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# Biomarkers in heart failure

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ARTICLE INFORMATION

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**Abbreviations**
**BNP:** brain natriuretic peptide
**NP:** natriuretic peptides
**NT-proBNP:** N-terminal prohormone of BNP

**ABSTRACT**
Heart failure is an increasingly prevalent disease, which requires additional blood tests that not only confirm what is clinically presumed, but also be useful in the prognostic evaluation of those who suffer from it. In this context, biomarkers with practical utility appeared in the heart failure guidelines, at the beginning of the year 2000. With diagnostic, prognostic and evolutionary indications in each clinical stage of this disease, both in acute and chronic stages, its use draws guidelines and strategies in the adequate treatment of these patients. In this review article, a brief approach to the subject is made.
*Keywords:* Heart failure, Cardiac biomarkers, Diagnosis, Prognosis

## *Biomarcadores en la falla cardíaca*

**RESUMEN**
*La insuficiencia o falla cardíaca es una enfermedad cada día más prevalente y precisa de complementarios que no solo confirmen lo presumido clínicamente, sino que también sean útiles en la evaluación pronóstica de quienes la padecen. En ese contexto aparecen en las guías de insuficiencia cardíaca, a inicios del año 2000, los biomarcadores con utilidad práctica. Con indicaciones diagnósticas, pronósticas y evolutivas, en cada momento clínico de esta enfermedad, tanto en fase aguda como crónica, su utilización traza pautas y estrategias en el tratamiento adecuado de estos enfermos. En este artículo de revisión se hace un breve acercamiento al tema.*
*Palabras clave: Insuficiencia cardíaca, Biomarcadores cardíacos, Diagnóstico, Pronóstico*

## INTRODUCTION

During the 30th Central American and Caribbean Congress of Cardiology and the 9th Cuban Congress of Cardiology, the First Cuban Symposium of Heart Failure was held. Its promoters were the members of the Cuban Group of Heart Failure created in June 2016, under the leadership of Ana Margarita Jerez Castro, MD, who for more than 15 years have been developing a commendable work in this cardiology subspecialty: the diagnosis, treatment and monitoring of patients with heart failure.

This first meeting was attended by Cuban speakers –well-known experts in the different elements that make up the physiopathology of this major syndrome and its multidisciplinary approach– who, through their talks,

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highlighted its multiple etiological factors, as well as the accompanying comorbidities, those that are so often overlooked throughout regular therapeutic practice.

The event was arranged in two working sessions; Initially, the lectures addressed key issues such as biomarkers in heart failure, the complexity of arrhythmias in patients with this disease, cardiotoxicity as an expression of heart failure in cancer patients and the genetic basis in such scenarios; In addition, the project: *Modelo Cubano de Unidades Integrales de Falla Cardíaca* (Cuban Reference of Integral Units of Heart Failure) was presented. In a second moment that took place in the afternoon, the topics discussed were related to: comorbidities associated with the disease (cardiorenal syndrome, anemia, iron deficiency), cardiomyopathies and non-pharmacological treatment of heart failure. The lecture "Diagnostic and Therapeutic Strategies for Heart Failure in Primary Health Care" brought the event to a close.

We were honored by the presence as speakers of the excellent teachers Margarita Dorantes Sánchez, MD, and Amalia Peix González, PhD; Besides, Hilda Roblejo Balbuena, MD, MSc; Xiomara Castello Villalón, MD, MSc; Yudmila Borges Moreno, MD, MSc; Aníbal González Trujillo, MD, Sheila Hechavarría Pouymiró, MD, Grisel Guevara Mirabal, MD, and Ana Margarita Jerez Castro, MD, MSc.

## DEFINITION

Heart failure is deemed to be a critical and ever-increasing public health problem, which appears not only as a result of myocardial overload or damage but also of a complex interplay between genetic, inflammatory, neurohormonal mechanisms and biochemical changes that activate cardiac myocytes, the interstitium or both; and increase the number of enzymes, hormones, biological substances and other markers, which generate stress, myocardial malfunction and cellular injury[1].

Decompensated heart failure is a widespread and heterogeneous disorder. Sometimes both diagnosis and treatment are challenging. Its precise assessment and identification in patients with dyspnea (the most common symptom for sufferers) can be difficult, and the risk is even greater when there is doubt about the diagnosis. Moreover, this diagnostic delay is associated with higher mortality. Consequently, heart failure does not only represent morbidity, but is associated with large health care costs. This is why improvements in diagnostic evaluation and treatment are essential, especially in view of the increasing incidence and prevalence of this condition within the community[2].

Although the diagnosis of heart failure is, and should always be, based on a thorough medical history and physical examination, complementary tests that support clinical judgment have been shown to improve the accuracy of the diagnosis and facilitate the prognosis and treatment of patients. These complementary tests must be quickly accessible, easy to interpret, additional to the clinical variables and other objective tests, as well as being cost effective so that they are truly useful. In this regard, over the last decade several biomarkers have emerged that facilitate the diagnosis, risk stratification and treatment of heart failure[3,4].

### Defining Biomarkers

As their name implies, biomarkers are biological markers that may include demographic characteris-

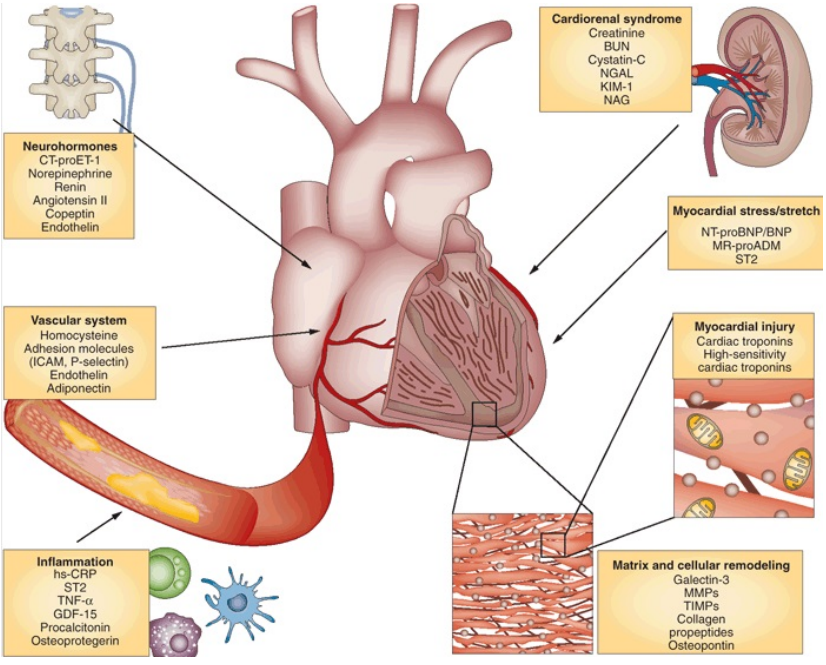


**Figure 1.** Variety of biomarkers in organs and tissues. Taken from Espinoza Silva, Valparaíso 2013[5].

tics, cardiac imaging studies, or even the identification of a specific genetic polymorphism. However, this term is applied to circulating molecules (**Figure 1**) which are determined by analyses that do not belong to the usual routine tests[3-5]. Natriuretic peptides (NP) are the most well studied and validated among the biomarkers used for heart failure. They are the benchmark against which all other markers of heart failure are compared.

NPs were incorporated into the diagnostic algorithm of the CI patient in the 2001 clinical practice guidelines[4] and in 2005 reference values for the diagnosis of acute heart failure were quoted for the first time (**Table**)[6,7].

Three basic criteria must be met for the use of biomarkers[8]: 1) they should be accurate, measurable, affordable to the practitioner, reasonable in cost, and measurable in the short term, 2) they should provide information, although it is not advisable to consider this as the only information available for the practitioner to assess and 3) the interpretation of its results and the subsequent medical decisions must be intelligent and well-balanced. In turn, these biomarkers must provide important information to meet the following criteria: to define the pathogenesis of heart failure, identify the groups most at risk for it, and help diagnose it, stratify the risk, and guide therapeutic behavior. Braunwald[1] classifies them into seven categories, six where he includes those who are well established and a seventh for new ones (**Figure 2**).

Up to this point we can summarize that a biomarker must meet three criteria to be of clinical use:

1. Have a reasonable cost and completion time.
2. Provide information not yet available for clinical evaluation.
3. Must be useful in making medical decisions.

In a survey by the *Sociedad Española de Cardiología* (Spanish Society of Cardiology)[9] conducted in January 2015, which included 107 public hospitals, with a population of more than 31 million inhabitants, NP determination was available in 65% of emergency departments, accounting for only 66% of the population receiving this group of services.

Based on expert consensus, the following cut-off points have been established to rule out acute heart failure according to NP values: BNP ≤100 pg/ml, NTproBNP ≤300 pg/ml (**Table**) and ≤120 pmol/L for MR-proANP (Mid-regional pro-atrial natriuretic peptide)[7].

## TYPES OF NATRIURETIC PEPTIDES

There are three types of NP[7,10,11]:

- A-type (atrial) natriuretic peptide (ANP), which occurs in the myocardium and has a systemic effect.
- B-type (brain) natriuretic peptide (BNP), which also occurs in the myocardium and has a systemic effect.
- C-type: natriuretic peptide (CNP), which occurs primarily in endothelial cells and acts as an autocrine and paracrine factor.

**Table.** Natriuretic peptide values, according to clinical scenario and age range.

| Context | NT-proBNP (pg/ml) | BNP (pg/ml) | Diagnostic value |
|---|---|---|---|
| **Emergency** | < 300 | < 100 | Very unlikely heart failure |
| < 50 years | 300 - 450 | 100 - 400 | Non-determinant. The clinical criterion of probability should prevail, taking into account other situations |
| 50-70 years | 300 - 900 | | |
| > 75 years | 300 - 1800 | | |
| < 50 years | > 450 | > 400 | Heart failure with high probability |
| 50-70 years | > 900 | | |
| > 75 years | > 1800 | | |
| **Outpatient** | < 125 | < 35 | Very unlikely heart failure |

BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

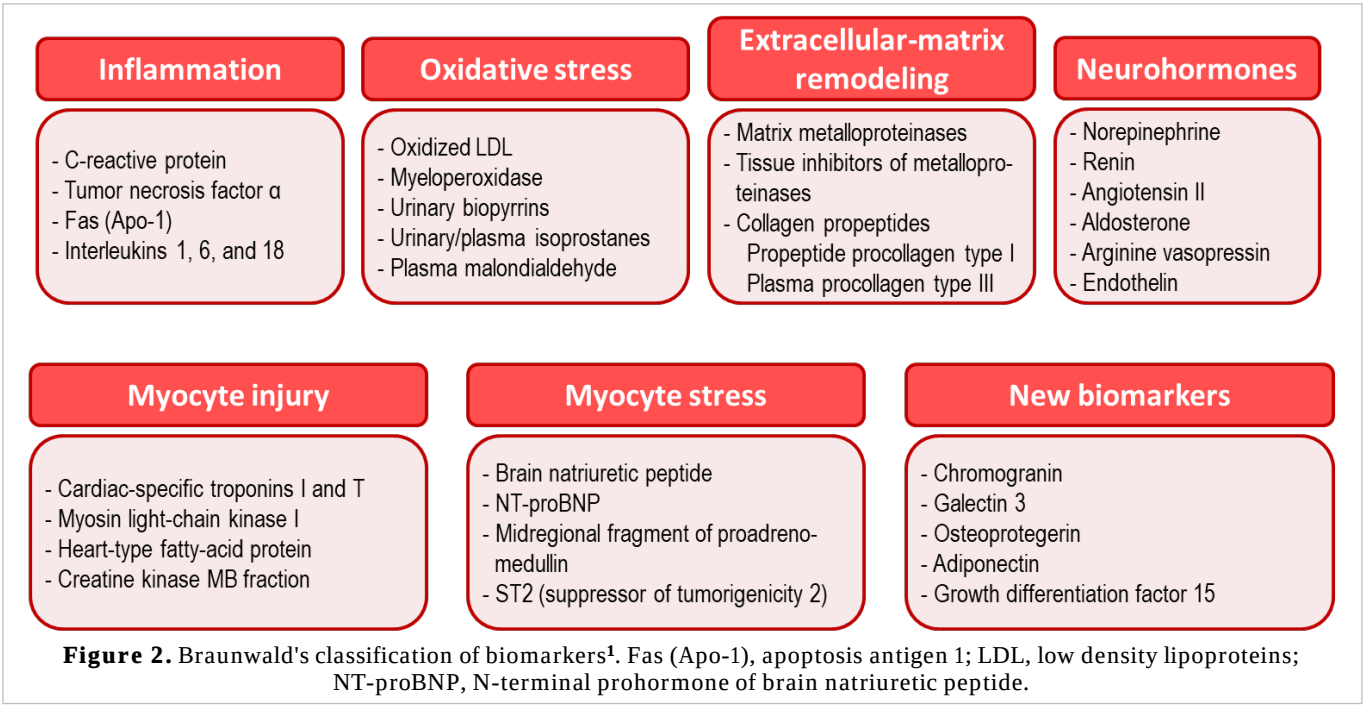


**Figure 2.** Braunwald's classification of biomarkers[1]. Fas (Apo-1), apoptosis antigen 1; LDL, low density lipoproteins; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

The effects of these NPs are mediated by their binding to 3 types of receptors, two functional and one of clearance[10,11]. The functional ones (natriuretic peptide receptor [NPR]) have been characterized as A-type (NPR-A) and B-type (NPR-B), and are expressed in the cardiovascular system and multiple organs (lung, kidney, skin and brain). Binding to these receptors stimulates the production of cyclic guanidine monophosphate (cGMP).

The circulating BNP is actively cleared by its binding to the C-type receptor (NPR-C) and by the action of neprilysin. This, in turn, is a neutral membrane endopeptidase that degrades the BNP ring structure, proBNP and preBNP, but not in NT-proBNP and causes proteolysis of these molecules. In homeostasis conditions, clearance by NPR-C binding predominates; but in conditions of volume or pressure overload (as in heart failure) neprilysin clearance predominates[11,12].

### B-Type natriuretic peptide groups

There are 3 major forms of B-type NP in circulation: the 76-amino acid NT-proBNP, which is biologically inactive; the 32-amino acid BNP, which is biologically active; and the precursor molecule, proBNP, which has 108 amino acids and biological activity that is about 10% of that of BNP[12].

These B-type NPs are produced in the atria and ventricles. The left ventricle is the main source, but production by the atria is significant. The half-life of BNP is 21 min and that of NT-proBNP is approximately 70 min. For this reason, the concentration of NT-proBNP is higher than that of BNP[13].

## TIMES TO QUANTIFY NATRIURETIC PEPTIDES

There are four key moments in heart failure where the quantification of NPs is of particular value: to make the diagnosis, to evaluate prognosis, during follow-up and treatment, and for on-going care.

### A. During diagnosis

Its measurement, added to clinical judgment, improves diagnostic accuracy over isolated clinical judgment, particularly in contexts of uncertainty. Its usefulness has been studied in patients where dyspnea is the main symptom at the medical appointment, and is primarily determined by the high negative predictive value for excluding heart failure, especially in patients with no prior diagnosis[14].

In short, a high value of BNP>400pg/ml, regardless of age, should lead to a probable diagnosis of heart failure (**Table**), with a positive predictive value of 86%[14].

AT the Emergency Room: Measurement of NP type B concentrations should be performed in all

patients attending for dyspnea, in whom there is suspicion of "de novo" heart failure (no previous diagnosis established)[15,16].

On outpatient basis: Measurement of NP concentrations should be accessible in outpatient clinics at the discretion of the physician in patients with clinically suspected "de novo" heart failure. It is recommended for patients with diagnostic doubt, after the initial clinical assessment. Ideally, the result should be available within 48 hours after the sample is obtained.

The result helps rule out the disease, if it is lower than the reference values (NT-proBNP<125 pg/ml and BNP<35 pg/ml); as lower concentrations have a negative predictive value between 96-99%. It is important to note that the initial request is preferable to echocardiography (due to accessibility and economic cost), especially if the latter takes more than 7 days to be performed; furthermore, a value higher than the exclusion values makes starting treatment for heart failure and the indication of the echocardiogram to define the presence of cardiopathy recommendable[3,4,6,17].

## B. To evaluate prognosis

Any increase in NP concentration should be interpreted not only as diagnostic support, but also as an alarm signal that provides short and medium-term risk information, complementary to clinical judgement. In any clinical practice scenario, the higher the concentration of NP, the higher the risk of complications and the worse the prognosis; therefore, its usefulness in assessing the prognosis applies mainly to patients with heart failure, but it should be acknowledged that the presence of high concentrations in other diseases, as a marker of stress and heart damage, also indicates an increased cardiovascular risk.

The measurement of NP as a risk assessment tool should not be performed routinely, but as an aid to clinical judgement, restricted to patients where the information it provides constrains therapeutic decision making[15].

At the Emergency Room: In hospitalized patients or patients attending the emergency department, the same criteria as in the previous section are applicable; Furthermore, the following situations may justify the use of NP when there is doubt about: a) deciding whether to admit the patient b) the degree of care and the specific admission unit, and c) the use or withdrawal of circulatory support devices or therapies.

Results interpretation: Absolute values of NT-proBNP above 5000 pg/ml are associated with a higher risk of serious complications. "The higher the NP concentration, the worse the prognosis". In the presence of extremely high concentrations of NP, but no signs of heart failure, the possibility of a serious cardiovascular stress condition, not attributable to this disease, should always be considered, as may occur in the case of sepsis or pulmonary thromboembolism[14-16].

On outpatient basis: For patients in outpatient clinics, the following situations may justify the measurement of NP1[17]:

- Chronic heart failure where the criteria for referral to a specialist, emergency room or hospital admission is in question.
- Patients assisted in advanced heart failure specialist consultations for therapeutic decisions, especially regarding the indication for heart transplantation and device implantation.

Results interpretation: It should be considered that NT-proBNP values above 1000 pg/ml suggest a higher risk of death or hospitalization. The increase in risk is linear; the higher the concentration, the higher the risk. Any value should be interpreted in the clinical context, taking into account modifying factors such as age and comorbidities[15-18].

## C. Follow-up and treatment

The usefulness of NPs has mainly been demonstrated in patients<75 years with systolic dysfunction. Studies to this effect have been conducted in specialized heart failure units, and their use should therefore only be considered in such a context and by trained personnel. Repetitive measurements of NP can also be assessed in specific circumstances, for decision making within specific protocols, and in support of clinical judgement[16].

At admission: In patients admitted for acute heart failure, the following recommendations are provided:

- For serial use of NPs, a value must be obtained on admission (within the first 24 hours), as changes in NPs must be interpreted in terms of relative reduction from the initial value.
- The reduction of NPs in relative terms is more

useful than in absolute terms; a 30% reduction represents the threshold that has been associated with a better outcome.
- Its measurement as a therapeutic guide, in periods between admission and discharge, is not justified and should be restricted to specific situations such as diuretic adjustment for congestion resolution.
- Its serial measurement should not be used to choose the time of hospital discharge; but it may help to support the clinical criteria for discharge, when considering the course of its concentrations.

On outpatient basis: In the follow-up of outpatients with heart failure, NP measurement is recommended within specialist units or consultations to:
- Confirm decompensations, in cases where there is reasonable clinical uncertainty[16].
- Optimize medical treatment. NPs can help to optimize medical treatment, based on the goal of achieving an NT-proBNP of less than 1000 pg/ml[17].
- In non-specialist practices, their use should be limited to the confirmation of decompensations in patients where a value is available in a clinically stable situation.

### D. On-going care

NPs provide relevant information for the different professionals engaged in the care of heart failure patients, which may be variable during their course [18-20]. The chronic nature and complexity of this disease imply the intervention of multidisciplinary teams, so it is important to contextualize the NP concentrations of each patient at each stage of their assessment. Hence the recommendation to record in the clinical history and medical reports all NP values obtained at any time during the course of the disease, and to include in discharge reports all values obtained throughout the hospitalization[18].

The ACC/AHA 2017 heart failure treatment guidelines show a graph on the sequence of indication of biomarkers in heart failure patients, which is worth checking[21].

## OTHER BIOMARKERS

### Highly sensitive troponins

Cardiac troponins are contractile proteins in the myocyte that are released into the circulation when there is cell damage[19], although they can also be elevated in situations other than coronary disease, and indicate myocardial damage. These include: local (myocarditis) and systemic (sepsis) inflammatory processes, toxic (anthracyclines), traumatic (heart contusion), excess adrenergic (strokes, Tako-Tsubo) and advanced renal failure. In addition, a large group of situations with mismatched energy demand and supply, without unstable or significant coronary disease[7,19].

The presence of circulating troponins, even at low concentrations, should be interpreted as a clear alarm signal reporting an increased risk of death in heart failure patients, as stated by Mallick and Januzzi[7] (**Figure 3**).

### Soluble ST2

It stands for tumorigenicity suppressor. ST2 is a member of the interleukin-1 (IL-1) receptor family. It is a protein that is upwardly regulated in the mechanical stress states of cardiac myocytes and has been shown to play an important role in myocardial hypertrophy and fibrosis[22]. This protein is also released by endothelial cells and may be involved in the development of atherosclerosis and high blood pressure[22].

According to Mallick and Januzzi[7], and Pascual-Figal *et al*[20], the PRIDE study showed the importance of NPs in relation to the diagnosis of heart failure, and concentrations of soluble ST2 showed a strong association with symptom severity and were almost linear with respect to short- and long-term mortality. Indeed, as shown in Figure 4, the higher the number of elevated biomarkers in heart failure patients, the higher the mortality[7].

### Galectin-3

It is a soluble peptide that is secreted by macrophages during phagocytosis, which secrete collagen, and is an important mediator in the initial phase of the process that leads to fibrosis in the heart and in other locations; furthermore, it has been shown to be elevated in patients with acute heart failure, thus representing a prognostic biomarker for future adverse events such as death and readmission[23]. This coincides with the findings of Mallick and Januzzi[7], who in the first study of galectin-3 determination in acute decompensated heart failure, PRIDE, included 559 patients, and found that the highest concentration of galectin-3 was a strong independent predictor of mortality at 60 days and readmission due to heart failure.

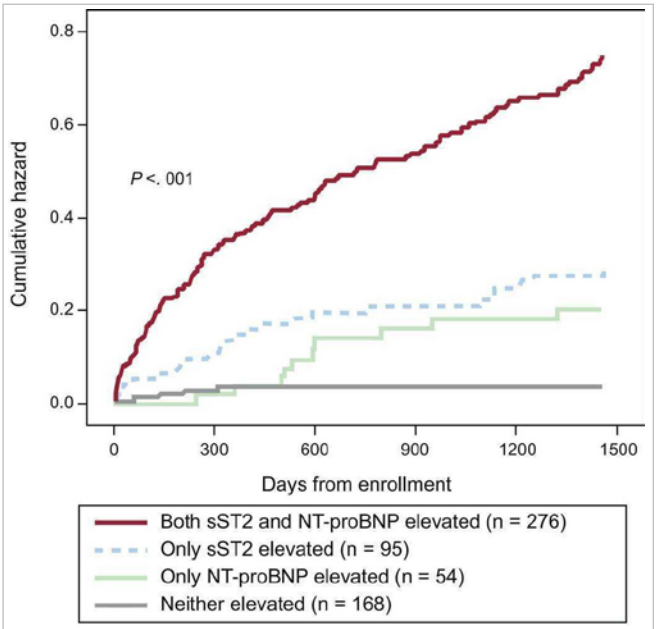


**Figure 3.** Risk of death after admission for acute decompensated heart failure as a function of soluble ST2 elevation (>35 ng/ml) and N-terminal prohormone of brain natriuretic propeptide (>1000 pg/ml) during 4 years of follow-up in the PRIDE study. NT-proBNP, N-terminal prohormone of brain natriuretic peptide; sST2: soluble ST2. Taken from Mallick and Januzzi[7] (Rev Esp Cardiol. 2015; 68:514-25), with permission from Elsevier.

### Mid-regional pro-adrenomedullin (MR-proADM)

Isolated for the first time from human pheochromocytoma cells, adrenomeduline is a peptide hormone with natriuretic, vasodilatory and hypotensive effects, mediated by cyclic adenosine monophosphate (cAMP), nitric oxide and renal prostaglandin systems[24]. It is expressed in many organ and tissue systems, including cardiovascular, renal, pulmonary, cerebrovascular, gastrointestinal and endocrine tissues[7,24]. According to Mallick and Januzzi[7], in the PRIDE study, MR-proADM had independent prognostic value for death, with a risk reclassification to 1 (HR 2.70; p<0.001) and 4 years (HR 1.51; p=0.03).

### Renal Biomarkers

Kidney dysfunction in patients with acute decompensated heart failure is fairly common and most often presents as acute kidney injury resulting in worsening of kidney function in up to 25% of patients, with significant elevation of plasma urea and creatinine and a reduction in glomerular filtration rate; it is therefore associated with a significantly increased risk of adverse events[25].

More recently, new biomarkers for estimating renal function have been assessed, such as cystatin C or beta trace protein BTP, to determine their ability to predict mortality in acute decompensated heart failure[7,25,26]. Both outperform serum creatinine by being more sensitive in detecting alterations in milder forms of renal dysfunction, thus providing a more accurate assessment of risk[7,25].

Other new biomarkers[7,25-28] have also been evaluated to identify renal injury in this same context and good results have been attained with neutrophilic gelatinase-associated lipocalin (NGAL), N-Acetyl-Beta-D-glucosaminidase and renal injury molecule-1. Apart from its usefulness for prognosis in this context, knowing the risk of acute renal injury could be useful to avoid exposure to nephrotoxic substances, such as intravenous contrast or certain nephrotoxic drugs[24-26].

## EPÍLOGO

It is important to stress that the usefulness of biomarkers in heart failure patients is very well established, from diagnosis, through the different stages of the disease, to prognostic estimation, which offers us a chronological curve that allows us to evaluate the patient's course and the effectiveness of the therapeutic strategies applied, all of which contributes to the best prognosis in these patients. In our country, given their availability, they would be indicated in the first medical appointment to evaluate the therapeutic response, especially in those cases where the cause is not yet well defined; and in young patients, in whom a positive therapeutic response would result in a better prognosis and a favorable change in the functional class.

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