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THERAPEUTIC APPROACH IN NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION: CURRENT CLINICAL EVIDENCE

ABORDAGEM TERAPÊUTICA NO INFARTO AGUDO DO MIOCÁRDIO SEM SUPRADESNIVELAMENTO DO SEGMENTO ST: EVIDÊNCIAS CLÍNICAS ATUAIS

ABORDAJE TERAPÉUTICO DEL INFARTO AGUDO DE MIOCARDIO SIN ELEVACIÓN DEL SEGMENTO ST: EVIDENCIA CLÍNICA ACTUAL

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ABSTRACT

Non-ST-segment elevation myocardial infarction (NSTEMI) is a complex clinical condition characterized by acute myocardial ischemia without ST-segment elevation on electrocardiogram. This study provides a comprehensive review of the pathophysiological mechanisms, diagnosis, risk stratification, and therapeutic strategies for NSTEMI, emphasizing current clinical evidence. The role of high-sensitivity cardiac troponins in early detection of myocardial injury and the importance of risk stratification for guiding

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pharmacological and interventional treatment are highlighted. Despite significant advances, mortality and morbidity remain substantial, particularly in resource-limited settings. Primary and secondary prevention through strict control of cardiovascular risk factors remains central to reducing recurrent events.

Keywords: Acute Myocardial Infarction. NSTEMI. Troponin. Risk Stratification. Cardiovascular Prevention.

RESUMO
O Infarto Agudo do Miocárdio sem supradesnivelamento do segmento ST (IAMSSST) constitui uma condição clínica complexa, caracterizada por isquemia miocárdica aguda sem elevação do segmento ST no eletrocardiograma. Este trabalho apresenta uma revisão abrangente sobre os mecanismos fisiopatológicos, diagnóstico, estratificação de risco e estratégias terapêuticas do IAMSSST, com ênfase nas evidências clínicas atuais. Destaca-se o papel das troponinas cardíacas de alta sensibilidade na detecção precoce de lesão miocárdica, bem como a importância da estratificação de risco para a escolha do tratamento farmacológico e intervencionista. Apesar dos avanços significativos, a mortalidade e morbidade associadas ainda são relevantes, principalmente em contextos com recursos limitados. A prevenção primária e secundária, por meio do controle rigoroso de fatores de risco cardiovasculares, permanece como elemento central para a redução de eventos recorrentes.

Palavras-chave: Infarto Agudo do Miocárdio. IAMSSST. Troponina. Estratificação de Risco. Prevenção Cardiovascular.

RESUMEN
El infarto agudo de miocardio sin elevación del segmento ST (IMSEST) es una afección clínica compleja que se caracteriza por isquemia miocárdica aguda sin elevación del segmento ST en el electrocardiograma. Este artículo presenta una revisión exhaustiva de los mecanismos fisiopatológicos, el diagnóstico, la estratificación del riesgo y las estrategias terapéuticas para el IMSEST, con énfasis en la evidencia clínica actual. Se destaca el papel de las troponinas cardíacas de alta sensibilidad en la detección temprana de la lesión miocárdica, así como la importancia de la estratificación del riesgo para la elección de tratamientos farmacológicos e intervencionistas. A pesar de los avances significativos, la mortalidad y la morbilidad asociadas siguen siendo significativas, especialmente en entornos con recursos limitados. La prevención primaria y secundaria, mediante un control riguroso de los factores de riesgo cardiovascular, sigue siendo fundamental para reducir los eventos recurrentes.

Palabras clave: Infarto Agudo de Miocardio. IMSEST. Troponina. Estratificación del Riesgo. Prevención Cardiovascular.

1 INTRODUCTION

Acute myocardial infarction (AMI) is one of the most severe clinical manifestations of acute coronary syndromes (ACS) and, for more than a century, has represented one of the greatest challenges of modern medicine due to its high morbidity and mortality. From the first clinical descriptions of coronary obstructions, such as those made by Herrick (1912), to the contemporary definitions established by international consensus, such as the Fourth Universal Definition of Myocardial Infarction (Thygesen et al., 2019), the understanding of pathophysiological mechanisms, diagnostic criteria, and therapeutic strategies has evolved substantially.

The terminology and clinical understanding of infarction have undergone relevant historical transformations. In the nineteenth century, De Mussy (1842) described manifestations of severe chest pain, which would later be correlated with angina pectoris and coronary syndromes. Decades later, Herrick (1912) consolidated the clinical concept of sudden coronary obstruction as a triggering event for infarction, relating severe, sudden, and prolonged chest pain to myocardial necrosis. These contributions were fundamental for the medical community to recognize AMI as a distinct clinical entity, with its own diagnostic and therapeutic implications.

Throughout the twentieth century, the evolution of knowledge about the pathophysiology of infarction brought new paradigms. Studies such as the one by DeWood et al. (1980) demonstrated, for the first time, that total coronary occlusion was present in most patients with transmural infarction in the first hours of evolution. This evidence reinforced the importance of coronary reperfusion as a central strategy in the treatment, later consolidated in fibrinolysis protocols and primary angioplasty.

On the other hand, the development of the concept of atherosclerosis as an inflammatory disease represented a crucial paradigm shift in cardiology. Ross (1999a; 1999b) pointed out that the atherosclerotic process is not limited to simple lipid accumulation, but involves complex mechanisms of chronic inflammation and immune response, determining plaque instability and predisposition to rupture. These findings were essential to consolidate the current understanding that acute coronary syndrome, including non-ST-segment elevation AMI (NSTEMI), often results from erosion or rupture of atherosclerotic plaque, followed by the formation of a subocclusive thrombus.

The diagnostic redefinition of infarction was also decisive for contemporary clinical practice. Alpert et al. (2000) published a consensus document that became a historical

milestone by redefining infarction based on the systematic use of myocardial necrosis markers, such as cardiac troponin, associated with clinical and electrocardiographic criteria. Subsequently, Thygesen et al. (2019) updated this definition, consolidating the role of high-sensitivity troponins as a fundamental diagnostic tool, especially in cases of NSTEMI, in which the absence of ST-segment elevation on the electrocardiogram makes the diagnosis more challenging.

From a pathophysiological point of view, NSTEMI occurs predominantly due to partial or intermittent coronary obstruction, with maintenance of residual flow, unlike ST-segment elevation infarction (STEMI), characterized by total and persistent coronary occlusion (Nicolau et al., 2018). This distinction has relevant therapeutic implications, since in STEMI, immediate reperfusion is mandatory, while in NSTEMI the intervention strategy is guided by clinical, hemodynamic, and laboratory risk stratification (Amsterdam et al., 2014).

In addition, the pathogenesis of AMI involves not only the mechanical occlusion of the coronary arteries, but also a complex process of reperfusion injury, in which the restoration of blood flow, paradoxically, can cause additional damage to the myocardium. Frank et al. (2012) point out that myocardial reperfusion injury results from oxidative stress, inflammation, and programmed cell death, which limits the benefits of revascularization and motivates research on cardioprotective adjuvant therapies.

The epidemiological context reinforces the importance of the theme. In Brazil, cardiovascular diseases remain the main cause of mortality, and acute myocardial infarction is among the most lethal events. Estimates from the Global Burden of Disease study show that, between 1990 and 2016, mortality from AMI showed significant regional variations, but remained high in all age groups (Ribeiro et al., 2019). This scenario highlights the need for constant updating of therapeutic protocols, based on international evidence, but adapted to the Brazilian reality.

Another relevant aspect is the chronobiology of AMI. Anderson et al. (1996) observed that the occurrence of infarction varies according to the time of day, being more frequent in the early hours of the morning, possibly due to hormonal and autonomic changes that favor atherosclerotic plaque instability and platelet aggregation. These findings suggest that environmental and physiological factors modulate the risk of acute events, reinforcing the complexity of the phenomenon.

From a physiological point of view, the heart is particularly vulnerable to ischemia due to the high metabolic demand of the myocardium and the limited capacity for cell regeneration

(Guyton; Hall, 2017). Opie (2004) emphasizes that cardiac homeostasis depends on a delicate balance between oxygen supply and consumption, and that any alteration in this relationship can trigger myocardial ischemia that is initially reversible, but which progresses to necrosis if prolonged.

In clinical practice, the absence of ST-segment elevation should not be interpreted as an absence of severity. White and Chew (2008) highlight that NSTEMI is associated with high rates of complications, including reinfarction, heart failure and sudden death, especially when not treated appropriately. Thus, effective and early therapeutic strategies are essential to reduce morbidity and mortality.

NSTEMI therapy involves multiple fronts, including hemodynamic stabilization, use of antiplatelet agents, anticoagulants, beta-blockers, statins, and, in selected cases, percutaneous coronary intervention (Amsterdam et al., 2014). Braunwald (1983) already highlighted, in his pioneering research, the importance of early reperfusion and limitation of the extent of infarction as determinants of the preservation of ventricular function and survival. Currently, these principles remain valid, although adapted to the clinical specificities of the NSTEMI.

In Brazil, national guidelines such as those of the Brazilian Society of Cardiology (Nicolau et al., 2018) offer specific recommendations on the diagnosis and management of infarction, incorporating international advances, but considering the particularities of the Brazilian health system. Nicolau (2004) also highlights that therapeutic individualization is fundamental, taking into account clinical characteristics, comorbidities and risk of hemorrhagic complications.

The pathophysiology of the atherosclerotic process also has direct therapeutic implications. Fonseca et al. (2004) explain that atherosclerotic plaque instability is a central factor in the triggering of infarction, so that pharmacological agents capable of modulating inflammation, stabilizing plaque and reducing thrombogenicity play an important role in secondary prevention.

Finally, the historical evolution of knowledge about AMI demonstrates a continuous process of integration between pathophysiological discoveries, technological advances, and clinical evidence. From the first descriptions of angina and coronary obstruction (De Mussy, 1842; Herrick, 1912) to the consolidation of reperfusion therapies and the definition of universal diagnosis (Alpert et al., 2000; Thygesen et al., 2019), the approach to non-ST-

segment elevation infarction reflects the maturity of cardiology as a science and the permanent need for updating in the face of new clinical challenges.

Thus, the present study aims to review the current clinical evidence on the therapeutic approach in non-ST-segment elevation acute myocardial infarction, with emphasis on the pathophysiological, diagnostic and therapeutic aspects that guide contemporary medical practice.

2 METHODOLOGY

The present study is characterized as an exploratory narrative literature review, whose main objective is to gather, analyze and discuss the current clinical evidence related to the therapeutic approach of non-ST-segment elevation acute myocardial infarction (NSTEMI). The choice of this methodology is justified by the fact that the theme involves extensive international scientific production, marked by historical, conceptual and therapeutic advances that need to be integrated in a critical way, in order to offer the reader a comprehensive and updated view.

According to Fonseca et al. (2004), the understanding of infarction requires not only the analysis of the immediate clinical aspects, but also of the underlying pathophysiology, including the role of atherosclerosis as a chronic inflammatory process (Ross, 1999a; 1999b). In this context, the literature review is adequate for the construction of a panorama that ranges from the pioneering clinical reports to the most recent universal definitions (Alpert et al., 2000; Thygesen et al., 2019), also incorporating international guidelines for conduct (Amsterdam et al., 2014) and the Brazilian epidemiological reality (Ribeiro et al., 2019).

2.1 TYPE OF STUDY AND RATIONALE

The study was conducted in the form of a narrative and descriptive review. This methodological choice is justified by the comprehensive nature of the theme and the need to rescue not only contemporary clinical trials, but also historical landmarks that underlie current knowledge. Unlike systematic reviews, which follow strict protocols, such as PRISMA, narrative review allows for greater flexibility in the integration of different types of sources, allowing the researcher to articulate classic and modern works, from pioneering reports, such as those of De Mussy (1842) and Herrick (1912), to consensus documents in contemporary cardiology (Thygesen et al., 2019).

As Guyton and Hall (2017) point out, the understanding of cardiovascular pathophysiology requires an integrative approach, in which physiological principles, epidemiological aspects, and therapeutic conducts are discussed in an interdependent manner. Thus, the option for a narrative review is in line with the central objective of deepening the clinical and scientific analysis of non-ST-segment elevation acute myocardial infarction (NSTEMI).

2.2 SEARCH STRATEGY AND SELECTION OF SOURCES

The bibliographic survey was conducted between March and June 2025 in databases recognized by the international scientific community, including **PubMed, Scopus, Web of Science, Scielo and LILACS**, as well as manuals and renowned textbooks in the area of cardiology and physiology.

The **descriptors used** (in Portuguese and English) were:

- "acute myocardial infarction";
- "non-ST-elevation myocardial infarction";
- "acute coronary syndromes";
- "atherosclerosis" / "atherosclerosis";
- "treatment" / "management";
- "myocardial reperfusion".

As **inclusion criteria**, articles, guidelines and books were selected that:

1. directly address the topic of acute myocardial infarction, especially NSTEMI;
2. brought relevant pathophysiological, epidemiological or therapeutic evidence;
3. were published in Portuguese, English, French or Spanish;
4. to present scientific recognition, through publication in indexed journals or consolidated publishers.

Duplicate studies, opinion articles without scientific support, and studies with low clinical relevance to the topic **were** excluded.

2.3 SOURCES USED

Among the classic studies rescued, the initial clinical descriptions of angina and coronary obstruction stand out (De Mussy, 1842; Herrick, 1912), the findings of coronary occlusion in the first hours of infarction (DeWood et al., 1980) and the theoretical formulations that consolidated atherosclerosis as a chronic inflammatory process (Ross, 1999a; 1999b).

In the field of diagnostic definitions, international consensus documents have been incorporated, such as the proposal to redefine infarction (Alpert et al., 2000) and the Fourth Universal Definition of Myocardial Infarction (Thygesen et al., 2019). Such references are essential milestones to contextualize the evolution of diagnostic criteria, especially in NSTEMI, in which the absence of ST-segment elevation on the electrocardiogram requires greater clinical and laboratory precision.

International therapeutic guidelines, such as those of the American Heart Association/American College of Cardiology (Amsterdam et al., 2014), and national ones, such as those of the Brazilian Society of Cardiology (Nicolau et al., 2018), which provide updated practical recommendations for the clinical management of AMI, were also considered. In addition, reference works in cardiac physiology (Opie, 2004; Guyton; Hall, 2017) and classic cardiology texts (Nicolau, 2004) were incorporated to support the pathophysiological and clinical analysis.

The Brazilian epidemiological panorama was discussed based on data presented by Ribeiro et al. (2019), who analyzed AMI mortality in Brazil between 1990 and 2016, providing fundamental subsidies for the contextualization of the national reality.

2.4 ANALYSIS PROCEDURE

The analysis process followed three main steps:

1. **Exploratory reading:** initial identification of the main themes, concepts and evidence of each work. At this point, we sought to recognize the role of each reference in the construction of knowledge about AMI.
2. **Selective reading:** critical deepening of the most relevant materials, with emphasis on those that specifically address the NSTEMI, such as diagnostic consensuses (Alpert et al., 2000; Thygesen et al., 2019) and treatment guidelines (Amsterdam et al., 2014; Nicolau et al., 2018).
3. **Interpretative and integrative reading:** The analysis was structured in thematic axes, in order to ensure greater clarity and consistency in the discussion. Topics covered include: **(i)** the pathophysiology of atherosclerosis (Ross, 1999a; Fonseca et al., 2004); **(ii)** myocardial physiology (Opie, 2004; Guyton; Hall, 2017); **(iii)** the mechanisms of reperfusion and associated myocardial injury (Braunwald, 1983; Frank et al., 2012); **(iv)** the historical evolution of the concept of infarction (De Mussy, 1842; Herrick, 1912; DeWood et al., 1980); **(v)** the diagnostic definitions proposed by

international consensus (Alpert et al., 2000; Thygesen et al., 2019); **(vi)** national and international management guidelines (Amsterdam et al., 2014; Nicolau et al., 2018); and **(vii)** the Brazilian epidemiological panorama (Ribeiro et al., 2019).

The critical analysis also contemplated the limitations inherent to each study. For example, although Herrick (1912) was a pioneer in clinically describing acute myocardial infarction, his report presented restrictions due to the lack of laboratory resources and imaging methods currently available. On the other hand, modern guidelines, although methodologically robust and based on ample scientific evidence, may have their applicability reduced due to different socioeconomic and structural contexts, as often occurs in developing countries.

2.5 METHODOLOGICAL LIMITATIONS

As this is a narrative review, this study did not follow strict protocols characteristic of systematic reviews, which implies greater subjectivity in the selection and analysis of sources. However, we sought to mitigate this limitation through the broad inclusion of classical and contemporary references, contemplating a historical and scientific spectrum capable of critically sustaining the discussion of the theme.

Another limitation is related to the constant updating of cardiology, an area in which new biomarkers, imaging techniques, and therapeutic strategies are continuously developed. This dynamism may make some of the evidence discussed here susceptible to future revisions. Even so, by integrating historical milestones and recent consensus (Alpert et al., 2000; Thygesen et al., 2019; Amsterdam et al., 2014), the present work ensures consistency, coherence and scientific relevance.

2.6 RELEVANCE OF THE METHODOLOGY

The choice for the narrative literature review proved to be adequate because it enables the recovery of the historical and scientific trajectory of knowledge about non-ST-segment elevation acute myocardial infarction (NSTEMI), ranging from the first clinical descriptions to the contemporary consensuses that guide medical practice. In addition, it allows us to understand the multifactorial complexity of the disease, which involves inflammatory, hemodynamic, physiological and therapeutic processes (Fuster et al., 1992; White; Chew, 2008).

The integration between classic and recent sources strengthens the reliability of the review, allowing the reader to visualize the evolution of cardiology and recognize the challenges that are still present. Thus, the methodology adopted contributes to the results of the study going beyond specific recommendations, configuring itself as a critical and comprehensive analysis of the current clinical evidence related to the therapeutic approach to NSTEMI.

3 RESULTS

The analysis of the literature on non-ST-elevation acute myocardial infarction (NSTEMI) shows significant advances in the understanding of its pathophysiological mechanisms, diagnostic criteria, and clinical management strategies. These advances reflect the evolutionary trajectory of knowledge, from the first clinical descriptions to the consolidation of contemporary guidelines that guide medical practice.

3.1 PATHOPHYSIOLOGY AND MECHANISMS OF NSTEMI

Non-ST-elevation acute myocardial infarction (NSTEMI) results largely from the rupture or erosion of an unstable atherosclerotic plaque, followed by the formation of a non-occlusive intracoronary thrombus, which culminates in persistent but non-transmural myocardial ischemia. In contrast, in ST-segment elevation infarction (STEMI), total coronary occlusion predominates, while in NSTEMI, variable degrees of partial obstruction and distal microembolization are observed, determining subendocardial necrosis (Fuster et al., 1992; Ross, 1999; Fonseca et al., 2004).

The classic studies by Ross (1999) consolidated the understanding that atherosclerosis is essentially a chronic inflammatory process, and not just a passive accumulation of lipids in the arterial wall. This perspective explains the instability of atherosclerotic plaques and the risk of acute events, even in patients without previously detected critical coronary stenosis.

Additionally, Opie (2004) and Guyton and Hall (2017) describe that the imbalance between oxygen supply and consumption can aggravate ischemic condition, especially in conditions of tachycardia, hypertension or metabolic overload. This pathophysiological phenomenon is particularly relevant in NSTEMI, since it does not always result from evident thrombotic occlusion, and may be associated with mechanisms such as vasospasm, endothelial dysfunction, or partial thrombosis.

3.2 DIAGNOSTICS AND RESETS

The evolution of the concept of myocardial infarction has been marked by significant advances in laboratory diagnosis and clinical criteria. The consensus document published by Alpert et al. (2000) represented a milestone in redefining infarction with the introduction of troponin as a central biomarker, conferring greater sensitivity and specificity to the detection of myocardial necrosis, especially in cases without ST-segment elevation.

Subsequently, the Fourth Universal Definition of Myocardial Infarction (Thygesen et al., 2019) consolidated the use of high-sensitivity troponins as a diagnostic standard, enabling the identification of previously imperceptible microinfarctions. This redefinition has been shown to be particularly relevant for patients with NSTEMI, in whom electrocardiographic alterations are often nonspecific or transient.

In addition to biochemical markers, risk stratification is guided by clinical and electrocardiographic parameters. Widimsky, Widimsky and Stroukova (1990) observed that episodes of recurrent unstable angina, called *stuttering* course, are often precursors of NSTEMI, emphasizing that clinical instability should direct early and intensive therapeutic interventions.

3.3 EPIDEMIOLOGY AND CLINICAL IMPACT

Mortality from acute myocardial infarction in Brazil remains an important public health challenge. Ribeiro et al. (2019), when analyzing data between 1990 and 2016, showed an overall reduction in mortality rates, but highlighted the persistence of regional inequalities, as well as limitations in access to advanced therapies. Considering that NSTEMI corresponds to a significant portion of acute coronary syndromes, these findings reinforce the need for prevention strategies and expansion of access to timely diagnosis and treatment throughout the national territory.

In addition, studies such as that by Anderson et al. (1996) have shown that the onset of ischemic events presents circadian variation, with a higher incidence in the early hours of the morning. This observation contributes to the understanding of the physiological and environmental factors that modulate the risk of NSTEMI, including elevated blood pressure, increased platelet activity, and increased catecholamine secretion during this period.

3.4 THERAPEUTIC STRATEGIES

NSTEMI therapeutics have evolved substantially in recent decades, combining pharmacological interventions and invasive strategies.

3.5 INITIAL PHARMACOLOGICAL MANAGEMENT

According to Amsterdam et al. (2014), North American guidelines recommend that the initial treatment of non-ST-elevation acute myocardial infarction (NSTEMI) include antiplatelet agents, such as acetylsalicylic acid and P2Y12 receptor inhibitors, as well as anticoagulants, such as heparins or fondaparinux. In addition to this regimen, beta-blockers, statins and, in selected cases, nitrates and angiotensin-converting enzyme (ACE) inhibitors are added. This approach aims to limit thrombus progression, reduce ischemic load, and promote atherosclerotic plaque stabilization.

White and Chew (2008) emphasize that the early introduction of dual antiplatelet therapy represented a milestone in the management of NSTEMI, by significantly reducing the occurrence of recurrent events and mortality. The association with anticoagulants enhances the prevention of thrombosis, but carries an increased risk of bleeding, thus requiring individualized evaluation and careful balancing between efficacy and safety.

3.6 INVASIVE STRATEGIES

The role of early percutaneous coronary intervention (PCI) in non-ST-elevation acute myocardial infarction (NSTEMI) has been consolidated through studies that compared invasive and conservative strategies. In pioneering investigations, DeWood et al. (1980) demonstrated the high prevalence of coronary occlusion in the early stages of transmural infarction, evidence that motivated the exploration of mechanical reperfusion as a therapeutic modality.

However, Braunwald (1983) pointed out that the limitation of the extent of the infarction and the preservation of ventricular function strongly depend on the speed of reperfusion. Although immediate PCI is mandatory in cases of ST-segment elevation AMI (STEMI), in NSTEMI the strategy should be guided by clinical risk stratification, as established by contemporary guidelines (Amsterdam et al., 2014).

Patients classified as high-risk, characterized by recurrent pain, hemodynamic instability, severe arrhythmias, or dynamic changes on the electrocardiogram, have proven benefit from the adoption of an early invasive strategy (<24h). Those with intermediate or low

risk, on the other hand, can be initially conducted conservatively, with subsequent selective invasive evaluation, according to clinical evolution.

3.7 ISCHEMIA AND REPERFUSION

Despite the benefits of reperfusion, Frank et al. (2012) point out that reperfusion injury remains a relevant clinical challenge, as it contributes to cell apoptosis, oxidative stress, and myocardial inflammation. These mechanisms help explain why, even after successful coronary intervention, some patients progress to persistent ventricular dysfunction.

In this context, Nicolau (2004) emphasizes that the ideal management of NSTEMI should integrate pharmacotherapy, selective reperfusion and clinical support measures, with individualized therapeutic decisions according to the risk profile of each patient.

3.8 INTEGRATION WITH HISTORICAL EVIDENCE

The evolution of knowledge about non-ST-elevation acute myocardial infarction (NSTEMI) cannot be dissociated from fundamental historical milestones. Herrick (1912) described, for the first time, the clinical manifestations resulting from sudden coronary obstruction, inaugurating the modern era of infarction diagnosis. Previously, De Mussy (1842) had already reported cases of typical angina, laying the groundwork for the correlation between chest pain and coronary heart disease.

These pioneering reports, associated with the contemporary understanding of atherosclerosis as a chronic inflammatory process (Ross, 1999; Fonseca et al., 2004) and the development of high-sensitivity biomarkers (Thygesen et al., 2019), have shaped the current diagnostic and therapeutic approach, basing clinical practice on evidence that integrates historical, pathophysiological, and technological advances.

3.9 SUMMARY OF RESULTS

Based on the analysis of the evidence, the main results can be summarized in four axes:

1. **Diagnostic advances:** The introduction of high-sensitivity troponin has allowed the identification of minor infarctions, common in NSTEMI, with greater accuracy (Alpert et al., 2000; Thygesen et al., 2019).

2. **Pathophysiological understanding:** Inflammatory atherosclerosis and rupture/erosion of unstable plaques explain most cases (Ross, 1999; Fuster et al., 1992).
3. **Clinical and epidemiological impact:** NSTEMI is highly prevalent, associated with significant mortality, especially in developing countries (Ribeiro et al., 2019).
4. **Current therapy:** Treatment combines dual antiplatelet therapy, anticoagulation and, in high-risk cases, early coronary intervention, always balancing risks and benefits (Amsterdam et al., 2014; White; Chew, 2008).

Thus, the results reinforce that the therapeutic approach in NSTEMI should be multifactorial, integrating early diagnosis, risk stratification, intensive pharmacological therapy, and selective revascularization.

4 DISCUSSION

Non-ST-elevation acute myocardial infarction (NSTEMI) represents one of the greatest therapeutic challenges within the spectrum of acute coronary syndrome (ACS), mainly due to its clinical, pathophysiological, and prognostic heterogeneity. Although knowledge about coronary heart disease has evolved since the first classical descriptions of angina and coronary occlusion (De Mussy, 1842; Herrick, 1912), there are still gaps regarding the standardization of optimal therapeutic management, especially when compared to ST-segment elevation infarction (STEMI).

From a historical point of view, the conceptual redefinition of myocardial infarction, proposed in the early 2000s, expanded the understanding of the disease by incorporating more sensitive and specific biomarkers, such as troponin, and consolidating diagnostic criteria applicable to both STEMI and NSTEMI (Alpert et al., 2000; Thygesen et al., 2019). This evolution has increased diagnostic accuracy, but it has also highlighted the complexity of management, particularly in NSTEMI, in which early diagnosis and risk stratification are determinants of prognosis.

The pathophysiology of NSTEMI is predominantly related to atherosclerotic plaque rupture or erosion with non-occlusive thrombus formation, resulting in myocardial ischemia without the classic persistent ST-segment elevation (Fuster et al., 1992; Fonseca et al., 2004). Unlike STEMI, which is characterized by total coronary obstruction (De Wood et al., 1980), NSTEMI is usually maintained in NSTEMI, albeit unstable, favoring recurrent chest pain and intermittent episodes of ischemia (Widimsky; Widimsky; Stroukova, 1990). This

pathophysiological characteristic justifies why the therapeutic approach, in this setting, prioritizes plaque stabilization and prevention of progression to total occlusion, rather than immediate reperfusion.

In this context, international guidelines, such as those of the American Heart Association (AHA) and the American College of Cardiology (ACC), emphasize the importance of early institution of pharmacological treatment with antiplatelet agents, anticoagulants, and anti-ischemic agents, associated with a careful evaluation of the need for invasive intervention (Amsterdam et al., 2014). This approach reflects the recognition that plaque instability and inflammation play a central role in the progression of the disease (Ross, 1999; Ross, 1999a).

Antiplatelet therapy is a fundamental pillar in the management of NSTEMI. The use of aspirin in combination with a P2Y12 receptor inhibitor significantly reduces recurrent ischemic events and cardiovascular mortality (Amsterdam et al., 2014; White; Chew, 2008). However, there is still debate regarding the choice of the most appropriate agent and the optimal duration of dual antiplatelet therapy, especially in patients at increased risk of bleeding. This dilemma reinforces the need for individualized strategies that consider both the vulnerability of the atherosclerotic plaque and the clinical profile of the patient.

Another essential component is anticoagulation in the acute phase. The use of unfractionated heparin, low molecular weight heparins, or fondaparinux is consolidated as an effective measure to prevent the spread of thrombus, especially in association with antiplatelet therapy (Amsterdam et al., 2014). However, anticoagulant selection should be guided by factors such as bleeding risk, drug availability, and planned invasive strategy.

Early percutaneous coronary intervention (PCI) is also a topic of debate at the NSTEMI. While in STEMI immediate reperfusion is mandatory (Nicolau et al., 2018), in NSTEMI the indication for PCI should be guided by risk stratification. Evidence indicates that high-risk patients — those with persistent troponin elevation, hemodynamic instability, dynamic changes in the electrocardiogram, or recurrent chest pain — have clinical benefit with an early invasive strategy (<24h). Patients with intermediate or low risk, on the other hand, can be managed conservatively initially, with subsequent selective invasive evaluation (Amsterdam et al., 2014; Nicolau, 2004).

Despite these recommendations, infarction-related mortality, both with and without ST-segment elevation, remains high in developing countries, such as Brazil (Ribeiro et al., 2019). This reality is partly due to the delay in recognizing symptoms, limited access to specialized

centers, and difficulties in adhering to prolonged treatment. In this sense, in addition to the individualized therapeutic choice, public health policies aimed at educating the population and expanding access to cardiology services are essential to reduce the impact of NSTEMI on cardiovascular mortality.

Another relevant aspect is reperfusion injury, defined as additional damage to the myocardium after blood flow is restored. Although more associated with STEMI, this phenomenon can also occur in patients with NSTEMI undergoing PCI, compromising the functional recovery of the left ventricle (Frank et al., 2012; Braunwald, 1983). This condition reinforces the need for adjuvant therapies, such as antioxidants and modulators of the inflammatory response, currently under investigation, which aim to attenuate the deleterious effects of reperfusion.

From a physiological point of view, the understanding of cellular and hemodynamic changes resulting from myocardial ischemia is essential to guide therapeutic approaches. As described by Guyton and Hall (2017) and Opie (2004), reduced oxygen intake triggers a cascade of events that include lactate accumulation, reduced contractility, arrhythmias, and, in prolonged cases, myocardial necrosis. Clinical management seeks to interrupt or minimize this cascade, justifying the use of antianginal drugs, such as beta-blockers and nitrates, in symptomatic control and preservation of ventricular function.

Additionally, the chronobiology of AMI should be considered. Anderson et al. (1996) demonstrated that the occurrence of infarction presents circadian variation, with a higher prevalence in the early hours of the morning, possibly due to peaks in blood pressure, heart rate and platelet activity. This finding suggests that the understanding of biological rhythms may guide more effective and personalized pharmacological strategies in the future.

In summary, the therapeutic approach of NSTEMI should be multifactorial, integrating early pharmacological treatment, risk stratification for invasive decision-making, secondary prevention, and public policies that expand access to diagnosis and treatment. Despite the advances achieved, challenges persist related to clinical heterogeneity, the risk of bleeding complications, and long-term treatment adherence. In this scenario, it is imperative that future research explores adjuvant therapies, more accurate risk biomarkers, and personalized medicine strategies, capable of optimizing clinical outcomes in NSTEMI.

5 CONCLUSION

Non-ST-segment elevation acute myocardial infarction (NSTEMI) represents one of the greatest contemporary challenges in clinical cardiology, both due to its high prevalence and its pathophysiological complexity and diversity of presentations. Unlike ST-segment elevation infarction, whose diagnosis and therapeutic approach are well established, NSTEMI requires careful interpretation of clinical, laboratory, and electrocardiographic findings, combined with quick and individualized decisions (Thygesen et al., 2019; Amsterdam et al., 2014).

From the pathophysiological point of view, it was evidenced throughout this study that NSTEMI is strongly associated with atherosclerosis and its inflammatory processes, a phenomenon recognized since Ross (1999) and widely consolidated in subsequent decades. The rupture or erosion of atheromatous plaques, accompanied by the formation of partially occlusive thrombi, constitutes the central mechanism of subendocardial ischemia, in contrast to the total occlusion typical of elevation AMI (Fuster et al., 1992; Fonseca et al., 2004). Although subtle in clinical presentation, these differences are decisive for the definition of the therapeutic strategy and for the prognosis.

In the diagnostic field, the advances obtained with the introduction and subsequent evolution of high-sensitivity cardiac troponins were decisive in redefining the concept of infarction and allowing the early detection of myocardial lesions. This evolution has provided more accurate diagnoses and timely interventions (Alpert et al., 2000; Thygesen et al., 2019). However, it brought with it new challenges, such as the differentiation between myocardial injury and infarction itself, always requiring a careful and contextualized clinical analysis.

Regarding treatment, current evidence reinforces the importance of early risk stratification and immediate implementation of pharmacological measures, including antiplatelet agents, anticoagulants, and high-potency statins (Amsterdam et al., 2014; White; Chew, 2008). In addition, early percutaneous coronary intervention, although not universally indicated as in elevation AMI, plays a crucial role in high-risk patients, characterized by hemodynamic instability, persistent elevation of necrosis markers, or recurrent ischemia. This integrated management contributes decisively to the reduction of mortality, which, despite significant advances, remains high in developing countries, as evidenced in the Brazilian scenario (Ribeiro et al., 2019).

Another relevant aspect refers to ischemic-reperfusion complications, which continue to limit the prognosis even in the face of successful interventions. Frank et al. (2012)

demonstrated that mechanisms such as oxidative stress, apoptosis, and myocardial inflammation contribute to persistent ventricular dysfunction, underscoring the need for new myocardial protection strategies. In this sense, ongoing research seeks adjuvant therapies capable of reducing the size of the infarct and preserving ventricular function, representing a promising field for the future.

In addition to immediate diagnosis and treatment, NSTEMI should be understood within a broader context of primary and secondary prevention. Strict control of cardiovascular risk factors, hypertension, diabetes mellitus, dyslipidemias, smoking, and sedentary lifestyle remains the most effective measure to reduce the incidence of new events (Ross, 1999; Fonseca et al., 2004). The promotion of healthy lifestyle habits and the implementation of effective public policies continue to represent fundamental pillars in the reduction of cardiovascular morbidity and mortality.

In summary, the therapeutic approach to NSTEMI has evolved substantially in recent decades, driven by diagnostic advances, greater pathophysiological clarity, and progressively more defined management protocols. However, relevant challenges remain, such as the control of reperfusion complications, the reduction of mortality in unequal health systems, and the need for personalized strategies based on individual risk. The future of cardiology points to increasingly precise medicine, based on advanced biomarkers, modern imaging methods and innovative pharmacological therapies, without losing sight of the essential principle of prevention as the most effective strategy against NSTEMI.

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