



(REVIEW ARTICLE)



Acute coronary syndrome: Definition, pathophysiology, diagnosis, and management

Erick Alexander Cabrera Estrada, Epitafio Rafael Mestre Sequeda *, Jairo Enrique Barcinilla Barros, John Alexander Caballero Ríos, Iris Michell Racedo Segura and Gabriela Lucia Lara Barreto

Department of Internal Medicine, Faculty of Health Sciences, Universidad Libre, Barranquilla.

World Journal of Advanced Research and Reviews, 2024, 21(01), 2537–2548

Publication history: Received on 18 December 2023; revised on 25 January 2024; accepted on 27 January 2024

Article DOI: <https://doi.org/10.30574/wjarr.2024.21.1.0352>

Abstract

Acute coronary syndrome (ACS) represents the most severe form of presentation of ischemic heart disease and imposes a significant burden on morbidity and mortality worldwide, particularly in low- and middle-income countries. Within the clinical spectrum of coronary syndrome are ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina. Although primarily caused by atherosclerotic plaque thrombosis or non-atherosclerotic causes, its pathophysiological mechanisms are not fully understood. Currently, the main mechanisms include plaque rupture, plaque erosion, calcified nodules, and non-atherosclerotic causes such as coronary vasospasm.

For ACS diagnosis, the electrocardiogram (ECG) is recommended primarily, along with high-sensitivity cardiac troponins (hs-cTn), following recommended algorithms to determine the testing interval. Non-invasive diagnostic tools such as echocardiography, computed tomography (CT), and cardiac magnetic resonance (CMR) are also available. These are mainly indicated in patients with inconclusive ECG and hs-cTn results and for establishing differential diagnoses.

The management of ACS should be multidisciplinary, encompassing pharmacological, invasive techniques, and non-pharmacological approaches. It should be individualized considering each patient's characteristics.

Keywords: Acute coronary syndrome; Myocardial Infarction; Plaque rupture; Troponins

1. Introduction

Coronary artery disease (CAD) and acute coronary syndromes (ACS) represent a significant global public health burden, contributing significantly to morbidity and mortality in the population [1]. Cardiovascular disease (CVD) is the most common cause of mortality and morbidity worldwide, primarily affecting low- and middle-income countries. ACS is often the initial manifestation of CVD, with an estimated 5.8 million new cases of ischemic heart disease in the European Society of Cardiology (ESC) member countries in 2019. The estimated median incidence is 293.3 cases per 100,000 individuals. Approximately 2.2 million deaths in women and 1.9 million deaths in men occur each year, constituting 38% of female CVD-related deaths and 44% of male deaths [2].

2. Methodology

A systematic review was carried out through the selection of original articles, available research reviews, written in English and / or Spanish, through recognized databases such as pubmed, scielo, science direct, wiley, plos one, among others. Regardless of its year of publication, using the search terms include acute coronary syndrome, myocardial Infarction, unstable angina.

* Corresponding author: Epitafio Rafael Mestre Sequeda

3. Results

3.1. Definition

ACS encompasses a significant group of clinical presentations with signs or symptoms, with or without electrocardiographic changes, and with or without acute elevations in cardiac troponin, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina [3].

The diagnosis of acute myocardial infarction (AMI) is associated with the release of cTn and is based on the fourth universal definition of infarction. It describes AMI as the presence of acute myocardial injury detected by an elevation in cardiac biomarkers in the context of evidence of acute myocardial ischemia. Unstable angina (UA) is defined as myocardial ischemia at rest or with minimal exertion in the absence of acute injury or necrosis of cardiomyocytes [4].

From a pathological standpoint, myocardial infarction is defined by the occurrence of myocardial cell death secondary to prolonged ischemia. The initial structural changes observed in cardiomyocytes include decreased glycogen deposits, the appearance of relaxed myofibrils, and sarcolemma rupture. These changes can be identified as early as the first 10 minutes of ischemia [4].

Cardiac troponins I (cTnI) and T (cTnT) are part of the contractile apparatus of myocardial cells and are expressed mainly in the heart. For example, it has not been reported to date that cTnI elevations occur due to damage in non-cardiac tissues, while cTnT may rise in the presence of damage to skeletal muscle. These are the biomarkers of choice for detecting myocardial damage. Other biomarkers such as creatine kinase-MB (CK-MB) have lower sensitivity and specificity. The presence of myocardial damage is indicated by the elevation of these biomarkers above the 99th percentile of the upper limit of normal. Damage can be acute when there is a dynamic increase or a descending pattern of cTn values above the 99th percentile, or chronic when cTn values are persistently elevated [4]. Various causes lead to the elevation of cardiac biomarker values, as illustrated in table 1.

Table 1 Causes of elevation in cardiac troponin values as a consequence of myocardial damage

Myocardial damage related to acute myocardial ischemia:
<ul style="list-style-type: none"> • Rupture of an atherosclerotic plaque with thrombosis
Myocardial damage related to acute myocardial ischemia resulting from an imbalance between oxygen supply and demand:
<ul style="list-style-type: none"> • Coronary spasm, microvascular dysfunction • Coronary embolism • Coronary dissection • Sustained bradyarrhythmia • Hypotension or shock • Respiratory failure • Severe anemia • Sustained tachyarrhythmia • Severe hypertension with or without left ventricular hypertrophy
Other causes of myocardial damage:
Cardiac conditions <ul style="list-style-type: none"> • Heart failure • Myocarditis • Cardiomyopathy (any type) • Tako-tsubo syndrome • Coronary revascularization procedure • Other cardiac procedures • Catheter ablation

- Defibrillator discharges
 - Cardiac contusion
- Systemic conditions
- Sepsis, infectious disease
 - Chronic kidney disease
 - Stroke, subarachnoid hemorrhage
 - Pulmonary embolism, pulmonary hypertension
 - Infiltrative diseases such as amyloidosis or sarcoidosis
 - Chemotherapeutic drugs
 - Critically ill patients
 - Strenuous exertion

Adapted from; Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018 Oct 30;72(18):2231-2264.

Clinically, ACS is characterized by the presence of prolonged angina (> 20 minutes) at rest; new-onset severe angina; angina increasing in frequency; or angina occurring after revascularization. Patients may also present asymptotically or with continuous nonspecific chest discomfort, hemodynamic instability, cardiogenic shock, or cardiac arrest [3]

Acute myocardial infarction can be classified into 5 types: Type 1 is limited to patients with atherothrombosis and is specified when plaque rupture or erosion leads to partial or complete coronary occlusion, myocardial ischemia, and necrosis. Type 2 myocardial infarction occurs when myocardial ischemia and necrosis result from an imbalance between oxygen supply and demand. Type 3 corresponds to sudden cardiac death where the probable cause is myocardial infarction, but death occurred before the diagnosis could be established. Type 4 infarction is subdivided into 3 classes: 4a involves a troponin elevation of 5 times above the 99th percentile after percutaneous coronary intervention; 4b involves stent thrombosis, and 4c involves stent restenosis. Type 5 infarction is associated with cardiac surgery [5].

3.2. Pathophysiology

The primary pathophysiological mechanisms underlying the development of ACS unstable angina include plaque rupture, erosion, and calcified nodules.

Atherosclerosis is the main mechanism implicated in the development of coronary syndromes and is considered a multi-step process. Endothelial dysfunction is essential for initiating atherosclerosis, allowing easy uptake of low-density lipoprotein (LDL) into the subendothelial space by binding with proteoglycans in the extracellular matrix. After this, modification and oxidation of LDL occur [6].

Following endothelial activation, various molecules such as selectins and adhesion molecules come into play, enabling the mobility and penetration of leukocytes into the subintimal space. These leukocytes then differentiate into macrophages and proceed to phagocytose oxidized LDL, triggering harmful inflammatory and oxidative responses. Additionally, there is activation and proliferation of vascular smooth muscle cells (VSMCs), which also exhibit phagocytic activity through the absorption of oxidized LDL [7].

3.2.1. Plaque Rupture

Plaque rupture is a critical phenomenon in coronary thrombosis and accounts for approximately 75% of all ACS cases. An association has been found between traditional cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and obesity, as well as non-traditional risk factors such as inflammation and genetic predisposition, in the formation of susceptible plaques. Different histological and structural characteristics confer a higher risk of rupture to plaques, such as thin fibrous caps (<65 μm), large lipid-rich cores, increased macrophage density, and neovascularization. Additionally, plaque susceptibility is heightened by the presence of intraplaque hemorrhage and calcification [8].

Plaque rupture occurs within a susceptible plaque, characterized by a fibrous cap with a lipid-rich core. Inflammatory cells, including macrophages and T lymphocytes, are located below the fibrous cap and contribute to ongoing inflammation and plaque remodeling. When the fibrous cap ruptures, exposing the lipid-laden core to the bloodstream, a series of events unfolds. Mechanical stress, inflammation, and extracellular matrix degradation are factors leading to plaque rupture. Shear stress and cyclic tension exerted on the plaque thin it and facilitate rupture. Chronic inflammation

on the plaque induces the release of proteolytic enzymes, mainly matrix metalloproteinases (MMP), which degrade extracellular matrix components [8].

The importance of inflammation has been demonstrated from plaque initiation to rupture development. Circulating monocytes bind to activated endothelial cells, move to the intima, differentiate into macrophages, internalize oxidized LDLs, and transform into foam cells, promoting the formation of a lipid-rich core. Inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) stimulate plaque vulnerability by promoting continuous inflammation. Plaque rupture is a crucial event in the development and progression of ACS. When plaque rupture occurs, the thrombogenic lipid-rich core is exposed to circulation, leading to platelet activation and aggregation. This results in the development of an occlusive thrombus causing myocardial ischemia and potentially myocardial infarction [9].

3.2.2. *Plaque Erosion*

Plaque erosion refers to thrombotic occlusion of a coronary artery without rupture of the fibrous cap. The relationship between plaque erosion and the occurrence of ACS has become more common. It has been established that approximately 20% of ACS patients exhibit plaque erosion; however, there is still a greater association with plaque rupture based on autopsy studies of cardiovascular events [10].

The pathogenesis of plaque erosion involves a combination of factors, including endothelial dysfunction, inflammation, and platelet activation. Endothelial dysfunction is associated with impaired nitric oxide availability and increased expression of adhesion molecules, leading to a prothrombotic state. On the other hand, inflammation stimulated by immune cell infiltration and activated endothelial cells induces greater instability in atherosclerotic plaques. It is noteworthy that comorbidities with systemic involvement, such as hypertension, dyslipidemia, and diabetes, induce a higher degree of inflammation and endothelial dysfunction, contributing to an increased risk of plaque erosion. The pathophysiology of plaque erosion can be divided into two steps. Firstly, alterations in local flow, innate immune activation through Toll-like receptor 2 activation, and endothelial cell apoptosis constitute the initial step. In the second step, activated endothelial cells produce chemokines such as interleukin-8, recruiting leukocytes and promoting the formation of neutrophil extracellular traps (NETs), thereby exacerbating endothelial cell damage and fostering local thrombus formation [11]. Patients with plaque erosion leading to ACS are often younger compared to those with rupture, and some studies suggest a higher prevalence of this phenomenon in females [12].

Eroded plaques exhibit histological features that differentiate them from ruptured plaques. Eroded plaques have a thick fibrous cap without evidence of rupture. Instead of a lipid core, they present superficial platelet-rich thrombi adhering to the intact endothelial surface. Eroded plaques contain a significant amount of extracellular matrix components such as proteoglycans and glycosaminoglycans instead of lipids and a lower number of inflammatory cells compared to ruptured plaques [13].

A stronger association has been found between eroded plaques and the development of non-ST-segment elevation myocardial infarction (NSTEMI), whereas this patient group has a lower risk of presenting with ST-segment elevation myocardial infarction (STEMI). Studies have demonstrated that plaque erosion is primarily located in the anterior descending artery (ADA), especially in the proximal and mid-segments [14].

3.2.3. *Calcified Nodule*

Calcified nodules are calcified structures within the coronary arteries that can contribute to luminal narrowing and the subsequent occurrence of ischemic events. Several biological processes surround the development of nodules, including inflammation, osteogenic transformation, and matrix remodeling. Continuous inflammatory states induce the release of proinflammatory cytokines and growth factors, stimulating the migration and differentiation of vascular smooth muscle cells, promoting the deposition of calcium phosphate crystals, leading to calcification [15].

Approximately 5.3% of SCAs are associated with the presence of calcified nodules. Various traditional cardiovascular risk factors such as advanced age, male gender, hypertension, dyslipidemia, and diabetes have been linked to the appearance of calcified nodules. It has been demonstrated that these conditions promote an imbalance between calcification inhibitors and promoters, inducing calcium deposition within the arterial wall [16].

In addition to plaque rupture, plaque erosion, and calcified nodules, other non-atherosclerotic causes of ACS have been identified, including coronary vasospasm, spontaneous coronary artery dissection, stress-induced cardiomyopathy, and embolism of the coronary artery from thrombi originating elsewhere in the body, causing obstruction [8].

3.3. Diagnosis

3.3.1. Medical History and Physical Examination:

Patients with ACS often report acute chest discomfort, the main symptom that can be described as pain, pressure, heaviness, or burning. Chest pain descriptors should be classified as cardiac, possibly cardiac, or probably non-cardiac. The use of the term "atypical chest pain" is currently discouraged. Symptoms equivalent to chest pain include dyspnea, epigastric pain, pain in the right or left arm, jaw, and neck. It is relevant to emphasize the widespread knowledge in the general population regarding ACS symptoms, primarily prolonged chest pain lasting more than 15 minutes and/or recurring within less than 1 hour. These characteristics should prompt urgent medical help-seeking [17].

A proper medical history and physical examination of patients with suspected ACS are crucial for differential diagnoses and establishing an appropriate approach. Vital signs should be immediately assessed at the first medical contact (FMC), including pulse verification, blood pressure measurement in both arms, proper cardiac and pulmonary auscultation, and evaluation of signs of heart and circulatory failure [17].

3.3.2. Diagnostic Tools:

The 12-lead ECG is the primary diagnostic tool for patients with suspected ACS. It is recommended to be performed immediately after the first medical contact, ideally within 10 minutes. Based on the interpretation, possible scenarios of ACS will be established, including non-ST-segment elevation and ST-segment elevation [18].

Patients with non-ST-segment elevation ACS (NSTEMI-ACS), experiencing chest pain or equivalents, may exhibit electrocardiographic abnormalities, including transient ST-segment elevation, persistent or transient ST-segment depression, and T-wave anomalies, including hyperacute T-waves, T-wave inversion, biphasic T-waves, flat T-waves, and pseudonormalization of the electrocardiogram. Some patients may also have normal electrocardiograms. Most of these patients will show a typical rise and fall in cardiac troponin levels and receive a diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI); another group of patients will maintain troponin levels below the 99th percentile and be classified as unstable angina [18].

In patients with suspected acute coronary syndrome with persistent ST-segment elevation, the priority will be the early implementation of reperfusion therapy. ST-segment elevation will be considered related to coronary artery occlusion if the following conditions are met:

New ST-segment elevation at the J point in at least 2 contiguous leads:

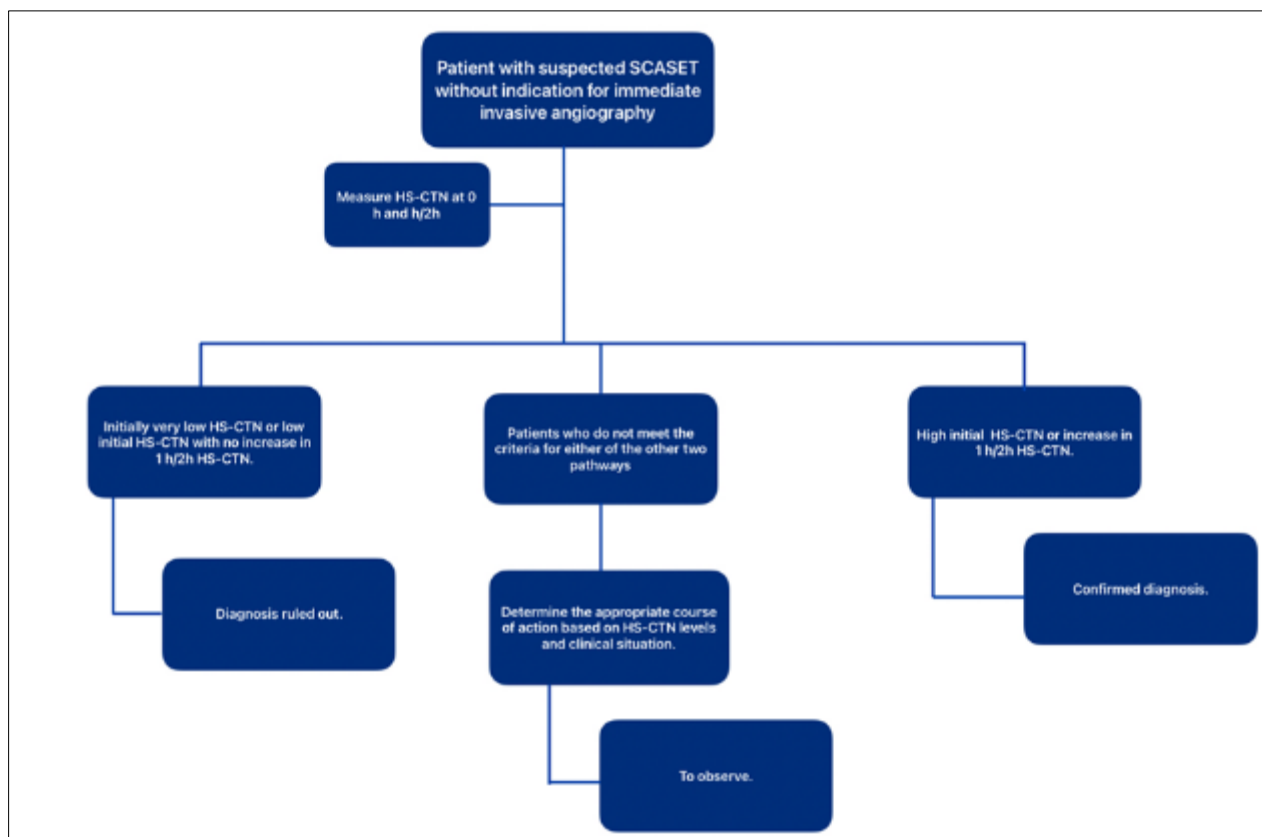
- ≥ 2.5 mm in men <40 years, ≥ 2 mm in men ≥ 40 years, or ≥ 1.5 mm in women regardless of age in leads V2-V3.

Patients with ACS without persistent ST-segment elevation generally present other characteristic ECG alterations that reinforce the diagnostic probability of ACS, including ST-segment depression and T-wave changes, especially prominent negative T-waves or biphasic T-waves [19].

Biomarkers

Biomarkers play a fundamental role in the diagnosis, risk stratification, and treatment of patients with suspected ACS. Currently, the measurement of a myocardial injury biomarker, ideally high-sensitivity cardiac troponin (hs-cTn), is recommended for all patients with suspected ACS²⁰. If the patient's clinical presentation is consistent with ACS, an increase and/or fall in cTn above the 99th percentile suggests the diagnosis of myocardial infarction (MI), considering the fourth universal definition of MI. In patients with MI, cTn levels rise rapidly when highly sensitive tests are used, usually within less than 1 hour, and remain elevated for a variable period. It is currently discouraged to use the terms "normal" and "abnormal" for troponins, and instead, the terms "elevated" and "not elevated" are preferred. It is also important to consider other possible etiologies causing troponin elevation mentioned earlier [20].

There are four main confounding factors in patients with NSTEMI-ACS that can alter the interpretation of cardiac troponin results: age, renal dysfunction, time since the onset of pain, and sex [21]. Due to its higher sensitivity and diagnostic accuracy for MI diagnosis, the use of hs-cTn allows for a shortened time to the second cTn assessment, significantly reducing the delay to diagnosis. The 0-hour/1-hour or 0-hour/2-hour algorithms are recommended (see figure 1) [22].



Adapted from: ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J Acute Cardiovasc Care. 2023

Figure 1 Diagnostic algorithm with hs-cTn

Additional tests are recommended after 3 hours if the first two measurements of hs-cTn in the 0-hour/1-hour algorithm are inconclusive and no alternative diagnoses explaining the clinical picture have been made²³. Currently, the use of biomarkers other than cTn for the diagnosis of ACS is not recommended. Among different biomarkers, only the creatine kinase myocardial band isoenzyme, myosin-binding protein C, and copeptin may be useful when used alongside cTn [23].

Non-Invasive Diagnostic Imaging

Echocardiography

Transthoracic echocardiography (TTE) is essential for identifying signs suggesting ongoing ischemia or prior myocardial infarction (MI). However, it should not cause delays in performing catheterization when there is an indication or suspicion of acute coronary artery occlusion. TTE is also useful for identifying alternative etiologies associated with chest pain, such as acute aortic disease, and indirect findings of pulmonary embolism. It is recommended that all patients with suspected ACS or hemodynamic instability undergo TTE to identify the cause and assess the function of the left and right ventricles, as well as the presence of mechanical complications [24].

In the pathophysiology of ischemia, regional wall motion abnormalities precede changes in the ECG and can be identified even if the patient presents several hours after an event. However, it is important to note that regional wall motion disorders are not only associated with myocardial ischemia but also with previous MI, myocarditis, left bundle branch block, and some cardiomyopathies [24].

Computed Tomography

Computed tomography (CT) is often used as a diagnostic tool to establish alternative differentials to ACS that are potentially life-threatening, such as pulmonary embolism or aortic dissection. Usually, CT has no relevance in patients with suspected acute coronary artery occlusion, where priority is given to angiography. Some studies have shown no

differences in hospital stay or admission duration when comparing coronary computed tomography angiography (CCTA) to the use of hs-cTn [25].

CCTA can be useful in some clinical scenarios, for example, in patients in observation areas where cTn and ECG results are inconclusive. A normal CCTA is useful for ruling out the presence of obstructive plaque as non-obstructive, having a high negative predictive value (NPV). CCTA is also useful for risk stratification in selected low-risk patients with NSTEMI. It is important to note that performing CCTA may be limited in patients with tachycardia, established coronary artery disease, previous stents, or extensive coronary calcification [26].

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (MRI) with or without stress testing details cardiac structure and function and has the ability to provide assessments of myocardial perfusion and describe the pattern of myocardial injury. It is considered the test of choice when patients have difficult echocardiographic windows that prevent proper assessment. Through MRI, infarcted regions can be directly observed, providing information about tissue scarring and viability. It is also useful for identifying the culprit vascular territory and confirming the diagnosis of myocarditis or Takotsubo cardiomyopathy, among other differentials. MRI is especially important for establishing the diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) after invasive angiography. It is also the preferred test for left ventricular thrombus evaluation [27].

4. Treatment

Treatment for acute coronary syndrome is essential to improve the patient's prognosis. From the moment of clinical presentation, there are established initial management strategies that will favour clinical evolution. The management of acute coronary syndrome can be divided according to acute or chronic phases and based on the selected strategy, into percutaneous, surgical, or pharmacological, taking into account diagnostic studies, coronary artery images, and the presence or absence of obstructive lesions in them [28].

4.1. Pre-hospital Treatment

It is necessary to recognize that a patient with chest pain represents a medical emergency until the diagnosis is established to define subsequent strategies. In an out-of-hospital scenario, ideally, there should be an action protocol that alerts the emergency medical service, including a physician or paramedic, as well as ambulance service, with the possibility of performing an electrocardiogram. Based on the findings, it will be decided whether to follow the ST-segment elevation acute coronary syndrome (STE-ACS) algorithm or the non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) algorithm. The former has higher mortality, so the reperfusion strategy and transfer to a 24-hour percutaneous coronary intervention (PCI) center should be prioritized. In the case of cardiac arrest with persistent ST-segment elevation, resuscitation maneuvers should be initiated, prioritizing transfer to a center with PCI. If there is hemodynamic instability after resuscitated cardiac arrest, immediate coronary arteriography should be performed. Percutaneous coronary intervention has shown improvement in angina symptoms in patients who have received antianginal or analgesic management [29].

Ambulances for patient transfer should have electrocardiographic monitoring, a defibrillator, at least one person with knowledge of basic and advanced cardiopulmonary resuscitation, and pharmacological therapy, including initiating antiplatelet therapy, supplementary oxygen if peripheral saturations are below 90%, sublingual nitrates for relief of ischemic symptoms, analgesic management with opioids (morphine) for persistent pain, and intravenous beta-blockers if the patient does not have signs of acute heart failure, has a systolic blood pressure greater than 120 mmHg, and has no other contraindications to improve myocardial oxygen consumption [30].

4.2. Acute Phase Treatment

Based on the electrocardiogram, clinical context, duration of clinical symptoms, and available resources, the best reperfusion strategy will be determined. In the context of STE-ACS, the priority is reperfusion therapy by primary PCI as the preferred choice. However, if it cannot be performed within the first 120 minutes from symptom onset, fibrinolysis should be performed within the initial 10 minutes from the diagnosis, with subsequent rescue PCI in case of unsuccessful fibrinolysis (ST-segment decrease less than 50% after 60-90 minutes of fibrinolytic therapy), hemodynamic or electrical instability, worsening of ischemia, or persistent chest pain. If successful fibrinolysis is achieved, an invasive strategy should be considered early (within the next 24 hours)[31]. In patients with NSTEMI-ACS, cardiovascular risk should be calculated to establish an immediate, early, or selective invasive strategy. Very-high-risk patients, including those with hemodynamic instability or cardiogenic shock, persistent or refractory chest pain to

medical management, acute heart failure presumably secondary to myocardial ischemia, life-threatening arrhythmias, or cardiac arrest after presentation, mechanical complications, or dynamic changes in the electrocardiogram suggestive of ischemia, require an immediate invasive strategy. In the high-risk category, patients with a confirmed diagnosis of NSTEMI, a GRACE score greater than 140, transient ST-segment elevation, or dynamic ST-segment or T-wave changes will benefit from an early invasive strategy. Patients who do not meet very-high-risk or high-risk criteria are candidates for selective invasive strategy. If there is no elevation of cardiac biomarkers and there is suspicion of unstable angina, an invasive or non-invasive strategy will be established based on medical judgment [32,33].

Regarding pharmacological management in this phase, antithrombotic treatment is a fundamental pillar in managing patients with acute coronary syndrome. The risk of thrombosis and bleeding should be evaluated to choose therapy. The bleeding risk will be assessed using the Academic Research Consortium on High Bleed Risk (ARC-HBR) scale [34]. Dual antiplatelet therapy (DAPT) is the therapy of choice in patients with acute coronary syndrome. Depending on the indication of each antiplatelet, the respective loading dose of acetylsalicylic acid should be indicated as soon as acute coronary syndrome is suspected. As for the loading dose of P2Y12 inhibitors, it will be considered in STE-ACS. Currently, there are no studies with statistically significant power to be routine treatment in NSTEMI-ACS, so loading is not recommended in this scenario. However, at the time of PCI, the loading dose should be given [35].

Parenteral anticoagulation is indicated in all patients with a diagnosis of acute coronary syndrome. In the context of STE-ACS undergoing PCI, unfractionated heparin during the procedure is recommended, with low-molecular-weight heparin and bivalirudin as alternatives. Fondaparinux is not recommended in this scenario. In NSTEMI-ACS, anticoagulation should also be initiated, with unfractionated heparin being the first option, followed by enoxaparin and fondaparinux [36].

Adjuvant treatment with high-intensity statins is beneficial, as is the use of beta-blockers if there is no contraindication to their use, and they should be initiated as soon as possible [37,38].

4.3. Invasive Treatment

Coronary angiography is the reperfusion therapy of choice, during which the interventional cardiologist should evaluate the anatomy of coronary lesions to establish the indication for coronary stent implantation. In case PCI cannot be performed, medical management and surgical management should be considered. The latter is indicated in lesions not susceptible to percutaneous approach, severe multivessel disease, and patient preference [39,40].

4.4. Chronic Treatment

Secondary prevention is essential in the chronic management of patients with acute coronary syndrome to improve the quality of life and reduce morbidity and mortality. This prevention is not only from a pharmacological perspective but also involves implementing habits that decrease the risk of experiencing a new event [41]

The initial phase of chronic treatment is cardiovascular rehabilitation, which should include all patients who have experienced acute coronary syndrome and should be initiated as soon as possible after the event. It should be rehabilitation led by trained personnel who evaluate the training plan based on anthropometric measurements, age, and the person's comorbidities. Psychological counseling should accompany physical therapy to prevent withdrawal from the rehabilitation plan [42,43]

Lifestyle management has clear benefits in reducing the recurrence of coronary events. Among these lifestyle changes is smoking cessation, which decreases the risk of recurrent infarction by 30-40% and the risk of death after acute coronary syndrome by 35-45%. A healthy diet, especially the Mediterranean diet, has been shown to reduce cardiovascular risk in all patients. Continuing physical activity after cardiovascular rehabilitation is crucial because sedentary behaviour increases cardiovascular risk [44].

Parenteral anticoagulation should be discontinued once percutaneous coronary intervention is performed, except in cases of confirmed left ventricular aneurysm with thrombus formation or atrial fibrillation requiring anticoagulation. In such cases, management with oral anticoagulation will be defined, keeping in mind that anticoagulation solely for acute coronary syndrome, without the described determinants to continue it, is not indicated [45].

In contrast to anticoagulation, dual antiplatelet therapy should be mandatory in the chronic management of patients with acute coronary syndrome, consisting of a potent P2Y12 inhibitor and aspirin for at least 12 months. In some scenarios, the duration of dual therapy can be decreased, extended, or modified according to the calculated bleeding and thrombotic risk; after dual management, aspirin will be continued indefinitely [46].

Pharmacological therapy for lipid lowering should be carried out in all patients with acute coronary syndrome, following the goals established in current dyslipidemia guidelines. Lower levels of low-density lipoprotein (LDL) cholesterol have been associated with a lower cardiovascular risk. For secondary prevention, the initial target is usually LDL levels below 55 mg/dL, with a 50% reduction from baseline. This therapy should be initiated as early as possible after acute coronary syndrome presentation, using high-intensity statin strategies. In patients with elevated LDL levels where achieving cholesterol goals with statin therapy alone is unlikely, ezetimibe should be initiated, as well as in patients with maximum statin doses that have not achieved cholesterol goals. If values persist above the established goal despite statin plus ezetimibe management, consideration should be given to initiating a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. The response to the initiation of each medication should be evaluated every 4-6 weeks [47, 48].

The indication for beta-blockers in patients with an ejection fraction less than or equal to 40% is clear; however, in patients with acute coronary syndrome and an ejection fraction greater than 40%, their benefit is not clear. In studies with patients with ejection fractions greater than 40%, the duration of therapy beyond the first year after uncomplicated acute coronary syndrome is controversial. It is estimated that there is no benefit from the medication after the first year of management; however, some studies have shown partial benefit to therapy lasting more than a year [49].

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) have demonstrated benefits in patients with acute coronary syndrome and other associated conditions such as ejection fraction less than or equal to 40%, chronic kidney disease, heart failure, or hypertension. There has been a demonstrated decrease in mortality at 30 days after the coronary event and a delay in cardiac remodeling [50]. The use of sodium-glucose co-transporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP1 RAs) have been shown to decrease major cardiovascular events in patients with associated conditions such as diabetes mellitus and heart failure [51].

5. Conclusion

Acute coronary syndrome is a serious cardiac condition that demands an immediate response and appropriate treatment. Early and accurate diagnosis, coupled with timely intervention, is crucial for enhancing outcomes and mitigating long-term risks. Long-term prevention and rehabilitation also play a fundamental role in the comprehensive management of this disease.

Compliance with ethical standards

Acknowledgments

Special thanks and sincere gratitude to all those who supported directly and otherwise to make the production of this manuscript possible.

Disclosure of conflict of interest

The authors do not declare conflicts of interest.

References

- [1] Theofilis P, Oikonomou E, Chasikidis C, Tsioufis K, Tousoulis D. Pathophysiology of Acute Coronary Syndromes- Diagnostic and Treatment Considerations. *Life (Basel)*. 2023; 13(7):1543. doi: 10.3390/life13071543.
- [2] Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, *et al*. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J* 2022; 43: 716–799. <https://doi.org/10.1093/eurheartj/ehab892>
- [3] Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, *et al*. ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J Acute Cardiovasc Care*. 2023; 22:zuad107. doi: 10.1093/ehjacc/zuad107
- [4] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth

Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol.* 2018; 72(18):2231-2264. doi: 10.1016/j.jacc.2018.08.1038.

- [5] Lindahl B, Mills NL. A new clinical classification of acute myocardial infarction. *Nat Med.* 2023; 29(9):2200-2205. doi: 10.1038/s41591-023-02513-2.
- [6] Gimbrone MA Jr, García-Cardena G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ Res.* 2016; 118(4):620-36. doi: 10.1161/CIRCRESAHA.115.306301.
- [7] Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, Tousoulis D. Inflammatory Mechanisms Contributing to Endothelial Dysfunction. *Biomedicines.* 2021; 9(7):781. doi: 10.3390/biomedicines9070781.
- [8] Yuan, D.; Chu, J.; Qian, J.; Lin, H.; Zhu, G.; Chen, F.; Liu, X. New Concepts on the Pathophysiology of Acute Coronary Syndrome. *Rev. Cardiovasc. Med.* 2023, 24, 112. <https://doi.org/10.31083/j.rcm2404112>.
- [9] Theofilis P, Oikonomou E, Chasikidis C, Tsioufis K, Tousoulis D. Pathophysiology of Acute Coronary Syndromes- Diagnostic and Treatment Considerations. *Life (Basel).* 2023; 13(7):1543. doi: 10.3390/life13071543.
- [10] Oikonomou E, Leopoulou M, Theofilis P, Antonopoulos AS, Siasos G, Latsios G, Mystakidi VC, Antoniadou C, Tousoulis D. A link between inflammation and thrombosis in atherosclerotic cardiovascular diseases: Clinical and therapeutic implications. *Atherosclerosis.* 2020; 309:16-26. doi: 10.1016/j.atherosclerosis.2020.07.027.
- [11] Fahed AC, Jang IK. Plaque erosion and acute coronary syndromes: phenotype, molecular characteristics and future directions. *Nat RevCardiol.* 2021; 18(10):724-734. doi: 10.1038/s41569-021-00542-3.
- [12] Kim HO, Kim CJ, Kim W, Cho JM, Soeda T, Takano M, et al. Relative risk of plaque erosion among different age and sex groups in patients with acute coronary syndrome. *J ThrombThrombolysis.* 2020; 49(3):352-359. doi: 10.1007/s11239-019-01969-9.
- [13] Sekimoto T, Mori H, Koba S, Arai T, Matsukawa N, Sakai R, et al. Clinical features and lipid profiles of plaque erosion over lipid-rich plaque versus fibrous plaque in patients with acute coronary syndrome. *Atherosclerosis.* 2022; 360:47-52. doi: 10.1016/j.atherosclerosis.2022.07.008.
- [14] Yamamoto E, Yonetsu T, Kakuta T, Soeda T, Saito Y, Yan BP, et al. Clinical and Laboratory Predictors for Plaque Erosion in Patients With Acute Coronary Syndromes. *J Am Heart Assoc.* 2019; 8(21):e012322. doi: 10.1161/JAHA.119.012322.
- [15] Sugane H, Kataoka Y, Otsuka F, Nakaoku Y, Nishimura K, Nakano H, et al. Cardiac outcomes in patients with acute coronary syndrome attributable to calcified nodule. *Atherosclerosis.* 2021; 318:70-75. doi: 10.1016/j.atherosclerosis.2020.11.005.
- [16] Torii S, Sato Y, Otsuka F, Kolodgie FD, Jinnouchi H, Sakamoto A, et al. Eruptive Calcified Nodules as a Potential Mechanism of Acute Coronary Thrombosis and Sudden Death. *J Am Coll Cardiol.* 2021; 77(13):1599-1611. doi: 10.1016/j.jacc.2021.02.016.
- [17] Bhatt DL, Lopes RD, Harrington RA. Diagnosis and Treatment of Acute Coronary Syndromes: A Review. *JAMA.* 2022; 327(7):662-675. doi: 10.1001/jama.2022.0358.
- [18] Hedayati T, Yadav N, Khanagavi J. Non-ST-Segment Acute Coronary Syndromes. *CardiolClin.* 2018; 36(1):37-52. doi: 10.1016/j.ccl.2017.08.003.
- [19] Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021; 42(14):1289-1367. doi: 10.1093/eurheartj/ehaa575.
- [20] Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, Mueller C. Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. *J Am Coll Cardiol.* 2017; 70(8):996-1012. doi: 10.1016/j.jacc.2017.07.718.
- [21] Boeddinghaus J, Twerenbold R, Nestelberger T, Badertscher P, Wildi K, Puelacher C, du Fay de Lavallaz J, et al. Clinical Validation of a Novel High-Sensitivity Cardiac Troponin I Assay for Early Diagnosis of Acute Myocardial Infarction. *Clin Chem.* 2018; 64(9):1347-1360. doi: 10.1373/clinchem.2018.286906.
- [22] Neumann JT, Twerenbold R, Ojeda F, Sörensen NA, Chapman AR, Shah ASV, et al. Application of High-Sensitivity Troponin in Suspected Myocardial Infarction. *N Engl J Med.* 2019; 380(26):2529-2540. doi: 10.1056/NEJMoa1803377.

- [23] Lopez-Ayala P, Nestelberger T, Boeddinghaus J, Koechlin L, Ratmann PD, Strebel I, et al. Novel Criteria for the Observe-Zone of the ESC 0/1h-hs-cTnT Algorithm. *Circulation*. 2021; 144(10):773-787. doi: 10.1161/CIRCULATIONAHA.120.052982.
- [24] Garg P, Underwood SR, Senior R, Greenwood JP, Plein S. Noninvasive cardiac imaging in suspected acute coronary syndrome. *Nat RevCardiol*. 2016; 13(5):266-75. doi: 10.1038/nrcardio.2016.18.
- [25] Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med*. 2012; 367(4):299-308. doi: 10.1056/NEJMoa1201161.
- [26] Lee KK, Bularga A, O'Brien R, Ferry AV, Doudesis D, Fujisawa T, et al. Troponin-Guided Coronary Computed Tomographic Angiography After Exclusion of Myocardial Infarction. *J Am Coll Cardiol*. 2021; 78(14):1407-1417. doi: 10.1016/j.jacc.2021.07.055.
- [27] Azarisman SM, Teo KS, Worthley MI, Worthley SG. Role of cardiovascular magnetic resonance in assessment of acute coronary syndrome. *World J Cardiol*. 2014; 6(6):405-14. doi: 10.4330/wjc.v6.i6.405.
- [28] Bergmark BA, Mathenge N, Merlini PA, Lawrence-Wright MB, Giugliano RP. Acute coronary syndromes. *Lancet*. 2022; 399(10332):1347-1358. doi: 10.1016/S0140-6736(21)02391-6.
- [29] Tolsma RT, de Koning ER, Fokkert MJ, van der Waarden NW, van 't Hof AW, Backus BE. Management of patients suspected for non-ST elevation-acute coronary syndrome in the prehospital phase. *Future Cardiol*. 2023; 19(13):639-647. doi: 10.2217/fca-2023-0049.
- [30] Solà-Muñoz S, Jorge M, Jiménez-Fàbrega X, Jiménez-Delgado S, Azeli Y, Marsal JR, et al. Prehospital stratification and prioritisation of non-ST-segment elevation acute coronary syndrome patients (NSTEACS): the MARIACHI scale. *Intern Emerg Med*. 2023; 18(5):1317-1327. doi: 10.1007/s11739-023-03274-z.
- [31] Atwood J. Management of Acute Coronary Syndrome. *Emerg Med Clin North Am*. 2022; 40(4):693-706. doi: 10.1016/j.emc.2022.06.008.
- [32] Jung J, Bord S. Emergency department management of non-ST-segment elevation myocardial infarction. *Emerg Med Pract*. 2020; 22(1):1-24.
- [33] Eggers KM, James SK, Jernberg T, Lindahl B. Timing of coronary angiography in patients with non-ST-elevation acute coronary syndrome: long-term clinical outcomes from the nationwide SWEDEHEART registry. *EuroIntervention*. 2022; 18(7):582-589. doi: 10.4244/EIJ-D-21-00982.
- [34] Urban P, Mehran R, Collieran R, Angiolillo DJ, Byrne RA, Capodanno D, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. *Circulation*. 2019; 140(3):240-261. doi: 10.1161/CIRCULATIONAHA.119.040167.
- [35] Landi A, Alasnag M, Heg D, Frigoli E, Malik FTN, Gomez-Blazquez I, et al. Abbreviated or Standard Dual Antiplatelet Therapy by Sex in Patients at High Bleeding Risk: A Prespecified Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol*. 2023; 22:e234316. doi: 10.1001/jamacardio.2023.4316.
- [36] Zeitouni M, Kerneis M, Nafee T, Collet JP, Silvain J, Montalescot G. Anticoagulation in Acute Coronary Syndrome-State of the Art. *ProgCardiovasc Dis*. 2018; 60(4-5):508-513. doi: 10.1016/j.pcad.2018.01.004.
- [37] Mahmood MM, Nawaz MJ. Prescription of statins after acute coronary syndrome; a single-centreobservational study. *J Pak Med Assoc*. 2023; 73(3):646-649. doi: 10.47391/JPMA.4328.
- [38] Sá FM, Morais J. Beta-blockers in acute coronary syndrome patients: The concept of 'gradient of benefit'. *Rev Port Cardiol (Engl Ed)*. 2021; 40(10):811-812. doi: 10.1016/j.repce.2021.10.017.
- [39] Gaba P, Christiansen EH, Nielsen PH, Murphy SA, O'Gara PT, Smith PK, et al. Percutaneous Coronary Intervention vs Coronary Artery Bypass Graft Surgery for Left Main Disease in Patients With and Without Acute Coronary Syndromes: A Pooled Analysis of 4 Randomized Clinical Trials. *JAMA Cardiol*. 2023; 8(7):631-639. doi: 10.1001/jamacardio.2023.1177.
- [40] Perera D, Clayton T, O'Kane PD, Greenwood JP, Weerackody R, Ryan M, et al. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. *N Engl J Med*. 2022; 387(15):1351-1360. doi: 10.1056/NEJMoa2206606.
- [41] Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020; 41(3):407-477. doi: 10.1093/eurheartj/ehz425.

- [42] Taylor RS, Dalal HM, McDonagh STJ. The role of cardiac rehabilitation in improving cardiovascular outcomes. *Nat Rev Cardiol.* 2022; 19(3):180-194. doi: 10.1038/s41569-021-00611-7.
- [43] Damluji AA, Forman DE, Wang TY, Chikwe J, Kunadian V, Rich MW, et al. American Heart Association Cardiovascular Disease in Older Populations Committee of the Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Radiology and Intervention; and Council on Lifestyle and Cardiometabolic Health. Management of Acute Coronary Syndrome in the Older Adult Population: A Scientific Statement From the American Heart Association. *Circulation.* 2023; 147(3):e32-e62. doi: 10.1161/CIR.0000000000001112.
- [44] Greco A, Adorni R, De Matteis C, D'Addario M, Fattirolli F, Franzelli C, et al. Latent change models of lifestyle in acute coronary syndrome patients: Are lifestyle changes associated with resilience changes? *HealthPsychol Open.* 2023; 10(1):20551029231167836. doi: 10.1177/20551029231167836.
- [45] Rath D, Geisler T. Optimal antiplatelet and anticoagulation strategies in acute coronary syndromes. *Herz.* 2020; 45(6):528-536. English. doi: 10.1007/s00059-020-04947-7.
- [46] Sharma R, Kumar P, Prashanth SP, Belagali Y. Dual Antiplatelet Therapy in Coronary Artery Disease. *Cardiol Ther.* 2020; 9(2):349-361. doi: 10.1007/s40119-020-00197-0
- [47] Wang Q, Liang C. Role of Lipid-Lowering Therapy in Low-Density Lipoprotein Cholesterol Goal Attainment: Focus on Patients With Acute Coronary Syndrome. *J Cardiovasc Pharmacol.* 2020; 76(6):658-670. doi: 10.1097/FJC.0000000000000914.
- [48] Koskinas KC, Mach F, Räber L. Lipid-lowering therapy and percutaneous coronary interventions. *EuroIntervention.* 2021; 16(17):1389-1403. doi: 10.4244/EIJ-D-20-00999.
- [49] Abi Khalil C, Zubaid M, Mekhaimar M, Asaad N, Mahfoud Z, Al Suwaidi J. Beta-blockers and Short-Term Cardiovascular Outcomes In Patients Hospitalized For Acute Coronary Syndrome and a Left Ventricular Ejection Fraction ≥ 40 . *Sci Rep.* 2020; 10(1):3520. doi: 10.1038/s41598-020-60528-y.
- [50] Li Z, Sun H, Hao Y, Liu H, Jin Z, Li L, et al. Renin-angiotensin system inhibition and In-hospital mortality in acute coronary syndrome patients with advanced renal dysfunction: Findings from CCC-ACS project and a nationwide electronic health record-based cohort in China. *Eur Heart J Qual Care Clin Outcomes.* 2023; 2:qcad006. doi: 10.1093/ehjqcco/qcad006.
- [51] Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol.* 2019; 7(10):776-785. doi: 10.1016/S2213-8587(19)30249-9