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REVIEW

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The diagnostic and prognostic value of copeptin in cardiovascular disease, current status, and prospective

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Abstract

Copeptin is a glycosylated peptide derived from the cleavage of the precursor of arginine-vasopressin. In contrast to arginine-vasopressin, copeptin is a stable molecule and can easily be measured using a simple rapid assay. The serum concentration of copeptin is increased in several clinical conditions, including hypertension, chronic kidney disease, and, of special interest in this review, in cardiovascular diseases. The diagnostic and prognostic value of copeptin in different cardiovascular diseases (acute coronary syndrome, stable coronary artery disease, congestive heart failure, and acute ischemic stroke) has been reviewed in this article, to provide an understanding of how its measurement may be applied to improve the management of these conditions.

KEYWORDS
biomarker, cardiovascular diseases, copeptin

1 | INTRODUCTION

Cardiovascular disease (CVD) is an important cause ofmorbidity and mortality in both men and women globally, and increasingly in developing countries, where it puts a huge burden on healthcare systems.[1,2] The incidence of death related to CVD has risen across the globe during recent decades.[3] Cerebrovascular disease and ischemic heart disease are 2 major causes of mortality and morbidity.[4] There are several established risk factors for CVD, which include: hypertension, cigarette smoking, diabetes mellitus, dyslipidemia, obesity, stress, high C-reactive protein and high red blood cell distribution width.[1] Within the last decade, a large number of new biomarkers for CVD risk have been identified. These novel biomarkers provide useful information and help clinicians to better identify high-risk individuals and may improve the speed and accuracy of diagnosis. They help plan better interventions for patients with CVD. Copeptin is a neurohormone and a novel biomarker for CVD, which has gained attention recently (Figure 1 and Table 1).

Copeptin is the C-terminal portion of provasopressin. It is a glycosylated polypeptide with 39 amino acids and a molecular weight of approximately 5 kDa and contains a leucine-rich core segment.[55] Copeptin is cosynthesized with

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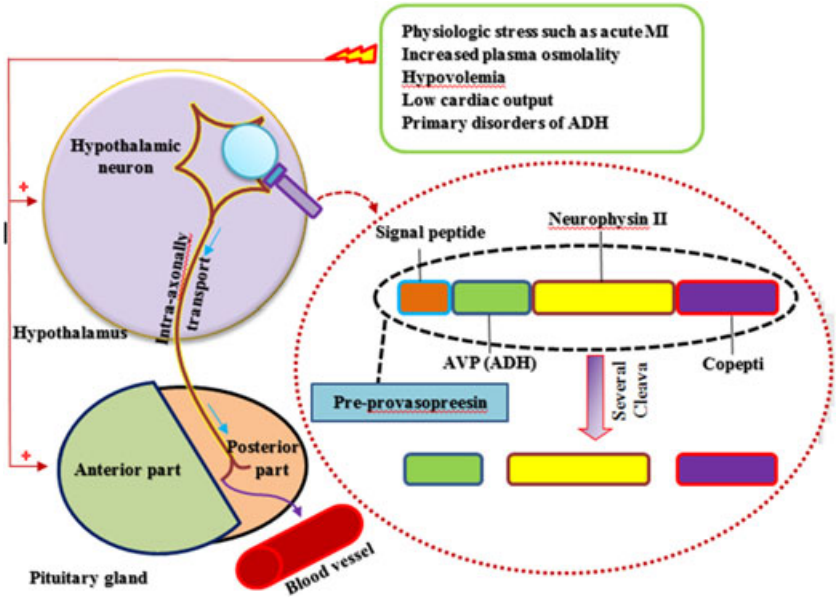

FIGURE 1 AVP and copeptin are synthesized in hypothalamic neurons as a preprovasopressin. Following several cleavages AVP and copeptin are transported intra-axonally to the posterior part of pituitary gland (neurohypophysis). Next, these hormones are released into blood flow in response to changing in hemodynamic state, plasma osmolality, and some other conditions. ADH, antidiuretic hormone; AVP, arginine-vasopressin; MI, myocardial infarction

arginine-vasopressin (AVP) hormone in the hypothalamus and is coreleased with AVP into the circulation from the neurohypophysis in equimolar quantities.[56] In contrast to AVP, copeptin remains stable at room temperature and can be measured relatively easily.[57] It has recently been proposed that copeptin could be used as a novel biomarker for a variety of diseases including CVD.[57] The purpose of this review is to summarize the results of recent studies that have investigated the diagnostic and prognostic potential of copeptin in CVD.

2 | AVP SYSTEM, BIOSYNTHESIS, AND FUNCTIONS

AVP, also known as an antidiuretic hormone, is a neuropeptide that is secreted in response to hypovolemia and elevated plasma osmolality from the hypothalamus.[58] AVP and copeptin are 2 important neurohormones involved in the AVP cascade system.[59] They are synthesized in hypothalamic neurons as a pre-pro-hormone called preprovasopressin. Following several cleavages, AVP and copeptin are generated and transported intra-axonally to the posterior part of the pituitary gland, the neurohypophysis.[60] They are released into the hypophyseal portal blood system in response to changes in the hemodynamic state and plasma osmolality.[60] Several studies have shown that there is a significant association between the plasma levels of copeptin and AVP.[61] AVP affects several tissues, including arterioles and collecting ducts in kidney via its receptors. Binding of AVP to the vasopressin receptor 1a (V1a) receptor has 3 consequences, including vasoconstriction and cardiac remodeling, increase in cardiac output, and reduction in systemic vascular resistance.[62,63] Binding of AVP to vasopressin receptor 1b (V1b) (also called V3) receptor leads to secretion of beta endorphin and adreno-corticotropic hormone. Binding of AVP to these receptors results in the antidiuretic effect in the collecting ducts in the kidney by reducing the clearance of water.[64] Copeptin may be considered to be a surrogate marker of AVP release. Its physiologic function is yet to be identified.[64]

Although measuring plasma AVP is of some clinical importance, it is unstable, undergoes rapid degradation, and hence its measurement requires careful sample collection and preservation.[65,66] In contrast, copeptin has greater stability and can be easily measured in peripheral blood, whilst its serum concentrations closely reflect the AVP level in the circulation.[65,66] Copeptin is routinely measured using a novel commercial sandwich immunoluminometric assay as described previously.[67] Copeptin level can fluctuate based on physiologic and pathologic conditions. In this regard, it was reported that plasma copeptin concentration increases during fasting, water deprivation, hypertonic saline infusion and different illnesses including CVD.[60,64] The median level of copeptin that was measured in healthy subjects in different studies is about 4.3 pmol/L (range, 0.4-44.3 pmol/L). Moreover, these median levels are significantly lower in women compared to men; however, the plasma levels of copeptin are age-independent among all groups.[60]

3 | DIAGNOSTIC AND PROGNOSTIC VALUE OF COPEPTIN IN ACUTE CORONARY SYNDROME

There are several traditional biomarkers for diagnosis of MI including troponin (T and I), creatine kinase-MuscleBrain

TABLE 1 Studies associated with copeptin and CVD

	Authors	Study population	Copeptin assessment method (assay kit)	Main findings
ACS	Keller et al[5]	1386 patients with suspected ACS	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Using both copeptin and troponin T provides NPV of 92.4% for acute MI diagnosis
	Maisel et al[6]	1967 patients with CP	Sandwich immunoluminometric assay (B.R.A.H.M.S)	normal copeptin and negative ruled out 58% of MI patients
	Reichlin et al[69]	487 patients with chest pain	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Sensitivity and NPV of using combination of copeptin and troponin T for diagnosis of MI was 98.8% and 99.7%, respectively
	Möckel et al[7]	902 suspected ACS patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	With using single measurement of troponin and copeptin can decide on patients discharge
	Khan et al[8]	980 MI patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	After MI AVP system become active
	Reinstadler et al[9]	54 STEMI patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin is correlated with size of infarct zone, LVEF and myocardial remodeling
	Kelly et al[10]	274 acute MI patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin is associated with ventricular remodeling and LVEF
	Voors et al[11]	224 HF patients after AMI	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Measuring copeptin, BNP and NT-proBNP together increase accuracy of outcome prediction in AMI patients
	O'Malley et al[12]	4432 NSTEMI patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Elevated copeptin is significantly associated with multiple cardiovascular risk factors
	Charpentier et al[13]	641 patients with CP	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Using combination of copeptin and troponin I improves sensitivity and NPV in diagnosis of MI
	Ray et al[14]	451 patients with CP	Sandwich immunoluminometric assay (B.R.A.H.M.S)	NPV in combination of negative troponin and elevated copeptin is about 98%
	Charpentier et al[15]	587 patients with CP	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Combination of troponin and copeptin provides high sensitivity and NPV in diagnosis of NSTEMI
	Folli et al[16]	472 patients with CP	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Using combination of copeptin and troponin improves sensitivity and NPV in diagnosis of MI
	Afzali et al[17]	230 patients with CP	Sandwich immunoluminometric assay (B.R.A.H.M.S)	NPV in combination of negative troponin and elevated copeptin is about 97.3%
	Chenevier-Gobeaux et al[18]	317 patients with CP	Sandwich immunoluminometric assay (B.R.A.H.M.S)	NPV in combination of negative troponin and elevated copeptin is about 99%
	Searle et al[19]	537 patients with cardiac chief complaints	Sandwich immunoluminometric assay (B.R.A.H.M.S)	NPV in combination of negative troponin and elevated copeptin is about 98.8%
	Sukul et al[20]	444 patients with CP	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Using combination of copeptin and troponin did not enhance diagnostic value
	Duchenne et al[21]	102 patients with chest pain (Trial registration number: NCT01334645)	Sandwich immunoluminometric assay (B.R.A.H.M.S)	measuring copeptin did not increase diagnostic value of other ACS biomarkers at admission
	Giannitsis et al[22]	(Trial registration number: NCT00953251)	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Using combination of copeptin and high-sensitivity troponin improved rapid ruling out of NSTEMI

(Continues)

TABLE 1 (Continued)

	Authors	Study population	Copeptin assessment method (assay kit)	Main findings
SCAD	Schnabel et al[23]	1781 SAP patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin were found to be moderate predictor
	Sabatine et al[24]	3717 SAP patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin was not independent predictor of outcome
	von Haehling et al[25]	1316 AMI and 1384 SAP patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin on admission was correlated with adverse outcome
HF	Stoiser et al[26]	268 DHF patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin was superior in prediction of outcome compared with BNP
	Neuhold et al[27]	786 chronic HF patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin in NYHA FC II and III was strongest predictor of mortality
	Neuhold et al[28]	181 chronic HF patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Decrease in copeptin during HF treatment
	Gegenhuber et al[29]	137 Acute HF patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	The ability of copeptin in prediction of death in next year was as strong as BNP
	Tentzeris et al[30]	172 HF patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Higher copeptin was significantly associated with more severe HF
	Alehagen et al[31]	470 HF patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Increased copeptin and NT-proBNP were correlated with higher risk of mortality
	Vondráková et al[32]	60 HF patients and 30 hypertensive patient	Sandwich immunoluminometric assay (B.R.A.H.M.S)	No correlation between copeptin and prognosis parameters
	Masson et al[33]	1237 chronic HF patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin was an independent HF prognostic factor
	Jia et al[34]	129 severe DHF	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin was an independent HF prognostic factor
	Yan et al[35]	meta-analysis	-	Increased copeptin is associated with increased risk of HF and mortality
	Zhang et al[36]	meta-analysis	-	Increased copeptin is associated with increased risk of HF and mortality
	Iwashita et al[37]	39 HF patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	There was a different regulation of copeptin in HF patients after treatment
	Adams et al[38]	20 stable HF patients (Trial registration number: NCT01346072)	Not mentioned	Patients with higher copeptin level showed better response to Tolvaptan which is AVP antagonist
Stroke	Urwyler et al[39]	362 AIS patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Increased copeptin is associated with increased risk of mortality and poor outcome
	Dong et al[40]	125 AIS patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Increased copeptin is associated with increased risk of mortality and poor outcome
	Katan et al[41]	362 AIS patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin improves predictive value of NIHSS score
	Katan et al[42]	107 TIA patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin level in patients with re-event was significantly higher
	Greisenegger et al[43]	1076 TIA or AIS patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Increased copeptin was associated with higher cerebrovascular re-event

(Continues)

TABLE 1 (Continued)

Authors	Study population	Copeptin assessment method (assay kit)	Main findings
Wendt et al[44]	561 patients with suspected stroke	Sandwich immunoluminometric assay (B.R.A.H.M.S)	No significant differences in copeptin neither between hemorrhagic and ischemic stroke
Perovic et al[45]	112 AIS patients and 63 controls	ELISA (CUSABIO)	There was a significant association between elevated copeptin and short-term adverse outcome
Tang et al[46]	405 AIS patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Increased copeptin was associated with higher stroke recurrence and severity
Tu et al[47]	4215 AIS patients	Sandwich immunoluminometric assay (B.R.A.H.M.S)	Copeptin and NT-proBNP can be helpful in prediction of mortality
Aksu et al[48]	126 cerebrovascular patients and 50 controls	Sandwich ELISA (EASTBIOPHARM)	Copeptin was not appropriate for discrimination cerebral infarction from cerebral hemorrhage
Zeng et al[49]	4302 AIS patients	Not mentioned	Copeptin gradually falls to baseline within 3-5 days after rising in the first day of stroke
Wannamethee et al[50]	3536 elderly men	Sandwich immunoluminometric assay (B.R.A.H.M.S)	There was a correlation between copeptin and incidence of stroke in men with DM
Bindila-Perisse et al[51]	146 patients with suspected ischemic stroke (Trial registration number: NCT01960478)	Not mentioned	Patients with cerebral infarction had higher but not significant copeptin level compared to those without
Choi et al[52]	meta-analysis	-	Increased copeptin in TIA or stroke patients is associated with increased risk of mortality and poor outcome
Xu et al[53]	meta-analysis	-	Increased copeptin in TIA or stroke patients is associated with increased risk of mortality
Jiao et al[54]	systematic review	-	Increased copeptin in TIA or stroke patients is associated with increased risk of mortality and poor outcome

ACS, acute coronary syndrome; AIS, acute ischemic stroke; AMI, acute myocardial infarction; AVP, arginine-vasopressin; BNP, B-type natriuretic peptide; CP, chest pain; CVD, cardiovascular disease; DHF, decompensated heart failure; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NIHSS, National institutes of Health Stroke Scale; NPV, negative predictive value; NSTEMI, non–ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; SCAD, stable coronary artery disease; SAP, stable angina pectoris

(MB) and serum myoglobin.[68] Troponin is the accepted "gold standard" biomarker for diagnosis of acute coronary syndrome (ACS). The main weakness of this biomarker is low sensitivity in the first hours after the onset of signs and symptoms due to its delayed release after myocardial necrosis.[68] The identification of a novel biomarker that is released rapidly and can be easily measured in minutes after the clinical onset of ACS is very important for early identification, risk assessment, and prognosis in these patients.

Copeptin, troponin T, creatine kinase-MB, and serum myoglobin were measured by Keller et al[5] in 1386 patients with suspected ACS; the measurement of both copeptin and troponin T within 3 hours after symptoms begin to show, showed a negative predictive value (NPV) of 92.4%. Maisel et al[6] investigated 1967 patients with chest pain and found that in patients with a non-diagnostic electrocardiogram, normal copeptin and negative troponin ruled out 58% of MI patients with 92.2% sensitivity and 99.2% NPV and reduced the average time required for a decision from 3 hours to 1.8 hours. Reichlin et al[69] studied 487 patients with chest pain suspected with MI and found that serum copeptin was elevated in patients positive for an MI. Using a combination of serum copeptin and troponin T for diagnosis of MI had a sensitivity and NPV of 98.8% and 99.7%, respectively. Furthermore, 902 suspected ACS patients were evaluated and followed up by Möckel et al in relation to deciding early discharge in patients with low to moderate risk by using a single measurement of troponin and copeptin levels. They found that if both copeptin and troponin on admission were negative, early discharge and reducing hospital stay would be safe in patients with low to moderate risk.[7] Khan et al[8] followed up 980 MI patients and measured copeptin and N-terminal brain natriuretic peptide (NT-BNP) and showed that copeptin was higher in patients who subsequently died, or developed heart failure (HF), when compared with controls. Reinstadler et al[9] studied 54 ST-segment myocardial infarction (STEMI) patients and reported that a high plasma copeptin level was correlated with a larger area of infarction and lower left ventricular ejection fraction and less myocardial remodeling. Consistent with these findings, Kelly et al[10] investigated 274 acute MI patients and reported that serum copeptin is associated with ventricular remodeling and left ventricular ejection fraction. In a further study, 224 patients with HF and a history of acute MI were evaluated. Serum copeptin, BNP, and NT-proBNP levels were all correlated with an adverse outcome and mortality. A doubling of the serum copeptin level was correlated with a 1.35 fold increased risk of adverse outcomes and 1.83 fold increased risk of mortality.[11] O'Malley et al[12] followed up 4432 patients with non-STEMI, in whom an elevated serum copeptin was significantly associated with multiple cardiovascular risk factors and increased risk of mortality and HF. Charpentier et al[13] investigated 641 patients with chest pain and after measuring copeptin and troponin, I found that compared with using troponin alone, using a combination of serum copeptin and troponin I significantly improved the sensitivity and NPV to 90.4% and 97.6%, respectively, but this sensitivity was not sufficiently robust to allow a rapid ruling out of non-STEMI patients. Ray et al[14] studied 451 patients with chest pain and coronary artery disease (CAD) history and reported that the NPV in patients with negative troponin together with a low serum concentration of copeptin (<10.7 pmol/L) was approximately 98%. In another study, Charpentier et al[15] investigated 587 patients with chest pain but with no ST-segment elevation and reported that using a combination of a sensitive troponin assay and serum copeptin provides very high sensitivity and NPV in the diagnosis of non-STEMI, particularly in patients with low thrombosis in myocardial infarction score. Folli et al studied 472 patients with chest pain and also found that the combination of copeptin and troponin improved the sensitivity and NPV of the diagnostic strategy. Furthermore, this combination of tests can provide a good indication of a life-threatening non-ACS cause of chest pain, such as aortic dissection.[16] Afzali et al[17] followed up 230 patients with chest pain and showed that an elevated serum copeptin concentration is correlated with acute MI in patients and combining copeptin with troponin improved NPV to 97.3%. Chenevier-Gobeaux et al[18] evaluated 317 patients with chest pain, and confirmed that in acute MI patients, serum copeptin concentrations were higher, and using both copeptin and troponin for ruling out acute MI, gave a high NPV of 99%. Searle et al[19] followed up 537 patients with cardiac symptoms and showed that in patients with a negative troponin the specificity, sensitivity, positive predictive value and NPV of measuring copeptin and troponin together were 64.2%, 76.9%, 6.9%, and 98.8%, respectively. In contrast to these findings, Sukul et al[20] investigated 444 patients with acute chest pain and reported that using a combined testing strategy of copeptin and troponin did not enhance the diagnostic value of troponin in these patients.[20] However, overall, these results support the proposition suggesting that copeptin could be a novel potent biomarker for ACS. Although the median level of plasma copeptin in several of the above studies was more than 20 pmol/L, the average of this level in patients with acute MI in above studies was about 15 pmol/L.

4 | ROLE OF COPEPTIN IN STABLE CAD

Using established CAD risk factors along with a blood biomarker is informative in risk stratification to identify high-risk patients and may also help in the prediction of prognosis in patients with stable angina pectoris (SAP). Schnabel et al measured multiple biomarkers including copeptin in 1781 SAP patients and reported that NT-proBNP, cystatin C, growth-differentiation factor-15, mid-regional-pro-atrial natriuretic peptide (MR-proANP), and mid-regional-pro adrenomedullin (MR-proADM) after adjustment for various parameters were found to be strong predictors of outcomes. In this study copeptin was found to be a moderate predictor.[23] Similarly, Sabatine et al evaluated 4 novel biomarkers: copeptin, MR-proANP, MR-proADM, and C-terminal pro-endothelin-1 (CT-proET-1) in 3717 SAP patients. They found that only MR-proANP, MR-proADM, and CT-proET-1 appeared to be independent predictors of outcomes.[24] von Haehling et al[25] studied 2700 patients (including 1316 acute MI and 1384 SAP patients) and found that elevation in serum copeptin at the time of hospital admission was significantly correlated with CVD adverse outcome during the subsequent 3 months, suggesting that copeptin, along with other biomarkers including troponin and established risk factors, also has a critical predictive value in stable CAD patients.

5 | CONGESTIVE HF

An increased serum BNP is associated with HF and recent studies have suggested that AVP is associated with the severity of HF.[26] Since copeptin is cosynthesized and -released with AVP, it has been hypothesized that serum copeptin could be correlated with HF too. Stoiser et al measured BNP and copeptin levels in 268 HF patients with a New York Heart Association (NYHA) functional class of III or IV and followed up these patients for a mean period of 15.8 months. During this period, some patients experienced worsening of HF and some died from complications of HF. Interestingly, the results of this study showed the superiority of copeptin level in prediction of death in comparison with BNP; however BNP was a better predictor of rehospitalization.[26] Neuhold et al investigated the serum concentrations of copeptin, BNP, and NT-proBNP in 786 patients with stable chronic HF across the entire spectrum of the NYHA functional class. They found a positive association between high copeptin levels and high risk of death in these patients. Moreover, in NYHA functional classes II and III, copeptin was found to be the strongest predictor of mortality. Further studies showed that copeptin was better at predicting outcomes than BNP for all NYHA functional classes.[27] In another study, 181 patients with chronic and unstable systolic HF were recruited and serum copeptin, BNP, MR-proADM, MR-proANP, and CT-proET-1 were measured before and after optimizing therapy. A reduction in serum copeptin and BNP, MR-proANP, and CT-proET-1 was observed during treatment.[28] Gegenhuber et al[29] studied 137 patients with acute HF and reported that the values of serum copeptin, MR-proANP, and MR-proADM were as strong as BNP in predicting 12 month mortality. To further support the potential for copeptin to be a novel biomarker in risk stratification of HF patients, Tentzeris et al followed up 172 patients with stable HF and measured the levels of copeptin and troponin T in these patients. They showed that elevated levels of serum copeptin were associated with more severe HF and both copeptin and troponin were strong predictors of outcomes.[30] Alehagen et al[31] investigated 470 HF patients for a mean period of 13 years and concluded that an increased plasma copeptin level and the combination of increased plasma copeptin level and NT-proBNP were correlated with a higher risk of mortality in these patients. Moreover, Masson et al measured the plasma concentrations of copeptin, MR-proADM, MR-proANP, and CT-proET-1 in 1237 stable and chronic HF patients and followed them up for clinical outcome. They concluded that these 4 biomarkers are independent predictors of prognosis in patients with HF.[33] Jia et al measured the level of copeptin and NT-proBNP in 129 severe acute decompensated HF patients and followed them up for 90 days. Results showed that these biomarkers were independent factors in predicting outcomes but NT-proBNP was the best.[34]

A recent meta-analysis by Yan et al[35] found that increased plasma concentrations of copeptin are associated with an increased risk of HF and all-cause mortality. They also reported that the risk of all-cause mortality is increased by 3% for every 1 pmol/L increment in copeptin level from its normal value. In another meta-analysis, Zhang et al[36] showed that there was a positive correlation between an increased serum copeptin and risk of mortality in patients with HF. Furthermore, Iwashita et al found that in 39 patients with HF who were admitted to hospital with a similar severity of HF, the initial levels of copeptin were very different. Thus, patients were divided into 3 categories: high level, midrange, and low level. Decrease in copeptin was only reported in the high level group after treatment, whereas in the low level group, copeptin was increased and in midrange group no changes were observed.[37] These results clearly suggest that copeptin could be a valid biomarker for both

prognosis and diagnosis in HF patients. The median plasma copeptin level mentioned in the above studies was greater than acute MI patients and was approximately 22 pmol/L in patients with HF.

6 | STROKE

In management of acute ischemic stroke (AIS) patients, an accurate assessment of risk for predicting clinical outcomes is crucial in selecting the appropriate therapeutic strategies and patient care.[39] There are several validated clinical score in AIS patients for evaluation of stroke severity. Biomarkers that are able to improve the power of these clinical scores would lead to more accurate risk stratification and outcome prediction. Urwyler et al evaluated the concentrations of copeptin and National Institute of Health Stroke Scale (NIHSS) score in 362 AIS patients and followed them up for 1 year. The results showed that serum copeptin could independently predict death in these patients and those who died had a higher level of copeptin in circulation. They also showed that using copeptin in combination with the NIHSS score could improve the predictive power of this scoring system.[39] Consistent with these results, another study on 362 patients found that AIS patients with unfavorable outcomes and patients who died had significantly higher serum copeptin at the time of hospital admission. Moreover, the results also showed that for prediction of outcome, copeptin was superior to glucose and C-reactive protein and improved the predictive value of the NIHSS score.[41] Furthermore, among 107 patients with transient ischemic attacks who were admitted to hospital, serum copeptin and cortisol were measured for investigating the association between the stress hormone and cerebrovascular recurrent events. Interestingly, they found that the copeptin level, but not cortisol, was significantly higher in patients with a re-event.[42] Greisenegger et al[43] also studied 1076 transient ischemic attacks or ischemic stroke patients and reported that in patients with an increased copeptin level, the risk of recurrent vascular event and death was higher, especially in patients with cardioembolic transient ischemic attacks or stroke.

To further investigate the prognostic value of copeptin in AIS patients, Wendt et al investigated 561 patients with suspected stroke and showed that there was no significant difference in copeptin between patients with a hemorrhagic or ischemic stroke, nor between stroke and other patients. However, a comparison between serum copeptin concentrations between patients who died and those who did not over the subsequent 3 months showed a significant difference between the two groups. Moreover, an elevation in copeptin was significantly associated with a higher NIHSS score.[44] A case control study was conducted by Perovic et al and serum copeptin compared between 112 patients with AIS and 63 controls. No significant difference in serum copeptin was found between the 2 groups; however there was a significant association between elevated copeptin and short-term adverse outcome. Further studies showed that there is an inverse association between increased copeptin levels and the Barthel index score that is used to identify short-term stroke outcomes.[45] Tang et al[46] found that in 405 patients with AIS, serum copeptin may be used as a predictor of severity and recurrence of a stroke. Tu et al[47] in a multicenter study on 4215 patients with AIS have reported that serum copeptin and NT-proBNP may be helpful in predicting mortality in these patients. Moreover, Wannamethee et al measured serum copeptin in 3536 men aged 60-79 years and followed up them for a mean period of 13 years and found that there was a correlation between the copeptin level and incidence of stroke only in men with diabetes mellitus, but not in the non-diabetic counterparts.[50] A systematic review and meta-analysis showed that increased serum copeptin concentration in stroke patients is positively associated with a higher risk of death and adverse outcomes.[52] And Jiao et al[54] and Xu et al[53] and have both confirmed these findings. Taken together, these results support the diagnostic and prognostic value of measuring serum copeptin in AIS. Although some of the above studies found the median level of plasma copeptin to be greater than 20 pmol/L, the average of this level in patients with acute stroke in the above studies was about 15 pmol/L.

7 | CONCLUSION

Copeptin is a hormone involved in the AVP system, is coreleased with AV, and may be of use as a surrogate marker of AVP release.[64] Several studies have investigated the relationship between copeptin and CVD. Several of these studies have shown that serum copeptin is increased in patients with CVD and this is associated with an increased risk of adverse outcomes, including mortality, in these patients. Copeptin either alone, but especially in combination with other cardiac biomarkers, can improve the determination of the diagnosis and prognosis of different CVDs including ACS, SCAID, HF, and ischemic stroke. The information gained from all these studies helps in the design of novel and potent cardiac biomarkers and has great clinical significance for the treatment of cardiovascular disorders.

CONFLICTS OF INTEREST

The authors have no financial conflicts of interest.

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