REVIEW

Copeptin in acute coronary syndromes and heart failure management: State of the art and future directions

Place de la copeptine dans la prise en charge du syndrome coronaire aigu et de l’insuffisance cardiaque : état des connaissances et perspectives futures

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Summary Over the past two decades, the use of multiple biomarkers has changed cardiovascular disease management. Recently, several trials have assessed the diagnostic and prognostic performances of copeptin, especially in patients with heart failure or acute coronary syndromes. Primary results are interesting, with copeptin looking promising for: the management of patients

KEYWORDS
Copeptin;
Acute coronary syndromes;

Abbreviations: ACS, acute coronary syndromes; AMI, acute myocardial infarction; AQ2, aquaporin 2 channel; AQ REV, aquaporin water channel containing vesicles; AVP, arginine vasopressin; BNP, B-type natriuretic peptide; cAMP, cyclic adenosine monophosphate; cCa2+, cytosolic calcium; CI, confidence interval; CMR, cardiac magnetic resonance; CPK, creatine phosphokinase; CPO, chest pain onset; ECG, electrocardiogram; ED, emergency department; Gq, G coupled protein q; Gs, G coupled protein s; H2O, water; HF, heart failure; HR, hazard ratio; IP3, phosphatidylinositol triphosphate; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; NPV, negative predictive value; NSTE-ACS, non-ST elevation acute coronary syndromes; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PKA, protein kinase A; PLCβ, phospholipase C β; PPV, positive predictive value; ROC, receiver operator characteristic; Se, sensitivity; Sp, specificity; STEMI, ST-segment elevation myocardial infarction; V1R, vasopressin V1 receptor; V2R, vasopressin V2 receptor.

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Copeptin in ACS and HF

Introduction

Over the past two decades, the introduction of multiple biomarkers has changed the landscape of cardiovascular diseases, especially in the management of patients with acute coronary syndromes (ACS) and heart failure (HF). Biomarkers can provide useful information for diagnostic, prognostic and therapeutic strategies.

In patients with chest pain, the predominant problem in clinical practice is to confirm or rule out a diagnosis of ACS as quickly as possible. This is important because:

• a high number of patients are referred to emergency departments (ED) due to suspected ACS;
• it is necessary to start early medical and/or invasive therapies in actual ACS patients in order to improve their prognosis.

Multiple biomarkers—including myoglobin, creatine phosphokinase (CPK) and CPK-MB—have been used in the past, but their delayed release after myocardial necrosis and/or their lack of specificity render them poorly exploitable in clinical practice and compromise their diagnostic performance. Currently, troponin assessment is the gold standard for the early detection of myocardial infarction (MI) and this has shown better aptitude (sensitivity, specificity, early detection) compared to older biomarkers. However, conventional troponin elevation usually still occurs relatively late (3–6 hours) after ACS onset, and multiple samplings are often required and recommended in those patients who present early (within 3 hours) after chest pain onset (CPO) [1–4]. In addition, since the recent introduction of high-sensitivity troponin, there has been an increase in sensitivity and an improvement in early detection, but a decrease in specificity in ACS management. Indeed, many causes (e.g. ACS, acute HF, pulmonary embolism, myocarditis and severe sepsis) could lead to myocardial necrosis and, subsequently, to increased troponin levels in practice [5].

In contrast to ACS, in HF management, the major issue is the prognostic evaluation of patients with chronic HF rather than the diagnosis of acute HF. Indeed, B-type natriuretic peptide (BNP) and N-terminal pro-hormone BNP (NT-proBNP) have shown to be highly specific of HF and have drastically simplified the management of patients referred to ED for dyspnoea or suspected HF [6–10]. By contrast, risk stratification remains a critical issue in HF management. Indeed, high-risk patients can therefore be considered for invasive strategies such as implantable assist devices and/or cardiac transplantation. Variables such as New York Heart Association (NYHA) class, right and left ventricular functions, BNP or variables obtained during cardiopulmonary exercise testing (e.g. VO2 max) have been associated with the outcome of chronic HF patients [8]. In spite of these advances, risk stratification of chronic HF patients needs further improvement. Indeed, there remains variability in prognosis, with some patients categorized as low risk who experience early major cardiac events and others categorized as high-risk who do not. In addition, since cardiopulmonary exercise testing is a time-consuming method that is rarely used for risk stratification in routine practice, some potent indicators may be lacking for an individual. As a consequence, there is a critical need for tools that may help physicians to guide therapeutic options in chronic HF, especially to better select patients who should be considered for invasive strategies.

Therefore, new biomarkers that can provide additional information may be of great interest in clinical practice to help physicians’ decisions [11,12]. Copeptin, a surrogate for arginine vasopressin (AVP) secretion is a novel biomarker that has shown great potential in cardiovascular diseases, especially ACS and chronic HF. In this review, we summarize the results of the main studies that have investigated the diagnostic and prognostic performances of copeptin in the settings of ACS and HF.
The roles of AVP and copeptin

AVP (also known as antidiuretic hormone [ADH]) is synthesized in the hypothalamus as a pre-pro-hormone, and is then transported to the neurohypophysis. It is released into the bloodstream from the posterior pituitary gland in response to changes in plasma osmolality and reduced cardiac output. AVP levels increase with most acute illnesses and/or stress and play crucial roles in acute HF and osmoregulation. The hypoperfusion of peripheral organs leads to AVP secretion in order to maintain circulatory homeostasis by promoting renal water reabsorption via the vasopressin V2 receptors located on the basolateral membrane of collecting duct cells of the kidney. Binding to these receptors, it activates adenylylate cyclase and leads to the generation of cyclic adenosine monophosphate (cAMP), thus decreasing water clearance by moving the aquaporin 2 channels from the cytosol to the cellular surface. Enhanced expression of aquaporin channels in the kidney contributes to the development of oedema and hyponatraemia. Vasopressin coupling to V1 receptors leads to an activation of the phosphatidylinositol pathway and mobilization of cytosolic calcium. Two subtypes exist: V1a receptors on various cell types (e.g. heart and vessels) and V1b in the anterior pituitary. V1a stimulation in the arterial system leads to:

- vasoconstriction and cardiac remodelling (by increasing afterload);
- decreased systemic vascular resistance;
- increased cardiac output [13,14].

The mechanism of action of AVP is shown in Fig. 1. The direct role of AVP in chronic HF is not fully understood. AVP is a regulator of fluid dynamics and an indicator of adequate hypothalmo-pituitary-adrenal axis activation. Robust data have shown that AVP is related to HF severity and outcomes [15]. During stress, AVP stimulation results in adrenocorticotropic hormone and cortisol secretion. AVP biomarkers have previously been shown to be rapid markers of individual stress levels, with good correlation with moderate stress [16]. Because many clinical situations induce activation of the hypothalamic stress axis, especially in cardiovascular disease, AVP markers will have a low specificity but a high-sensitivity for individual disease such as ACS. However, AVP is unstable (short half-life and 90% bound to platelets) so it is not a reliable marker.

Copeptin, the C-peptide portion of pre-pro-vasopressin (Fig. 2), is a 39-amino acid glycoprotein that is more stable than AVP, and is secreted in equimolar amounts. The exact function of copeptin is unknown. This peptide is easily measurable in peripheral blood, and represents a surrogate marker for AVP release in various clinical situations [17–19]. It has emerged as a potential biomarker in various cardiac diseases such as HF and ACS.

Copeptin in ACS

The diagnosis and risk stratification in patients presenting with suspected non-ST elevation ACS (NSTE-ACS) usually rely on cardiac troponins (I and T) as biomarkers [1,2]. Troponins are currently considered the gold standard for the detection of myocardial necrosis; they have also been shown to be strong indicators of prognosis in this setting [3,4,20]. Nevertheless, the major weakness of these biomarkers is their delayed release after cell necrosis that consequently alters their diagnostic performance early after CPO. Owing to the high proportion of patients who present in ED with suspected ACS, new troponin assays have been developed to overcome this major limitation. High-sensitivity troponins allow earlier detection and have shown superiority in ACS diagnosis compared to conventional troponins [21,22]. As a consequence, high-sensitivity troponins are now used as the reference for patients presenting with chest pain and/or suspected ACS [21,22]. However, copeptin, by its independent pathophysiology and its rapid release after ACS, could further improve diagnostic accuracy in this setting.

Copeptin and prognosis in ACS

Copeptin has first been studied in order to investigate its prognostic potential in ACS (Table 1). In patients presenting with MI, copeptin has been shown to be a strong predictor of worse outcome and a prognostic marker of death [20,23]. Of note, its relevance was increased when used in combination with other biomarkers (NT-proBNP and troponins) [20,23]. The pathophysiological background of troponins, natriuretic peptides and copeptin reflects different characteristics of cardiac homeostasis. Therefore a combination of biomarkers may give more information than a unique biomarker [23]. Others studies have shown that copeptin can predict left ventricular dysfunction and clinical events related to HF in survivors of MI [20,24–27].

Copeptin and diagnosis in ACS

Recently, several authors have focused on the diagnostic performance of copeptin in the setting of NSTE-ACS and chest pain. As endogenous stress is increased at the onset of ACS, copeptin could identify ACS patients when other biomarkers are still negative. The use of a ‘dual-marker’ strategy in order to rapidly rule out a diagnosis of ACS in patients presenting with chest pain has been studied in several large trials (Table 2) [28–32]. It should, however, be emphasized that most large studies have used conventional troponins as a reference rather than high-sensitivity troponins.

The first study that tested the additional diagnostic performance of copeptin in early evaluation of patient presenting with suspected ACS was conducted by Reichlin et al. [29]. In their study, which included 487 patients with suspected ACS (within 12 hours after symptom onset), they report that the combination of copeptin and troponin T improved the area under the receiver operator characteristics curve from 0.86 to 0.97 (compared to troponin alone) for the diagnosis of MI. In addition, negativity of both biomarkers (troponin T <0.01 μg/L and copeptin <14 pmol/L) had a sensitivity of 98.8% and a negative predictive value (NPV) of 99.7% to correctly rule out ACS.

In 2010, Keller et al. [30] published concordant results. Altogether, 1386 patients with suspected ACS were enrolled in this multicentre study. Blood samples and electrocardiograms (ECGs) were obtained at admission and after 3 and 6 hours. In this study, 37.3% of the cohort had CPO <3 hours, 58.2% <6 hours and 73.4% <12 hours [30]. The diagnosis of
Copeptin was excluded in 65.2% of patients, while a discharge diagnosis of MI was made in 21.6% of patients. In the subgroup of patients with CPO < 3 hours (those patients who may benefit the most from copeptin evaluation), conventional troponin levels rose significantly during the first 6 hours after admission \((P < 0.001)\) while copeptin levels decreased from its peak (at admission) during the same period \((P < 0.001)\). In the whole population, levels of troponin reached a maximum 12 hours after CPO in MI patients. In contrast, the copeptin level was five times higher when CPO was < 3 hours, and decreased 12 hours after CPO. The authors showed that the diagnostic value of troponin increased over time after CPO, but copeptin had the strongest diagnostic performance and discriminatory power in patients with CPO < 3 hours. A combination of troponin T and copeptin resulted in higher sensitivity and NPV. The association of copeptin with troponin I (more sensitive than troponin T, but not as sensitive as high-sensitivity troponin) further improved sensitivity and NPV (98.3 and 99.0% respectively) in patients presenting within 3 hours after CPO but at the cost of reduced positive predictive value (PPV) and specificity. In conclusion, the authors suggested that the use of troponin and copeptin improves diagnostic performance, especially within the first hours after CPO.

The Copeptin Helps in the early detection Of Patients with acute myocardial Infarction (CHOPIN) trial [31]
included 1967 patients who presented with CPO <6 hours in a 16-centre prospective study. The hypothesis was that a copeptin level <14 pmol/L at admission in association with conventional troponin I and an ECG would rule out the diagnosis of ACS in patients presenting with chest pain. Of these patients, 75% presented within 3 hours of symptom onset. The final diagnoses were ACS (14.4%), cardiovascular non-ACS (21.0%), a non-cardiac diagnosis (30.5%) and unclassified cause (34.2%). Of note, 65.5% of the patients experienced chest pain lasting >30 minutes. Among ACS patients who had a normal troponin I value at admission, copeptin was elevated (median 129.2 pmol/L for ST-segment elevation MI [STEMI] and 17.8 pmol/L for non-ST elevation MI [NSTEMI]), whereas it was low (8.7 pmol/L).

Table 1 Major studies focusing on the prognostic value of copeptin in ACS patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Endpoint and results</th>
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<tbody>
<tr>
<td>O’Malley et al., 2014 [20]</td>
<td>4432 patients with NSTE-ACS</td>
<td>To assess the prognostic value of copeptin compared to natriuretic peptides and cardiac troponin Follow-up: 1 year Cardiac troponin I was the strongest predictor of all events Copeptin was associated with cardiovascular mortality (HR: 1.52, 95% CI: 1.10–2.11) and HF (HR: 1.70, 95% CI: 1.18–2.43), but not with MI (HR: 1.17, 95% CI: 0.89–1.54) after adjustment for cofounders Additional value on top of BNP and cardiac troponin I</td>
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<tr>
<td>Khan et al., 2007 [23]</td>
<td>980 MI patients</td>
<td>To assess the prognostic value of copeptin compared to natriuretic peptides Follow-up: 342 days Copeptin was predictive of the primary endpoint (death or HF; OR: 2.33, 95% CI: 1.55–3.49) Stronger prediction when added to NT-proBNP</td>
</tr>
<tr>
<td>Kelly et al., 2008 [24]</td>
<td>274 MI survivors</td>
<td>Association between copeptin levels and LV function or HF Follow-up: 155 days Copeptin predicted LV dysfunction and clinical events related to HF in post-MI patients (OR: 3.01, 95% CI: 1.10–8.21)</td>
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<tr>
<td>Voors et al., 2009 [26]</td>
<td>224 patients with HF after MI</td>
<td>Investigate the prognostic value of copeptin on mortality and morbidity Follow-up: 1 year Multivariate analysis showed that copeptin was independently correlated with mortality (OR: 1.83, 95% CI: 1.26–2.64)</td>
</tr>
<tr>
<td>Reinstadler et al., 2003 [25]</td>
<td>54 STEMI patients</td>
<td>Correlation between copeptin and infarct size or myocardial function (by CMR) Follow-up: 4 months High copeptin levels correlated with lower LVEF, greater infarct size and adverse remodelling</td>
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</table>

BNP: B-type natriuretic peptide; CI: confidence interval; CMR: cardiac magnetic resonance; HF: heart failure; HR: hazard ratio; LV: left ventricular; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTE-ACS: non-ST elevation acute coronary syndromes; NT-proBNP: N-terminal pro-hormone B-type natriuretic peptide; OR, odds ratio; STEMl: ST-segment elevation myocardial infarction.
for other diagnosis. Copeptin was also elevated in ACS patients whose troponin I at admission was elevated. Troponin I levels peaked at 8–10 hours, while copeptin levels peaked at 0–2 hours. For patients without MI, both markers remained low throughout 0–30 hours. The NPV of a normal troponin I value associated with a non-diagnostic ECG and a copeptin level <14 pmol/L was excellent (99.2%); sensitivity was 92.2% and specificity was 62.6%. Interestingly, negativity of both markers allowed physicians to rule out ACS in 58% of patients with no additional blood samples, thus reducing the time to decision from 2.96 to 1.80 hours. The authors concluded that the combination of copeptin and troponin I at admission provides a strong NPV and allows the avoidance of additional biological testing, thus improving decision-making in patients with chest pain presenting at ED.

The BiC-8 study [32] is probably the most relevant copeptin biomarker study as it was a large-scale randomized trial and high-sensitivity troponin was used as a reference. It was the first prospective, randomized study to assess the safety of an early discharge after ruling out MI with a single combined test of high-sensitivity troponin and copeptin. Altogether, 902 patients with signs and symptoms of ACS and negative troponin were randomized 1:1 to standard care (n = 451) or a new process that incorporated copeptin (n = 451). STEMI patients were excluded, as were those who required hospitalization. Copeptin was measured at admission, and a value ≥10 pmol/L was considered positive. Patients with negative troponin and negative copeptin were discharged into ambulant care. The primary endpoint was the proportion of combined major adverse cardiac events (MACE) within 30 days. Of note, 43.2% of patients had CPO <3 hours, 54.8% <6 hours and 64.0% <12 hours. Around 40% of the patients were discharged early from ED: 67.6% in the copeptin group and 12.0% in the standard care group (P < 0.001). The use of copeptin as a biomarker did not impact on the final diagnosis in this study. NSTEMI was retained as the final diagnosis in 90 patients (19.9%) in

<table>
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<tr>
<th>Reference</th>
<th>Patients</th>
<th>Troponin assay</th>
<th>High-sensitivity troponin?</th>
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<tr>
<td>Reichlin et al., 2009 [29]</td>
<td>487 patients with suspected ACS</td>
<td>Troponin T</td>
<td>No</td>
<td>Improvement of the AUC from 0.86 using troponin alone to 0.97 using troponin plus copeptin for the diagnosis of MI. Negativity of both copeptin and troponin had a high-sensitivity (98.8%) and NPV (99.7%)</td>
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<tr>
<td>Keller et al., 2010 [30]</td>
<td>1386 patients with suspected ACS</td>
<td>Troponins T and I</td>
<td>No</td>
<td>Copeptin, alone and especially when added with troponin, improved diagnostic performance with high-sensitivity (98.3%) and NPV (99.0%) in patients presenting early after CPO</td>
</tr>
<tr>
<td>Maisel et al., 2013 [31]</td>
<td>1967 patients presenting with chest pain at ED</td>
<td>Troponin I</td>
<td>No</td>
<td>Negativity of both copeptin and troponin and a non-diagnostic ECG had a high-sensitivity (92.2%) and NPV (99.2%), allowing AMI to be ruled out early in 58% of patients with no additional blood sample, reducing time to decision from 2.96 to 1.80 hours</td>
</tr>
<tr>
<td>Mockel et al., 2015 [32]</td>
<td>902 suspected ACS</td>
<td>Troponin T in 6 sites</td>
<td>Yes in 6 sites No in 1 site</td>
<td>Prospective, randomized controlled trial comparing standard care versus standard care + copeptin (early discharge if negative). Follow-up: 30 days. In the copeptin group, discharged copeptin-negative patients had a very low event rate (0.6%). Proportion of MACE was similar in both groups (standard care versus copeptin group: 5.17% versus 5.19%)</td>
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ACS: acute coronary syndromes; AMI: acute myocardial infarction; AUC: area under the receiver operator characteristic curve; CPO: chest pain onset; ECG: electrocardiogram; ED: emergency department; MACE: major adverse cardiac events; NPV: negative predictive value.
To summarize, copeptin has no place in the diagnosis of STEMI (diagnostic and reperfusion therapy decisions are based on ECG alone) or in ‘late presenters’ after CPO in suspected NSTE-ACS (diagnosis can be based on troponins alone). The use of copeptin in suspected NSTE-ACS has been shown to slightly improve the sensitivity and NPV of troponins in ‘early presenters’ after CPO (<3 hours) even when a high-sensitivity troponin is used as the reference, but at the cost of a decrease in specificity [33,34]. The possibility of a safe early discharge should, however, be better demonstrated before widely recommending such a strategy in clinical practice [35]. In addition, adapting therapies and management on the result of copeptin dosage has not been adequately studied and should be further explored. Therefore, routine copeptin use in ‘early presenters’ is not currently recommended [36] due to a lack of robust data showing a relevant additional value compared to high-sensitivity troponins. According to the latest guidelines [36] a unique measurement of high-sensitivity troponins below the 99th percentile can allow immediate discharge.

**Copeptin in HF**

Despite recent improvements, the prognostic evaluation of patients with stable but severe chronic systolic HF remains a critical and imperfect issue in clinical practice. Due to the lack of heart transplants in real life and the relatively high-risk of serious adverse complications related to cardiac assistance and cardiac transplantation, it is important to identify those patients who may benefit the most from such therapies.

Several trials have shown that copeptin is a promising predictor of outcomes in acute and chronic HF (Table 3). Stoiser et al. [37] were the first to compare copeptin with the usual natriuretic peptides in a cohort of 268 patients with advanced decompensated HF. All patients were NYHA functional class III or IV. The observation period was 15.8 ± 6.6 months. Of these 268 patients, 83 died during follow-up and 122 experienced worsening of HF (145 patients reached the combined endpoint of death or worsening of HF). In multivariable analyses, copeptin was an independent predictor of mortality ($P<0.0001$), re-hospitalization for HF ($P=0.05$) and the combined endpoint ($P<0.0001$). Copeptin was superior to BNP for predicting mortality and the combined endpoint, but BNP was the best predictor for re-hospitalization due to HF. The authors concluded that measurement of copeptin is a good marker to predict outcomes in patients with decompensated HF, and could be superior to natriuretic peptides.

However, the predictive value of copeptin in the entire spectrum of HF is not clear, especially in patients with stable chronic HF. An observational study published in 2008 included 786 such patients (mean left ventricular ejection fraction [LVEF] 25%) [38]. After the 2-year follow-up, 233 patients (30%) had experienced all-cause mortality. A multivariable model for survival showed that NYHA functional class ($P=0.0005$), glomerular filtration rate ($P=0.0005$), systolic blood pressure ($P=0.0055$) and female gender ($P=0.014$) predicted death. NYHA class was the strongest predictor of death and this variable was dichotomized to

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**Figure 3.** Sensitivities (Se), specificities (Sp), positive predictive values (PPV) and negative predictive values (NPV) for the diagnosis of acute coronary syndromes (ACS) with cardiac troponin, alone and in combination with copeptin, and high-sensitivity cardiac troponin T, alone and in combination with copeptin. Adapted from the data of Raskovaova et al. [33].

The standard group and 96 patients (21.3%) in the copeptin group, which was not statistically different. During the 30-day follow-up, 46 patients experienced a MACE (5.2% in both groups). The use of copeptin allowed physicians to discharge patients without ACS earlier, and this strategy was safe. Indeed, among patients who experienced a MACE in the copeptin group, only two patients were discharged from the ED early (0.6%). No MI or death occurred in the discharge copeptin-negative patients of the copeptin group. The authors concluded that, with an attentive clinical examination and risk stratification (i.e. low-to-intermediate) in patients presenting with a suspected ACS, those with negative troponin and negative copeptin could safely be discharged from ED. This strategy therefore allowed a significant reduction in the length of hospital stay. One major limitation of the study should, however, be highlighted: there was a high number of cross-overs ($n=71$) in the copeptin-negative group. Therefore, the results of this study should be interpreted with caution.

A recent meta-analysis [33], which included all but the BIC-8 studies ($n=8740$ patients), was published in 2014. They investigated the diagnostic accuracy of copeptin in combination with cardiac troponin to rule out MI in ED. This meta-analysis reported that the use of copeptin significantly improved the sensitivity (from 87 to 96%), but at the cost of a decrease in specificity (from 84 to 56%). Of note, the sensitivity improvement was less, but still significantly improved (from 91 to 98%), when high-sensitivity cardiac troponin T was used as the reference (Fig. 3). In this case, the specificity was also significantly reduced (from 75 to 50%).

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Table 3  Major studies focusing on the prognostic value of copeptin in HF patients.

<table>
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<td>Stoiser et al., 2006 [37]</td>
<td>268 patients with decompensated HF (NYHA III or IV)</td>
<td>Follow-up: 15.8 ± 6.6 months Copeptin independently predicts mortality (P &lt; 0.0001), re-hospitalization for HF (P = 0.05) and combined endpoint (P &lt; 0.0001) It was superior to BNP for predicting mortality and combined endpoint</td>
</tr>
<tr>
<td>Neuhold et al., 2008 [38]</td>
<td>786 patients with stable chronic HF (mean LVEF 25%)</td>
<td>Follow-up: 2 years Copeptin was the most potent predictor of all-cause death in NYHA II (HR: 1.014, 95% CI: 1.007–1.021; P = 0.0001) and NYHA III (HR: 1.010, 95% CI: 1.003–1.017; P = 0.0039) patients It was superior to BNP in these subgroups</td>
</tr>
<tr>
<td>Tentzeris et al., 2011 [39]</td>
<td>172 patients with stable HF</td>
<td>Follow-up: 42.5 months High copeptin (&gt;16.4 pmol/L) was an independent predictor of poor outcome: all-cause mortality and hospitalization for HF (HR: 2.51, 95% CI: 1.66–3.79; P &lt; 0.001) It was even more discriminant when added to other biomarkers such as troponins and NT-proBNP</td>
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BNP: B-type natriuretic peptide; CI: confidence interval; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-hormone B-type natriuretic peptide; NYHA: New York Heart Association.

analyse the predictive value of copeptin at different stages. In NYHA II and III patients, copeptin was the most potent single predictor of death (P = 0.0001 and P = 0.0039, respectively), whereas in stage IV patients, sodium level and glomerular filtration rate were the most powerful predictors of mortality and copeptin did not show any additional value in this subgroup.

Tentzeris et al. [39] investigated the combined role of copeptin and cardiac troponin T to identify high-risk patients with stable chronic HF (n = 172). LVEF was <45% in all cases and, for 55.8% of the patients, was <35%. The primary endpoint was a composite of all-cause mortality or hospitalization for decompensated HF. High troponin T was a significant predictor of poor outcome (hazard ratio [HR] 2.96, 95% confidence interval [CI] 1.88–4.64; P < 0.001), as was high copeptin level (HR: 2.51, 95% CI: 1.66–3.79; P < 0.001). A copeptin level >16.4 pg/mL was an independent predictor of worse outcome (adjusted for age, sex, NYHA class, renal function and plasma level of NT-proBNP). Adding copeptin to other biomarkers improved model discrimination. Patients with increased levels of both parameters (troponin T and copeptin) had higher rates of mortality and adverse events. The authors concluded that, in association with troponin T, copeptin could help physicians identify patients at risk of death or acute HF.

To summarize, copeptin looks promising for the risk stratification improvement of patients with chronic systolic HF. However, this biomarker and its incremental value on top of ‘classic’ prognostic indicators (NYHA class, LVEF, BNP, creatinine, VO2 max) need to be further validated in large studies and, for now, physicians’ decisions cannot rely on copeptin levels in routine practice. To the best of our knowledge, no trial has studied the predictive value of copeptin in HF with preserved ejection fraction.

**Future directions and multimarker approach**

Biomarkers can provide important information for diagnostic, prognostic and therapeutic strategies and their related adverse events. Although these markers offer great opportunities, they are related to various physiopathological processes and clinical presentations. A perfect single biomarker is very unlikely to be found, but a multimarker approach, where each biomarker provides insight into various underlying pathways, could be a powerful tool for tailored and targeted therapies in each patient [28]. A tandem approach with biomarkers and others multimodal or imaging tools should also provide additional risk stratification and evaluation of disease progression before symptom onset, thus allowing more effective preventive strategies. The ultimate goal would be to improve patient outcomes rather than creating greater complexity.

Several trials have assessed the diagnostic and prognostic value of copeptin in various cardiovascular diseases, especially HF and ACS. Primary results show that copeptin is promising for the risk stratification of HF patients and the management of patients who present at ED early after CPO. It should, however, be emphasized that the additional value of copeptin over high-sensitivity troponins remains a matter of debate. Further studies are required to precisely define the specific role of copeptin in chronic HF and ACS. For now,
guidelines do not recommend the systematic use of copeptin in these settings.

Disclosure of interest

Dr Goldstein has received fees from Thermo Fisher for acting as a speaker and on an advisory board. The other authors declare that they have no conflicts of interest concerning this article.

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