# Hyponatremia - Early differential diagnosis, management and prognosis

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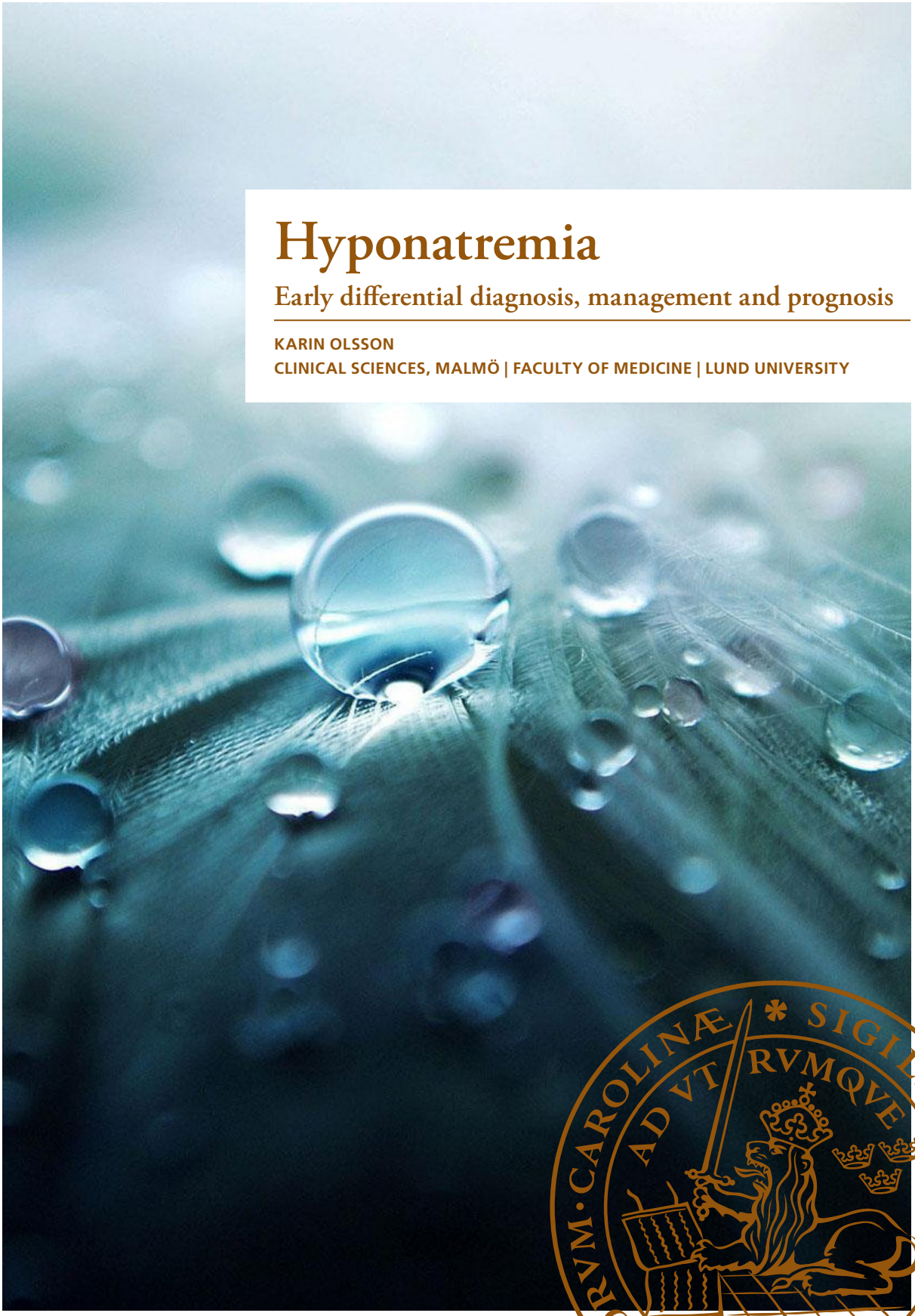

# Hyponatremia

## Early differential diagnosis, management and prognosis

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CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

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**KARIN OLSSON** works at the Department of Endocrinology, Skåne University Hospital. Hyponatremia is the most common electrolyte disturbance. This thesis examines the epidemiology of hyponatremia and current routine management. New methods are examined for evaluation of volume status using biomarkers and bioreactance measurement. The results indicate that MR-proANP, apelin and bioreactance measurement may be valuable in early management. Hyponatremia is a risk factor for future cardiovascular disease and all-cause mortality even at mild levels near the reference interval.

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Karin Olsson

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UNIVERSITY

DOCTORAL DISSERTATION

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**Abstract**

Hyponatremia is the most common electrolyte imbalance. It is associated with increased morbidity and in-hospital mortality. An effective early management is dependent on knowledge of epidemiology in the current population, accurate assessment of patient volume status and efficient diagnostic investigation.

I) Prevalence of hyponatremia was investigated in an unselected population presenting to the Emergency department. Four groups of hyponatremia severity were established: Group 1: P-Na <120mM, Group 2: 120-124mM, Group 3:125-129mM, Group 4:130-134mM and 100 patients from each group were included. (Patients in Group 2-4 matched to Group 1 for age, gender, ER visit calender month.) Hyponatremia (P-Na <135mmol/L) was identified in 3% of the entire emergency population. Leading etiologies being SIADH and thiazide diuretics. Patients in Group 1 were 3.6 times (CI95%:1.9-6.8) more likely to be on thiazide diuretics compared to Group 4. Only 31 % of patients in Group 1 was evaluated with basic laboratory investigation (P-osm, U-osm, U-Na).

II) Initial treatment of hyponatremia is based on clinical evaluation of patient volume status, but an accurate assessment is difficult, particularly differentiating between hypovolemia and euvolemia. Biomarkers were evaluated in the diagnosis (MR-proANP, MR-proADM, copeptin, proET-1, NT-proBNP). A total of 81 patients were included and a well substantiated volume status could be determined in 72 patients. A significant association was observed between MR-proANP and volemic state (p=0.0001). Using logistic regression, MR-proANP was significantly related to euvolemia in multivariate backward elimination model (OR:2.45 per SD of MR-proANP, 95% CI 1.22-4.91, p=0.012.) Copeptin levels were not associated with a diagnosis of SIADH or volemic state.

III) Further study on early management and differentiation between patient volume groups were performed using Apelin, urine-metoxycathecholaminer and bioreactance measurement of stroke volume index (SVI) after passive leg raise test. An increase in SVI ≥ 10% was defined as a sign of volume responsiveness (i.e hypovolemia). Blood and urine samples were analysed at baseline and during infusion of isotonic sodium chloride (1000ml/10h) 4h, 12h, 24h and daily until discharge. In total 8 patients were included (4 hypovolemic, 4 euvolemic), median P-Na 120 mM, 79 years of age. Apelin was significantly higher in hypovolemic patients (299 vs 175 ng/ml, p=0.021). All hypovolemic, but no euvolemic patients had a level >250 ng/ml. All patients in the hypovolemic group increased their stroke volume after passive leg raise.

IV) The aim of this study was to examine prevalence of hyponatremia in a large community-based cohort and association with future morbidity and mortality. In total, 22 267 individuals from the Malmö Preventive Project (MPP) cohort were included. Median follow-up time 34 years. Hyponatremia (S-Na<135mM) was observed in 166 subjects (0.7%). Hyponatremia was associated with increased all-cause mortality after adjusting for cardiovascular risk factors even when comparing “borderline” hyponatremia (S-Na 135-136) with normonatremia, HR 1.332 (1.184-1.499) p<0.001. There was also an association between hyponatremia and incident coronary artery disease (CAD) both with hyponatremia and borderline hyponatremia (e.g.S-Na135-136mM), HR:1.320 (1.127-1.545), p=0.001.

Conclusions: The results of the papers included in this thesis, indicate that MR-proANP, apelin and bioreactance measurement may be valuable in early management of hyponatremia, especially determination of patient volume status. Hyponatremia is a risk factor for future cardiovascular disease and all-cause mortality even at mild levels near the reference range.



**Key words: Hyponatremia; Copeptin; MRproANP; Apelin ; Bioreactance; Morbidity; Mortality**

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*"Hyponatremia: the final frontier.*
*To boldly go where no one has gone before."*
*Adapted from Star Trek the tv-series*

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II. Olsson K, Enhörning S, Öhlin B, Melander O. Hyponatremia in the Emergency Department: Could biomarkers help in diagnosis and treatment? *Open Journal of Emergency Medicine. 2016 (4):11-22*.

III. Olsson K, Löndahl M, Melander O, Katzman P. Bioreactance and Apelin in the management of severe hyponatremia. *Open Journal of Emergency Medicine, 2021(9):1-10.*

IV. Olsson K, Löndahl M, Katzman P, Melander O. Mild hyponatremia is associated with future cardiovascular morbidity and death: a populations-based study. *Manuscript form*

Reprints of the papers are enclosed at the end of this thesis with permission from the publishers.

# Abbreviations

| | |
|---|---|
| ACTH | Adrenocorticotropic hormone |
| ADH | Antidiuretic hormone |
| BP | Blood pressure |
| CAD | Coronary artery disease |
| CI | Confidence interval |
| CO | Cardiac output |
| CRH | Corticotropin-releasing hormone |
| CRP | C-reactive protein |
| eGFR | Estimated glomerular filtration rate |
| ELISA | Enzyme-linked immunosorbent assay |
| GnRH | Gonadotropin releasing hormone |
| Hb | Haemoglobin |
| HDL | High density lipoprotein |
| HPA | Hypothalamic–pituitary–adrenal axis |
| HR | Hazard ratio |
| MPP | Malmö Preventive Project |
| MR-proADM | Midregional proadrenomedullin |
| MR-proANP | Midregional pronatriuretic peptide |
| NaCl | Sodium chloride |
| NT-proBNP | N-terminal probrain natriuretic peptide |
| OR | Odds ratio |
| proET-1 | Proendothelin-1 |
| P-Na | Plasma sodium |
| P-osm | Plasma osmolality |
| RAAS | Renin- angiotensin-aldosterone system |
| SD | Standard deviation |
| SIADH | Syndrome of inappropriate ADH secretion |
| SSRI | Selective serotonin reuptake inhibitor |
| SV | Stroke volume |
| SVI | Stroke volume index |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TSH | Thyroid stimulating hormone |
| U-K | Urine-potassium |
| U-Na | Urine sodium |
| U-osm | Urine osmolality |

# Introduction

Hyponatremia is the most common electrolyte disturbance associated with considerable morbidity and increased mortality in patients [1][2]. The pathophysiology is complex and effective clinical evaluation demanding. Much remain unexplored and a deeper understanding of this electrolyte disturbance is needed. The aim of this thesis is to describe prevalence, patient characteristics, early evaluation and management in hyponatremia while examining new diagnostic tools.

Body water content is distributed between three major compartments: the intracellular, extracellular and vascular compartment [3].

Water can move freely across almost all cell membranes in the body. Particles that cannot pass the membrane exert an osmotic effect, moving water between compartments to achieve equilibrium. Sodium is the major extracellular solute and changes in plasma osmolality and volume is therefore often a question of sodium and water volumes. Osmolality is closely safe guarded within a narrow interval and complex hormonal-, renal-, and cardiovascular systems uphold the balance.

Despite this complex array of regulatory systems, and interconnected adaptative systems, salt-water balance can sometimes become disturbed, resulting in hyponatremia. Hyponatremia can be a sign of too much total body water in relation to sodium (hypervolemic hyponatremia), too little salt and/or water (hypovolemic hyponatremia) or a disturbed balance between salt/water volumes even though the total body water amount is normal (euvolemic hyponatremia). Even if all these different conditions result in hyponatremia the underlying pathophysiological causes and treatments differ. Effective management of hyponatremia therefore depend on an accurate determination of total water and sodium volumes.

To further develop early effective management of hyponatremia we sought a broader understanding of salt and water volume balance, its hormonal regulation, clinical evaluation and prognosis.

# Regulation of body fluid status and osmolality

Osmolality and sodium levels are regulated through several systems (Figure 1) [4-6]. Baroreceptors in the carotids and aorta, detect changes in circulating blood volume and blood pressure and activate the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS). Activation of baroreceptors decreases perfusion to the kidneys, increases reabsorption of sodium and water in the kidney and increases thirst. Changes in osmolality and blood volume stimulate secretion of vasopressin from the pituitary gland. The hormone mediates vasoconstriction and reabsorption of water in the kidneys. Stimuli from the central nervous system also affect vasopressin secretion, for example nausea and pain and natriuretic peptides (including brain natriuretic peptide, BNP) are excreted from the cardiac atrium as response to dilatation of the heart, causing increased natriuresis (excretion of sodium through the kidneys).

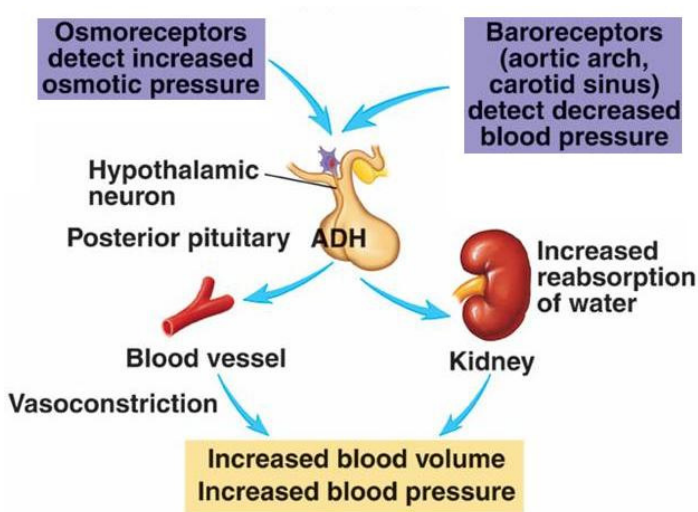


**Figure 1. Vasopressin effects.** (Copyright McGraw-Hill Companies Inc.)

# Vasopressin

Vasopressin, the key hormone in regulating body water homeostasis, has existed for over 700 million years and has been identified in diverse organism such as worms, insects, fish and mammals [7]. Peptides vary by only a few amino acids exhibiting a remarkable stability (Figure 2). This could be conceived as a sign of how critical preservation of water homeostasis has been since the early dawn of multicellular organisms.

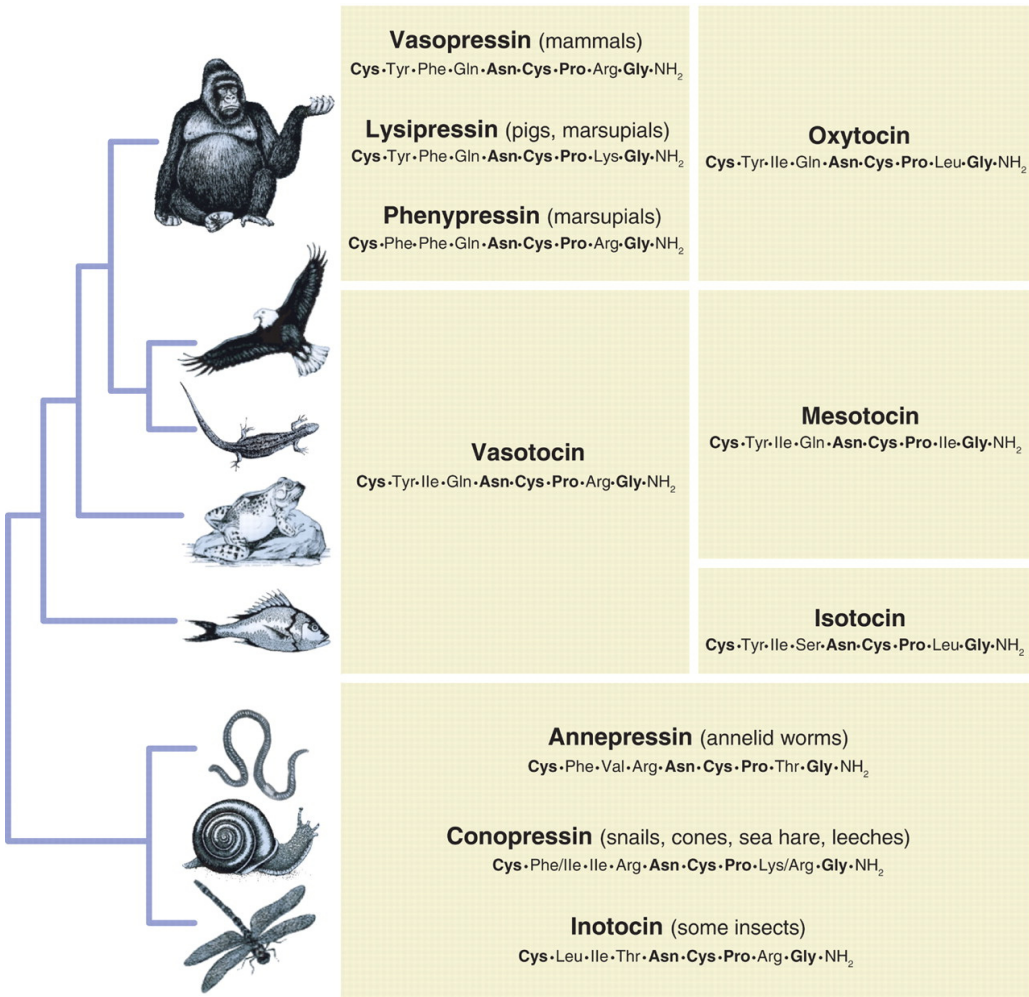


**Figure 2. Evolution of vasopressin**

Vasopressin and oxytocin homologes existed over 700 million years ago and has been identified in diverse organisms. Peptides vary by only few amino acids exhibiting a remarkable stability over evolution. (Donaldson et al Science 2008)

## Vasopressin and copeptin

Vasopressin (also called Arginine Vasopressin or antidiuretic hormone, ADH) is synthesized in the supraoptic and paraventricular nuclei in the hypothalamus [8][9]. Secretory granules containing the pre-hormone, preprovasopressin, migrate down the axons in the pituitary stalk into the posterior lobe of the pituitary gland. Here they are stored until the appropriate stimuli. During transport the prohormone undergoes enzymatic cleavage. Some secretory granules produced in the paraventricular nuclei enter the cerebrospinal fluid and portal capillaries in the median eminence (Figure 3).

Preprovasopressin is cleaved during axonal vesicular transport into vasopressin (AVP), neurophysin II and copeptin (Figure 4).

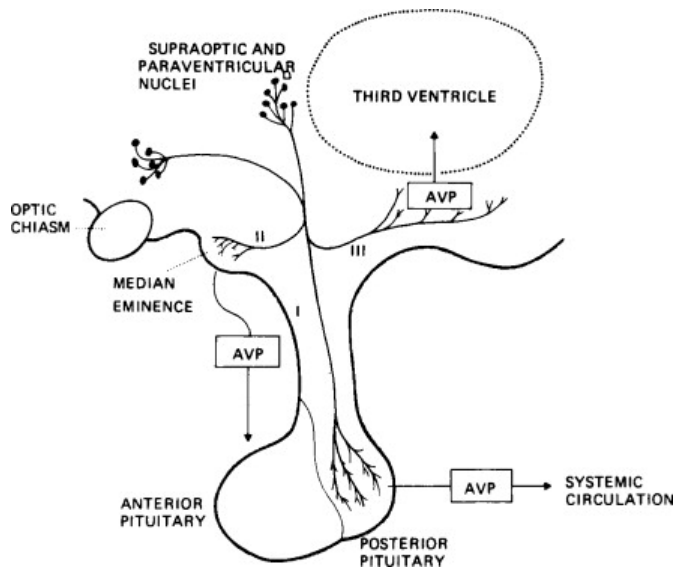


**Figure 3: Neuronal pathways of vasopressin secretion in the hypothalamus and posterior pituitary.** Vasopressin is synthesized in supraoptic and paraventricular nuclei of the hypothalamus. Secretory granules travel via three pathways. The major tract terminates in the posterior pituitary lobe (I), the other two supplies the median eminence (II) and the floor of the third ventricle (III). (Copyrigth Baylis and Robertson, 1980).

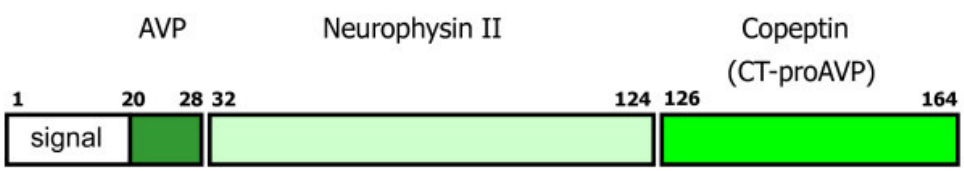


**Figure 4: Preprovasopressin**.(Copyright Creative Commons. Morgenthaler, BMC Medicine 2012.)

Vasopressin is unstable in vitro, largely attached to platelets, making it difficult to analyse reliably. The hormone has a short half-life in circulation of 15 minutes and is rapidly metabolized in the liver and kidney. Copeptin the C-terminal portion of preprovasopressin is a 39-aminoacid glycoprotein which is believed to play a role in the intracellular transport and enzymatic maturation of preprovasopressin [10]. It is released from the posterior part of the pituitary gland equimolar to vasopressin. Unlike vasopressin, copeptin is stable and can be measured reliably making it ideal as a surrogate marker for vasopressin.

## Vasopressin and body fluid balance

*Osmoreceptors*

The major stimuli for vasopressin secretion are hyperosmolality and effective circulating volume depletion. In general, the plasma sodium concentration is the primary osmotic determinant and thus has the primary influence on vasopressin secretion [11].

Osmoreceptors located in the supraoptic nuclei of the hypothalamus are activated by alterations in the osmotic gradient between plasma and intracellular content [12]. They are extremely sensitive and react to changes in plasma osmolality of as little as 1% (Figure 5). Plasma osmolality is normally kept within a narrow span and does not vary more than 1-2% despite wide fluctuations in water intake. The osmotic threshold for vasopressin secretion is about 280 mOsm/kg. Above this level there is a swift and linear rise in vasopressin secretion resulting in water retention. (Figure 5). Below the osmotic threshold there is only low levels of circulating vasopressin and the urine is maximally diluted. The system is effective and after a large water intake more than 80% of excess water is excreted within 4 hours [13].

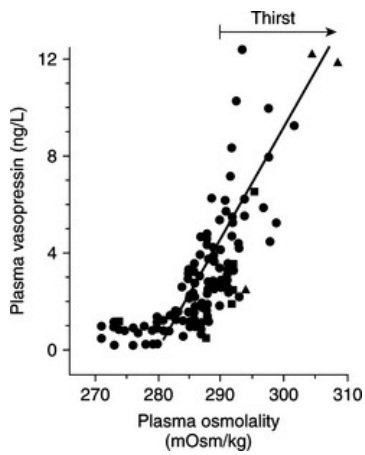


**Figure 5. Relationship of plasma vasopressin concentration to plasma osmolality.**
(Copyright Robertson GL Am J Med 72:339, 1982)

Osmoreceptors also exist in the upper small bowel but are believed to primarily be associated with regulation of thirst [14]. However, the ingestion of hypertonic sodium chloride solution leads to an increase in vasopressin secretion. This response can be prevented in experimental models by lesions in the splanchnic nerves [15].

*Baroreceptors*

Parasympathetic afferent baroreceptors located in the carotid sinus and aortic arch affect the vasomotor center in the medulla and subsequently vasopressin secretion by neurons in the paraventricular area of the brain. Receptors also exist in the left atrium, but these are less important in humans than other animals [11].

Baroreceptors function as pressure receptors thus reacting to decreases in mean arterial pressure. The sensitivity in baroreceptors is different from that of osmoreceptors. Acute small decreases in circulating volume has little effect on vasopressin secretion and instead stimulate renin and norepinephrine increase. However once hypotension occurs there is a marked rise in vasopressin secretion to even higher levels than induced by hyperosmolality (Figure 6).

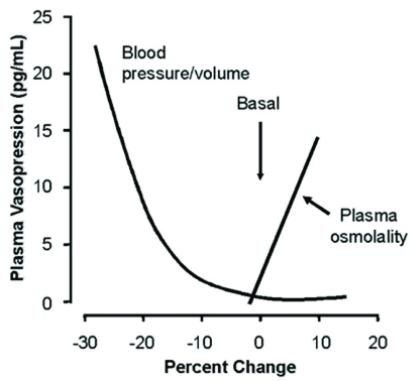


**Figure 6. Decreases in active circulating volume stimulate vasopressin secretion.**
(Copyright Stricker et al, Fundamental Neuroscience 2nd ed 2003;1011-1029.)

*Interaction osmoreceptors-baroreceptors*

Input from osmoreceptors and baroreceptors converge in supraoptic and paraventricular nuclei. Volume depletion potentiates vasopressin secretion in response to concomitant hyperosmolality (Figure 7). At the same time stimulatory input from baroreceptors can prevent normalization of vasopressin when plasma osmolality is normal, leading to water retention and hyponatremia.

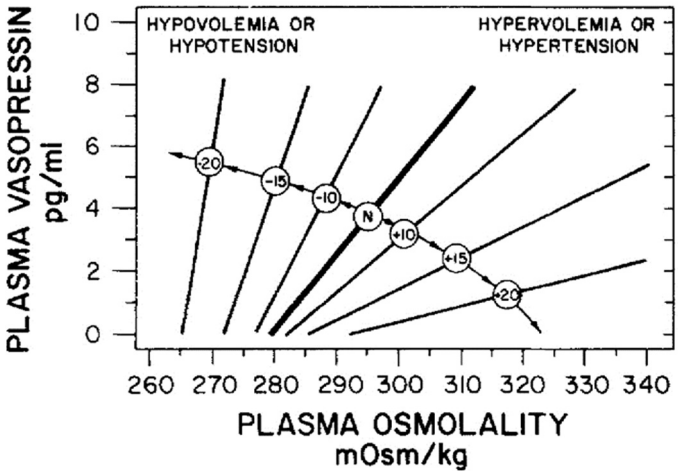


**Figure 7. The influence of hemodynamic state on osmoregulation.**
Both the slope of the curve and the osmotic threshold for vasopressin secretion is affected by volume status. (Copyright Robertson GL et al. Kidney Int. 1976.)

*Thirst*

In addition to hyperosmolality and volume depletion thirst plays an important part in the regulation of total body fluid. The osmotic threshold for thirst is higher than that for vasopression secretion (Figure 5). It is controlled by receptors centrally.

Thirst is one of the most powerful behavioural drives in humans. It increases rapidly at plasma osmolality levels above 290 mOsm/kg, becoming very intense around 300 mOsm/kg. Ingestion of water leads to a suppression of thirst and vasopressin withing 10-20 minutes *before* a reduction in plasma osmolality [16][17]. This response is physiologically appropriate since there is a delay before ingested water is absorbed. If stimulation of thirst and vasopressin secretion prevailed uninterrupted until normalization of osmolality, overcompensation and hypoosmolality would ensue. Oropharyngeal mechanoreceptors are stimulated by swallowing large volumes of fluid leading to cessation of thirst by signals to the median preoptic nucleus in the lamina terminalis [18]. Acid-sensing taste receptor cells on the tongue, the sour taste sensors, also respond to water ingestion [19].

Osmoreceptors in the small bowel and liver also regulate thirst. However, much is still unknown when it comes to thirst regulation.

*Other factors affecting vasopressin secretion*

Nausea is one of the strongest stimuli for vasopressin secretion and can increase levels up to 500 times. Pain and stress, for example in a postoperative setting, is also known to stimulate elevated vasopressin levels persisting for days [8][9].

Pregnancy lowers the osmoreceptor threshold for vasopressin release and thirst. Elevated circulating levels of Angiotensin II is detected by Angiotensin II receptors in the hypothalamus [20].

## Effects of vasopressin

Secretion of vasopressin leads to vasoconstriction, water reabsorption in the kidney and platelet aggregation [21].

There are two major receptors for vasopressin: $V_1$ and $V_2$. Activation of $V_1$-receptors in the kidneys, brain, liver, and smooth muscle cells leads to vasoconstriction, prostaglandin release, platelet aggregation, glycogenolysis and gluconeogenesis [22]. The $V_{1b}$-receptor is expressed in the anterior pituitary resulting in release of adrenocorticotropic hormone (ACTH) in response to vasopressin stimulation. The vasopressin induced release of ACTH is resistant to glucocorticoid feedback inhibition as seen in the CRH-ACTH-cortisol axis. $V_2$-receptors mediate an antidiuretic response in the kidney.

## Vasopressin and the metabolic syndrome

Vasopressin plays a role in the pathophysiology of the metabolic syndrome (Figure 8) [23]. Activation of the hypothalamic-pituitary-adrenal axis along with CRH (corticotropin-releasing hormone) may have a role in the pathogenesis of insulin resistance and metabolic syndrome. Vasopressin acts as an amplifier of ACTH release from the anterior pituitary [24][25]. Vasopressin also stimulates cortisol release directly by activation of $V_{1b}$-receptors in the adrenal cortex. Cortisol causes insulin resistance, stimulates glucagon secretion and glycogenolysis and induces a stress-related increase in appetite.

Vasopressin also activates $V_{1b}$-receptors in the adrenal glands to increase epinephrine levels and $V_{1a}$-receptors in the liver stimulating glycogenolysis. The secretion of glucagon is increased through $V_{1b}$-receptors on α-cells in the pancreas and insulin release from β-cells in the presence of glucose is potentiated [26][27]. Osmotic stimulation of vasopressin by infusion of hypertonic NaCl results in a higher hyperglycemic response in an oral glucose challenge [28].

Vasopressin is associated with diabetes and triglyceride levels [29]. Elevated copeptin concentrations independently predict diabetes and abdominal obesity [30][31].

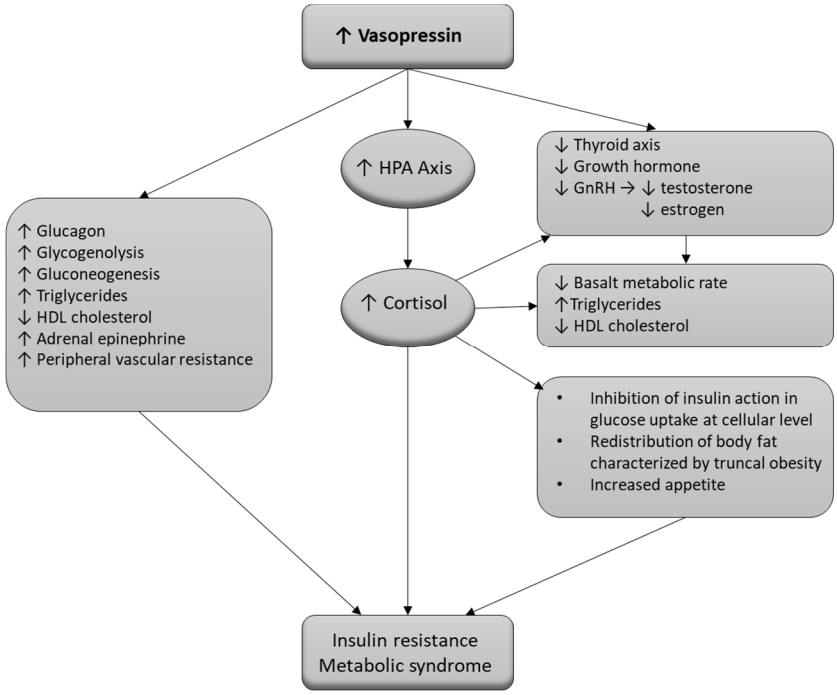


**Figure 8. Vasopressin and the metabolic syndrome.**
(Copyright Adapted by the author from Saleem et al. J Clin Endocrinol Metab 2009)

# Apelin

Apelin is another hormone involved in the regulation of plasma osmolality and fluid balance. Apelin is co-localized with vasopressin in hypothalamic neuron and receptors for both hormones are expressed by the same cells [32][33]. Apelin counteracts the effects of vasopressin leading to increased aquaresis, decreased thirst and decreased vasopressin secretion. Increased plasma osmolality simultaneously raises plasma vasopressin levels and decreases plasma apelin levels in control subjects.

Apelin is not only synthesized by cells in the central nervous system, but also in the upper gastrointestinal tract, lungs, heart, and kidneys. It is produced in mammary glands and expression increases up to 20 times during pregnancy and lactation. Obese patients with hyperinsulinemia have a large secretion from adipose tissue.

The preprohormone of apelin undergoes enzymatic cleavage into active forms of apelin. The 36-amino-acid apelin appears to be the parent peptide but different apelin forms have different receptor binding affinities and cause different intracellular reactions after binding with the apelin receptor. The apelin receptor is a G protein-coupled receptor and can be found in different parts of the body; central nervous system (hypothalamus, basal ganglia, cortex), gastrointestinal tract (pancreas, stomach, duodenum, jejunum), cardiovascular system (cardiomyocytes, vascular endothelial and smooth muscles) liver, lungs, kidneys and mammary glands [34].

## Vasopressin and apelin in aging

The elderly have an increased risk of dehydration due to decreased fluid intake but also increased fluid losses. An aging kidney has a decreased ability to concentrate urine and a resistance to the effect of vasopressin on the kidney. Thirst sensation itself is reduced [35].

The normal aging process also affects vasopressin and apelin secretion. Vasopressin levels are increased, and plasma apelin levels are decreased. When the neuron is stimulated by changes in osmolality vasopressin and apelin levels are static [36].

# Hyponatremia

## Epidemiology

Hyponatremia is the most common disturbance of electrolyte and water homeostasis, with a reported prevalence of up to 30% in hospitalized patients [37][38]. Severe hyponatremia (P-Na<120 mmol/L) is seen in 1% of patients. Prevalence increases with age. Different aetiologies can dominate in different clinical settings. It is therefore important to be familiar with the epidemiology in the specific current environment. Several different conditions and diseases can cause hyponatremia. The most common cause of hyponatremia in hospitalized patients is SIADH (syndrome of inappropriate ADH secretion) but heart failure, treatment with diuretics and cancer are also important etiologies (Table 1). SIADH is characterized by an inappropriate vasopressin secretion in relation to plasma osmolality. It can be caused by cancer (sometimes through ectopic vasopressin production) or drugs (for example carbamazepine and SSRI). A specific treatment for SIADH exists, vasopressin receptor antagonists, also known as vaptans.

| Cause | Specific disorder |
|---|---|
| Central nervous system disorders | Vascular diseases (thrombosis, embolism, hemorrhage, vasculitis)<br>Trauma (subdural hematoma, subarachnoid or intracranial hemorrhage)<br>Tumor<br>Hydrocephalus<br>Infection (meningitis, encephalitis, brain abscess)<br>Acute intermittent porphyria<br>Lupus erythematosus<br>Postoperative transsphenoidal hypophysectomy<br>Schizophrenia |
| Neoplasms with ectopic hormone production | Small-cell carcinoma of the lung<br>Pharyngeal carcinoma<br>Pancreatic carcinoma<br>Thymoma<br>Lymphoma, Hodgkin's disease, reticulum cell sarcoma<br>Bladder carcinoma |
| Pulmonary disease | Pneumonia<br>Lung abscess<br>Bronchiectasis<br>Tuberculosis |
| *Drugs* | |
| Endocrine disease | Pituitary tumor<br>Hypothyroidism<br>Adrenal insufficiency |
| Other | Positive pressure ventilation<br>Acquired immune deficiency syndrome<br>Idiopathic SIADH of the elderly |

**Table 1. Causes of hyponatremia** (Copyright Josiassen et al Expert Opin. Pharmacother. 2010).

# Management

All algorithms for diagnosis and treatment of hyponatremia are based on an early correct evaluation of volume status (Figure 9) [39]. A euvolemic patient with urinary-sodium (U-Na) above 40 mOsm/kg needs water restriction and maybe vasopressin receptor antagonists (vaptans). A hypovolemic patient with U-Na > 40 mOsm/kg should be given extra fluids, for example infusion of isotonic sodium chloride. Evaluation of volume status is key to early management.

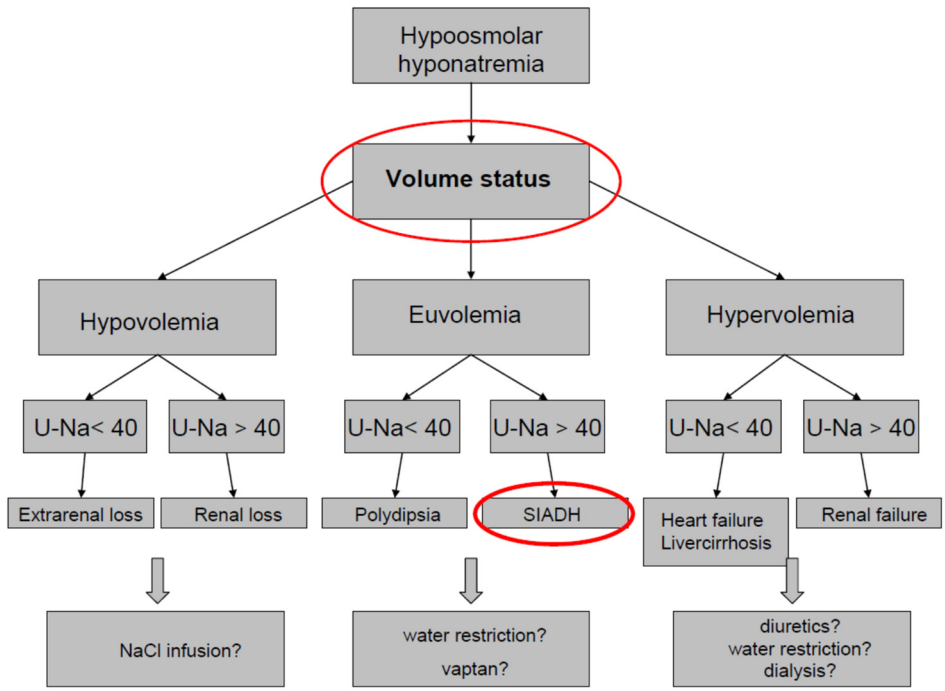


**Figure 9**. **Diagnostic algorithm for hyponatremia.** (Paper II) (Copyright Olsson K et al OJEM 2016).

# Morbidity and mortality

Patients with hyponatremia, even of mild to moderate severity, have an increased in-hospital mortality compared to normonatremic controls [40]. Hyponatremia has been associated with an increased mortality in conditions such as pneumonia, heart failure, acute myocardial infarction and cancer [41-43]. These studies have however not been able to determine whether hyponatremia contributes directly to the poor outcome or if it is just a marker of severity of underlying comorbidities. Correction

of hyponatremia at discharge decreased the odds of 30-day readmission or death in a study by Donzé et al. on patients with congestive heart failure [44]. No randomized studies exist and it is not known if the results may have been impacted by selection bias or if the population of heart failure patients are representative for patients with hyponatremia at large.

# Evaluating patient volume status

It is difficult to evaluate patient volume status even for experienced clinicians, especially differentiating between euvolemia and hypovolemia. No golden standard exists [45-47].

Systematic analysis of publications noted a limited value of classical vital signs in determination of hypovolemia in the Emergency department [48]. Results from standardized phlebotomy studies cannot be translated to an often elderly population with concurrent illnesses, drug use, pain, nausea and stress. Severe postural dizziness may increase the suspicion for hypovolemia. However, vital signs as supine hypotension and tachycardia are lacking in most hypovolemic and dehydrated subjects. Physical signs such as dryness of the mouth, decreased skin turgor and slow capillary filling are helpful when present concomitantly (Table 2). A comprehensive clinical evaluation that considers all medical history and laboratory analysis in conjunction with physical examination remains the best strategy.

| Physical Finding | Source, y | Grade of Study | Definition of Abnormal Finding | Sensitivity, % | Specificity, % | Positive LR (95% CI) | Negative LR (95% CI) |
|---|---|---|---|---|---|---|---|
| Postural vital signs | Johnson et al,[35] 1995 | C | Pulse increment >30 beats/min | 43 | 75 | 1.7 (0.7-4.0) | 0.8 (0.5-1.3) |
| | Johnson et al,[35] 1995 | C | Postural hypotension (systolic blood pressure decline >20 mm Hg) | 29 | 81 | 1.5 (0.5-4.6) | 0.9 (0.6-1.3) |
| Skin, eyes, and mucous membranes | Eaton et al,[33] 1994 | A | Dry axilla | 50 | 82 | 2.8 (1.4-5.4) | 0.6 (0.4-1.0) |
| | Gross et al,[34] 1992 | B | Mucous membranes of mouth and nose dry | 85 | 58 | 2.0 (1.0-4.0) | 0.3 (0.1-0.6) |
| | Gross et al,[34] 1992 | B | Tongue dry | 59 | 73 | 2.1 (0.8-5.8) | 0.6 (0.3-1.0) |
| | Gross et al,[34] 1992 | B | Longitudinal furrows on tongue | 85 | 58 | 2.0 (1.0-4.0) | 0.3 (0.1-0.6) |
| | Gross et al,[34] 1992 | B | Sunken eyes | 62 | 82 | 3.4 (1.0-12.2) | 0.5 (0.3-0.7) |
| Neurological findings | Gross et al,[34] 1992 | B | Confusion present | 57 | 73 | 2.1 (0.8-5.7) | 0.6 (0.4-1.0) |
| | Gross et al,[34] 1992 | B | Upper or lower extremity weakness present | 43 | 82 | 2.3 (0.6-8.6) | 0.7 (0.5-1.0) |
| | Gross et al,[34] 1992 | B | Speech not clear or expressive | 56 | 82 | 3.1 (0.9-11.1) | 0.5 (0.4-0.8) |
| Capillary refill time | Schriger and Baraff,[36] 1991 | C | Capillary refill time greater than age- and sex-specific upper normal limit (see "Results") | 34 | 95 | 6.9 (3.2-14.9) | 0.7 (0.5-0.9) |

**Table 2. Diagnostic accuracy of physical signs for hypovolemia not due to blood loss.**

Laboratory tests can help to distinguish between hypovolemia and euvolemia. The normal response by the kidneys to hypoosmolality is to maximally dilute the urine resulting in a urine-osmolality below 100 mOsm/kg as a result of an appropriately and completely suppressed vasopressin secretion. However, vasopressin can be stimulated by volume depletion (for example gastrointestinal losses, diuretics, osmotic diuresis in diabetes, SIADH, hypothyroidism, Addisons disease or congestive heart failure) which affects urine-osmolality [49].

Urine sodium (U-Na) < 30 mmol/L in spot sample is indicative of hypovolemia, whereas U-Na>30 mmol/L is often seen in SIADH [46][50]. However, a urine sample is not always available in the acute setting, especially in dehydrated patients, and the result can be affected by sodium intake and treatment with diuretics. It is not uncommon for elderly patients with salt-depletion and SIADH to present with a low U-Na [51]. Fenske et al. observed a sensitivity of 82% but specificity of only 53% for U-Na above 30 mmol/L in SIADH [52]. A combination of fractional excretion of sodium and urea (U-Na or U-urea/U-krea) may improve the evaluation to some degree [53].

The difficulty in determining patient fluid status does not only affect the management of hyponatremic patients. In septicaemia hypotension may be fluid responsive or require inotropic drugs. Different methods have been evaluated in Critical Care use reaching recommendation from the European Society on Intensive Care Medicine for providing support in bedside diagnosis [54].

Invasive techniques can be used for diagnosis and monitoring. Thermodilution via pulmonary artery catheter is considered the “gold standard” in stroke volume (SV) and cardiac output (CO) measuring techniques. Boluses of ice-cold fluid are injected into the right atrium, and blood temperature is measured by a thermal filament on the catheter in the pulmonary artery and used to calculate SV. These methods are exact but hardly appropriate in circulatory stable hyponatremic patients in the Emergency Department. Transthoracic or transoesophageal echocardiography can be used but requires experienced users.

A passive leg raise test is a way of evaluating the effect of an artificial fluid bolus on cardiac output. The technique involves raising a patient´s legs 45° to transfer blood from the lower extremities to the thoracic cavity. This equals a fluid bolus of 200-300 ml. Studies have validated the accuracy in using the method for identifying fluid responsiveness [55]. The Frank-Starling curve depicts the relationship between preload and stroke volume. (Figure 10). If stroke volume increases > 10% after a fluid bolus the patient is fluid responsive. If stroke volume increases <10% the peak of the Frank-Starling curve has been reached and further fluid treatment will not improve cardiac output [56].

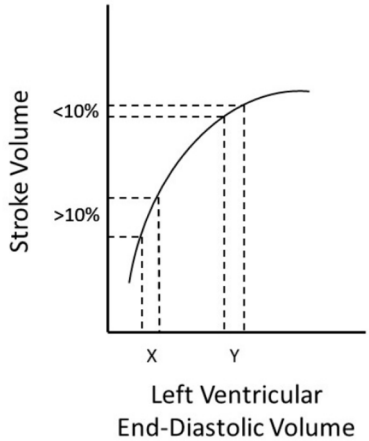


**Figure 10. Frank-Starling curve depicting the relationship between preload and stroke volume** (Copyright Russell et al. J Clin Med 2020).

# Bioreactance

Bioreactance is a bedside system designed for measurement of cardiovascular parameters. The device is connected to the patient with four double-electrodes on the chest wall (Figure 11). An alternating electric current passes between the outer electrodes and the inner electrodes sensing the resulting voltage signal (Figure 12). Comparison of the phase shift is proportional to aortic flow [57]. Heart rate, stroke volume, mean arterial pressure, cardiac output and total peripheral resistance is registered. A passive leg raise test can be performed while the difference in stroke volume index is examined. A stroke volume index increase ≥10% is considered a sign of fluid responsiveness i.e. hypovolemia.

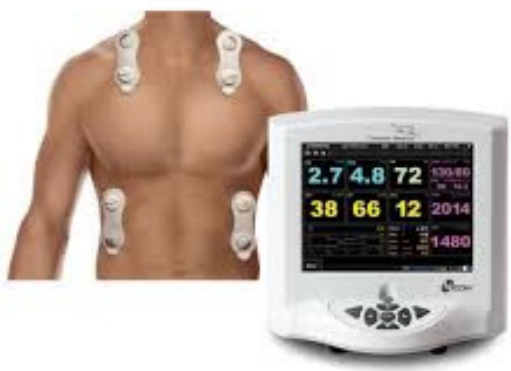


**Figure 11.** Bioreactance electrode placement and portable device. (Copyright Cheetah NICOM).

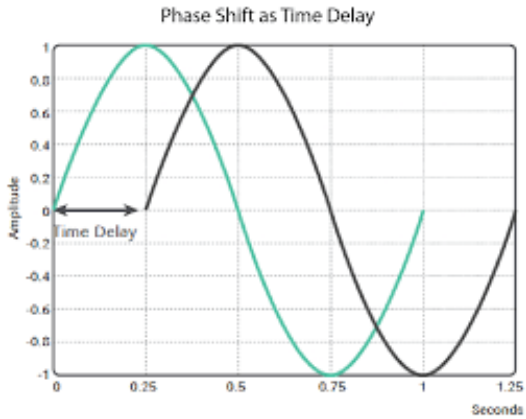


**Figure 12**. **Phase shift.** The thorax oppose the change in electrical voltage creating a time delay and thus a phase shift between the applied current and the measured voltage. The phase shift is highly correlated with aortic blood flow and stroke volume can be calculated. (Copyright Cheetah, NICOM).

# Biomarkers

## Copeptin and apelin

Copeptin has been evaluated in the differential diagnosis of hyponatremia. A low copeptin level was seen in hyponatremia due to polydipsia but could not be used to differentiate between hypovolemic and euvolemic patients [52][58].

Apelin has not previously been evaluated in determination of patient volume status or early differentiation between different etiologies behind hyponatremia.

## Natriuretic peptides

The natriuretic peptide N-terminal pro-brain natriuretic peptide (NT-proBNP) is the most extensively studied natriuretic peptide and is in widespread use in clinical practice for screening and treatment monitoring of heart failure [59].

Atrial natriuretic peptide (ANP) is found in a concentration 10- to 50-fold higher than BNP concentrations. In a small study of 40 patients by Coenraad et al, significantly lower ANP concentrations were found in hypovolemic and euvolemic patients with hyponatremia compared to controls, whereas hypervolemia was associated with higher levels [60]. Cardiovascular studies on orthostatic stress have shown a reduction in ANP concentrations following head-up tilt tests, indicating a possible effect of mild hypovolemia on ANP [61].

## Adrenomedullin

Adrenomedullin (ADM) is a potent vasodilator with natriuretic effect. It is produced in the heart, adrenal glands, lungs, kidneys and brain in response to pressure/volume strain. Higher levels of ADM have been found in cerebrospinal fluid after subarachnoid haemorrhage in patients with hyponatremia [62]. It has to our knowledge not been evaluated in determination of patient volume status.

## Endothelin-1

Endothelin-1 is a potent vasoconstrictor produced in endothelial cells and decreases sodium excretion by altering the hemodynamics of the kidneys. A small pilot study by Kamoi et al. has indicated higher levels in hypovolemic patients versus controls, but with a wide distribution [63].

# Aims

The general aim of this thesis was to gain further knowledge of the characteristics of patients with hyponatremia, from presentation to the Emergency department to the long-time prognosis. We also wanted to examine methods of differential diagnosis of hyponatremia to improve management.

I. To examine the characteristics of patients presenting to the Emergency department with various degrees of hyponatremia.
II. To examine if biomarkers can distinguish between volume states and SIADH diagnosis in early evaluation of hyponatremia.
III. To evaluate the usefulness of bioreactance measurement and apelin in early differentiation between hypo- and euvolemia in patients with severe hyponatremia.
IV. To examine the prevalence of hyponatremia in a large community-based cohort and its association with future morbidity and mortality.

# Methods

## Study Sites

Patients were recruited from the Emergency department at Skåne University Hospital (**Paper I, II, III**). The hospital, with a total of 1750 beds, serves 560 000 inhabitants with 400 visits per day to the Emergency departments. Patients from all specialities were included in the study (surgery, orthopeadics, general internal medicine, neurology).

The cohort 'Malmö Preventive Project' (MPP) was used in **Paper IV** [64][65]. This prospective community-based study was established in Malmö 1974-92 and individuals were followed until 2014. Physical examination, blood samples and a questionnaire were included in baseline evaluation. A total of 22 444 men and 10 902 women were included with an overall annual participation rate of 71%. All patients with a baseline serum sodium value in MPP were included in the study for **Paper IV**.

## Study design

### Paper I

The study was designed as a retrospective hospital record study. A laboratory database search was conducted for all patients visiting the Emergency department at Skåne University Hospital between May 2009 and Oct 2010, with a P-Na <135 mmol/L.

Patients were divided into four groups based on severity of hyponatremia: Group 1: P-Na<120 mmol/L, Group 2: P-Na 120-124 mmol/L, Group 3: P-Na 125-129 mmol/L and Group 4: P-Na 130-134 mmol/L. One hundred patients from each group were matched to Group 1 for gender, age, calendar-month of emergency room visit. Hospital records were audited, and investigations, treatments, likely underlying causes and in-hospital outcomes were registered. The study was approved by the Ethics Committee in Lund.

## Paper II

Blood samples were collected from an unselected patient population at entry to the Emergency departments at Skåne University Hospital after a written consent. Inclusions were made between Sept 2009 and May 2010. If plasma sodium was ≤125 mmol/L the sample was frozen and stored in -80°C for further analysis of biomarkers. If hyperglycaemia was present a corrected sodium level was calculated. Only patients who were admitted for in-hospital care were included to ensure sufficient foundation for subsequent evaluation. Hospital records and routine clinical analysis were audited after patient discharge, blinded for biomarker and bioreactance results.

Biomarkers of cardiovascular load (MR-proANP, NT-proBNP, pro Endothelin-1 and MR-ADM) and osmotic stress (copeptin) of interest in the pathogenesis of hyponatremia were examined. Biomarker levels were evaluated for assessment of volume status and underlying causes of hyponatremia, for example SIADH. The study was approved by the Ethics Committee in Lund.

## Paper III

Patients older than 50 years of age and serum sodium concentration of ≤ 125 mmol/L were recruited from the Emergency Department, Skåne University Hospital, Lund between June 2015-Dec 2016. Informed written consent was obtained. Patients with seizures, uncompensated heart failure, eGFR < 30 ml/min, systolic blood pressure < 90 mmHg, ongoing gastrointestinal losses, or a hemoglobin concentration below 100 g/L were excluded, as were patients who had received an intravenous infusion of sodium chloride before inclusion.

Blood, and urine samples were collected at baseline and routine treatment was then initiated with 1000ml isotonic sodium chloride over 10 h. Drugs suspected of aggravating or causing hyponatremia were withheld. Plasma and urine sodium, osmolality and biomarkers were collected at 4h, 12h, 24h and daily until discharge and stored at -80°C until analysis. Biomarkers of cardiovascular load (NT-proBNP), osmotic stress (copeptin, apelin) and mineralocorticoid status (aldosterone, renin) were evaluated. Sympathetic activity was investigated by urine methoxycatecholamine to creatinine ratio in urine fractions.

Patient volume status was examined using bioreactance measurement (Cheetah Medical, USA) in semi-recumbent position and after passive leg raise.

Clinical assessment, hospital records, biomarkers and bioreactance were evaluated after hospital discharge for assessment of volume status and underlying causes of hyponatremia. The study was approved by the Ethics Committee in Lund.

### Paper IV

In the Malmö Preventive Project (MPP) participants were subjected to baseline physical examination (including height, weight and blood pressure), blood samples were taken after overnight fast and analysed using routine methods at the Department of Clinical Chemistry, Malmö. Participants answered a comprehensive questionnaire centred on medical history, lifestyle, diet, occupation, and family history of cardiovascular disease.

The MPP participants were followed through record linkage with national registers including the National Cause of Death registers regarding in-hospital care, cardiovascular events and cause of death. Cases were retrieved through linkage with the Swedish National Hospital Discharge Register (SNHDR) and hospitalizations with associated International Classification of Diseases codes (ICD-codes) were registered.

All patients with a measured serum sodium <135 mmol/L were included in the current study. End points of all-cause mortality, incident coronary artery disease (CAD) and new onset heart failure were compared between groups with different levels of hyponatremia.

The MPP study was approved in its original form by the Ethics Committee in Lund. A complementary application for the current study was reviewed and accepted.

## Laboratory measurements

Sodium analysis was performed in venous blood either with an accredited method using ion selective electrodes on Roche Cobas c501 instrument or with the bed-side blood gas analyser Radiometer ABL 800 Flex. (**Paper I, II, III**) [66].

Mid-regional pro-atrial natriuretic peptide (MR-proANP), copeptin, mid-regional pro-adrenomedullin (MR-proADM) and pro-endothelin-1 (proET-1) were measured on fully automated immunoassay systems (Kryptor, Thermo Fisher). N-terminal pro-brain natriuretic peptide (NT-proBNP) was analysed using the Dimension RxL N-BNP (Dade-Behring, Germany). **(Paper II, III)** [10][67-71].

Apelin was analysed using ELISA (Ray Biotech Inc, Norcross GA, USA) [72][73].

Urine catecholamines were measured on liquid chromatography-mass spectrometry [74].

## Bioreactance measurement

Bioreactance measurement were performed using the NICOM system (Cheetah Medical, Portland, OR, USA) [57]. Baseline values including heart rate, stroke volume, mean arterial pressure and blood pressure, were registered with patients in a 45ºsemi-recumbent position. The device then calculated cardiac output and total peripheral resistance. A passive leg raise test was performed by lowering the head to a flat position and elevating the legs to 45º. An increase in stroke volume index (SVI=SV/body surface area) ≥10% was considered a sign of fluid responsiveness i.e. hypovolemia.

## Statistics

Data was analysed using the SPSS statistical software (version 19-25, SPSS Inc., Chicago, Ill.) Group wise differences in continuous variables were calculated with Mann-Whitney U-test and group wise differences in categorical variables were calculated using Chi-Square test or Fisher´s exact test where appropriate. A p-value $< 0.05$ was considered as statistically significant. Trends across groups were evaluated using logistic regression.

For the analysis of biomarkers, we used crude and multivariate linear regression models with backward elimination of covariates (p-value for retention $<0.10$). Due to skewed distribution biomarkers were ln-transformed before entered into the linear and logistic regressions.

Incident morbidity and mortality was analyzed using Cox regression with crude and multivariate models. In multivariate models, retained covariates were included using backward elimination (p-value for retention $p<0.10$).

# Results

## Paper I

The aim of this study was to examine the characteristics of patients presenting to the Emergency department with hyponatremia, to describe the initial investigation and management and evaluate the underlying causes of hyponatremia.

The prevalence of hyponatremia (P-Na<135 mmol/L) was 3% of all patients presenting to the Emergency departments, Skåne University Hospital. The median age was 74 years with a female predominance, 65%. P-Na values ranged between 100-134 mmol/L. Patient's chief complaint and reason for seeking medical care ranged from abdominal pain to neurological symptoms. Only a minority of patients had been referred to the hospital because of diagnosed hyponatremia. Symptoms linked to hyponatremia (fatigue, vertigo, nausea, balance disorders, convulsions and headache) was significantly more common with lower P-Na values (p for trend <0.001). All but one patient suffered from chronic hyponatremia (developed over more than 48h). Drugs known to cause hyponatremia were common in the study population.

Basic laboratory investigation (serum-osmolality, urine-osmolality and urine-sodium) was ordered in 31% (Group 1:P-Na<120 mM), 10% (Group 2: 120-124mM) and 3% (Group 3: 125-129mM). Evaluation of body fluid status was performed in 38% of patients (Group 1).

First line treatment consisted of isotonic sodium chloride infusions (60%) and/or discontinuation of predisposing drugs (28%). If treatment was altered or new modalities were added they were considered "second line" therapies. Fluid restriction (40%) and sodium chloride pills (48%) were common. The P-Na correction rate exceeded 10 mmol/L/24h in 27% of patients with P-Na<120mM.

The leading aetiologies were thiazide diuretics (17%) and SIADH (17%) (Figure 13). It was however common with multiple underlying causes of hyponatremia (Figure 14). The likelihood of being on thiazide diuretics increased with hyponatremia severity (p<0.0001). Patients in Group 1 (P-Na <120 mmol/L) were 3.6 times (CI95%:1.9-6.8) more likely to be on thiazide diuretics compared to Group 4 (P-Na 130-134 mmol/L).

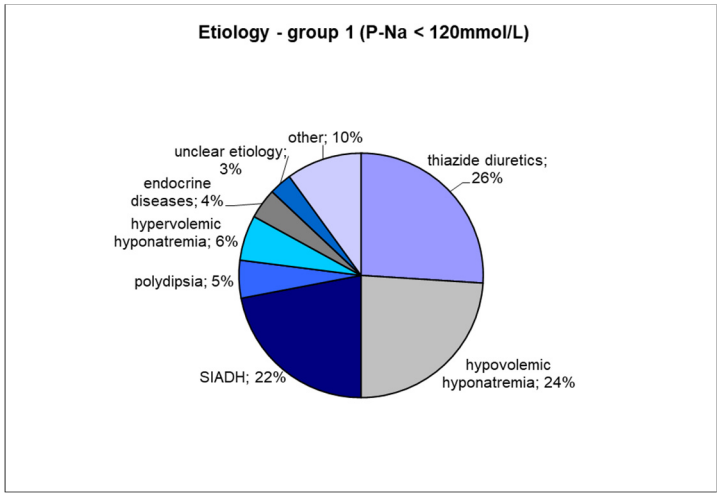


**Figure 13. Underlying causes of hyponatremia in Group 1 (P-Na <120 mmol/L).**

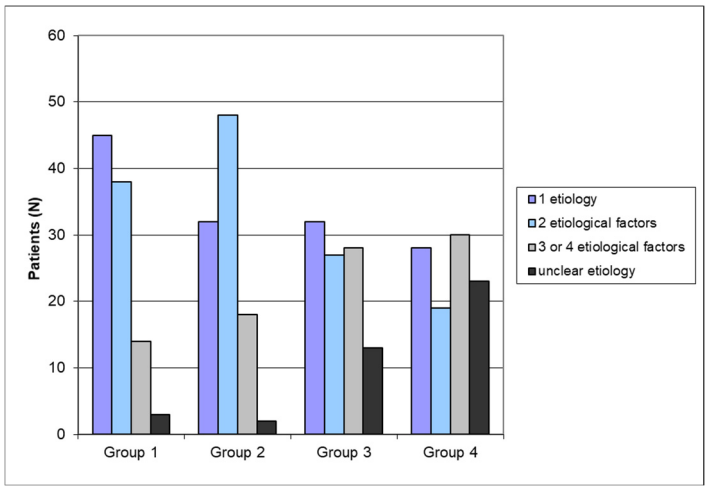


**Figure 14. Number of underlying causes in subgroups of hyponatremia.**

In hospital mortality ranged between 2-7% between groups without significant difference. Hospital length of stay increased with severe hyponatremia (p for trend<0.001).

A follow-up sodium level after discharge was planned in 55% of patients with P-Na<120 mmol/L.

# Paper II

The aim of this study was to examine the use of biomarkers in early determination of volume status and SIADH diagnosis.

A total of 81 patients were included. A well substantiated volemic state (hypo- eu- or hypervolemia) could be established in 72 patients and all analyses involving volume groups were performed in this subgroup. Hypovolemia was noted in 29%, euvolemia 53% and hypervolemia 18% of patients. The underlying cause of hyponatremia was often found to be multifactorial and the most common underlying causes were SIADH, gastrointestinal losses, diuretics and heart failure (Paper II, Table 1).

A significant association was observed between MR-proANP levels and volemic state in linear regression analysis (beta-coefficient 0.30 SD of MR-proANP per volemia class, 95% CI 0.15-0.44, p=0.0001). In a multivariate backward elimination model (entering age, gender, thiazide or loop diuretics, heart failure, cirrhosis, oedema, gastrointestinal losses and MR-proANP), MR-proANP remained significantly related to volemic state (beta-coefficient 0.18 per SD increment of MR-proANP per volemia class, 95%CI 0.04-0.32, p=0.012). The distinction between mild hypovolemia and euvolemia is clinically more challenging and data was analysed with respect to hypo- or euvolemia (n=59) using logistic regression. In crude analysis MR-proANP was significantly related to euvolemia (OR:2.54 per SD increment of MR-proANP, 95%CI 1.32-4.86, p=0.005) and remained after the multivariate backward elimination modelling (Table 3). There was however overlap in MR-proANP levels between volemic groups. (Figure 15).

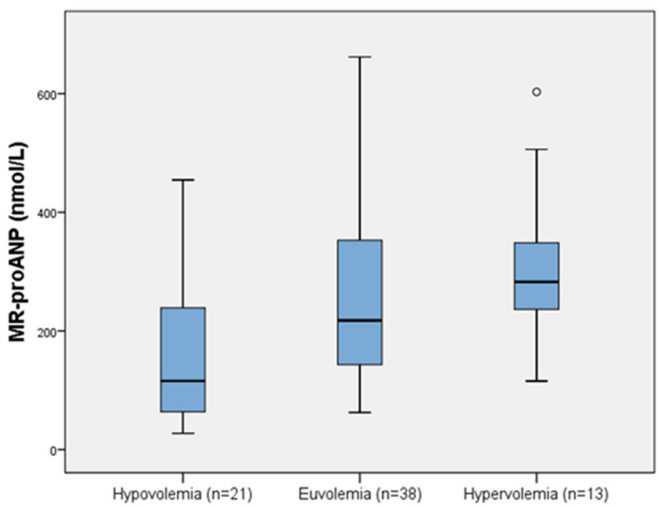


**Figure 15. MR-proANP levels in different volume status groups.**

**Table 3. Biomarkers and subdivision of hyponatremia.**

| | *Volume status* | | *SIADH vs other causes* |
|---|---|---|---|
| | **Hypo/eu/hypervolemi** (p-value)* | **Hypo vs euvolemia** (p-value)** | *(p-value)*** |
| *ET-1* | 0.352 | 0.772 | *0.457* |
| *MR-proADM* | 0.625 | 0.337 | *0.479* |
| *MR-proANP* | **p < 0.001** | **0.005** | *0.971* |
| *NT-proBNP* | **p < 0.006** | 0.159 | *0.282* |
| *Copeptin* | 0.875 | 0.371 | 0.286 |

(*crude linear regression, **crude logistic regression)

Copeptin levels were higher in patients with SIADH (31.99 pmol/L (IQR6.6-96.8)) compared to the entire study population (24.7 pmol/L (IQR 8.5-75.4) but the difference was nonsignificant (Figure 16). No linear association was found between copeptin value and volemic state.

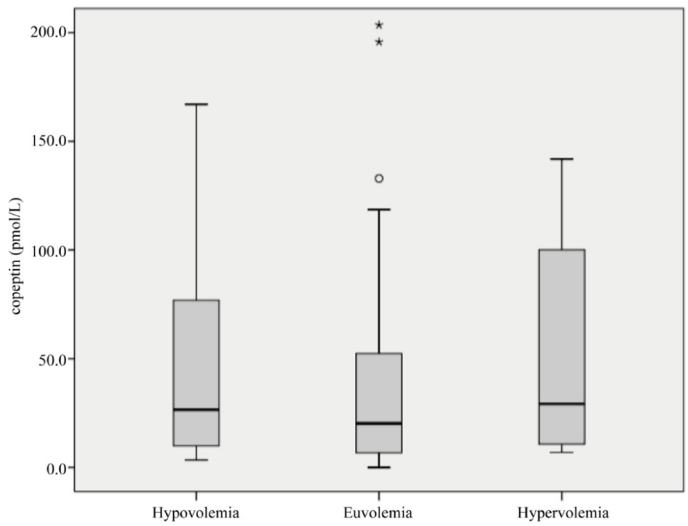


**Figure 16.** Copeptin levels in different volemic states.

# Paper III

The aim of this study was to evaluate the usefulness of bioreactance measurement and apelin in early differentiation between hypo- and euvolemia in patients with severe hyponatremia.

A total of 8 patients were included (4 hypovolemic and 4 euvolemic) (Table 4). Median age 79 (63-88) years and baseline sodium level 120 (107-123) mmol/L.

Apelin was significantly higher in the hypovolemic group 299 (265-433) ng/ml vs 175 (147-228) ng/ml in the euvolemic group, p=0.021 (Figure 17). The apelin concentration was above 250 ng/ml in all hypovolemic patients.

Copeptin was similar between volume groups (Figure 17). Copeptin to plasma sodium ratios, to examine "inappropriate vasopressin release", did not statistically significantly differ between hypo- and euvolemic patients.

There was no statistically significant difference at baseline between stroke volume, cardiac output, mean arterial pressure and thoracic fluid content in volume groups. However, all patients in the hypovolemic group increased their stroke volume after passive leg raise.

**Table 4. Baseline characteristics hypovolemia vs euvolemia.**

| | **Hypovolemia (n=4)** Value (min-max) | **Euvolemia (n=4)** Value (min-max) | p-value |
|---|---|---|---|
| Age (years) | 76 (63-88) | 80 (70-86) | 0.564 |
| Gender (female) | 4 | 2 | 0.105 |
| BP systolic (mmHg) | 145 (130-169) | 158 (150-200) | 0.191 |
| BP diastolic (mmHg) | 76 (70-80) | 103 (74-110) | 0.081 |
| Heart rate (beats/min) | 79 (60-92) | 79 (70-87) | 1.000 |
| TSH (mU/L) | 1.3 (1-4) | 1.4 (1.0-37.0) | 0.663 |
| T4 (mU/L) | 15 (12-18) | 20 (2-27) | 0.309 |
| T3 (mU/L) | 3.7 (3-5) | 3.4 (1-4) | 0.564 |
| cortisol (mmol/L) | 421 (191-821) | 540 (283-582) | 0.564 |
| ACTH (pmol/L) | 3.6 (2-12) | 5.1 (3-15) | 0.289 |
| Hb (g/L) | 122 (102-164) | 140 (128-142) | 0.386 |
| Potassium (mmol/L) | 3.9 (2.9-4.5) | 4.2 (4.0-4.5) | 0.189 |
| creatinine (mmol/L) | 101 (52-153) | 69 (45-92) | 0.248 |
| glucose (mmol/L) | 6.0 (5-13) | 6.5 (5.8-8.0) | 0.564 |
| CRP (mg/L) | 3 (1-6) | 2 (1-5) | 0.663 |
| P-osm (mOsm/kg) | 263 (261-288) | 251 (237-277) | 0.146 |
| U-osm (mOsm/kg) | 236 (204-269) | 537 (290-600) | **0.021** |
| U-Na (mmol/L) | 24 (20-34) | 82 (44-149) | **0.020** |
| U-K (mmol/L) | 24 (23-36) | 31 (19-46) | 0.724 |
| U-Methoxynorepinephrine/creatinine | 291 (191-430) | 199 (168-674) | 0.386 |
| U-Methoxyepinephrine/creatinine | 104 (54-219) | 141 (111-211) | 0.564 |

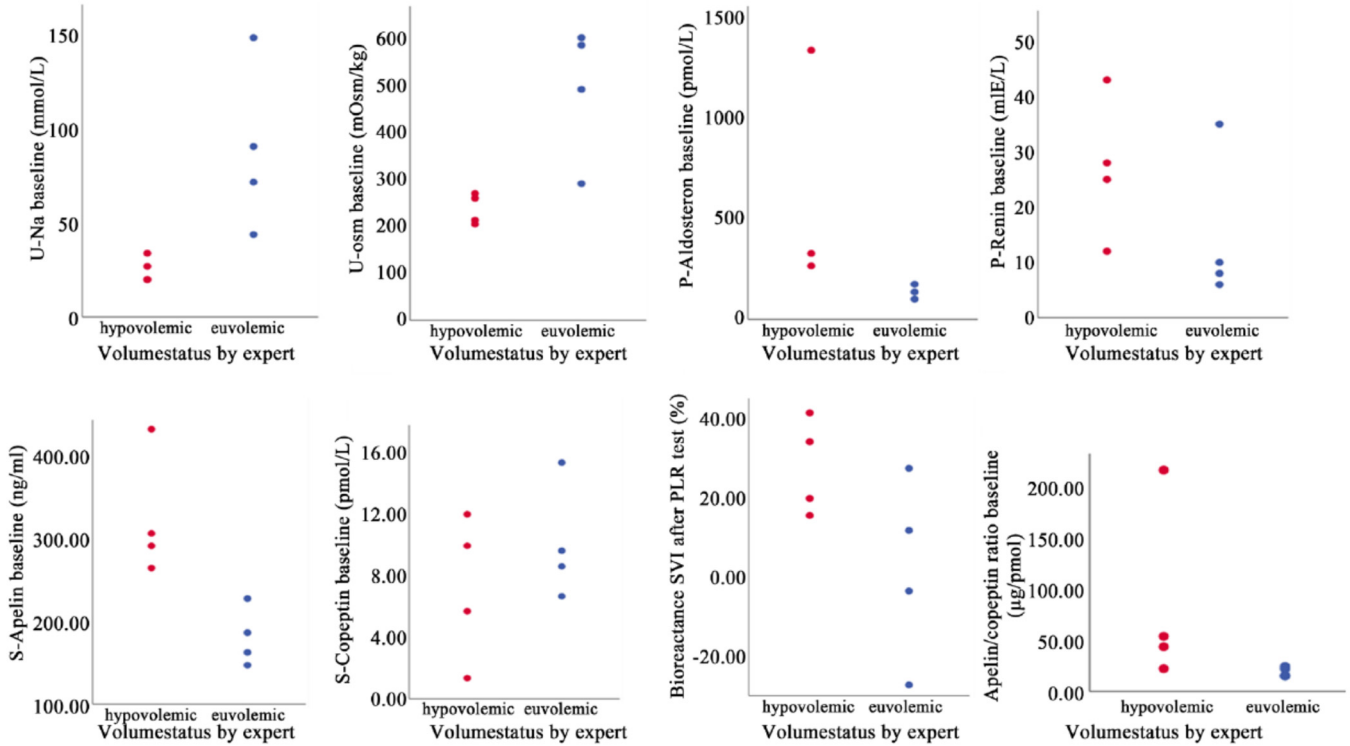


**Figure 17. Baseline biomarker levels in patients with hypo- versus euvolemic hyponatremia.**
Bioreactance analysis of stroke volume index after passive leg raise test.

# Paper IV

The aim of this study was to examine the prevalence of hyponatremia in a large community-based cohort and association with future morbidity and mortality.

A total of 22 444 men and 10 902 women were included in Malmö Preventive Project (MPP) between 1974-1992. Serum sodium was analysed in 22 267 of the MPP participants (75% men) (Figure 18).

Hyponatremia classified as S-Na <135 mmol/L, was present in 166 subjects (0.7%), median S-Na 133 mmol/L (IQR 131-134). Patients were grouped by sodium level into normonatremia (S-Na 135-145, n=21 410), hyponatremia (S-Na<135mmol/L, n=166) and mild hyponatremia (S-Na 130-134 mmol/L, n=148). Sodium levels at borderline hyponatremia (S-Na=135 and S-Na 136 mmol/L) were also examined.

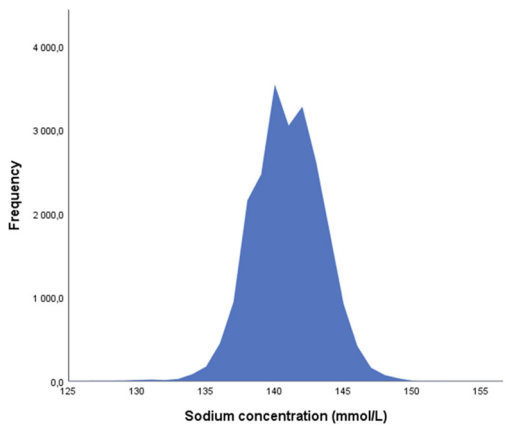


**Figure 18.** Distribution of serum sodium in the population.

During the follow-up period 9577 (29%) of study participants died, 5073 developed coronary artery disease CAD, 2520 suffered from stroke and 1709 were diagnosed with incident heart failure.

Hyponatremia versus normonatremic individuals demonstrated a higher all-cause mortality risk after adjustment for age and gender but not in fully adjusted model (age, gender, diabetes, smoking, hypertension, cholesterol) (Table 5). However borderline hyponatremia was significantly associated with all-cause mortality, crude and in adjusted model. S-Na 135 mmol/L HR:1.708 (1.384-2.107) p<0.001 and S-Na 136 mmol/L HR: 1.215 (1.055-1.399) p=0.007.

The association remained in individuals with S-Na 135 mmol/L even after exclusion of individuals >50 years of age, previous CAD, stroke, heart failure, diabetes, hypertension *and* adjusting for cardiovascular risk factors and fasting glucose, heart rate, potassium and creatinine at baseline: HR1.507 (1.064-2.136) p=0.021. All-cause mortality rates for different hyponatremia levels were plotted in Kaplan-Meier curves (Figure 19).

Incident CAD (coronary artery disease) during follow-up time was increased in patients with hyponatremia but also in mild or borderline hyponatremic groups, both crude and after adjustment (Table 5) (Figure 20).

**Table 5. Relationships between hyponatremia and all-cause mortality, CAD, stroke and heart failure.**

| | Hypo- vs normonatremia (S-Na<135) | Mild hypo- vs normonatremia (S-Na 130-134) | Borderline hyponatremia vs normonatremia (S-Na 135-136) |
|---|---|---|---|
| **All-cause mortality** | 1.397 (1.119-1.743) **p=0.003**<br>1.220 (0.976-1.524) p=0.080 | 1.440 (1.144-1.813 **p=0.002**<br>1.236 (0.981-1.559) p=0.072 | 1.335 (1.187-1.502) **p<0.001**<br>1.332 (1.184-1.499**) p<0.001** |
| **Incident CAD** | 1.799 (1.372-2.359) **p<0.001**<br>1.469 (1.119-1.928) **p=0.006** | 1.892 (1.427-2.507) **p<0.001**<br>1.524 (1.148-2.023) **p=0.004** | 1.360 (1.162-1.592) **p<0.001**<br>1.320 (1.127-1.545) **p=0.001** |
| **Incident heart failure** | 1.312 (0.760-2.264) p=0.330<br>1.044 (0.603-1.806) p=0.879 | 1.354 (0.767-2.389) p=0.296<br>1.037 (0.586-1.836) p=0.901 | 1.271 (0.951-1.700) p=0.105<br>1.264 (0.945-1.691) p=0.115 |
| **Stroke** | 1.189 (0.780-1.813) p=0.420<br>1.386 (0.911-2.109) p=0.128 | 1.488 (0.968-2.286) p=0.070<br>1.248 (0.811-1.922) p=0.314 | 0.839 (0.637-1.104) p=0.210<br>0.827 80.628-1.089) p=0.176 |

Crude analysis in first row, adjusted Cox regression models in second (hazard ratio, 95% confidence interval, p-value). Adjusted for age, gender, diabetes, composite hypertension, smoking, total cholesterol. Prevalent CAD, heart failure or stroke excluded in respective analysis.

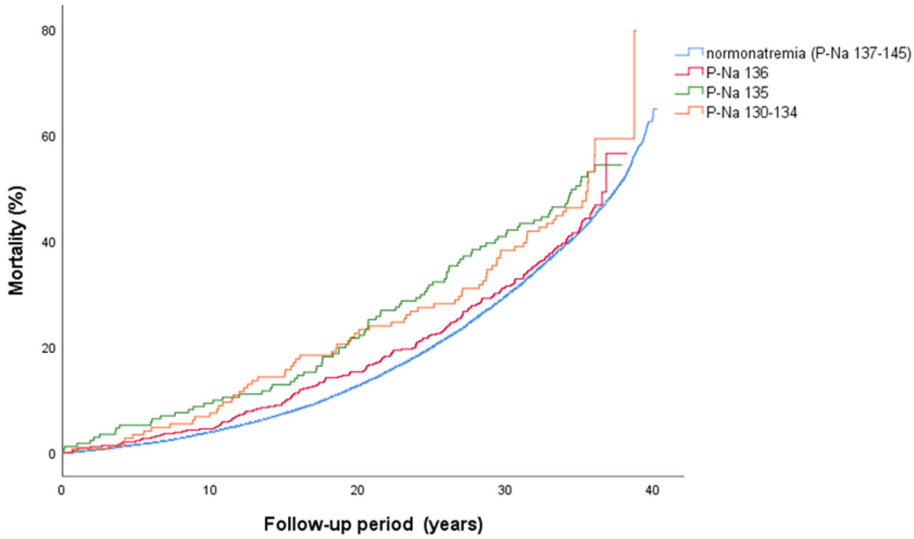


**Figure 19**. Crude all-cause mortality in different levels of mild hyponatremia and lower normal reference range of S-Na

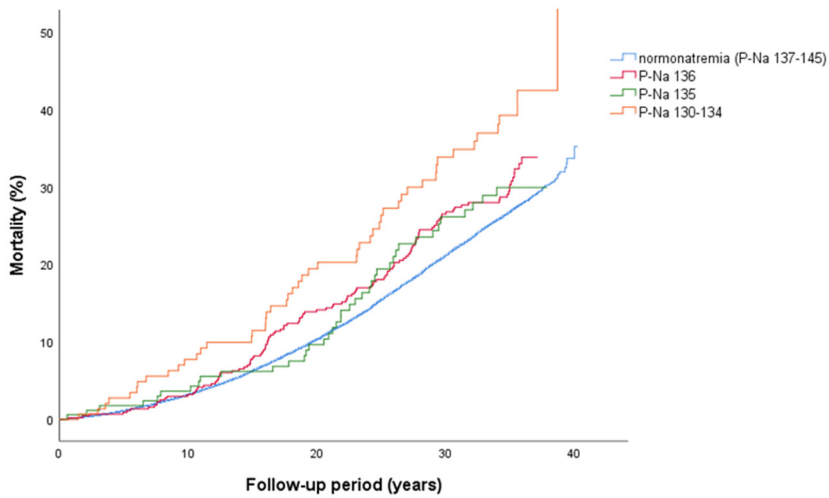


**Figure 20.** Incidence of CAD in different levels of mild hyponatremia and lower normal reference range of S-Na Follow-up period to first CAD event or death or emigration or last follow-up date. (Prevalent CAD excluded).

# Discussion and clinical implications

The overall aim of this thesis has been to gain an overview over the epidemiology of hyponatremia. To evaluate current routine management and identify problem areas of high clinical importance.

In Paper I the absence of methods for swift and accurate differential diagnosis of hyponatremia and patient volume status to guide initial treatment became evident. Even in retrospective studies of hospital records distinguishing between different diagnoses was difficult. A low frequency of basic laboratory investigation (S-osm, U-osm, U-Na) added to this. Only 31% of patients with P-Na < 120 mmol/L were evaluated. Hyponatremia was not a diagnosis in focus but rather a fact noted in overpass. At discharge 55% of patients with a severe hyponatremia were planned for a follow-up sodium level.

First-line treatment of hyponatremia consisted of isotonic sodium chloride infusion (46%) and/or discontinuation of predisposing drug treatments (28%). Since diuretic use was the most common identified underlying cause this would be adequate. However, recommended P-Na correction rates were exceeded in the first 24 hours in 27% of patients with severe hyponatremia. Insufficient re-evaluation after treatment initiation may be responsible.

After diuretic use, the second most common underlying cause of hyponatremia was SIADH (17%). Fluid restriction was prescribed as a first line treatment in 9% of patients. If treatment was altered or new modalities were added they were considered “second line” therapies. Fluid restriction increased to 40% and sodium chloride pills were given to 48%. The change in therapy form and increased use of fluid restriction in “second line” therapy may reflect the difficulty in early diagnosis of SIADH, a diagnosis for which water restriction is more effective than saline infusion. Treatment with sodium chloride pills was common even though there is no scientific evidence supporting the use of sodium chloride pills in SIADH. In the study two patients received tolvaptan after a hospital-stay of 6 and 7 days respectively. An early accurate diagnosis of SIADH could have resulted in a more effective management and shorter hospital length of stay.

The question of improving early patient evaluation led to Paper II and III. Management of hyponatremia is dependent on volume status. We decided to examine the use of biomarkers and bioreactance. Since normal regulation and pathophysiology in hyponatremia is complex different avenues were explored.

Biomarkers involved in cardiovascular pressure load (NT-proBNP, MR-proANP), vascular stress (pro-ET, MR-proADM) and osmolality (copeptin, apelin) were examined. MR-proANP levels were significantly associated with volemic state and even more importantly the level of MR-proANP could distinguish hypovolemia from euvolemia which is the greatest challenge in clinical practice. MR-proANP was significantly related to euvolemia with an odds ratio of 2.5 per SD of MR-proANP compared to hypovolemia.

Apelin levels were significantly higher in hypovolemic patients ((299 vs 175 ng/ml), p=0.021). All hypovolemic, but none of the euvolemic patients, had a level above 250 ng/ml. Apelin is thus a promising future biomarker in the early management of severe hyponatremia. The small study population size unfortunately limits firmer conclusions. Elevated apelin levels have been noted in patients with nephrogenic diabetes insipidus however apelin levels have not been compared between hypo- and euvolemic hyponatremia patients [75].

According to our studies copeptin could not be used to distinguish between different volume groups or confirm SIADH diagnosis. (Paper II, III). This is in accordance with a previous publication [52]. Calculating the apelin/copeptin ratio did not add any information compared to apelin alone, possibly due to the many non-osmotic stimuli for vasopressin secretion.

Apart from biomarkers we wanted to explore other methods for evaluation of volume status. (Paper III) To be useful in clinical practice evaluation must be swift, easy and non-user dependable. Bioreactance measurement has not previously been studied in hyponatremia but used in cardiovascular unstable sepsis patients [57]. In our study we used the same definition for fluid responsiveness and hypovolemia (stroke volume index increase ≥ 10% after passive leg raise), as suggested by the manufacturer and used in studies. Whether this is accurate in a circulatory stable, aged population is not known. All patients in the hypovolemic group increased their stroke volume after passive leg raise. However, two patients in the euvolemic group also increased SVI, one of them borderline to the definition of a positive test (SVI increased 12%). Perhaps a definition of 15-20% increase in SVI after leg raise is more correct. Further studies are needed but bioreactance may offer a complement to bedside evaluation of volume status.

Working with studies on the early management and diagnosis of hyponatremia raised questions regarding the negative effects of hyponatremia. Hyponatremia is a known risk factor for increased morbidity and mortality, but it remained to be examined at what level this negative effect is noticed and whether the association is direct or a marker of severity of underlying comorbidities. The MPP cohort allowed for a unique longitudinal study of hyponatremia in a large community-based cohort with a median follow-up time of 34 years. The results showed an association between hyponatremia and all-cause mortality and coronary artery disease. Even more interestingly these associations were evident in borderline hyponatremia (S-

Na 135-136) after adjusting for cardiovascular risk factors (age, gender, diabetes, hypertension, smoking, cholesterol) and excluding previous coronary artery disease from analysis. (Adjusted all-cause mortality in borderline group, HR:1.332 (1.184-1.499), p<0.001, adjusted CAD HR:1.320 (1.127-1.545), p=0.001).

Our study does not allow for firm conclusions regarding causality. It is however interesting to note an association was still seen between mild hyponatremia and CAD after sub analysis in patients ≤50 years, excluding individuals with preexisting medical conditions and adjusting for cardiovascular risk factors, fasting glucose, heart rate, potassium, and creatinine (HR:2.042 (1.282-3.252), p=0.003).

The results indicate that mild and borderline hyponatremia should be recognized as a risk factor for future morbidity. Individuals could benefit from an early structured examination and elimination of risk factors.

We can only speculate in the underlying pathophysiology. Hyponatremia could be a result of increased activity of vasopressin- and/or renin-angiotensin-aldosterone systems. Fasting blood glucose (after exclusion of diabetes) and potassium levels were significantly disparate in individuals with hyponatremia versus normonatremia. This could be a sign of elevated vasopressin and aldosterone levels given the association between high vasopressin and hyperglycemia and the effect of aldosterone on urinary potassium secretion[20][31].

Current reference levels of sodium can be questioned. The difference between analytical versus physiological normal reference ranges should be discussed. Wald et al noted lowest in-hospital mortality in patients with P-Na 138-142 mmol/L in the U-shaped association between P-Na at admission and mortality [40]. In our study (Paper IV) there seemed to be a dividing point at S-Na ≤136 mmol/L.

This thesis has added to the base of knowledge on hyponatremia. An unselected population in the Emergency Department had not previously been studied and biomarkers MR-proANP and apelin, and bioreactance measurement had not been evaluated in diagnosis of patient volume status. Much remain to be examined but we have unveiled a few new facts about this complex and elusive electrolyte disturbance.

# Conclusions and future perspective

- Hyponatremia is common in an unselected population in the Emergency department. Thiazide diuretics and SIADH are common underlying causes.
- Frequency of adequate diagnostic testing was low, even in severe hyponatremia.
- Correction rates commonly exceeded recommended levels. Routine use of sodium chloride infusions as first line treatment without sufficient follow-up may therefore be questioned.
- MR-proANP and apelin may be promising biomarkers for distinguishing between hypovolemia and euvolemia in hyponatremic patients.
- Copeptin levels cannot diagnose SIADH in the Emergency Department.
- Bioreactance measurements may offer a supplement to bedside evaluation of volume status.
- Hyponatremia is a risk factor for cardiovascular death and coronary artery disease, also in the long term. Even mild hyponatremia is associated with increased risks and should be recognized as a risk factor for future morbidity.

Larger confirmatory studies on apelin, MR-proANP and bioreactance measurements in the early management of hyponatremia are essential.

Future studies are needed to explore the association between hyponatremia and cardiovascular death and morbidity. Pathophysiological models need to be investigated further. Whether hyponatremia is a causative factor or early sign of underlying subclinical disease is yet unknown.

# Populärvetenskaplig sammanfattning

Hyponatremi, låg natrium-saltnivå i blodet, är vanligt och drabbar upp till 30% av patienter som vårdas på sjukhus. Saltrubbningen kan ge symptom som trötthet, illamående, yrsel och balanssvårigheter. Förekomst av hyponatremi ökar dödlighet på sjukhus. För att behandla rubbningen rätt är det viktigt att tidigt avgöra orsaken och fastställa om patienten har brist på både salt *och* vatten, brist på salt men normal mängd vatten, eller har ett överskott av vatten som späder ut saltet. Detta är svårt även för erfarna läkare och riskerar fördröja rätt behandling. Brist på både salt och vatten behandlas med saltinnehållande dropp medan man vid normal mängd vatten istället kan behöva minska vätskeintaget för att komma till rätta med saltrubbningen. I avhandlingen har vi kartlagt vilka bakomliggande orsaker till hyponatremi som förekommer på akutmottagningen och undersökt nya metoder för bedömning av patienterna.

Hyponatremi förekommer hos 3% av alla patienter som söker akutmottagningen, oberoende av anledning till att de söker vård eller om de kräver vidare vård på sjukhus eller återgår hem. De vanligaste orsakerna är vätskedrivande mediciner och SIADH (ett tillstånd med ökad nivå av hormonet vasopressin som reglerar salt-vattenbalansen i kroppen).

Vi undersökte nya metoder för att tidigt kunna bestämma mängden salt och vatten genom att mäta markörer i blod och urin. Nivån av ämnena MR-proANP och apelin kunde särskilja patienter med brist på både vatten och salt från de med normal total mängd vatten. Vi använde även en ny metod, kallad bioreaktans, för beräkning av blodflödet från hjärtat genom elektroder som sätts på bröstkorgen. Resultaten visade att metoden kan bistå läkaren i den tidiga, så viktiga, bedömningen av patienten.

I den senaste studien undersökte vi de framtida konsekvenserna av hyponatremi och fann att patienter med till och med lätt sänkt natriumsalt hade en ökad risk för död och framtida hjärtkärlsjukdom.

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