowing back. (1)

Aorta, the largest and main artery in the body, emerges from the left ventricle of the heart and supplies arterial branches throughout the body. Myocardium, which is the muscular tissue of the heart, is supplied with blood from the coronary arteries that arise from the coronary sinus at the aortic root, and converge towards the heart apex. Two coronary arteries, namely the left main coronary artery (LMCA) and the right coronary artery (RCA), are responsible for supplying the heart, and they branch further into the smaller vessels, until they reach every cell in the heart. The initial section of the LMCA, splits into two branches, the left circular artery (LCx), and the left anterior descending artery (LAD). **(Figure. 1)** (2)

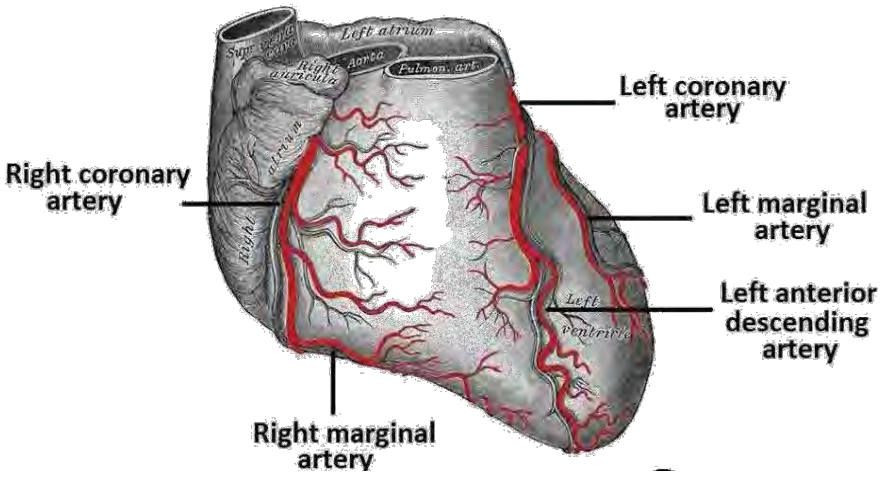


Figure 1. Coronary circulation [internet image] (4)

The right coronary artery supplies blood to the right atrium, the right ventricle, the sinoatrial, and the atrioventricular node. The RCA further branches into the acute marginal artery (AM) and the right posterior descending artery (PD), which supply blood to the interatrial septum, a

part of the left atrium, the postero-inferior third of the interventricular septum, and a part of the posterior portion of the left ventricle. The PD and the AM, along with the LAD, supply blood to the septum of the heart. The LMCA and its branches, the LAD and LCx supply blood to the left atrium and the left ventricle. The LAD supplies blood to the front and left sides of the heart, while the LCx is responsible for the blood supply to the left atrium and the posterior-lateral aspect of the left ventricle. Other small branches of the coronary arteries include the obtuse marginal artery, the diagonal branch, and the septal branch. **(Figure 2)** (2)

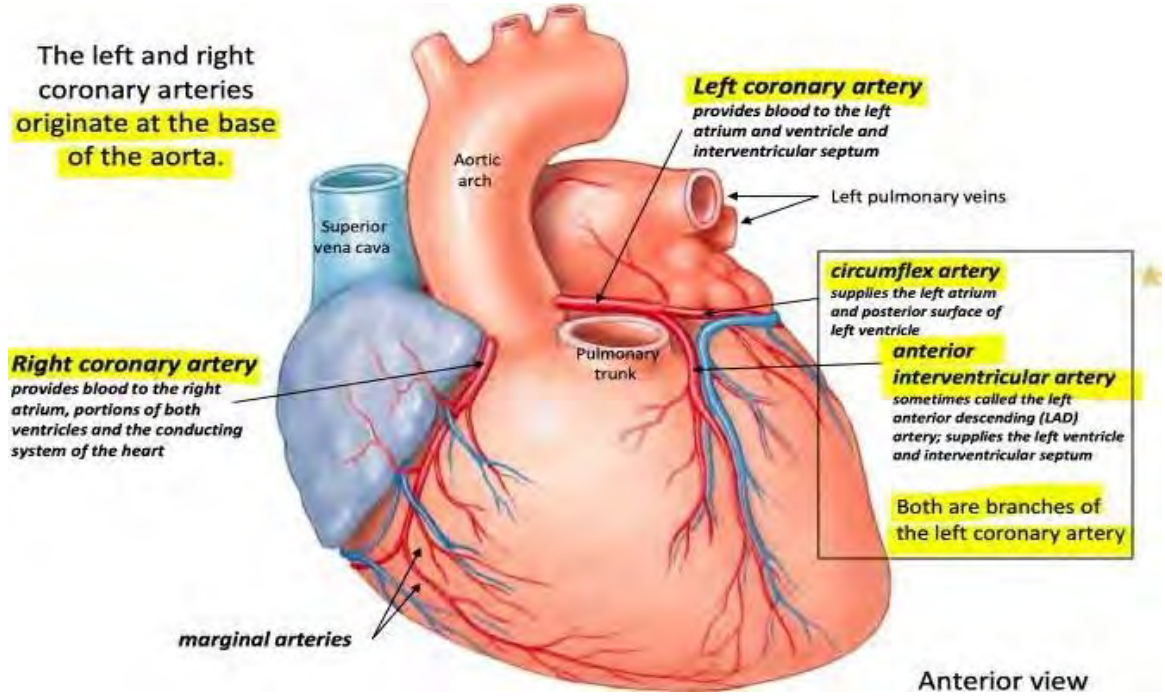


Figure 2. Major coronary arteries and patterns of blood flow [internet image] (5)

1.2. Coronary Circulation

On average, the heart beats 100,000 times within 24 hours, with each beat causing the heart to contract and pump blood into the bloodstream. The left ventricle of the heart plays a vital role in generating the arterial blood pressure, which affects the blood flow throughout the systemic circulation. Additionally, this ventricle utilizes most of the oxygen delivered via the coronary arteries to sustain the optimal cardiac function. Myocardial contractions are intricately linked to the coronary blood flow, and the successful delivery of oxygen depends on maintaining a balance between supply and demand. This equilibrium is essential for the proper functioning of the heart muscles and cells. **Figure 3** illustrates the trends in the coronary pressure under the normal and stress conditions. (3)

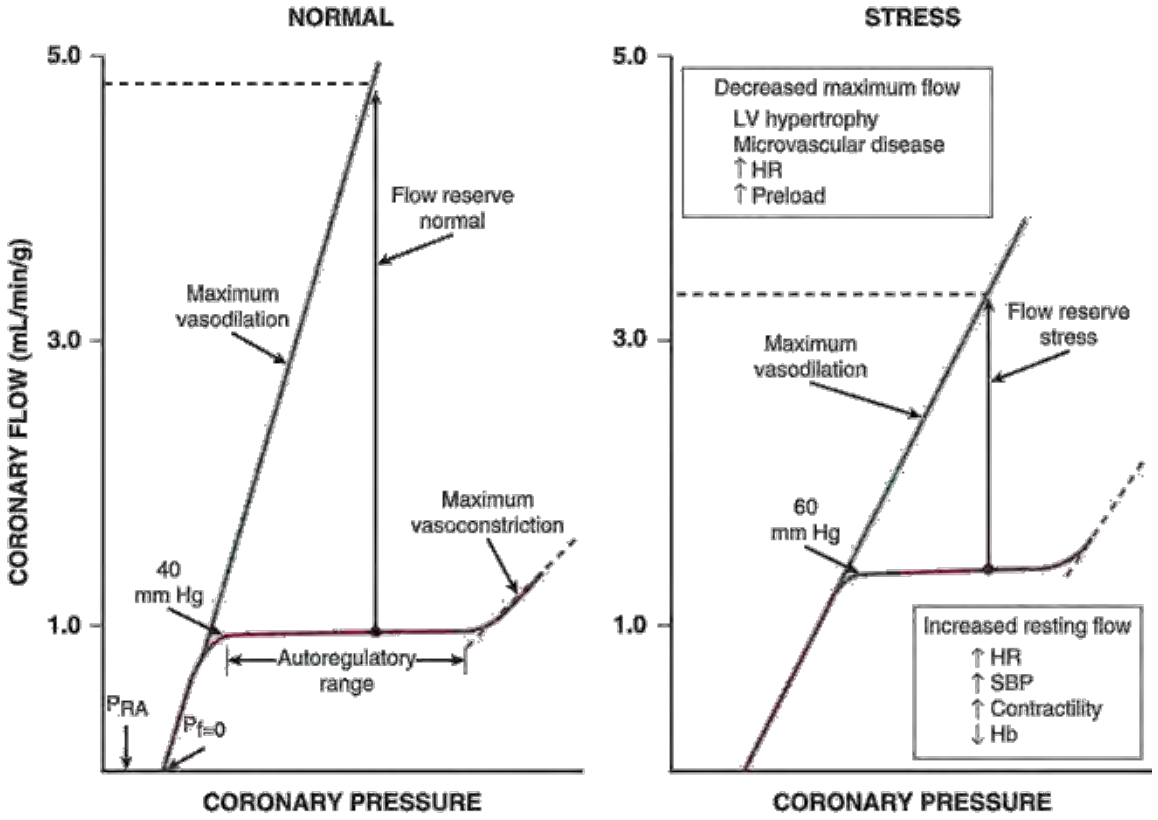


Figure 3. Coronary pressure [internet image] (6)

Under normal conditions, the heart is able to maintain a consistent blood flow as the regional coronary pressure fluctuations span a broad range, while the global determinants of oxygen consumption remain constant (shown in **Figure 3** as the red line). However, when the pressure falls below the lower cut-off for the autoregulatory pressure (roughly 40 mmHg), the subendocardial vessels undergo the maximal vasodilation, which can lead to the development of myocardial ischemia. During the vasodilation (depicted as the blue line in **Figure 3**), the blood flow increases four to five times above the resting value at the normal arterial pressure. In the individuals experiencing stress, such as a rapid heart rate, the compressive determinants of the coronary resistance increase, the time required for diastolic perfusion decreases, and the maximal vasodilated flow is reduced. (3)

Throughout a person's life, the regular balance of the oxygen and nutrition supply can be disrupted by the formation of atherosclerotic plaques within the coronary arteries. When these arteries begin to narrow, the blood flow necessary to sustain normal physiological activities becomes inadequate. As a response to an increased demand for myocardial oxygen, the resting flow rates also increase, and the reserves and the ratio of resting coronary flow follow suit. However, this can result in ischemia at the higher coronary pressures, and insufficient oxygen

in the cardiac tissue can trigger transient spasm-like heart pain. (7) Initially, pain occurs only during the higher levels of physical exertion. However, as the constriction of the coronary arteries increases, pain can occur more frequently and can even be triggered by the normal daily activities that don't require much physical exertion. (7, 8)

1.3. Atherosclerosis

The vast majority of cardiovascular diseases (CVD) are primarily caused by atherosclerosis, which is an underlying pathological process. The term "cardiovascular diseases" refers to a wide range of conditions that impact either the heart or the blood vessels. This group includes various heart conditions such as coronary artery disease (CAD), congenital heart disease, rheumatic heart disease, and cerebrovascular disease, as well as the blood vessels such as those related to hypertension and the conditions affecting cerebral, carotid, and peripheral circulation. The most prevalent subtypes of CVD are ischemic heart disease or coronary artery disease, stroke, and peripheral artery disease. (9)

Lesions in the coronary arteries cause coronary artery disease, which is the most common and dangerous form of atherosclerotic cardiovascular disease in the middle-aged individuals. **(Figure 4)** Although the lesions in the cerebral and peripheral arteries occur a decade or two later, the atherosclerosis process in these arteries is similar to that in the coronary arteries. (9)

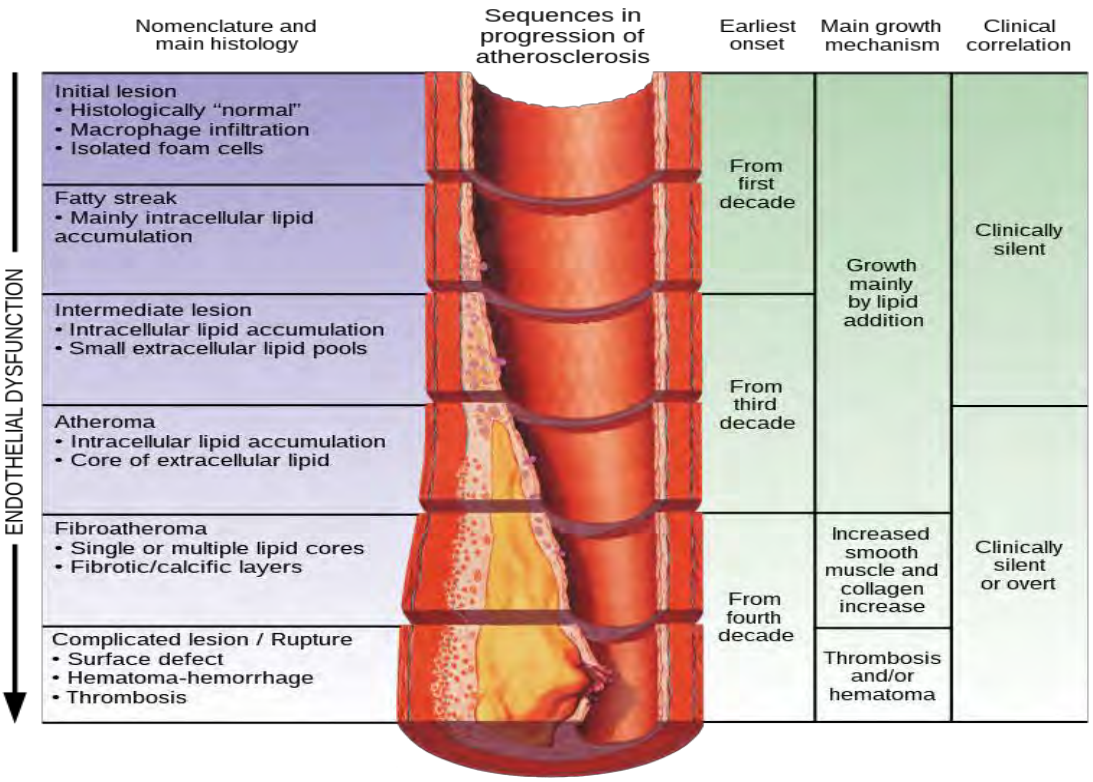


Figure 4. Atherosclerosis [internet image] (10)

Atherosclerosis is known to impact the large and medium-sized arteries, including the coronary, carotid, and cerebral arteries, their branches, and the major arteries in the extremities. It was once viewed solely as a cholesterol storage disease, but it is now understood to be an inflammatory disorder as well. (11) Plaque is the primary characteristic of atherosclerosis and is composed of the lipids, the inflammatory infiltrates, the smooth muscle cells, and the connective tissue. Disruption of normal endothelial function caused by injury or infection can lead to the formation of the atherosclerotic lesions referred to as the "fatty streaks." These streaks on the artery wall typically consist of the macrophages and the T lymphocytes embedded in a thin layer of lipids. Macrophages ingest the lipids and transform into the activated foam cells that produce various chemoattractant chemicals, cytokines, and growth factors. As more lymphocytes are attracted to the lesion, the number of the effector molecules amplifies, thereby sustaining the inflammatory response. The repeated cycle results in the development of a fatty core surrounded by a fibrous matrix that stabilizes the plaque structure. Plaque is typically found in the arterial locations such as the branches, the bends, and the bifurcations, which are exposed to the low or the disturbed blood flow that exerts the low or the oscillatory shear stress on the vessel wall. (10)

Various forms of plaque exist, but they are often classified into the stable and the unstable categories in the clinical practice. Atherosclerotic plaque rupture is the underlying pathological mechanism of the plaque stability and instability. (12) Stable plaques tend to increase in size gradually or remain in their original location for the extended periods. In contrast, the unstable plaques are more susceptible to spontaneous erosion, rupture, or fissuring, leading to acute thrombosis, occlusion, or infarction before stenosis takes place. Stable and unstable plaques have distinct characteristics and some of these features can be visualized by using cardiac imaging techniques, such as computed tomography angiography. (13)

Progression of coronary atherosclerosis is typically associated with an increase in calcification. Degree of coronary calcification is one of the most commonly used imaging biomarkers. (14,15) In the past decade, there has been increasing interest in using the coronary artery calcium (CAC) measurement as a tool for the risk assessment of coronary artery disease and atherosclerotic cardiovascular diseases. Calcium accumulation within the plaque leads to its increased brittleness and susceptibility to rupture. Once rupture occurs, the released lipid content from the plaque acts as a trigger for clot formation. Plaque formation and rupture manifest as various cardiovascular diseases, which is an umbrella term encompassing a range

of conditions affecting the heart and the blood vessels. Recent advances in coronary computed tomography imaging have enabled detailed cardiovascular risk stratification based on the plaque characteristics. (16)

1.4. Epidemiology of cardiovascular diseases in Europe

Cardiovascular diseases arise from a multitude of cardiometabolic, behavioral, environmental, and social risk factors. The term "risk factors" in the context of coronary artery disease was first introduced during the Framingham Heart Study, whose findings were first published in 1957**.** (17, 18)

Today, it is widely accepted that multiple interrelated risk factors contribute to the development of cardiovascular diseases rather than a single factor being solely responsible. The Framingham Heart Study conducted on the Caucasian populations, identified several traditional risk factors, including smoking, high blood pressure, and elevated cholesterol levels, and confirmed their causal association with coronary artery disease. Subsequent cohort studies have furthered our understanding of these risk factors and their impact on the CVD incidence. To effectively prevent and manage coronary artery disease, it is crucial to understand and accurately quantify the contribution of these key risk factors at all levels. (19) The FINRISK study aimed to identify the risk factors for chronic diseases, including cardiovascular diseases, and has made significant contributions to the understanding of the risk factors in Finland. The study has involved the large population samples, and its findings have led to the several public health interventions in Finland, such as the tobacco control policies, the dietary recommendations, and the improved treatment of hypertension and dyslipidemia. Other countries have also conducted the similar cohort studies, such as the British Regional Heart Study and the Scottish Heart Health Study among the others. These studies have contributed to a better understanding of the risk factors associated with cardiovascular diseases and have helped to develop the effective prevention and treatment strategies. (20) Several cohort studies, including ULSAM, PIVUS, POEM, EpiHealth, and SCAPIS, were conducted at Uppsala University in Sweden. Additionally, in New Zealand, the PREDICT-CVD cohort study was established in 2002 in the primary care to assess the effectiveness of the Framingham risk model. (21)

Studies mentioned above have classified risk factors into two broad categories: non-modifiable and modifiable risk factors. Non-modifiable risk factors include age, sex, race, and family history of coronary artery disease, which cannot be changed. On the other hand, modifiable

risk factors such as hypertension, hyperlipidemia, diabetes, obesity, smoking, poor diet, sedentary lifestyle, and stress can be altered through the lifestyle changes or the medical interventions. (17) Non-modifiable risk factors are known to be the strong predictors of CAD and can account for up to 63% to 80% of the variability in the prognostic performance. On the other hand, modifiable risk factors have a more modest contribution to CAD risk prediction, but their control can substantially reduce CAD events. (19)

Regarding age, coronary artery disease prevalence increases after 35 years of age in both sexes. Men have a higher risk compared to women, but coronary artery disease remains the leading cause of death among women. Approximately one in three female deaths is caused by cardiovascular diseases. The prevalence of non-obstructive and obstructive CAD differs between the sexes, with non-obstructive CAD being found in 57% of cases in women and obstructive CAD being more common in men. Proposed mechanisms for CAD in women include coronary microvascular dysfunction, altered endothelial tone, structural changes, and an altered response to vasodilator stimuli. Estrogen is thought to have a protective role in the coronary vasoreactivity and to promote plaque stabilization through its anti-inflammatory effect on atherosclerosis. However, a disparity still exists in health outcomes between men and women, which is attributed to a lack of awareness and understanding of CAD in women and more focus on obstructive CAD in men. (22, 23) Family history is a significant non-modifiable risk factor for CAD. Individuals with a family history of premature cardiac disease, particularly those occurring before the age of 50, have an increased risk of CAD mortality. (24, 25)

However, despite the availability of effective medications, as much as one-third of patients with CAD do not receive optimal medication interventions, which would lead to a substantial reduction in CAD events. (26) Doctors have a pivotal role in the pharmacologic management of modifiable risk factors such as hypertension, hyperlipidemia, diabetes, and smoking cessation. Dietary education and obesity seem to be equally important in the risk reduction. Physical inactivity and a sedentary lifestyle are estimated to contribute to 12.2% of myocardial infarction cases in the INTERHEART study. (27)

Non-traditional risk factors, such as non-alcoholic fatty liver disease, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, thyroid disease, and chronic kidney disease (CKD), have also been studied. CKD has been found to be an independent risk factor for CAD due to the high levels of pro-inflammatory mediators, oxidative stress, and decreased nitric oxide production leading to endothelial dysfunction. Patients with CKD may

experience silent myocardial infarctions more frequently, likely due to the higher incidence of diabetic and uremic neuropathy. The American Heart Association Guideline for the Primary Prevention of Cardiovascular Disease considers chronic kidney disease with a glomerular filtration rate (GFR) of 15-59 as a risk-enhancing factor. (28)

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. By 2030, the statistical projections estimate that around 23.6 million people will die each year from this group of diseases. In Europe alone, more than 60 million potential years of life are lost annually due to CVD. While more women than men die from CVD in absolute terms, the age-standardized rates of morbidity and mortality, which adjust for age structure, are higher in men than in women. (29) Currently, there are over 6 million new cases of cardiovascular diseases reported in the EU and over 11 million cases in Europe annually. While traditional risk factors such as smoking, alcohol consumption, and mean blood cholesterol levels continue to be the primary contributors, there has been a considerable increase in the prevalence of the other risk factors such as overweight or obesity and diabetes in the recent decades. (30) CAD is the most prominent subtype of cardiovascular diseases and remains the primary cause of death, with predictions suggesting it will continue to be the leading cause of mortality. (31, 32)

Cardiovascular diseases remain the leading cause of death in the majority of European countries, although cancer deaths exceed those from cardiovascular diseases in some countries. Disparities in data coverage, morbidity, treatment outcomes, and mortality from CVD still exist across Europe, largely due to economic development and healthcare system improvements. The European Society of Cardiology (ESC) regularly publishes annual reports and provides policymakers with scientific knowledge about cardiovascular diseases to create the evidence-based policies for heart health. Mortality indicators accurately measure the burden of CVD, with proportional mortality accounting for 45% and 39% of female and male deaths, respectively, in ESC member countries. The total number of cardiovascular deaths across all ESC member countries exceeds cancer deaths for both sexes. However, 15 ESC high-income countries have more male cancer deaths than CVD deaths, and five ESC member countries have more female cancer deaths than CVD deaths. Disparities still exist between the high- and middle-income countries in the proportion of premature deaths before the 70 years of age caused by CVD. (30)

Age-standardized mortality rates (ASMRs) for CVDs have been decreasing in Europe since 1990, with a decline of 47% in males and 42% in females. High-income countries have seen

reductions in ASMRs of over 50% in both sexes, while the middle-income countries have seen smaller declines, not exceeding 15%. Some countries have even experienced increases in ASMRs. Despite the mentioned progress, disparities in the CVD mortality rates remain between high- and middle-income countries. (33)

A health gap has emerged over time between European countries, with a notable East/West divide in terms of morbidity and mortality. Health behaviors and psychosocial factors are considered the key factors contributing to these differences in the health status and the mortality rates. (34) The "East-West Health Gap" has been identified as a significant challenge for the European Union (EU), and it has been extensively discussed in the literature. The EU has undergone structural changes since 1992, and until January 31, 2020, it was composed of 28 member countries, which decreased following the United Kingdom's withdrawal from the union. On May 1, 2004, ten new member states mostly from Eastern Europe joined the European Union, which is known as the EU-25 enlargement. Avgerinos et al. issued a warning prior to the EU-25 enlargement that the inclusion of the new members with the varying levels of the development and the political backgrounds would significantly impact the EU's healthcare policy. The authors stressed the importance of narrowing the health gap, addressing the specific health concerns, and enhancing the evaluation of the health system performance. (35) McKee and Nolte highlighted that the new member states faced significant health challenges and emphasized the need for the policies that would improve both the economic and the health outcomes to narrow the health gap with these countries. (36)

Enlargement of the European Union had various impacts on the health status and the health indicators of the member countries. Overall, there was a decline in the ASMR and an increase in the life expectancy and the healthy life expectancy for EU-28 members. However, the EU-25 and EU-27 enlargements resulted in the statistically significant worsening of all age-sex standardized rates and life expectancies. Similarly, the EU-28 enlargement showed a similar tendency compared to the EU-15. Despite the changes in the composition over the years, the EU's health status is improving. However, the enlargements in 2004, 2007, and 2013 have led to a decrease in the average health of EU states. (37)

The burden of cardiovascular diseases in the new EU member states is higher than in the older member states, which is not unexpected given that epidemiological shift from infectious diseases to chronic diseases occurred earlier in the Western European countries than in the

Eastern European countries. (38) Since the 1970s, there was a rapid decline in cardiovascular mortality in Western Europe, but this trend was not observed in Central Europe and the former communist countries. Ongoing structural reforms in the CEE countries have been accompanied by the economic and political instability and crises, which further impede the processes of the epidemiological transition and cardiovascular health. Although the countries of the former Soviet Union experienced a significant deterioration in cardiovascular health, some CEE countries like Poland, Czechia, Slovakia, Hungary, and Slovenia have demonstrated tendencies of reversal and improvements in the cardiovascular health indicators. Trend towards reduction in cardiovascular diseases is attributable to improved medical care and treatment, leading to lower case-fatality ratios, as well as better primary prevention and management of risk factors, which has reduced incidence rates of the disease. (39)

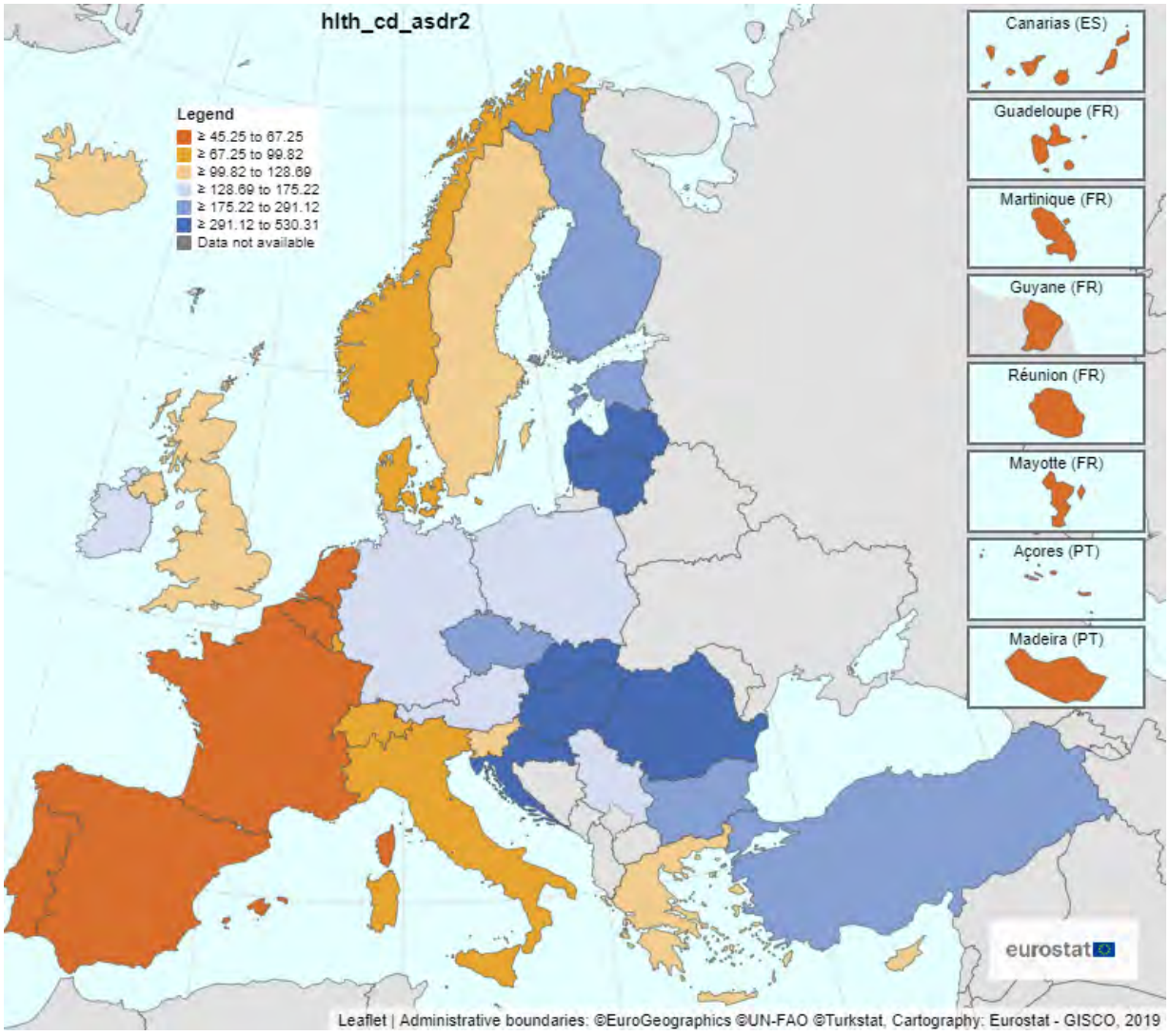


Figure 5. Death due to coronary heart diseases [internet image] (40)

France, a traditionally low cardiovascular risk country, has the lowest age-standardized mortality rate per 100,000 population for CAD in both sexes, with 77 deaths in males and 32 deaths in females. In contrast, Lithuania has the highest mortality rate, with 700 deaths per 100,000 males and 429 deaths per 100,000 females. This results in a nine-fold difference in men and a 13-fold difference in women when comparing France to Lithuania. Among European countries that are not members of the EU, Israel has the lowest ASMR for CAD, with 115 deaths per 100,000 in males and 67 deaths per 100,000 in females, while Ukraine has the highest, with 1,102 deaths per 100,000 in males and 727 deaths per 100,000 in females. This represents an almost 10-fold difference in men and an almost 11-fold difference in women between these two countries. (39)

1.5. Burden of cardiovascular diseases in the Republic of Croatia

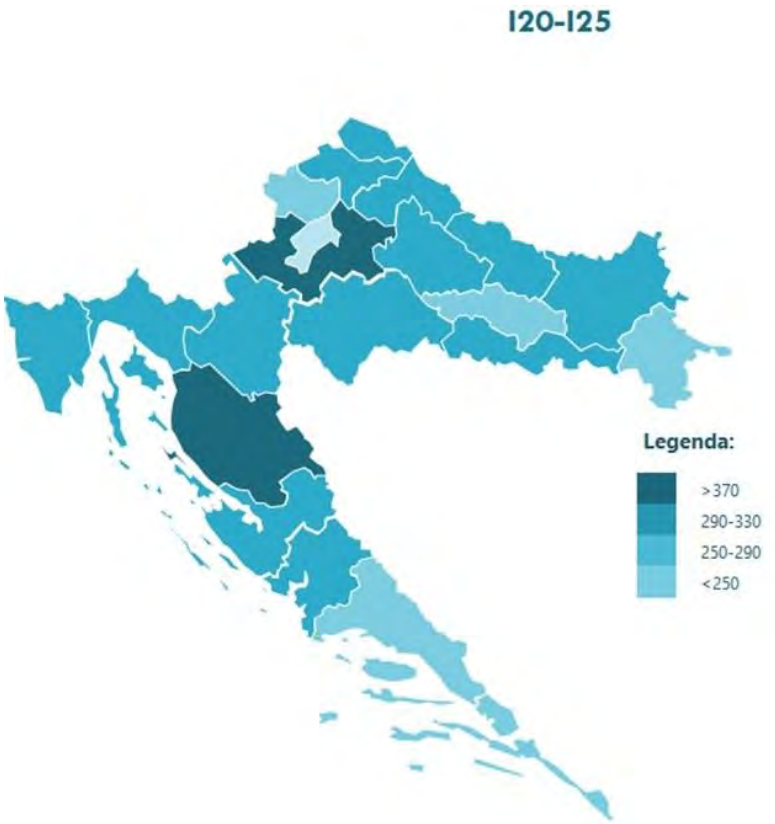
Despite Croatia's geographic and historical ties to the Mediterranean basin and its traditional association with the low cardiovascular risk, it falls within the medium- to the high-risk country group in the terms of cardiovascular mortality. The burden of CVD in Croatia is more similar to that of the other ex-socialist countries in CEE, including Bulgaria, the Czech Republic, Estonia, Latvia, Lithuania, Hungary, Poland, Romania, Slovenia, and the Slovak Republic. (41)

Croatia's two predominant climate regions, the Continental and the Mediterranean, exhibit differences in the burden of cardiovascular diseases. The prevalence of cardiovascular diseases in the Continental region is generally higher compared to the Mediterranean region. This difference may be attributed to factors such as a higher prevalence of smoking, a sedentary lifestyle, and unhealthy diet habits in the Continental region. Conversely, the Mediterranean region has a relatively lower burden of cardiovascular diseases, which is often attributed to the cardio-protective effects of the Mediterranean diet. The diet is rich in fruits, vegetables, whole grains, legumes, and fish. (42) The extent to which the Mediterranean lifestyle and diet affect the risk of cardiovascular diseases is still a subject of a debate. While many studies suggest that the regional and the lifestyle differences can have a significant impact on the development of cardiovascular diseases, the true extent of the effect of the Mediterranean diet and lifestyle remains debated**.** (43–45) According to the most studies, the Mediterranean diet, which is characterized by a high consumption of vegetables, olive oil, and fish, and the Mediterranean lifestyle are particularly advantageous for cardiovascular health. This is likely due to the presence of antioxidants, fiber, and healthy fats, along with the regular exercise (43, 44, 46)

In general, the mortality and morbidity patterns in Croatia are similar to those found in the transitional countries rather than in the Mediterranean countries, such as Italy, Spain, and France. Despite a decline in the CVD mortality rate over the last fifteen years, cardiovascular diseases continue to contribute significantly to overall mortality and morbidity in Croatia. They remain the leading cause of death and disability in both the coastal and continental areas. (47)

Last year, cardiovascular diseases were the primary cause of death in Croatia, making up 36% of all deaths, with cancer being the second most common cause, accounting for 21.6% of deaths. Moreover, when stratified by sex, the data showed that CVD was responsible for 41.80% of deaths among women and 32.07% among men. (48) When the most recent data were compared to 2016, there was a slight reduction in proportional mortality of cardiovascular diseases among both men and women. The proportion of deaths attributable to CVDs decreased from 50.1% to 41.80% in women (a decrease of 10%) and from 39.7% to 32.07% in men (a decrease of 7%). Despite the previously mentioned reduction in proportional mortality, Croatia still faces a significant burden of cardiovascular diseases. (48) Since 2000, a decreasing trend has been observed in Croatia for cardiovascular mortality, although the reduction was more pronounced for cerebrovascular disease than coronary artery disease. Specifically, from 2000 to 2014, there was a 45.2% decrease in overall cardiovascular disease mortality, with cerebrovascular disease mortality decreasing by 47.6% and coronary heart disease mortality decreasing by 28.8%. The absolute values of CVD mortality rates per 100,000 inhabitants decreased from 572.7 to 314, while for CAD, it decreased from 201.0 to 143.2. (49)

Inequalities in CVD prevalence, mortality, and access to the adequate cardiovascular care exist within and between EU countries, often resulting from the social and the economic factors. In 2019, the ASMRs from cardiovascular diseases in Croatia was 572.8 per 100,000, which is considered high when compared to the other European countries. Additionally, this rate is above the European average of 387.6. The sex specific ASMRs in Croatia is also high, with females having the ASMRs of 509.4 and males having the ASMRs of 648.7 per 100,000. The European average for males is 438.8, and for females, it is 132.12. The range for the total ASMR averages across Europe is vast, with France having the lowest rate of 190.4, and the Czech Republic having the highest rate 1051.8. (50)



Županija	I20-I25
Grad Zagreb	245,0
Dubrovačko-neretvanska	264,6
Krapinsko-zagorska	345,9
Splitsko-dalmatinska	249,4
Požeško-slavonska	361,3
Vukovarsko-srijemska	370,3
Sisačko-moslavačka	328,9
Karlovačka	288,2
Bjelovarsko-bilogorska	400,2
Istarska	268,7
Koprivničko-križevačka	392,7
Primorsko-goranska	264,0
Virovitičko-podravska	393,8
Zadarska	230,4
Osječko-baranjska	368,4
Brodsko-posavska	336,7
Međimurska	243,4
Šibensko-kninska	266,1
Varaždinska	349,2
Ličko-senjska	320,3
Zagrebačka	287,8

Figure 6. Distribution of age standardized cardiovascular mortality rate according to counties [internet image] (48)

As illustrated in the **Figure 6**, the latest mortality data for cardiovascular diseases, expressed as the ASMRs, demonstrate a non-uniform distribution throughout Croatia, characterized by a persistent East-West gradient. The continental region generally exhibits the higher mortality rates compared to the low-risk Mediterranean region counties. Zagreb and Mediumurje County, despite being located in the continental region, have the mortality rates that are similar to those observed in the coastal region of Croatia. Across all counties, cardiovascular diseases consistently emerge as the leading cause of death. For example, Bjelovar-Bilogora County reports the highest proportion of cardiovascular disease-related deaths at 49.7%, whereas Šibenik-Knin County records the lowest at 37.7%. Moreover, significant disparities exist in age-standardized rates of total mortality among counties. Virovitica-Podravina County exhibits the highest rate at 1363.2/100,000, while Zadar County reports the lowest at 799.7/100,000. When examining mortality rates from cardiovascular diseases, distinct geographical patterns emerge. Coastal regions generally exhibit lower rates compared to their inland counterparts. For example, mortality rates from ischemic heart disease are notably higher in Požega-Slavonia County (228.9) than in Zadar County (88.4). Furthermore, gender-

based disparities are evident, with males consistently experiencing higher mortality rates from cardiovascular diseases. Additionally, hypertension-related mortality rates tend to be higher in females in certain counties. (51)

Morbidity and mortality patterns of cardiovascular disease can be attributed to both preventive and curative medicine. In Croatia, curative medicine is well-established, and the rate of percutaneous coronary interventions (PCI) per 100,000 inhabitants is high and comparable to that in the more economically developed EU countries. (52) In contrast to the well-developed curative medicine system, Croatia faces high burden from the traditional cardiovascular risk factors, which are significantly higher compared to the other EU countries. There are also differences in the prevalence of the risk factors between the regions and by sex. In men, high blood pressure is the most prominent risk factor, followed by smoking, physical inactivity, high alcohol consumption, inadequate nutrition, and obesity. (51)

Behavior-related risk factors account for more than half of all the deaths, and the preventable mortality rates from CAD and stroke are double the EU average. Compared to the EU, Croatia shows higher disparities in dietary risks (26% vs. 18%), which consist of 14 different components, including the fruit and vegetable consumption. Tobacco is another significant cardiovascular risk factor in Croatia compared to the EU (20% vs. 17%), while alcohol contributes 7% (EU 6%). Low physical activity contributes equally to the EU and Croatia (3%). When the individual contribution of each risk factor is analyzed, the overall number of deaths (24,281) is not the same as the sum of each risk factor taken individually (28,899), as a single death may be attributable to the multiple risk factors. These findings suggest that comprehensive prevention measures are not being taken systematically through a comprehensive program and that preventive medicine lags behind curative medicine in Croatia. (53)

1.6 International Survey of Acute Coronary Syndromes in the Transitional Countries – literature review

The term "transition" refers to the period between an authoritarian political regime and a democratic regime. While it is generally assumed that transitions have distinct beginnings and endings, the flexibility of the process makes it challenging to draw a clear demarcation**.** (54) The fall of communism in the past 30 years has brought about significant changes in Europe,

affecting the complex determinants of health. Despite this, there remains a clear east-west gap in the health outcomes across Europe. While the life expectancy in Western Europe has increased significantly due to a reduction in mortality in the older age groups, Eastern Europe has progressed only modestly and continues to lag behind. (55)

Cardiovascular health presents a significant challenge for the transitional countries, which continue to strive towards achieving the standardized mortality and morbidity rates that are comparable to those in the Western European countries. While the cardiovascular mortality rates have decreased across Europe over the past decade, there remains a significant variability, with the CEE countries continuing to experience a higher burden compared to the Western European countries. Improvements in cardiovascular health in Western Europe have been associated with the advancements in the modern cardiovascular treatment, as well as the efforts at all levels of prevention. (56) Although preventive strategies and medical interventions are both essential for improving cardiovascular health, their relative contribution may vary depending on the country. A previous IMPACT model suggests that reducing the major risk factors accounts for more than half of the decline in the number of coronary heart disease deaths, while the evidence-based medical therapies account for less than a half. This highlights the critical role of the comprehensive prevention measures in reducing the burden of cardiovascular disease. (57–59)

The University of Bologna serves as the data coordination center for the International Survey of Acute Coronary Syndromes in the Transitional Countries (ISACS-TC) (ClinicalTrials.gov, NCT01218776). The study commenced in 2010 and is scheduled to conclude in December 2026. The survey is both retrospective and prospective, with an estimated enrollment of 36,000 participants, aimed at collecting data on patients with acute coronary syndromes in the countries with transitioning economies in CEE. The primary objective of the study is to optimize internationally recommended therapies for ACS in these countries, with all-cause mortality within 30 days, 6 months, and one year as the primary outcome measure. Secondary outcome measures include cardiovascular mortality within the same time frames, recurrent myocardial infarction, the pharmacogenetic and the cardiovascular genetic studies associated with the clinical outcomes, and adherence to the internationally recommended therapies across the participating countries. (60)

The ISACS-TC project has gained the support of 112 collaborating centers across 17 countries

with the economies in transition, including Albania, Bosnia and Herzegovina, Belarus, Bulgaria, Croatia, Hungary, Kosovo, Latvia, Lithuania, Macedonia, Moldova, Montenegro, Romania, the Russian Federation, Serbia, Slovakia, Slovenia, and Ukraine. A total of 47 cluster sites in 11 CEE countries participated in the project. Of these, 22 tertiary healthcare services provided the advanced medical investigation and treatment, such as PCI and/or cardiac surgery, while 19 secondary healthcare services provided the intensive care in the critical coronary care units. Each participating hospital obtained an approval from their respective local research ethics committee for the study. (60)

The focus of the ISACS-TC project is on ACS, as it represents one of the most complex areas of cardiovascular diseases. ACS is associated with a range of clinical presentations of cardiovascular diseases, from the ST-segment elevation myocardial infarction (STEMI) to non-ST-elevation myocardial infarction (NSTEMI) or unstable angina (UA). ACSs share the common underlying mechanisms in the terms of pathophysiology and are almost always associated with the rupture of an atherosclerotic plaque and the partial or complete thrombosis of the related coronary artery. (61) ACS is a major cause of cardiovascular morbidity and mortality, leading to a significant healthcare cost. However, data on the ACS management and therapies in CEE countries are still lacking, and there is a need for further efforts to improve clinical outcomes. Geographical disparities in the acute cardiovascular care and the outcomes for ACS persist both between and within the European countries. The ISACS-TC was launched to examine whether differences in the clinical and ethnic factors or the healthcare organizations contribute to these disparities. The registry provides detailed information on the patients' clinical, demographic, metabolic, and health status. Clinically relevant data that significantly influence the primary and secondary outcomes were selected for publication, based on the aggregated country-specific data. The inclusion of patients from some of the EU's founding members increases the data's generalizability. ISACS-TC examines the effect of the risk factors on the clinical outcomes in the countries with economies in transition, with a focus on the age groups and the sex stratification. A pattern of reversed risk was observed among the age categories, indicating that the association between age and the outcomes is not linear. Clinical outcomes such as the overall and cardiovascular mortality are associated with the multiple predictors, and a multiplicative model is more likely to explain these outcomes than an additive model. The ISACS-TC project aims to promote the healthcare equity within the transitional countries. The rationale and design of the project were published by Bugiardini et al. in 2014. (60)

Some research papers focused on the country-specific data from Bosnia and Herzegovina (62, 63)**,** Romania, (64) Croatia (65–68)**,** Serbia (64) the risk factors such age and sex (69–75), the comorbidities (76,77) and the different treatment options. (78, 79)

Study conducted by Ricci et al. examined the clinical characteristics of the young patients with ACS within a cohort of 14,931 patients from October 2010 to April 2016. The study focused on the patients up to 45 years of age, of whom 1,182 (8%) were included, with a mean age of 40.3 years, and 15.8% were women. The primary outcome was all-cause mortality at 30 days. The results showed that STEMI was the most common clinical manifestation in young patients (68% versus 59.6%). Young patients had a higher incidence of insignificant coronary artery disease (11.4% versus 10.1%) and a lesser extent of significant disease (single vessel, 62.7% versus 46.6%). The incidence of 30-day death was significantly lower in young patients (1.3% versus 6.9% in older patients). After adjusting for baseline and clinical differences, age at 45 years was a predictor of survival in men (OR, 0.24; 95% CI, 0.10–0.58), but not in women (OR, 1.35; 95% CI, 0.50-3.62). This reversed risk pattern between sexes persisted even after adjusting for in-hospital medications and reperfusion therapy. Additionally, the study found that younger women had worser outcomes than men of a similar age (OR, 6.03; 95% CI, 2.07–17.53). (69)

Pokrajčić Z et al**.** analyzed the sex differences in the presentation, treatment, and clinical outcomes among the patients with ACS after PCI. Their study focused on in-hospital mortality in men and women with ACS and its relationship with age (65 years). Study included 5,140 patients from 3 primary PCI hospitals from January 2010 to June 2015. Women had a higher mortality rate in the younger age group (OR 1.52, 95% CI: 1.01–2.29), but there was no sex difference in the older group. In-hospital mortality from ACS was similar among older men and women. (80)

Vasiljević Z. investigated sex differences in clinical characteristics, treatment, and in-hospital mortality among patients with STEMI in Serbia. From October 2010 to September 2013, 2,348 patients were treated in 19 hospitals. Women were older than man, with a higher prevalence of family history of coronary artery disease, hypertension, and diabetes. They were less likely to be smokers and more likely to have a prior angina and history of heart failure. Significantly fewer women than men presented within 2 h from symptom onset. Also, a significantly lower

proportion of women was treated with aspirin (91.3% vs 94.3%), clopidogrel (88% vs. 91%), heparins (61.6% vs. 66.5%) and PCI (62.1% vs. 69.7%). In-hospital mortality was significantly higher in women than men, and after adjustment for the potential confounders, women had a 97% higher risk of in-hospital mortality. (81)

Cenko et al. conducted a study to investigate the association between sex, acute heart failure, and the related outcomes after STEMI in patients without prior history of heart failure. The study included 10,443 patients (3,112 women) from the ISACS-TC registry. After adjusting for covariates, the incidence of de novo heart failure was significantly higher for women than men, and women with de novo heart failure had a higher 30-day mortality rate than men. (73)

Also Cenko et al. conducted a study to investigate if female sex is a treatment effect modifier of blood flow and related 30-day mortality after primary PCI for STEMI, and if the magnitude of the effect on outcomes differs depending on a delay to hospital presentation. They enrolled 2,596 patients from the ISACS-TC registry from 2010 to 2016, and found that female sex was associated with the higher rates of suboptimal post-PCI thrombolysis in myocardial infarction flow, grades 0 to 2, and 72% higher mortality. The sex gap in mortality was no longer significant for the patients with hospital presentations lasting 120 minutes. So they concluded that the delay to hospital presentation and the suboptimal post-PCI TIMI flow grade are variables independently associated with excess mortality in women. (82)

The Croatian branch of the ISACS-CT registry aimed to address the gaps in the knowledge regarding the clinical management of ACS at a national level. (66, 83) The results of the Croatian branch of the ISACS-CT registry, which enrolled 3,066 ACS patients from January 2013 to May 2018, showed that women with ACS were older, had a longer delay from the symptom onset to the hospital admission, and were more burdened with comorbidities. The study found that while there were no sex differences in the administration of beta blockers, ACE inhibitors, or statins in the first 24 hours, coronary angiography was performed in a smaller percentage of female patients (86% vs. 92%), and less women underwent primary PCI (67% vs. 77%). After multivariate regression, only age over 65 years (OR=3.61), chronic kidney disease (OR=1.85), and primary PCI (OR=0.49) remained associated with in-hospital mortality. (83)

Another study aimed to investigate the characteristics of myocardial infarction with non-obstructive coronary arteries (MINOCA) in ACS patients in the ISACS-CT registry. The study

aimed to determine the characteristics of MINOCA and compare them with age and sex-matched patients with UA, NSTEMI, and STEMI. MINOCA patients were primarily classified as UA and NSTEMI at clinical presentation, but had fewer comorbidities, more pronounced chest pain symptoms, a shorter time from symptom onset to hospitalization, and lower levels of statin and antiaggregating prescriptions at the hospital admission and the hospital discharge. In-hospital mortality confirmed MINOCA as low-risk, but a long-term follow-up is needed to learn about longer-term outcomes. (66)

A study published in 2018 from the Croatian branch of the ISACS-CT registry examined the sex differences in the mortality rates during the hospitalization and at a 1-year follow-up among the patients with ACS. The study showed that women who were admitted to the hospital were older, had more comorbidities, and experienced longer delays in seeking medical care compared to men. It was noted that there were no sex differences in terms of achieving a reduced ejection fraction below 40% during hospitalization. However, women with STEMI had significantly worser outcomes in the acute phase. During the follow-up period, no significant difference between sexes was found in terms of the all-cause mortality or the various cardiovascular endpoints. Factors such as age, the ejection fraction at discharge, and the primary PCI were identified as significant predictors of the survival, after adjusting for the type of acute coronary event and sex. (67)

In a 2018 study published by Pavasović et al**.**, aimed to examine the potential benefits of the early percutaneous coronary intervention within 24 hours of the admission for the elderly patients (>75 years) with NSTEMI. The primary endpoint of the study was a combination of 30-day mortality and severe left ventricular systolic dysfunction. The results showed that after adjusting for the various factors including age, sex, renal function, risk factors, clinical presentation, prior cardiovascular disease, and in-hospital medical therapy within 24 hours, early PCI reduced the occurrence of the primary endpoint in the cohort. The occurrence of severe left ventricular systolic dysfunction and 30-day mortality was also reduced in the PCI group compared to the medical therapy group. The study concluded that elderly patients treated with early PCI had lower rates of the primary and secondary endpoints compared to those treated with the medical therapy. There was no significant difference in the occurrence of the bleeding events between the two groups. (68)

1.7 Coronary artery disease

In medical texts and clinical settings, coronary artery disease is often referred to by various synonymous terms, such as coronary heart disease, ischemic heart disease, myocardial ischemia, or simply heart disease. Clinically, CAD can manifest in numerous ways, but the primary classification distinguishes ACS from chronic ischemic heart disease. Subcategories of chronic ischemic heart disease include stable angina, variant angina, and silent myocardial ischemia, while ACS encompasses NSTEMI and STEMI. **(Figure 7)** (84)

CAD results from the compromised blood flow in the coronary arteries due to the narrowing of the inner diameter by the atherosclerotic plaque. As atherosclerosis progresses, the blood flow is reduced, depriving cells of the necessary nutrients and oxygen. This inadequate blood flow leads to ischemia, which further disrupts the cellular functions. Extended ischemia results in the irreversible damage to the heart tissue, manifesting clinically as a heart attack and causing necrosis or cell death at the histological level. Clinically significant narrowing of the coronary arteries typically occurs in the initial segments of the larger arteries. Atherosclerosis complications can involve the subsequent rupture or erosion of the atherosclerotic plaque. (85) Partial occlusion of the coronary artery, characterized by 50-70% narrowing, presents clinically as UA. The optimal treatment solution for the intermediate coronary lesions has long been a challenge in interventional cardiology. Although coronary angiography is considered the "gold standard" for assessing coronary anatomy, it has significant limitations in evaluating lesion severity. Borderline lesions, with 50-70% stenosis, are particularly difficult to assess. (86)

Currently, both non-invasive and invasive methods are available for the clinical evaluation of the cardiac patients. Non-invasive techniques include the myocardial stress perfusion imaging and the stress echocardiography, while the novel invasive tests such as fractional flow reserve (FFR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT) offer valuable insight**.** (87, 88) Invasive methods are especially beneficial because they can be performed during coronary angiography on patients with borderline lesions. FFR is the most accessible method to identify the intermediate lesions requiring intervention and to minimize the unnecessary procedures with potential complications. (89) Diminished blood flow in the specific regions of the heart compromises the delivery of oxygen and nutrients, causing the heart to rely on an alternative oxygen substitute, such as lactic acid, to maintain function. The build-up of lactic acid in the heart muscle presents clinically as pain. In some patients,

myocardial ischemia may result from an imbalance between the myocardial oxygen consumption and supply without the fixed coronary artery obstruction, potentially leading to coronary artery spasm, severe anemia, cardiac arrhythmias, severe hypertension, or hypotension. (90) It is important to note that plaque formation is a lengthy process that often goes unnoticed and can span years. The term "cardiovascular continuum" was first introduced by Dzau et al. in 1991 to emphasize the sequence of events that starts with a well-known risk factor and culminates in cardiovascular death. (91)

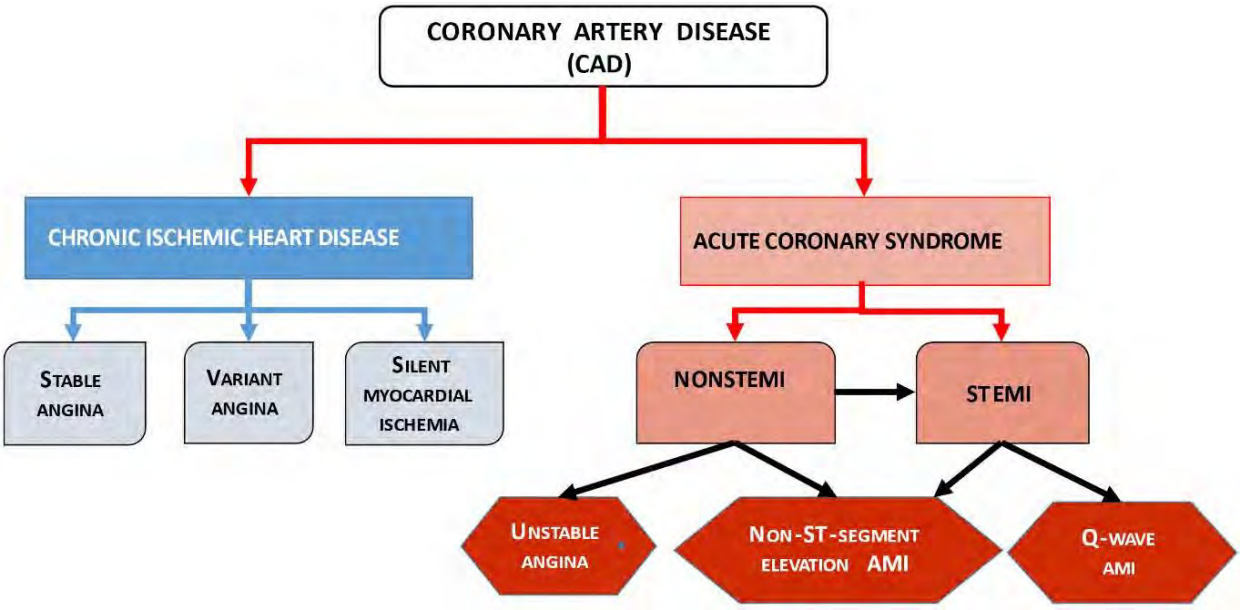


Figure 7. Clinical presentation of ischemic heart disease – acute coronary syndrome and chronic ischemic disease (acquired and modified from: www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.)

CAD can manifest as either chronic ischemic heart disease or acute coronary syndrome. Chronic coronary syndrome (CCS) can present as silent myocardial ischemia, stable angina pectoris, or variant angina pectoris. For all patients suspected of having CCS, pre-test probability and clinical likelihood of coronary artery disease should be assessed. Based on these evaluations, high-risk patients can be identified and undergo the functional or anatomical non-invasive tests to confirm or rule out CAD. (91, 92)

ACS represents the clinical manifestation of CAD and is typically a consequence of plaque disruption in the coronary arteries. STEMI, which is caused by a complete coronary artery occlusion, accounts for approximately 30% of ACS cases. ACS without significant ST-

segment elevation on electrocardiography, known as NSTE-ACS, makes up around 70% of ACS cases. **(Figure 7)** (93)

Myocardial infarction leads to reduced or completely halted blood flow to a portion of the myocardium. It can manifest as a "silent" event or as a severe incident that results in hemodynamic collapse and sudden death. The majority of heart attacks are caused by underlying coronary artery disease, where atherosclerosis contributes to a long-term oxygen imbalance in the myocardium and tissue death. Diagnosis typically relies on the clinical examination, the ischemic changes in the ECG, and the elevated biochemical markers (troponins). (94,95) Rapid diagnosis is crucial, as mortality is the highest within the first hour, and the prompt interventions are most effective since the heart muscle cells begin to die after 20 minutes of complete blood flow cessation. Patients with MI often present with typical chest pain, while the likelihood of developing atypical symptoms increases with age, female sex, diabetes, and dementia. (84, 93)

UA is a significant public health issue affecting a large portion of the global population. With UA, pain is unpredictable and arises from varying levels of physical activity. It can occur with minimal exertion, at rest, or even be triggered by intense emotions. Patients typically describe pain as intense, uncomfortable pressure, chest tightness, or burning or sharp pain radiating to the neck, lower jaw, left shoulder, left arm, or back. Pain usually lasts between 2 to 30 minutes. UA necessitates the immediate treatment and the evaluation for signs of ischemia or potential myocardial infarction. Patients may present with or without ECG changes indicative of ischemia. UA differs pathologically from the other ACS because the ischemic tissue perfusion remains sufficient to prevent heart muscle cell death. In the early stages of the disease, the plaque impedes blood flow to the myocardium, causing pain and shortness of breath during the more strenuous activities. As narrowing worsens, pain starts to occur during daily activities such as walking faster, climbing stairs, exposure to cold, and at rest. (96–98)

NSTEMI should be considered in patients who exhibit symptoms similar to those of unstable angina and have elevated troponin levels. Often, the elevation of troponins may not be apparent during the initial clinical presentation, making UA and NSTEMI difficult to distinguish at first evaluation. Typical NSTEMI symptoms include the pressure-like pain that occurs at rest or during exertion, usually lasting no more than 20 minutes. Patients may experience pain in their hands, neck, and lower jaw. Accompanying symptoms can include shortness of breath, nausea

or vomiting, fatigue, or sweating. Some patients may also exhibit atypical symptoms such as chest pain that worsens with breathing, abdominal pain, indigestion, or isolated difficulty breathing. NSTEMI is ultimately diagnosed based on the clinical symptoms, the elevated cardiac troponins, and the electrocardiogram changes. ECG findings suggestive of NSTEMI include the transient ST-segment elevation, the ST depression, or a new T-wave inversion. A follow-up ECG should be performed at the predetermined intervals or if the symptoms reoccur. (99,100) NSTEMI has been increasingly diagnosed in recent years, and this has been especially contributed to the aging world population and the introduction of the highly sensitive troponin tests. NSTEMI diagnosis can only be made if acute myocardial injury is defined as an increase and/or a decrease in cardiac troponin (cTn) above the upper reference limit (99%) in the combination with acute myocardial ischemia. (101) According to the new guidelines for NSTEMI it is important to evaluate the clinical context in which the troponin value is obtained and applied according to the recommended guidelines in order to be able to make the correct diagnosis and define the therapeutic strategies. (102) Cardiac troponins are crucial independent markers for determining the short- and the long-term prognoses, evaluating disease progression, and assessing the risk of death within the first 42 days. The risk of death in the first 42 days is directly proportional to the cardiac troponin levels. (103)

STEMI is the most critical and life-threatening condition in the patients with CAD. It involves death of the heart cells due to prolonged ischemia caused by a complete blockage of the coronary artery by a blood clot. Myocardial tissue death can lead to severe complications such as cardiac arrest, cardiogenic shock, hemodynamically unstable arrhythmias, heart failure, and death. STEMI is characterized by persistent chest pain (lasting > 20 minutes) that may radiate to the arm, neck, jaw, back, abdomen, or shoulder, and a variety of atypical presentations such as fever, nausea, vomiting, shortness of breath, abdominal pain, and fainting. The severity of symptoms can be influenced by the emotional stress levels. Atypical symptoms may be observed in the patients with diabetes, the elderly, and women. (104)

The ECG is the primary diagnostic tool for the patients presenting with chest pain. Initial findings may include the transient ST-segment elevation lasting over 20 minutes, the atrioventricular or interventricular abnormalities, the ischemic ST-T changes, various arrhythmias, or even normal results. Stenocardia followed by J-point elevation in two or more contiguous leads, ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V2 – V3 and / or ≥ 1 mm (0.1 mV) in the other contiguous chest leads or the limb leads is characteristic

of STEMI. (99) Reperfusion treatment is the preferred initial therapy for ACS, as it alleviates chest pain, stabilizes the patient, and reduces the ischemia symptoms. PCI is recommended within 90 minutes of the first medical contact at a PCI center or within 120 minutes if the patient is transferred to another hospital. Early reperfusion methods in STEMI have significantly reduced the mortality rates, with advances ranging from fibrinolytic therapy to PCI. Prompt and complete reperfusion preserves the myocardial tissue and the ventricular function, greatly impacting the long-term survival in the STEMI patients. (104)

1.8 Management of ACS

Current guidelines provide the comprehensive management strategies for ACS, emphasizing the importance of the evidence-based medicine in the daily clinical practice. ACS management focuses on the early diagnosis, the risk stratification, the timely mechanical and pharmacological reperfusion, the novel antithrombotic therapies, and the awareness of bleeding complications, especially in treating the STEMI and the NSTEMI patients. It is crucial to differentiate the STEMI from the NSTEMI and the UA patients. Treatment of ACS demands an urgency and commences at the patient's initial contact. Goals include an emergency and the long-term objectives. (101,105)

Emergency treatment aims to improve the coronary blood flow, while long-term goals encompass the lifestyle interventions, the risk factor management, and the efforts to enhance the heart function and minimize the reinfarction risk. Physicians and cardiologist tailor drug and procedure combinations according to the patient characteristics and risk stratification within the ACS spectrum. Special attention is required for the patients with a higher risk-benefit ratio, such as those with cardiogenic shock due to ACS or the particular subgroups of UA or NSTEMI patients at a higher risk of the negative outcomes. (102,103)

For the emergency treatment, the accurate diagnosis and the prompt anti-aggregation therapy are critical. The best myocardial reperfusion method should be selected based on the patient characteristics, including fibrinolysis, PCI, or coronary artery bypass graft surgery (CABG). (104,105) Antiplatelet therapy has long been considered essential for managing patients with acute coronary syndrome. However, atherothrombosis is a complex process, encompassing various stages of the plaque formation, from the early fatty streaks to the rupture-prone plaques, involving the multiple cellular and molecular events. Therefore, to reduce the risk of the

ischemic complications, it is crucial to target different pathways of the platelet activation. (104,105)

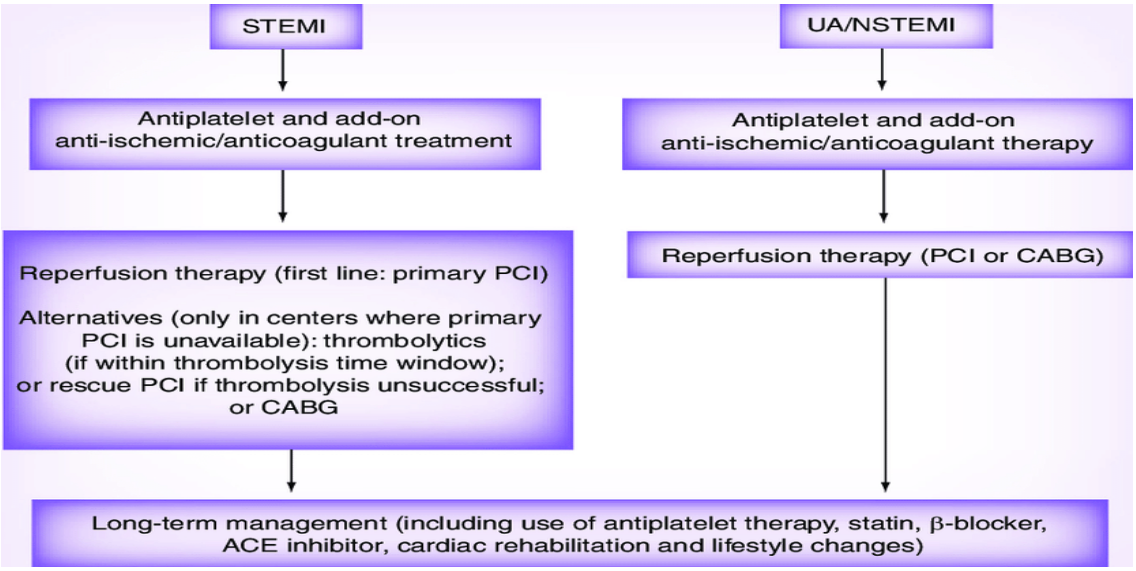


Figure 8. Emergency and long-term treatment goals in acute coronary syndrome (acquired and modified from: researchgate.net/figure/Initial-and-long-term-management)

Antiplatelet drugs inhibit the platelet function via various mechanisms, including acetylsalicylic acid inhibiting cyclooxygenase-1 and Clopidogrel, Ticagrelor, and Prasugrel targeting P2Y12 ADP receptors on the platelet membrane. (106–108)

PCI is the preferred method over fibrinolysis; however, it may not always be available. A meta-analysis of 23 randomized clinical trials found that primary PCI reduced the short- and the long-term adverse outcomes, including death, more effectively than fibrinolysis. (109) Currently, fibrinolytics are seldom used and are typically administered in the areas with the underdeveloped PCI networks. Modern guidelines recommend primary PCI for the patients with the symptoms lasting less than 12 hours (Class I) and a consideration up to 48 hours after the symptom onset (Class IIB). For NSTEMI revascularization, the timing of PCI varies based on the patient's clinical presentation. Very high-risk patients should undergo immediate invasive coronary angiography (<2h). These patients include those who are hemodynamically unstable or in cardiogenic shock, experiencing recurrent stenosis, life-threatening arrhythmias, mechanical complications, or ST-segment elevation in aVR >1 mm and precordial ST depression. High-risk patients, such as those with a confirmed NSTEMI diagnosis, the resuscitated patients without ST-segment elevation, or a GRACE score >140, should receive early invasive strategy with coronary angiography performed within 24 hours of the hospital admission. For patients without the symptom recurrence and who do not meet the very high or

high-risk criteria, a selective invasive strategy should be applied. (101)

Early treatment stages often involve antithrombotic therapy (usually in the cath-lab), which includes administering a heparin drug to prevent blood clots. Combining anticoagulation with anti-aggregation drugs is more effective in reducing recurrent thrombotic events in ACS than using only anti-aggregation platelets. (110) Current revascularization guidelines suggest that certain ACS patients meeting the specific criteria should CABG. Candidates for urgent CABG include patients with a patent infarction related artery (IRA) but unsuitable anatomy for PCI, a significant myocardial region at risk, or cardiogenic shock. Additionally, patients with large infarcts or who do not receive timely revascularization remain at risk for the mechanical complications of acute MI (e.g., myocardial wall rupture, ventricular septal rupture, pseudoaneurysm, or true aneurysm) and should also be considered for CABG. **(Figure 9)** (111)

Long-term treatment goals encompass the lifestyle interventions and the risk factor control, which are crucial for managing the patients who have survived MI. Altering lifelong habits can be challenging, and implementing and maintaining these changes demands considerable time and effort. Patients can control some risk factors, such as smoking cessation, achieving therapeutic goals in blood pressure control and body weight regulation, and engaging in the regular physical activity. (28) During the chronic phase of the disease, pharmacological treatment aims to prevent heart failure, control coronary disease, prevent sudden cardiac death, and manage angina. Antithrombotic treatment, beta-blockers, ACE inhibitors, and statins have demonstrated a positive impact on survival and reinfarction prevention. (112–115)

Dual antiplatelet therapy for up to 12 months post-ACS has been particularly beneficial in patients treated with PCI, as it reduces the risk of stent thrombosis, myocardial infarction, and cardiovascular death. Latest guidelines prefer Prasugrel or Ticagrelor over Clopidogrel due to their faster onset of action, greater inhibition of platelet activity with less interindividual variability, and better bioavailability after application. (116) Beta-blockers are considered a secondary prevention medication. They decrease myocardial oxygen demand by reducing heart rate, blood pressure, and myocardial contractility, thus effectively relieving ischemic symptoms in patients with ACS. A meta-analysis of 82 randomized beta-blocker clinical trials in patients with acute or previous MI n showed a significant reduction in long-term mortality**.** (119)

In patients with specific conditions such as heart failure, diabetes, hypertension, and chronic kidney disease, the early-stage treatment with ACE inhibitors after myocardial infarction has proven beneficial for the long-term therapy. The AIRE study evaluated the efficacy of ACE inhibitor therapy, resulting in a 36% reduction in mortality and an 11.4% absolute mortality reduction in survivors of an MI. (117) The AIREX study, an extension of the AIRE study, demonstrated that a treatment with ramipril for about one year, initiated early post-MI in the patients with heart failure, results in a sustained survival benefit over many years and offers, on average, an additional year of life. (118) Statins are a group of hypolipidemic drugs that reduce blood cholesterol levels. Their greatest therapeutic potential lies in the plaque stabilization. Besides the plaque stabilization, statins have been shown to have the anti-inflammatory effects and improve the endothelial and platelet function. (119,120) Patients undergoing percutaneous PCI and subsequently treated with statins experienced a significantly lower rate of the target vessel revascularization, even after adjusting for LDL-c levels. **(Figure 9)** (121)

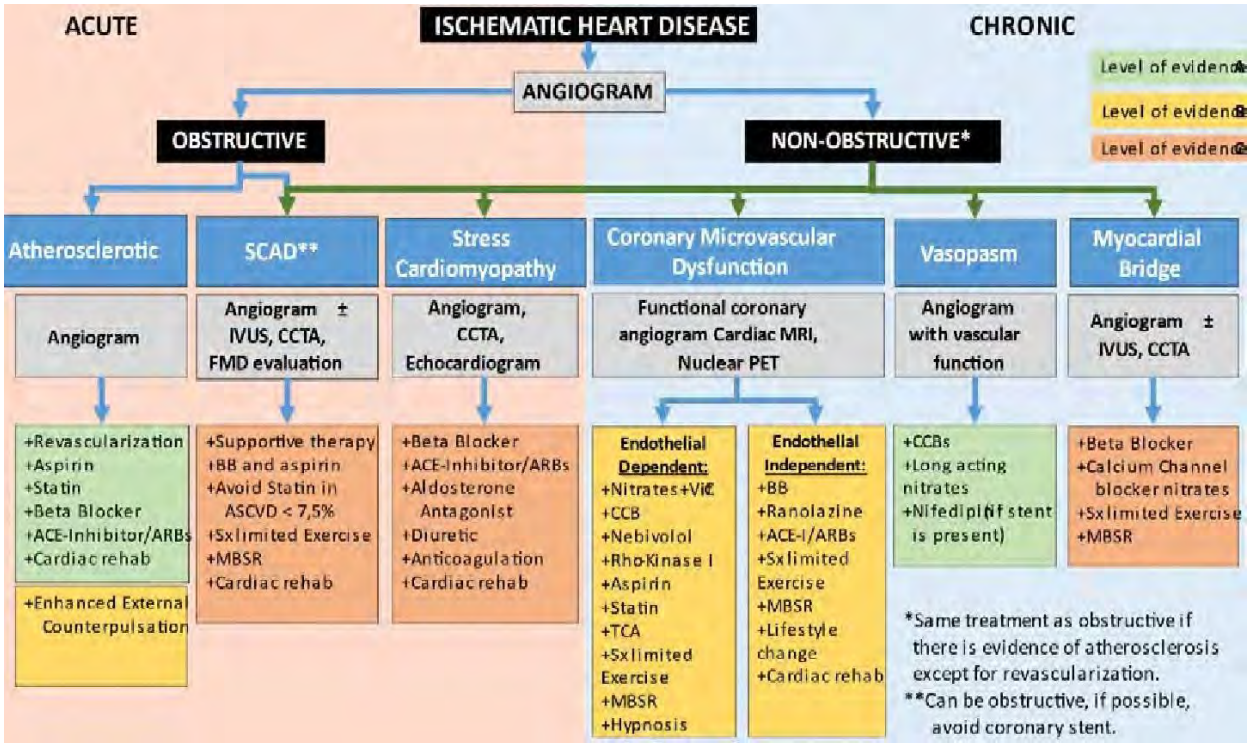


Figure 9. Clinical management of obstructive and non-obstructive ischemic heart disease (acquired and modified from: www.researchgate.net/figure/Evaluation-and-management-of-ischemic-heart-disease)

1.9 Risk factors for increased mortality in ACS in the post PCI setting

Over the past few decades, the secondary prevention measures, the strict guidelines, the early revascularization procedures, and the antithrombotic therapies have all significantly improved the prognosis for the patients with ACS. PCIs are the most common revascularization procedures performed worldwide, and along with the stent implantation, they are considered the most suitable approach for ACS. PCI has been proven to enhance prognosis in the ACS patients and is widely used in those with multiple vessels and complex, acute, or stable CAD. The extensive clinical presentation of ACS poses challenges for a study design, ranging from cardiac arrest, electrical or hemodynamic instability with cardiogenic shock due to the ongoing ischemia or the mechanical complications, to patients who are pain-free at the time of the presentation. (122)

Despite the advances in the care, the ACS hospital survivors still experience the various late adverse cardiac events. Endpoint definitions can vary among the studies, including the single or composite outcomes, and the follow-up times can be short (30 days, 60 days) or longer (months or years). One proven and reliable indicator of the appropriateness and the effectiveness of the diagnostic and the therapeutic process for AMI patients is 30-day mortality, which includes deaths during the index or the subsequent hospitalizations. (124–126)

Although STEMI and NSTEMI patients share similar risk factors and pathophysiology, there are notable differences in the short and long-term outcomes. (127,128) In general, the patients with STEMI have the higher in-hospital mortality rates and the worser short-term outcomes, while the NSTEMI patients have poorer long-term prognoses. (129–131) The potential causes explaining these differences are not yet fully understood, but various path mechanisms have been proposed. NSTEMI patients tend to have a worser clinical risk profile (i.e., they are significantly older, have more comorbidities, and a more frequent history of CAD), higher rates of recurrent ischemia, and are less likely to receive the guideline-recommended treatment strategies at discharge. (127, 129, 131)

Yan et al. provided the evidence on the prevalence and associated factors of mortality after PCI for the adult STEMI patients. (132) Chacko et al. conducted a meta-analysis of the randomized clinical trials among the STEMI patients, estimating the effects and the benefits of PCI. The reduction in mortality with PCI has been confirmed in the various studies for the STEMI patients, but the role of PCI remains controversial for the other patients within the ACS

spectrum. The authors analyzed the benefits of PCI in three groups of patients with unstable CAD: post-MI patients who did not receive immediate revascularization; patients who underwent primary PCI for STEMI but had the residual coronary lesions; and patients who experienced a NSTEMI. Patients from the ISCHEMIA trial, presented in 2019, were also included in this study. The authors confirmed that PCI prevents death, cardiac death, and MI in the patients with unstable CAD. In contrast, for the patients with stable CAD, PCI shows no evidence of impacting any of these outcomes. (133) In their 2016 study Sanchis et al. examined the elderly patients with NSTEMI and compared the effectiveness of the conservative and invasive treatment approaches. The study's main objective was to assess the 2.5-year composite endpoint of all-cause mortality and the readmissions for cardiac reasons. The results of the study showed that the invasive management did not significantly alter the long-term outcomes in the comorbid elderly patients with NSTEMI. (134)

Sawano et al. examined 30-day and 1-year outcomes of the ACS hospital survivors using a Japanese nationwide cohort. The study population included 20,042 ACS patients who underwent PCI in 2017: STEMI (51%), NSTEMI 3,027 (15%) and UA (34%). The overall 30-day all-cause, cardiac, and non-cardiac mortality rates were 3.0%, 2.4%, and 0.6%, respectively. The overall 1-year incidence of all-cause, cardiac, and non-cardiac death was 7.1%, 4.2%, and 2.8%, respectively. (135)

Hosseiny et al. studied the mortality patterns in 1,313 STEMI patients treated with PCI between 2006-2013. The average follow-up was 3.5 years, and the patients' mean age was 62.3±13.one years, with 22.5% being female. Over the follow-up, 181 patients (13.7%) died, with 3.4% in the first 7 days, mostly from cardiogenic shock, and 3.9% between 7 days and one year, mainly due to the cardiovascular causes and cancer. After one year, the mean annual mortality rate was 2.05%, with 36% from the cardiovascular causes and 52% from the non-cardiovascular causes, including 29% cancer deaths. Key predictors of the long-term mortality included age ≥75, diabetes, prior PCI, cardiogenic shock, eGFR <60, and the treatment delay. The 1-year mortality rate was 7.3% and 2.05% annually after that, with causes shifting from the cardiovascular to the non-cardiovascular over time. (136)

1.9.1. Bundle block

Bundle block is also a predictor of an unfavorable outcome in the ACS patients. The effect of a left bundle branch block (LBBB) on the outcome differs from that of a right bundle branch

block (RBBB). Prior research has shown that RBBB occurs more frequently than LBBB because the Purkinje fibers of the right bundle branch are longer and structurally thinner than those of the left bundle branch. (137,138) This difference might contribute to RBBB's higher susceptibility to myocardial ischemia compared to LBBB in ACS. It remains unclear whether the new permanent RBBB should be used as an independent variable for the long-term prognosis of the new-onset STEMI patients following primary PCI. The Third Universal Definition of Myocardial Infarction from 2012 defines it as the rise and/or fall of cardiac troponin, the symptoms of ischemia, the significant ST-T changes, and the new LBBB. However, RBBB was recently recognized as an important prognostic factor and is now included in the new universal definition of MI. The latest study indicates that patients with RBBB have a larger area of myocardium (i.e., septum) in ischemia, which could explain the worst outcomes. (139–141)

Previous guidelines recommended a similar treatment for the STEMI patients and those with new or presumably new LBBB, including the immediate reperfusion therapy, preferably PCI. (142) However, more recent guidelines also included the RBBB patients, but with the lower-level evidence. The prevalence of RBBB in ACS is 6–10%**.** (143–147) In-hospital mortality for both BBB types was around 15–20%, significantly higher than in the STEMI patients or the other ACS patients with the normal QRS duration (144,146,147) In more recent studies, the hospital mortality remains highest in patients with BBB, particularly new-onset RBBB. However, limitations of these studies include the small samples, the non-contemporaneous populations, the populations from randomized clinical trials rather than the real-life settings, and the ethnically different populations.

Timoteo et al**.** assessed the varying effects of RBBB and LBBB on the prognosis for the patients with ACS. The study involved the consecutive patients from a single-center registry of ACS. Baseline ECG characteristics, such as the normal QRS, LBBB, or RBBB, were analyzed, and the primary outcome was one-year all-cause mortality. Of the 3,990 patients (mean age 64, 72% male), 3.4% had LBBB and 4.3% had RBBB. Medical treatment was similar, but angioplasty was performed less frequently. In a multivariate analysis, only RBBB (HR 1.66, 95% CI 1.14–2.40, p = 0.007) was independently associated with all-cause mortality. (148)

Yang et al. studied the long-term prognosis of the new-onset STEMI patients who underwent PCI, focusing on the predictive value of the permanent RBBB and LBBB. Of the 547 patients, 29 had permanent LBBB, 51 had permanent RBBB, and 467 had no BBB. The primary

endpoint was major adverse cardiac and cerebrovascular event. After a 43.93-month follow-up, the new-onset RBBB patients had a higher risk of MACCEs than the new-onset LBBB patients (p=0.021). (149)

1.9.2. Age

The pathophysiology of ACS varies between the elderly and the younger patients. Although there isn't a universally accepted definition of "elderly," a cutoff of 75 years was used in two cohorts (150,151) Elderly patients represent a large and growing proportion of the ACS patients admitted to hospitals. Aging is associated with the structural and functional changes in coronary arteries, such as the luminal enlargement, calcification, and intima-media thickening. Vascular stiffness and endothelial function also increase with age. Older patients have predominantly calcified lesions, while younger patients have a higher prevalence of rupture/dissection and culprit lesions with more thrombus. Age is associated with more severe CAD, higher MVD and LAD incidence, but no major age-related differences in lesion characteristics. (152)

Increased mortality among the elderly patients can be attributed to the various predictors, such as the high-risk baseline demographic and clinical features, including diabetes, hypertension, renal failure, anemia, cardiogenic shock, cognitive dysfunction, peripheral arterial disease, longer door-to-balloon time and higher baseline brain natriuretic peptide. Clinical presentation varies based on the degree and duration of obstruction and includes both the NSTEMI and STEMI patients. Detailed clinical evaluation is crucial since the elderly patients often exhibit the non-typical clinical presentations, leading to a delayed diagnosis and a worser prognoses. With an aging population, understanding the relative risks and benefits of interventions for elderly ACS patients is vital. (153)

Recent ESC guidelines recommend invasive coronary angiography for most elderly NSTEMI patients. (101) Although the invasive treatment for NSTEMI is supported by numerous studies, physicians often prefer conservative strategies over invasive approaches in the patients aged 80 or older, as advanced age is an independent predictor for the conservative treatment. However, this approach is not backed by the available clinical evidence, and the studies focused on the invasive strategies among the elderly remain limited. To date, there are four randomized clinical trials comparing the invasive and the conservative treatment strategies in the elderly NSTE-ACS patients: the Italian Elderly ACS study n=313 (151), the After Eighty study n=457,

(154) the MOSCA study n=106, (161) and the RINCAL trial n=251. (155) These trials have produced the conflicting results, with the After Eighty study showing a 52% risk reduction with an invasive strategy (HR=0.48, 95% CI: 0.37-0.63) and the other three studies showing no difference between two treatment strategies.

The randomized controlled trial conducted by Bach et al. showed that an early-invasive strategy could improve the ischemic outcomes in the elderly patients (age >65) with unstable angina and NSTEMI. The study involved 2,220 patients who were assigned to either an early-invasive or conservative management strategy. The study found that the early-invasive strategy resulted in a significant reduction in death or MI at 6 months among the patients 65 years of age and older compared to the conservative strategy. (156)

The study conducted by de Boer et al. in 2022 evaluated the final survival benefit of primary PCI versus thrombolytic therapy in the STEMI patients over 75 years of age. The study included 46 patients who were randomly assigned to PCI and 41 to thrombolysis, with no significant differences in the baseline variables. After a maximum follow-up of 20 years, all patients had passed away, and the patients randomized to PCI had a mean final survival benefit of 1.5 years compared to thrombolysis (p=0.15). Therefore, the life expectancy of elderly STEMI patients increases by 28.8% with primary PCI. (157)

Recent studies have focused on evaluating predictors of clinical outcomes in octogenarians with STEMI who underwent PCI. One Dutch study found that cardiogenic shock at initial admission was the most direct predictor of 30-day and 1-year mortality. Age and post-procedural TIMI flow 3 were also identified as independent predictors of mortality at 30 days and one year. (158) In a Japanese study of PCI for STEMI in elderly patients aged ≥75 years, Sakai et al. identified several independent predictors of 30-day mortality, including overt cardiogenic shock upon arrival, anterior MI, unsuccessful reperfusion, age over 85 years, and female sex. (159)

In the TRIANA trial**,** researchers have compared PCI and fibrinolysis in very old patients (mean age of 81 years) with STEMI. The trial found that PCI was associated with a non-significant reduction in the composite primary endpoint of all-cause mortality, re-infarction, or disabling stroke at 30 days, as well as the non-significant reductions in death, re-infarction, or disabling stroke. Recurrent ischemia was less common in the PCI-treated patients, and there were no differences in major bleeds. A pooled analysis with previous reperfusion trials in older

patients showed an advantage of PCI over fibrinolysis in reducing death, re-infarction, or stroke at 30 days. (150)

In the APEX-AMI Trial, Gharacholou et al. in examined the impact of age on treatment and outcomes in STEMI patients treated with PCI. The study included patients aged 75 years or older and found that older patients had a higher prevalence of comorbidities, worser angiographic success after PCI, and a higher rate of complications during hospitalization. Age was also found to be the strongest independent predictor of short term mortality, with the higher rates of mortality and composite outcomes observed in the older patients. (160)

1.9.3 Gender

There is evidence that CAD pathophysiology and clinical manifestations of atherosclerosis are different in women. (161) Although men generally have a higher risk for the development of the disease, multiple registries around the world consistently show that women are at a much higher risk of adverse outcomes than men. However, the results are arguable whether female sex is an independent contributor to this observation or whether the higher risk differences are attributable to baseline characteristics and comorbidities. (162–164)

Idris et al**.** studied the influence of sex among 3,178 (25% female) consecutive ACS patients who underwent PCI at Liverpool Hospital, Sydney, from 2003 to 2010. Outcomes were late events, including mortality, MI, and bleeding. Among the patients under 55 years of age (n = 988), mortality and bleeding were higher in females (6.0% vs. 3.0%, p = 0.028) and (26% vs. 14%, p = 0.001), respectively. Still, sex had no effect on mortality or bleeding in the patients older than 55 years of age. However, in the multivariable regression analysis, female sex was not an independent predictor of mortality but was a significant predictor of bleeding (OR = 1.84, 95% CI: 1.38–2.45). The authors concluded that bleeding and mortality were higher in the younger females with ACS who underwent PCI. While females had more post-PCI bleeding events, which were associated with late mortality, sex per se was not an independent predictor for mortality. (165)

Ferrante et al. 2011 studied the sex differences in the long-term outcomes for PCI patients. Of 481 STEMI patients, 138 (28.7%) were women, who were older and had more health issues than men. Women had a higher incidence of death, nonfatal myocardial infarction, and hospitalization for heart failure. After propensity score matching, the hazard of the composite

endpoint was attenuated. Researchers conclude that women undergoing PCI had worser long-term outcomes compared to men, but the observed difference is largely attributable to differences in their baseline cardiovascular profile. (166)

Pancholy SB et al. 2014 conducted a meta-analysis to compare the sex disparity in survival in STEMI patients treated with PCI. Studies were included if PCI was the treatment option, if PCI was performed within 12 hours of symptom onset, and if sex-specific in-hospital and/or 1-year mortality were reported. The primary outcomes were non-specific in-hospital mortality and 1-year all-cause mortality. Risk ratios (RRs) of mortality were used for the previously mentioned time points. Of the 149 studies identified, 35 met inclusion criteria, representing 18,555 women and 49,981 men. In the unadjusted analyses, women had a 95% higher risk for in-hospital mortality (RR 1.93, 95% CI, 1.75–2.14) and a 58% higher risk for 1-year all-cause mortality (RR, 1.58, 95% CI, 1.36–1.84). However, the adjusted RRs between women's sex and all-cause mortality were lower but still significantly higher for in-hospital mortality (RR, 1.48; 95% CI, 1.07-2.05). The risk for 1-year mortality in women was no longer significant (RR, 0.90; 95% CI, 0.69-1.17). Researchers concluded that increased mortality in the women was likely confounded by the baseline CVD risk factors and the differences in the clinical profiles among the male and female STEMI patients. (167)

1.9.4 Glomerular Filtration Rate

Chronic kidney disease represents a global public health problem. (168) Kidney function is a strong risk factor for the fatal and nonfatal cardiovascular events, with the patients requiring the long-term renal replacement therapy at the particularly high risk. (169) There is a limited accuracy in using the serum creatinine level as an indicator of kidney function on account of the fact that it varies by age, sex, race, and lean body mass. As a result, the National Kidney Foundation recommends using the estimates of GFR determined from the validated equations instead of the serum creatinine levels to define decreased kidney function. (170) Recent studies suggest that even mildly decreased kidney function is an independent predictor of long-term mortality in the patients who have known or suspected coronary artery disease. (171–173)

In spite of a higher risk of the adverse outcomes, the patients with CKD are often treated less aggressively than the patients with normal renal function. Patients with CKD are also less likely to receive P2Y12 receptor blockers or aspirin and are less likely to undergo reperfusion or

revascularization. (174) The ISCHEMIA CKD trial included 777 patients with advanced renal insufficiency (eGFR 30 mL/min), a subpopulation of the larger ISCHEMIA trial population. As opposed to the main population, an early routine invasive strategy did not reduce the incidence of death or MI, and an excess of stroke, death, or the initiation of dialysis was observed compared to the initial approach with medical therapy alone. Authors concluded that PCI benefit window for CKD patients still remains narrow. (175)

Chen et al. in 2020 investigated the relationships between chronic kidney disease, and the prognosis of the NSTEMI patients treated PCI. The study included 8,197 individuals and analyzed 2,159 patients (average age: 64.23 ± 10.25 years; 73.7% male). The primary outcome measure was the number of in-hospital net adverse clinical events (NACE), while secondary outcomes included NACE and death from any cause during the follow-up period. The study observed 39 (1.8%) hospitalized patients with NACE. During the 3.23 ± 1.55-year follow-up, 1.7% mortality and 4.2% NACE were reported. Severe CKD was found to result in a significant rate of in-hospital NACE in NSTE-ACS patients after PCI. (176)

In their article published in 2012, Campbell NG et al**.** investigated whether mild renal impairment is an independent predictor of survival in the STEMI patients. The median follow-up time was 2.6 for 601 patients. Mortality after 30 days and one year was 5.7% and 12.5%, respectively. After adjustment for age and comorbidities, mild renal impairment was a strong independent predictor, compared with an eGFR ≥90 ml/min/1.73 m2 (HR 2.79, 95% CI 1.98 to 3.92, $p < 0.001$), and deteriorating kidney function was a strong predictor of death after both 30 days and one year of follow-up. (177)

1.9.5 Culprit lesion in acute coronary syndrome

Culprit lesion is the lesion responsible for coronary stenosis and for the subsequent symptoms. (178) Within cardiovascular continuum 50% cut-off is used to classify lesions as obstructive (stenosis >50 %) or nonobstructive (stenosis <50 %). This culprit lesion is often characterized by intraluminal filling defects consistent with thrombus, plaque ulceration and irregularity, dissection, and impaired flow. (179) Beside the term culprit lesion, a term culprit vessel has been introduced into the clinical practice. Culprit coronary vessel is defined as any vessel with an acute thrombotic total or subtotal occlusion. (180,181) These lesions are readily identified, and an attempt is made to re-establish blood flow with the use of thrombectomy, balloon angioplasty, or placement of one or more stents. Its early recognition enables appropriate

treatment in the patients with multivessel disease. In addition to culprit lesion(s), about 50% of the STEMI patients have one or more obstructive lesions remote from the area of infarction (ie, "non-culprit" lesions). Patients with STEMI and multivessel coronary artery disease who undergo PCI are most commonly treated with PCI to the culprit lesion only. (181,182) However, such strategy in multivessel coronary artery disease remains questionable. According to the current guidelines this approach is justified. Nonetheless, recently alternative approaches have been tested against this according to guidelines currently valid approach. The aim of the CvLPRIT trial was to evaluate PCI of the infarct-related artery compared with a complete revascularization among the patients with ST-segment elevation myocardial infarction. (183) Among patients with STEMI, complete revascularization appears beneficial at reducing major adverse cardiac events with a significant difference in overall composite outcomes between these two groups of patients after 12 months follow-up. However, stratified outcome analysis revealed no significant difference in all-cause mortality, IM, repeated revascularization, heart failure and total infarct size. Although underpowered, this study provided a clear direction after 5,6 years follow-up where complete revascularization was associated with a reduction in death or MI. Complete revascularization is associated with an increase in acute non-infarct artery MI, however, these were small events which were detectable by magnetic resonance imaging and did not increase a total infarct size. (184)

Some recent studies evaluated the association of culprit lesion location with outcomes of culprit-lesion-only PCI with optional staged revascularization vs immediate multivessel PCI in patients with multivessel disease, myocardial infarction, and cardiogenic shock. (185) At one year, culprit-lesion-only vs immediate multivessel PCI was associated with a significantly reduced risk of death in the left main or proximal left anterior descending artery but not the other-culprit-lesion location group. Therefore, the post-hock CULPRIT-SHOCK sub study revealed that these patients may especially benefit from culprit-lesion-only PCI with optional staged revascularization. These results are not in line with the recommendation that patients at cardiogenic shock should be treated at all, culprit and non-culprit lesions. DANAMI-3—PRIMULTI, Danish open-label, randomized controlled trial conducted at two university hospitals aimed to study the clinical outcome of the patients with STEMI treated with fractional flow reserve guided complete revascularization versus treatment of the infarct-related artery only. (186) The latest guideline of the 2017 ESC recommends routine revascularization of non-culprit lesions in STEMI before a hospital discharge, but still not at the initial admission or at initial intervention, however the level of the recommendation is still not high enough to be

clinically implemented universally. (107) Recently non-invasive approaches with coronary computed tomography angiography have been added to the standard of care in order to improve the diagnostic sensitivity in detection of culprit lesions with promising results. (187,188)

Stratification by culprit vessel affects the clinical outcome for ACS patients in post-PCI setting. Culprit vessel is easily identified in the STEMI patients and opposed to the clinically more challenging NSTEMI patients and those with MVD. Among the NSTEMI patients electrocardiographic changes may be transient, absent, or even misleading. (189) The nonexistence of the classic ST-segment elevation in the NSTEMI patients, despite the presence of totally occluded culprit artery, lead to either delay in or no revascularization. (190) According to large study of NSTE-ACS and MVD, the culprit lesion appeared unclear by coronary angiography in >10% of patients. (191)

The LMCA supplies the around 70% myocardium in the patients with right dominant type and 100% in the patients with left dominant type. (1) Left main stem disease is identified in up to 5% of diagnostic angiography cases and is associated with a significant morbidity and mortality due to the proportion of myocardium at risk, carrying large prognostic significance. (192) Treatment strategies for LMCA disease must therefore be efficacious and robust. Initial experience with PCI in treating LMCA disease using the older-generation stents and a limited use of the contemporary imaging modalities had demonstrated poorer outcomes, leading to CABG being considered the gold-standard therapy. However, the newer-generation drug-eluting stents, the more advanced intravascular imaging modalities, and a better patient selection, have meant that PCI is now considered to be a viable alternative to CABG, and its use is increasing in the patients with LMCA disease. (192)

Culprit vessel, such as LAD, RCA and LCx, are associated with different clinical outcomes in the patients with myocardial infarction. The LAD artery is the largest artery which supplies 45-55% of the left ventricle muscle. Revascularization guidelines use the LAD occlusion location to determine the best treatment options. Stenosis of the proximal LAD artery is known under the name “widow maker”. According to the one-year study, LAD infarctions had the highest increased risk of death, heart failure and stroke compared with RCA infarctions, which had the lowest risk. (193,194) ESC Guidelines from 2017 recommend a “heart team debate“ for the patients with stable coronary artery disease and proximal LAD disease and confer a class I for percutaneous and surgical treatment. In contrast, with lesion in the proximal RCA or LCx,

stenting is preferred choice. (104)

In 2006 article published in "American hearth journal" evaluated relationship between the infarct artery location and the clinical outcomes after (30 days and one year) in the patients who underwent PCI because of myocardial infarction. A total of 2,082 patients from CADILLAC trial were included in the study. They have similar baseline characteristic, and distribution of IRA was LAD, 37%, LCX 18% and RCA 46%. Patients with anterior vs nonanterior infarction had significantly higher mortality at 30 days (3.4% vs 1.3%, P= 0.0006) and one year (6.5% vs 2.9%, P < 0.0001). Also in the multivariate analysis, LAD infarction come out as a strong independent predictor of 1-year mortality. (195)

A Swedish analysis published by Entezarjou et al. in 2018 evaluated the impact IRA on a short-term and a long-term prognosis in the patients with STEMI. Total of 29 832 patients from SCAA registry who underwent PCI between 2003 and 2014 were enrolled in this analysis. Based on the culprit artery, the patients were stratified into three groups, and they have investigated 30 days and 1-year mortality outcome. One-year outcome shown that LAD as the culprit artery had the highest risk for MACE, while RCA had the lowest. Additionally, the investigators concluded that the culprit artery had no significant influence on 1-year mortality if the patient survived the first month. Another interesting conclusion from this study was that female sex and multivessel disease were significant high-risk sub-groups with respect to one year survival. (194)

2. Hypothesis

Gender, age, decreased glomerular filtration rate, bundle branch block in the electrocardiogram and the LAD as the infarction related artery are important predictors for first year clinical outcomes in ACS patients who undergo primary percutaneous coronary interventions.

3. Aims and purpose of the research

Despite significant advancements in in-hospital outcomes for patients with acute coronary syndrome, considerable disparities persist both within and between European countries. These discrepancies are particularly noticeable in CEE countries, likely due to the unique characteristics of their healthcare systems. Even though mortality rates from acute coronary syndrome have substantially declined in the EU, CEE patients continue to experience poorer clinical outcomes compared to their Western European counterparts. Transitional countries are working to close this health gap by investigating country-specific predictors that may be causally linked to inferior clinical outcomes.

We hypothesised that male gender, increased age, decreased glomerular filtration rate, bundle branch block in the electrocardiogram, and LAD as the infarction artery related will be significantly associated with one month and one-year mortality in ACS patients who undergo primary percutaneous coronary interventions. The aims of this study share similarities with objectives of ISACS-TC which include definition of patient and treatment characteristics in order to examine whether differences in clinical and ethnic factors or healthcare organization may mediate the observed disparities in outcomes. Risk factors included into analysis, both modifiable and non-modifiable, were selected based on their availability within clinical setting and previous studies in transitional countries.

Our research consists of the following aims:

1. The major aim is to identify predictors, demographic and clinical, for lethal outcome or hospitalisation/reinfarction within one month and first year in ACS patients who undergo primary percutaneous coronary interventions.
2. The specific aim is to quantify the association of these predictors with mortality risk during the two follow-up periods (one month and one year) by estimating the odds ratios after adjusting for potential confounders.

The results of this study can be applied for evaluation of clinical practice for post-PCI ACS patients in University Hospital Centre Zagreb and for comparison of clinical outcome with similar research from other transitional countries.

4. Materials and methodology

4.1. Data collection and patients

Data collection for this PhD study was conducted retrospectively as part of study The International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC registry) supported by University of Bologna, Bologna, Italy. This ongoing observational retrospective and prospective cohort (2010 - 2026), aims to analyse data of patients with ACS in transitional countries, and to optimize internationally guideline-recommended therapies.

Aims of ISACS-TC study included; (i) documentation of the characteristics of all patients presenting to the ISACS-TC centres with STEMI or NSTEMI, (ii) documentation of in-hospital outcome, and outcome rates at 6 month and one year, (iii) documentation of invasive procedures and procedure-associated complications, and (iv) documentation of therapeutic regimens and investigation conformity of treatment with already established guidelines. Total sample size was estimated at 36,000 participants.

University Hospital Centre Zagreb, Croatia was one of ISACS-TC centers included in the cohort and institutional ethical approval was obtained for this multicentric and multi-national study. All patients have provided written consent before they were enrolled in the registry. Additional written consent with their approval for the survey being contacted was requested during the first year after the hospitalization. Further study details as provided by the CINECA http://isacs-ct.cine1ca.org/.

4.1.1 Study setting and inclusion/exclusion criteria

The study was conducted in the Department of Cardiovascular Diseases, University Hospital Centre Zagreb (Rebro) in period from January 1, 2013, and December 31, 2017. This medical center is tertiary hospital, and the source population cannot be numerated. Croatia has a universal healthcare system providing a form of mandatory public insurance to all population. There are no administrative boundaries regarding the use of medical services according to county of residency and patients from entire Croatian territory can be admitted to University Hospital Centre Zagreb. Therefore, within the study period, all patients attending this hospital

and meet the eligibility criteria were included in the study. This convenience sampling method is consistent with policies and procedures previously described by the Registry of Patient Registries. (196)

Inclusion criteria were adult than 18 years and diagnosis of acute coronary syndromes without previous history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting who underwent invasive coronarography, and ad hoc PCI. Exclusion criteria were underage patients, those not able to give informed consent or those loss to follow-up. The appropriateness of inclusion criteria was evaluated by cardiologists who obtained medical history, conducted clinical examination, and evaluated electrocardiogram, cardiac biomarkers and PCI findings.

4.2. Methods

4.2.1. Definition of acute coronary syndrome

Clinical evaluation of coronary artery disease includes several modalities, such as EKG, echocardiography, cardiac catheterization, and blood analyses. Selection of tests varies on the clinical context in which patients are presented. In this study, after the clinical examination each patient mandatory underwent ECG procedure and the analysis of cardiac enzymes. ACS included diagnosis of unstable angina, NSTEMI and STEMI and they were confirmed if following criteria were fulfilled.

Unstable angina was verified if following criteria were present: (i) ECG changes (ST-segment changes, and/or T-wave inversion), (ii) negative cardiac enzymes, and (iii) one of these symptoms, new onset of angina, accelerated angina and angina at rest in the previous 48h.

NSTEMI was defined according to presence of following criteria: (i) ECG changes (ST-segment depression ≥ 0.5 mm in ≥2 contiguous leads or T-wave inversion >1 mm in leads with predominant R waves, (ii) detection of rise/and or fall of cardiac biomarkers, (iii) typical symptoms of myocardial ischaemia, and (iv) imaging evidence of new regional wall motion abnormality.

STEMI was defined if following criteria were present: (i) ECG changes: elevation J-point

elevation in two or more contiguous leads, ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V2 - V3 and / or ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads (ii) acute onset of typical stenocardia [≥20 min], and (iii) detection of positive myocardial markers.

The diagnosis of UA, STEMI and NSTEMI were validated according to ESC guidelines. (101, 104)

In-hospital treatment included routine medical therapy as well as reperfusion treatment, percutaneous coronary intervention. PCI was performed according to standard procedures. All the patients were given 300 mg aspirin and 300-600 mg clopidogrel before PCI, and 1000 IU/kg heparin during intervention. Administering of GPIIb-IIIa receptor antagonist followed the surgeon's instruction, and the drug-eluting stent was implanted according to PCI guidelines. During PCI the presence of significant coronary disease was defined as a stenosis of at least 50% in a major epicardial vessel. Coronary thrombus was defined as an intraluminal filling defect, or an area of contrast staining noted within the stenosis. Multivessel disease was defined as at least 2 main branches of the epicardial coronary artery with≥50% stenotic lesions or≥50% stenosis in the left main coronary artery. Patients were given dual antiplatelet therapy for 12 months after interventions. Other drugs such as statins and angiotensin-converting- enzyme inhibitors were administered according to the patients' clinical conditions. Patients were followed up by telephone or at medical record withing previously mentioned time intervals.

4.2.2. Definition of predictors and clinical outcomes

4.2.2.1. Predictors or patients' characteristics

For each patient several variables/predictors were obtained from demographic data and clinical data (GFR, BBB, infarction related artery group obtained during routine clinical work).

(i) ***Demographic data*** – age and sex (male/female). Age was obtained as absolute number and for the purpose of analysis it was classified into following age categories: up to 45 years, 46 - 65 years and 66 and over.

(ii) ***Estimated glomerular filtration rate*** - was used as indicator of renal function. Based on this value patients were divided in six groups according to CGA Staging: G5 Very

severe, or end-stage kidney failure (<15), G4 Severely reduced kidney function (15-29), G3b Moderately reduced kidney function (30-44), G3a Moderately reduced kidney function (45-59), G2 Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease (60-89), and G1 Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease (90+).

(iii) ***Bundle block***- based on ECG findings or new bundle branch blocks were reported.

(iv) ***Infarction related artery (culprit vessel)*** **–** data were obtained during PCI procedure and presented for right coronary artery, left anterior descending artery and left circular artery.

4.2.2.2. Clinical outcomes

The primary outcome measure was all-cause mortality within 30 days of hospital admission, with another assessment conducted at one year. The secondary outcome was hospitalization/reinfarction during the same periods. The 30-day mortality was selected based on previous studies from the ISACS-TC registry since it enriches the data over that acquired during the index hospitalization while mitigating survivor bias. Throughout each follow-up, we recorded hospitalizations/reinfarctions and survival statuses either during ambulatory checks or through phone contact. In our statistical analysis, we presented primary and secondary outcomes separately as mortality and hospitalisation.

4.3. Statistical Analysis

Descriptive and analytic methods were used in the statistical analysis. To test the normality of data distribution, we used both Kolmogorov-Smirnov and Shapiro-Wilk test when required. Data were presented as absolute frequencies, percentages, mean, standard deviation, minimum and maximum value, variance or interquartile range. According to the normality of data distribution, we used parametric or nonparametric tests. Hence, for exploring the impact of continuous variables over the outcome we used Mann-Whitney U-test, whereas for the categorical variables we used Chi-square test. Furthermore, to estimate the relationships between the observed variables and categories we used the McNemar's and Chi-square tests. (197, 198)

Clinical outcomes in this study were hospitalization and cardiovascular death or survival and

for the purpose of analysis we secondary used and recoded already collected data. We used the logistic regression to predict the binary outcome (survived or died) of the ACS patients' treatment in the post PCI setting during two follow-up periods - one month and one year. To estimate the relationship between one non-metric (binary) dependent variable and a group of metric or non-metric independent variables, we used predictors available in selected clinical setting and previously used in the similar studies, such as age, sex, BBB, GFR categories and lesion site.

Procedure for the variable selection was enter method and all variables in a block are entered in a single step for the logistic regression analysis. For logistic regression, variable age was dichotomized in two categories; the first one above 65 years, and second one above 75 years, as previously described. BBB was coded as yes or no, while for GFR normal kidney function was used as reference level. For the lesion site, the infarction related arteries were categorised in the reference category (RCA or LCx) versus LAD. Beta coefficient of the independent variables represents the difference in log odds compared to the reference category and they were expressed as the odds ratios and presented with the confidence intervals (CI). (197,199)

For all tests used in the analysis, the level of significance was a-priori set to 5%, which provides a 95% confidence interval for accepting or rejecting our hypothesis, by observing the p-values of a two-sided tests. Analyses were conducted by using the SPSS statistical software (version 21.0, SPSS Inc., Chicago, IL, USA).

5 . Results

5.1. Demographic data - descriptive statistic

A total of 704 patients met the inclusion criteria as previously described, but there is some missing data for certain variables.

Table 1. Age distribution

	Statistic	Std. Error
Mean	64.06	0.44
95% CI	63.19 - 64.93	
5% Trimmed mean	64.11	
Median	64.00	
Variance	147.91	
Std. deviation (SD)	12.16	
Minimum – Maximum	28.0 - 94.0	
Range	66.0	
Interquartile range	18.0	
Skewness	-0.07	0.09
Kurtosis	-0.55	0.18

Average age was 64.06 years with a SD of 12.162 years but the age span was large. The minimum age value was 28 years, while the maximum age value was 94 years with 95% CI 63.19 – 64.93 years. Among total of 704 patients, 6.7% were up to 45 years old (n = 47), 47.9% were between 46 - 65 years old (n = 337), while 45.4% were 66 and over (n = 320). Among the selected patients (n=704), 72.1% were male (n=507), and 27.9% were female (n=197).

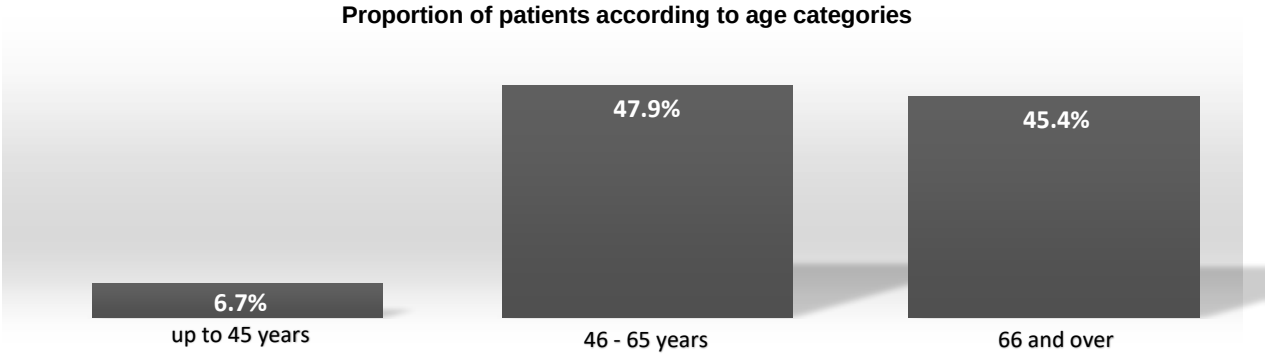


Figure 10. Proportion of patients according to age categories.

5.2. Clinical data – descriptive and analytic statistic

Bundle block – Among total 704 patients, 631 patients had data about bundle block – there 31 with bundle block (4.9%) and 95.1% without (N = 600).

Table 2. Glomerular filtration rate

	Statistic	Std. Error
Mean	74.623	0.897
95% Confidence Interval for	72.860 – 76.386	
5% Trimmed Mean	74.026	
Median	72.800	
Variance	567.599	
Standard deviation	23.824	
Minimum	8.3	
Maximum	195.6	
Range	187.3	
Interquartile Range	30.2	
Skewness	0.584	0.092
Kurtosis	1.559	0.184

Average value of GFR was 74.62 with a standard deviation of 23.82. The minimum value of the indicator was 8.3, the maximum value is 195.6 while the confidence interval was from 72.86 to 76.39.

Table 3. Glomerular filtration rate categories

	GFR categories	N	%
G5	Very severe or end-stage kidney failure (<15)	2	0.3
G4	Severely reduced kidney function (15-29)	14	2.0
G3b	Moderately reduced kidney function (30-44)	42	6.0
G3a	Moderately reduced kidney function (45-59)	127	18.0
G2	Mildly reduced kidney function and other findings (as for stage 1) point to kidney disease	349	49.6
G1	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease	170	24.1
	Total	704	100

As much as 75.9% of patients had impaired renal function while only 24.1% had had normal kidney function. Mildly reduced kidney function was observed among 49.6%, while 24% patients had moderately reduced kidney function. Severely and very severe GFR categories were present in 2.3% patients.

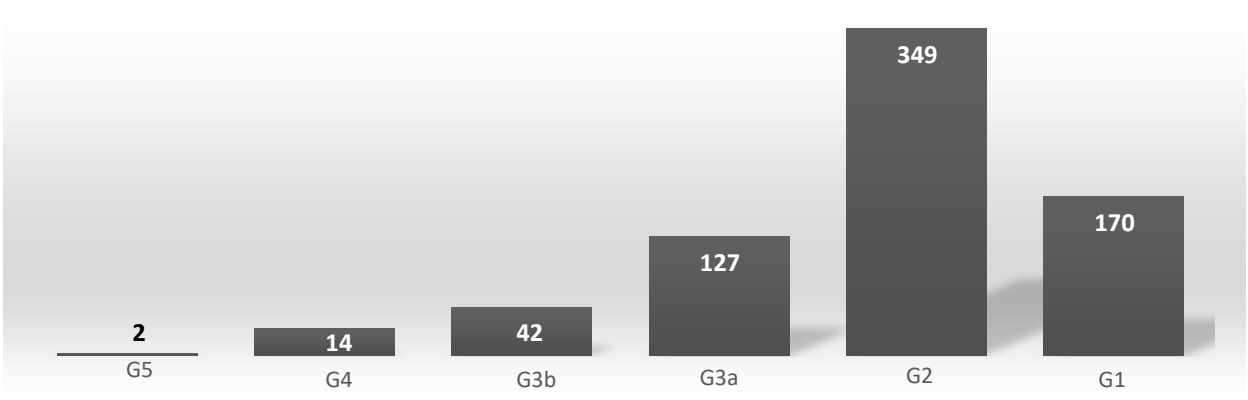


Figure 11. Number of patients according to GFR categories

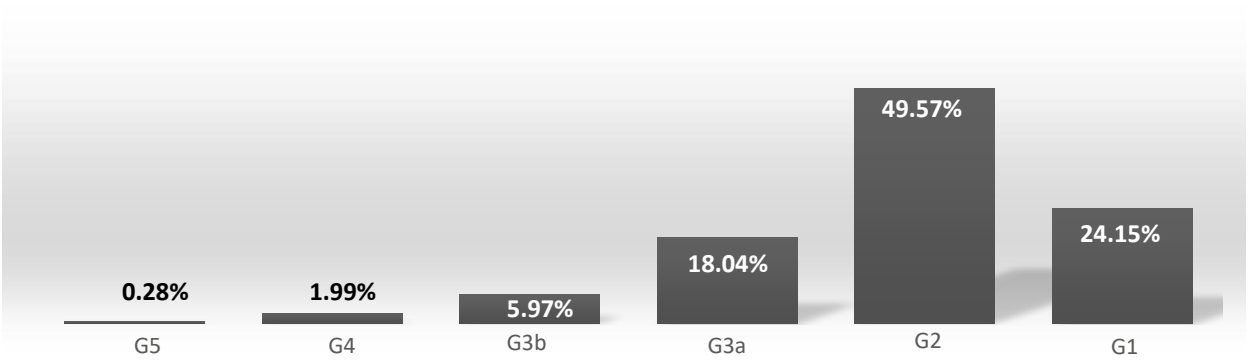


Figure 12. The proportion (%) of patients according to GFR categories

Table 4. GFR categories according to age categories

Age categories /Years	GFR categories												Total	
	<15 or		15-29		30-44		45-59		60-89		90+			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
up to 45	0	0.0	1	7.1	1	2.4	3	2.4	27	7.7	18	10.6	50	7.1
46 – 65	1	50.0	4	28.6	8	19.0	44	34.6	181	51.9	100	58.8	338	48.0
66 and over	1	50.0	9	64.3	33	78.6	80	63.0	141	40.4	52	30.6	316	44.9
Total	2	100	14	100	42	100	127	100	349	100	170	100	704	100

According to the distribution of age categories and GFR categories (N=704), there was statistically significant difference $\chi 2$ (10, N = 704) = 57.354. Higher proportion of participants in older age categories have higher proportion of GFR categories indicative for moderately or severe reduction in kidney function suggesting an association between old age and impaired kidney function ($p<0.001$). **(Table 4)**

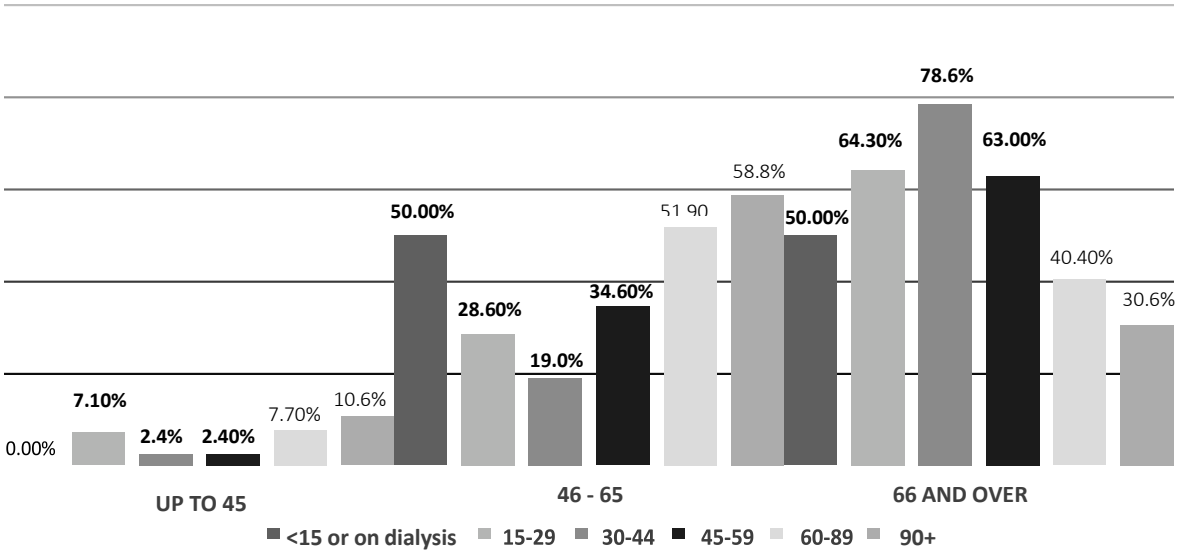


Figure 13. GFR categories and age categories

Table 5. GFR categories according to sex

Gender	GFR categories												Total	
	<15 or on dialysis		15-29		30-44		45-59		60-89		90+			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Male	1	50.0	8	57.1	20	47.6	75	59.1	271	77.7	144	84.7	519	73.7
Female	1	50.0	6	42.9	22	52.4	52	40.9	78	22.3	26	15.3	185	26.3
Total	2	100	14	100	42	100	127	100	349	100	170	100	704	100

A chi-square test was conducted to examine the association between gender and GFR categories among a sample size of N=704 participants. The analysis revealed a statistically significant association, $\chi 2(5, N = 704) = 44.808$, $p<0.001$. The proportions of GFR categories indicative of severely or moderately reduced kidney function were lower in female subjects, and association between gender and GFR categories was significant. **(Table 5)**

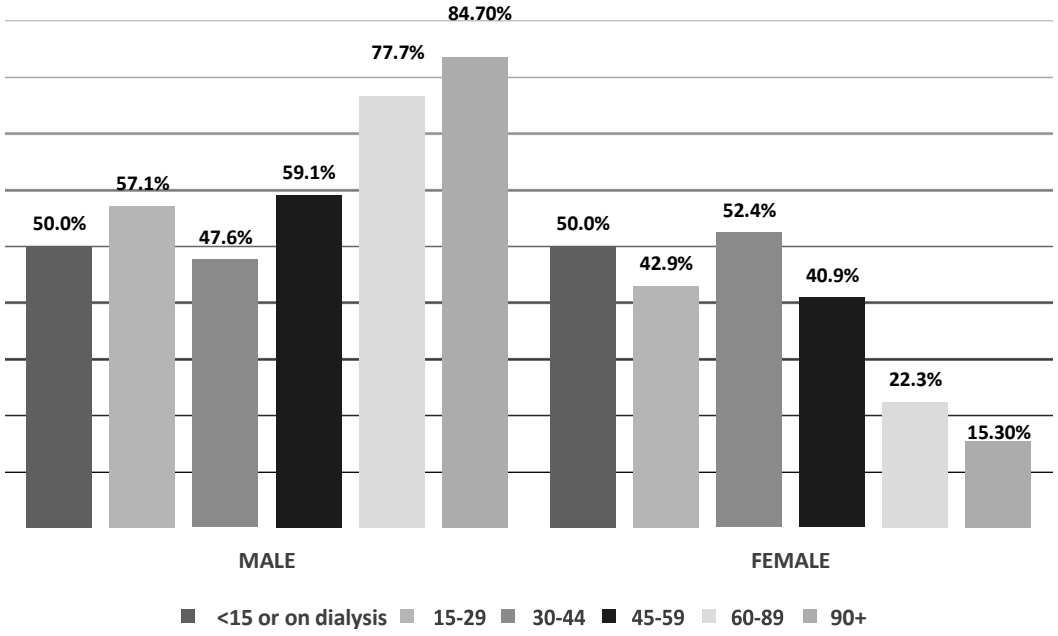


Figure 14. GFR categories and age categories

Table 6. GFR categories and bundle block

Bundle block	GFR categories												Total	
	<15 or on dialysis		15-29		30-44		45-59		60-89		90+			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Yes	0	0.0	1	9.1	2	5.7	6	6.3	15	5.6	3	2.0	27	4.8
No	2	100.0	10	90.9	33	94.3	89	93.7	255	94.4	144	98.0	533	95.2
Total	2	100	11	100	35	100	95	100	270	100	147	100	560	100

A chi-square test was conducted to examine the association between bundle block and GFR categories among a sample size of N = 560 participants. The analysis did not reveal a statistically significant association, $\chi^2(5, N = 560) = 3.8$ between bundle block and GFR categories $p = 0.570$. **(Table 6)**

Table 7. Severely reduced renal function and hospitalization (one month)

Hospitalization	GFR categories		Total	
	<15	15-29	N	%
Yes	5	11	16	72.8
No	1	5	6	27.2
Total	6	16	22	100

A chi-square test was conducted to examine the association between hospitalization (one month) and GFR categories among a sample size of N = 704 participants. The analysis revealed a statistically significant association, $\chi 2(4, N = 704) = 22.384$, $p<0.001$ between hospitalization one month and GFR categories. Hospitalized patients exhibited higher proportions of GFR categories indicative of severely or moderately reduced kidney function. **(Table 7)**

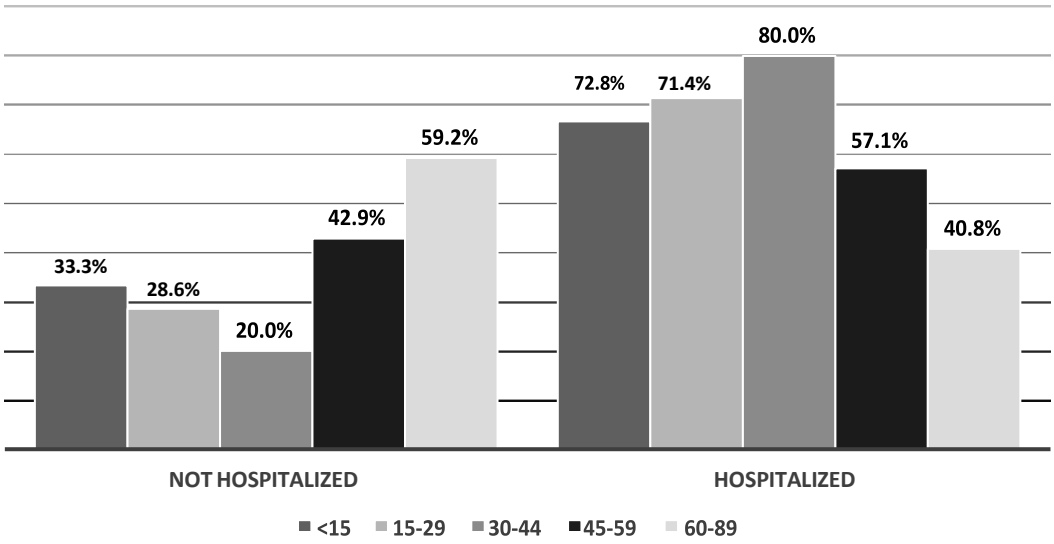


Figure 15. GFR categories and one month hospitalization

Table 8. GFR categories and hospitalization (one year)

Hospitalization	<15	15-29	30-44	45-59	60-89	90+	Total
Yes	1	1	11	28	39	19	99
No	2	7	10	36	165	95	315
Total	3	8	21	64	204	114	414

A chi-square test was conducted to examine the association between hospitalization (one year) and GFR categories. The analysis revealed a statistically significant association, $\chi 2(4, N = 414)$ 25.958, $p<0.001$ between hospitalization (one year) and GFR. Additionally, the proportion of GFR categories indicative of severely or moderately reduced kidney function was higher in hospitalized subjects. **(Table 8)**

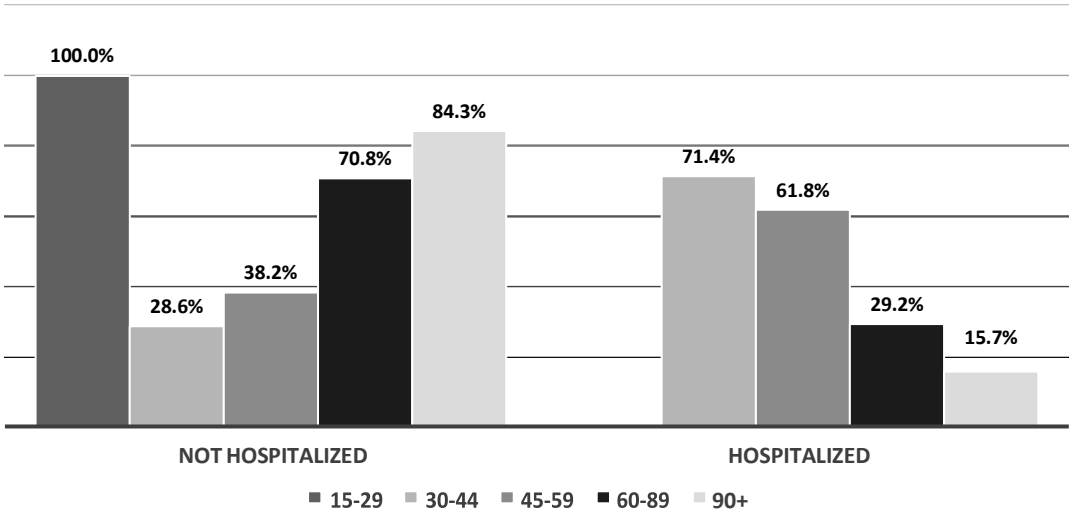


Figure 16. GFR categories and one year hospitalization

5.3. Mortality after one month and one year – descriptive and analytic statistics

5.3.1. Mortality after one month

Table 9. Mortality within one month and one year follow-up

	Alive	Dead	Total
One month	667	37	704
One year	471	81	552

Mortality rate for one month was 5.25% (n=37) and for one year 14.67% (n=81). When data were further analysed according to sex, after one month of follow-up, among 507 males 23 died, while among females 14 of 197 died. Proportion of males and females who died were similar. (p=0.32)

After one year of follow-up among 381 males 53 died and among 171 females 28 died. The proportions males and females who died were similar. (p=0.51) As per the McNemar test, a significant difference was observed in the number of patients who passed away at the one-month (n = 37) and one-year (n = 81) follow-up periods ($p < 0.05$).

Age was further stratified in age categories (up to 45 years, 46 – 65 years, 66 and over) and survival status after one month was presented as absolute numbers and percentages of dead or alive patients. There was no significant difference in proportion of dead and alive in up to 45 age group (p=0.85), 45-65 group (p=0.92), and 66 and over group. (p=0.32)

Table 10. Mortality (one month) and age categories

	Alive		Dead		Total	
	N	%	N	%	N	%
up to 45 years	47	7.04	0	0	47	6.7
46 – 65 years	331	98.21	6	1.78	337	47.9
66 and over	289	90.31	31	9.68	320	45.4
Total	667	100	37	100	704	100

A chi-square test was conducted to examine the association between age categories and one-month survival. The analysis revealed a statistically significant association, $\chi 2(2, N = 704)$ 14.700, $p<0.001$ between age categories and one-month survival. Among deceased individuals, the proportion of patients in older age groups (66 and over) was significantly higher compared to other age groups**. (Table 10)**

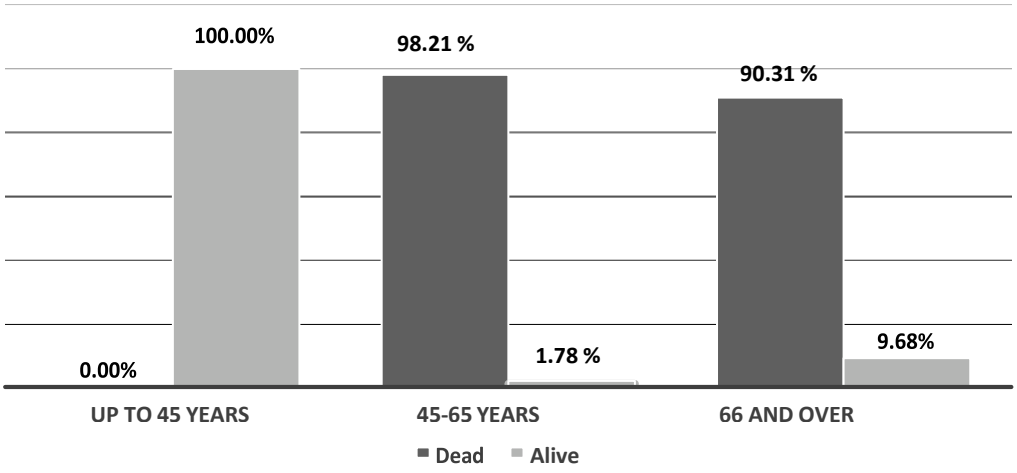


Figure 17. Mortality (one month) and age categories

Table 11. Mortality (one month) and gender

	Alive		Dead		Total	
	N	%	N	%	N	%
Male	482	95.06	25	4.9	507	100
Female	185	93.91	12	6.09	197	100
Total	667	94,74	37	5,26	704	100

A chi-square test was conducted to examine the association between gender and one-month survival. The analysis revealed no statistically significant association, $\chi 2(1, N = 704) = 0.989$, $p = 0.320$ between gender and one-month survival. **(Table 11)**

Table 12. Mortality (one month) and bundle block

Bundle block	Alive		Dead		Total	
	N	%	N	%	N	%
Yes	2	6.67	34	7.20	36	7.17
No	28	93.33	438	92.8	466	92.83
Total	30	100	472	100	502	100

A chi-square test was conducted to examine the association between bundle block and one-month mortality. The analysis revealed no statistically significant association, $\chi 2(1, N = 502) = 0.457$, $p = 0.499$ between bundle block and one-month mortality. **(Table 12)**

Table 13. Mortality (one month) and hospitalization one month

Hospitalization	Alive		Dead		Total	
	N	%	N	%	N	%
Yes	31	83.78	45	6.74	76	10.79
No	6	16.21	622	93.25	628	89.21
Total	36	100	667	100	664	100

A chi-square test was conducted to examine the association between one-month hospitalization and outcome (dead/alive). The analysis revealed a statistically significant association, $\chi 2(1, N = 704)$ 31.271, $p<0.001$ between one-month hospitalization and outcome (dead/alive), with most of the deceased patients being hospitalized**. (Table 13)**

Table 14. Risk Estimate

	Value	Lower	Upper
For cohort patient status (one month) = Alive	1.630	1.362	61.951
N of valid cases	704		

Table 15. Mortality (one month) and GFR categories

GFR categories	Alive		Dead		Total	
	N	%	N	%	N	%
<15	5	0.78	2	5.41	7	1.03
15-29	11	1.71	3	8.11	14	2.06
30-44	41	6.37	9	6.37	50	7.34
45-59	104	16.15	13	35.14	117	17.18
60-89	316	49.07	9	24.32	325	47.72
90+	167	25.93	1	2.70	168	24.67
Total	644	100	37	100	681	100

A chi-square test was conducted to examine the association between GFR categories and one-month mortality. The analysis revealed a statistically significant association, $\chi 2(4, N = 681)59.400$, $p < 0.001$. between GFR categories and one-month mortality. The highest proportion of patients who died was observed in GFR category 30-44. **(Table 15)**

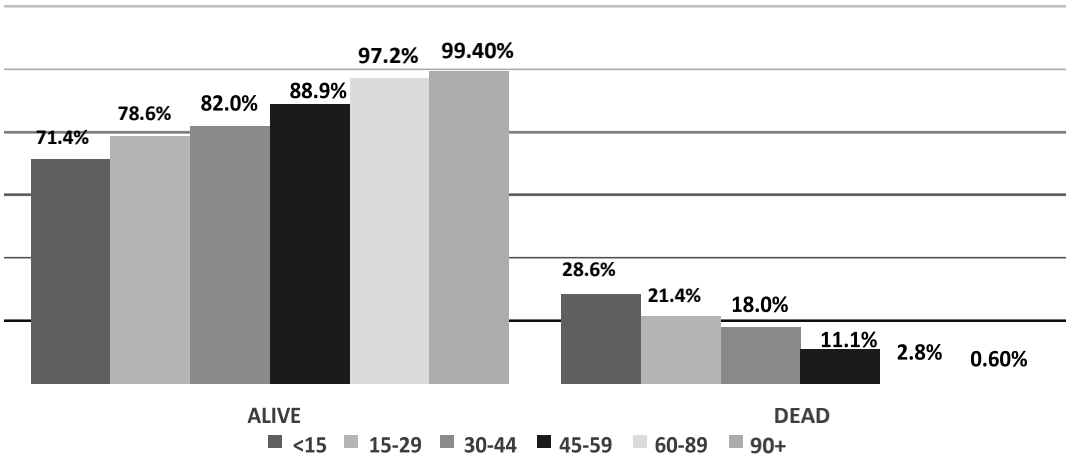


Figure 18. Mortality (one month) and GFR categories

Lowest proportion of alive patients was in <15 category, while the highest was in 90+ category.

Table 16. Mortality (one month) and hospitalisation vs. LAD, RCA and LCx

		LAD		RCA		LCx		Total		p
		N	%	N	%	N	%	N	%	
Mortality (one month)	**Alive**	319	93.21	236	96.32	112	95.72	667	94.74	0.303
	Dead	23	6,79	9	3.37	5	4.27	37	5.26	
	Total	342	100	245	100	117	100	704	100	
Hospital (one month)	**Yes**	38	11.11	24	9.79	14	11.96	76	10.79	0.652
	No	304	88.89	221	90.21	103	88.04	628	89.21	
	Total	342	100	245	100	117	100	704	100	

No significant difference was among infarction related arteries and one month mortality (p = 0.303) and infarction related arteries and one month hospitalisation. (p=0.652) (**Table 16**)

5.3.2. One-year mortality

Table 17. Mortality (one year) and age categories

	Alive		Dead		Total	
	N	%	N	%	N	%
up to 45 years	20	95.23	1	4.76	21	3.81
46 – 65 years	230	92.36	19	7.63	249	45.11
66 and over	221	78.36	61	21.64	282	51.08
Total	471	85.32	81	14.67	552	100

A chi-square test was conducted to examine the association between age categories and one-year mortality. The analysis revealed a statistically significant association, $\chi 2(2, N = 552) = 16.500$, $p < 0.00$ between age categories and one-year mortality. The proportion of patients who died in the older age category was significantly higher, with as much as 21.64% aged 66 and over died within one year. **(Table 17)**

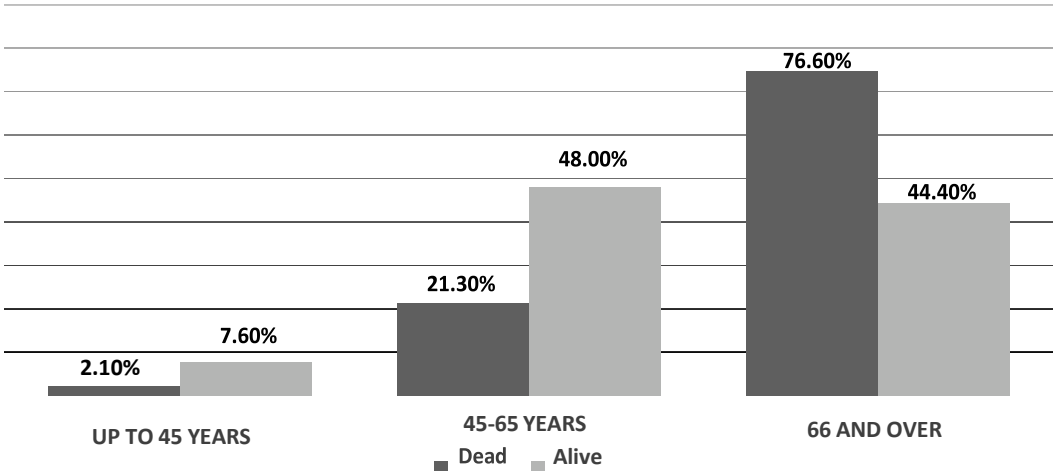


Figure 19. Mortality (one year) and age categories

Table 18. Mortality (one year) according to gender

	Alive		Dead		Total	
	N	%	N	%	N	%
Male	329	86.35	52	13.65	381	100
Female	142	83.94	29	16.06	171	100
Total	471	85.32	81	14.67	552	100

Among males 86.35 % were alive, while 13.65 % died. Among females 83.94 % were alive while 16.06 % died. The chi-square test was conducted to examine the association between

gender and one-year survival. The analysis revealed no statistically significant association, $\chi 2(1, N = 552) = 1.875$, $p = 0.171$ between gender and one-year survival. The proportions of males and females who died were similar**. (Table 18)**

Table 19. Mortality (one year) and bundle block

	Alive		Dead		Total	
	N	%	N	%	N	%
Yes	27	81.82	6	18.18	33	100
No	316	84.49	58	15.51	374	100
Total	343	84.28	64	15.72	407	100

A chi-square test was conducted to examine the association between bundle block and one-year survival. The analysis revealed no statistically significant association, $\chi 2(1, N = 407) = 0.412$, $p = 0.521$. **(Table 19)**

Table 20. Mortality (one year) and hospitalization (one year)

Hospitalization	Alive		Dead		Total	
	N	%	N	%	N	%
Yes	94	56.62	72	43.38	166	100
No	377	97.66	9	2.34	386	100
Total	471	85.32	81	14.67	552	100

A chi-square test was conducted to examine the association between hospitalization and survival status. The analysis revealed a statistically significant difference, $\chi 2(1, N = 552) = 37.457$, $p < 0.001$. difference between the proportion of patients who were hospitalized and survival status. Most of the patients who died were hospitalized**. (Table 20)**

Table 21. Mortality (one year) and GFR categories

GFR categories	Alive		Dead		Total	
	N	%	N	%	N	%
<15	3	75.00	1	25.00	4	100
15-29	8	72.73	3	27.27	11	100
30-44	21	58.33	15	41.67	36	100
45-59	69	69.00	31	31.00	100	100
60-89	230	90.55	24	9.45	254	100
90+	130	94.89	7	5.11	137	100
Total	461	85.06	81	14.94	542	100

After one year of follow-up 14.94% patients died. There is an increase in percentage of patients who died in categories with reduced kidney function. In 90+ groups only 5.11% patients died as opposed to groups with very severe and severely reduced kidney function where 25% and 27.27% percentage of patients died. **(Table 21)** A chi-square test was conducted to examine the association between GFR categories and mortality. The analysis revealed a statistically significant difference, $\chi 2(4, N = 542) = 65.524$, $p < 0.001$ in the proportion of patients who died according to GFR categories. The highest proportion of deceased patients was observed in the 45-69 category, accounting for 41.67% of deaths**.**

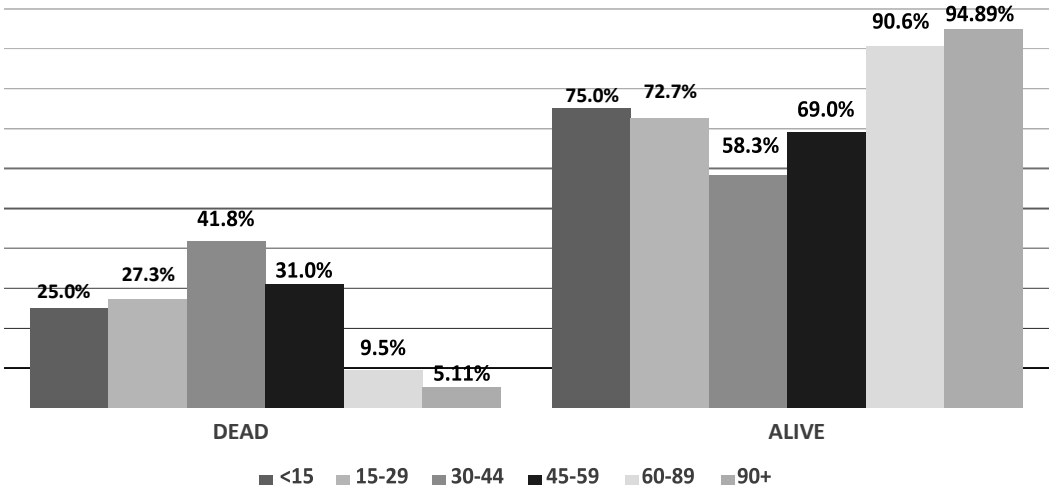


Figure 20. Mortality (one year) and GFR categories

Table 22. Mortality and hospitalisation (one year) vs. LAD, RCA and LCx

		LAD		RCA		LCx		Total		p
		N	%	N	%	N	%	N	%	
Mortality (one month)	**Alive**	205	80.08	163	90.05	103	86.56	471	85.32	0.019
	Dead	51	19.92	18	9.95	12	10.43	81	14.67	
	Total	256	100	181	100	115	100	552	100.00	
Hospital (one month)	**Yes**	95	37.01	38	20.99	33	28.69	166	30.07	0.000
	No	161	62.89	143	79.01	82	71.31	386	69.92	
	Total	256	100	181	100	115	100	552	100.00	

Among 552 patients followed-up for one year 471 survived (85.32 %) while 81 died (14.67 %). During one year follow up period 166 patients were hospitalized, a 386 was not hospitalized. The observed differences according to the infarction site were statistically different for mortality and hospitalisation ($p<0.001$).

5.4. Logistic regression models for one month and one year mortality

5.4.1. Logistic regression model for one month mortality

Two logistic regression models with infarction artery as predictor were selected according to age categories, the first one with age (>65) and the second one with (>75).

Table 23. Logistic regression model for one month mortality with age (>65)

	B	S.E.	Wald	df	Sig.	OR	95% CI for OR	
							Lower	Upper
Age (>65)	1.178	0.545	4.670	1	0.031	**3.248**	1.116	9.456
Gender	0.336	0.514	0.427	1	0.513	1.400	0.511	3.836
Bundle block	-0.309	0.766	0.162	1	0.687	0.734	0.164	3.295
GFR cat.	1.776	0.810	4.805	1	**0.028**	**5.908**	1.207	28.915
LAD vs. RCA/LCx	1.381	0.502	7.555	1	**0.006**	**3.978**	1.486	10.648
Constant	-24.456	4009.39	0.000	1	0.995	0.000		

Model summary: -2 Log likelihood 111,983a Cox & Snell R Square 0,273 Nagelkerke R Square 0,467, Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

Table 23 presents the findings of a logistic regression model examining factors influencing one-month mortality among individuals over 65 years old. Age, GFR and infarction artery (LAD vs. RCA/Lcx) were significant predictors of one month mortality. Patients (>65) had OR 3,248 compared with younger age group, while higher GFR category was associated with 5,908 odd ratio for fatal outcome. LAD as infarction site was associated with 3,978 higher odds ratio for fatal outcome compared with RCA/LCx.

Table 24. Logistic regression model for one month mortality – age >75

	B	S.E.	Wald	df	Sig.	OR	95% CI for OR	
							Lower	Upper
Age (>75)	1.399	0.518	7.294	1	**0.007**	**4.052**	1.468	11.187
Gender	0.138	0.499	0.077	1	0.782	1.148	0.432	3.050
Bundle block	-0.528	0.804	0.432	1	0.511	0.590	0.122	2.849
GFR cat.	1.683	0.799	4.434	1	**0.035**	**5.384**	1.124	25.801
LAD vs. RCA/LCx	1.354	0.505	7.183	1	**0.007**	**3.873**	1.439	10.424
Constant	-23.779	4049.12	0.000	1	0.995	0.000		

Model summary: 2 Log likelihood 109,376a Cox & Snell R Square 0,283, Nagelkerke R Square 0,484 Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

Table 24 presents the findings of a logistic regression model examining factors influencing one-month mortality among individuals over 75 years old. The analysis reveals significant associations between mortality and age, GFR and infarction artery (LAD vs. RCA/Lcx). Patients (>75) had odds ratio 4,052 compared with younger age group, while higher GFR category was associated with 5,384 odd ratio for fatal outcome. LAD as infarction site was associated with 3,873 higher odds ratio for fatal outcome compared with RCA/LCx. However, gender and bundle block do not demonstrate significant associations with one-month mortality in this analysis.

5.4.2. Logistic regression model for one year mortality

Table 25. Logistic regression model for one year mortality - age >65

	B	S.E.	Wald	df	Sig.	OR	95% CI for OR	
							Lower	Upper
Age (>65)	0.526	0.674	0.609	1	0.435	**1.692**	0.451	6.347
Gender	0.076	0.703	0.012	1	0.914	**1.079**	0.272	4.283
Bundle block	-0.984	1.156	0.724	1	0.395	0.374	0.039	3.601
GFR cat.	0.733	1.168	0.394	1	0.530	**2.082**	0.211	20.553
LAD vs. RCA/LCx	1.535	1.111	1.909	1	0.167	**4.643**	0.526	40.995
Constant	-22.946	2837.71	0.000	1	0.994	0.000		

Model summary: -2 Log likelihood 59,538a Cox & Snell R Square 0,177 Nagelkerke R Square 0,500a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

Table 25 displays the results of a logistic regression model examining factors associated with one-year mortality in individuals aged over 65. Among the variables investigated, several predictors had odds ratio higher than 1 which suggest increased risk, such as age (>65) 1, 692, gender 1,079, GFR category 2,082 and LAD vs. RCA/LCx but neither one of them reached the level of statistical significance.

Table 26. Logistic regression model for one year mortality - age >75

	B	S.E.	Wald	df	Sig.	OR	95% CI for OR	
							Lower	Upper
Age (>75)	1.866	0.719	6.733	1	**0.009**	**6.461**	1.579	26.445
Gender	-0.276	0.759	0.132	1	0.717	0.759	0.171	3.361
Bundle block	-0.653	1.212	0.290	1	0.590	0.521	0.048	5.602
GFR cat.	0.312	1.210	0.067	1	0.796	**1.367**	0.128	14.642
LAD vs. RCA/LCx	1.348	1.179	1.308	1	0.253	**3.850**	0.382	38.809
Constant	-22.490	2785.55	0.000	1	0.994	0.000		

Model summary: -2 Log likelihood 53,071a Cox & Snell R Square 0,199 Nagelkerke R Square 0,560a. Estimation terminated at iteration number 20 because maximum iterations has been reached. Final solution cannot be found.

Table 26 presents the results of a logistic regression model examining the factors associated with one-year mortality in individuals aged over. Notably, age over 75 ($p = 0.009$) emerges as a significant predictor of mortality, indicating a higher likelihood of mortality with advancing age. Other variables such as gender, bundle block, GFR category, and LAD vs. RCA/LCx suggested increased risk for fatal outcome but these predictors did not reach the level of statistical significance.

6. Discussion

This study aimed to examine disparities in clinical outcomes among ACS patients who underwent primary PCI in a tertiary medical institution. The study design was based on the objectives of ISACS-TC and previous studies in transitional countries. These objectives aimed to define patient and treatment characteristics to investigate whether differences in clinical factors, ethnicity, or healthcare organization could influence the outcomes. Our research included one major aim and several specific aims, focusing on both modifiable and non-modifiable cardiovascular risk factors. These factors were selected based on their availability within clinical settings and the findings of previous studies in transitional countries.

Objective of this research was to identify demographic clinical parameters that are specific predictors for worse outcome within first year in ACS patients who underwent PCI at the University Hospital Centre Zagreb. To address this objective, we hypothesized that specific factors would be significantly associated with one-month and one-year mortality in ACS patients who underwent primary PCI. These factors included gender, age, reduced glomerular filtration rate, BBB, and LAD as the infarction artery site. Furthermore, we quantified the association of these factors in four logistic regression models in terms of risk estimates, such as odds ratios, while adjusting for potential confounders. Age, GFR, and LAD were confirmed as statistically significant predictors in the one-month mortality model, while only age reached significance in the one-year model.

During the study period, spanning from January 1st, 2013, to December 31st, 2017, a total sample size of 704 patients diagnosed with ACS who fulfilled the inclusion criteria were enrolled. This sample size is categorically considered as medium when placed in the context of medical research, as larger studies typically encompass sample sizes of 1000 or more. (200) Risk factors selected in this study and study details were provided by the CINECA http://isacs-ct.cineca.org/, but in this research methodology levels of selected variables, such as age, sex, BBB, GFR, and LAD as the infarction artery, were adjusted to capacity to collect data in clinical setting. First, we described the demographic data of the study population. The age range was quite broad, spanning from 28 to 94 years, with an average age of 64.06 years. **(Table 1)** The majority of patients in this retrospective study fell into the middle-age category (46-65 years), comprising 47.7% of the total, while 45.4% were classified as older patients (66

years and above). **(Figure 10)** Similar findings were observed in other studies. For example, in a recent study by Ahmed I et al. with a comparable sample size, a significant proportion of middle-aged patients, aged between 55 and 64 years, were observed, with ages ranging from 15 to 85 years (201). Ahmed F et al. found that 48.7% of their patients fell into the middle- aged category, ranging from 50 to 69 years. (202)

In a study by Vasiljevic et al., published in 2014 and based on data from the Serbian branch of the ISACS registry, the mean age of the overall population was calculated to be 62.1 years. (76) Another study involving 14,931 patients diagnosed with ACS and enrolled in the ISACS-TC registry between October 2010 and April 2016 reported a mean age of 62.6 years (64). Compared to our study, where the average age was 64 years, similar studies on other populations had different average ages, ranging from 50.5 years to 63.3 years, but none exceeded 65 years, which is generally considered the cut-off for the older age category in most studies (201,202) However, in one recent study by Ferrante G et al. on the Italian population, the average age was higher at 66.2 years. (170) This difference can be partly attributed to the high life expectancy in Italy, which has been steadily increasing over the past 50 years and reached 83.86 years in 2022. (203)

Furthermore, disparities in patient demographics were observed, with a higher proportion of male patients (72.4%) compared to female patients (27.6%). Sex is a recognized major risk factor for MI, as highlighted in various cardiovascular mortality studies, where male patients tend to have a higher risk. (169-171) The male-to-female patient ratio of 72.4% in this study is lower than that reported in the study by Ahmed I et al. (83%) but comparable to the study by Wang JC et al. (73%), and higher than the research conducted by Ahmed F. et al. (70.5%), Pacaric et al. (55%), Vasiljevic Z. et al. (65%), and Ferrante G. et al. (70.7%) (201-203,76, 170). In a previously mentioned study encompassing 14,931 ACS patients from the ISACS-TC registry between 2010 and 2016, women accounted for 31.6%. (64). Idris et al. studied the influence of sex among 3,178 (25% female) ACS patients who underwent PCI at Liverpool Hospital, Sydney, from 2003 to 2010. (173)

In our study, the representation of women, at 27.6%, is significantly lower than the estimated proportion of 51.3% in the general population. In Croatia, there has been a notable fluctuation in the male-to-female ratio over the years, showing a trend of increasing from 1950 to 2020, where it peaked at 93.1 males for every 100 females in 2020 (49). Furthermore, rates of

revascularization procedures, including PCI, are typically and significantly lower in women compared to men. (204–208) Another plausible explanation for the higher representation of men in our study sample could be the underreporting of ACS cases in women, leading to misclassification bias. Furthermore, some studies suggest that the clinical symptoms of coronary disease in women are occasionally vague and underestimated. While quantifying the impact of systematic errors on the study's outcomes is challenging, it is crucial to exercise caution regarding potential biases and to account for sex differences in symptom presentation among patients with ACS. (206-208) Preferences among specific patient groups may also contribute, as a previous study has noted such a trend among younger male patients admitted to PCI in the City of Zagreb. (209)

Following the descriptive analysis of demographic data, we proceeded to conduct both descriptive and analytical studies of clinical data, encompassing bundle block and GFR **(Table 2, Table 3),** as well as GFR stratified by age categories **(Table 4),** sex **(Table 5),** bundle block **(Table 6),** and hospitalization at one month **(Table 7)** and one year **(Table 8).**

In our study, we examined the prevalence of BBB, regardless of whether it was left or right-sided. However, it's important to emphasize that the impact of a LBBB differs from that of RBBB. (138,139) Furthermore, it's worth noting that right BBB has only been recently acknowledged as a significant prognostic factor and is now incorporated into the updated universal definition of myocardial infarction. (95) The most recent research suggests that patients with RBBB may have a larger area of myocardial ischemia, leading to more unfavourable outcomes. (139–141) Nevertheless, studies have argued that left and right BBB should be treated as equivalent when determining the need for urgent angiography in patients suspected of having. (104) In a study comprising 8,771 ACS patients, with an average age of 66.1 years, it was noted that 4.1% exhibited LBBB, while 5% exhibited RBBB. These observations were linked to an unfavourable prognosis, influencing patient outcomes not only during their hospitalization but also over the long term. The prevalence of RBBB in the context of ACS has been reported to range from 6% to 10%. (148, 149) In the study of Timoteo et al**.** of the 3,990 ACS patients, 3.4% had LBBB and 4.3% had RBBB. (148) The proportion of bundle branch blocks in our study was only 4.9%, which is lower compared to other studies. A recent study by Yang et al. aimed to evaluate the potential predictive value of permanent RBBB and LBBB for the longer-term prognosis in patients who underwent PCI for STEMI. The findings suggest that the presence of new-onset permanent RBBB in these patients is

independently associated with a higher risk of MACCEs and all-cause mortality in the longer term. However, the study did not identify a correlation between the occurrence of no BBB, new permanent LBBB, or RBBB and the severity of coronary artery lesions. (149)

CKD poses a substantial public health challenge on both a global scale and within Croatia. (168,210) In our examined population, a decline in kidney function was highly prevalent, affecting a significant portion of patients. Nearly three-quarters of patients (75.9%) were categorized as having decreased renal function. Among these individuals, 49.6% had mild reductions, while 24% showed moderate reductions. A relatively small minority of patients (2.3%) were categorized as having severely and very severely reduced GFR levels **(Table 3)**. The limited presence of patients in these severely and very severely reduced GFR categories can be attributed to the high mortality rate observed within this subgroup. (211) This percentage is higher than the reported figures for ACS patients on chronic dialysis who were hospitalized between 2003 and 2018, as per the administrative Lombardy Health Database in Italy, where only 1.2% were categorized in a similar manner. (212)

Renal dysfunction is a common concern among patients undergoing PCI. In a retrospective study conducted by Patel et al. spanning from 2006 to 2012 and utilizing the National Inpatient Sample Database in the USA, temporal trends in coronary angiography and PCI were analysed among patients categorized into three groups: those without CKD, those with advanced CKD (CKD III–V), and those with end-stage renal disease presenting with ACS. The majority of patients, accounting for approximately two-thirds, did not exhibit renal dysfunction. (213) This findings are in contrasts with our study, where a significant portion of the studied population (two-third) exhibited some degree of renal dysfunction.

The significant prevalence of diminished kidney function in our study population comes as no surprise, as impaired kidney function is widely recognized for its role in promoting atherosclerosis, a fundamental process underlying the majority of cardiovascular diseases and aging. (171) The natural aging process is linked to age-related changes in the kidneys, which encompass a decrease in functional glomeruli, reduced cortical volume, and the emergence of enlarged kidney cysts. In a healthy kidney, the glomerular filtration rate decreases at an average rate of 6.3 mL/min/1.73 m2 per decade. (214) The literature underscores a strong connection between chronic kidney disease and cardiovascular disease, often described as a vicious cycle. Oxidative stress in CKD shows an inverse relationship with kidney function, signifying that

oxidative stress plays a crucial role in the age-related decline in renal function. Particularly noteworthy is the robust association between oxidative stress, end-stage renal disease, and elevated mortality rates, all of which are closely intertwined with cardiovascular disease. (211)

In our study, it was observed that up to two-thirds of patients exhibited impaired renal function. Notably, the prevalence of reduced kidney function was more pronounced among older patients, with those aged 65 years and above showing the highest percentage, as indicated in the data **(Table 4)**. Conversely, younger patients, particularly those up to 45 years of age, exhibited the lowest percentage of moderate and severe kidney function reduction. Our findings underscore the prevalence of reduced kidney function among ACS patients, with the moderate category being particularly noteworthy, accounting for 24%, as shown in **Table 3**. Furthermore, advanced age was found to be correlated with a higher percentage of moderate and severe reductions in kidney function. This connection is further substantiated by the significant relationship between glomerular filtration rate and age categories, as illustrated in **Table 4** and **Figure 13.** The decline in kidney function became more pronounced with increasing age, consistent with the results of previous research studies. (175–177, 179)

A gender-based difference in GFR was also noted, with a significantly higher number of males than females displaying moderate to severe reductions in renal function. This association was found to be statistically significant. **(Table 5)** This finding can be supported by previous epidemiological research. Swartling et al. concluded that compared to women, men had an increased risk of CKD progression, as well as cardiovascular and all-cause mortality.
(215) In another study Toth-Manikowski et al. aslo reported that the risk of atherosclerotic events, incident heart failure, and cardiovascular and all-cause mortality was lower in women compared to men. (216) According to findings from the Lombardy Health Database, the proportion of males (65%) was also higher than the proportion of females. (212)

Another risk factor examined in this research, bundle branch block, was not found to be significantly associated with a decrease in renal function. **(Table 6)** Timoteo et al. also reported the varying effects of RBBB and LBBB on prognosis for patients with ACS. (148) Some of the studies that aimed to assess the association between bundle branch block and the prognosis of ACS patients have several limitations. These limitations include small sample sizes, non-contemporaneous populations, populations derived from randomized clinical trials rather than real-life settings, and ethnically diverse populations. (147,149) Nonetheless, it is quite possible

that in our study, the prevalence of bundle branch block was underreported, and a larger sample size might uncover potential significant associations.

A decrease in renal function is highly prevalent and significantly associated with the outcomes of hospitalization within one month and one year. **(Table 7, Table 8)** These findings are consistent with prior research. In a study published in 2004 that involved 247,888 patients, the association between the rate of kidney function decline and the risk of hospitalization was investigated. The results demonstrated that patients with moderate and severe eGFR decline had an increased risk of hospitalizations, readmissions, and prolonged lengths of stay. (217) In our study, hospitalized patients displayed a higher proportion of GFR categories indicative of moderately or severely reduced kidney function. To be more specific, 72.8% of patients with severely reduced renal function were hospitalized, while only 27.2% of patients with the same GFR were not hospitalized. **(Tables 7)** These results are in line with the findings of previous research studies, which have indicated that kidney dysfunction elevates the risk of hospitalization. (218) Overall, hospitalized patients are more commonly categorized into the moderate or severely reduced kidney function group. **(Table 7, Table 8)** It should be noted that even mild renal disease should be considered a significant risk factor for cardiovascular complications following a myocardial infarction. (219)

We also conducted descriptive and analytical statistics for other study outcomes, one-month and one-year mortality. The observed one-month mortality rate was documented at 5.15%, while the corresponding one-year mortality rate stood at 14.43% **(Table 9)**. One-month mortality rates among ACS patients vary significantly across different geographic regions, with figures ranging from 5.3% in the Czech Republic to as high as 15.3% in Latvia. (220) From the ISACS-TC registry, several papers have been published that report one-month mortality rates. In a study by D. Trninic and M. Dilic et al. based on data from the ISACS-TC registry (Bosnia and Serbia branch), mortality rate was reported as 5.5%. (64) Furthermore, a distinct study conducted by Ricci et al. conducted a subgroup analysis focusing on young women (≤45 years) who suffered from ACS. This analysis utilized data from the ISACS-TC registry. The primary focus of this research was the 30-day all-cause mortality rate. Interestingly, the study revealed that young women experiencing ACS had a higher 30-day mortality rate compared to their male counterparts, despite receiving similar quality-of-care and undergoing equivalent in-hospital procedures. While youth emerged as an independent predictor of reduced 30-day mortality in men, it did not exhibit a similar association among women. Among young patients

(≤45 years), the overall 30-day all-cause mortality rate was calculated at 1.3% (0.7% for men and 4.8% for women), while older patients demonstrated an overall 30-day all-cause mortality rate of 6.9% (5.9% for men and 9% for women). Subsequent regression analysis within the young patient cohort clarified that the only variable significantly associated with 30-day mortality was female gender, even after adjusting for the utilization of guideline-recommended medications and reperfusion therapy. (70)

Furthermore, Cenko et al. conducted a study that assessed the advantages and potential risks of an early invasive strategy in comparison to a conservative approach in both female and male patients. This study was based on data derived from the ISACS-TC database. The primary endpoint of this investigation focused on a composite measure that included 30-day mortality and severe left ventricular dysfunction. It's worth noting that the different methodology used in this study may limit the comparability of results. The research findings revealed 30-day mortality rates of 2.0% for male participants and 4.4% for female participants. (221)

In another study utilizing the ISACS TS registry, Bugiardini et al. conducted research to compare the effects of early versus delayed administration of oral beta-blockers on 30-day mortality among ACS patients. They reported in-hospital mortality rates of 1.5%, 2.7%, and 4.0% based on the timing of beta-blocker administration (<6 hours, 6-24 hours, and >24 hours). (80) In a Japanese study by Sawano et al. involving ACS patients, the overall 30-day all-cause mortality rate was 3.0%. (138)

One notable study, the World Health Organization's MONICA Project, conducted in mid-1990s, offers a robust international comparison of MI outcomes in 31 countries. This project assessed 30-day mortality rates, aiming to mitigate in-hospital mortality biases. While this project underscores challenges for future research, its cross-sectional analyses suggest that care quality played a role in the high mortality rates from coronary artery disease in Eastern Europe. However, these analyses struggled to disentangle the effects of care from those of coronary artery disease risk factors and socio-economic factors. Detailed examinations of 10-year changes in mortality and case-fatality rates related to care quality within the 31 populations studied in the MONICA project yielded ambiguous results. Improvements in coronary care were positively correlated with reductions in 30-day case-fatality rates. (222)

Data for two follow-up periods were further analysed, taking into account variables such as

sex, age, bundle block, GFR, infarction artery, and hospitalization. For the analysis, age was stratified into three distinct categories: up to 45 years, 46 - 65 years, and 66 and above. **(Table 10)** Among the patients who died, a substantial proportion, 83.7% belonged to the oldest age group 66 years and over. This observation was significant and expected, as age is a confirmed significant predictor of one-month mortality in ACS patients who undergo PCI. The pathophysiology of ACS in elderly patients differs from that in younger individuals and can explain the increased mortality. As people age, vascular stiffness and endothelial dysfunction also increase. Older patients are more likely to have calcified lesions, while younger patients have a higher prevalence of rupture/dissection and culprit lesions with more thrombus. (152) The APEX-AMI trial investigated the influence of age on treatment and outcomes in patients aged ≥75 years with treated with PCI. The study concluded that age was the most significant predictor of short-term mortality. (160)

At the one-month follow-up, the mortality rates for both males and females were similar (p=0.32). **(Table 11)** A similar non-significant association was found between one- month mortality and bundle block. **(Table 12)** in contrast to hospitalization, which exhibited a significant association, as the majority of deceased patients were hospitalized. **(Table 13)** One-month mortality and GFR categories were significantly associated, and as expected, the highest proportion of patients who died (34.5%) were in the 30-44 GFR category. **(Table 15**) This association is consistent with the results of previous studies. A study published in 2002, based on a convenience sample of four large ACS trial databases (GUSTO IIb, GUSTO III, PARAGON, PURSUIT), confirmed that patients with abnormal renal function had higher mortality at both 30 and 180 days, regardless of ST-segment status. (223) Campbell et al evaluated whether mild renal impairment is an independent predictor of survival and found that it was a strong independent predictor of mortality compared to normal kidney function. (177) Our study also revealed a significant association between GFR categories and one-month mortality **(Figure 18)**, with the highest proportion of deaths observed in patients with moderately reduced kidney function (GFR category 30-44 or Stage III b). Similarly, there was a significant difference in the proportion of patients who died based on their GFR categories, with the highest proportion of deaths observed within the first year in patients with moderately reduced kidney function, GFR category 45-59 or Stage IIIa. Patients with moderate reductions in kidney function (GFR category 45-59 or Stage IIIa) may sometimes receive inadequate attention in terms of healthcare compared to patients with more severe renal impairment. It's possible that doctors underestimate the fact that patients with moderate reductions in kidney

function also have a higher risk of developing further complications such as bleeding, reinfarction, heart failure, or cerebrovascular events. Consequently, these patients may not receive the recommended standard of care and clinical follow-up, increasing their risk of unfavourable outcomes. Existing literature also suggests that these patients may not receive adequate medical treatments and may have a more limited potential benefit from PCI. The findings of the ISCHEMIA CKD trial, provide support for these observations. (224). It should be noted that while PCI has proven effective as a treatment for ACS patients, it can lead to acute kidney injury, which can significantly impact survival time. (225)

In five TIMI trials involving ACS patients, a notable and graded association between 30-day and 6-month mortality and reduced GFR was observed. In multivariable analysis, GFR remained independently associated with 30-day and 6-month mortality after adjusting for differences in baseline characteristics and the trials used for the analysis. The study also revealed that for each decrease of 10 mL/min/1.73 m2 in GFR, there was a 19% increase in the risk of mortality at 30 days and a 16% increase in the risk of mortality at 6 months. (216)
We also examined the association between one-month mortality and hospitalization with the infarction-related artery. **(Table 16**) A statistically significant link was observed between one-month hospitalization and mortality, with the majority of deceased patients been hospitalized. The influence of the culprit vessel on clinical outcomes after primary PCI remains a topic of interest. In 2018, Entezarjou et al. conducted a study aimed at elucidating the impact of the culprit vessel on clinical outcomes following PCI. The study involved 29,832 patients with no prior cardiac issues who underwent primary PCI between 2003 and 2014. They were categorized into three groups based on the culprit vessel: RCA, LAD, and LCx. The primary outcome assessed was 1-year mortality. The study's findings indicated that LAD infarctions exhibited a relatively higher adjusted mortality rate, along with an elevated risk of heart failure, stroke, and death. (194) Although there is a potential link between infarction-related arteries and an increased risk of mortality, our research did not identify statistically significant associations between the LAD/RCA/LCx, and one-month mortality. It's worth noting that the LAD group had the highest proportion of patient deaths, even though statistical significance was not achieved. **(Table 16)**

Similar to the analysis for one-month mortality, we conducted descriptive and analytical statistical analyses for one-year mortality. During this follow-up period, mortality also exhibited an increase with age. Among the patients who died, a substantial proportion,

specifically 75.3% (61 out of 81), belonged to the oldest age group (65 years and over), and this association with age categories was statistically significant. **(Table 17)** Our findings of a 21.64% correlation between individuals aged >65 and one-year mortality is consistent with previous research. Claessen et al. conducted a more extensive observational study, revealing that octogenarians undergoing primary PCI experienced a one-year mortality rate of 28.2%. (226) In a Brazilian study titled " The ERICO Study," an overall one-year mortality rate of 12.0% was observed in a sample of post-ACS patients. The study identified age, and diabetes as independent predictors of one-year survival for both overall and cardiovascular-related causes (227) Our findings reflect a similar outcome with a one-year mortality rate of 14.67%. The one-year mortality observed in our study was within a range comparable to the reported figures in the Polish Registry of Acute Coronary Syndromes, which ranged between 14.5% and 19.1%. (225) Sawano et al. also investigated the one-year outcomes of survivors from ACS hospitalizations. Their study included a population of 20,042 patients who underwent PCI in 2017. The overall one-year incidence of all-cause mortality was reported at 7.1%. (138)

In our study, the mortality rate increases with age categories, ranging from 4% in the category up to 45 years of age to 21.64% in the 66 and over category. **(Table 17)** There was no significant difference in the proportion of males and females who died. Gender- related disparities in outcomes among post-PCI patients are frequently reported and the subject of ongoing discussion. A large number of studies have examined the survival disparities between genders in patients with ACS treated with PCI. (228) Observed differences are explained by baseline characteristics, but they could also reflect pathophysiological and anatomical differences between men and women. (162)

While men have a higher risk of developing coronary artery disease, women have been shown to experience higher rates of adverse outcomes. The studies on mortality risk for ACS patients according to sex are not consistent, and further stratification is needed according to age categories. (170–175) Vaccarino et al. reported that younger women, but not older women, have higher rates of death during hospitalization than men of the same age. (229) According to a systematic review and meta-analysis published in 2023, women with ACS experience delays in time to treatment more often than men. They are also less likely to be treated invasively. Women have worse crude short- and long-term all-cause mortality, but after adjustment for multiple covariates, a less significant gender difference has been observed. Considering the

difference between crude and adjusted mortality, the authors concluded that further investigations are needed to understand the gender-related influence of particular risk factors on the outcomes of ACS. (230)

Similar to one-month mortality, bundle block did not have a significant influence on the outcome. **(Table 19)** These findings align with other studies, including a 2004 study based on the Swedish Register, which also assessed the impact of BBB on one-year mortality in acute myocardial infarction patients. Although there was a higher unadjusted relative risk of one-year mortality in patients with BBB compared to those without, this association did not remain statistically significant after adjusting for propensity score. (231) In our study BBB in all four models (**Table 23, Table 24, Table 25, Table 26)** had OR < 1 suggesting that, when adjusted to other confounders, it did not contribute to risk increase which is not in line with previous research of Timoteo et al. (148) and Yang et. al. (149). Nonetheless, it's essential to underscore the significance of methodological considerations and the influence of both identified and unforeseen biases when interpreting measures of associations.

The increase in mortality with age is a consistent finding in prior research. Similarly, as in one month, hospitalization was significantly associated with one-year mortality, since most of the patients who died were hospitalized. **(Table 20)** When studying patient outcomes, it is crucial to consider the association between hospitalization and kidney function in individuals who have recently experienced ACS. Patients with ACS who also exhibit impaired kidney function frequently contend with concurrent medical conditions like diabetes or hypertension, further complicating their treatment and elevating the likelihood of hospitalization. Moreover, they are less inclined to receive the suitable therapeutic interventions. (232)

Furthermore, we examined the link between one-year mortality and GFR categories, revealing variations in the mortality rates among different GFR categories. Notably, the 30-44 GFR category exhibited the highest mortality rate at 41.67%, which was significantly different from the mortality rates in the other age categories. **(Table 21)** Our study findings are consistent with prior research, which identified renal dysfunction as a significant predictor of one-year mortality. In a previous study, it was reported that one-year all-cause mortality rates were 2.8%, 6.4%, 14.5%, and 40.9% for patients with normal renal function, mild, moderate, and severe renal dysfunction, respectively. (232)

One of the study's aims was to evaluate the connection between the affected coronary artery and the study's outcomes, which encompassed mortality and hospitalization. **(Table 22)** In cases of MI, the outcome is not solely determined by the location of the infarction but also by the specific site of occlusion within the coronary artery. (233) Both STEMI and NSTEMI are associated with the rupture of atherosclerotic plaques, which are frequently prone to vulnerability, resulting in intracoronary thrombosis. (234) Recent studies have suggested that a significant portion of AMI tend to happen in the left anterior descending and right coronary artery territory. (235)

In contrast to the one-month follow-up, at the one-year follow-up, significant associations emerged between the infarction artery and both mortality and hospitalization rates. **(Table 22**) The LAD group had the highest mortality rate, along with the highest rate of hospitalization. Several research studies have explored outcome disparities between anterior and non-anterior myocardial infarctions by categorizing patients based on their ECG patterns. These investigations have consistently revealed that anterior infarctions are linked to elevated cardiac mortality rates compared to inferior infarctions. In a study led by Brener J, the focus was on angiographic findings in patients with MI. This study revealed that proximal LAD infarctions were associated with poorer outcomes, larger infarct sizes, and a more significant reduction in global ejection fraction. (236)

One of the most extensive studies that sought to measure the impact of the culprit artery on outcomes following PCI was carried out using data from the SWEDEHEART registry. The research revealed that LAD and LCx infarctions were linked to a relatively higher adjusted mortality rate when compared to RCA infarctions. Specifically, LAD infarctions were associated with an elevated risk of heart failure, stroke, and mortality. However, it's important to note that the influence of the culprit vessel on mortality was limited after the first month. (194) Our findings are consistent with these observations; however, there is a distinction in the relationship between the infarction artery and hospitalization within one month **(Table 16)** compared to one-year mortality **(Table 22)**. During the one-month follow-up, no significant association was observed. Several factors could contribute to this outcome, including potential bias, confounding variables, and methodological limitations. Additionally, it's important to consider the influence of effect modifiers and clinical practice. Early, clinical decisions often rely on a binary perception of stenosis with a cutoff of 50%. However, the role of FFR in interventional cardiology is steadily gaining importance. FFR emphasizes the importance of

functional testing and evaluating the hemodynamic impact of lesions, rather than solely relying on the traditional visual estimation of stenosis percentage. (237) Our results indicate that mortality is influenced by numerous factors, and additional research is required to uncover these factors comprehensively. Expanding the sample size may unveil associations that remained undetected in a smaller study. However, it's essential to recognize that mortality is a complex event shaped by various variables, encompassing both conventional risk factors and non- conventional ones, which may exert additive, multiplicative, or interactive effects.

We performed multivariate logistic regression analyses that encompassed all demographic and clinical variables to assess the risk of one-month and one-year mortality during the follow-up periods. By incorporating all these variables into the models, we were able to adeptly account for potential confounding factors. This comprehensive approach enhances our understanding of the multitude of factors that influence mortality outcomes, enabling a more accurate evaluation of the specific variables' true impact on one-month and one-year mortality during the follow-up periods. **(Table 23, Table 24, Table 25, Table 26)** For our analysis, we developed two distinct models for each outcome, namely one-month and one-year mortality. This division was necessitated by the categorization of age into two groups: >65 and >75 years. It's important to note that the selection of age cutoffs in research can vary, and although there isn't a universally accepted definition of older patients, many studies commonly employ cutoffs of 65 and 75 years to differentiate age groups and evaluate their influence on different outcomes. (238–241) This approach enables us to examine the effects of age in a more detailed manner and gain a deeper understanding of its impact on mortality within the context of our study. In their study, Bach et al. presented findings specific to two age groups: individuals aged 65 and those aged 75. (159) A cut-off of 75 years of age was used in two large cohorts (152,153) as well as Japanese study of PCI (158) and APEX-AMI Trial. (160) In total, there were four logistic regression models, each considering two age thresholds (>65 and >75 groups) and two distinct outcomes: one-month and one-year mortality.

In the initial set of models employing a cutoff age of 65 **(Table 23),** age, GFR category, and the site of infarction artery (LAD vs. RCA/LCx) emerged as significant predictors of one-month mortality. However, sex and BBB did not achieve statistical significance in these models. It's important to highlight that the role of sex is becoming increasingly emphasized in research. The observed variations in the outcomes of ischemic heart disease may be attributed to differences in the underlying pathophysiology between men and women. Traditional

cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, and cigarette smoking may interact differently with the coronary anatomy in men and women. (242)

Nevertheless, age appears as a strong predictor of outcomes. The odds ratio for patients aged over 65 was 3.248, signifying a greater risk of mortality among older patients in contrast to their younger counterparts. Previous risk models based on 15,904 stabilized STEMI or NSTEMI patients who were randomized in the SYMPHONY and 2nd SYMPHONY trials, similarly recognized age as the most significant factor linked to mortality, explaining approximately 45% of the observed outcomes. (243) Age was also validated as a significant risk factor for cardiovascular death in a 10-year follow-up study involving coronary patients. (244) Moreover, in our model there was a notably higher odds ratio of 5.908 for patients in the higher GFR category when compared to those in the lower GFR category. These results align with previous studies that have consistently reported elevated rates of cardiac events and cardiovascular mortality in post-ACS patients with renal impairment. (223,245–247)

In the study conducted by Ferrante G et al., it was determined that the GFR emerged as a noteworthy predictor of one-month mortality. (170) In a meta-analysis conducted in 2013, which encompassed a total of 27,610 post MI patients, data were pooled from four major randomized trials (VALIANT, EPHESUS, OPTIMAAL, and CAPRICORN). The consistent findings from this meta-analysis consistently affirmed that GFR serves as a strong and independent predictor of unfavorable outcomes in post-MI patients.(248) The site of infarction artery emerged as a significant predictor of one-month mortality, revealing that patients who experienced LAD infarctions had a 3.978-fold higher odds of mortality compared to those with RCA/LCx infarctions. **(Table 23)** Gender did not emerge as a significant predictor of one month mortality, consistent with the results of a study conducted by D. Trninić and M. Dilić et al., which was based on ISACS patients from Bosnia and Serbia. (63)

In another logistic regression model focusing on one-month mortality using a cutoff age of 75, significant associations were established for age, GFR, and the infarction artery (LAD vs. RCA/LCx) with mortality. Patients in the older age group exhibited an odds ratio of 4.052 for adverse outcomes in comparison to the younger age group. Those in the higher GFR category had an odds ratio of 5.384. Furthermore, the infarction site demonstrated a significant association with one-month mortality, where the LAD as the culprit lesion had a 3.873-fold higher odds ratio for adverse outcomes compared to RCA/LCx. **(Table 24)** Age was also

identified as the primary predictor of 30-day mortality in MI patients treated with PCI in the APEX-AMI trial. (160)

We utilized logistic regression models to evaluate the association between various predictors and one-year mortality. **(Table 25, Table 26)** These models were employed to investigate the link between predictors, which included age (>65, >75), gender, bundle block, GFR category, and LAD vs. RCA/LCx, with one-year mortality. While several predictors displayed similar directions and odds ratios greater than 1, suggesting an increased risk of one-year mortality, none of them reached statistical significance in the >65 age model. The odds ratios and corresponding confidence intervals were as follows: age >65 (OR = 1.692, 95% CI = 0.451-6.347), gender (OR = 1.079, 95% CI = 0.272-4.283), bundle block (OR = 0.374, 95% CI = 0.039-3.601), GFR category (OR = 2.082, 95% CI = 0.211-20.553), and LAD vs. RCA/LCx (OR = 4.643, 95% CI = 0.526-40.995). **(Table 25)**

In the logistic regression model for one-year mortality, it was found that age >75 was significantly associated with the outcome. **(Table 26)** The odds ratios from the model indicated an increased risk for age (6.461), GFR category (1.367), and LAD vs. RCA/LCx (3.850), all of which pointed towards a heightened risk for a fatal outcome. **(Table 26)** Additionally, it's worth noting that the clinical evidence for the treatment of ACS in the elderly is less robust than in patients younger than 75 years, underscoring the importance of considering age as a significant factor in clinical decision-making for this population. (249)

In this particular model, focusing on patients aged >75, sex was not found to be significantly associated with the outcome. This finding is in contrast to the results observed in all other models, where men had a lower risk compared to women (as indicated by OR=1.4 in **Table 23**, OR=1.14 in **Table 24**, and OR=1.07 in **Table 25**, with an odds ratio of 0.759 in **Table 26**).

These findings align with previous studies conducted within the ISACS-TC project, which consistently indicated increased risks for women. (73-75) Indeed, it's crucial to acknowledge that the risk of cardiovascular events and survival rates can vary significantly across different age groups. For example, a study published in 2001 delved into sex differences in survival following myocardial infarction at various age intervals, including the 1-year overall survival rate. The findings from this research showed that only women under the age of 50 had a significantly lower 1-year survival rate compared to men of the same age. Interestingly, women

older than 70 years had a slight survival advantage. The authors of the study attributed the excess mortality among young women to the presence of diabetes, underscoring the multifaceted nature of risk factors and outcomes in cardiovascular health. (250) However, gender-related disparities persist, and it is observed that women with ACS tend to experience worse outcomes compared to men. (251)

In all four models, which included age (>65 and >75), declining renal function, and LAD as predictors, an increased risk was consistently indicated, although the association did not consistently reach statistical significance across all models. (**Table 23, Table 24, Table 25, Table 26)** In summary, the R-squared values across all models ranged up to 0.56, suggesting that the chosen predictors collectively explain a substantial portion of the outcome variability. However, the role of gender in terms of increased risk remains inconclusive. Both gender and age are non-modifiable factors that exert a significant influence on clinical outcomes in ACS. The pathophysiology of coronary artery disease and the clinical manifestations of atherosclerosis provide support for the existence of differences in how these factors affect women in comparison to men. (166) While men tend to have a higher risk of developing coronary artery disease, numerous registries from around the world consistently show that women face a significantly greater risk of adverse outcomes than men when they do develop the disease. However, an important question remains: whether female gender independently contributes to these observations, or if the differences in risk can be attributed to baseline characteristics and comorbidities. (167- 169)

Chronic kidney disease has a detrimental impact on the survival of ACS patients. While PCI can enhance the prognosis of ACS patients with CKD, it's crucial to recognize that individuals with renal insufficiency are at an elevated risk of experiencing post-procedural complications. Balancing the benefits of PCI with the increased risks in this patient population is a crucial consideration in clinical decision-making. (252) A prior study has indeed confirmed the association between a decrease in glomerular filtration rate and mortality in patients with acute coronary syndrome. (253) It's important to highlight that recent studies have indicated that even mild declines in kidney function serve as independent predictors of long-term mortality in individuals with known or suspected coronary artery disease. This underscores the significance of monitoring renal function as part of the comprehensive assessment and management of cardiovascular health. (177-179) It is plausible that patients with reduced renal function may receive less aggressive treatment in comparison to those with normal renal function. Such

differences in medical management could potentially contribute to an increased risk of mortality.

The significance of the LAD artery in coronary circulation is notable, as it provides blood supply to a significant portion of the left ventricle muscle, typically ranging from 45% to 55%. (1) Although data on clinical outcomes among ACS patients treated with PCI and categorized by the culprit vessel are limited, previous studies have consistently affirmed an elevated risk of mortality associated with the involvement of the LAD artery. This underscores the importance of recognizing the clinical implications of LAD involvement in ACS cases. (201,202). The results in our study align with the findings of research conducted by Bassan et al. where lesions in the LAD were more frequent than those in the RCA and Cx arteries. (254) This contrasts with earlier studies by Pierard et al. and Ghanim et al., in which the RCA and Cx arteries were more often responsible for myocardial infarction. (255)

A study conducted by Vasiljević Z et al., based on the ISACS TS registry Serbian branch, did demonstrate higher mortality rates in cases of anterior infarctions compared to posterior infarctions, potentially suggesting more frequent involvement of the left anterior descending artery. However, it's important to note that the distribution of mortality by specific vessels was not presented in that particular study. (83) In contrast to the findings of our current research, the study conducted by Ferrante G et al. did not identify LAD artery involvement and intervention as predictors of in-hospital mortality, death from any cause, or long-term mortality after a follow-up period of 4.9 years. (256) In a study conducted by Wang JC et al., the majority of myocardial infarctions were found to occur in RCA at 44% and LAD artery at 39%. The study also revealed specific details about the location of occlusions within these arteries. In the case of the RCA, the most common occlusion site was the middle segment, with 50% of occlusions located within 45 mm of the ostium. For the LAD artery, all occlusions occurred in the proximal and middle segments, with 50% located within 25 mm of the ostium and 90% within 40 mm of the ostium. Regarding the LCx artery, 50% of occlusions were found within 25 mm of the ostium. The study's authors concluded that for every 10 mm distal to the ostium, the risk of occlusion significantly decreases. (202) In the study conducted by Ahmed F et al.,it was found that 52.1% of cases were attributed to LAD, followed by RCA with 26.6%, and Cx with 21.3 %. (203) In terms of distribution, the results of this study are similar to the results of mortality based on affected arteries in our study. However, there is a discrepancy when it comes to hospitalizations, as RCA was more frequently identified as the primary cause. In

conclusion, LAD was identified as the most common infarction artery, and the odds ratios in this study suggest an increased risk for mortality during both follow-up periods.

When comparing the logistic regressions for one-month and one-year survival, some predictive factors lose their significance at the one-year follow-up. This phenomenon can be attributed to the fact that the initial one-month interval represents the period of greatest risk for post-myocardial infarction patients, during which the impact of various predictive factors may be more pronounced. However, as time progresses, the influence of these factors tends to diminish. A plausible explanation for this trend lies in the consistent adherence of patients to their optimal medical therapy (OMT) over time. As patients adhere to OMT for a longer duration, its effects become more pronounced. Numerous studies have demonstrated that OMT in post-ACS patients leads to reduced morbidity and mortality rates. This highlights the importance of long-term adherence to optimal medical therapy in improving outcomes for these patients. (257–259) It's important to highlight that a significant number of patients who have experienced their first myocardial infarction often make substantial lifestyle changes. These changes commonly include quitting smoking, losing weight, adopting a healthier diet, and engaging in regular physical activity. These lifestyle modifications can significantly contribute to improved outcomes and overall cardiovascular health. (260,261) Despite the diminishing influence of predictive factors over time, the logistic regression models for one-year survival still indicate an increased risk of a fatal outcome, although to a lesser extent compared to the one-month interval. This suggests that certain factors continue to play a role in influencing longer-term survival outcomes for patients after a myocardial infarction, albeit with a reduced impact compared to the acute phase.

In the course of this research, certain limitations and biases were encountered. The study was conducted at a tertiary medical institution, the University Hospital Centre Zagreb. Patients from the City of Zagreb and its surrounding areas, as well as from other regions, were eligible for admission to this hospital, regardless of their place of residence. As a result, it was not possible to accurately enumerate the source population, which introduced biases into the research and limited its generalizability. It's important to note that this research did not differ in terms of patient selection from other similar studies, as the healthcare system in Croatia permits unrestricted access to tertiary health centers. Unfortunately, data regarding patients' residences were unavailable, but it is reasonable to assume that the majority of patients resided in the City of Zagreb and the neighboring counties. Differences may exist between patients from the

capital of Zagreb and those from other counties in terms of clinical characteristics. The potential for misclassification bias cannot be entirely ruled out. However, the potential impact of misclassification bias is relatively low due to the acute nature of ACS and the implementation of guidelines. The diagnosis of ACS is associated with high accuracy, although it includes both STEMI and NSTEMI patients. We lack precise data on the number of cases where the culprit vessel could not be identified, but previous research suggests that this is more likely in NSTEMI patients. (195) While culprit arteries were identified, specific data on the exact segment of culprit lesions (e.g., proximal or distal) were not reported. The involvement of different segments could potentially influence clinical outcomes, but the specific direction of this influence cannot be estimated. Previous research has also suggested the possibility of implicit biases and a higher rate of hospital admissions among younger males. (209)

Despite the acknowledged limitations and biases, this research carries significant strengths. It is a part of the larger study "The International Survey of Acute Coronary Syndromes in Transitional Countries," which was established at the University of Bologna, Italy. The ISACS-TC registry was established as a comprehensive retrospective and prospective cohort study, providing valuable context and depth to the research findings. All 17 participating countries, including Bosnia and Herzegovina**,** Romania, Croatia, and Serbia followed the same methodology for data collection and applied internationally recommended therapies in patient treatment. This consistent approach enhances the generalizability of the study's results. Time frames for follow-up were 30 days, 6 months and one year. Risk factors included age, gender, comorbidities and different treatment options. The primary outcome measures of the ISACS-TC registry also encompassed cardiovascular mortality within the one-year follow-up time frame. This inclusion facilitates comparisons of the study's results with those of other research conducted in transitional countries. In our study, the one-month mortality rate was recorded at 5.15%, while the one-year mortality rate was at 14.43%. Furthermore, the significant risk factors associated with mortality in the one-month model were found to be age, renal dysfunction, and the left anterior descending artery as the site of infarction.

7. Conclusion

This observational retrospective study was based on ISACS-TC registry data and possesses a strong methodological foundation. Risk factors, both modifiable and non-modifiable, were included in the analysis based on their availability within the clinical setting and previous studies in transitional countries. The study spanned from 2013 to 2017 and included a sample size of >700 patients for the majority of analyses. Since University Hospital Centre Zagreb is a tertiary hospital, the source population cannot be enumerated. Consequently, all patients who attended this hospital and met the eligibility criteria were included in the study. Age, GFR, and LAD as the culprit artery were consistently confirmed as significant predictors of one-month and one-year mortality in the majority of analyses. After conducting initial descriptive and analytic statistics, we performed four logistic regression models with two different age cut-offs (>65 and >75) and two follow-up periods. Age, GFR, and LAD as the culprit exhibited odds ratios indicative of an increased risk of mortality within the studied periods. While the majority of risk factors were significant in the one-month model, with the exception of age in the >75 model, they did not reach significance in the one-year period. Gender was a variable that did not consistently show a significant risk in all four models. These results align with previous studies, suggesting that age, a decrease in renal function, and LAD as the culprit are associated with mortality. However, some other variables that could influence the study's outcome in a longer follow-up period, such as comorbidities, optimal medical treatment, and certain procedure-related issues, were not included in this study. Despite these limitations, all results are in accordance with previous studies.

8. Abstract

Among patients with acute coronary syndrome (ACS), there are considerable disparities among European countries in gender and clinical parameters during the first-year follow-up. These differences are particularly notable in Central and Eastern European countries as opposed to their Western European counterparts. This study was conducted at the Department of Cardiovascular Diseases at the University Hospital Centre Zagreb from January 1, 2013, and December 31, 2017. The aim of this PhD thesis is to identify predictors of ACS patients who underwent primary PCI for one year follow-up. We hypothesed that male gender, age, decreased glomerular filtration rate (GFR), bundle branch block, and left anterior descending artery (LAD) as the infarction artery will be significantly associated with one-month and one-year mortality. The sampling method was convenient and all patients who fulfilled diagnostic and interventional criteria were included in the analyses. Sample size was more than 700 patients for the majority of analyses. Age, GFR, and LAD as the culprit artery were significant predictors for one-month and one-year mortality in the majority of analyses. Following descriptive and analytic statistics, for two follow-up periods we constructed four logistic regression models with two age cut-offs, >65 and >75 years of age. Odds rations for age, GFR, and LAD indicated increased risk for mortality. Although majority of risk factors, with the exception of age were in the >75 model, were statistically significant in the one-month models, they did not achieve significance in one-year period. Gender was not significant predictor in all four models. Our results were in line with previous studies, emphasizing the need for more comprehensive treatment and follow-up algorithms for patients with identified predictors of adverse outcomes. Data collection adjusted to clinical setting would improve clinical outcomes and efficiency of secondary prevention.

9. Abstract (in Croatian)

Spol i klinički parametri u prvoj godini praćenja ishoda liječenja u pacijenata s akutnim koronarnim sindromom

Igor Tagasovski, 2024

Kod pacijenata s akutnim koronarnim sindromom (AKS) postoji značajna varijacija u spolu i kliničkim parametrima tijekom prve godine praćenja. Cilj istraživanja je identificirati prediktore smrtnosti kod pacijenata koji su prebolili infarkt. Istraživanje je provedeno na Odjelu za kardiovaskularne bolesti Sveučilišne bolnice u Zagrebu od 2013. do 2017.godine. Hipoteza je da muški spol, dob, smanjena glomerularna filtracija (GFR), blok grane te lijeva prednja silazna arterija (LAD) kao infarktna arterija mogu biti značajno povezani s jednomjesečnom i jednogodišnjom smrtnošću. Dob, GFR i LAD bili su značajni prediktori za jednomjesečnu i jednogodišnju smrtnost u većini analiza. Nakon statističkih analiza, konstruirana su četiri logistička regresijska modela s dvije dobi (stariji od 65 i stariji od 75 godina) za dva razdoblja praćenja. Dob, GFR i LAD ukazivali su na povećan rizik smrtnosti. Iako je većina čimbenika rizika, osim dobi, bila statistički značajna u modelima za mjesec dana nisu postigli značajnost u jednogodišnjem razdoblju. Spol nije bio značajan prediktor u sva četiri modela. Rezultati su u skladu s prethodnim istraživanjima u vezi s povećanim rizikom za GFR i LAD, naglašavajući potrebu za sveobuhvatnijom terapijom i metodologijom praćenja pacijenata s AKS-om. Prikupljanje podataka prilagođeno kliničkom okruženju moglo bi poboljšati kliničke ishode i učinkovitost sekundarne prevencije.

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11. Biography

Igor Tagasovski was born in Skopje, Macedonia, on October 20, 1988, and received his education by completing the gymnasium of natural sciences. Subsequently, he graduated in record time from the Medical Faculty of the University "St. Cyril and Methodius" in Skopje in 2013. Throughout his studies, he spent every summer gaining practical experience in hospitals in Skopje and abroad, including Malta/Italy/Ireland/Turkey/Slovenia/Lithuania, and thereby acquiring valuable professional insights. Following his practice and successful completion of the state exam, he secured a position in 2014 at the cardiology department of the University Hospital "8-Septembar. Embarking on his specialization in cardiology in June 2015, he joined the Department of Cardiovascular Diseases at the University Hospital Center Zagreb. In 2017, he enrolled in the PhD study of Biomedicine and Health at the School of Medicine, University of Zagreb. To date, Igor Tagasovski has authored several professional and scientific papers published in both domestic and international journals. He has actively participated in numerous national and international congresses and courses. In late 2020, he successfully passed the specialist exam in cardiology, and since then, he has been practicing as a cardiologist in Zagreb, currently holding a position at the Clinic for Cardiovascular Medicine, Magdalena.