Chapter 1

ACUTE CORONARY SYNDROME

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Acute Coronary Syndrome (ACS) refers to a set of heart conditions characterized by the obstruction of the coronary arteries, potentially leading to acute myocardial infarction. These conditions represent a group of severe clinical problems that affect millions of people worldwide. There are two types of

ischemia caused by ACS: ischemia due to elevated ST segments and ischemia caused by an excess demand for oxygen in relation to the capacity of the coronary arteries (Carey, 2016). Both types can be identified through cardiovascular exams performed in hospital emergencies. The ECG has the necessary sensitivity to detect specific markers, occurring when ischemia causes cell death in cardiac tissue, and these residues are identified through blood tests. In the context of medical urgency and emergency, ACS is one of the main causes of hospitalization and mortality in emergency services (Wang *et al*., 2021).

ACS causes changes in specific markers on the ECG, such as elevated ST segment levels. The electrocardiogram shows these changes, and the analysis of ST segment levels is crucial for diagnosing the syndrome. Studies show that the mortality of patients with elevated ST segment levels is higher than those with low levels of this marker. Immediate treatment aims to restore blood flow to the heart. The latest trends in the diagnosis and treatment of ACS involve advanced imaging techniques, such as coronary angiography and echocardiography (ECG), in addition to thorough physical and laboratory examinations, aiming to establish an accurate differential diagnosis. Therapeutic management includes both drug therapy, with antiplatelet and anticoagulant agents, and invasive interventions, such as angioplasty and coronary artery bypass surgery (Amiri, 2019). Patients affected by ACS require continuous monitoring due to the risk of cardiac, mechanical, and thromboembolic complications (Thomas *et al*., 2021).

Recent technological advances have improved the diagnostic and prognostic accuracy of ACS. The use of techniques such as computed tomography for coronary artery calcium assessment and carotid ultrasound for atherosclerotic plaque analysis has proven effective (Falk *et al*., 2013). Additionally, the role of NK cells in modulating the inflammatory response and preventing cardiac fibrosis has emerged as a promising therapeutic approach (Kumrić *et al*., 2020). These advances provide a more precise and personalized approach to the treatment of cardiovascular disease. Acute Coronary Syndrome remains a significant challenge for healthcare systems due to its complexity and impact on cardiovascular morbidity and mortality. Recent advances in diagnostic and therapeutic techniques have improved clinical management and patient outcomes, promoting a more precise and personalized approach to treating this critical condition (Kumar *et al*., 2021).

EPIDEMIOLOGY

Acute Coronary Syndrome (ACS) is the leading cause of mortality worldwide. The global incidence of ACS exceeds 20 million cases per year (Simoni *et al*.., 2023). After an ACS event, the risk of future events remains high, as patients who have had a myocardial infarction (MI) are five to six times more likely to have another MI compared to those who have never had coronary heart disease (Pottle, 2020). Despite the significant incidence of cardiovascular disease, mortality from ischemic heart disease has decreased in the general

population over the past 40 years, likely due to technological medical advancements and the refinement of major guidelines (Khraishah *et al*.., 2023). However, this reduction in mortality is more pronounced in men than in women, and the prevalence and incidence of MI in younger women (under 55 years) have increased dramatically compared to men of similar age (Khraishah *et al*.., 2023).

Studies on acute coronary syndrome (ACS) reveal significant variations in the presentation and outcomes of the disease. Men tend to manifest ACS at younger ages, while women often develop the condition post-menopause, presenting atypical symptoms that can delay diagnosis (Haider *et al*.., 2020). More developed regions generally show better survival rates, reflecting disparities in access to healthcare (Pottle, 2020). Additionally, environmental factors such as air pollution have been associated with increases in ACS incidence, more severely affecting urban populations (Mills; Pope, 2022). Elderly individuals and those with pre-existing conditions are particularly vulnerable to the adverse effects of pollution (Mills & Pope, 2022). Socioeconomic disparities also influence outcomes, with patients from lower socioeconomic classes presenting higher incidences of severe complications and worse post-event recovery (Simoni *et al*.., 2023). These demographic nuances are crucial for personalizing ACS prevention and treatment strategies, aiming to improve outcomes for all affected groups (Viana *et al*.., 2020; Zhang *et al*.., 2022).

Various factors contribute to the observed differences in mortality trends and outcomes of acute coronary syndrome (ACS) between men and women. These factors include biological aspects, variations in symptom presentation, associated comorbidities, and social and lifestyle influences. One of the most important biological factors is the difference in coronary artery size between men and women. Women have significantly smaller epicardial coronary arteries, which can affect the clinical presentation and outcomes of ACS. Additionally, dysregulation of DNA methylation (DNAm) can contribute to adverse changes in gene expression, affecting various cardiovascular risk factors, including obesity, atherosclerosis, inflammation, hypertension, dyslipidemia, and glucose metabolism. These factors collectively increase the risk of developing coronary artery disease (CAD) in women (Haider *et al*.., 2019).

The manifestation of symptoms in men and women also differs significantly. While precordial pain is the most common symptom in more than 80% of ACS cases for both sexes, women are more likely to present atypical symptoms, often attributing their symptoms to non-cardiac conditions such as esophageal acid reflux, stress, or anxiety. This difference in symptom presentation can lead to delayed or incorrect diagnosis in women, negatively affecting clinical outcomes. Young women with ACS often have a higher prevalence of comorbidities such as depression, hypertension, diabetes, and obesity compared to men of the same age group (Haider *et al*., 2019). These associated conditions can complicate the treatment and management of ACS, resulting in worse outcomes. For example, the presence of depression can influence treatment adherence and recovery after a cardiac event.

Social and lifestyle factors also play a crucial role in the differences in mortality and outcomes of ACS between men and women. Differences in access to healthcare and awareness of heart diseases can influence early detection and effective treatment of ACS. Additionally, lifestyle practices such as diet and physical activity levels can vary significantly between men and women, impacting the risk of developing CAD and other cardiovascular problems (Haider *et al.*, 2019). These biological factors, differences in symptom presentation, prevalence of comorbidities, and social and lifestyle influences combine to explain the observed differences in mortality and outcomes of ACS between men and women.

Risk factors for developing cardiovascular diseases are similar between men and women, although there are variations in the prevalence, incidence, and age of manifestation of these diseases according to sex (Haider *et al.*., 2020). Factors such as hypertension, diabetes, smoking, and high cholesterol contribute to the development of cardiovascular diseases in both sexes. However, the frequency with which these factors appear and the age at which diseases manifest can differ between the sexes.

Women with ACS are generally older and have multiple comorbidities (Haider et al., 2020). Studies suggest that women with ACS are generally 8 to 10 years older than men with the same clinical condition (Khraishah *et al.*, 2023). Additionally, women who smoke and/or have diabetes are at higher risk of ACS compared to men with the same comorbidities (Haider *et al.*, 2020). In the global case-control INTERHEART study with 27,000 individuals from 52 countries, it was observed that women with diabetes were 4.3 times more likely to suffer a myocardial infarction (MI) compared to non-diabetic women, while men with diabetes had a 2.7 times higher risk of MI compared to non-diabetic men (Khraishah *et al.*, 2023). Young women tend to have a poorer pre-event quality of life than men of the same age (Haider *et al.*, 2020). Another important finding is that younger women (under 65 years) with a maternal history of MI have a four times higher risk of ACS compared to men of the same age or older women (Haider *et al.*, 2020).

In terms of socioeconomic risks, women hospitalized for cardiovascular events tend to have greater social frailty, lower socioeconomic status, higher incidence of depression, and greater occurrence of physical problems compared to hospitalized men (Haider *et al.*, 2020). An alternative analysis notes that men and women have significant differences in gut microbiota, specifically in levels of trimethylamine N-oxide, which may contribute to survival after ACS. One study observed 30-day event-free survival for women and six-month event-free survival for men, related to the previously mentioned compound (Haider *et al.*, 2020).

Pregnancy-related complications also increase women›s cardiovascular risk. Studies show that the risk of coronary artery disease (CAD) is higher in women with a history of preeclampsia, placental abruption, gestational hypertension, and gestational diabetes (Haider *et al.*, 2020). Additionally, ethnic and racial factors also influence the risk of ACS. Generally, Black women in the United States have a higher prevalence of traditional cardiovascular disease risk factors, including diabetes, hypertension, and smoking, compared to non-Hispanic White women (Khraishah *et al.*, 2023).

Young women may be more likely to have systemic inflammatory disorders (SID), conferring a high risk of MI and cardiovascular mortality. Among 2,097 patients aged ≤ 50 years who presented with an MI episode, 53 (2.5%) had an SID diagnosis, distributed as follows: 64% psoriasis, 23% systemic lupus erythematosus, 9% rheumatoid arthritis, and 4% other SIDs (Khraishah *et al.*, 2023). These varied effects of sex, age, environmental, and hereditary influences on the development of ACS highlight the condition›s complexity.

Crucial statistics on acute coronary syndrome reveal significant disparities and multiple determining factors. Women often have higher mortality rates due to less typical symptoms and underdiagnosis compared to men (Haider *et al.*, 2020). Patients with cognitive impairment have higher in-hospital mortality and increased rates of cardiovascular complications, reflecting the complexity of clinical outcomes in these cases (Pottle, 2020). The adverse influence of environmental factors such as air pollution and emotional stress exacerbates the risk of severe complications and mortality among individuals with acute coronary syndrome (Mills & Pope, 2022). Socioeconomic disparities persist over time, with patients of lower socioeconomic status facing worse clinical outcomes and higher mortality, highlighting the need for interventions to reduce these inequalities (Simoni *et al.*, 2023). Delays in recognizing symptoms and implementing appropriate treatments significantly contribute to high mortality rates among patients with acute coronary syndrome (Viana *et al.*, 2020). Additionally, glycemic variability emerges as a significant risk factor for adverse cardiovascular events, underscoring the importance of stringent glycemic control in the effective clinical management of this condition (Zhang *et al.*, 2022). These findings highlight the multifactorial complexity of ACS and emphasize the need for integrated and personalized approaches to improve clinical outcomes and reduce the mortality associated with this severe cardiovascular condition.

Over the past four decades, age-adjusted mortality for cardiovascular diseases (CVD) has steadily decreased. However, this decrease has been less pronounced in women than in men. Cardiovascular diseases remain the leading cause of morbidity and mortality in Europe, accounting for 49% of deaths in women and 40% of deaths in men (Haider *et al.*, 2019). Recent studies report a significant increase in case fatality rates of acute coronary syndromes (ACS) in young women under 55, while mortality from coronary artery disease (CAD) has decreased in younger men. A recent meta-analysis concluded that the risk of CAD is higher in women with a history of preeclampsia, placental abruption, gestational hypertension, and diabetes. These trends may vary among different populations and regions due to factors such as access to healthcare, prevalence of specific risk factors, and lifestyle practices (Haider *et al.*, 2019).

DIAGNOSIS

Acute coronary syndrome (ACS) has a sudden onset and rapid development, which can lead to life-threatening malignant conditions at any moment (Wang *et al.*, 2020). The morbidity and mortality of ACS compel emergency physicians to work with limited time to determine the course of action, significantly altering the disease›s progression. Rapid diagnosis is essential in any patient presenting with chest pain or anginal equivalent in the emergency room and is based on a series of findings that collectively lead to a definitive conclusion (Geyer *et al.*, 2020). The diagnosis is not always straightforward, as many patients may present with atypical symptoms and show no changes in supplementary tests.

The main complaint of a patient with ACS is unstable precordial, retrosternal, or diffuse anginal chest pain. The pain has a sudden onset, is moderate to intense, and is described as a tightness or burning sensation (Amiri, 2019). The pain may radiate to the epigastrium, upper limbs, shoulders, back, and neck, and may also cause epigastric pain, nausea, vomiting, sweating, dyspepsia, hypotension, and syncope (Amiri, 2019). The physical examination is generally nonspecific, resembling that of patients with acute myocardial infarction (AMI), and may reveal arterial hypotension (SBP < 85 mmHg), sweating and clammy skin, tachycardia (> 100 bpm), systolic murmurs of mitral origin, and pulmonary crackles (Amiri, 2019; Goldschmied *et al.*, 2024).

Chest pain is the main symptom of ischemia, but ischemia can also present as anginal equivalents: epigastric pain, dyspepsia, dyspnea, nausea and vomiting, sweating, hypotension, and syncope. Patients with acute coronary syndrome (ACS) often exhibit symptoms and signs of myocardial ischemia at rest with minimal exertion. These symptoms and signs are similar to those of chronic angina, with retrosternal chest pain that may radiate to the jaw, left shoulder, and arm. Dyspnea, nausea, sweating, and syncope may accompany chest pain or be the only acute symptoms. About one-third of AMI patients do not present with chest pain; these patients tend to be older, female, diabetic, and at higher risk of subsequent mortality. Although chest pain is the main symptom, up to 30% of patients may not experience chest pain, with elderly patients (> 75 years), women, and those with diabetes, chronic kidney disease, or dementia more commonly presenting with anginal equivalents in the emergency department with atypical complaints, including epigastric pain, dyspepsia, dyspnea, and rarely syncope. Patients may even present with generalized weakness or mental confusion. Delays in diagnosis have been well-documented and often lead to delays in therapy. Patients ≥ 75 years old have higher in-hospital mortality and are more likely to have heart failure associated with myocardial infarction, with the risk progressively increasing in each successive age group from 36% at 65-69 years old to 65% in those ≥ 85 years old (Goldschmied *et al.*, 2024).

In recent years, various innovative technologies and techniques have emerged for the diagnosis of Acute Coronary Syndrome (ACS), enhancing precision and early detection.

Laboratory diagnosis is performed using cardiac biomarkers, complete blood count, and lipid profile. Cardiac biomarkers are called myocardial necrosis markers (MNM), the main ones being troponin, myoglobin, and CK-MB. Troponin is the primary cardiac biomarker of cellular content, released after myocardial necrosis; it is a regulatory protein complex found only in the myocardium, with two main isoforms: cardiac troponin T (cTnT) and cardiac troponin I (cTnI), with cTnT being the most sensitive. After myocardial injury, serum troponin concentration begins to rise between 3-6 hours, peaking at 24 hours, and normalizing between 7-14 days (Moeckel, 2019; Wang *et al*., 2020; Goldschmied *et al*., 2024).

Myoglobin is another type of cellular origin cardiac biomarker used to guide the diagnosis of ACS. It is a protein involved in oxygen storage found in both muscles and myocardium, indicating injuries in striated skeletal or cardiac muscle. Its serum concentration rises earlier compared to troponin, starting 2-3 hours after injury and peaking at 8-12 hours. Its use is always associated with troponin values, as together they increase the negative predictive value of myocardial injury (Geyer *et al*., 2020; Gajardo, Lillo-Moya, and Llancaqueo, 2024). The enzyme creatine kinase-MB (CK-MB) is an isoenzyme of creatine kinase (CK) present in striated skeletal muscle but primarily in cardiac muscle. Its serum elevation occurs 4-6 hours after myocardial injury, peaking between 12-20 hours. It is a less specific test, always requested in conjunction with troponin or in situations where troponin is unavailable (Moeckel, 2019; Geyer *et al*., 2020).

Patients with a history of cardiovascular disease and unstable angina first exhibit increased serum concentrations of myoglobin, followed by troponin, and finally CK-MB (Moeckel, 2019; Amiri, 2019). Patients with ACS may present elevated erythrocyte sedimentation rate and leukocytosis with a left shift (Amiri, 2019). Total and fractional cholesterol and triglycerides should be collected to assess the presence of dyslipidemia, as it is a risk factor for cardiovascular diseases and a predictor of ischemia due to atheroma plaque in confirmed ACS cases (Moeckel, 2019; Amiri, 2019; Goldschmied *et al*., 2024).

Among imaging tests, the electrocardiogram (ECG) is the initial and most important test and should be performed within 10 minutes of the admission of patients with typical ACS signs and symptoms (Moeckel, 2019). The ECG is a sensitive and specific test for detecting ischemic changes, suggesting infarctions due to complete or partial obstructions (Moeckel, 2019). The condition most closely linked to ACS is ST-segment elevation myocardial infarction (STEMI), indicating infarction due to complete myocardial obstruction (Moeckel, 2019). If the initial ECG is inconclusive, another ECG should be performed after 5-10 minutes. If the patient remains under observation, the ECG should be repeated every 3 hours for a total period of 12 hours or whenever there are changes in the patient›s clinical condition (Moeckel, 2019).

Patients with a normal ECG still have a 2% risk of presenting with ACS (Khraishah et al., 2023). Patients with nonspecific ECG changes but anginal symptoms have up to a 9% chance of having ACS (Khraishah *et al*., 2023). Transthoracic echocardiography

(TTE) should be performed on all patients with suspected ACS as it is easy to perform, non-invasive, and has high sensitivity and specificity in identifying ventricular contractility abnormalities, ejection fraction, and mechanical complications that may be involved in the syndrome. Computed tomography angiography (CTA) is the diagnostic test of choice for assessing the extent of injury, perfusion, and prognosis in patients with ACS, especially those with non-ST-segment elevation (NSTEMI) (Kakizaki *et al*., 2022).

To assist in the reliable diagnosis of chest pain and therapeutic strategy in the emergency setting, the HEART score was developed (Moeckel, 2019). This score estimates the probability of major cardiovascular disorders within 6 weeks in patients with suspected ACS, especially those with nonspecific chest pain and normal ECG and troponins. It is used in the emergency setting, evaluating clinical history, ECG results, age, risk factors for heart disease, and serum troponin level (Moeckel, 2019). Each variable consists of 2 points, corresponding to a maximum score of 10 points. The higher the score, the greater the suspicion of ACS, and patients should be admitted to intensive care units and monitored (Moeckel, 2019; Khraishah *et al*., 2023).

Differentiating anginal pain is essential. Among the differential diagnoses, pulmonary thromboembolism is the main one, being a high morbidity and mortality syndrome, presenting dyspnea as the main symptom that differs from ACS, even with elevated serum troponins (Moeckel, 2019; Amiri, 2019). Acute aortic syndromes, represented by the triad of acute aortic dissection, intramural hematoma, and penetrating ulcer, have low incidence but strongly fit as differential diagnoses after excluding ACS (Moeckel, 2019; Amiri, 2019). Pericarditis is a low-prevalence condition, affecting only 5% of the general population, but it presents typical pleuritic chest pain in sharp stabs located in the anterior chest, worsening with inspiration or coughing (Moeckel, 2019; Amiri, 2019). Cardiac tamponade generates anginal pain similar to pericarditis but is strongly associated with acute conditions post-cardiological invasive procedures, such as biopsies, surgeries, pacemaker implants, angioplasty, and even AMI (Moeckel, 2019; Amiri, 2019). Pneumothorax also causes sudden chest pain, but associated with ventilatory-dependent dyspnea and worsening with exertion (Moeckel, 2019; Amiri, 2019).

Other technologies that demonstrate advances in ACS diagnosis include machine learning algorithms, which have shown great potential in predicting major adverse cardiac events (MACE) and acute coronary artery occlusion (ACAO). These algorithms outperform the accuracy of the «TropOut» score, which does not use troponin, by utilizing a wide range of clinical and pre-clinical data, quickly identifying at-risk patients even without troponin availability (Goldschmied *et al*., 2024). Additionally, metabolomics also stands out as an innovative tool for accurate and less invasive ACS and coronary artery disease (CAD) diagnoses, using techniques such as nuclear magnetic resonance (NMR) and mass spectrometry (MS) to identify new biomarkers, improving diagnostic and prognostic accuracy (Amiri, 2019). Recently, non-coding RNAs (ncRNAs), such as microRNAs

(miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have also emerged as promising biomarkers for ACS due to their stability in the blood, contributing to early detection, accurate diagnosis, and personalized treatment (Wang *et al.*, 2020).

Additionally, besides biomarkers, imaging tests have also advanced, such as optical coherence tomography (OCT), a high-resolution imaging technique used in the diagnosis of acute coronary syndrome (ACS) to identify three main types of atherosclerotic plaques: plaque rupture (PR), plaque erosion (PE), and calcified nodules (CN). It allows for a detailed examination of the internal structures of coronary arteries, offering an accurate diagnosis of the causes of ACS and significantly influencing the prognosis of patients. Patients with PE have better prognoses after percutaneous coronary intervention (PCI) compared to those with PR, while patients with CN have the worst clinical outcomes, including higher incidence of major adverse cardiac events (MACE) and cardiovascular mortality. OCT also allows for adjustments in PCI strategy during emergencies, improving procedural outcomes (Kondo*et al.*, 2023). Studies indicate that fractional flow reserve derived from OCT (OCT-FFR) has a robust correlation with wire-based FFR and is associated with the presence of functional ischemia. Low OCT-FFR values have been linked to target vessel failure (TVF), and its inclusion in post-PCI evaluations may improve the detection of at-risk patients, optimizing clinical outcomes (Kakizaki *et al.*, 2022).

The adoption of these new technologies and techniques has considerably improved the accuracy of diagnoses and early identification of ACS. The increased sensitivity of biomarkers allows for faster and more accurate detection of cardiac muscle injuries, while advanced imaging methods enable a detailed analysis of the heart›s structure and function (Geyer *et al.*, 2020; Moeckel, 2019; Gajardo, Lillo-Moya; Llancaqueo, 2024; Kondo *et al.*, 2023; Kakizaki *et al.*, 2022). Additionally, the use of ncRNAs as biomarkers adds a new perspective to the detection and prediction of ACS, further personalizing patient treatment and improving clinical outcomes (Wang *et al.*, 2020). In summary, recent advances in highly sensitive biomarkers, cutting-edge imaging techniques, and the discovery of non-coding RNAs have revolutionized the diagnosis of Acute Coronary Syndrome. These innovations enable a more accurate and early approach, fundamental for effective management and improved patient outcomes (Geyer *et al.*, 2020; Moeckel, 2019; Gajardo, Lillo-Moya; Llancaqueo, 2024; Kondo *et al.*, 2023; Kakizaki *et al.*, 2022; Wang *et al.*, 2020).

TREATMENT

The treatment of acute coronary syndrome (ACS) is essential and should focus on early detection, risk stratification, and immediate intervention, aiming to reduce cardiac damage, improve clinical outcomes, and prevent severe complications. ACS is one of the leading causes of cardiovascular morbidity and mortality worldwide, with increasing importance given the aging population (Crea;Libby, 2017). Following the diagnosis of ACS, the initial

therapeutic approach includes supportive measures, antithrombotic and anticoagulant drug therapy, and invasive or conservative reperfusion strategies. Patients with ACS require early risk stratification to guide the search for the best intervention, considering their needs. Therapeutic adjustments also need to be made, as despite inflammation playing the main role in the pathophysiology of ACS, other underlying mechanisms need to be considered: plaque rupture with systemic inflammation, plaque rupture without systemic inflammation, plaque erosion, and plaque without thrombus; allowing for the implementation of precise and personalized therapeutic approaches according to the etiology (Crea ; Libby, 2017).

Historically, aspirin has been the first-line antithrombotic treatment in cardiovascular diseases. Subsequently, new antiplatelet agents, including P2Y12 inhibitors, were evaluated in addition to aspirin. The choice of the optimal antiplatelet strategy after ACS or PCI at the individual level is a conundrum that requires stratification of ischemic and hemorrhagic risks (Guedeney *et al.*, 2020). Among conventional pharmacological treatments, antiplatelet agents, especially P2Y12 receptor inhibitors (clopidogrel, prasugrel, and ticagrelor), stand out for preventing platelet aggregation and suppressing systemic inflammation (Thomas *et al.*, 2021).

Large randomized clinical trials and recent meta-analyses have demonstrated that dual therapy based on a non-vitamin K oral anticoagulant and a P2Y12 inhibitor is superior to triple therapy based on a vitamin K antagonist with dual antiplatelet therapy (DAPT) for preventing bleeding. However, several of these trials also reported an increase, although not significant, in coronary ischemic events in case of aspirin discontinuation (Guedeney *et al.*, 2020). In a recent study, clopidogrel and ticagrelor were predominantly used as P2Y12 inhibitors based on single antiplatelet therapy. Given the significant proportion of patients with an inadequate response to clopidogrel therapy, as detected by platelet function or genetic tests, concerns have arisen regarding its use as single antiplatelet therapy, particularly in patients without a history of oral anticoagulants (OAC) (Guedeney *et al.*, 2020). In a retrospective study based on the Israeli Acute Coronary Syndrome Survey (ACSIS) registry, patients after ACS present a particularly increased risk of recurrent cardiovascular events (Grinberg *et al.*, 2022). However, strategies based on P2Y12 inhibitors› genotype or platelet function testing did not result in a significant reduction of ischemic complications in dedicated trials, suggesting that clopidogrel alone can be safely used in these patients. Consistently, no significant interaction was found between the effect of early aspirin discontinuation and prolonged single antiplatelet therapy with clopidogrel or ticagrelor in patients who do not require chronic OAC (Guedeney *et al.*, 2020).

The results of early aspirin discontinuation on safety and efficacy events remained consistent according to the type of P2Y12 inhibitors predominantly used (i.e., clopidogrel vs. ticagrelor). Furthermore, the optimal timing for aspirin discontinuation remains unclear. In all trials with patients presenting an underlying indication for chronic OAC, aspirin use was allowed during Percutaneous Coronary Intervention (PCI) and before randomization, which

generally occurs between four hours after the arterial sheath removal and up to 14 days after PCI/ACS. On the other hand, in studies including patients without an indication for chronic OAC, aspirin discontinuations occurred one month or three months after randomization (weighted mean DAPT duration of 1.7 months). Notably, no significant interaction was found in the effect of aspirin discontinuation between one month and three months (Guedeney *et al.*, 2020).

In ACS caused by plaque rupture with inflammation, colchicine, an antirheumatic drug, was able to reduce cardiovascular events in a medium-sized open-label randomized study (Crea; Libby, 2017). Colchicine›s mechanism of action is related to the activation of the NLRP3 inflammasome, resulting in a reduction of interleukin IL-1β and interleukin 18 (Wang et al., 2020). A large phase III study (n>10,000) determined a 15% reduction in the primary endpoint of myocardial infarction and a 30% reduction in revascularization procedures in the group that received canakinumab, an anti-IL-1β monoclonal antibody, every three months in patients with a history of MI and CRP > 2mg/L, reinforcing the contribution of inflammation to the atherosclerotic process (Crea; Libby, 2017).

IL-1β inhibition with canakinumab has shown success in treating residual inflammatory risk (RIR) in coronary arteries, raising the potential implication of anti-inflammatory therapy in ACS patients. Reducing inflammation through cytokine inhibition such as IL-1β may help stabilize atherosclerotic plaques and reduce the risk of acute cardiovascular events. This therapeutic approach represents a new perspective in treating ACS, focusing not only on reducing cholesterol but also on modulating the inflammatory response (Wang *et al.*., 2020).

Studies indicate that the use of anacetrapib, a potent inhibitor of cholesterol ester transfer protein (CETP), in ACS due to plaque rupture without inflammation, not only increases high-density lipoprotein (HDL) but also reduces low-density lipoprotein (LDL). However, more studies are needed to attribute event reduction to HDL increase, possibly associated with atherosclerotic plaque stabilization. Statins and ezetimibe can also reduce cholesterol crystal formation. Cyclodextrin has been used to combat cholesterol crystal accumulation by solubilizing them (Crea; Libby, 2017).

Currently, the treatment of epicardial spasm, the main contributor to atherosclerotic plaque instability in ACS patients without thrombus in plaques, uses long-acting nitrates and calcium channel blockers. However, many patients do not respond to these vasodilators. Understanding post-receptor mechanisms responsible for nervous system hyperreactivity and epicardial spasm is necessary to create new therapeutic alternatives (Crea; Libby, 2017).

Immunological and inflammatory dysfunctions have been associated with the pathogenesis of acute coronary syndrome. Studies show that inflammation plays an important role in the development and progression of cardiovascular diseases, including acute coronary syndrome. The activation of the immune system and the inflammatory response can contribute to the formation of atherosclerotic plaques and the instability of

these plaques, leading to acute events such as myocardial infarction. It is important to consider these aspects in the treatment and prevention of acute coronary syndrome (Wang *et al*., 2020).

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