CAT
Critically Appraised Topic

Title: The measurement of copeptin: clinical relevance?

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CLINICAL BOTTOM LINE

Arginine vasopressin (AVP) and copeptin are derived from the same precursor peptide. The exact function of copeptin is unknown. Copeptin has been proposed as a stable, surrogate marker of AVP and can be measured with a sandwich immunoassay. Both copeptin and AVP are responsive to osmotic stimuli and somatic stress. Here we investigated the clinically relevant use of the measurement of copeptin.

Copeptin can be used as a valuable and reliable diagnostic marker in the differential diagnosis of diabetes insipidus and primary polydipsia. Determination of basal copeptin levels is recommended to differentiate nephrogenic DI from central DI and primary polydipsia. An overnight water deprivation test or hypertonic osmotic stimulation can further differentiate between central DI or primary polydipsia. There is no relevant diagnostic utility of copeptin in the differentiation of hyponatremia.
Somatic stress is another major determinant of unspecific copeptin regulation. High copeptin levels are associated with poor functional outcome and mortality. Since the prediction of risk of poor outcome often remains complicated, copeptin can aid in the assessment of outcome and be used as a prognostic marker in various acute diseases like sepsis, cardiovascular disease, ischemic stroke and traumatic brain injury. Copeptin has been put forward as predictive marker for renal function in chronic kidney disease, autosomal dominant polycystic kidney disease and diabetes mellitus.

To date, the measurement of copeptin is not yet implemented in routine clinical practice. It's a fast, accurate but quite expensive biomarker. The feasibility of implementing the copeptin assay in routine laboratory practice and the possibility of reimbursement needs further investigation.

CLINICAL/DIAGNOSTIC SCENARIO

Diabetes insipidus (DI) is characterized by the inability to appropriately concentrate urine in response to volume and osmolar stimuli. The main causes for DI are decreased AVP production (central DI) or decreased renal response to AVP (nephrogenic DI). The determination of the underlying disease pathology in patients with polyuria and altered plasma osmolality is often difficult. Polyuria can be related to insufficient AVP (central DI), reduced sensitivity to AVP (nephrogenic DI), or excessive water intake (primary polydipsia). Differentiation of these disorders is important since treatment strategies vary and wrong treatment can have deleterious consequences.

The golden standard in the differential diagnosis of polyuria polydipsia has been the water deprivation test with indirect assessment of the AVP activity by measurement of the urine concentration capacity during a prolonged dehydration period.[1] This procedure has its limitations: firstly, chronic polyuria itself can affect renal concentration capacity through a washout mechanism of the renal concentration capacity or downregulation of kidney aquaporin (AQP)-2 water channels. Secondly, patients with real AVP deficiency may concentrate their urine to almost normal levels. Thirdly, patients with acquired nephrogenic DI are often not completely resistant to AVP. Fourthly, the proposed cut-off levels were post hoc derived on a small patient cohort (n=29)[1] and were never prospectively validated.[2]

Direct measurement of AVP activity was hoped to overcome the limitations of this indirect approach to detect renal concentration. Despite promising first results disappointing test results derived from recent investigations showing that AVP measurements pointed toward a correct diagnosis in only 38%.[2] Reasons are that an accurate definition of normal physiological relationship of AVP has long been missed and several technical limitations of the AVP assay per se, resulting in a high pre-analytical instability.[2] Therefore the AVP assay never entered routine clinical practice. Measurement of plasma copeptin concentration has been shown to be useful in the investigation of these AVP-related disorders. Additionally, utilization of copeptin has been proposed in the assessment of syndrome of inappropriate antidiuretic (SIAD).

On the other hand, through its characteristics as a marker of stress, copeptin provides a unique measure of the individual stress burden and could operate as a prognostic marker in different acute diseases. Copeptin has been reported to aid in the prognosis or diagnosis of several cardiac disorders such as acute coronary syndrome, stable coronary artery disease, congestive heart failure, and acute ischemic stroke.
The rationale for a presumed prognostic value of copeptin is due to the positive correlation of the individual stress level with the magnitude of the stressor, or the severity of the illness. Copeptin more subtly reflects individual stress level than plasma cortisol in patients with increasing disease-related stress.

One more problem stability of the calibration curve, which is 15 days, and the stability of the kit of one month[3] which can cause difficulties when demand is limited.

To date, the measurement of copeptin is not yet implemented in routine clinical practice until more data from clinical trials is available to support altering clinical management based on these results. The serum concentration of copeptin is increased in several clinical conditions. The purpose of this project is to evaluate the possible clinically relevant use of the promising biomarker copeptin.

QUESTION(S)

1) Copeptin: synthesis, physiology, function and what is normal?
2) In which clinical settings the measurement of copeptin could take place?
3) How can copeptin be implemented in routine clinical practice?

SEARCH TERMS

1) MeSH Database (PubMed): MeSH term: ""copeptins" [Supplementary Concept]"
2) PubMed Clinical Queries (from 1966; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi): Systematic Reviews; Clinical Queries using Research Methodology Filters (diagnosis + specific, diagnosis + sensitive, prognosis + specific): "copeptins"
3) Pubmed (Medline; from 1966), SUMSearch (http://sumsearch.uthscsa.edu/), The National Institute for Clinical Excellence (http://www.nice.org.uk/), Cochrane (http://www.update-software.com/cochrane)
4) *UpToDate Online: copeptin*

Filter: English, Human

RELEVANT EVIDENCE/REFERENCES

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Package insert: BRAHMS Copeptin proAVP Kryptor. ThermoFisher Scientific, Ver. R01 09/2015

6) Posters, "grey literature", presentations

3. ThermoFischer. *Data Sheet B ·R ·A ·H ·M ·S Copeptin ProAVP*.; 2015.

Question 1: Copeptin: synthesis, physiology, function and what is normal?

1. Synthesis and physiology

The AVP hormone is synthesized as part of a 164 amino acid vasopressin precursor protein in the magnocellular neurons located in the supraoptic (SON) and paraventricular nucleus (PVN) (Figure 1a). This vasopressin precursor consists of a signal peptide, the AVP moiety, neurophysin-2 and copeptin, a 39 amino acid long glycosylated peptide with a leucine-rich core segment (Figure 1b). The gene that encodes this precursor is located on the short arm of chromosome 20 (20p13).[2]

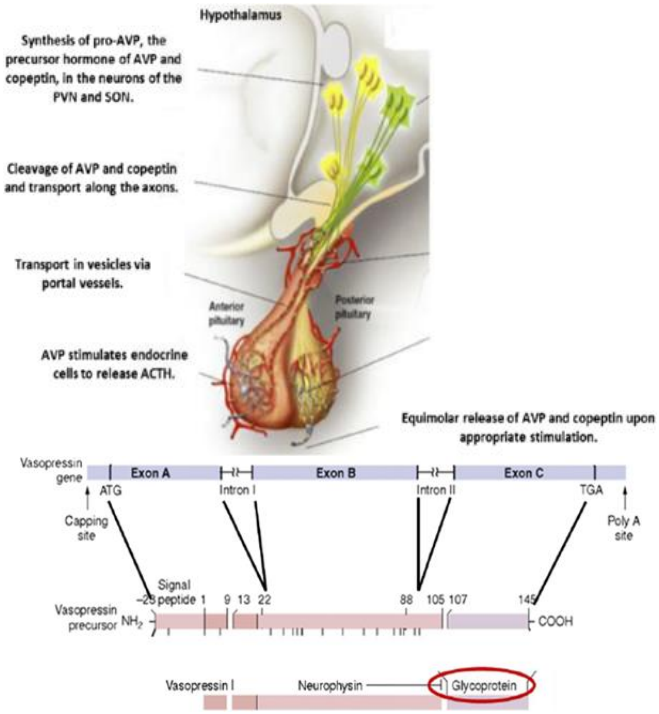

Figure 1: *(a) Synthesis of Arginine Vasopressin (AVP) and copeptin (b) Arginine Vasopressin (AVP) gene and its protein products. (Christ-Crain et al, 2019[2])*

The pro-AVP is synthesized in the magnocellular neurons and processed in the endoplasmatic reticulum by the removal of the signal peptide and the addition of a carbohydrate chain. Additional posttranslational processing occurs during the transport of the precursor protein down to axon terminals in the posterior pituitary. AVP is enzymatically cleaved form copeptin and neurophysin-2 and stored in neurosecretory granules in the posterior pituitary.[2]

The main stimulus for the release of vasopressin are dehydration resulting in an increase in plasma osmolality and an decrease in extracellular volume.[2] For the same change in osmolality, sodium has a larger influence on vasopressin secretion than does urea or glucose. Other stimuli for vasopressin secretion are stress situations where AVP acts synergistically with corticotropin-releasing hormone to stimulate adrenocorticotropic hormone (ACTH) release from the anterior pituitary.[2]

Copeptin is rapidly eliminated from the circulation. This rapid elimination no longer happens ex vivo. Copeptin has a two-times-longer half-life in relation to AVP.[4] No specific copeptin receptor or copeptin elimination mechanisms are known. Copeptin can be measured in urine which indicates a (partial) renal elimination.[5]

2. Function of copeptin[2]

The role of copeptin remains unclear. Early studies suggested a role as a prolactin-releasing factor, but the results were inconclusive. Recent data postulate copeptin to be a chaperone-like molecule which is involved in the structural formation of proAVP. It is reported to interact with the calnexin/calreticulin system which monitors protein folding an interacts with glycosylated proteins. This decreases the formation of inactive hormones and increases the formation of active hormones. The tight regulation of copeptin in the circulation raises the idea that copeptin may have a specific peripheral function, although experimental data prove no evidence for this. Importantly, copeptin responds as rapidly as AVP to osmotic, hemodynamic an unspecific stress-related stimulus which may be explained by its equimolar production together with AVP.

3. Normal range and physiological response

The normal range of copeptin was first established in 359 healthy volunteers in normo-osmotic baseline conditions.[6] Median copeptin plasma concentration were reported to be 4,2 pmol/L with a 99th percentile of 13,5 pmol/L.[6] These values were confirmed in larger populations[7,8] (Table 1). Men show slightly higher values than women, with a difference in median value of only 1 pmol/L.[6,7] A large population of around 5000 individuals showed a 97,5 percentile of 13 pmol/L and a 99th percentile of 18,9 pmol/L.[8]

AUTHOR	N	MEDIAN	97,5TH PERCENTILE	99TH PERCENTILE	MALE	FEMALE
ADULT						
MORGENTHALER ET AL. (2006)[6]	359	4,2 (1,7-13,8)	11,25	13,5	5,2	3,7
BHANDARI ET AL. (2009)[7]	706				4,3	3,2
KELLER ET AL. 2010[8]	5000		13	18,9		
KHAN ET AL. 2007[9]	700	3,8 (0,44-44,3)				
MULLER ET AL. 2007[10]	50	5,0 (3,5-8,3)				
ENHORNING ET AL 2019[11]	55	5,33 (3,45-7,14)				
PEDIATRIC		MEAN				
TULI ET AL. 2015[12]	53	5,2 (2,4-6,8)				

Table 1: *Overview of the normal range of copeptin (copeptin in pmol/L)*

In healthy subjects, copeptin is regulated within the normal range but may fluctuate according to physiological conditions. Copeptin increases towards higher values in the normal range during fasting and during exercise and declines rapidly in vivo towards low normal values after intake of water.[6,11] Copeptin shows the same behavior to osmotic and hemodynamic stimuli as demonstrated for AVP. One study showed a stronger correlation between copeptin and serum osmolality (r = 0.77) than between AVP and serum osmolality (r = 0.49).[13]
Copeptin levels show no correlation with age[2,7], and no circadian variability.[2] Copeptin release seems not to be affected by food intake or the menstrual cycle of woman, suggesting that copeptin measurements are quite robust and can be reliably interpreted independently of time point of withdrawal, prandial status or menstrual cycle.[2]

Question 2: In which clinical settings the measurement of copeptin could take place?

1. Fluid balance

1.1. Polyuria Polydipsia syndrome – Diabetes insipidus

The value of direct copeptin measurement in the whole spectrum of polyuria polydipsia syndrome has been evaluated in several studies either through osmotic stimulation (water deprivation test and hypertonic saline infusion) or non-osmotic stimulation (arginine stimulated copeptin measurements and pituitary surgery).[2] Used protocols are displayed in Attachment I.

During an overnight water deprivation test, direct measurement of copeptin reliably separated patients with complete nephrogenic DI (>20 pmol/L) and central DI (<2,6 pmol/L) based on a single baseline measurement.[14] Water deprivation alone showed difficulties with the differentiation between patients with partial CDI and PP due to the limited osmotic stimulation. Copeptin measured during the water deprivation test yielded a better differentiation compared to the indirect water deprivation test or direct AVP measurement.[14] One study (n = 55) tested the diagnostic potential of copeptin in a modified water deprivation test followed by hypertonic saline infusion.[15] This modified test guaranteed a sufficient osmotic stimulus for evaluation of osmotically induced copeptin and AVP activity. Post-hoc analysis revealed that without prior thirsting, a single baseline copeptin level > 21.4 pmol/L differentiated NDI from other etiologies with 100% sensitivity and specificity, whereas an osmotically stimulated copeptin value >4.9 pmol/L differentiated between patients with PP and patients with partial CDI with 94.0% specificity and 94.4% sensitivity.[2] This cut-off level was validated in an international multicenter trial including 156 patients with diabetes insipidus or primary polydipsia.[16]

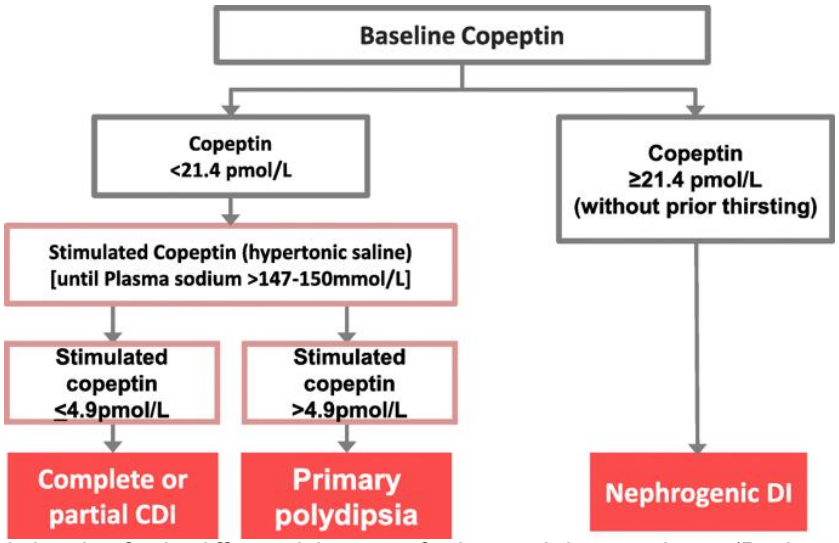

Figure 2: *Proposed algorithm for the differential diagnosis of polyuria polydipsia syndrome. (Fenske et al. 2018*[16]*)*

A third approach for osmotic stimulation is the hypertonic saline infusion test, using a 3% saline infusion test without prior thirsting. Hypertonic saline infusion leads to a correct diagnosis in 97% (95% CI: 92-99) of the patients using the copeptin cutoff level of >4.9 pmol/l, which was superior to the diagnostic accuracy of the indirect water deprivation test of 77% (95%CI: 69-83; $p < 0.001$).[16] The diagnostic accuracy of hypertonic saline stimulated copeptin was similarly accurate in distinguishing patients with partial DI from patients with primary polydipsia with a correct diagnosis in 95%, compared to 73% with the water deprivation test. This hypertonic saline test plus copeptin measurement might replace the indirect water deprivation test in the differential diagnosis of polyuria polydipsia syndrome and a recommended diagnostic workflow algorithm is displayed in Figure 2.[2] The hypertonic saline infusion test is based on the induction of hypernatremia and has, therefore, several caveats: the rise in sodium can be associated with adverse effects, the test requires close monitoring of sodium levels and is contraindicated in some patients (e.g. with heart failure or epilepsy).

Arginine is known to stimulate various hormones secreted by the anterior and posterior pituitary. Arginine stimulation is already used as a simple and well-tolerated tool to diagnose growth hormone deficiency. In a study including 92 healthy volunteers and children as well as 96 patients with either diabetes insipidus or primary polydipsia, the study showed that an arginine-stimulated copeptin measurements can be an accurate test for DI.[17] A copeptin cutoff of 3,8 pmol/L at 60 min after arginine infusion had an optimal accuracy of 93% to diagnose diabetes insipidus (Figure 3).[17] The test was safe and had a convenient tolerability profile: mild nausea was common, but adverse effects such as vertigo, headache and malaise were negligible during arginine stimulation.

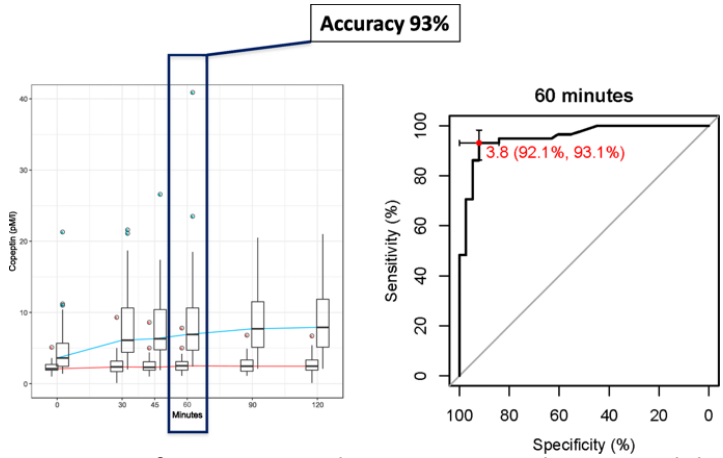

Figure 3: (a) *Copeptin concentrations after arginine stimulation in patients with primary polydipsia (blue) as compared to patients with central diabetes insipidus (red). (b)ROC curve for copeptin upon arginine infusion for the diagnosis of central diabetes insipidus. (Winzeler et. al 2019*[17]*)*

When comparing patients with complete versus partial DI, those with complete disease showed a negligible copeptin increase, whereas those with partial disease tended to have greater increased copeptin concentrations (both at baseline and after stimulation).[17] However, because treatment of complete versus partial diabetes insipidus does not differ, this distinction is not clinically relevant.[2,17]

A prospective head-to-head comparison between a hypertonic saline infusion without prior thirsting and arginine stimulation is ongoing. Special cases of DI patients with osmoreceptor dysfunction where thirst is also impaired,

and hypodipsia can result in serious complications associated with hyperosmolality were not included. These patients usually develop hypernatremia as they fail to increase their daily fluid intake and could be evaluated with a direct copeptin measurement to differentiate between CDI and NDI.[2]

Transsphenoidal surgery can lead to transient central DI in up to 30% of cases and permanent central DI in 2-10%.[18] In a prospective multicenter trial with patients undergoing pituitary surgery (n=205) a post hoc derived copeptin cut-off level of <2,5 pmol/L, at 1-day postoperative, had a positive predictive value for development of postoperative DI of 81% and a specificity of 97%, while a level of >30 pmol/L excluded it with a negative predictive value of 95% and a sensitivity of 94%[18]. Copeptin can be used as a predictive marker for the development of postoperative DI and postoperative management after pituitary surgery where the surgery itself fungates as a stress test.

TEST	DIAGNOSTIC ACCURACY	COPEPTIN VALUES		
		Central DI	Nephrogenic DI	Primary Polydipsia
INDIRECT WATER DEPRIVATION TEST	70-76,6% [14,16]	-	-	-
DIRECT WATER DEPRIVATION TEST (AVP)	38% [14]	-	-	-
DIRECT WATER DEPRIVATION TEST (COPEPTIN)	72% [14]	<2,9 pmol/L	>20 pmol/L	
HYPERTONIC SALINE INFUSION (COPEPTIN)	96,5%[16]	<4,9 pmol/L	>21,9 pmol/L†	>4,9 pmol/L
ARGININE STIMULATED COPEPTIN MEASUREMENTS	93 % [17]	<3,8 pmol/L	-	>3,8 pmol/L
TRANSSPHENOIDAL SURGERY	-	<2,5 pmol/L	-	-

Table 2: *Overview diagnostic accuracy for diabetes insipidus per test; †: baseline copeptin measurement without prior thirsting or hypertonic saline infusion*

1.2. Hyponatremia

Copeptin has been proposed and evaluated as a readily available and stable diagnostic marker. Despite this, several studies showed no diagnostic utility of copeptin in the differentiation of hyponatremia.[2]

Copeptin levels widely overlap between different etiologies of hyponatremia and show a large variability within single categories, especially in SIAD.[2] It was postulated that copeptin may provide a good tool to detect underlying malignancies in SIAD. However, a study evaluated data from 146 hospitalized patients with SIAD, copeptin levels were not higher in patients with cancer-related versus -unrelated SIADH.[2] Hyponatremia in cancer patients is not only caused by paraneoplastic AVP secretion, but also by other condition seen in non–cancer patients: comorbidities, medication or symptoms as vomiting, nausea, dehydration or stress.[2]

As mentioned above, as a marker of stress, copeptin is known to be elevated due to stress and acute conditions such as pneumonia, stroke, or heart failure. The non-osmotic stress-related copeptin stimulus in acute hospitalized hyponatremic patients may, therefore, confound the osmotic or paraneoplastic impulse.

2. Marker of stress in different acute diseases

Copeptin might also play a role as a surrogate marker for AVP-release indicating the individual stress responses, because AVP is a potent synergistic factor of the hypothalamo-pituitary-adrenal (HPA) axis. Copeptin is not organ-specific, but rather is a non-specific marker of acute illness and disease severity.

2.1. Sepsis - Infection

Copeptin levels in ICU patients with sepsis and septic shock, copeptin concentrations were significantly increased (median 79,5 pmol/L (10,6-228; P <0.001) compared with those of healthy individuals.[6] Copeptin levels showed a stepwise increase from patients without infections to patients with sepsis, severe sepsis and septic shock. The median copeptin value on admission in the group of non-survivors was significantly higher as compared to the group of survivors whereas copeptin was an independent predictor for development of septic shock.[19]
Copeptin has repeatedly been shown to accurately predict mortality independently of clinical risk prediction by various scores (Attachment 2). The largest study includes 1740 patients and showed the superior accuracy of copeptin for 28-day mortality when compared to the CRB-65 score and the inflammatory biomarkers CRP and procalcitonin.[20]

2.2. Cardiovascular disease

Copeptin plasma concentration are usually elevated in acute cardiac conditions such as AMI, myocarditis and heart failure. Copeptin is not elevated in patients with unstable angina.[21]

2.2.1. Hearth failure (HF)

Several meta-analyses show that increased concentrations of copeptin are associated with increased risk of HF and all-cause mortality. [22–24] One meta-analysis reported that the risk of all-cause mortality is increased by 3% for every 1 pmol/L increment in copeptin from its normal value.[22] Copeptin has similar prognostic value as compared to NT-proBNP for all-cause mortality in patients with HF.[23] These results suggest that copeptin could be a valid biomarker for both prognosis and diagnosis of HF patients.

2.2.2. Acute Coronary Syndrome

As a single variable, copeptin has only modest diagnostic accuracy for AMI. [21,25] However, as a dual-marker strategy it provides a substantial benefit with conventional cTn, it increases the diagnostic accuracy and particularly the negative predictive value.[21] When used with a sensitive or high sensitive cTn assay it only provides a small increment in sensitivity, at the expense of specificity. [21,25,26] Adding copeptin to hs-cTnT significantly decreased the NPV in a NSTEMI setting.[26] The overall diagnostic accuracy as quantified by the AUC was not increased[26] or increased only marginally by the additional use of copeptin to hs-TnT.[21] Some indicate that the advantage of dual marker strategy appears insignificant when hs-TnT assays are used, while others say the diagnostic and prognostic accuracy are significantly improved.[26] The use of a combined assessment of hs-cTnT and copeptin would take place in emergency department setting to rule out AMI without performing serial testing for troponin due to its higher sensitivity. In settings where only a conventional cTn assay is available, the use of the dual-marker strategy is recommended for the rapid rule-out of AMI by current ESC-guidelines.[27]

2.2.3. Aortic Valve Stenosis (AVS)

One review suggested that copeptin could be used as an objective risk stratifier in the setting of severe AVS to prevent excess mortality and morbidity in asymptomatic cases as well as unnecessary aortic valvular intervention in cases with a vague or ambiguous symptomatology.[28] Reversible causes of copeptin elevation and changes in volume status should be corrected first before evaluation of patients with severe AVS based on copeptin guidance.[28]

2.3. Renal impairment

2.3.1. Chronic Kidney Disease

In patients with chronic kidney disease, plasma copeptin levels inversely correlate with decreasing glomerular filtration rate.[29,30] An increased level of copeptin independently predicts development of both CKD and other specified kidney diseases, suggesting that copeptin can be used to identify individuals at risk for kidney disease development. [31] (cfr. 2.3.2 and 3.1.)

2.3.2. Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD leads to the development of end stage renal disease through irreversible loss of glomeruli. AVP leads to production of cAMP, which is known as a stimulator of cyst formation and growth. A cross-sectional study with patients with ADPKD (n = 102) showed that copeptin levels correlated with 24-h albuminuria, with glomerular filtration rate, and with the renal blood flow, independent of age, sex and diuretic use. Another cohort study in more than 200 patients copeptin was a predictor for larger decrease in glomerular filtration rate during a median follow-up of 8,5 years.[2]

2.4. Acute Ischemic Stroke and Traumatic Brain Injury

There is no significant difference in copeptin between patients with a hemorrhagic or ischemic stroke, nor between stroke and other patients.[32] But serum copeptin could independently predict death in patients with AIS and patients who died had a higher level of copeptin in circulation. Copeptin level was significantly higher in patients with re-event.[32] There elevated copeptin concentrations are positively associated with a higher risk of death and adverse outcomes, serum copeptin may be used as a predictor of severity and recurrence of a stroke.[32,33]

The use of copeptin in combination with the National Institute of Health Stroke Scale (NIHSS) score improved the predictive power of this scoring system.[32] In the Copeptin for Risk Stratification in Acute Stroke (CoRisk) score the numeric increase in AUC curves between the predictive models without and with copeptin was modest (0,816 vs. 0,819 p<0,001).[34] The inclusion of copeptin in the model was associated with an net reclassification index (NRI) of 46% indicating that copeptin allowed improvement in risk reclassification in almost every second patient.[34]

Copeptin levels were significantly associated with poor neurological outcomes and mortality in patients with TBI after adjustment for important prognostic factors such as age, sex, and initial injury severty.[35]

Brain edema plays a critical role in the pathophysiology and morbidity of a wide variety of nervous system disorders including stroke, infection and metabolic disorders.[33] Previous studies identified that vasopressin plays a role in the formation of brain edema and ischemic neuronal injury as blocking of vasopressin receptors attenuates brain edema in ischemic and ischemic and traumatic injury mice models and space-occupying cerebral edema was associated with higher copeptin values.[33,35]

Early measurement of plasma copeptin could provide better prognostic information about functional outcome and mortality in patients with acute stroke[32,33] and traumatic brain injury.[35] Since the prediction of risk of poor outcome remains complicated and mostly depends on underlying conditions or clinical parameters.

3. Other

3.1. Diabetes Mellitus

High copeptin levels in patients with diabetes mellitus predicted a decline in kidney function during follow-up. Copeptin measured in patients with newly diagnosed type 2 diabetes was a predictor for development of chronic kidney disease during a 10 years follow-up. Copeptin was associated with the risk of severe renal outcomes independent of relevant covariates such as age, duration of diabetes, blood pressure, and baseline levels of HbA1c.[2]

3.2. Stress of the newborn

Umbilical cord copeptin measurements have been suggested to be higher in infants with intrauterine growth restriction (IUGR)[36] but was not confirmed by another study[37]. Umbilical cord blood copeptin seems to reflect perinatal stress associated with delivery mode.[36]

3.3. Psychological stress

Two studies in healthy volunteers have shown that copeptin increases upon psychological stress to a much smaller extent than observed in response to somatic stress.[2]

Question 3: How can copeptin be implemented in routine clinical practice?

1. Available tests and test principle
   - Immunoluminometric assay (LIA) or an automated chemiluminescence sandwich immunoassay (BRAHMS Copeptin proAVP Kryptor by ThermoFisher Scientific, CE marked) developed by Morgenthaler et al in 2006.[6] 50 µL of serum or plasma (EDTA or heparin) is needed for the measurement of copeptin, no preanalytical procedures are required. The copeptin assay has a lower detection limit of 0,69 pmol/L. Intra- and interassay coefficient of variation (CV) are shown in Table 3. The kit has a calibration stability of 15 days and an onboard stability of 29 days.[3]

CONCENTRATION RANGE	INTRA-ASSAY CV %	INTER-ASSAY CV %
2.0 – 4.0 PMOL/L	< 15.0	< 18.0
4.0 – 15.0 PMOL/L	< 8.0	< 10.0
15.0 – 50.0 PMOL/L	< 4.0	< 5.0
>50.0 PMOL/L	< 3.0	< 5.0
OUT OF RANGE SAMPLES (> 500 PMOL/L)	< 4.0	< 6.0

Table 3: *Intra- and interassay variability of Copeptin proAVP Kryptor by ThermoFischer Scientific*

   - Sandwich enzyme-linked immunosorbent assay (ELISA) kit with a detection limit of 0.024 ng/mL and an interassay CV of 12% (EASTBIOPHARM, Hangzhou Eastbiopharm Co. Ltd.)

2. Clinical utility of copeptin:

As a more stable surrogate biomarker of AVP release, the clinical utility of copeptin of differentiating polyuria and water balance disorders has been demonstrated in a number of studies. Although the indirect water-deprivation test is considered the current reference standard for the evaluation of DI, direct measurement of saline or arginine stimulated copeptin was shown to be more accurate than the water-deprivation test. A useful diagnostic algorithm to help guide clinicians to use a copeptin-based diagnostic approach is displayed in Figure 2. Expert consultation is still needed due to the fact that patients with psychogenic polydipsia will either have a normal response to water deprivation or, in long-standing cases, show a pattern suggestive of mild nephrogenic DI and mixed forms of DI can exist, and both central and peripheral DI may be incomplete, complicating the interpretation of results.
With implementation of copeptin, the test protocol can be greatly simplified. The majority of patients preferred the hypertonic saline stimulation with copeptin measurements over the classical water deprivation test, despite the fact that side effects were slightly more common in the hypertonic saline test phase.[18]

For the use in cardiovascular disease further studies are required to convincingly establish a clinically relevant increase in diagnostic performance that would then justify routine clinical use of copeptin. In settings where a conventional cTn assay is available, the use of the dual-marker strategy is recommended for the rapid rule-out of AMI. In settings where a hs-cTn is used, the added value of copeptin seems limited and, it is unlikely that simultaneous measurement of copeptin and hs-cTn can be cost-effective. Interestingly, copeptin in combination with the NIHSS-score improved the predictive power[32] and improved the risk reclassification (CoRisk score) in every second patient.[34] The practical use in routine clinical setting must be further evaluated. In all other settings, further investigation for the clinically relevant use are required that would justify routine clinical use of copeptin.

There are some limitations in the measurement of copeptin:
- Influence of comorbidities and several diseases
- The use of AVP receptor antagonist therapy
- Ectopic bronchial carcinoma may lead to copeptin secretion

- Circulating antianimal antibodies in patients exposed to animal antigens

3. Cost of copeptin assay

When using the copeptin proAVP assay from ThermoFisher and counting for an expected monthly request rate of 2 to 3, we estimate a monthly reagent cost of €108,3-151,6 (VAT included). This number is based on 2 to 3 samples with addition of one control level for each analyzed sample and a semimonthly calibration rate[3] with one control after each calibration. When adding personnel cost, we estimate a monthly cost of €240,3-316,6. An added cost for controls and calibrator needs to be taken into account.

Administration of L-arginine-hydrochloride (21%) for the arginine induced stimulation of copeptin is available for € 4,68 (VAT included). A 500 ml 0,9% sodium chloride solution costs less than €2,00. When comparing an arginine stimulation test to a water deprivation test, the reduced length of stay in the hospital, paired with a reduced personnel cost, is another advantage.

Product	Cost (VAT excl.)	+ 21% VAT
BRAHMS Copeptin pro AVP reagent kit (50 determinations)	€ 895	€ 1082,95
BRAHMS Copeptin pro AVP Calibrator kit (6 vails)	€ 220	€ 266,20
BRAHMS Copeptin pro AVP Control kit (2 levels, 3 vails for each level)	€ 280	€ 338,80

Table 4: Cost copeptin proAVP Kryptor by ThermoFisher Scientific. (Thermo Fisher Diagnostics)

TO DO/ACTIONS

1) Consideration and review of the feasibility of implementing the copeptin assay in LAG UZ Leuven.
2) Reimbursement for copeptin test in polyuria polydipsia syndrome RIZIV.

ATTACHMENTS

Attachment 1

Protocols (in)direct water deprivation with AVP or copeptin measurements

TEST	DESCRIPTION
Indirect water deprivation[16]	As is standard for the water-deprivation test, a 17-hour fluid restriction started at midnight, or at 6 a.m., in patients with known or suspected complete diabetes insipidus. Every 2 hours, vital signs and body weight were monitored, and urine was collected for measurement of volume and osmolality. Blood samples were obtained at 8 a.m. and immediately before the administration of desmopressin (1 hour before the end of the test). For safety reasons, the water-deprivation test was stopped early in patients who met one of the following criteria: a decrease in body weight of more than 3%, symptoms of orthostatic hypo- tension with an increase in heart rate or a de- crease in mean arterial blood pressure of more than 15%, or an increase in plasma sodium level of 150 mmol or more per liter. At 4 p.m., or when the test was stopped, each patient received 2 µg of desmopressin intravenously, and a final urine specimen for osmolality measurement was Results according to the protocol of Miller et al.
Direct water deprivation[14]	Fluid intake was stopped at 2400 h for a total period of 16 h to reach the osmotic endpoints necessary for a robust osmotic stimulation of AVP release. At 1600 h, all subjects received an iv injection of 4 µg desmopressin and were allowed to drink up to 0.5 liter of mineral or tap water. In patients, the test was finished at 1900 h, and in controls the final samples were collected 60 min after the desmopressin injection.
Modified water deprivation[15]	All patients underwent a standardized water deprivation test starting at 0800 h, without prior fluid restriction, according to the Robertson et al. protocol, as long as baseline plasma sodium did not exceed 147 mmol/L. The test was stopped when plasma sodium exceeded 147 mmol/L. If plasma sodium levels increased greater than 147 mmol/L or were greater than 147 mmol/L at baseline, and urine osmolality remained less than 300 mmol/kg H_2O, the test was discontinued and a desmopressin challenge (2 µg i.v was performed). Urine osmolality was measured before and 1 hour after desmopressin injection. If plasma sodium did not exceed 147 mmol/L by thirsting alone by 1300 h, patients received a 3% saline infusion at 0.1 mL/kg body weight/min and blood

	was sampled every 30 minutes thereafter for measurement of plasma sodium, osmolality, AVP, and copeptin. The test was terminated when plasma sodium exceeded 147 mmol/L.
Hypertonic saline infusion[16]	Hypertonic saline is given as a bolus dose of 250 ml over 10–15 min, followed by a slower infusion rate of 0.15 ml/kg/min. Serum sodium and osmolality are measured every 30 min and the infusion is terminated once the serum sodium was >150 mmol/L. At this point, copeptin is measured and the patient is asked to drink water at 30 ml/kg within 30 min followed by an intravenous infusion of 5% glucose at 500 ml/h for one hour. Serum sodium is once more measured to ensure its return to normal values.
Arginine stimulation	After an overnight fast of 8h and fluid restriction of 2h. L-arginine-hydrochloride 21% at a dose of 0,5 g/kg bodyweight, diluted in 500 mL of 0,9% sodium chloride solution was infused over 30 minutes.

Attachment 2: [20]

TABLE 2 Studies evaluating copeptin as a prognostic parameter in community-acquired pneumonia (CAP)

Study	Patients n	Design	End-point	Copeptin cut-off pmol·L^{-1}	AUC	Comments on prognostic value of copeptin
MULLER [80]	373	Prospective, CAP in ED	6-week mortality	53	0.68	Independent of PSI score, superior to CRP, PCT
KRUGER [81]	589	Prospective, in- and outpatients with CAP	28-day mortality	29	0.86	Independent of CRB-65 score, predicted shock or mechanical ventilation
MASIA [82]	173	Prospective, in- and outpatients with CAP	28-day mortality	19	0.75	Independent of PSI score, predicted ICU admission/complications
SCHUETZ [78]	925	Prospective, CAP in ED	Combined death, ICU admission, empyema within 30 days	36	0.70	
KRUGER [79]	1740	Prospective, in- and outpatients with CAP	28-day mortality	29	0.84	Superior to CRB-65, CRP, PCT
KOLDITZ [84]	51	Prospective, hospitalised CAP	Combined 7-day mortality/ICU admission	35	0.81	Superior to CRB-65 score, proADM, PCT; Improved 2007 ATS/IDSA minor criteria
			Clinical instability on day 4	25	0.74	

AUC: area under the curve; ED: emergency department; PSI: Pneumonia Severity Index; CRP: C-reactive protein; PCT: procalcitonin; CRB-65: confusion, respiratory rate ⩾30 min^{-1}, blood pressure <90/⩾60 mmHg, age >65 years; ICU: intensive care unit; proADM: proadrenomedullin; ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America.