Editorial

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Copeptin in critical illness

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In this issue of *Clinical Chemistry and Laboratory Medicine* (*CCLM*), Bolignano and colleagues present an extensive review on copeptin, the C-terminal fragment of the provasopresin peptide (CTproAVP), as a surrogate biomarker of arginine vasopressin [1]. Copeptin is co-released from the hypothalamus in an equimolar ratio with the hypothalamic stress hormone vasopressin, and hence secretion is activated not only by changes in plasma osmolality and circulating blood volume, but also by stress and inflammatory states.

Copeptin reflects the stress response during critical illness. Its plasmatic concentration has been associated with mortality in several acute disease states. The acute-phase response to critical illness is characterized by an abrupt and massive release of stress hormones, including adrenocorticotropic hormone and cortisol, catecholamines, vasopressin, glucagon, and growth hormone [2]. In the acute stage of critical illness, this response can maintain effective circulation and tissue oxygenation, and increase the production of energy substrates. Persistent systemic inflammation may result in tissue hypoxia and cell damage causing multiple organ dysfunctions and failure. With the body primed by this persistent pro-inflammatory state with hypercatabolism, several drugs, such as propofol, glucocorticoids and catecholamines may further enhance the tissue damage [3]. In the chronic stage of critical illness, the hormonal profile changes substantially with inappropriately low vasopressin levels, onset of the sick euthyroid syndrome, and reduced adrenal responsiveness to adrenocorticotropic hormone, often despite hypercortisolemia. In sepsis, few endocrine systems are so rapidly activated and then are so rapidly exhausted as the vasopressin axis [4].

Copeptin plasmatic levels correlate with the release of acute phase cytokines interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and have been used to improve prognostication in several neurological and non-neurological acute diseases in the intensive care unit [5] or to improve patients' triage in the emergency department [6, 7]. In community-acquired pneumonia, copeptin has been shown to be a good predictor of short- and long-term all-cause mortality, superior to inflammatory markers, and at least comparable to "the confusion, respiratory rate, blood pressure, and age over 65 years (CRB-65)" score [8, 9]. In severe chronic obstructive pulmonary disease, copeptin is an independent predictor of acute exacerbation together with chronic obstructive pulmonary disease assessment test (CAT). Importantly, copeptin and CAT scores are both independent predictors of 6-month mortality in such patients. In ventilator-associated pneumonia, a major complication in critically ill patients undergoing mechanical ventilation, copeptin is significantly elevated in non-survivors and moderately predicts survival [10]. In patients with sepsis, copeptin concentration gradually increases with the severity of the disease [11]. Plasma concentrations in septic shock can be more than 30-fold higher than in healthy individuals and more than six-fold higher than in patients with systemic inflammation not related to infection [11]. However, these findings are not uniformly reported. Despite vasopressin levels being expected to increase early in septic shock because hypotension is the most potent stimulus of increased synthesis and release of vasopressin, vasopressin plasma concentrations may not be different in adult patients with and without shock, indicating that the vasopressin system is dysfunctional in severe sepsis [12]. In this condition, the correlation between the vasopressin and copeptin plasmatic levels can be suboptimal, possibly as a consequence of renal dysfunction [12], or reduced vasopressin synthesis and secretion [13]. In children with septic shock, vasopressin and copeptin levels may not robust markers for severity and clinical outcomes [14]. Copeptin is also increased in several acute neurological illnesses, such as acute ischemic stroke [15, 16], spontaneous cerebral hemorrhage [17–19] and brain trauma [20]. Copeptin, measured within the first 24 h after stroke onset, improves neurologic prognostication after ischemic stroke adding predictive information for functional outcome and mortality at 3 months beyond age and stroke severity measured with the NIH Stroke Scale score [16]. In patients with severe brain trauma, copeptin does not reflect the urinary sodium excretion or sodium plasma levels, indicating an uncoupling of

copeptin-vasopressin release and renal water excretion, but is correlated with injury severity [21]. Copeptin combined with high-sensitive cardiac troponin T may help in ruling out acute myocardial infarction in patients with acute chest pain of early onset [22, 23] and non-ST-elevation myocardial infarction (NSTEMI) in older patients [24], facilitating safe early discharge from the hospital [25]. The relevancy of copeptin measurement is debated in NSTEMI patients with troponin I below the 99th centile at presentation [26]. Copeptin may help prognostication in patients presenting with dyspnea in the emergency department [27] or in patients with non-ST-segment elevation acute coronary syndrome [28].

Copeptin plasmatic levels reflect the severity of illness rather than changes in plasma osmolality; as such, copeptin is a promising prognostic biomarker in critical illness. However, the way for biomarkers towards impacting on clinical practices is like long-distance running; few biomarkers reach the finish line [29]. Future studies should evaluate if copeptin measurement adds predictive information to established standard risk markers, allowing *clinical risk reclassification* of patients into higher or lower risk categories [30].

Conflict of interest statement

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References

1. Bolignano D, Cabassi A, Fiaccadori E, Ghigo E, Pasquali R, Peracino A, et al. Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. Clin Chem Lab Med 2014;52:1447–56.
2. Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet 2004;364:545–8.
3. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intens Care Med 2003;29:1417–25.
4. Russell JA. Vasopressin and its copilot copeptin in sepsis and septic shock. Crit Care Med 2009;37:749–50.
5. Katan M, Christ-Crain M. The stress hormone copeptin: a new prognostic biomarker in acute illness. Swiss Med Weekly 2010;140:w13101.
6. Nickel CH, Bingisser R, Morgenthaler NG. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. BMC Med 2012;10:7.
7. Nickel CH, Messmer AS, Geigy N, Misch F, Mueller B, Dusemund F, et al. Stress markers predict mortality in patients with nonspecific complaints presenting to the emergency department and may be a useful risk stratification tool to support disposition planning. Acad Emerg Med 2013;20:670–9.
8. Kruger S, Ewig S, Giersdorf S, Hartmann O, Suttorp N, Welte T. Cardiovascular and inflammatory biomarkers to predict short- and long-term survival in community-acquired pneumonia: results from the German Competence Network, CAPNETZ. Am J Respir Crit Care Med 2010;182:1426–34.
9. Kolditz M, Halank M, Schulte-Hubbert B, Bergmann S, Albrecht S, Hoffken G. Copeptin predicts clinical deterioration and persistent instability in community-acquired pneumonia. Respir Med 2012;106:1320–8.
10. Boeck L, Eggimann P, Smyrnios N, Pargger H, Thakkar N, Siegemund M, et al. The Sequential Organ Failure Assessment score and copeptin for predicting survival in ventilator-associated pneumonia. J Crit Care 2012;27:523,e521–9.
11. Morgenthaler NG, Muller B, Struck J, Bergmann A, Redl H, Christ-Crain M. Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock. Shock 2007;28:219–26.
12. Jochberger S, Dorler J, Luckner G, Mayr VD, Wenzel V, Ulmer H, et al. The vasopressin and copeptin response to infection, severe sepsis, and septic shock. Crit Care Med 2009;37:476–82.
13. Oliveira-Pelegrin GR, Basso PJ, Rocha MJ. Cellular bioenergetics changes in magnocellular neurons may affect copeptin expression in the late phase of sepsis. J Neuroimmunol 2014;267:28–34.
14. Lee JH, Chan YH, Lai OF, Puthucheary J. Vasopressin and copeptin levels in children with sepsis and septic shock. Intens Care Med 2013;39:747–53.
15. Katan M, Fluri F, Morgenthaler NG, Schuetz P, Zweifel C, Bingisser R, et al. Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. Ann Neurol 2009;66:799–808.
16. De Marchis GM, Katan M, Weck A, Fluri F, Foerch C, Findling O, et al. Copeptin adds prognostic information after ischemic stroke: results from the CoRisk study. Neurology 2013;80:1278–86.
17. Zhu XD, Chen JS, Zhou F, Liu QC, Chen G, Zhang JM. Detection of copeptin in peripheral blood of patients with aneurysmal subarachnoid hemorrhage. Crit Care 2011;15:R288.
18. Fung C, De Marchis GM, Katan M, Seiler M, Arnold M, Gralla J, et al. Copeptin as a marker for severity and prognosis of aneurysmal subarachnoid hemorrhage. PloS One 2013;8:e53191.
19. Zweifel C, Katan M, Schuetz P, Siegemund M, Morgenthaler NG, Merlo A, et al. Copeptin is associated with mortality and outcome in patients with acute intracerebral hemorrhage. BMC Neurol 2010;10:34.
20. Dong XQ, Huang M, Yang SB, Yu WH, Zhang ZY. Copeptin is associated with mortality in patients with traumatic brain injury. J Trauma 2011;71:1194–8.
21. Kleindienst A, Brabant G, Morgenthaler NG, Dixit KC, Parsch H, Buchfelder M. Following brain trauma, copeptin, a stable peptide derived from the AVP precusor, does not reflect osmoregu-

lation but correlates with injury severity. Acta Neurochir Suppl 2010;106:221–4.
22. Lippi G, Plebani M, Di Somma S, Monzani V, Tubaro M, Volpe M, et al. Considerations for early acute myocardial infarction rule-out for emergency department chest pain patients: the case of copeptin. Clin Chem Lab Med 2012;50:243–53.
23. Sebbane M, Lefebvre S, Kuster N, Jreige R, Jacques E, Badiou S, et al. Early rule out of acute myocardial infarction in ED patients: value of combined high-sensitivity cardiac troponin T and ultrasensitive copeptin assays at admission. Am J Emerg Med 2013;31:1302–8.
24. Bahrmann P, Bahrmann A, Breithardt OA, Daniel WG, Christ M, Sieber CC, et al. Additional diagnostic and prognostic value of copeptin ultra-sensitive for diagnosis of non-ST-elevation myocardial infarction in older patients presenting to the emergency department. Clin Chem Lab Med 2013;51:1307–19.
25. Mockel M, Searle J, Hamm C, Slagman A, Blankenberg S, Huber K, et al. Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study. Eur Heart J 2014. [Epub ahead of print 30 Apr 2014].
26. Duchenne J, Mestres S, Dublanchet N, Combaret N, Marceau G, Caumon L, et al. Diagnostic accuracy of copeptin sensitivity and specificity in patients with suspected non-ST-elevation myocardial infarction with troponin I below the 99th centile at presentation. Br Med J Open 2014;4:e004449.
27. Vetrone F, Santarelli S, Russo V, Lalle I, De Berardinis B, Magrini L, et al. Copeptin decrease from admission to discharge has favorable prognostic value for 90-day events in patients admitted with dyspnea. Clin Chem Lab Med 2014;52:1457–64.
28. O'Malley RG, Bonaca MP, Scirica BM, Murphy SA, Jarolim P, Sabatine MS, et al. Prognostic performance of multiple biomarkers in patients with non-ST elevation acute coronary syndrome: analysis from MERLIN-TIMI 36. J Am College Cardiol 2014;63:1644–53.
29. Plebani M, Melichar B. Quo vadis, biomarkers? Clin Chem Lab Med 2014;52:761–4.
30. Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:2408–16.

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