

# Coronary lesion pattern and outcome of elderly and very elderly patients with acute coronary syndrome

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UNIVERSITY OF SPLIT



**UNIVERSITY OF SPLIT  
SCHOOL OF MEDICINE**

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**CORONARY LESION PATTERN AND OUTCOME OF ELDERLY AND VERY  
ELDERLY PATIENTS WITH ACUTE CORONARY SYNDROME**

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Sizi cok seviyorum canim ailem.*

## **LIST OF ABBREVIATION**

AHA – American Heart Association  
AMI - Acute myocardial infarction  
ACS – Acute coronary syndrome  
CABG - Coronary artery bypass grafting  
CAD – Coronary artery disease  
CCS - Canadian Cardiovascular Society  
CK - Creatine Kinase  
CK-MB - Creatine Kinase-MB  
CKD - Chronic kidney disease  
COPD - Chronic obstructive pulmonary disease  
cTn - Cardiac troponin  
CVD – Cardiovascular disease  
CX – Circumflex artery  
DAPT – Dual antiplatelet therapy  
DES - Drug-eluting stent  
ECG - Electrocardiogram  
ESC – European Society of Cardiology  
HF – Heart failure  
Hs-cTn – high-sensitivity cardiac Troponin  
LAD – Left artery descending  
LBBB – Left bundle branch block  
LCA - left circumflex artery  
LM – Left main coronary artery  
MI - Myocardial infarction  
NSTEMI – Non-ST-elevation myocardial infarction  
NYHA - New York Heart association  
PAD - Peripheral artery disease  
PCI – Percutaneous coronary intervention  
PM – Pacemaker  
RBBB – Right bundle branch block  
RCA – Right coronary artery  
STEMI - ST-elevation myocardial infarction

TIMI - Thrombolysis in myocardial infarction

TTE - Transthoracic echocardiography

UA – Unstable angina

UFH - Unfractionated heparin

## **1. INTRODUCTION**

## 1.1. General

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, with the 2013 Global Burden of Disease research indicating that CVD caused 17.3 million deaths worldwide (1,2). In comparison, CVD accounts for 45 percent of all deaths in Europe, with 4 million deaths each year. Although CVD mortality rates have declined in Western nations during the previous four decades, this ailment still accounts for about half of all fatalities in Europe (3,4). However, the focus will be on one of the most common kinds of CVD, coronary artery disease (CAD), often known as acute coronary syndrome (ACS). ACS kills around 1.7 million people in Europe each year, accounting for 20% of all fatalities (4).

In a study of nearly 3.7 million patients, Neuman JT, *et al.* found a decrease in ACS in Germany from 2005 to 2015, but coronary angiographies and procedures increased. The study also revealed an interesting statistic about the increasing age of ACS patients (5). These findings will intensify in the next decades as Germany ages. In addition, prospective and randomized clinical trials of ACS rarely incorporate geriatric characteristics including frailty, cognitive function, multimorbidity, and polypharmacy, which can affect outcomes. Elderly ACS patients over 75 have a higher risk of ischemia outcomes and procedure-related complications, making therapy difficult. Older patients are complex and at high-risk, requiring a multifaceted treatment approach compared to younger patients. ACS treatment in older adults is even more complicated. Due to anatomic complexity, physiological susceptibility, aging (especially geriatric disorders), life span and health care aims vary (6,7).

In addition to these facts, it is critical to note that Germany is one of the EU nations where demographic change has advanced the fastest. Between 1990 and 2014, the number of people in Germany aged 65 and over increased by approximately 5.2 million to 17.1 million. This represents an increase of about 43% within 24 years, while the increase in the total population was 6%. There are many factors that contribute to the trend of an aging population. First, in 2020, the 1960s baby boom generation will have reached retirement age. This leads to a rightward shift of the average age towards older ages. Second, since the 19th century, the life expectancy of Germans has doubled because of improved living conditions (8).

Finally, Germany's persistently low birth rates are contributing to this trend. This leads to the conclusion that in Germany, more than a quarter of the population is 65 or older. Furthermore, due to increased life expectancy, this aging trend is accompanied by an increase in the number of so-called oldest people. The number of people 80 years old in Germany in 2014. was 4.5 million, which represents 6% of the population. According to the Federal Statistical Office of Germany, their population will grow to approximately 9.9 million people



by 2050. In 2050, this will account for 13% of the population. In conclusion, the demographic change underlines the importance of studies about elderly patients, especially in Germany since the trend in aging is significantly higher than in other European countries (8).

Overall, due to the regional demographic changes and the increasing importance of elderly patients in the treatment of CAD, we thought to evaluate the coronary lesion pattern and outcome of PCI procedures in patients with ACS over the age of 75 years and compared these results to younger patients.

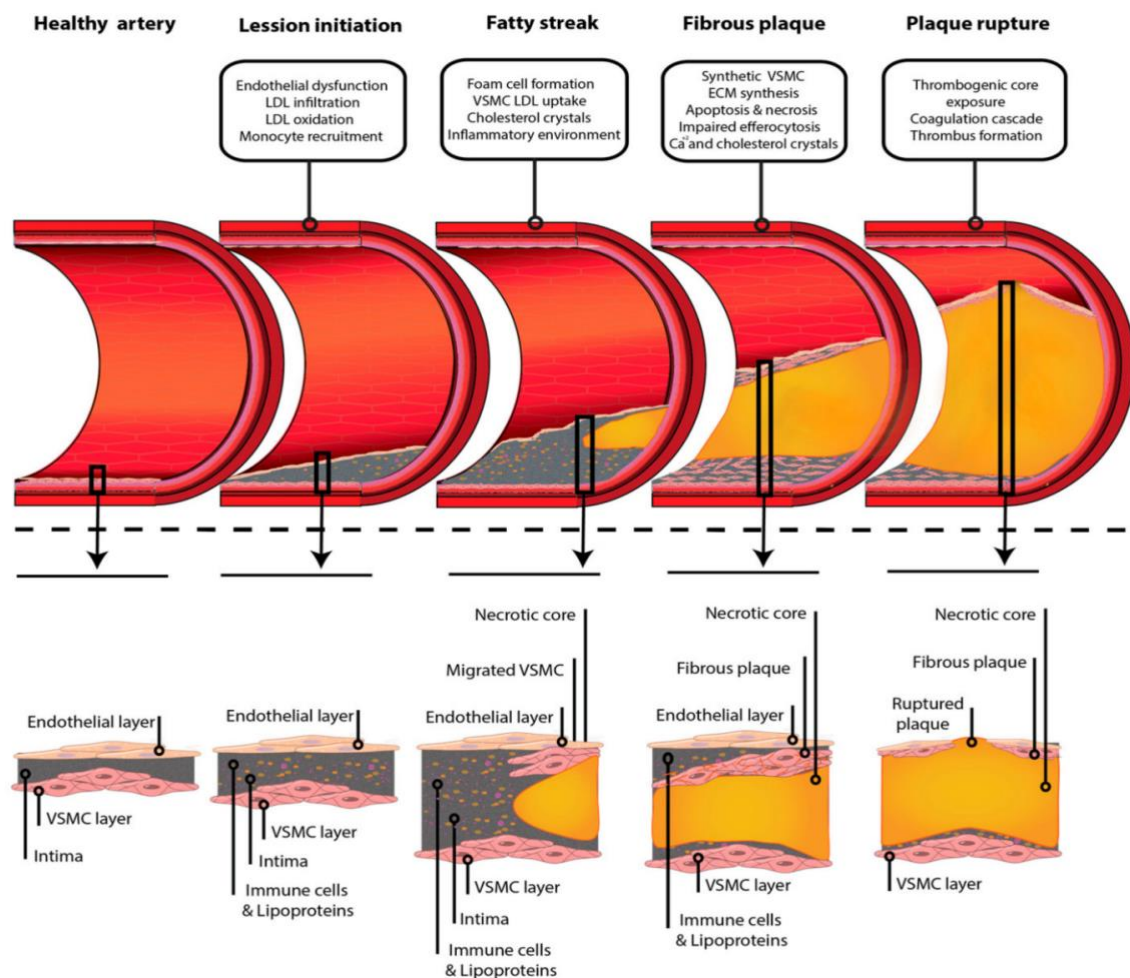
## **1.2. Acute coronary syndrome**

The term ACS summarizes the stages of coronary heart disease that are immediately life-threatening and manifest as unstable angina (UA), acute myocardial infarction (AMI) or sudden cardiac death (9).

The pathophysiological mechanism for these syndromes begins with the process of a buildup of atheromatous plaques within the coronary arteries, which develop and progress for decades prior to the acute event, as shown in Figure 1. This atherosclerotic process can be described as a low-grade inflammatory condition of the tunica intima of arteries that is accelerated by risk factors such as hypertension, hypercholesterinemia, diabetes mellitus, obesity, smoking, an unhealthy diet, family history, and genetics (10).

In detail, the pathological mechanism includes mechanical injuries amplified by the mentioned risk factors, which can result in endothelial injury. The initial factor beginning the process of atherosclerotic is the plaque formation. Especially bifurcations of arteries are prone to the effects of physical force, i.e., the bifurcation of the left main coronary artery (LM) and the left anterior descending artery (LAD). Following the endothelial injury, lipoprotein molecules enter the endothelium and are oxidated to modified lipoproteins. Since oxidized cholesterol is highly toxic, it is phagocytosed by the vessel wall macrophages. The oxidized lipids trigger a series of proinflammatory reactions, perpetuating the activation and recruitment of monocytes and macrophages and inflammatory cells. The following lipid uptake by macrophages leads to the formation of foam cells, which cause a fatty streak in the arterial wall. As a consequence of production of growth factors by the foam cells, vascular smooth muscle cells (VSMC) migrate from the tunica media to the intima, the surface of the plaque. This creates a fibrous cap in the lumen of the vessel, which is one of the hallmarks of advanced

atherosclerosis. In this phase, a plaque regression is unlikely to happen and the plaque stability and its vulnerability is directly connected to the thickness and cellularity of the fibrous cap (10).



**Figure 1.** Schematic representation of atheroma plaque development underlying the crucial changes that contribute to its development from a healthy artery to plaque rupture.  
 SOURCE: Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of Atherosclerosis. *Int J Mol Sci.* 2022 Jan;23(6):3346.

Another hallmark of advanced atherosclerosis is the necrotic core that forms the nucleus of atherosclerotic plaques. During the transition from fatty streak to intimal growing plaques, atheroma plaques exhibit a cell-free and lipid-rich necrotic core. As a result of increased apoptosis of macrophages within the plaque and subsequent accumulation, this necrotic core grows. After cell death, Metalloproteases are released and shrink the size of the fibrous cap, thus increasing the vulnerability of the plaque. A vulnerable plaque is considered when the lesion has a thin fibrous cap, a large necrotic core, and an increased inflammatory response because it is constantly exposed to the pro-atherogenic environment. This vulnerability correlates with a high susceptibility to rupture when exposed to the hemodynamic forces. Plaque rupture is the most often responsible for ACS, regardless of clinical presentation, age, sex, or

continent. A plaque rupture or fissure exposes subendothelial collagen and triggers a coagulation cascade, which leads to thrombus formation (Figure 1) (10,11).

Consequently, decreased blood flow caused by coronary blockade and/or distal embolization of thrombus into the coronary microcirculation results in a sudden imbalance between myocardial oxygen consumption and its demand. This leads to AMI, which is defined as sudden ischemic death of myocardial tissue. Sustained ischemia of these cells activates a wavefront of cardiomyocyte death that extends from the subendocardium to the subepicardium (11). Clinically, myocardial infarction (MI) is defined by evidence of elevated cardiac troponin (cTn) levels with at least one value above the 99th percentile of the upper reference limit and is considered acute when there is a dynamic of cTn levels as evidenced by an increase and/or decrease in cTn levels (12).

Depending on the clinical, pathological, and prognostic differences, myocardial infarction (MI) is classified into different types. Type 1 MI is presented by rupture or erosion of the atherosclerotic plaque with resultant intraluminal thrombus formation in single or several coronary arteries. As described previously, this can lead to coronary blockage and/or distal coronary embolism resulting in myocyte necrosis. Type 2 MI is defined as ischemic myocardial injury resulting from an imbalance between myocardial oxygen demand and supply. The imbalance may be multifactorial and related to either decreased myocardial perfusion due to fixed atherosclerotic obstruction without plaque rupture, but also to coronary artery spasm, coronary microvascular dysfunction, coronary embolism, or coronary artery dissection. By definition, acute atherothrombotic plaque dysfunction is not a feature of type 2 MI. Type 3 MI includes patients who suffer sudden cardiac death that is fatal MI, but die before blood samples can be obtained for cardiac biomarkers or before an increase in these markers can be detected. Finally, types 4 and 5 include patients with coronary procedure-related myocardial injury. Type 4 MI is associated with PCI induced myocardial injury, whereas type 5 MI is associated with coronary artery bypass grafting (CABG)-induced myocardial injury (13).

ACS, characterized by a sudden imbalance between the oxygen consumption and oxygen demand of the heart, includes STEMI (ST -elevation myocardial infarction), NSTEMI (Non- ST -elevation myocardial infarction), and UA (12,14).

The predominant mechanism of MI is the imbalance of oxygen demand and supply. Depending on whether the thrombus in the coronary artery is totally or partially occluded, STEMI reflects acute total or subtotal coronary occlusion (type 1 MI), whereas NSTEMI shows partial coronary occlusion (type 2 MI) resulting from chronic CAD. In comparison, UA usually

results from exacerbation of fixed atherosclerotic stenosis, without acute cardiomyocyte injury or necrosis, and may progress to AMI or stable situation (12,14).

In addition to this pathophysiological classification, STEMI and NSTEMI are defined by characteristic symptoms associated with myocardial ischemia and elevated blood cTn levels. The main difference with UA is that cTn levels are not elevated in UA, although symptoms and electrocardiography (ECG) findings may suggest NSTEMI. This difference results from damage to the myocardium, which is present in NSTEMI but not in UA. Therefore, the increase in cTn values is not present in UA. Patients have a lower risk of dying with unstable angina and appear to benefit less from intensified antiplatelet treatment and invasive strategies within 72 hours (15–19).

An important characteristic clinical sign that links all three is acute chest discomfort, which is the hallmark and leading symptom of ACS. Anginal symptoms are described as pain, pressure, tightness, and burning. In general, the three main manifestations of ACS are resting angina, new-onset angina, and crescendo angina. Resting angina refers to chest pain that occurs at rest and lasts longer than 20 minutes. New-onset angina (*de novo*) is the occurrence of angina of at least moderate severity (Canadian Cardiovascular Society [CCS] class II or III) within the past three months. Crescendo angina refers to destabilization of preexisting stable angina in terms of frequency, duration, and lower threshold (increase by at least one CCS class to at least class III) (20).

The above CCS classes grade the severity of angina and are useful to assess the urgency and impact of treatment based on the change in functional class. The four classes indicate the level of physical activity that triggers anginal symptoms. Class I signifies that normal physical activity, such as walking, does not cause angina, but strenuous or prolonged exertion can trigger angina. Class II represents mild limitation of normal physical activity, with angina occurring during activities such as fast walking or climbing stairs, especially after meals. Class III represents marked limitation of normal physical activity, with angina occurring with minimal exertion, such as walking on level ground. Finally, Class IV signifies an inability to engage in any physical activity without experiencing discomfort. In this class, anginal symptoms can occur even at rest. All in all, this classification system enables a standardized evaluation of the impact of angina on daily activities, with higher classes denoting more severe limitations in physical activity as a result of anginal symptoms (20).

Myocardial ischemia manifests not only as angina pectoris but also as anginal equivalents and may also be silent. The latter is usually detected by ECG or cardiac imaging but lacks clinical signs. Angina pectoris is a typical chest discomfort, characterized by a

retrosternal sensation of pain, pressure, or heaviness that may radiate intermittently or persistently to an adjacent area of the body. The pain may radiate to the left and/or right arm, intrascapular area, neck, or jaw, increasing the likelihood of AMI. Elderly patients or patients with diabetes mellitus in particular may have an altered ability to specify the location of discomfort, which can complicate the diagnostic process (20,21).

Anginal equivalents, on the other hand, are symptoms other than chest discomfort, such as diaphoresis, nausea, or epigastric pain. These additional symptoms are consequences of either acute ischemic left ventricular dysfunction or arrhythmias manifesting as dyspnea, palpitations, extreme fatigue, or syncope. In addition, atypical symptoms without chest discomfort may occur, but other major symptoms including isolated epigastric pain, indigestion-like symptoms, and isolated dyspnea or fatigue (14,20).

Atypical symptoms are more frequently noted in elderly patients, women, and in patients with diabetes mellitus, chronic kidney disease (CKD), or dementia. Women, in particular, are less likely to have chest discomfort and instead present with atypical symptoms (12,14,20). Overall, the diagnostic performance of chest pain characteristics for MI is limited in patients who present to the emergency department with suspected MI. Physical examination may reveal signs of noncoronary causes of angina, for example, pulmonary embolism, acute aortic syndromes, myopericarditis, aortic stenosis. Other findings may indicate extracardiac pathologies, including pneumonia, pneumothorax, or musculoskeletal disorders. In addition, the symptom of chest pain, which may be triggered by increased pressure on the chest wall, is associated with a significant negative predictive value for NSTEMI (21).

In addition to physical examination, other diagnostic tools are needed to assess AMI, such as laboratory values and ECG. In STEMI, the ECG shows a sustained ST-segment elevation over 20 minutes accompanied by acute chest pain. NSTEMI patients show acute chest discomfort without ST-segment elevation on the ECG (12,19).

In the following sections, the terms NSTEMI and STEMI are discussed in more detail, with particular attention to ACS in elderly patients.

### **1.3. Acute coronary syndrome without ST-Elevation**

NSTEMI is defined as the absence of ST-segment elevation and increased cTn values accompanied by anginal symptoms and other acute events. In individuals with suspected NSTEMI, the physical examination is usually normal. However, a more specific tool used primarily in patients with suspected ACS is the resting ECG (12-lead), which should be

performed within ten minutes of the patient's coming in the emergency department (22). As mentioned previously, an ECG in the setting of NSTEMI may show characteristic abnormalities, such as ST-segment depression, transient ST-segment elevation, and T-wave changes, but may also be within the physiological limits in some patients (more than 30%). Additional leads should be recorded if the standard leads are indeterminate and the patient shows signs suggestive of MI. The additional leads V7, V8, and V9 may detect left circumflex artery (LCA) occlusion, and leads V3R and V4R may display right ventricular MI. In contrast, persistent ST-segment elevation in patients with suggestive signs indicates STEMI and requires immediate reperfusion (20,23).

To complete the diagnostic of patients with suspected NSTEMI, the acquisition of biomarkers is of immense importance. In particular, measurement of the biomarker of cardiomyocyte injury, ideally the high-sensitivity cTn (hs-cTn) level, must be measured in all patients with suspected NSTEMI (12,24).

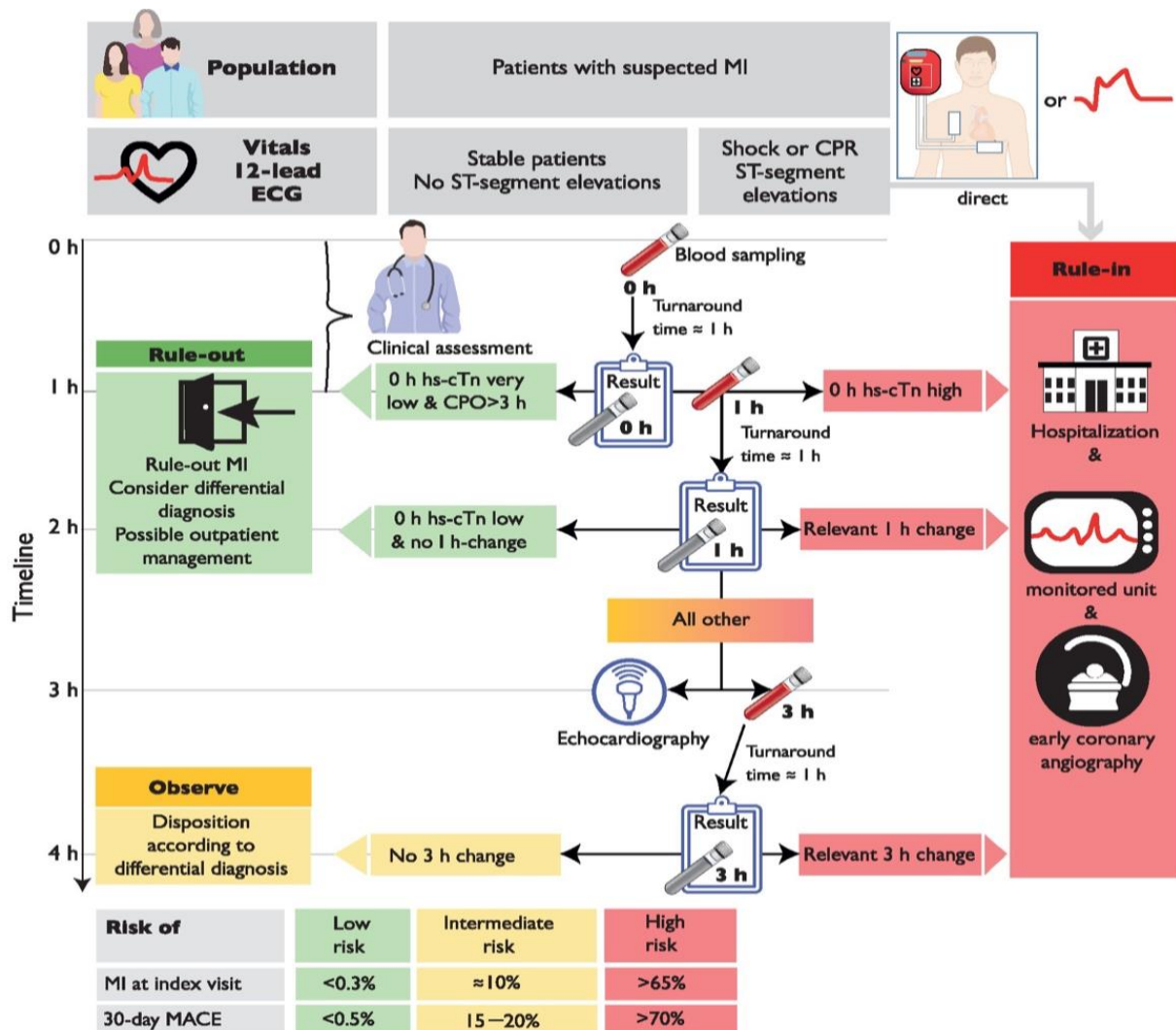
Troponin is a complex of three proteins with subunits troponin C, troponin I, and troponin T. Since cTn C isoforms are also found in skeletal tissue, it has no specificity as a cardiac marker. Cardiac troponin I and T are more specific and are therefore used as hs-cTn markers for cardiac damage. Nevertheless, cTn I and T cannot be used as definitive markers of myocardial ischemia because troponin release can also occur as a consequence of nonischemic damage, for example, in pericarditis, hypertrophic cardiomyopathy, congestive heart failure, and tachy- or bradyarrhythmias. In addition, neurologic conditions such as stroke or subarachnoid hemorrhage or drug toxicity may also increase troponin levels causing a false positive result. Troponin T in particular may also be elevated in patients with renal failure without clinical signs of myocardial damage (14).

In general, cTn levels rise rapidly in patients with MI within 1 hour of the onset of typical symptoms when high-sensitivity assays are used. Troponin levels peak after approximately 12 to 48 hours and remain elevated for days to weeks. If a dynamic increase in hs-cTn levels is above the 99th percentile of healthy individuals, this may indicate MI if the clinical picture is also consistent with myocardial ischemia. The clinical picture includes angina pectoris, new ischemic changes in the 12-lead ECG, and/or other factors (20,24,25).

Technological advances have ameliorate the capacity to identify and quantify cardiomyocyte injury by refining cTn assays. High-sensitivity assays for cTn I and T improve diagnostic accuracy for MI at the time of presentation compared with conventional assays,

particularly in patients presenting early after the onset of chest pain, and allow faster 'rule-in' and 'rule-out' of MI (12,26–28).

The early rule-out approach excludes MI in patients with cTn levels below a risk stratification threshold of 5 ng/L at presentation unless they presented within 2 hours of symptom onset and the test was repeated 3 hours after presentation. Patients with cTn levels above 5 ng/L at presentation are considered “ruled-in” and should be retested 3 hours later. This algorithm is shown in Figure 2. MI is ruled out if the concentrations are constant and remain below the 99th percentile of the diagnostic threshold. Rapid diagnosis of MI using the "ruling-in" or "ruling-out" technique allows earlier initiation of treatment and improves overall patient outcomes (28–30).



**Figure 2.** Timing of the blood draws and clinical decisions when using the European Society of Cardiology 0 h/1 h algorithm.

SOURCE: Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021 Apr 7;42(14):1289–367.

Patients not qualified for the “rule-in” or “rule-out” algorithm should be observed. This group of patients requires a third measurement of hs-cTn at 3 hours and transthoracic echocardiography (TTE) should be considered. TTE is recommended for the evaluation of patients with NSTEMI to detect morphologic and functional cardiac abnormalities suggestive of myocardial ischemia or necrosis. These wall motion abnormalities will present as hypokinesia, akinesia, or dyskinesia and are very early signs of MI. These changes occur before the enzyme or ECG changes, so the absence of these TTE findings is 95% predictive of no MI (31,32).

All in all, for the diagnostic evaluation of NSTEMI, the ESC recommends a detailed anamnesis and clinical assessment of symptoms, a 12-lead ECG, and serial measurement of cTn I and T at 0 h, 1 h, and 3 h, if necessary, to detect dynamic changes. Lastly, measurement of CK /CK- MB and imaging with TTE are also important in the diagnostic evaluation of NSTEMI (12,33).

In terms of outcome, the increase in cTn levels in patients with NSTEMI is an important marker reflecting the high short-term risk of death or nonfatal MI. In this context, a study by Haaf *et al.* comparing cTn T and I found higher accuracy of high-sensitivity cTn T compared with high-sensitivity cTn I in predicting long-term mortality (34).

Other important biomarkers in the diagnostic approach in patients with suspected MI are creatine kinase (CK) and its myocardial band isoenzyme (CK-MB). CK-MB is found predominantly in the myocardium, increases 4 to 6 hours after the onset of cardiomyocyte necrosis, and may remain elevated for 24 to 48 hours. The CK-MB shows relative sensitivity but limited cardiac specificity because it is also found in skeletal muscle. For the diagnostic evaluation of NSTEMI, CK-MB may be of clinical relevance in certain clinical situations when used in combination with cTn I and T. Because CK-MB falls more rapidly after MI, it may be useful for predicting cardiomyocyte injury and as an early determinant of reinfarction (35,36).

In addition, other laboratory values, including estimated glomerular filtration rate, serum creatinine, glucose, and B-type natriuretic peptide might add important information regarding possible outcomes. They should be determined in all patients with NSTEMI and are key elements of the Global Registry of Acute Coronary Events (GRACE) risk score. The GRACE risk score predicts the mortality in the hospital and within 6 months after discharge. The score includes eight variables for risk prediction, such as age, systolic blood pressure, pulse rate, serum creatinine, cardiac arrest at admission, elevated cardiac biomarkers, ST deviation, and lastly Killip class at presentation. For different patient groups, there are several GRACE risk scores, each predicting different outcomes (20,37–39).



In the context of risk assessment at MI, NSTEMI is highly associated with comorbidities and therefore has higher short- and long-term mortality than other coronary syndromes. Mortality in the early stages after NSTEMI is more likely to be due to ischemic or thrombotic events, whereas mortality in the later stages of NSTEMI is more attributable to the progression of atherosclerosis and noncardiovascular causes. This increases the importance of early risk stratification to develop appropriate treatment options (12,14,20,40).

### **1.3.1. Therapy of NSTEMI**

In general, relief of pain, dyspnea, and anxiety is important in patients with MI and is usually among the first treatment options in prehospital care or the emergency department. Relieving chest pain is not only important for comfort, but also decreases sympathetic nervous system activation as subsequent vasoconstriction increases cardiac workload. Opioids such as morphine are commonly used. Still, morphine is absorbed more slowly, its antiplatelet effect is delayed, and in susceptible patients it might result with early treatment failure (41). In addition, administration of oxygen is indicated in hypoxic patients when oxygen saturation is below 90% or when patients are in respiratory distress. The use of oxygen when oxygen saturation is above 90% is not recommended due to evidence that hyperoxia can be harmful in uncomplicated MI (42). Finally, anxiety, which is a natural reaction to the pain and circumstances following a MI, should be relieved by reassuring patients or mild anxiolytics such as benzodiazepines in very anxious patients (20).

Administration of nitroglycerin is recommended in patients with signs of heart failure or uncontrolled hypertension. Furthermore, patients with persistent ischemic symptoms should receive treatment with beta-blockers, which should be continued as chronic therapy unless the patient has overt heart failure (12,20,43).

### **1.3.2. Pharmacological Therapy**

Vulnerable atherosclerotic plaques in the coronary arteries causing ACS may trigger thrombus formation and worsen the diagnosis and prognosis of MI. Platelet activation and the coagulation cascade play an important role in the early phase and progression of ACS. Since this process is partly controlled by platelets, the treatment of MI in the acute phase should always include antiplatelet agents. Currently, there are three different classes of antiplatelet agents used for therapy during and after MI. First, the cyclooxygenase-1 (COX -1) inhibitor, aspirin; second, the adenosine diphosphate P2Y12 receptor antagonists, clopidogrel, prasugrel,

ticagrelor, and cangrelor. And finally, the glycoprotein IIb/IIIa inhibitors (GPI), abciximab, eptifibatide, or tirofiban (12,14).

Dual antiplatelet therapy (DAPT), which includes aspirin and a potent P2Y<sub>12</sub> receptor inhibitor such as ticagrelor or prasugrel, is recommended as standard therapy for NSTEMI patients. The initial dose of aspirin for a MI patient is 150-300 mg, for ticagrelor 180 mg, for prasugrel 60 mg, and for clopidogrel 300-600 mg (12,44).

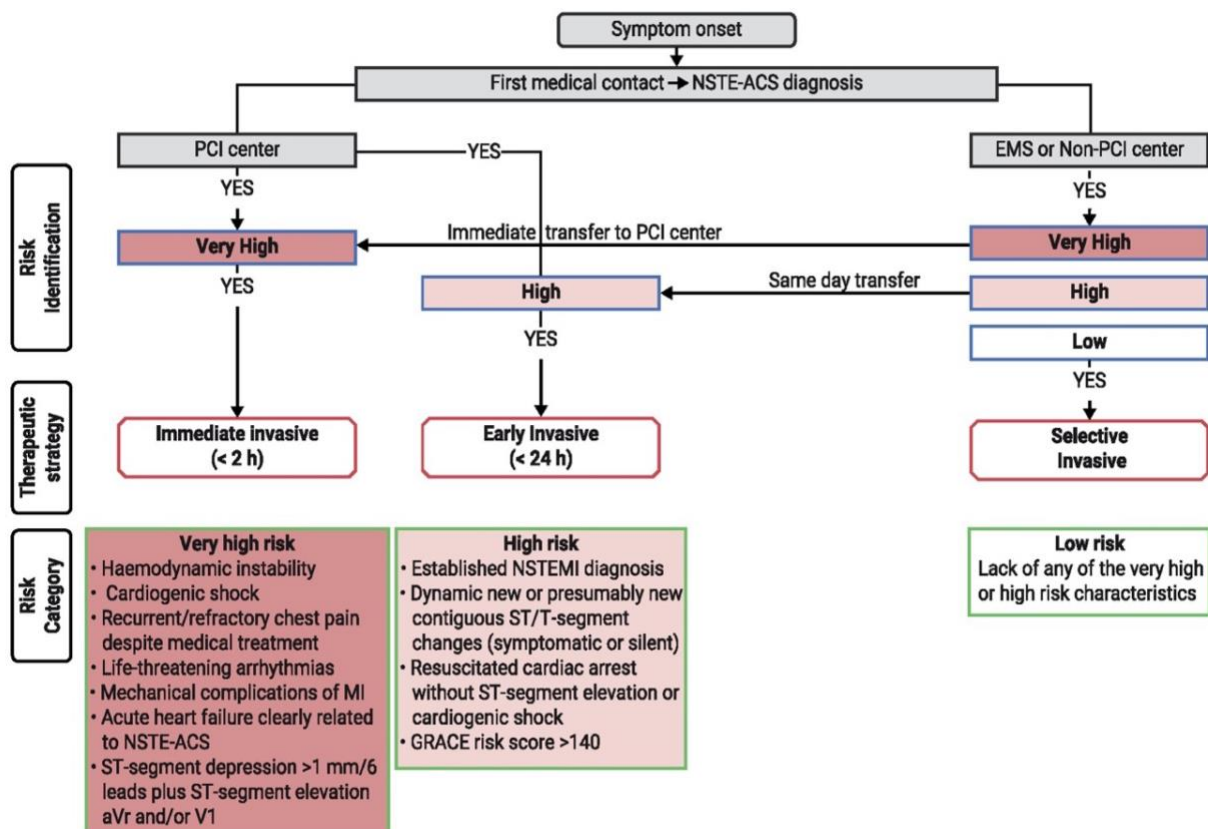
Ticagrelor and prasugrel are more potent and have a faster onset of action compared with clopidogrel. However, prasugrel is contraindicated in patients older than 75 years of age, body weight less than 60 kg, and in patients with a history of stroke or transient ischemic attack. Ticagrelor, on the other hand, may cause transient dyspnea but is still recommended for all patients with ACS, regardless of whether the patient is to be treated invasively or conservatively. A contraindication to ticagrelor or prasugrel leads to an indication for the less effective clopidogrel. The antiplatelet agent clopidogrel shows beneficial effects when given in addition to aspirin, although the risk of major bleeding is increased in these patients (12,14,45,46).

Besides antiplatelet therapy, anticoagulation is also important in MI to inhibit the activated coagulation cascade. In NSTEMI an anticoagulant such as unfractionated heparin (UFH) is indicated at the time of diagnosis and especially during invasive revascularization therapy (12).

Postinterventional and maintenance therapy for NSTEMI patients includes DAPT consisting of lifelong aspirin therapy and an additional potent P2Y<sub>12</sub> receptor inhibitor for 12 months (47). In NSTEMI patients with stent implantation and a high risk of bleeding, the P2Y<sub>12</sub> receptor inhibitor should be discontinued after 3-6 months. Doses for maintenance therapy include 75-100 mg for aspirin, 60/90 mg for ticagrelor, and 10 mg for prasugrel. In NSTEMI patients with AF undergoing PCI, antithrombotic therapy consists of triple therapy for up to 1 week after PCI, including DAPT (aspirin and P2Y<sub>12</sub> receptor inhibitor) and a NOAK. Non-vitamin K antagonist oral anticoagulants (NOAKs) include apixaban, dabigatran, edoxaban, and rivaroxaban. They are important in the inhibition of thrombin production induced by plaque rupture in the coronary artery. After 1 week of triple therapy, dual therapy with a NOAK and single antiplatelet therapy (preferably clopidogrel) is initiated for up to 12 months, and beyond that, NOAK therapy alone is further recommended (12,14,15,17,33).

### 1.3.3. Invasive treatment

After initiating treatment with antianginal, antiplatelet, and anticoagulant agents, patients are advised to undergo PCI and are therefore classified into 3 pathways. To initiate invasive treatment in NSTEMI patients, initial risk stratification is recommended, in which the risk criteria of NSTEMI patients are assessed and divided into 3 groups (Figure 3). The groups are classified as very high, high, and low risk, with criteria including hs-cTn measurements, GRACE risk score > 140, and dynamic or suspected new ST-segment changes. The appropriate group leads to the appropriate treatment for the individual patient and its timing, as shown in Figure 3. Highly unstable patients at very high risk require immediate invasive angiography within 2 hours if at least one of the very high-risk criteria shown in Figure 3 applies. An early invasive strategy within 24 hours is recommended in high-risk patients who meet at least one criterion, such as a GRACE risk score > 140, an established NSTEMI diagnosis, or other criteria shown in Figure 3. In low-risk patients, a selective invasive strategy is recommended after appropriate ischemia testing or evidence of obstructive CAD (12).



**Figure 3.** Selection of non-ST-segment elevation acute coronary syndrome treatment strategy and timing according to initial risk stratification.

SOURCE: Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289–367.

Revascularization strategies for NSTEMI patients do not differ from invasive assessment and revascularization strategies for other manifestations of CAD. NSTEMI patients benefit from early intervention, but if time to PCI is delayed, fondaparinux is recommended, and an unfractionated heparin (UFH) bolus is given during PCI (12).

The main technical aspects of invasive revascularization in NSTEMI patients are similar to those in STEMI patients and are discussed in more detail in the section on the treatment of STEMI. The exception is revascularization therapy with fibrinolytics, which is not recommended in NSTEMI patients. Of patients with NSTEMI, 5-10% require coronary artery bypass grafting (CABG). Compared with PCI, CABG shows a significant reduction in the risk of mortality, MI, or stroke. In this context, an optimal timing for nonurgent CABG in NSTEMI patients has not been established and should be assessed individually (12,48,49).

#### **1.4. Acute coronary syndrome with ST- Elevation**

Management of STEMI, including diagnosis and treatment, begins with initial medical contact. As with NSTEMI, the diagnosis of STEMI is based on symptoms of myocardial ischemia such as chest discomfort and signs in ECG recordings. 12-lead ECG recording and routine blood sampling for serum markers should be performed as soon as possible if STEMI is suspected (50).

A typical ECG recording of a STEMI confirms the diagnosis with a specificity of 91%. At least 2 additional 12-lead ECGs should be recorded to confirm the diagnosis (16). The characteristic finding of STEMI on ECG is ST-segment elevation, which indicates ongoing ACS if at least 2 contiguous leads display ST-segment elevations. In men younger than 40 years, these elevations (measured at the J-point) are  $\geq 2.5$  mm, and in men older than 40 years,  $\geq 2$  mm. In women, the ST-segment elevations in leads V2 and V3 are  $\geq 1.5$  mm and/or  $\geq 1$  mm in the other leads. If posterior MI is suspected, the use of additional posterior chest wall leads V7, V8, and V9 should be considered. If inferior MI is suspected, the use of additional right precordial leads V3R and V4R should be considered. After recording a 12-lead ECG, it is recommended that ECG monitoring with defibrillator capacity be initiated as soon as possible to detect life-threatening arrhythmias and to allow rapid defibrillation if needed (51).

### 1.4.1. Therapy of STEMI

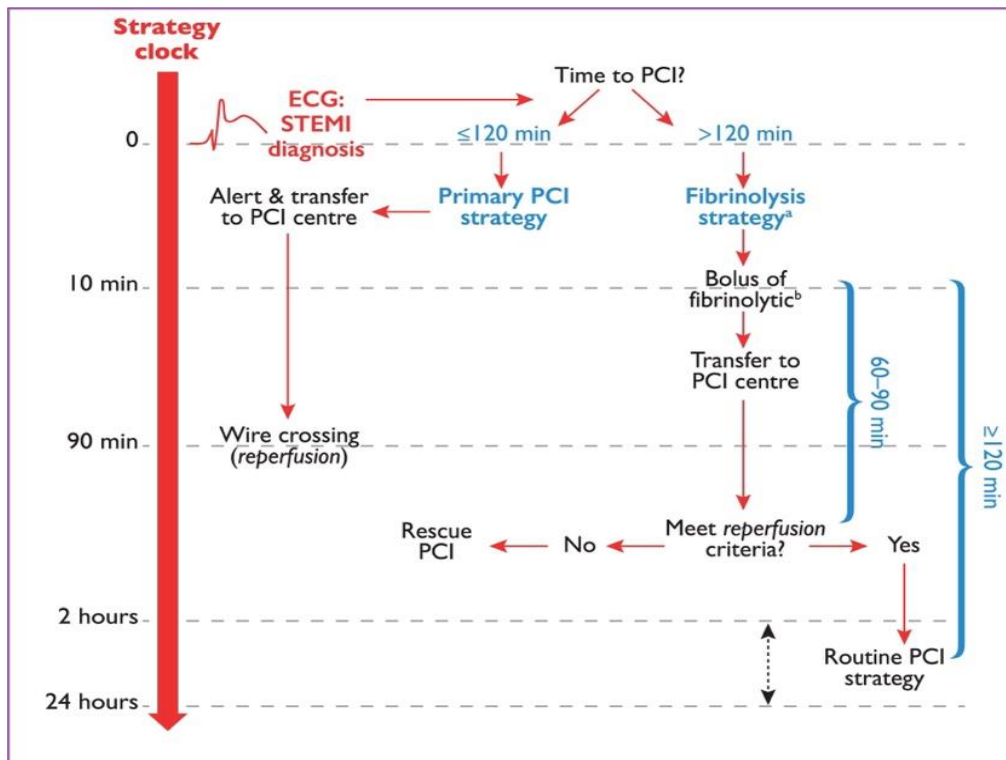
Unlike NSTEMI, invasive treatment for STEMI does not include risk stratification to determine time intervals of invasive reperfusion therapy. Rapid diagnosis of STEMI is critical to initiate reperfusion therapy as soon as possible (43).

Pharmacologic therapy is similar to strategies used in NSTEMI. As part of periprocedural management, antiplatelet therapy with DAPT is recommended in patients undergoing PCI. Potent P2Y<sub>12</sub> receptor inhibitors such as ticagrelor and prasugrel are administered along with aspirin once a diagnosis of STEMI has been made. In addition, cangrelor administration should be considered in patients not receiving P2Y<sub>12</sub> receptor inhibitors (52). Routine use of GPI in primary PCI is also not recommended but should be considered when there is evidence of no-reflow or thrombotic complication (43).

In addition to antiplatelet therapy, anticoagulant therapy is recommended for all patients during the primary PCI and should include the use of UFH and enoxaparin, but fondaparinux is not recommended. In this context, the administration of clopidogrel in early treatment may have a beneficial effect on PCI (43,53).

In STEMI patients, the treatment strategy of choice is revascularization with primary PCI. This should take place as soon as the diagnosis of STEMI is made by the first medical contact, usually the emergency medical system. Reperfusion therapy is indicated in all patients with persistent ST-segment elevation and symptoms of myocardial ischemia of less than 12 hours' duration. In the treatment of STEMI, the most important parameter is time, because “time is muscle” in terms of myocardial cell damage by MI. Therefore, different time frames for reperfusion strategies are estimated for the time after diagnosis, as shown in Figure 4 (12,20).

Patients transferred to a primary PCI-capable centers should receive a primary PCI within 60 minutes or less. For patients transferred to PCI-capable hospitals from hospitals without the PCI option, the maximum time to primary PCI should be minutes. In general, the goal of  $\leq 120$  minutes from the onset of diagnosis to primary PCI represents the maximum expected delay. If primary PCI is not possible within this time frame ( $\geq 120$  minutes), fibrinolysis therapy should be initiated within 10 minutes. After 60–90 minutes, an evaluation of fibrinolysis therapy should be performed to distinguish other treatment options. Failure of fibrinolysis at this stage would indicate immediate rescue PCI, whereas success of fibrinolytics would result in routine PCI between 2 and 24 hours after initiation of fibrinolysis. These target times according to reperfusion strategy are shown in Figure 4 (43,54).



**Figure 4.** Maximum target times according to reperfusion strategy selection in patients presenting via EMS or in a non-PCI center.

SOURCE: Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289–367.

### 1.4.2. Primary percutaneous coronary intervention

In STEMI patients, primary PCI is the preferred reperfusion therapy, which is superior to fibrinolytic treatment because it reduces mortality, reinfarction, and stroke (26). In the procedure of PCI, the access site via the radial artery is preferred because the risk of bleeding is lower compared with the transfemoral approach. During primary PCI, coronary stenting of the infarct related artery is the preferred technique and is recommended over balloon angioplasty (55). Stenting with new-generation drug-eluting stents (DES) is recommended over bare-metal stents because the former reduces the risk of targeted reintervention and all-cause mortality compared with bare-metal stents (56). The routine use of thrombus aspiration during primary PCI is not recommended because no benefit to clinical outcomes has been demonstrated. While it is usually recommended to treat the artery related to the infarction (culprit vessel), the evidence for preventive revascularization of other significant stenoses in the coronary arteries is conflicting. Approximately 50% of STEMI patients have multivessel disease, so revascularization of other arteries should be considered before hospital discharge or even during primary PCI. This is supported by studies showing the benefit of complete revascularization in terms of a significant reduction in primary outcomes and repeated revascularizations (43,57,58).

### **1.4.3. Fibrinolysis and pharmacoinvasive strategy**

Although primary PCI is the preferred reperfusion strategy for the majority of patients with STEMI, fibrinolytic therapy is an important alternative strategy. If primary PCI cannot be initiated in a timely manner ( $\leq 120$  minutes), fibrinolytic therapy should be started within 10 minutes of the diagnosis of STEMI if contraindications are not present. If contraindications are present, the life-saving effects of fibrinolytic agents should be weighed against the life-threatening side effects. Transfer to the primary PCI should be considered sooner if the patient presents after 3 hours, because the clinical benefit and efficacy of fibrinolytic therapy diminish with increasing time from symptom onset. In general, the patient should be transferred to a PCI center regardless of the success or failure of fibrinolysis. In case of failure of fibrinolysis, reocclusion, or reinfarction, immediate angiography and rescue PCI is indicated. On the other hand, successful fibrinolysis does not exclude a transfer to a PCI center, as early routine angiography followed by PCI is recommended in these patients (59). Early routine angiography after fibrinolysis shows a lower rate of reinfarction and recurrent ischemia. Additional PCI, benefits with a decrease in adverse events such as stroke or major bleeding (60). All in all, this procedure should be performed in a time frame of 2-24 hours (43).

However, fibrin-specific agents for fibrinolysis include tenecteplase, alteplase, or reteplase and are recommended, with tenecteplase given at half the dose in patients older than 75 years (54). Co-therapy with fibrinolysis includes antiplatelet agents and anticoagulants. The former include aspirin and clopidogrel, which reduce the risk of cardiovascular events and overall mortality in patients receiving fibrinolysis therapy (61). Anticoagulation co-therapy is recommended until revascularization (if performed) or for the duration of hospitalization of up to 8 days. In this context, enoxaparin is preferred over UFH and is administered intravenously at baseline, followed by subcutaneous administration until PCI (43,62).

In general, fibrinolytic therapy is associated with a slightly increased risk of intracranial hemorrhage, so special attention should be paid to contraindications to fibrinolytic therapy. These include previous intracranial hemorrhage, stroke, ischemic stroke in the previous 6 months, central nervous system damage or neoplasm, recent major trauma, surgery, or head injury within 1 month, and other factors that militate against fibrinolytic therapy (43,54).

### **1.4.4. Coronary artery bypass graft surgery**

CABG surgery should be considered in patients with an infarct-related artery with unsuitable anatomy for PCI and also for large myocardial areas at risk or cardiogenic shock. The time to reperfusion is long, therefore the probability of myocardial recovery affecting

prognosis is low and surgical risks are increased. Studies show a higher mortality rate in patients undergoing early CABG, with the highest mortality in patients in whom surgery was performed on day MI. Therefore, a waiting period of 3 or more days is recommended in hemodynamically stable patients who are not at high risk for recurrent ischemic events (43,63).

## **1.5. Acute coronary syndrome in elderly**

The current incidence and prevalence of ACS in elderly patients older than 75 years is unknown. However, in the United States, patients older than 75 years account for approximately 30% to 40% of all hospitalizations with ACS (6).

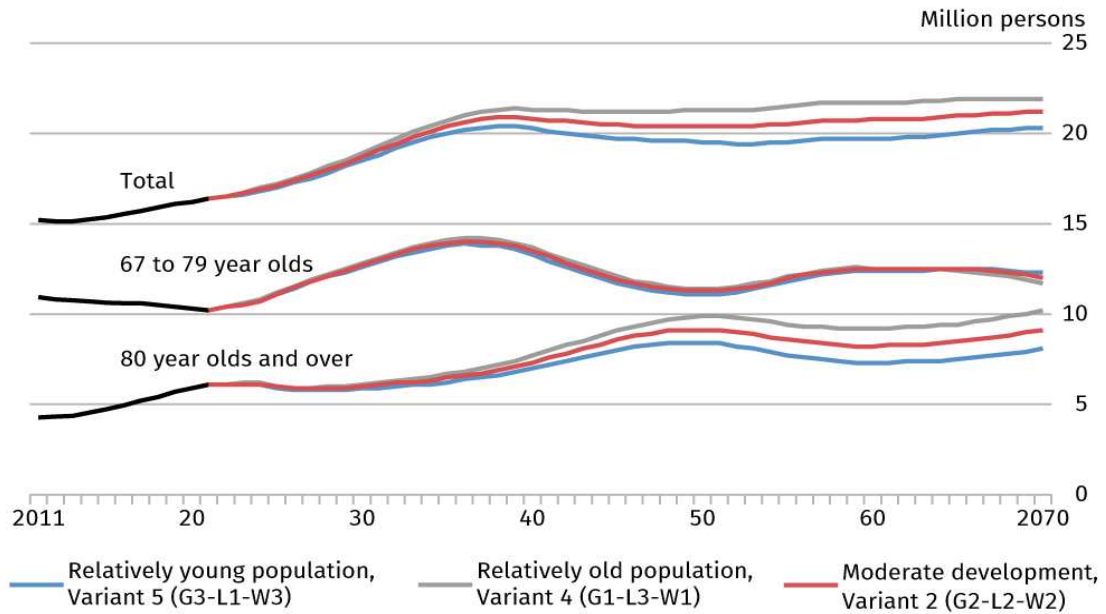
Due to improved prevention and treatment, the number of deaths from cardiovascular disease is steadily declining in Western countries. Paradoxically, the incidence of ACS in the elderly is predicted to increase for three reasons. First, the increased life expectancy of the population. According to the Federal Statistical Office in Germany, life expectancy has doubled since the 19th century due to better living conditions. This trend toward an aging population can be seen in the life expectancy of today's newborns. A newborn boy may expect a life expectancy of 78 years, while girls can live to 83 years. Compared to 1960, when life expectancy was 68 years for boys and 72 years for girls, the increasing trend toward an aging population shows an increase in life expectancy of about 10 years for both sexes. The average age at death in Germany has thus risen linearly over the last 60 years (64,65).

Second, the increasing number of people over 65 in the population, which is due to an advanced demographic change in Germany. Today, more than one in four people in Germany is 60 or older. In 2050, this proportion will already have risen to more than one-third. This means a 23-26% increase in the number of people over 67 and a 12% increase in the number of people over 80 by 2050, as shown in Figure 5 (65,66).



### Population aged 67 years or over

From 2022, results of the 15th coordinated population projection



© Statistisches Bundesamt (Destatis), 2022

**Figure 5.** Aging of the German population until 2070.

SOURCE: [https://www.destatis.de/EN/Press/2022/12/PE22\\_511\\_124.html](https://www.destatis.de/EN/Press/2022/12/PE22_511_124.html)

Finally, because of improved therapies, there are increasing numbers of older adults with a history of CAD. This also suggests that ACS is becoming more common in the latter stages of life (67,68). The increase in ACS with age is accompanied by a concomitant increase in the incidence of CVD with increasing age. According to an update of the American Heart Association (AHA) in 2019 by Benjamin *et al.*, the incidence of CVD in patients aged 40 to 60 years averaged 35–40%. In patients aged 60–80 years, the incidence was 75–78%, whereas it exceeded 85% in patients older than 80 years. In addition, the mortality rate of CAD in the 75–84 age group is almost twice that in the 65–74 age group (69,70).

The high mortality rates in older age groups are directly attributable to age-related risk factors. These include age-related pathophysiologic mechanisms that cause cardiovascular aging and other causes such as frailty. One pathophysiological mechanism associated with aging is impaired endothelial function. This mechanism is mediated mainly by decreased nitric oxide bioavailability. Consequently, the decline is associated with decreased vasodilation and a reduced ability of, for example, the coronary arteries to upregulate coronary blood flow in response to increased oxygen demand by the myocardium. As a result, older adults are at increased risk of type 2 MI and NSTEMI (71). In this context, type 2 MI has a higher mortality compared with type 1 MI, which is due to early and noncardiovascular death (72).

Another pathophysiological mechanism associated with aging is the increase in reactive oxygen species. This contributes not only to a further decrease in nitric oxide bioavailability and consequently to increased endothelial dysfunction, but also to the persistence of chronic systemic inflammation. Aging is also associated with immune system dysregulations, which include high blood levels of proinflammatory immunogenic stimuli. These changes contribute to chronic inflammation during aging, which is one of the most common age-related changes (73–75).

All in all, impaired endothelial function and age-related chronic inflammation are major drivers of atherosclerosis and thereby contribute to an increasing prevalence of CAD in older people (6).

Other age-related alterations in the cardiovascular system encompass a gradual decline in attainable maximum heart rate and a reduced sensitivity to  $\beta$ -adrenergic activation, both contributing to diminished cardiac output during periods of stress. Under normal circumstances this decrease is not directly linked to ischemia, but in elderly patients with CAD the susceptibility to acute and chronic heart failure increases. Moreover, the aging process is also associated with an inclination towards thrombosis rather than fibrinolysis, resulting in an imbalanced equilibrium. Consequently, elderly are more prone to the development of venous thromboembolic disorders and arterial clot formations. This includes the occurrence of coronary thrombosis, which can lead to type 1 myocardial infarction, as well as the formation of left atrial thrombi in patients with atrial fibrillation (76–78).

In the elderly population, the prevalence of all types of MI is generally higher due to the underlying pathophysiological changes associated with aging. Elderly individuals presenting with ACS often exhibit a range of diminished functional reserve, varying from modest impairment to severe deterioration. The clinical manifestation, course of the disease, treatment decisions, prognosis, and response to ACS therapy may be significantly influenced by the presence of one or more geriatric syndromes. These syndromes refer to age-related physiological vulnerabilities that set older patients apart from younger patients. Geriatric syndromes encompass frailty, multimorbidity, polypharmacy, and cognitive impairment, all of which contribute to the complexity of managing ACS in the elderly (6).

Frailty is defined by physiological deterioration of multiple organ systems and consequent increased susceptibility to stressors. Therefore, frailty is related to adverse outcomes such as falls, delirium, and disability (79,80). It is more common in women than in men and in frail with CVD because of chronic inflammation at older ages (81,82). Frail patients with CVD tend to have poorer outcomes and tolerate medications and procedures more poorly.

Finally, frailty in older people with NSTEMI who receive invasive angiography leads to an increase in all-cause mortality, stroke, major bleeding at one year, and MI, (77,83).

Other geriatric syndromes include multimorbidity, defined as  $\geq 2$  chronic diseases occurring simultaneously. It is prevalent in older people with CVD, affecting approximately 70% of all adults older than 75 years (84). Thus, ACS occurs in association with multiple comorbidities, that may conflict with therapeutic strategy. In addition, the elderly with multiple comorbidities are often associated with polypharmacy, defined as the chronic use of  $\geq 5$  medications, which ultimately increases the risk of adverse drug interactions and hospitalizations (6,85). Lastly, cognitive impairment or dementia as another geriatric syndrome in elderly are in the setting of ACS associated with deterioration in cognitive function after an acute event (6).

All in all, geriatric syndromes have an impact on health outcomes of elderly patients with ACS. In addition, ACS may also exacerbate the burden of underlying geriatric syndromes. A holistic approach to the management of ACS addresses the rather complex issues associated with ACS in elderly and involves an personalized access to treatment that scrutinize coexisting medical conditions and overlapping health care aspects (6,86).

ACS, including STEMI and NSTEMI, is associated with increased morbidity and death in elderly patients. In patients older than 85 years, mortality is at least three times higher than in younger patients younger than 65 years (87). In particular, for NSTEMI, mortality is at least twice as high in patients older than 75 years compared with patients younger than 75 years (88). Therefore, in patients diagnosed with NSTEMI, age is a predictor of in-hospital and 6-month mortality. STEMI is generally less common than NSTEMI in elderly patients and has significant in-hospital mortality (89).

After an ACS event, elderly people with a higher burden of geriatric syndromes are generally more vulnerable to disability, loss of independence, and impaired quality of life and ability to care for themselves. Therefore, patient-centered goals and outcomes must always be evaluated with a focus on quality of life. It is crucial to acknowledge that critical outcomes in guiding the management of ACS among older patients burdened with geriatric syndromes or end-stage cardiovascular disease include goals related to the time spent at home and other personal preferences that contribute to an improved quality of life (90).

Thus, good assessment and individualized treatment are important in the management of ACS in elderly. However, because of the historical underrepresentation of elderly patients with ACS in clinical trials, there is a lack of specific pharmacologic and invasive treatment

guidelines for elderly patients. Therefore, the following sections provide recommendations and results of clinical trials, which are described in more detail in subsequent sections (91,92).

### **1.5.1. Symptoms and diagnosis in elderly patients**

In the evaluation of a suspected ACS in elderly patients first step should be the classification of symptoms (93). In this patient group, symptoms are more likely to be affected by geriatric syndromes, which diminish the diagnostic specificity and sensitivity. The clinical presentation of elderly with ACS is usually not associated with chest pain. Symptoms in this group of patients are most commonly atypical, with dyspnea being the most common, whereas syncope, presyncope, malaise, or confusion are less frequently encountered. Therefore, initial diagnosis of ACS in elderly patients with atypical symptoms is complicated by misdiagnosis. This leads to undertreatment, not only because of their higher susceptibility to complications, but also because these patients are less likely to receive effective pharmacotherapy for MI compared with patients with typical symptoms. Ultimately, elderly ACS patients with atypical presentation experience higher hospital morbidity and mortality (12,94). A national study by Hsia *et al.* showed that chest pain in those over 80 years is more likely to have an underlying noncardiac cause in more than half of the patients. Therefore, the majority of chest pain that occurs as a typical symptom of ACS is not an ACS (95).

Besides the evaluation of clinical symptoms, ECG and biomarkers are the key steps in the initial evaluation of ACS. Nevertheless, most elderly people already have some abnormalities in their baseline ECG, which often complicates ECG interpretation when ACS is suspected. In addition, hs-cTn assays provide a significant diagnostic performance for the presence of ACS in elderly patients and help identify the cause of injury and indicate myocardial ischemia. Numerous asymptomatic elderly adults are identified with biomarkers that are chronically high or fluctuate outside the diagnostic values for MI. Fluctuations in hs-cTn levels are associated with age-related decline in renal function, hormonal changes, and body composition changes. Chronically high hs-cTn levels are associated with fibrosis and progressive changes in left ventricular structure, which are common in the elderly. Therefore, assay specificity is reduced in elderly patients, and evaluation of the rise and fall of hs-cTn is critical in this patient population (96–99).

Finally, because of the particular complexity of elderly patients presenting with suspected ACS, the diagnosis of ACS in the elderly usually cannot be confirmed or ruled out by history, physical examination, and ECG alone (100).

Decisions about the management of elderly patients should be based on ischemic and bleeding risk, estimated life expectancy, comorbidities, need for noncardiac interventions, quality of life, frailty, cognitive and functional impairment, patient values and preferences, and estimated risks and benefits of revascularization (101).

### **1.5.2. Pharmacotherapy in elderly patients**

Physiological changes associated with aging impact the pharmacokinetics and pharmacodynamics of various medications used for ACS. In the elderly, alterations in vascular and myocardial function can result in an amplified response to specific drugs, thereby influencing their pharmacodynamics (76). Therefore, geriatric syndromes, increased atherothrombotic risk, and higher bleeding risk in older adults must be considered in the medical therapy for ACS in elderly patients (102).

According to recent revascularization guidelines, clopidogrel is preferred as a P2Y<sub>12</sub> inhibitor in elderly patients with DAPT therapy after ACS due to its lower bleeding risk compared with ticagrelor (103). Further therapy with  $\beta$ -blockers may be beneficial because of their antiischemic effect but should be administered with caution in elderly patients because of their side effects including bradycardia and heart failure in the acute setting (104).

All in all, elderly patients are a high-risk group requiring careful evaluation of ischemic and bleeding risk. Therefore, antithrombotic treatment should be based on an individualized strategy considering age, comorbidities, frailty, and patient preferences (102).

### **1.5.3. Percutaneous revascularization in elderly patients**

PCI is considered the optimal reperfusion strategy because of the minimized risk of bleeding but is used in only a small proportion of patients with STEMI older than 85 years of age, although the primary PCI is associated with a significant reduction in mortality, reinfarction, and stroke in elderly STEMI patients compared with the fibrinolysis strategy (105,106).

Although revascularization rates are low in elderly adults, early primary PCI is beneficial in older adults (107). In this regard, invasive strategy is superior to conservative treatment in older NSTEMI patients in terms of reducing MI and recurrent revascularization (108). In addition, invasive therapy may reduce mortality at the expense of a higher risk of bleeding (109). Therefore, the radial access should be superior to the femoral approach during PCI in elderly patients to reduce the risk of bleeding and also to reduce the risk of acute kidney injury as a complication of coronary intervention with contrast agents (6,110).

Cardiovascular and noncardiovascular risk evaluation before reperfusion therapy is critical to achieve optimal outcomes in elderly patients with NSTEMI (27). Therefore, risk assessment scores such as the GRACE score, which is heavily age-weighted, are used (111). This leads to the classification of elderly patients with NSTEMI as high-risk and consideration of early invasive therapy to reduce the incidence of recurrent ischemia and recurrent revascularization and shorten the length of hospital stay (103).

In this context, the frailty of patients with STEMI and NSTEMI should also be investigated because frailty is associated with increased mortality and is associated with more difficult angiographic findings, such as severe calcifications or high-risk lesions, regardless of age (112,113). In addition, frail adults among NSTEMI patients have a higher incidence of unfavorable clinical outcomes compared with robust patients, including MI, repeat revascularization, stroke, significant bleeding, and all-cause death at 1 year (83).

All in all, optimal reperfusion therapy for elderly patients with ACS is similar to that for younger patients and includes PCI.

#### **1.5.4. Surgical revascularization in elderly patients**

Most surgical risk scores, as well as other risk stratification systems, do not incorporate an assessment of frailty or other geriatric syndromes, which are major determinants of outcomes following cardiac surgery in elderly patients. Frailty is associated with an increased likelihood of in-hospital death and is an independent predictor of serious complications after CABG (114,115).

Compared with CABG, PCI is associated with increased mortality with advanced age. In addition, CABG is associated with a lower risk of primary outcome in older patients with LM or multivessel CAD. This advantage is mainly due to a lower risk of repeated revascularization and MI (116,117). Nevertheless, a cardiac team that includes geriatric expertise is recommended for the revascularization strategy in elderly patients to assess frailty, multimorbidity, cognition, and other age-related elements of care (6).

Finally, procedural complications are more likely to occur during revascularization with both PCI and CABG in elderly patients, including MI, heart failure, stroke, renal failure, and bleeding (118).



## **2. OBJECTIVES**



## **2.1. Aims of the study**

The aim of the study was to evaluate the coronary lesion pattern, details of percutaneous intervention and assessment of the short-term outcomes in old and very old patients with ACS in comparison to younger patients.

## **2.2. Hypothesis**

Elderly patients can safely and effectively undergo percutaneous coronary intervention for acute coronary syndrome.

### **3. SUBJECTS AND METHODS**

### **3.1. Study design and subjects**

The Department for Cardiology and Angiology at the REGIOMED Hospital Coburg in Germany served as the site for this retrospective monocentric study. Between 01.01.2022 and 01.10.2022, the study's obtained data were gathered from the hospital information system (Orbis). Since the collected data was made anonymous, no inferences about specific patient data are possible. Patients with ACS followed by PCI or coronary angiography are included in the data sets gathered. They were all treated in accordance with the most recent recommendations made by the European Society of Cardiology (ESC). These patients were split into the young group and elderly group. All patients equal or over 75 years old who had ACS followed by PCI or coronary angiography between January 2022 and October 2022 make up the elderly group. All patients with ACS followed by PCI or coronary angiography who are younger than 75 years old are included in the young group.

### **3.2. Variables**

From the above-mentioned data set we received multiple parameters. We used sex and age as standard characteristics. Further parameters include risk factors, concomitant diseases, previous cardiac diseases and revascularization, ECG at admission, Ultrasound findings, laboratory values, mean hospital stay, and mortality. Additionally, data on coronary intervention and following complications, and mortality have been gathered.

### **3.3. Statistical analysis**

The statistical analyses were performed using IBM-SPSS version 28.0 (IBM Corp. Released 2021, Version 28.0. Armonk, NY, USA) and JASP Version 0.16.3 (JASP Team, University of Amsterdam, Amsterdam, The Netherlands). Normal continuous variables are presented as mean  $\pm$  standard deviations. Categorical variables are presented as number and percentage of total. For our study the statistical significance is determined as  $P < 0.05$ . Normally distributed data was compared with the Student T Test. The data was presented using mean and standard deviation.

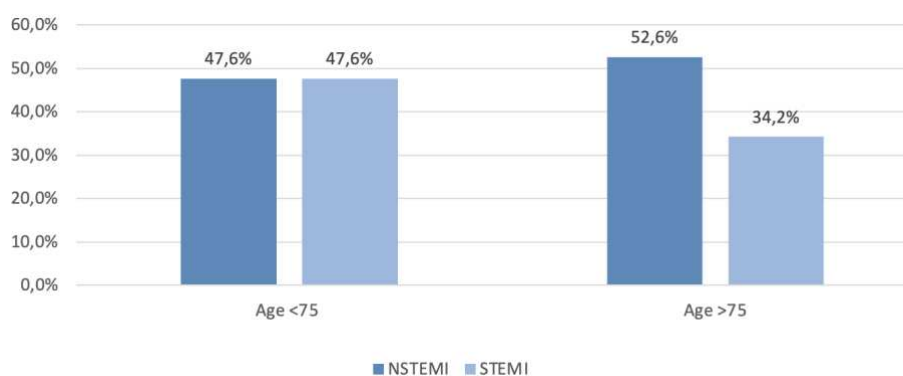
### **3.5 Ethical approval**

This study was ethically approved by the Institutional Review Board of the REGIOMED Medical School on 16<sup>th</sup> November 2022. All data and rights of patients were protected in accordance with the World Medical Association Helsinki declaration of 2013.

## **4. RESULTS**

## 4.1 Differences in age groups

The final study comprised 101 patients who underwent PCI or coronary angiography as part of their treatment for ACS (29 females (28.7%) and 72 males (71.3%)). Age ranged from 41 to 97 years old, with a mean age of 69 years. A total of 38 patients were equal or older than 75 years (elderly group) comparing to 63 patients (62.4%) in the younger group. In the young group, 47.6 percent (30 patients) and in the elderly group, 52.6 percent (20 patients), were diagnosed with NSTEMI (Figure 6). Contrarily, in the elderly group, 34.2 percent (13 patients) and in the young group, 47.6 percent (30 patients) suffered from STEMI (Figure 6). While the remaining patients—3 from the young group and 5 from the elderly group—had coronary angiography to rule out an occlusion, these individuals received PCI.



**Figure 6.** Comparison of the number of patients diagnosed with NSTEMI or STEMI in the elderly (Age  $\geq$ 75 years) and young group (Age <75 years).

Table 1 shows the comparison of the risk factors, comorbidities and previous cardiac diseases of both groups. Risk factors in both groups were comparable. Obesity shows a higher incidence in younger patients and arterial hypertension represents a higher incidence in the elderly group (Table 1), but was also statistically comparable.

Table 1 shows our comparison of the concurrent disorders that affected both groups. The prevalence of chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), and stroke between the two age groups does not differ significantly. Intriguingly, the elderly group had a significantly higher prevalence of CKD, whereas the young group had a higher incidence of COPD and PAD.

In addition, our study included the comparison of previous cardiac diseases in both groups. The results in Table 1 show no significant differences between the elderly and young group. However, the incidence of previous CAD with one-, two- or three-vessel disease was higher in the elderly group compared with the young group. Previous one-vessel disease included 15.8% in the elderly and 3.2% in the young group, whereas previous two-vessel

disease included 7.9% in the elderly and 6.4% in the young group, and lastly previous three-vessel disease included 18.4% in the elderly and 11.1% in the young group. Additionally, previous three-vessel disease was the most common form of CAD in both groups. Patients with heart insufficiency and a New York Heart association (NYHA) classification of over class II showed a higher incidence in the elderly group in comparison to the young group. Furthermore, previous AMI, Arrhythmias, Pacemaker, previous PCI or CABG also showed a higher incidence in the elderly group, as seen in Table 1.

**Table 1.** Comparison of risk factors, comorbidities and previous cardiac diseases of the young and elderly group.

<b>Comorbidities</b>	<b>&lt;75 (N=63)</b>	<b>&gt;75 (N=38)</b>	<b>P values*</b>
Diabetes (%)	20 (31.8)	13 (34.2)	0.440
Dyslipidemia (%)	40 (63.4)	26 (68.4)	0.175
Arterial Hypertension (%)	47 (74.6)	37 (97.4)	0.115
Obesity (%)	33 (52.4)	17 (44.7)	0.743
COPD <sup>a</sup> (%)	5 (8.0)	3 (7.9)	0.994
PAD <sup>b</sup> (%)	11 (17.5)	4 (10.5)	0.347
Stroke (%)	1 (1.6)	2 (5.3)	0.297
CKD <sup>c</sup> (%)	7 (11.1)	15 (39.5)	0.001
Previous CAD <sup>d</sup> (%)	13 (20.6)	16 (42.1)	0.878
Previous HF <sup>e</sup> with NYHA > II <sup>o</sup> <sup>f</sup> (%)	23 (36.5)	22 (57.9)	0.118
Previous AMI <sup>g</sup> (%)	15 (23.8)	17 (44.7)	0.878
Arrhythmia (%)	6 (9.5)	16 (42.1)	0.440
PM <sup>h</sup> (%)	1 (1.6)	3 (7.9)	0.440
Previous PCI <sup>i</sup> (%)	12 (19.0)	16 (42.1)	0.878
Previous CABG <sup>j</sup> (%)	3 (4.8)	3 (7.9)	0.440

Data is presented as absolute numbers or median and interquartile range.

\* Independent T-Test

<sup>a</sup> Chronic obstructive pulmonary disease, <sup>b</sup> Peripheral artery disease, <sup>c</sup> Chronic kidney disease, <sup>d</sup> Coronary artery disease, <sup>e</sup> Heart failure, <sup>f</sup> New York Heart Association, <sup>g</sup> Acute Myocardial Infarction, <sup>h</sup> Pacemaker,

<sup>i</sup> Percutaneous coronary intervention, <sup>j</sup> Coronary artery bypass grafting

The evaluation of ECG of all the patients admitted to the hospital shows a higher incidence of ST-segment elevation in the young group (44.4%) in comparison to the elderly group (29.0%), whereas ST-segment depression showed a higher incidence in the elderly group (15.8%) compared to the young group (14.3%). When evaluating the Ultrasound findings of all the patients admitted to the hospital, our results show no significant differences between the two groups (Table 2).

**Table 2.** Comparison of Ultrasound findings of the young and elderly group.

<b>At admission</b>	<b>&lt;75 (N=63)</b>	<b>&gt;75 (N=38)</b>	<b>P values*</b>
Mean Ejection fraction (SD)	46.61 ± 13.45	48.57 ± 12.92	0.718
Malformation of valves >II° (%)	4 (6.4)	4 (10.5)	0.606
Mean Troponin values (SD)	0.727 ± 1.40	0.544 ± 1.25	0.599

Data is presented as absolute numbers or median and interquartile range.

\* Independent T-Test

With a mean hospital stay of 9.76 days ( $\pm 7.21$ ) the elderly group showed a significantly higher duration of hospital stay ( $P=0.043$ ) in comparison to the young group with 7.17 days ( $\pm 5.39$ ).

## 4.2 Coronary intervention

The coronary intervention included PCI and/or solely coronary angiography. 88.89% of the young group and 63.16% of the elderly group received an implantation of DES, with the number of mean implanted DES of  $1.86 \pm 1.34$  in the young group and  $1.87 \pm 2.21$  in the elderly group (Table 3). Therefore, the young group had a significantly higher rate of implanted DES ( $P=0.002$ ) than the elderly group (Table 3). The mean implanted DES and mean contrast agent volume during the PCI showed no significant differences between the two age groups, as seen in Table 3.

**Table 3.** Comparison of coronary intervention outcomes of the young and elderly group.

<b>Coronary intervention</b>	<b>&lt;75 (N=63)</b>	<b>&gt;75 (N=38)</b>	<b>P values*</b>
Implanted DES <sup>a</sup> (%)	56 (88.9)	24 (63.2)	0.002
Mean implanted DES <sup>a</sup> (SD)	$1.86 \pm 1.34$	$1.87 \pm 2.21$	0.975
Mean contrast agent volume during PCI (ml)	$162.70 \pm 67.53$	$0.66 \pm 0.48$	0.872

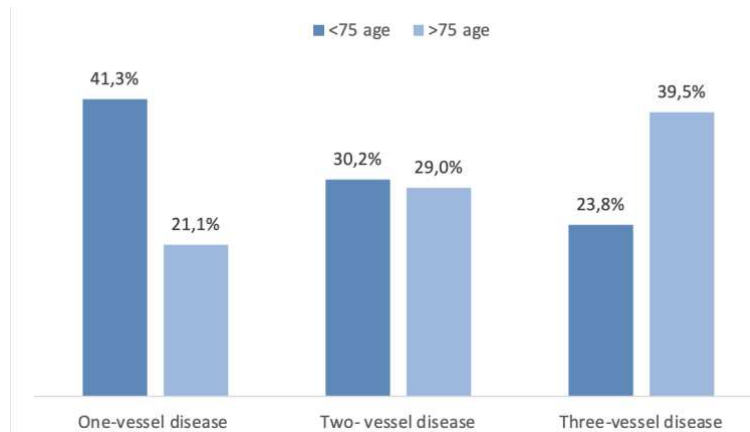
Data is presented as absolute numbers or median and interquartile range.

\* Independent T-Test

<sup>a</sup> Drug Eluting Stent

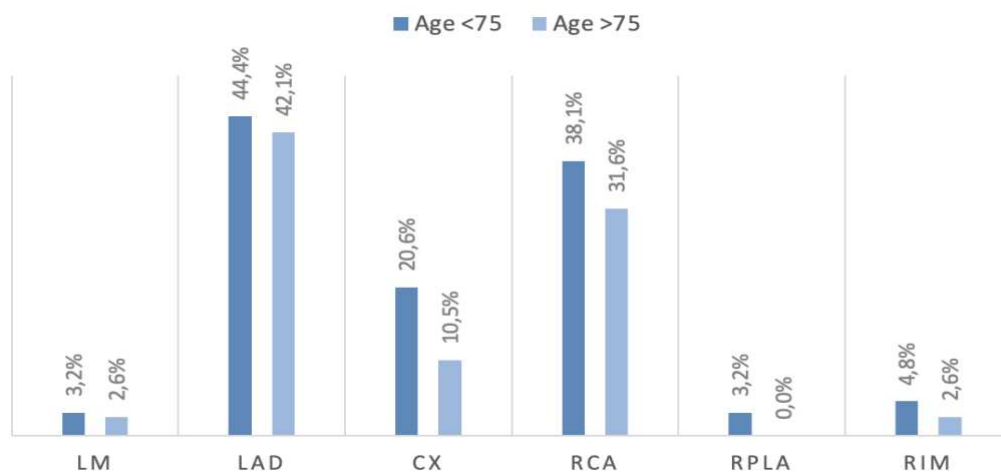
We found more three-vessel CAD in the elderly group (39.5%), whereas one-vessel disease was more pronounced in the younger group (41.3%) (Figure 7).





**Figure 7.** Comparison of one-, two-, and three-vessel diseases indicating a PCI in the young and elderly group.

CABG intervention was not induced in any patient of this study. Regarding coronary lesion pattern our results show the highest rate of coronary artery occlusion in the LAD in both groups. The second highest rate of occlusion occurred in the right coronary artery (RCA) and the third most common location of occlusion was found in the circumflex artery (CX) (Figure 8). All three, showed no significant difference between the two groups. LM, right posterolateral artery and ramus intermedius also showed no significant difference between the groups.



**Figure 8.** Coronary lesion location and intervention with PCI in the young and elderly group. Legend: LM-Left Main coronary artery, LAD-Left anterior descending artery, CX-Circumflex artery, RCA-Right coronary artery, RPLA-Right posterolateral artery, RIM-Ramus intermedius

### 4.3 Complications

As shown in table 4, the complications with the highest incidence in both groups was pneumonia and other complications including urinary tract infections etc. Furthermore, the incidence of repeated coronary intervention within a year was significantly higher in the young group in comparison to the elderly group with a *P* value of 0.010. All in all, complications in

both age groups showed no significant difference, although the incidence of complications in the elderly group was higher than in the younger group (Table 4).

**Table 4.** Comparison of complication outcomes of the young and elderly group.

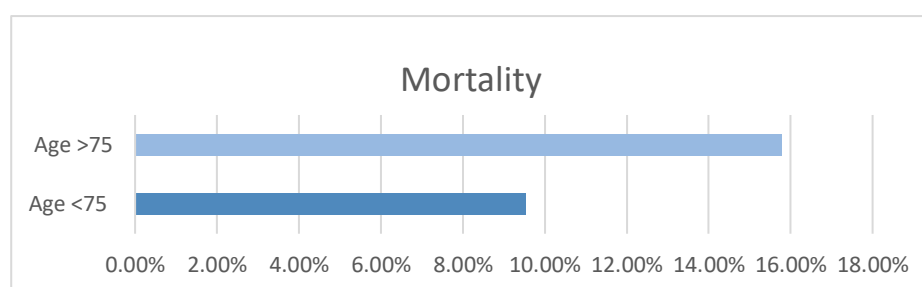
Complications	<75 (N=63)	>75 (N=38)	P values*
Cardiogenic shock (%)	6 (9.5)	3 (7.9)	0.199
Bleeding (%)	4 (6.4)	3 (7.9)	0.770
Reinfarction (%)	0	1 (2.6)	0.199
Ventilation of Patient (%)	8 (12.7)	7 (18.4)	0.199
Pneumonia (%)	11 (17.5)	10 (26.3)	0.293
Myocarditis (%)	1 (1.6)	3 (7.9)	0.118
Acute kidney injury (%)	3 (4.8)	5 (13.2)	0.133
Dialysis (%)	3 (4.8)	1 (2.6)	0.599
Reanimation (%)	4 (6.4)	2 (5.3)	0.825
PM-Indication/Implantation <sup>a</sup> (%)	4 (6.4)	5 (13.2)	0.249
Covid-19 Infection during stay (%)	6 (9.5)	1 (2.6)	0.190
Other complications (%)	22 (34.9)	19 (50)	0.138
Repeated coronary intervention within a year (%)	16 (25.4)	2 (5.3)	0.010

Data is presented as absolute numbers or median and interquartile range.

\* Independent T-Test

<sup>a</sup> PM-Pacemaker

Our study also examined the prevalence of mortality in both groups by using the hospital information system (Orbis) to assess mortality rates up to 60 days after coronary intervention. Our results show that the incidence of mortality was higher in the elderly group than in the young group (Figure 9). With a *P* value of 0.351, significance between the 2 groups was not demonstrated.



**Figure 9.** Comparison of Mortality in the elderly and young group.

## **5. DISCUSSION**

In this study, we aimed to compare younger (<75 years) and older ( $\geq$ 75 years) patients who underwent PCI or coronary angiography as part of their treatment for ACS at the REGIOMED hospital in Coburg. The findings revealed age-related differences in risk factors, concurrent diseases, prior cardiac diseases, intervention outcomes, complications, and mortality.

The elderly group comprised of patients aged 75 and older was smaller than the young group, which consisted of patients under 75 years of age. NSTEMI was more prevalent in the elderly population, whereas STEMI was more prevalent in the younger population. These results suggest that the manifestation of ACS varies by age group. This is further supported by prior research demonstrating a higher incidence of NSTEMI in older patients and STEMI in younger patients (75,126,127).

In terms of risk factors, the elderly group demonstrated a higher incidence of arterial hypertension, while the younger group demonstrated a higher incidence of obesity. These findings are consistent with previous research indicating a link between aging and the onset of arterial hypertension, as well as an increasing prevalence of obesity among younger individuals (128,129).

The comparison of comorbidities revealed that the young group had a higher incidence of COPD and PAD, while the elderly group had a higher incidence of stroke. It also demonstrated a significantly higher prevalence of CKD compared to the younger group. Regarding aging-related changes in elderly patients, these results are consistent with earlier studies indicating an increase in comorbidities among elderly ACS patients (130).

The evaluation of previous cardiac diseases revealed that the elderly had a higher incidence of CAD than the young. In addition, the prevalence of heart insufficiency (NYHA class II or higher), previous AMI, arrhythmias, pacemaker, previous PCI, or CABG was higher in the elderly group. These results suggest that elderly patients with ACS have a higher prevalence of preexisting cardiac conditions and complications. A review by Izzo *et al.*, demonstrating the role of oxidative stress in cardiovascular aging and cardiovascular diseases, demonstrates these age-related cardiovascular changes in great detail (131).

However, risk factors, concurrent diseases, and previous cardiac diseases do not differ significantly between the two age groups.

The comparison of coronary intervention outcomes revealed a significantly higher rate of stent implantation in the young group in comparison to the elderly group. This indicates that younger patients were more inclined to receive this procedure. These findings may be due to a variety of factors, including the complexity of coronary lesions, comorbidities, and patient

preferences, all of which could impact treatment decisions. Furthermore, our study showed a higher incidence of one-vessel disease in the young group and a high incidence of three-vessel disease in the elderly group. Similar results have been reported in a study by Chen *et al.*, displaying the safety and effectiveness of PCI in elderly patients (119).

The analysis of complications revealed that both groups had a higher incidence of pneumonia and unspecified other complications. However, the young group had a significantly higher rate of repeated coronary intervention within a year, suggesting that older patients may not be referred to a cardiology specialist or coronary angiography again. Other studies indicate that elderly patients are more prone to complications than younger patients (127,132).

Regarding mortality, the incidence of death after PCI was higher in the elderly group, but this difference was not statistically significant.

In conclusion, this study sheds light on age-related differences in patients treated for ACS with PCI or coronary angiography. Our findings highlight the similarities between younger and older age groups in terms of risk factors, comorbidities, and complications. Our findings reveal no statistically significant differences in complications and mortality after coronary intervention, demonstrating the safety and efficacy of PCI in the elderly.

However, it is essential to note that the study had some limitations. Its retrospective methodology and relatively small sample size are examples. Consequently, larger cohorts and prospective designs are required to confirm our findings and investigate additional factors that may contribute to age-related differences in ACS treatment.

## **6. CONCLUSION**

Our findings suggest that PCI or coronary angiography is a safe and effective treatment for elderly patients over the age of 75 because complications and mortality are comparable to younger individuals. Elderly patients shouldn't be denied coronary treatments as good outcomes might be anticipated.

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## **9. SUMMARY**

**Objectives:** The purpose of this study was to compare acute coronary syndrome patients who were old or very old ( $\geq 75$  years) to younger patients in terms of coronary pathology, comorbidities, coronary intervention, and the short-term outcome following PCI.

**Materials and Methods:** This retrospective monocentric investigation was performed between January 1 and October 1, 2022, and included all patients who were treated invasively for their acute coronary syndrome. Patients were divided into two groups: patients equal to or over 75 years old (elderly group) and patients under 75 years old (young group).

We compared risk factors, cardiac and extra comorbidities, ECG, ultrasound, laboratory results, complications after angiography, death and outcome of coronary intervention in these two groups.

**Results:** The final study comprised 101 patients who underwent PCI or coronary angiography as part of their treatment for ACS (29 females (28.7%) and 72 males (71.3%). The age ranged from 41 to 97 years, with a mean age of 69 ( $\pm 13$  years). When compared to the elderly group, the younger group had more patients (63 patients (62.4%) vs. 38 patients (37.6%). Regarding risk factors and comorbidities, there were no significant differences between the groups, except for a significantly higher incidence of CKD in the elderly group. In contrast to the younger group, we found older patients to have more severe CAD. For the treatment of their ACS, more patients in the younger group had stents implanted (56 patients (88.9%) vs. 24 patients (63.2%),  $P=0.002$ ). Both groups' complications and short-term mortality rates were comparable.

**Conclusion:** Our findings suggest that PCI or coronary angiography is a safe and effective treatment for elderly patients over the age of 75 because complications and mortality are comparable to younger individuals. Since a considerable portion of this vulnerable patient group might be predicted to have positive outcomes from coronary procedures, elderly patients shouldn't be denied access to invasive treatment of their ACS.

## **10. CROATIAN SUMMARY**

**Ciljevi:** Svrha ove studije bila je usporediti bolesnike s akutnim koronarnim sindromom koji su bili stari ili vrlo stari ( $\geq 75$  godina) s mlađim bolesnicima u pogledu koronarne patologije, komorbiditeta, koronarne intervencije i kratkoročnih ishoda nakon PCI postupka.

**Materijali i metode:** Ova retrospektivna monocentrična studija provedena je od 1. siječnja do 1. listopada 2022. godine i uključila je sve bolesnike koji su bili invazivno liječeni zbog svog akutnog koronarnog sindroma. Bolesnici su podijeljeni u dvije skupine: bolesnici koji su stari jednako ili preko 75 godina (starija skupina) i bolesnici mlađi od 75 godina (mlađa skupina). Usporedili smo čimbenike rizika, srčane i dodatne komorbiditete, EKG, ultrazvuk, laboratorijske rezultate, komplikacije nakon angiografije, smrtnost i ishod koronarne intervencije u ovim dvjema skupinama.

**Rezultati:** Završna studija obuhvatila je 101 bolesnika koji su podvrgnuti PCI postupku ili koronarnoj angiografiji kao dio njihovog liječenja za ACS (29 žena (28,7%) i 72 muškarca (71,3%). Dob se kretala od 41 do 97 godina, s prosječnom dobi od 69 ( $\pm 13$  godina). Uspoređujući s starijom skupinom, mlađa skupina imala je više bolesnika (63 bolesnika (62,4%) naspram 38 bolesnika (37,6%). Što se tiče čimbenika rizika i komorbiditeta, nije bilo značajnih razlika između skupina, osim znatno veće učestalosti kronične bolesti bubrega (CKD) u starijoj skupini. Nasuprot mlađoj skupini, primijetili smo da stariji bolesnici imaju teži oblik koronarne arterijske bolesti (CAD). U liječenju njihovog ACS-a, više bolesnika u mlađoj skupini imalo je ugrađene stentove (56 bolesnika (88,9%) naspram 24 bolesnika (63,2%),  $P=0,002$ ). Komplikacije i stope kratkoročne smrtnosti bile su usporedive u obje skupine.

**Zaključak:** Naši rezultati sugeriraju da je PCI ili koronarna angiografija siguran i učinkovit tretman za starije bolesnike starije od 75 godina jer su komplikacije i smrtnost slični mlađim osobama. Budući da se značajan broj ove ranjive skupine bolesnika može očekivati s pozitivnim ishodom koronarnih postupaka, starijim bolesnicima ne bi trebalo uskratiti pristup invazivnom liječenju njihovog ACS-a.