



REVIEW ARTICLE

## Mid-regional pro-adrenomedullin and ST2 in heart failure: Contributions to diagnosis and prognosis



Daniela Lopes<sup>a</sup>, Luiz Menezes Falcão<sup>b,\*</sup>

<sup>a</sup> University Hospital Santa Maria/CHLN, Lisbon, Portugal

<sup>b</sup> University Hospital Santa Maria/CHLN, Faculty of Medicine of Lisbon, Lisbon, Portugal

Received 5 October 2016; accepted 21 November 2016

### KEYWORDS

Heart failure;  
Biomarkers;  
NT-proBNP;  
Mid-regional  
pro-adrenomedullin;  
ST2;  
sST2

**Abstract** Heart failure has a high prevalence in developed countries. It is a frequent cause of hospital admission and has an important impact on morbidity, mortality and healthcare costs. Biomarkers have been widely studied in heart failure, as they improve diagnosis and prognostic assessment. Natriuretic peptides are already a part of daily clinical practice but several other biomarkers are being studied. This review focuses on mid-regional pro-adrenomedullin (MR-proADM) and ST2. Neither of these biomarkers is useful in the diagnosis of acute heart failure. However, both have considerable short- and long-term prognostic value in patients with acute and with stable chronic heart failure. The utility of these two biomarkers in guiding heart failure treatment is yet to be established. ST2 appears to have some advantages compared to MR-proADM, because it is more closely associated with ventricular remodeling and fibrosis.

© 2017 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. All rights reserved.

### PALAVRAS-CHAVE

Insuficiência  
cardíaca;  
Biomarcadores;  
NT-proBNP;  
Adrenomedulina;  
ST2;  
sST2

### A MR-proadrenomedulina e o ST2 na insuficiência cardíaca: contribuição para o diagnóstico e prognóstico

**Resumo** A insuficiência cardíaca tem uma elevada prevalência nos países desenvolvidos. Trata-se de uma causa frequente de internamento hospitalar com importante impacto na morbidade, mortalidade e custos dos cuidados de saúde. Os biomarcadores têm contribuído para a avaliação diagnóstica e prognóstica na insuficiência cardíaca. Os peptídeos natriuréticos fazem já parte da prática clínica diária, mas há vários outros biomarcadores que têm vindo a ser estudados. Este artigo pretende avaliar a importância da MR-proadrenomedulina e do ST2. Nenhum

\* Corresponding author.

E-mail address: [luizmfalcao@sapo.pt](mailto:luizmfalcao@sapo.pt) (L. Menezes Falcão).

destes biomarcadores se tem revelado útil para o diagnóstico da insuficiência cardíaca aguda. Também não está estabelecida ainda a utilidade dos dois biomarcadores na terapêutica guiada da insuficiência cardíaca. Contudo, ambos têm importante valor prognóstico em doentes com insuficiência cardíaca aguda ou insuficiência cardíaca crónica. O uso combinado com os péptidos natriuréticos pode permitir uma melhor estratificação de risco na insuficiência cardíaca. © 2017 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L.U. Todos os direitos reservados.

#### List of abbreviations

ADM	adrenomedullin
ACEIs	angiotensin-converting enzyme inhibitors
ARBs	angiotensin receptor blockers
AUC	area under the curve
BNP	B-type natriuretic peptide
ED	emergency department
HF	heart failure
IL-1	interleukin-1
IL-33	interleukin-33
MR-proADM	mid-regional pro-adrenomedullin
NT-proBNP	N-terminal pro-B-type natriuretic peptide
ST2	suppression of tumorigenicity 2
sST2	soluble ST2

## Introduction

In the most recent European Society of Cardiology (ESC) guidelines,<sup>1</sup> heart failure (HF) is defined as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. This definition of HF restricts itself to stages at which clinical symptoms are apparent.<sup>1</sup> In recent decades, there have been notable advances in the prevention, diagnosis and treatment of cardiovascular disease. However, HF still has a significant impact, as it results in frequent hospitalizations, reduced life expectancy and high expenditure in healthcare systems.<sup>2</sup> HF has an estimated prevalence of 1-2% in the adult population of developed countries, but the number of cases in the elderly is higher, affecting at least 10% of individuals aged 70 years or older.<sup>1</sup>

Considering that the symptoms and signs described are non-specific, the diagnosis of acute HF is not always easy and differential diagnosis can be complicated. The presence of comorbidities such as pulmonary infection also complicates diagnosis due to overlapping symptoms.<sup>3</sup> Therefore, the use of biomarkers to provide more accurate diagnosis

has been widely studied. Ideally, biomarkers should provide information that is not given by clinical assessment or routine exams, thereby helping medical decisions. They should also be highly sensitive and specific, as well as easily measured, with reasonable costs and rapidly available results.<sup>3</sup> The part played by biomarkers is not limited to the diagnosis of HF, as they may also be useful in prognostic assessment.

Natriuretic peptides, especially B-type natriuretic peptide (BNP) and its precursor N-terminal pro-B-type natriuretic peptide (NT-proBNP), are currently used in clinical practice and their measurement is recommended by the ESC guidelines for the diagnosis and assessment of HF.<sup>1</sup> Their use in the diagnosis of acute HF in patients presenting with acute dyspnea in the emergency department (ED) has been validated by several studies.<sup>4</sup> Both BNP and NT-proBNP are very precise in identifying acute HF and their addition to routine clinical assessment is clearly advantageous.<sup>5-7</sup> In terms of diagnostic value, there is no statistical difference between the two biomarkers.<sup>8</sup> Natriuretic peptides are also useful in the prognostic assessment of patients hospitalized due to acute HF: higher BNP and NT-proBNP concentrations are associated with higher mortality.<sup>9-11</sup> In patients with stable chronic HF, measurement of natriuretic peptides is also an important follow-up tool.<sup>12,13</sup> Natriuretic peptide-guided therapy has been the subject of considerable study.<sup>14</sup> Adjusting therapy in order to attain lower BNP and NT-proBNP levels has been found to be associated with lower hospitalization and mortality rates.<sup>15,16</sup>

Despite their important role in HF, natriuretic peptides show some limitations. They are elevated in other conditions as well as HF, such as valvular heart disease, pulmonary hypertension, pulmonary thromboembolism, atrial fibrillation and sepsis.<sup>4,17</sup> Age and kidney failure increase natriuretic peptide levels, while obesity is associated with lower levels.<sup>4,17</sup> These situations can give values in a gray area that requires particularly careful analysis. The investigation of new biomarkers that can complement natriuretic peptides has been the subject of considerable attention.

This review focuses on two interesting and promising biomarkers currently under study: adrenomedullin (ADM), mainly a myocyte strain marker, and ST2, mainly a cardiac remodeling marker. These biomarkers reflect different pathological pathways. Their diagnostic and prognostic value will be examined, as will their importance in monitoring of therapy and patient follow-up.

## Adrenomedullin

ADM is a 52-amino acid peptide belonging to the calcitonin gene-related peptide family.<sup>18,19</sup> The ADM gene encodes a 185-amino acid preprohormone, which, after cleavage, generates a 164-amino acid prohormone, pro-ADM; pro-ADM is then processed, forming ADM<sup>18,19</sup> and mid-regional pro-adrenomedullin (MR-proADM) (Figure 1). ADM is secreted in various tissues, including the heart, lungs, central nervous system, kidneys and gastrointestinal organs; it is also expressed in endothelial cells, vascular smooth muscle cells, fibroblasts and adipocytes.<sup>18,19</sup> ADM has a hypotensive effect: it stimulates diuresis and natriuresis and also causes vasodilation, lowering blood pressure.<sup>18</sup> In HF, as a consequence of pressure/volume overload and ventricular wall stretching, the ADM gene is upregulated in cardiac myocytes. The resulting high ADM levels appear to have a protective effect in the myocardium, as they lead to a decrease in preload and afterload.<sup>19</sup> Some studies suggest that ADM additionally inhibits cell growth and hypertrophy; it has also been associated with reductions in remodeling and fibrosis.<sup>19,20</sup>

ADM, like natriuretic peptides and many other vasoactive peptides, is cleaved by neprilysin, a ubiquitous enzyme that is mainly expressed in the proximal tubules of nephrons.<sup>21</sup> Inhibition of neprilysin has been studied as a way to enhance endogenous neurohumoral systems that are diuretic and natriuretic and able to inhibit hypertrophy and fibrosis in HF.<sup>22</sup>

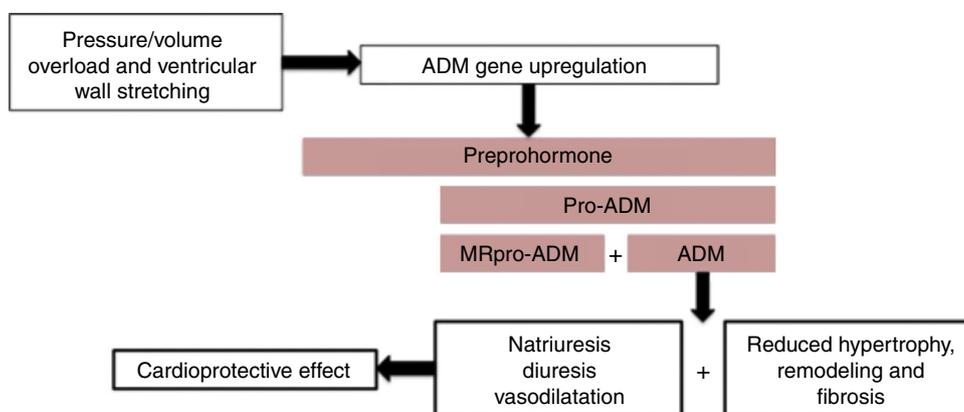
Clinical use of ADM was limited for some time because of the *in vitro* instability of this biomarker: its half-life is short and it is quickly removed from the circulation.<sup>19</sup> This problem was solved by the use of MR-proADM, a stable fragment of pro-ADM whose concentrations reflect those of ADM.<sup>19</sup>

## Diagnostic value of MR-proADM in acute heart failure

Regarding the use of MR-proADM in the diagnosis of acute HF, it should be borne in mind that this biomarker is also increased in other conditions, such as systemic and pulmonary hypertension, following myocardial infarction, kidney failure and sepsis.<sup>18,19</sup> In order to determine the diagnostic value of MR-proADM, Dieplinger et al. measured its levels in patients who attended the ED with acute dyspnea.<sup>23</sup> It was concluded that MR-proADM had no statistically significant value in the diagnosis of acute HF and was clearly inferior to NT-proBNP.<sup>23</sup> Another study confirmed the lack of specificity of MR-proADM in the diagnosis of acute HF.<sup>24</sup> Therefore, MR-proADM appears to have no practical utility in the diagnosis of acute HF and its measurement has no advantage over the established natriuretic peptides.

## Prognostic value of MR-proADM in acute heart failure

Several studies have shown that MR-proADM can be used in the prognostic assessment of patients with acute HF<sup>19</sup> (Table 1). The BACH study by Maisel et al., involving a large number of patients presenting to the ED with acute dyspnea, analyzed whether MR-proADM was related to 90-day survival.<sup>25</sup> Survivors had lower MR-proADM levels than those who died.<sup>25</sup> Furthermore, for predicting 90-day survival, MR-proADM had an area under the curve (AUC) on receiver operating characteristic analysis of 0.67, which was slightly superior to BNP (AUC 0.61) and NT-proBNP (AUC 0.66).<sup>25</sup> The prognostic accuracy of MR-proADM levels, assessed in blood samples taken on admission to the ED, was 73%, which was higher than for BNP and NT-proBNP (62% and 64%, respectively).<sup>25</sup>



**Figure 1** Schematic representation of the production and actions of adrenomedullin (ADM) in heart failure (HF). The pressure/volume overload and ventricular wall stretching seen in HF lead to upregulation of the ADM gene. The preprohormone undergoes cleavage, forming pro-ADM, which is further processed to ADM. ADM causes natriuresis, diuresis, and vasodilation. It is also associated with reduced hypertrophy, ventricular remodeling and fibrosis. The actions of ADM thus have a cardioprotective effect. Due to its *in vitro* instability, ADM levels cannot be measured directly, but cleavage of pro-ADM also produces mid-regional pro-adrenomedullin, a stable fragment that is easily measured and whose concentrations reflect those of ADM. ADM: adrenomedullin; MR-proADM: mid-regional pro-adrenomedullin.

**Table 1** Studies assessing the prognostic value of MR-proADM in acute heart failure.

Study	Setting	No. of patients	Primary endpoint	Main conclusions
Maisel et al. <sup>25</sup>	Patients presenting to the ED with dyspnea	1641	90-day mortality	MR-proADM had an AUC of 0.67, which was marginally superior to BNP (AUC 0.61) and NT-proBNP (AUC 0.66)
Peacock et al. <sup>26</sup>	Patients presenting to the ED with dyspnea	1641	14-day mortality	With an AUC of 0.72, MR-proADM was superior to both BNP (0.48) and NT-proBNP (0.59)
Travaglini et al. <sup>27</sup>	Patients presenting to the ED with dyspnea	501	30- and 90-day mortality	MR-proADM values at admission and at 72 hours significantly predicted 30-day mortality ( $p < 0.001$ ) and 90-day mortality ( $p < 0.0001$ )

AUC: area under the curve on receiver operating characteristic analysis; BNP: B-type natriuretic peptide; ED: emergency department; MR-proADM: mid-regional pro-adrenomedullin; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

In a subsequent sub-analysis of the BACH study assessing the prognostic value of ADM in the shorter term,<sup>26</sup> MR-proADM was superior to natriuretic peptides in predicting 14-day mortality; the AUC for BNP and NT-proBNP was, respectively, 0.48 and 0.59, while MR-proADM had an AUC of 0.74.<sup>26</sup> As the latter value is considerably superior to the AUC observed for predicting 90-day mortality, this biomarker seems to be more useful in shorter-term prognostic assessment. It is important to note that in the above study treatment was similar in survivors and in those who died within 14 days; this shows the importance of identifying patients with worse prognosis, who may need more aggressive treatment and surveillance.<sup>26</sup> The Verifying Dyspnea study<sup>27</sup> also confirmed the prognostic value of MR-proADM. In the group of patients with acute HF, MR-proADM levels in the ED and at 72 hours after admission had an AUC for 90-day mortality of 0.76 ( $p < 0.005$ ) and 0.77 ( $p < 0.05$ ), respectively.<sup>27</sup> Moreover, reassessment of MR-proADM 72 hours after admission was superior to a single measurement.<sup>27</sup>

These studies show that MR-proADM is a good prognostic marker in patients hospitalized due to acute HF and, in some reports, is even superior to natriuretic peptides. Hence, MR-proADM can be complementary to natriuretic peptides and its measurement may be useful. It is important to point out that MR-proADM levels vary according to certain patient characteristics. Women, older patients, and those with kidney failure and systolic dysfunction have higher MR-proADM levels, while like natriuretic peptides, levels decrease with higher body mass index.<sup>28,29</sup>

### MR-proADM in follow-up and biomarker-guided therapy

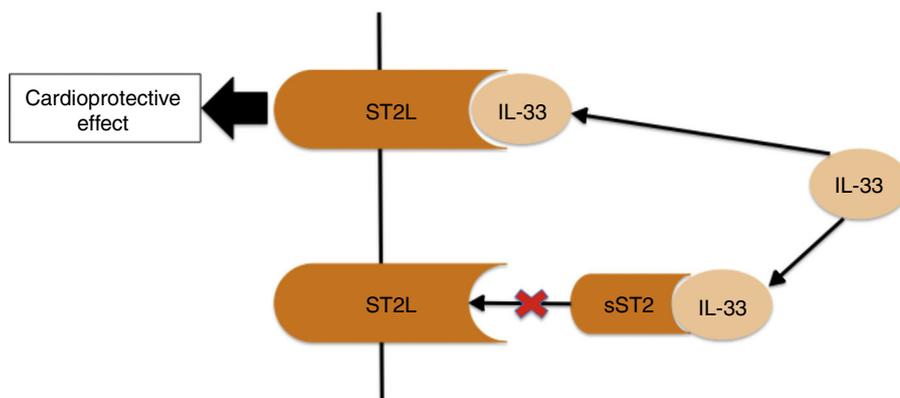
Assessment of MR-proADM appears to be useful in the follow-up of patients with stable chronic HF. Von Haehling et al.<sup>28</sup> measured MR-proADM and NT-proBNP in patients with chronic HF, under medication and clinically stable. Higher MR-proADM levels were seen in patients in more advanced NYHA classes and these higher levels were also

associated with increased mortality ( $p < 0.0001$ ).<sup>28</sup> Concerning 12-month mortality, MR-proADM had a similar value to NT-proBNP; however, for three-month mortality MR-proADM was shown to be superior to NT-proBNP.<sup>28</sup> Once again MR-proADM appears to be more useful in short-term assessment. The use of MR-proADM together with clinical assessment and natriuretic peptides had a better prognostic value than the individual use of any of these variables ( $p < 0.0009$ ).<sup>28</sup> Masson et al., in the GISSI-HF study,<sup>29</sup> found that higher concentrations of MR-proADM were associated with an increased risk of mortality or hospitalization for cardiovascular causes ( $p < 0.0001$ ). In this study, NT-proBNP and MR-proADM had similar value in prognostic assessment.<sup>29</sup> Xue et al. recently confirmed these results, concluding that MR-proADM levels were strong predictors of mortality ( $p < 0.0001$ ).<sup>30</sup> Considering all these studies, MR-proADM is a good prognostic marker even in patients with stable chronic HF, and is useful as a follow-up tool.

MR-proADM values change with some medications, and lower levels are observed in patients treated with diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and beta-blockers.<sup>29</sup> Richards et al. showed that patients with chronic HF who had higher MR-proADM levels particularly benefited from the use of carvedilol.<sup>31</sup> Nevertheless, there is no evidence that MR-proADM can be used in a biomarker-guided therapeutic strategy.

### ST2

ST2 is a member of the IL-1 receptor family. There are two main isoforms: a transmembrane receptor (ST2L) and a soluble receptor (sST2). ST2L includes an extracellular domain, a transmembrane segment and an intracellular domain. sST2, which lacks the transmembrane and intracellular domains, is a circulating isoform that can be detected in serum. The ligand of ST2 is interleukin-33 (IL-33), an interleukin-1-like cytokine that is secreted by most cells in response to damage. IL-33 exerts its biological actions only when it binds to the ST2L isoform. However, circulating sST2 acts as a



**Figure 2** Schematic representation of the interleukin-33 (IL-33)/ST2 pathway. IL-33 exerts its biological actions when it binds to the ST2L isoform. In situations of myocardial stress, the IL-33/ST2L interaction appears to have a cardioprotective effect. Soluble ST2 acts as a decoy receptor, preventing the beneficial effects of IL-33/ST2L signaling. IL-33: interleukin-33; sST2: soluble ST2.

decoy receptor, binding to IL-33 and blocking the IL-33/ST2L interaction, which inhibits the action of IL-33<sup>32</sup> (Figure 2).

The IL-33/ST2 complex participates in the immune response through the activation of Th2 effector cells and the release of Th2-related cytokines. IL-33/ST2 thus plays a role in various inflammatory diseases, including asthma and rheumatoid arthritis.<sup>32</sup> Recently, it was discovered that IL-33/ST2 is also expressed in cardiac fibroblasts and cardiomyocytes.<sup>32</sup> Expression is increased in response to myocardial stress, and this appears to have a cardioprotective effect, reducing myocardial fibrosis, preventing cardiomyocyte hypertrophy, reducing apoptosis, and improving myocardial function.<sup>32</sup> The beneficial effects of IL-33 are exerted specifically through the ST2L receptor and are blocked when IL-33 binds to the decoy receptor sST2, which occurs when sST2 levels are increased.<sup>32,33</sup> This explains why higher sST2 levels are associated with remodeling, fibrosis and hypertrophy in patients with cardiac disease, especially HF and ischemic heart disease.<sup>32</sup> In view of this, several studies have measured circulating sST2 levels in patients with HF, in order to determine the utility of this biomarker.

### Diagnostic value of ST2 in acute heart failure

Regarding the diagnostic value of sST2 in acute HF, it is important to note that sST2 levels are increased in other cardiovascular diseases besides HF, such as hypertension, ischemic heart disease and valvular heart disease.<sup>33</sup> Higher concentrations of sST2 are also seen in several inflammatory diseases, including asthma, rheumatoid arthritis and systemic erythematosus lupus, and in sepsis.<sup>33</sup> In the PRIDE study,<sup>34</sup> the sST2 levels of patients presenting to the ED with acute dyspnea were measured in order to determine its diagnostic value for acute HF. Although sST2 concentrations were higher in patients with acute HF than in those with non-cardiac dyspnea, sST2 was not found to have a statistically significant diagnostic value; likewise, it was clearly inferior to NT-proBNP in the diagnosis of acute HF.<sup>34</sup> Accordingly, it can be concluded that sST2 measurement is not useful for the diagnosis of acute HF and does not present advantages

over the established natriuretic peptides, which has been confirmed in more recent studies.<sup>23,35</sup>

### Prognostic value of ST2 in acute heart failure

sST2 levels in patients hospitalized due to acute HF, measured at admission and discharge, can be used for prognostic assessment<sup>36</sup> (Table 2). The PRIDE study<sup>34</sup> showed that high sST2 concentrations were clearly associated with increased one-year mortality. Likewise, patients with sST2 levels above the median value had 11-fold greater odds for death ( $p < 0.0005$ ).<sup>34</sup> sST2 was also superior to NT-proBNP in predicting one-year mortality risk ( $p < 0.05$ ), but the best value was obtained by using these two biomarkers together.<sup>34</sup> Rehman et al.<sup>37</sup> confirmed the correlation between higher sST2 and worse prognosis and also showed that sST2 levels increased with higher NYHA class.<sup>37</sup> More recently, Friões et al.<sup>38</sup> concluded that higher sST2 concentrations in patients with acute HF were associated with greater risk of six-month mortality or readmission. In this study, sST2 and BNP had similar values but, again, the best value was attained by using the two biomarkers together.<sup>38</sup>

Monitoring of sST2 values through serial measurements appears to be particularly useful, increasing the prognostic power of this biomarker.<sup>39</sup> Bayes-Genis et al.<sup>40</sup> studied a small group of patients with acute HF and measured their sST2 values at discharge and two weeks later. Patients with a greater decrease in sST2 two weeks after discharge had a better prognosis.<sup>40</sup> Another study measured sST2 at admission in the ED and 48 hours later, concluding that sST2 levels clearly separated those who survived from those who did not.<sup>40</sup> Likewise, the percentage of sST2 decrease predicted long term mortality.<sup>41</sup>

It can be concluded that sST2 is a good prognostic marker, both short- and long-term, in patients hospitalized for acute HF. Also, the addition of sST2 to natriuretic peptides is superior to the use of natriuretic peptides alone. It is important to emphasize that repeated monitoring of sST2 levels is more useful than a single measurement, and its low biological variability increases its potential for serial testing and patient monitoring.<sup>42</sup> It has also recently been shown that the prognostic value of sST2 is not influenced by renal

**Table 2** Studies assessing the prognostic value of ST2 in acute heart failure.

Study	Setting	No. of patients	Primary endpoint	Main conclusions
Januzzi et al. <sup>34</sup>	Dyspneic patients in the ED	599	1-year mortality	High ST2 levels associated with increased 1-year mortality
Rehman et al. <sup>37</sup>	Patients in the ED with acute HF	346	1-year mortality	Higher ST2 levels are found in patients in higher NYHA class and correlate with worse prognosis
Friões et al. <sup>38</sup>	Patients hospitalized with acute HF	195	6-month mortality or readmission	Higher ST2 concentrations associated with higher risk of 6-month mortality or readmission
Bayes-Genis et al. <sup>40</sup>	Ambulatory patients with recent decompensated HF	48	1-year cardiovascular death, hospital admission for HF or heart transplantation	A greater decrease in ST2 levels two weeks after discharge associated with better outcome
Breidhardt et al. <sup>41</sup>	Patients in the ED with acute HF	207	1-year mortality	ED and serial ST2 measurements are independent predictors of 1-year mortality in acute HF

ED: emergency department; HF: heart failure; NYHA: New York Heart Association.

function.<sup>43</sup> It should be noted that higher sST2 levels are associated with decreased ejection fraction, left ventricular enlargement and hypokinesia, which suggests its potential for the assessment of ventricular remodeling.<sup>44</sup>

### ST2 in follow-up and biomarker-guided therapy

sST2 assessment may also be useful as a follow-up measure in patients with stable chronic HF.<sup>45</sup> The Penn Heart Failure study, which determined sST2 levels in patients with chronic HF, concluded that higher sST2 concentrations (>36.3 ng/ml) were associated with a higher risk of mortality or heart transplantation ( $p < 0.0001$ ).<sup>46</sup> Although the prognostic value of sST2 was similar to that of NT-proBNP, the combination of the two biomarkers was superior to their use individually,<sup>46</sup> and was a useful complement to conventional clinical assessment, enabling better classification of patients in appropriate risk categories.<sup>46</sup> Bayes-Genis et al.,<sup>47</sup> whose study showed comparable results, subsequently confirmed these findings. In the Val-HeFT trial, elevated sST2 levels in patients with chronic HF were significantly ( $p < 0.0001$ ) correlated with increased morbidity, mortality and hospitalization for decompensated HF,<sup>48</sup> while in the PROTECT study,<sup>49</sup> patients with increased sST2 during follow-up had earlier cardiovascular complications ( $p = 0.009$ ). This study reached another important conclusion: sST2 levels below a cutoff of 35 ng/ml were associated with lower left ventricular end-diastolic volume.<sup>49</sup> This links sST2 with left ventricular remodeling and suggests the potential of this biomarker in surveillance of structural heart changes.<sup>49</sup> Hence, sST2 has prognostic value in patients with chronic HF, as it identifies those at higher risk, particularly when used together with natriuretic peptides, and could thus be used as a follow-up strategy in these patients.

Patients under HF treatment including ACEIs, ARBs, mineralocorticoid receptor antagonists and beta-blockers show

**Table 3** Clinical usefulness of natriuretic peptides, adrenomedullin and ST2 in patients with heart failure.

Biomarker	Diagnosis	Prognosis	Follow-up	Therapy guidance
BNP/NT-proBNP	+++	++	++	+
MR-proADM	-	++	++	-
sST2	-	++	++	-

+ indicates utility; - indicates lack of data suggesting utility.

lower concentrations of sST2.<sup>50</sup> This association has led to the hypothesis that this biomarker can be used as a treatment guide in HF. Beta-blockers have shown a substantial effect on sST2 levels.<sup>48</sup> Exploring this link, Gaggin et al.<sup>51</sup> observed that, in patients with elevated sST2 levels, those under higher beta-blocker doses had lower mortality, suggesting that high sST2 levels may identify patients who will benefit from higher treatment doses. In another study, spironolactone therapy was significantly beneficial for patients hospitalized with acute HF who had elevated sST2.<sup>52</sup> However, there is insufficient data to support the clinical use of sST2 in biomarker-tailored therapy.<sup>50</sup>

### Discussion and conclusions

Natriuretic peptides are a part of daily clinical practice, not only for the large number of patients hospitalized with decompensated HF, and their utility has been confirmed in various studies. They are an important tool in the diagnosis of acute HF, as well as in prognostic assessment. They have a promising role in biomarker-guided therapy, though this is still not recommended by clinical guidelines. Several other biomarkers that can complement natriuretic peptides have been studied. A multimarker strategy appears to be bene-

ficial, which is another incentive for thorough investigation of new molecules.<sup>53,54</sup>

Considering the studies analyzed in this work, it can be concluded that measurement of MR-proADM and sST2 is not of significant help in the diagnostic assessment of patients hospitalized with HF.

Regarding risk stratification, the best results can be found in the MOCA study,<sup>55</sup> in which these biomarkers were able to identify patients with higher mortality risk, who need enhanced surveillance and more aggressive therapeutic strategies. The addition of sST2 and MR-proADM to the natriuretic peptides helps to determine both short- and long-term prognosis. sST2 and MR-proADM can be used in the follow-up of patients with stable chronic HF. In these patients, MR-proADM and sST2 appear to be equivalent or, in some cases, superior to natriuretic peptides, and can be used in conjunction with them in follow-up. Unlike for natriuretic peptides, studies proving the clinical utility of sST2 and MR-proADM in biomarker-guided therapy are still lacking. These conclusions are summarized in Table 3.

sST2 appears to have some advantages compared to MR-proADM. Some studies on sST2 have shown that this biomarker is linked to ventricular remodeling: elevated sST2 levels are associated with an enlarged and hypokinetic left ventricle. This suggests that natriuretic peptides could be more useful when assessed in conjunction with sST2 than with MR-proADM.

Despite the benefits of these two biomarkers, many questions remain to be answered. For instance, the cutoff values indicating good or bad prognosis are of considerable importance. Biomarker values usually reach their peak in the acute phase and then decrease during stabilization, reaching lower levels in patients with stable chronic HF.

For sST2, 35 ng/ml is the cutoff validated in both acute and chronic HF. This biomarker is most widely used to classify patients with chronic HF.<sup>56,57</sup> By contrast, there is no agreed threshold for MR-proADM in either acute or chronic HF patients. It is consequently a priority to define cutoff values that can be applied to the general population, enabling widespread clinical use of these biomarkers.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## References

- Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–200.
- Braunwald E. Heart failure. *JACC: Heart Fail*. 2013;1:1–20.
- Choudhary R, Iqbal N, Khusro F, et al. Heart failure biomarkers. *J Cardiovasc Transl Res*. 2013;6:471–84.
- Iqbal N, Wentworth B, Choudhary R, et al. Cardiac biomarkers: new tools for heart failure management. *Cardiovasc Diagn Ther*. 2012;2:147–64.
- Maisel A, Krishnaswamy P, Nowak R, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161–7.
- Januzzi J, Camargo C, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol*. 2005;95:948–54.
- Januzzi J, Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J*. 2006;27:330–7.
- Roberts E, Ludman A, Dworzynski K, et al. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *Br Med J*. 2015;350:h910.
- Fonarow G, Peacock W, Phillips C, et al. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:1943–50.
- Di Somma S, Magrini L, Pittoni V, et al. In-hospital percentage BNP reduction is highly predictive for adverse events in patients admitted for acute heart failure: the Italian RED Study. *Crit Care*. 2010;14:R116.
- Januzzi J, Sakhuja R, O'Donoghue M, et al. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. *JAMA Intern Med*. 2006;166:315–20.
- Masson S, Latini R, Anand I, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem*. 2006;52.
- Nishiyama K, Tsutomoto T, Yamaji M, et al. Biological variation of brain natriuretic peptide and cardiac events in stable outpatients with nonischemic chronic heart failure. *Circ J*. 2011;75:341–7.
- Troughton R, Felker G, Januzzi J. Natriuretic peptide-guided heart failure management. *Eur Heart J*. 2014;35:16–24.
- Savarese G, Trimarco B, Dellegrottaglie S, et al. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2686 patients in 12 randomized trials. *PLOS ONE*. 2013;8:e58287.
- Troughton R, Frampton C, La Rocca H, et al. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. *Eur Heart J*. 2014. <http://dx.doi.org/10.1093/eurheartj/ehu090>.
- Gaggin H, Januzzi J. Biomarkers and diagnostics in heart failure. *Biochim Biophys Acta*. 2013;1832:2442–50.
- Jougasaki M, Burnett J. Adrenomedullin: potential in physiology and pathophysiology. *Life Sci*. 2000;66:855–72.
- Potocki M, Ziller R, Mueller C. Mid-regional pro-adrenomedullin in acute heart failure: a better biomarker or just another biomarker. *Curr Heart Fail Rep*. 2012;9:244–51.
- Niu P, Shindo T, Iwata H, et al. Protective effects of endogenous adrenomedullin on cardiac hypertrophy, fibrosis and renal damage. *Circulation*. 2004;109:1789–94.
- Bayes-Genis A, Morant-Talamante N, Lupón J. Nephrylysin and natriuretic peptide regulation in heart failure. *Curr Heart Fail Rep*. 2016;13:151–7.
- McMurray J. Nephrylysin inhibition to treat heart failure: a tale of science, serendipity, and second chances. *Eur J Heart Fail*. 2015;17:242–7.
- Dieplinger B, Gegenhuber A, Haltmayer M, et al. Evaluation of novel biomarkers for the diagnosis of acute destabilized heart failure in patients with shortness of breath. *Heart*. 2009;95:1508–13.
- Shah R, Truong Q, Gaggin H, et al. Mid-regional pro-atrial natriuretic peptide and pro-adrenomedullin testing for the diagnostic and prognostic evaluation of patients with acute dyspnea. *Eur Heart J*. 2012;33:2197–205.

25. Maisel A, Mueller C, Nowak R, et al. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol*. 2010;55:2062–76.
26. Peacock WF, Nowak R, Christenson R, et al. Short-term mortality risk in emergency department acute heart failure. *Acad Emerg Med*. 2011;18:947–58.
27. Travaglino F, Russo V, De Berardinis B, et al. Thirty and ninety days mortality predictive value of admission and in-hospital procalcitonin and mid-regional pro-adrenomedullin testing in patients with dyspnea. Results from the VERifying DYspnea trial. *Am J Emerg Med*. 2014;32:334–41.
28. Von Haehling S, Filippatos G, Papassotiropoulos J, et al. Mid-regional pro-adrenomedullin as a novel predictor of mortality in patients with chronic heart failure. *Eur J Heart Fail*. 2010;12:484–91.
29. Masson S, Latini R, Carbonieri E, et al. The predictive value of stable precursor fragments of vasoactive peptides in patients with chronic heart failure: data from the GISSI-heart failure (GISSI-HF) trial. *Eur J Heart Fail*. 2010;12:338–47.
30. Xue Y, Taub P, Iqbal N, et al. Mid-region pro-adrenomedullin adds predictive value to clinical predictors and Framingham risk score for long-term mortality in stable outpatients with heart failure. *Eur J Heart Fail*. 2013;13:43–9.
31. Richards A, Doughty R, Nicholls M, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. *J Am Coll Cardiol*. 2001;37.
32. Pascual-Figal D, Januzzi J. The biology of ST2: the International ST2 Consensus Panel. *Am J Cardiol*. 2015;115:3B–7B.
33. Dieplinger B, Mueller T. Soluble ST2 in heart failure. *Clin Chim Acta*. 2014, <http://dx.doi.org/10.1016/j.cca.09.021>.
34. Januzzi J, Peacock W, Maisel A, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. *J Am Coll Cardiol*. 2007;50:607–13.
35. Henry-Okafor Q, Collins SP, Jenkins CA, et al. Soluble ST2 as a diagnostic and prognostic marker for acute heart failure syndromes. *Open Biomark J*. 2012;5:1–8.
36. Maisel A, Richards A, Pascual-Figal D, et al. Serial ST2 testing in hospitalized patients with acute heart failure. *Am J Cardiol*. 2015;115:32B–7B.
37. Rehman S, Mueller T, Januzzi J. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. *J Am Coll Cardiol*. 2008;52:1458–65.
38. Friões F, Lourenço P, Laszczynska O, et al. Prognostic value of sST2 added to BNP in acute heart failure with preserved or reduced ejection fraction. *Clin Res Cardiol*. 2015. <http://link.springer.com/article/10.1007%2Fs00392-015-0811-x>
39. Januzzi J, Mebazaa A, Di Somma S. ST2 and prognosis in acutely decompensated heart failure: the International ST2 Consensus Panel. *Am J Cardiol*. 2015;115:26B–31B.
40. Bayes-Genis A, Pascual-Figal D, Januzzi J, et al. Soluble ST2 monitoring provides additional risk stratification for outpatients with decompensated heart failure. *Rev Esp Cardiol*. 2010;63:1171–8.
41. Breidthardt T, Balmelli C, Twerenbold R, et al. Heart failure therapy-induced early ST2 changes may offer long-term therapy guidance. *J Card Fail*. 2013;19.
42. Wu A, Wians F, Jaffe A. Biological variation of galectin-3 and soluble ST2 for chronic heart failure: implication on interpretation of test results. *Am Heart J*. 2013;165:995–9.
43. Bayes-Genis A, Zamora E, De Antonio M, et al. Soluble ST2 serum concentration and renal function in heart failure. *J Card Fail*. 2013;19:768–75.
44. Shah R, Chen-Tournoux A, Picard M, et al. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. *Circ: Heart Fail*. 2009;2:311–9.
45. Bayes-Genis A, Zhang Y, Ky B. ST2 and patient prognosis in chronic heart failure. *Am J Cardiol*. 2015;115:64B–9B.
46. Ky B, French B, McCloskey K, et al. High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. *Circ: Heart Fail*. 2011;4:180–7.
47. Bayes-Genis A, Antonio M, Galán A, et al. Combined use of high-sensitivity ST2 and NT-proBNP to improve the prediction of death in heart failure. *Eur J Heart Fail*. 2012;14:32–8.
48. Anand I, Rector T, Kuskowski M, et al. Prognostic value of soluble ST2 in the Valsartan Heart Failure trial. *Circ: Heart Fail*. 2014;7:418–26.
49. Gaggin H, Szymonifka J, Bhardwaj A, et al. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. *JACC: Heart Fail*. 2014;2:65–72.
50. Januzzi J, Pascual-Figal D, Daniels L. ST2 testing for chronic heart failure therapy monitoring: the International ST2 Consensus Panel. *Am J Cardiol*. 2015;115:70B–5B.
51. Gaggin H, Motiwala S, Bhardwaj A, et al. Soluble concentrations of the interleukin receptor family member ST2 and  $\beta$ -blocker therapy in chronic heart failure. *Circ: Heart Fail*. 2013;6:1206–13.
52. Maisel A, Xue Y, Van Veldhuisen D, et al. Effect of spironolactone on 30-day death and heart failure rehospitalization (from the COACH study). *Am J Cardiol*. 2014;114:737–42.
53. Ahmad T, Fiuzat M, Pencina M, et al. Charting a roadmap for heart failure biomarker studies. *JACC: Heart Fail*. 2014;2:477–88.
54. Ky B, French B, Levy WC, et al. Multiple biomarkers for risk prediction in chronic heart failure. *Circ: Heart Fail*. 2012;5:183–90.
55. Lassus J, Gayat E, Mueller C, et al. Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: the Multinational Observational Cohort on Acute Heart Failure (MOCA) study. *Int J Cardiol*. 2013, <http://dx.doi.org/10.1016/j.ijcard.2013.01.228>.
56. Felker G, Fiuzat M, Thompson V, et al. Soluble ST2 in ambulatory patients with heart failure: association with functional capacity and long-term outcomes. *Circ: Heart Fail*. 2013;6:1172–9.
57. Daniels L, Bayes-Genis A. Using ST2 in cardiovascular patients: a review. *Future Cardiol*. 2014;10:525–39.