Chronic heart failure secondary to ventricular dysfunction is characterized by neurohormonal activation, reflected mainly as increased sympathetic and renin-angiotensin system activation. Increased plasma levels of several neurohormones have been associated with increased morbidity and mortality. Neurohormone activation is part of the mechanism of compensation that is activated to maintain hemodynamic stability when heart output is reduced. Despite the initial benefits of this mechanism, neurohormone activation has been shown to contribute to progressive impairment of ventricular function and symptoms of heart failure, such that the greater the degree of activation, the worse the prognosis.

Despite their important implications for prognosis, plasma neurohormone levels are not measured in clinical practice as part of the clinical evaluation of patients with heart failure. Medical treatment with ACE inhibitors and beta blockers, by lowering the plasma levels of some neurohormones, reduces their prognostic usefulness in establishing risk. Thus, no ideal biomarker is yet available that is stable and easy to measure, and that accurately established risk in patients with heart failure. Such a marker should also have an acceptable cost/benefit ratio.

**Key words:** Ventricular dysfunction. Neurohumoral activation. Heart failure.

**INTRODUCTION**

Heart failure is a growing health problem which consumes a great deal of economic resources. Its high prevalence is due to the fact that the long-term evolution of different types of heart disease can induce heart failure. Despite the most recent therapeutic advances, it still carries very high mortality and morbidity, especially when it is secondary to left ventricular dysfunction.

Compensation mechanisms are activated when cardiac output drops, mediated by the activation of a
series of hormones and peptides that act in the kidney, the peripheral vascular system, and the myocardium itself. There is also an immune reaction, with the release of cytokines, inflammatory mediators and growth factors, that is activated both at the systemic and tissue level. These mediators partly help to perpetuate ventricular dysfunction, thus having an important role in prognosis.\textsuperscript{5,6} (Table 1).

The neurohormones and mediators activated in heart failure can be grouped into two major groups that have opposite activity. First, those which increase contractility and heart rate produce peripheral vasoconstriction, promote liquid retention, and, in the tissues, induce proliferative responses. This activity is mediated by the increase in sympathetic activity and activation of the renin-angiotensin-aldosterone system, vasopressin and endothelin. Second, other mediators, such as natriuretic peptides, adrenomedullin and cytokines, induce opposite responses and cause vasodilation and diuretic effects, reduce cellular proliferation and induce apoptosis. High plasma concentrations of some of these mediators, such as norepinephrine and angiotensin, directly contribute to increasing mortality in heart failure, whereas it is believed that other hormones are only indirect markers of greater severity.\textsuperscript{7,8}

Although in clinical practice determining neurohormone values in serum has been of limited use, knowledge concerning them has made it possible to improve and develop new treatments for heart failure. We review the prognostic value of the different neurohormones and mediators activated in heart failure.

**NOREPINEPHRINE**

An increased level of norepinephrine in peripheral blood was one of the first neurohormonal changes detected in heart failure.\textsuperscript{9} The origin of its activation is multifactorial; on the one hand, the decline in cardiac output, through activation of vascular baroreceptors, increases its release in the central nervous system; on the other, the activation of the renin-angiotensin system (RAS) also activates the release of norepinephrine. This increased release, together with the reduction in its reabsorption in the nerve terminals, leads to an increase in plasmatic norepinephrine concentrations.\textsuperscript{10,11} As the sympathetic system is activated, heart rate and contractility increase, so increasing heart output. It also causes strong peripheral vasoconstriction that helps maintain blood pressure. Nevertheless, this entails an increase in oxygen consumption and cardiac effort that contributes in the long run to the progressive deterioration of ventricular function. Furthermore, norepinephrine can cause myocardial necrosis and cell death by apoptosis, which aggravates ventricular dysfunction. Thus, it is thought that this actively contributes to the poor prognosis of these patients.\textsuperscript{12}

High values of norepinephrine have been traditionally associated with worse prognosis in heart failure. In the 1960s, it had already been observed that its concentrations increased in parallel to the deterioration

### TABLE 1. Neurohormones and Peptides Activated in Heart Failure Directly or Indirectly Associated With Greater Mortality*  
<table>
<thead>
<tr>
<th>Markers Directly or Indirectly Related to Poor Prognosis in Heart Failure</th>
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<tr>
<td>Neurohormones</td>
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<tr>
<td>Norepinephrine</td>
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<td>Plasma renin activity</td>
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<td>Angiotensin II</td>
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<td>Aldosterone</td>
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<td>Arginine-vasopressin</td>
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<td>Natriuretic peptide</td>
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<td>Peptides activated in the endothelium</td>
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<td>Endothelin</td>
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<td>TNF-(\alpha)</td>
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<td>Interleukin 6</td>
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<td>Adrenomedullin</td>
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<td>Lymphocyte adhesion molecules</td>
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<td>Oxidative stress markers</td>
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<td>NADPH oxidase</td>
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<td>Uric acid</td>
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<tr>
<td>Myocardial injury markers</td>
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<td>Troponins</td>
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*TNF-\(\alpha\) indicates tumor necrosis factor-\(\alpha\); LDL, low-density lipoproteins; NADPH, reduced nicotinamide adenine dinucleotide phosphate.
in the functional class of the New York Heart Association (NYHA), such that patients with higher values presented more severe symptoms and greater mortality. In various studies, high plasma values of norepinephrine were significantly correlated with higher ventricular pressures and pulmonary resistance, as well as with a worse cardiac index.

When the factors that determined the prognosis of patients with heart failure who participated in the V-HeFT studies were analyzed, high values of norepinephrine were identified together with the ejection fraction (EF) and maximum oxygen consumption peak as the strongest mortality predictors. It was also observed that even though norepinephrine values were reduced during the first year of treatment with enalapril compared to placebo, in the long-term these increased progressively in both groups, indicating that activation of the sympathetic system persisted.

Similarly, both the CONSENSUS study (Cooperative North Scandinavian Enalapril Survival Study) as well as the SOLVD study (Studies of Left Ventricular Dysfunction), demonstrated that patients with norepinephrine values higher than the median of the population studied presented greater mortality. Furthermore, the SOLVD prevention study showed that even in patients with asymptomatic left ventricular dysfunction, high values of norepinephrine were associated with a greater incidence of heart failure and mortality.

It should be emphasized that whereas in some studies the prognostic value of high norepinephrine concentrations was reduced when the patient was being treated with angiotensin-converting enzyme (ACE) inhibitors or beta-blockers (BB), in others this was identified as an independent predictor of mortality unrelated to pharmacological treatment for heart failure. However, it should be pointed out that although some patients with severe ventricular dysfunction and signs of advanced heart failure do not present high values of norepinephrine, they still have a poor prognosis.

The clinical usefulness of determining the values of norepinephrine for the prognosis of heart failure is affected by several factors. In addition to sample extraction measurements and variability in the course of the disease, treatment with drugs that also modulate the activation of the sympathetic system, such as ACE inhibitors and BB, modifies the prognostic value of plasma norepinephrine concentrations.

**PLASMA RENIN ACTIVITY**

Renin release is the first step in RAS activation and this activates a cascade of stimuli that leads to angiotensin II formation which mediates most of the undesirable effects secondary to RAS activation. Renal hypoperfusion and activation of the sympathetic system are the most frequent cause of renin release in the juxtaglomerular apparatus of the kidney.

Although activation of renin increases as heart failure worsens, its release is influenced by various factors such as the use of diuretics and diets low in sodium, which strongly increases its activity. The SOLVD-prevention study made it possible to demonstrate that some asymptomatic patients with left ventricular dysfunction could already present RAS activation. Nevertheless, plasma renin activity (PRA) was closely related to the use of diuretics. Although RAS is a dynamic system whose activation can vary in response to different hemodynamic situations, PRA tends to remain high due to chronic treatment with ACE inhibitors and diuretics. As ACE inhibitors lower the values of angiotensin II by a negative feedback mechanism, they increase PRA, and thus its prognostic value changes.

In the V-HeFT II study, in which the value of the different neurohormones was analyzed for prognosis of heart failure, high PRA values were associated with high mortality at 4-year follow-up. Nevertheless, in the same study, the prognostic value PRA was reduced in the presence of ACE inhibitors. In the SAVE study (Survival and Ventricular Enlargement), carried out in patients with postinfarction left ventricular dysfunction, PRA increase was identified as an independent predictor of mortality or future heart failure decompensations. In this study, from 1-year follow-up onwards, patients with PRA increase had a greater incidence of death or reinfarction, regardless of whether they were being treated with ACE inhibitors. Various studies have demonstrated that BB reduce plasma renin, which contributes to better control of neurohormonal activation and partly neutralizes the prognostic value of its increase. Thus, PRA, when increased, is a marker of poor prognosis that indicates the degree of activation of RAS, but its clinical usefulness is limited by its great variability in response to medical treatment and by the hemodynamic situation of the patient.

**ANGIOTENSIN II**

Angiotensin II is an octapeptide that constitutes the final link in RAS activation. It is a powerful peripheral vasoconstrictor and an important stimulator of fibrosis and myocardial hypertrophy. It also activates the release of other hormones, such as aldosterone and vasopressin, that help to retain liquid, and norepinephrine and endothelin, which also are very powerful vasoconstrictors. Thus, angiotensin II plays an important role in the progression of ventricular dysfunction. The final step that gives rise to angiotensin II formation is the action of ACE that activates the transformation/conversion of angiotensin I into angiotensin II. In addition, ACE activates degradation of bradykinins, which have a vasodilator
effect, and this helps to strengthen vasoconstriction induced by angiotensin II.

Various studies have demonstrated that an angiotensin II increase in plasma is associated with greater mortality in patients with heart failure. In the CONSENSUS study, patients in the placebo group who died had significantly higher serum values of angiotensin II, aldosterone, atrial natriuretic peptide (ANP) and norepinephrine. This relationship between neurohormone values and mortality changed in the group that received enalapril treatment, since the values of all the neurohormones was lowered in this group, especially angiotensin II, and this reduction in neurohormonal activation was the leading cause of reduction in observed mortality.

Despite the great impact of ACE inhibitors on reducing mortality in heart failure, in the long term fairly high mortality and a high index of readmissions persist. In fact, various studies have demonstrated angiotensin II escape events, despite treatment with ACE inhibitors. Neurohormonal reactivation, greater mortality and a higher number of readmissions for heart failure (Figure 1) was found in these patients.

The prognostic value of angiotensin II, although higher than that of PRA, is also modified by pharmacological treatment, such that the values of angiotensin II are reduced by treatment with ACE inhibitors and BB. On the other hand, they increase with angiotensin II receptor antagonists (ARA-II), because they prevent its binding to the AT1 receptor, thus leading to overestimating its activation.

**ALDOSTERONE**

Aldosterone is a hormone that acts by reabsorbing sodium and water in the distal tubule, interacts with the sympathetic system increasing vascular tone, and promotes myocardial hypertrophy and fibrosis. Aldosterone activation in heart failure is part of neurohumoral activation, such that angiotensin II is the main stimulator of its release; the role of vasopressin and endothelin, that can also activate it, is less important. Similar to angiotensin II, an aldosterone escape event has also been described, with an increase in its plasma values independently of treatment with ACE inhibitors.

Various multicenter studies have reported a relationship between high values of aldosterone and greater mortality, although possibly this is a weaker risk marker than angiotensin or norepinephrine. Nevertheless, treatment with aldosterone antagonists associated with ACE inhibitors has proven to reduce mortality significantly, both in patients with advanced heart failure and post-AMI.

**ARGININE-VASOPRESSIN**

Arginine-vasopressin acts through 2 receptors: when combined with the V1 receptor it has a powerful vasoconstricting effect and with the V2 receptor it increases the reabsorption of water, reducing diuresis, which promotes hyposmolarity and hyponatremia. Its plasma values increase as heart failure worsens, and angiotensin II and diuretic treatment contribute to its activation. Its prognostic value is less than other neurohormones, which means that for practical purposes it has not been utilized in hospitals as a marker of severity of heart failure.

**ENDOTHELIN**

Endothelin (ET-1) is a peptide released by the endothelium with a powerful vasoconstricting effect. Its synthesis is activated by gene transcription in the form of preproendothelin, which then becomes proendothelin or big endothelin. This is finally converted by endothelin converting enzyme into ET-1, that is, the active peptide. Angiotensin II is a powerful activator of ET-1 gene expression, although this is also activated by vasopressin, adrenaline, thrombin, and some cytokines. Some physical stimuli such as increased venous pressure, left ventricle filling pressures and ischemia, which are all present in heart failure, also increase it. ET-1 gene expression diminishes in response to nitric oxide and natriuretic peptides.

Endothelin has different effects depending on the receptor it binds to. Thus, through the endothelium...
ET<sub>B</sub> receptor it causes vasodilation upon activating the release of nitric oxide and prostacyclins, whereas when binding to the ET<sub>B</sub> and ET<sub>B</sub> receptors found in vascular smooth muscle fiber, it induces vasoconstriction. A predominance of ET receptors<sub>B</sub> has been described in heart failure that promotes vasoconstriction and endothelial dysfunction. This is especially relevant in pulmonary circulation, where it induces hyperplasia of the intima and contributes to remodeling of pulmonary vessels, promoting pulmonary hypertension.32

Pro-endothelin and ET-1 plasma values are high in heart failure, and their increase has been correlated with the degree of pulmonary hypertension, NYHA functional class and severity of heart failure. Pro-ET-1 is more stable in plasma than ET-1 and so has been frequently utilized as an indirect measurement of ET-1 activation. High pro-ET-1 values have been associated with greater mortality in various studies, such that patients with heart failure and pro-ET-1 plasma values higher than 4.3 fmol/mL had an annual mortality higher than 70%. Nevertheless, despite these impressive results, the determination of ET-1 has not proven to have a predictive value higher than that of other neurohormones when identifying patients with a greater risk of death or need for cardiac transplant.19

**ATRIAL NATRIURETIC PEPTIDE**

Atrial natriuretic peptide is mainly released in the atrium upon increasing pressure on the wall, and in smaller quantities in the kidney. Thus, its plasma values can also increase with maneuvers that increase intra-atrial pressure, such as water immersion or in sodium-rich diets. Its expression also increases in response to other hormones in heart failure, such as angiotensin II and endothelin.

In particular, the action of ANP includes vasodilation and reduction of peripheral resistance, inducing, in addition, increases in natriuresis and diuresis. This improvement in hemodynamic profile is due to the fact that it reduces the values of norepinephrine, angiotensin and aldosterone. Nevertheless, despite increases in circulating values of ANP, as heart failure worsens its beneficial effects are attenuated. It is thought that this occurs by downregulation of its receptors and by a change in its degradation. Its release in plasma is quite early, such that high values of ANP have been detected in patients with left ventricular dysfunction, despite being asymptomatic and not presenting any clinical decompensation.13

Its usefulness in assessing the prognosis of heart failure has been demonstrated in various studies, where high values of ANP have been associated with a significant increase in mortality.18 The SAVE study demonstrated that post-AMI patients with left ventricular dysfunction who presented elevated ANP at discharge had worse prognosis during follow-up.23

Due to its beneficial effects, ANP is considered to be an indirect marker of severity of heart failure and that it does not directly contribute to its poor prognosis. Despite this, it has been demonstrated that its values increase especially in decompensated heart failure, whereas it tends to normalize when the patient is stabilized and fluid overload disappears. As occurs with other neurohormones, pharmacological treatment of heart failure varies ANP plasma concentrations and modifies its prognostic value.

**BRAIN NATRIURETIC PEPTIDE**

Brain natriuretic peptide (BNP) is released in ventricular myocytes upon pressure increase in the ventricular wall, making it a very sensitive marker of left ventricular dysfunction. The action of BNP is similar to that of ANP, having a vasodilator effect and increasing diuresis. Currently, it is possible to determine the values of BNP and those of pro-BNP (N-BNP). This is a more stable precursor which is also elevated in the plasma of patients with heart failure. Both are considered to be indirect markers of severity of heart failure. Its introduction in clinical practice is relatively recent but, due to its high sensitivity and specificity for diagnosing left ventricular dysfunction, its use is constantly increasing.40,41

Furthermore, because it can be quickly determined, it has been used to improve diagnostic efficacy in emergency situations, where it helps to differentiate dyspnea of cardiac origin from one of pulmonary origin. In this way unnecessary complementary tests and admissions can be avoided.42,43

High values of BNP have also proven useful in determining the prognosis of heart failure during its development. It is effective both in asymptomatic patients or those with few symptoms, in whom high values of BNP were identified as independent predictors of mortality at 2 years, as well as in patients with advanced heart failure, where high values of BNP at the time of discharge made it possible to identify patients with greater mortality or need for readmission for heart failure.44-48 In the Val-HEFT study, where 5010 patients received valsartan or placebo in addition to conventional treatment, the high values of BNP were associated with a greater incidence of events at 2-year follow-up.20 Given its high predictive power, it has been suggested that BNP values can be of use in guiding individual medical treatment. Thus, patients with high values of BNP; despite optimized medical treatment, should be considered high-risk and therefore candidates for
other therapeutic options.\textsuperscript{49} As occurs with other hormones, heart failure treatment can modify the prognostic value of BNP. In fact, it has already been demonstrated that treatment with ACE inhibitors and BB reduces the concentrations of pro-BNP, lowering its predictive value.\textsuperscript{20} Despite the initial enthusiasm raised by the determination of BNP and its rapid spread, the variability of its values over time remains unknown. Furthermore, it is difficult to reach a consensus for the BNP cut-off value that would be suitable for the diagnosis of heart failure. This means that we still lack the information necessary to generalize its use in clinical practice.

\textbf{ADRENOMEDULLIN}

Adrenomedullin is a peptide released by the endothelium with a powerful positive vasodilator and inotropic effect. High values of plasmatic adrenomedullin have been detected in heart failure and its increase has been associated with greater mortality in patients with moderate heart failure.\textsuperscript{50} As with natriuretic peptides, it is thought to be an indirect marker of severity, although it is still not very clearly known what role it plays in neurohumoral activation in these patients.

\textbf{TUMOR NECROSIS FACTOR ALPHA}

In addition to neurohumoral activation, it has been confirmed that inflammation mediators are also activated in heart failure with important systemic and local repercussions; the origin of this inflammatory reaction is probably multifactorial.\textsuperscript{51} Tumor necrosis factor (TNF-\(\alpha\)) is a low molecular weight peptide that is activated through gene transcription factors. The majority of its actions are carried out through receptors located in target cells, where there are two types of receptors, I and II. These receptors can sometimes be found in the circulation in a soluble form, as occurs in heart failure. The release of TNF-\(\alpha\) is activated in response to various mediators, such as certain mitogens, angiotensin II and other cytokines; it is also activated in the presence of free radicals and during hypoxia. Tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) acts by activating inducible nitric oxide synthase (iNOS) and releases large quantities of nitric oxide, which has a vasodilator effect, negative inotropic effects, and forms cytotoxic free radicals.

Locally, TNF-\(\alpha\) is part of the inflammatory response activated after a myocardial injury, and thus is part of the initial repair response. However, TNF-\(\alpha\) expression has also been detected in experimental models of left ventricular pressure overload.\textsuperscript{52} In fact, TNF-\(\alpha\) promotes ventricular remodeling since it triggers signals that activate cellular proliferation, growth factors, adhesion molecules and, finally, apoptosis signals.\textsuperscript{4,53} In this regard, expression of TNF-\(\alpha\) mRNA has been detected in the myocardial tissue of hearts extracted at the time of cardiac transplant. Furthermore, numerous experimental studies conducted with transgenic mice overexpressing TNF-\(\alpha\) have demonstrated that such mice present dilatation and severe ventricular dysfunction, which is associated with early death.\textsuperscript{56}

TNF-\(\alpha\) was the first cytokine found to be elevated in the plasma of patients with severe heart failure, the highest values of TNF-\(\alpha\) being associated with a greater degree of neurohumoral activation and more marked cachexia.\textsuperscript{54} Various studies have demonstrated that high values of TNF-\(\alpha\) and its soluble receptors are associated with worse prognosis. In fact, its values in peripheral blood increase as heart failure worsens\textsuperscript{55,56} (Figure 2). Although it was initially believed, based on experimental studies, that TNF-\(\alpha\) contributed directly to progressive deterioration of ventricular function, the blocking of its activity with etanercept (synthetic receptor of TNF-\(\alpha\)), or infliximab (a chimerical monoclonal anti-TNF-\(\alpha\) antibody) has not proven to reduce mortality in patients with heart failure as was expected.

The prognostic value of TNF-\(\alpha\) and its receptors is also modified by medical treatment, especially with BB, that significantly reduce the concentration of TNF and its receptor sTNF-R2.\textsuperscript{57}

\textbf{INTERLEUKIN 6}

In addition to TNF-\(\alpha\), other cytokines, such as interleukin 6 (IL-6), are also elevated in patients with heart failure.\textsuperscript{4} Like all cytokines, IL-6 is a low molecular weight peptide activated through transcription factors and it presents autocrine or paracrine activity through target cell receptors. It is activated in response to various stimuli, such as angiotensin II, other cytokines, especially TNF-\(\alpha\), and when hypoxia is present. Like TNF-\(\alpha\), it releases large quantities of nitric oxide through the activation of iNOS.\textsuperscript{58}

Its values increase progressively as heart failure symptoms worsen. Thus, as with TNF-\(\alpha\), high values of IL-6 have been detected in patients with left ventricular dysfunction and few symptoms, which increase as NYHA functional class worsens (Figure 2). Several studies have shown that high values of IL-6 are a marker of poor prognosis\textsuperscript{56,57} and are correlated with increases in right cavity pressure and persistence of ventricular dysfunction during follow-up.\textsuperscript{59} Thus, in clinically stable patients with compensated heart failure, high values of IL-6 were associated with greater mortality or symptoms of heart failure decompensation during follow-up (Figure 3). As with
other prognosis markers, medical treatment, especially with BB, modifies IL-6 plasma concentrations, thus reducing its prognostic value.57

**ADHESION MOLECULES**

As part of the immune and inflammatory response triggered in heart failure, adhesion molecules should be mentioned. They have a mediating role between endothelial cells, lymphocytes, and circulating blood platelets, and also mediate the biological action of cytokines. High values of soluble intercellular adhesion molecule-1 (sICAM-1) have been associated with poor prognosis in heart failure patients.60 In a recent study, an increase in other soluble adhesion factors, such as vascular cellular adhesion molecule-1 (VCAM-1) and P-selectin, in addition to ICAM-1, has also been associated with worse prognosis in heart failure. Although the values of the 3 adhesion molecules were correlated inversely with EF in this study, only the values of P-selectin were identified as independent predictors of new events during follow-up.61 Despite these very initial results, the clinical usefulness of these markers is still uncertain.

**OXIDATIVE STRESS**

Oxidative stress is increased in heart failure, partly due to the strong increase in nitric oxide values secondary to the activation of iNOS and partly to the reduction in antioxidant activity. Increases in nitric oxide can lead to toxicity, since it gives rise to the production of oxygen free radicals that are cytotoxic, increase oxidative stress and reduce aerobic cellular metabolism, which can reduce the contractile capacity of myocytes. This increase in oxidative stress contributes to ventricular dysfunction, by mediating apoptosis and necrosis, and to the endothelial dysfunction62,63 typical of heart failure patients.

The increase in certain oxidative stress markers, such as low-density lipoprotein cholesterol (LDL-C), xanthinoxidase or uric acid, are elevated in patients with heart failure and their increase has been associated with greater mortality.64,65

Furthermore, improvements in ventricular remodeling have been demonstrated with antioxidant drug treatment.66 The clinical usefulness of these markers is
TROPONINS

Troponins are proteins that regulate cardiac contraction and do not circulate in the peripheral blood in normal conditions. Nevertheless, in the presence of myocardial injury, especially when the cellular membrane is injured, they can pass into the blood, thus being a very sensitive marker of myocardial necrosis. There are two types of troponin, T and I. Both are routinely used as prognosis markers in acute coronary syndromes. In addition to ischemic heart disease, high plasma values of both troponins have also been detected in patients with severe heart failure, and increases in troponin T and troponin I have been associated with a worse prognosis. In fact, in a recent study, troponin values were higher the worse the NYHA functional class, with values higher than 0.04 ng/mL being associated with greater mortality. Even though values of troponin T decreased in response to medical treatment and to improvement in symptoms, their high values at the time of patient admission were independent predictors of death or readmission after a year.67,68 Thus, this new marker has potential to establish the prognosis of patients with heart failure, although there is still little information available in this field.

CONCLUSION

The usefulness of these biological markers in heart failure treatment is still very limited (Figure 4) in clinical practice. In fact, the ideal marker should be, on the one hand, easy to determine, highly reliable, have little variability in response to medical treatment, and be cost effective. On the other hand, it should reflect changes in the clinical situation of the patient and have a very high predictive value regarding the evolution of heart failure. For now, this ideal marker remains unavailable, which means that research in this field should continue, in particular epidemiology validation studies.

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