ORIGINAL ARTICLE

Role of copeptin in diagnosis and outcome prediction in patients with heart failure: a systematic review and meta-analysis

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ABSTRACT

Background/Context: Heart failure (HF) is a heterogeneous condition characterized by increased morbidity and mortality.

Objective: This systematic review and meta-analysis of 19 studies was conducted to evaluate the role of copeptin in diagnosis and outcome prediction in HF patients.

Materials and methods: A systematic literature search for clinical trials reporting copeptin levels in HF patients was performed using EMBASE, PubMed, Cochrane Register of Controlled Trials, and Google Scholar. Articles from databases published by 2 January 2022, that met the selection criteria were retrieved and reviewed. The random effects model was used for analyses.

Results: Pooled analysis found higher mean copeptin levels in HF vs. non-HF populations (43.6 ± 46.4 vs. 21.4 ± 21.4; MD = 20.48; 95% CI: 9.22 to 31.74; p < 0.001). Pooled analysis of copeptin concentrations stratified by ejection fraction showed higher concentrations in HFrEF vs. HFpEF (17.4 ± 7.1 vs. 10.1 ± 5.5; MD = −4.69; 95% CI: −7.58 to −1.81; p = 0.001). Copeptin level was higher in patients with mortality/acute HF-related hospitalization vs. stable patients (31.3 ± 23.7 vs. 20.4 ± 12.8; MD = −13.06; 95% CI: −25.28 to −0.84; p = 0.04). Higher copeptin concentrations were associated with mortality and observed in all follow-up periods (p < 0.05).

Conclusions: The present meta-analysis showed that elevated copeptin plasma concentrations observed in HF patients are associated with an increased risk of all-cause mortality, thus copeptin may serve as a predictor of outcome in HF.

1. Introduction

Heart failure (HF) is a heterogeneous condition characterized by increased morbidity and mortality (Ziaeian and Fonarow 2016), with estimated prevalence of 1% to 2% of adult individuals (Groenewegen et al. 2020). Approximately 50% of HF patients have preserved left ventricular (LV) ejection fracture (HFrEF) and the remainder have reduced LV ejection fracture (HFpEF) (Dunlay et al. 2017). HF accounts for 1% to 2% of all hospital admissions and is the most common diagnosis in hospitalized patients aged ≥65 (Braunwald 2015).

Current guidelines recommend measurement of plasma concentration of B-type natriuretic peptide (BNP), its physiologically inactive metabolite, N-terminal pro-B-type natriuretic peptide (NT-proBNP), or mid-regional pro-atrial natriuretic peptide as an initial test to rule out the diagnosis of HF (McDonagh et al. 2021). Natriuretic peptides (NPs) are elevated as a consequence of the ventricular wall stress, which occurs in HF (Duchnowski et al. 2019), and serve as accurate predictors of outcome as well as for risk stratification in HF (Maisel et al. 2008). However, NPs increase with age, have strong correlation with renal dysfunction (Fabian et al. 2012) and can be elevated due to several other cardiac and non-cardiac factors associated with increased ventricular wall stress. Conversely, as a function of metabolic consumption, lower NPs are observed in obese patients, and the use of lower cut-off concentrations is required with body mass index (BMI) above 35 (Mueller et al. 2019). Therefore, novel biomarkers of HF have been examined.

Arginine vasopressin (AVP), an antidiuretic hormone secreted in response to hypovolemia, is increased in HF and correlates with the severity of the disease (Nakamura et al. 2006) and reflects the important role of neuroendocrine activity in the pathophysiology of HF (Francis et al. 1984). As measurement
of plasma AVP is challenging (Preibisz et al. 1983), copeptin, the stable, easily measured C-terminal synthetic fragment of pro-AVP, was proven to serve as surrogate biomarker for AVP (Morgenthaler et al. 2006). Several studies reported that copeptin is an independent predictor of mortality and re-hospitalization in patients with chronic (Neuhold et al. 2008, Alehagen et al. 2011) and decompensated HF (Potocki et al. 2010, Babroudi et al. 2020). Some described copeptin as superior to well-established BNP and NT-proBNP in assessment of HF (Neuhold et al. 2008, Voors et al. 2009). Copeptin showed promising results as prognostic biomarker of HF after acute myocardial infarction (Kelly et al. 2008, Voors et al. 2009) and of adverse events in both HFpEF and HFrEF populations (Xu et al. 2018). Therefore, we conducted a systematic review with meta-analysis to evaluate the role of copeptin in diagnosis and outcome prediction in HF patients.

**Clinical significance**

In the present study, we found copeptin levels to be correlated with all-cause mortality and HF-related re-hospitalizations in HF patients. Copeptin may serve as predictor of outcome in HF, together with established NPs. Further studies are necessary to fully evaluate the added value of copeptin in diagnosis and outcome prediction in HF patients.

**2. Materials and methods**

This systematic review and meta-analysis was performed in accordance with the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al. 2021). A PRISMA checklist is presented in Table S1. Owing to the character of the study, ethical approval or patient consent was not required for this meta-analysis.

**2.1. Literature search**

Two reviewers (S.A. and M.S.) independently searched the EMBASE, PubMed, Cochrane Register of Controlled Trials and Google Scholar databases from inception to 2 January 2022 for papers published in English. Discrepancies between reviewers were discussed with other authors to achieve full consensus. Databases were searched using the following keywords: ‘copeptin’ OR ‘neurohypophysis hormone’ OR ‘C-terminal pro-vasopressin’ OR ‘heart failure’ OR ‘HF’ OR ‘cardiac failure’ OR ‘cardiac insufficiency’ OR ‘cardiomyopathy’. Search strategies were modified for each database using free text terms and controlled vocabularies. Finally, we manually checked the reference lists from each publication to identify additional eligible studies.

**2.2. Study selection criteria**

The selection of all studies was independently decided by two reviewers (L.S. and A.G.) according to the predefined selection criteria. Included studies were required to meet the following criteria: to be focussed on the value of copeptin in predicting mortality in patients with HF, or focussed on the copeptin levels in: HF vs. non-HF patients; preserved vs. reduced systolic function in HF patients; stable patients vs. mortality/acute HF-related hospitalizations.

**2.3. Data extraction**

Two authors (L.S. and A.G.) independently extracted data from eligible studies. For this purpose, they use predefined Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA). Any potential disagreements were resolved by discussion with a third reviewer (L.S.). Extracted data included: (1) study characteristics (i.e., first author, year of publication, country, study design, inclusion and exclusion criteria, primary outcomes, findings); (2) participant characteristics (i.e., number of participants, age, sex); (3) primary study outcomes: copeptin levels in HF vs. control group; and (4) secondary outcomes (i.e., copeptin levels in preserved vs. reduced systolic function in stable HF vs. mortality/acute HF-related hospitalization; and copeptin levels in survivors at follow-up).

**2.4. Risk of bias assessment**

For each study, the risk of bias was assessed at the study level by 2 independent reviewers using the Cochrane ROBINS-I bias assessment tool (Sterne et al. 2016). The ROBINS-I tool examines seven bias domains due to: (1) confounding; (2) selection of participants; (3) classification of interventions; (4) deviations from intended interventions; (5) missing data; (6) measurement of outcomes; and (7) selection of the reported result. The Robvis application was used to visualize the risk of bias assessments (McGuinness and Higgins 2021).

**2.5. Statistical analysis**

All statistical analyses were performed using Stata software, version 15.0 (College Station, TX, USA) and the Cochrane Collaboration Review Manager Software version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration). Significance was defined as \( p < 0.05 \). For dichotomous data, we used odds ratios (ORs) or risk ratios (RRs) as the effect measure with 95% confidence intervals (CIs). For continuous data, we used mean differences (MDs) with 95% CI. When the continuous outcome was reported in a study as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. (2005). Heterogeneity between studies was assessed by the Cochrane Q test and I\(^2\) statistic. I\(^2\) values of 25%, 50%, and 75% were considered low, moderate, and high, respectively (Higgins et al. 2011). The random effects model was used for the analyses (Higgins et al. 1997). To evaluate the potential for publication bias, we plotted values against associated standard errors (Egger et al. 1997) and used Begg's test to assess
the symmetry of the resulting funnel plot (Begg and Mazumdar 1994). We considered publication bias present when the \( p \)-value was <0.1 in the asymmetry test. However, publication bias was not evaluated if <10 studies occurred in a subgroup of this analysis.

### 3. Results

#### 3.1. Study characteristics

The flow chart of the literature search and the study selection process is shown in Figure 1. Overall, the combined search identified 5,322 articles, of which 5249 were rejected based upon the title and abstract evaluation. The remaining 73 articles underwent full-text evaluation; 54 were excluded because they were reviews, did not have sufficient data or did not have comparator group. Finally, 19 studies (Stoiser et al. 2006, Gegenhuber et al. 2007, Neuhold et al. 2008, Dieplinger et al. 2009, Peacock et al. 2011, Tentzeris et al. 2011, Loncar et al. 2012, Mason et al. 2013, Pozsonyi et al. 2015, Hage et al. 2015, Bahrmann et al. 2016, Herrero-Puente et al. 2017, Jia et al. 2017, Kilicgedik et al. 2017, Guer et al. 2017, Goliasch et al. 2018, Duengen et al. 2018, Xu et al. 2018, Ozmen et al. 2021) including 5,562 patients and published between 2006 and 2021 were included. Of the total population, 63.3% were male.

#### 3.2. Meta-analysis outcomes

Four studies examined copeptin plasma concentrations in HF vs. control groups. Pooled analysis showed that the mean copeptin levels were higher in HF vs. non-HF populations (43.6 ± 46.4 vs. 21.4 ± 21.4, respectively; \( MD = 20.48; 95\% CI: 9.22 \text{ to } 31.74; I^2 = 98\%; p < 0.001 \); Figure 2).

Pooled analysis of copeptin concentrations stratified by LV ejection fraction found higher concentrations in HFrEF vs. HFpEF patients (17.4 ± 7.1 vs. 10.1 ± 5.5, respectively; \( MD = −4.69; 95\% CI: −7.58 \text{ to } −1.81; I^2 = 95\%; p = 0.001 \); Figure 3).

Additional four studies found that copeptin levels were higher in patients with mortality/acute HF-related
hospitalization vs. stable patients (31.3 ± 23.7 vs. 20.4 ± 12.8, respectively; MD = −13.06; 95% CI: −25.28 to −0.84; I² = 99%; p = 0.04; Figure 4).

A detailed analysis of survival in different follow-up periods is presented in Table 1. Higher copeptin concentrations were associated with mortality and were observed in all follow-up periods (p < 0.05).

### 4. Discussion

In our meta-analysis of nineteen studies, we found copeptin to be a very strong predictor of HF diagnosis as well as to be associated with reduced ejection fraction in HF patients. Higher copeptin concentrations also identified those who would subsequently die or be re-admitted due to HF, as compared to those without diagnosis of HF or who were in stable condition. Additionally, higher copeptin concentrations were strongly prognostic for subsequent mortality in all periods, ranging from 14 days to 5 years.

Increased activity of the vasopressin system has an important impact on the pathophysiology of HF (Francis et al. 1984). AVP, a nonapeptide, is synthetized in the supraoptic and paraventricular nuclei of the hypothalamus as pre-pro-AVP, which is then cleaved into pro-AVP. Subsequently, pro-AVP is cleaved into AVP, inactive copeptin and neurophysin-II, all of which are released in equimolar amounts (Demiselle et al. 2020). Neurophysin-II participates in transport of AVP to the neurohypophysis, where AVP is stored. The physiological role of copeptin, a 39-aminoacid glycoprotein, remains uncertain, but is hypothesized to assist in pro-AVP formation (Balling and Gustafsson 2014).

AVP is secreted from the neurohypophysis in response to increased plasma osmolality, decreased sodium concentration, low cardiac output, hypotension, or hypovolemia, although the non-osmotic stimuli are thought to be the primary cause of elevated AVP in HF (Oghlakian and Klapholz 2009, Mason et al. 2013, Guer et al. 2017). Elevated AVP acutely promotes vasoconstriction, as well as water retention via renal V2 receptors. Chronic AVP elevation results in cardiomyocyte hypertrophy and myocardial remodelling via V1A-receptors (Izumi et al. 2014).

Circulating AVP has a short half-life, is mostly bound to platelets, requires specialist laboratory analysis, such that its use as a clinically available prognostic biomarker is limited (Preibisz et al. 1983). Conversely, copeptin, characterized by longer half-life, greater stability, and less demanding analysis, is used as surrogate marker (Morgenthaler et al. 2006). Copeptin concentrations do not seem to be age-dependent (Bhandari et al. 2009), however, there is a stronger correlation between copeptin and estimated glomerular filtration rate (eGFR) in males vs. females (Bhandari et al. 2009, Vargas et al. 2021). Copeptin elevation is correlated with the presence of diabetes mellitus (Enhoerning et al. 2010), renal dysfunction (Bhandari et al. 2009), left atrial
size and deceleration time, although not with diastolic dysfunction (Bhandari et al. 2009, Hage et al. 2015).

Several studies showed that copeptin is elevated in HF patients compared to those without HF (Dieplinger et al. 2009, Mason et al. 2013, Bahrman et al. 2016, Guer et al. 2017). Yet its ability to predict HF remains uncertain. Recent study and meta-analysis linked elevated copeptin with increased risk of HF (Yan et al. 2017, Schill et al. 2021), suggesting its potential use as a diagnostic tool. On the contrary, some reported no positive correlation between copeptin and HF incidence (Wannamethee et al. 2014). Nevertheless, NT-proBNP, increased in HF patients, was described as superior to copeptin in diagnosis of HF (Winther et al. 2017).

We showed, consistent with previous papers (Wannamethee et al. 2014, Zhang et al. 2017, Yan et al. 2017, Winther et al. 2017), that copeptin is a strong independent predictor of all-cause mortality in HF as well as HF-related re-hospitalization in HF (Stoiser et al. 2006, Jia et al. 2017, Duengen et al. 2018, Ozmen et al. 2021). Other studies reported different outcomes. One described copeptin as inferior to BNP in prediction of HF re-hospitalization in chronic HF (Stoiser et al. 2006) Another study reported NT-proBNP as the only independent predictor of re-hospitalization due to cardiac causes in patients with de novo HF (Molvin et al. 2019). Although we found copeptin to be useful in the prediction of HF re-hospitalization, its independency for this calculation remains unclear.

While some suggested that the predictive value of copeptin is equivalent to NT-proBNP (Neuhold et al. 2008, Maisel et al. 2011, Zhang et al. 2017, Jia et al. 2017), others reported no correlation between the markers (Pozsonyi et al. 2015). This may be the consequence that the predictive value of both biomarkers may be related to disease severity in HF patients. For example, the correlation between copeptin and New York Heart Association (NYHA) class (Jia et al. 2017) suggests that BNP may act as predictor of outcome in early HF stages, whereas copeptin may be more useful in advanced HF (Stoiser et al. 2006). Initially strong prognostic abilities of copeptin seem to become less accurate over time, whereas improved NPs performance was observed during follow-up period. Therefore, copeptin, as marker of hemodynamic status, may be superior to NPs in predicting short-term mortality (Peacock et al. 2011, Jia et al. 2017). Overall, use of copeptin in prediction of adverse events was proven to increase the prognostic value of NPs (Maisel et al. 2011, Pozsonyi et al. 2015, Duengen et al. 2018), thus multi-marker approach was recommended (Dieplinger et al. 2009, Yan et al. 2017, Molvin et al. 2019).

Studies comprised different subgroups of HF patients. Copeptin was shown to predict adverse events in individuals presenting with dyspnea as symptom of acute HF (Dieplinger et al. 2009, Winther et al. 2017), those admitted due to decompensated HF (Jia et al. 2017, Duengen et al. 2018, Protasov et al. 2019, Ozmen et al. 2021) and those, mostly elderly, suffering from chronic HF (Stoiser et al. 2006, Mason et al. 2013). Furthermore, elevated copeptin levels were found to be associated with increased mortality in HF patients after acute myocardial infarction (Voors et al. 2009).

The mean follow-up period of studies included in our meta-analysis varies from 14 days to 5 years. It is of clinical importance that copeptin shows predictive value regarding both short- and long-term mortality. Moreover, one study reported copeptin as able to predict all-cause mortality within the mean follow-up period of 13 years (Alehagen et al. 2011). Long-term mortality prediction is useful in patients with chronic HF. In acute settings though, short-term prediction, e.g., 14 days, is vital to identify high-risk patients requiring immediate intervention or intensive care unit admission (Pozsonyi et al. 2015).

Some limitations of our meta-analysis are to be acknowledged. Firstly, relatively small number of studies was included. Secondly, considerable heterogeneity was observed, as we analyzed studies comprising patients with higher NYHA-class and acute HF together with studies examining patients with lower NYHA-class and stable, chronic HF. For this reason, included studies differed regarding copeptin cut-off concentrations. Thirdly, we compared studies with different endpoints – CV vs. all-cause mortality. Fourthly, laboratory techniques used for measurements differed per study. Fifthly, we presented limited information about polled studies, e.g., thresholds of LV ejection fraction were not included. Sixthly, we did not consider BNP, as we concentrated on comparison between copeptin and NT-proBNP. Finally, we focussed on ability of copeptin to predict all-cause mortality instead of overall HF related adverse events. Thereby further trials should be conducted to fully evaluate copeptin performance.

5. Conclusions

Results from the present meta-analysis showed that elevated copeptin plasma concentrations observed in HF patients are associated with increased risk of all-cause mortality. Therefore, copeptin may serve as predictor of outcome in HF, potentially improving prognostic value of established NPs.

Authors contributions

Conceptualization, M.J.J., A.D., and L.S.; methodology, M.J.J., A.D., and L.S.; software, L.S. and M.P.; validation, M.J.J., A.D., and L.S.; formal analysis, M.J.J. and L.S.; investigation, S.A., M.S., L.S.; resources, L.S.; data curation, M.P., S.A., M.S.; writing - original draft preparation, J.M.Z., A.G., L.S.; writing - review and editing, J.M.Z., A.G., M.J.J., S.A., M.S., A.D., MP, PD., F.W.P., Z.R., L.S.; visualization, L.S.; supervision, L.S. and M.J.J.; project administration, L.S.; funding acquisition, M.J.J. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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