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# Biomarkers of myocardial injury

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Acronyms
**ACS:** acute coronary syndrome
heart failure (HF
**BNP:** brain natriuretic peptide
**cTn:** cardiac troponin
**ECG:** electrocardiogram
**hs:** highly sensitive
**MI:** myocardial infarction
**miRNA:** microRNA
**NPs:** natriuretic peptides
**NPV:** negative predictive value
**NT-proBNP:** amino-terminal fraction of the brain propeptide
**PCI:** percutaneous coronary intervention

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**ABSTRACT**
Acute chest pain is a frequent symptom in emergency services. The serial measurements of cardiac biomarkers, in their assessment, aid diagnosis, risk stratification, and have prognostic and therapeutic implications. A review of biomarkers of myocardial injury is proposed: cardiac troponins, creatine kinase MB fraction, natriuretic peptides and other novel cardiac biomarkers; as well as their behavior in acute coronary syndrome and other heart diseases. They are an essential tool for the evaluation of patients with chest pain, in addition to the clinical method, mainly cardiac troponins because of its high sensitivity and negative predictive value.
***Key words:*** Chest pain, Cardiac biomarkers, Diagnosis, Acute coronary syndrome

## *Biomarcadores de daño miocárdico*

**RESUMEN**
El dolor torácico agudo es un síntoma frecuente en los servicios de urgencia. Las determinaciones seriadas de biomarcadores cardíacos en su valoración, ayuda al diagnóstico, a estratificar el riesgo, y tiene implicaciones pronósticas y terapéuticas. Se propone una revisión sobre los biomarcadores de daño miocárdico: troponinas cardíacas, creatinquinasa fracción MB, péptidos natriuréticos y otros nuevos biomarcadores cardíacos; así como su comportamiento en el síndrome coronario agudo y otras cardiopatías. Son una herramienta esencial para la valoración de pacientes con dolor torácico, como complemento de la clínica, fundamentalmente las troponinas cardíacas, por su alta sensibilidad y el valor predictivo negativo.
***Palabras clave:*** Dolor torácico, Biomarcadores cardíacos, Diagnóstico, Síndrome coronario agudo

## INTRODUCTION

Acute chest pain is one of the most common symptoms found in emergency services. Early assessment facilitates the immediate implementation of diagnostic and therapeutic algorithms, which are critical for a favorable prognosis. Conversely, a prolonged time of chest pain assessment, in the emergency

room, not only worsens prognosis, but increases labor and costs. Thus, patients with chest pain, suggestive of myocardial ischemia, should undergo (in addition to clinical and electrocardiographic assessment) serial measurements of cardiac biomarkers, which help to stratify risk and establish the diagnosis[1].

These biomarkers are proteins, structural components of cells that are released into the circulation when myocardial injury occurs[2]. They are biological parameters that, when quantified, indicate if a normal or pathological process is taking place, or provide an idea of the possible therapeutic response of the patient. Therefore, they play a key role in the diagnosis, risk stratification and treatment of patients with chest pain that is suggestive of acute coronary syndrome (ACS), and symptoms of heart failure (HF) exacerbation[2].

These biomarkers are central in the new definition of myocardial infarction (MI), formulated by the American College of Cardiology (ACC) and the European Society of Cardiology (ESC). Myocardial injury is detected through sensitive and specific biomarkers when they increase their concentration[3]. The histological evidence of necrotic myocardial injury may also be detected in clinical conditions associated with non-ischemic myocardial injury, as in HF, renal failure, myocarditis, arrhythmias, pulmonary embolism, or in percutaneous or surgical coronary procedures without events. These cases must not be regarded as MI or complications of the procedures, but as myocardial injury[3].

Research in this area has provided a long list of new patients who may need the determination of markers of myocardial injury, but not all of them meet the time and clinical use criteria. Understanding and mastery in advancing these new noninvasive tests is essential to obtain better results in the care of patients with cardiovascular diseases[4].

## Cardiac troponin (cTn)

### Conventional cardiac troponins

The cTnI and cTnT are components of the myocardial cell contractile apparatus which are found almost exclusively in the heart. Although increased biomarkers in blood indicate an injury resulting in necrosis of the myocardial cells, they do not indicate the underlying mechanism[5]. Several possibilities have been suggested for the release of myocardial structural proteins, including a normal recovery of myocardial cells, apoptosis, cell release of troponin degradation products, increased cell wall permeability, formation and release of membrane blisters and myocyte necrosis[4,6].

Over the last 2 decades, cTn has emerged as the preferred biomarker for noninvasive determination of myocardial injury[7]. The current definition of acute myocardial infarction (AMI) in a clinical setting, being consistent with myocardial ischemia, requires the finding of a rise or fall pattern in the value of a biomarker of myocardial injury or necrosis, preferably troponin, due to its high sensitivity and specificity. At least one of the values of troponin should be located above the 99$^{th}$ percentile of the upper reference limit (URL), according to the method used in each laboratory. In the first evaluation, blood samples should be taken to measure the cTn and then repeat it at 3-6 hours. Subsequent samples are needed if there are more ischemic events, or when the time of symptom onset is not precise.

However, many acute and chronic conditions, different from ACS, produce small elevations in the levels of cTn, for example, myopericarditis, toxic injury, excessive cardiac workload, among others[8-10]. Chronic conditions include chronic kidney disease and HF, with a marked increase in cTn, but without acute changes in their values[3,11-14].

It is important to note that in patients with a high probability of AMI, who are treated long after the onset of symptoms, it is not necessary a pattern of rising or falling in the levels of cTn for diagnosis, because they may be found near the threshold of the concentration-time curve of cTn or of the slow decline of this curve[11].

In an observational study of patients with symptoms of chest pain consistent with ACS, who underwent a rapid diagnostic protocol for identifying low-risk groups, its usefulness was demonstrated by combining the findings on the electrocardiogram (ECG) with cTnT determinations on admission and at 2 hours, and the calculation of TIMI index[15]. Low risk was defined when ECG and cTnT were negative, and the TIMI index was 0. This protocol has high sensitivity and high negative predictive power.

In relation to percutaneous coronary intervention

(PCI), the most sensitive marker in detecting myocardial damage is increased cTnI or T[16]. The MI related to PCI is defined by elevated cTn titers > 5 x 99th percentile URL in patients with normal baseline values (≤ 99 percentile URL), or an increase in cTn > 20% if baseline values were high and stable, or decreasing[3].

The prognostic implications of cTn elevation after PCI are not entirely clear. Studies by Gómez-Hospital *et al.*[16], Fuchs *et al.*[17] and Cavallini *et al.*[18] showed that any increase in cTn detected after PCI have no prognostic implications for medium or long term monitoring, as it is associated with minimal myocardial damage. Meanwhile, Fuchs *et al.*[17] and Nallamothu *et al.*[19] conclude that an increase in these biomarkers after PCI increases the risk of short-term complications (nosocomial); although Nallamothu *et al.*[19] believes it occurs when the value of cTn is more than 8 times its cutoff.

The difference of the study published by Gómez-Hospital *et al.*[16] is that it adds the value of creatine kinase-MB (CK-MB), which allow us to differentiate the minimum myocardial damage (prognosis unchanged) from myonecrosis (major myocardial damage). This study concludes that in patients with stable or unstable coronary heart disease, with negative markers of myocardial damage before the procedure, an increase in troponin without an increase in CK-MB during PCI is not associated with adverse cardiac events during long term follow-up. By contrast, the concomitant increase of troponin I and CK-MB is associated with increased mortality during follow-up. This would suggest the need to determine the CK-MB after all PCI to be able to assess the influence of this procedure on the prognosis of myocardial damage.

Moreover, Prasad *et al.*[20] demonstrated the lower sensitivity of cTnI for the detection of myocardial damage after PCI, which means that cTnT detects a greater damage.

The role of cTn in the diagnosis of AMI is eclipsed in the spectrum of HF for its persistent elevation in this disease. In case of a sharp increase in cTn during an episode of acute HF, type 1 AMI (rupture-ulceration of the plaque) must be ruled out, although there are frequent reports of the presence of high concentrations of cTn in acute and chronic HF unrelated to this type of AMI[21].

The release of troponin into the bloodstream is common in diabetic patients or patients with extensive atherosclerosis via: endothelial dysfunction, subendocardial ischemia (aggravated by anemia or hypotension), high ventricular filling pressures and myocardial stiffness. Since the typical clinical manifestations suggestive of ischemia are not always present, it will be appropriate to perform serial measurements to place the values in the context of its elevation[21].

Shave *et al.*[22], in a review on the elevation of cTn in physical exercise, conclude that it is probably due to a benign phenomenon associated with cTn dripping by the myocyte membrane instead of its necrosis. This conclusion should be considered with caution, given the lack of adequate long-term monitoring in elite high performance athletes[23]. There is increasing evidence that in some of these athletes, after several years of practice, abnormalities may appear in the right ventricle such as enlargement, dysfunction and lethal arrhythmias[23,24]. These athletes are clinically and genetically distinct from patients with arrhythmogenic right ventricular dysplasia and family cardiomyopathies. One hypothesis is the tension that is created in this ventricle, which sometimes leads to myocardial necrosis that, while small, justify the elevation of cTn after exercise[25]; the cumulative effect of these episodes of necrosis leads to a fibrosis resulting in dysfunction of the right ventricle and favors lethal arrhythmias[23,25].

Extracardiac causes of cTn release into the bloodstream are, among others: muscular dystrophies, systemic inflammatory or autoimmune processes, and renal failure. The relationship between the latter with the elevation of these markers and myocardial damage is caused by the very systemic involvement of the disease, and not due to a decrease in glomerular filtration rate[21].

**High-sensitivity cardiac troponins**

The industry has improved the ability to detect minimum amounts of cTn. Today we have a new generation of cTn measurement methods which are highly sensitive or ultrasensitive (hs-cTn) and are displacing conventional ones[26]. They have improved the diagnostic sensitivity, especially in the first hours after the onset of symptoms[27].

If less than 6 hours have passed since the pain episode, a second determination of hs-cTn is advised

within 3 hours of arrival at the emergency room. On the other hand, if more than 6 hours have passed since the pain episode, a single negative determination of hs-cTn is sufficient to rule out myocardial necrosis. The hs-cTn have an independent predictive value for prognosis and mortality in the short and medium term[28,29].

The hs-cTn also have controversial aspects. The increased sensitivity of the method comes at the expense of less specificity and positive predictive value, which increases the number of false-positive results [30-32]. Of the patients who visit the emergency room with chest pain and show increased hs-cTn in the early hours of the onset of symptoms, only 50-80% have a final diagnosis of AMI[27]. Hence the need to always consider the value of the hs-cTn within a specific clinical context, and always after ruling out other serious causes that may have induced an increase in the concentrations of this marker.

With the advent of the hs-cTn, the causes of cTn elevation that are not related to ACS have become more common in patients coming to the emergency department with chest pain[33]. In the case of chronic HF, a large number of patients have chronically high cTn values, a fact that increases with the use of hs-cTn. Those with high levels or steadily rising curves, or both, will have worse outcomes than those showing steady values[21].

A study published in the Journal of The American Heart Association[34] compared the diagnostic ability of conventional cTn with hs-cTn in a population attending an emergency department with suspected AMI. The 99th percentile was used as cutoff. Sensitivity and specificity were 89 and 80% for the former and 91 and 74% for the hs-cTn. It is concluded that, in an unselected patient population attending an emergency department, the diagnostic yield of both troponins is not different. With the hs-cTn, more heart diseases are detected; however, they do not predict, independently, either emergency readmissions or mortality from any cause. These results may seem to contradict other studies examining the diagnostic efficacy of the hs-cTn; however, they have been conducted in selected populations of patients with chest pain and high prevalence of the disease.

The PITAGORAS study[35] is a Spanish multicenter study that evaluated the high-sensitivity troponin T (hs-TnT) in patients with chest pain and normal conventional troponin. The main results indicate that clinical history and ECG are the basic tools for the diagnosis of ACS in these patients, although the absence of detectable amounts of hs-TnT has a high negative predictive value (NPV) that could be clinically useful. Furthermore, in patients coming to the emergency department due to chest pain, without damage or with minimal myocardial damage that is not detectable with standard troponin, hs-TnT provides information on the diagnosis and prognosis; therefore, it may help in decision making.

In summary, the hs-TnT has improved the diagnosis of ACS in patients presenting with chest pain and normal conventional cTn, preferably within the early hours[36].

**Creatine kinase-MB (CK-MB)**

The third definition of myocardial infarction[3] indicates that in case there is no cTn test available, the best alternative is CK-MB, measured by the mass test. As with troponin, a high value of CK-MB > 99 percentile URL is designated as the decision threshold for the diagnosis of MI, and specific values should be used for sex[37,38].

In the case of AMI associated with PCI, it may be establish by an increase in creatine kinase (CK), and its isoform CK-MB, 3 times the normal value. An increase that is associated with reduced survival during follow up[16]. In the study of Gómez-Hospital *et al.*[16], the increase in CK-MB was associated with myonecrosis and this, in turn, with significant alterations of coronary circulation in a particular territory, as the phenomenon of no-reflow or the occlusion of the side branch, causing structural damage to the myocardium. In this study it is concluded that in a group of patients with stable or unstable coronary disease, with negative markers for myocardial damage prior to the procedure, an increase of troponin without an increase in CK-MB during PCI is not associated with adverse cardiac events during long-term monitoring. By contrast, the concomitant increase of troponin I and CK-MB is associated with increased mortality during follow-up. This would suggest the need to determine the CK-MB after all PCI to assess the influence on the prognosis of the myocardial damage produced by PCI.

**Natriuretic peptides (NPs)**

Natriuretic peptides, called cardiac hormones, are also used as markers of myocardial injury. They include atrial natriuretic peptide (secreted primarily by atrial myocytes), the brain natriuretic peptide (BNP), secreted by the ventricular myocyte (the name is because it was first isolated from porcine brain), and C-type natriuretic peptide (expressed primarily in endothelial cells)[1,39].

The BNP and its inactive form or amino-terminal fraction of the brain propeptide (NT-proBNP), are derived in turn from a precursor (proBNP), which is released into the circulation from ventricular myocytes in response to increased wall stress, such as myocardial ischemia[39], although there are differences in kinetic and analytical parameters, their clinical roles are the same[40].

The NPs are synthesized from polypeptide precursors, and together with the sympathetic nervous system and other hormones play an important role in homeostasis[41]. The physiological effects of BNP include peripheral vasodilatation, stimulation of natriuresis, inhibition of the sympathetic nervous system and renin-angiotensin-aldosterone system, and growth of long bones, among others[1,42].

This makes the BNP a useful diagnostic marker for various pathophysiological conditions. NP concentrations have been found under stress, trauma, hypotension and severe sepsis, multiple organ failure, intrinsic myocardial disorders and hypertension and pulmonary embolism[40,43,44].

NPs are sensitive as diagnostic tools, but lack specificity for excluding or including patients with ACS. They could provide prognostic information in ACS, independent of classical risk stratification, and their role in the early diagnosis of acute chest pain is controversial. The episodes of myocardial ischemia increase the ventricular wall stress and NPs are released into bloodstream, in addition to ischemia itself which also facilitates their release[45]. Thus, they can be detected before myocyte necrosis occurs, or in the absence of it. Therefore, they are detectable in patients with ACS and normal or still normal hs-TnT, which could give an additional value to BNP, increasing the sensitivity of early diagnosis of ischemic chest pain when added to the detection of traditional markers[46].

Studies across the spectrum of ACS, including patients with normal troponin, have shown that an increase in NPs is associated with increased risk of cardiovascular events. Moreover, in some of these studies, the prognostic value was additional to that provided by troponin. Specifically, in patients with chest pain and normal troponin, who were assessed in chest pain units, elevated NT-proBNP increased the risk of death or AMI at one year of monitoring[47,48]. It has been suggested that low levels of NT-proBNP and normal troponin in chest pain could identify lower risk patients who could be released from the emergency room[49,50]. Similarly, in primary prevention, an increase in NPs identified asymptomatic ischemia[51].

In this sense, when analyzing the role of NT-proBNP, added to the determination of the hs-TnT in the diagnosis and short-term prognosis of patients with chest pain in the emergency room, who had normal values of conventional cTn in two serial measurements (6 and 8 hours), Sanchis *et al.*[36] found that NT-proBNP showed a marginal value for the assessment of chest pain of uncertain origin, when the hs-TnT is used. Therefore, it has no additional diagnostic value to predict the diagnosis or estimate the prognosis. Among the reasons that attempt to explain these results is that in the ACS the peak NT-proBNP appears between 16 and 24 hours after the onset of the symptoms[52]; it is possible that a determination at 24 hours would have increased the predictive value.

These results contradict those obtained by Truong *et al.*[53] and Melki *et al.*[54], who concluded that the additional measurement of NT-proBNP improve the diagnostic[53] prognostic[54] ability in the initial care of patients assessed with hs-TnT tests. The cutoffs chosen for NT-proBNP by Sanchis *et al.*[36], Truong *et al.*[53] and Melki *et al.*[54] were 125, 50 and 300 ng/l, respectively. Which were randomly selected, as there are no established reference values for use in the diagnosis of ACS and none of these studies has assessed the many influencing factors when considering what NP values are normal (age, sex, lean body mass, renal failure)[1,55].

The relationship of BNP with the binomial myocardial ischemia–left ventricular systolic dysfunction (LVSD) was studied by Nadir *et al.*[56], who concluded, in 3 separate populations, that a disproportionately high value of BNP for the degree of LVSD may be due to an unsuspected ischemia; and a very low value of this biomarker may be useful to exclude ischemia in the presence of such dysfunction.

The clinical utility of BNP has been established in different clinical situations in the context of asympto-

matic LVSD and clinical HF, and has been assessed as a possible method for screening LVSD[57,58].

In HF, the secretion of these peptides increases with disease progression. Therefore, the measurement of their plasma concentration has become a useful diagnostic and prognostic tool, and a tool for assessing the response to treatment. Thus, the determination of BNP or NT-proBNP is included in the diagnostic algorithm of acute and chronic HF, recommended in current clinical practice guidelines. The main value of this determination lies in its high NPV, which allows us to rule out HF when their concentrations are not increased[59].

However, although low levels of BNP (<100 pg/ml) exclude HF, and very high levels (>400 pg/ml) strongly support the diagnosis, there is a large gray zone (values between 100 and 400 pg/ml) where there is diagnostic uncertainty[58].

With regard to the usefulness of BNP in HF, the early detection of LVSD is still an issue to be elucidated. Lobos *et al.*[58] conclude that BNP may be useful for the early diagnosis of LVSD in patients at high risk of HF in primary health care, with similar values of sensitivity and specificity. When using a cutoff of 71 pg/ml a high NPV is reached (> 96%). BNP levels <100 pg/ml (or NT-proBNP <300 pg/ml) allow us to rule out HF in 9 out of 10 cases.

The PROBE-HF study[60] found a sensitivity of 100% and a NPV of 99.5% for detecting asymptomatic ventricular dysfunction (moderate or severe systolic and diastolic) using the NT-proBNP with a better cutoff of 125 pg/ml.

In this regard, Jacob *et al.*[61], taking into account the data from the Epidemiology Acute Heart Failure Emergency (EAHFE)[62], analyzed the prognostic value of BNP in patients with acute HF who were treated in emergency departments, and concluded that although the determination of BNP has prognostic value in a particular individual who complains of acute HF in the emergency room, it is without interest due to the fact that in patients where the BNP is not determined the prognosis is similar, with no impact on survival. The same authors[61,62] point out that many of the reviewed literature agree that there are still questions to be answered in this area, such as assessing the possible clinical, therapeutic and economic implications of this intervention.

In summary, the utility of BNP in HF is as follows:

a) The determination of BNP is very useful in patients with dyspnea to rule out its cardiac origin (NPV 98%), so it is now included in the initial diagnostic algorithm of HF in clinical practice guidelines.
b) In asymptomatic patients, there are doubts about its relevance in screening for LVSD, so it does not seem appropriate in the low-risk population (low prevalence of the disease).
c) In certain high-risk subgroups, positive screening results have been reported, but there is some heterogeneity and there are few studies in the field of primary health care.

**New Biomarkers**

There are dozens of new markers of myocardial injury, which reflect a variety of pathophysiological pathways that are altered in patients with ACS, and are associated with a potential increase in risk[63-65]. They include markers of ischemia and inflammation (ischemia modified albumin, heart-fatty acid-binding protein, myeloperoxidase), vascular dysfunction (metalloproteinase-9, pregnancy-associated plasma protein A), biomechanical stress (ST2, copeptin, growth differentiation factor, GDF-15), homeostasis (fibrinogen, plasminogen activator inhibitor-1) and those related to lipid metabolism (lipoprotein-associated phospholipase A2). For a variety of reasons, it is impossible to achieve widespread clinical use in most of these new markers. Some of them might consistently improve the established markers (**Table**).

In a study of suspected cases of ACS[63], none of the more than 10 new biomarkers that were tested approached the sensitivity of cTn in the diagnosis of AMI. Of these, only the GDF-15, which is released in the myocyte during ischemia and reperfusion, has shown promising results. In cohorts of patients with chest pain[63] and non-ST segment elevation ACS[64], the high level of GDF-15 is associated with increased risk of death and AMI, regardless of changes in the ECG, the cTn or high NP. Furthermore, it has been studied in patients undergoing heart surgery[65], where it predicts postoperative morbidity and mortality.

Another non-specific inflammatory marker, which has been extensively assessed in ACS, is the C-reactive protein. It has been shown that although it is not specific for the diagnosis of ACS, their increased levels

**Table.** Diagnostic and prognostic utility and clinical implications of new biomarkers[9,33,40,48-51,59,66].

| New biomarkers | Diagnosis ACS/AMI | Prognosis | Clinical implications |
|---|---|---|---|
| Ischemia modified albumin | */- | * | - |
| Heart-fatty acid-binding protein | */- | ** | - |
| Growth differentiating factor, GDF-15 | **/- | ** | * |
| Pregnancy-associated plasma protein A | */- | - | - |
| Myeloperoxidase | */- | ** | - |
| ST2 | */- | * | - |
| Lysosomal phospholipase A2 | */- | ** | * |
| Copeptin | */- | * | - |
| Fibrinogen | */- | ** | - |
| Plasminogen activator inhibitor-1 | */- | - | - |
| D-dimer | */- | - | - |

**Leyend.** -: absence of evidence, *: contradictory evidence, **: no conclusive evidence.

are associated with poor prognosis in patients with ACS[66]. Experimental and clinical evidence suggests that inflammation plays a crucial role in the initiation and progression of atherosclerosis, and it remains unclear whether inflammation simply accompanies the atherosclerotic process or has a greater role. Based on this, the high sensitivity C-reactive protein is promising; with it, groups at high risk of recurrent cardiovascular events have been identified in patients with manifest atherosclerosis[67].

## MicroRNA

The microRNA (miRNA) has emerged as the most promising biomarker in cardiovascular disease. They are noncoding small molecules, which act as negative regulators of gene expression[68], and are involved in a wide range of biological processes and in the control of important cell functions[69].

The identification of specific miRNAs as important regulators of cell biology has opened new possibilities in clinical practice, using them as tools in the diagnosis, prognosis and therapeutic strategy[68]. It has been shown that miRNAs play a physiological role in cardiovascular homeostasis and in the pathogenesis of cardiovascular diseases. High or low expressions of them are cause or consequence of pathological processes[70,71]. Several of these biomarkers, have promising potential as miRNA-423-5p, which is expressed in cardiac myocytes and increases in the blood of patients with HF, as well as miRNA-145, -155, -92ª, -17 and -126, which are significantly altered in patients with coronary artery disease compared with the control group[72].

The cardiac expression of miRNA after an AMI is evident in the miRNA-1, -29b, -126, and -499, with low expression one week after AMI; these miRNA recover their basic regular expression at 14 days of the ACS[73]. In contrast, another study showed that miRNA-1 and -206 are increased over a period of weeks after the AMI in the ventricle[74].

The miRNA reduction in periinfarct zone may reflect a viable myocardium[75]. In samples from human heart, it was found that the miRNA-1 and -133a/b had low expression in the infarcted tissue and the miRNA-1 had a high expression in remote tissue. In addition, a high expression of miRNA-21, -214 and -233, and a low expression of miRNA-29b and -143 were found in border areas of the infarcted myocardium in humans[76].

The AMI can induce a specific expression pattern of miRNA that would be directly related to a specific damage in myocardial cells, making these a potential therapeutic target to reduce myocardial damage, and influence the adverse remodeling and the clinical scenario of the AMI[75].

Currently, there are approximately 20 clinical studies designed to investigate whether circulating miRNAs may serve as biomarkers of myocardial injury. Expression levels of circulating miRNAs in cardiovascular disease, their early onset and stability, make

them highly suitable as biomarkers for ACS.

The association of circulating miRNA with myocardial injuries has recently been shown[77]. Compared to cTn, miRNAs are detectable in the circulation earlier, after an AMI (this is because the cTn are part of the myofibrillar contractile apparatus that are large protein complexes, and miRNA are small proteins that are released in a controlled way, which explains the difference in time to discharge after AMI). This may help in the diagnosis of AMI and the revascularization therapy[75].

Three studies have investigated the miRNAs in patients coming to the emergency room with chest pain that is suggestive of AMI[78-80]. In a comparison of several miRNAs, they showed an increase in the specificity and sensitivity in diagnosing AMI[78,81]. Even when combined with hs-TnT and a clinical pattern (medical history and cardiovascular risk factors), the miRNAs added discriminative power. This supports the theory that they can be used as markers for early independent diagnosis of ACS. The combined assessment of circulating miRNAs and cTn could be used to increase the specificity and sensitivity in the diagnosis of AMI.

In conclusion, miRNAs are promising for symptomatic and asymptomatic coronary artery disease, and provide valuable information for diagnosis and prognosis in these patients. They could replace established biomarkers, but some challenges in their routine clinical use will have to be overcome. First, it is necessary to achieve a greater understanding of their blood composition and second, improve the technical problems in their determination[82].

Meanwhile, Lin *et al.*[83], in a review of the evidence on the use of novel biomarkers in the diagnosis of ACS in patients with chest pain suggestive of myocardial ischemia, conclude that there is little evidence of routine use of new biomarkers; however, when combined with cTn, several of them have the potential to improve the sensitivity of diagnosing ACS.

### Multimarker strategy

The correct approach to follow in ACS management is closely linked to its early detection, for a proper stratification of prognosis[84]. In a study by Bhardwaj *et al.*[33], aimed at evaluating the role of new biomarkers versus established biomarkers in the diagnostic course of ACS, patients coming to the emergency room with chest pain were studied, evaluating the diagnostic value of 5 biomarkers, NT-proBNP, ischemia modified albumin, heart protein linked to fatty acid, hs-cTnI and free fatty acids to detect patients with ACS, compared with cTnT. In these patients, it was concluded that neither modified albumin nor heart protein linked to fatty acid detected or excluded the ACS; while the NP-proBNP, hs-cTnI and free fatty acids added diagnostic information to cTnT.

Another study compares the cTn alone with a dual strategy (TnT plus PN)[53], with the goal of improving the diagnosis of ACS in a single blood sample and providing physiological information of cardiovascular disease in patients presenting to the emergency department with chest pain. It showed that patients with ACS had higher concentrations of each biomarker compared with those patients who did have ACS ($p < 0.01$). By adding the NP, specifically the NT-proBNP, to both troponin (cTn and hs-TnT), the episodes were reclassified. The results with dual negative strategy improved sensitivity (cTnT from 38% to 83-86%, the hs-TnT from 59 to 86-90%) and negative predictive value (cTn from 94% to 97-98%, hs-TnT from 96 to 97-98%) for ACS patients. It was concluded that in patients with a low to intermediate probability of ACS, the combination of NP with cTn or hs-TnT improves the diagnostic ability and allows a reclassification of patients with suspected ACS. These data contrast with the findings presented by Sanchis *et al.*[36], as discussed above.

## CONCLUSIONS

Biomarkers are an essential tool for the assessment of patients with chest pain. Nothing beats common sense and clinical assessment in each situation. So far, it is difficult to surpass the high sensitivity and almost 100% NPV for the detection of myocardial damage that is achieved with the new measuring methods of hs-cTn. Further studies are needed, with specific designs, to go deeply into the use of the available biomarkers.

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