

# The measurement of copeptin: clinical relevance?

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# SUMMARY



**INTRODUCTION**



**QUESTIONS**

1 - 3



**TO DO/ACTIONS**



# INTRODUCTION – DIABETES INSIPIDUS

Increase water output and excretion of relatively dilute urine (<300 mOsm/kg)

Central diabetes insipidus

- Deficient secretion of ADH

Nephrogenic diabetes insipidus

- Normal ADH secretion but varying degrees of renal resistance to its effect

Primary polydipsia

- Primary increase in water intake
- Middle-aged women and psychiatric illnesses
- Hypothalamic lesions that effect thirst center



# INTRODUCTION - CAUSES OF DIABETES INSIPIDUS

## CENTRAL DIABETES INSIPIDUS

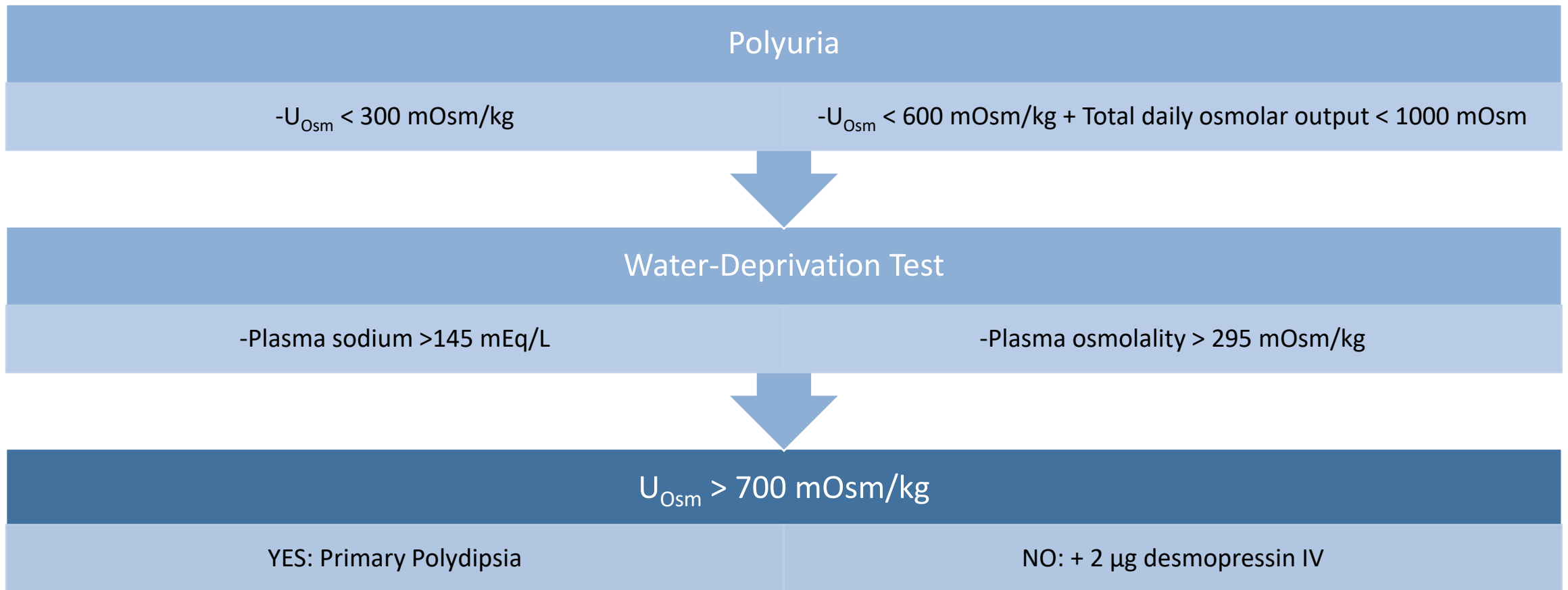
- Idiopathic (30-50%)
- Trauma or neurosurgery
- Familial/Congenital
  - Familial DI
  - Wolfram syndrome
  - PCSK1-deficiency
  - Congenital hypopituitarism, midline abnormalities
- Cancer

## NEPHROGENIC DIABETES INSIPIDUS

- Hereditary
  - AVPR2 mutation – X-linked
  - AQP-2 mutation
- Lithium toxicity
- Hypercalcemia
- Hypokalemia



# INTRODUCTION – WATER-DEPRIVATION TEST





# INTRODUCTION – WATER-DEPRIVATION TEST

## Opname en verloop

De dorstproef bestaat uit 2 delen:

**Deel 1: eigenlijke dorsten:** 12 tot 24 uur, bestaat uit aantal tests:

- Meten urinedebiet en afnemen urinestaal (elk uur)
- Gewicht noteren (elk uur)
- Bloeddruk meten (elk uur)
- Bloedafname (elke 2 uur)
- Eventueel afname plasma-ADH op het einde

**Deel 2: beoordelen van effect van desmopressine** (Minirin): 2 uur

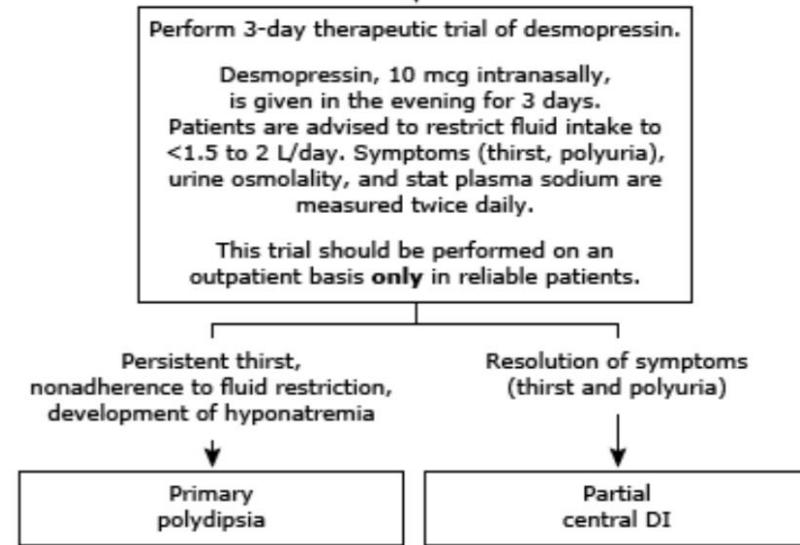
Na een aantal uren zonder urineconcentratie of als uw lichaamsgewicht meer dan 3 % daalt, krijgt u 2 µg Minirin (0,5 ampul) toegediend. 1 en 2 uur later worden dan nogmaals bovenstaande tests afgenomen.

De totale duur van het dorsten wordt door de arts bepaald. Na de test mag u naar huis. Uw arts bespreekt de resultaten met u tijdens een consultatie enkele weken later.



# INTRODUCTION – WATER-DEPRIVATION TEST

<b>Inset 2: Judging the response to desmopressin</b>
Urine osmolality rises <15% to a value <300 mosmol/kg: <b>complete nephrogenic DI</b>
Urine osmolality rises 15 to 45% to a value <300 mosmol/kg: <b>partial nephrogenic DI</b>
Urine osmolality more than doubles (ie, rises by >100%): <b>complete central DI</b>
Urine osmolality rises 15 to 100% to a value >300 mosmol/kg: <b>partial central DI</b>
Minimal or no rise in urine osmolality and a value >300 mosmol/kg: <b>nondiagnostic</b>  When the test is nondiagnostic, the etiology of polyuria is usually partial central DI or primary polydipsia



TEST

DIAGNOSTIC  
ACCURACY

INDIRECT WATER DEPRIVATION TEST

70-76,6%



# CAT: QUESTIONS

1

COPEPTIN:  
SYNTHESIS,  
PHYSIOLOGY AND  
WHAT IS NORMAL?

2

IN WHICH CLINICAL  
SETTINGS THE  
MEASUREMENT OF  
COPEPTIN COULD  
TAKE PLACE?

3

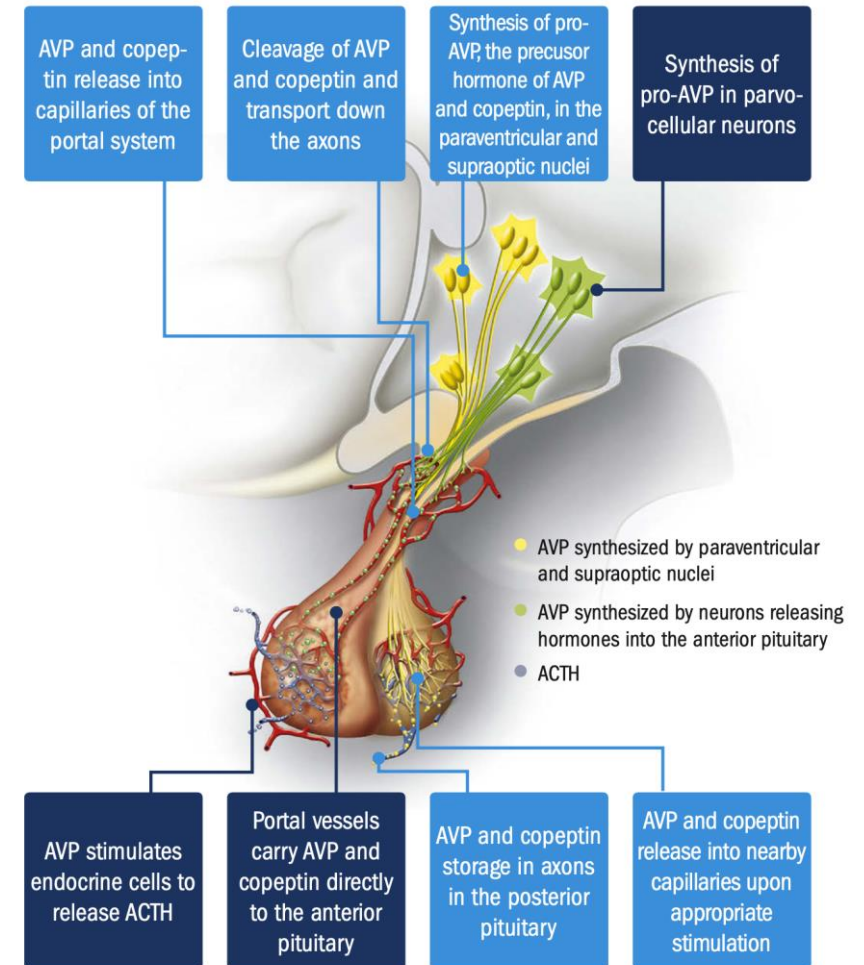
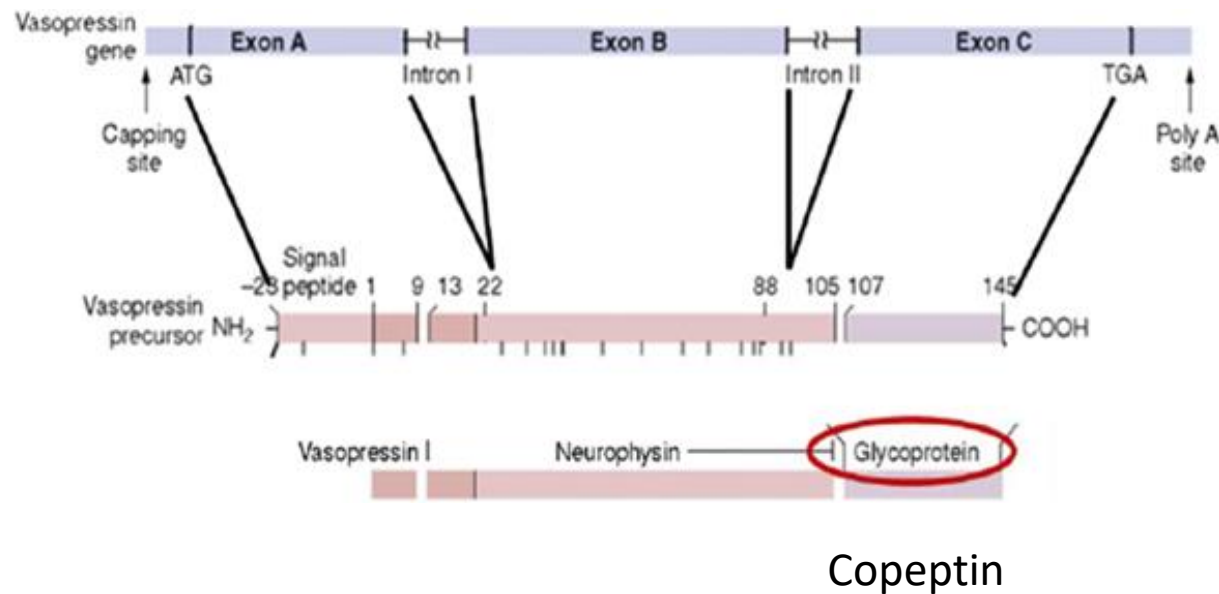
HOW CAN  
COPEPTIN BE  
IMPLEMENTED IN  
ROUTINE CLINICAL  
PRACTICE?



# 1

# SYNTHESIS

## AVP and Copeptin Release in Hypothalamus and Pituitary and its Effects

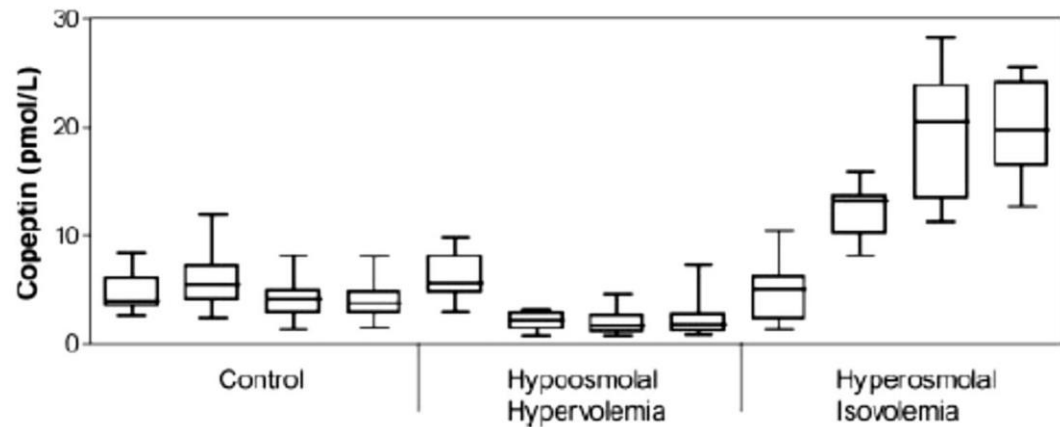


# 1

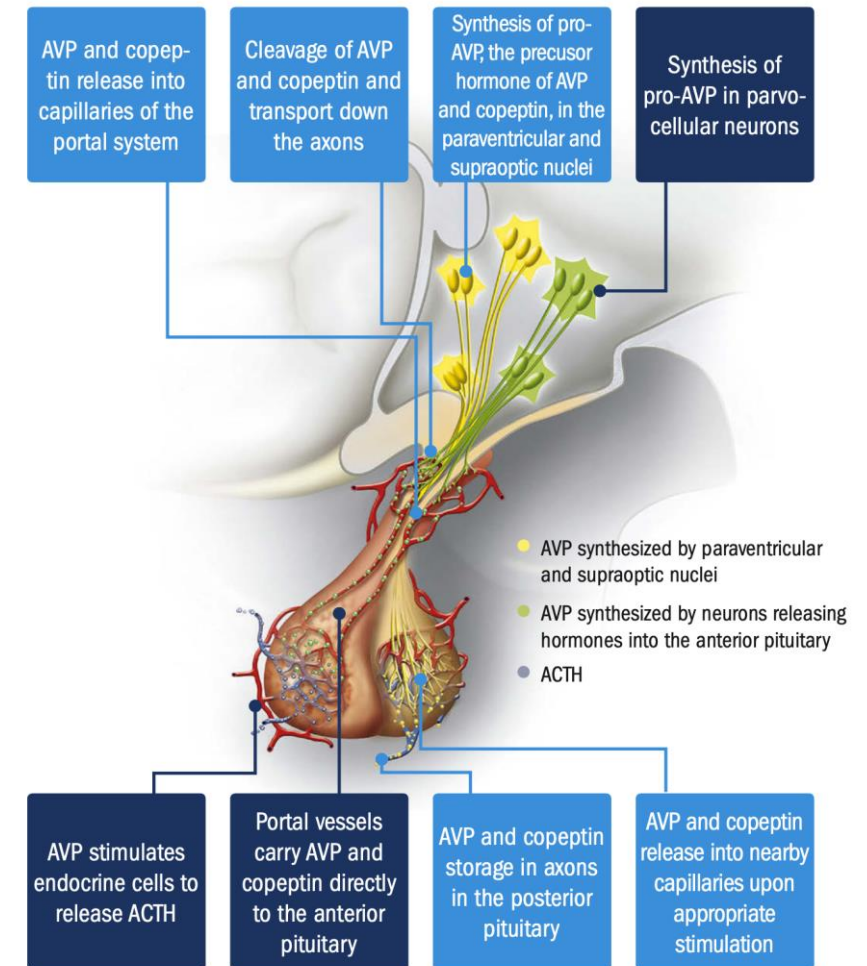
# PHYSIOLOGY AND FUNCTION

## • Stimuli

- Decrease plasma osmolality
- Decrease extracellular fluid
- Stress



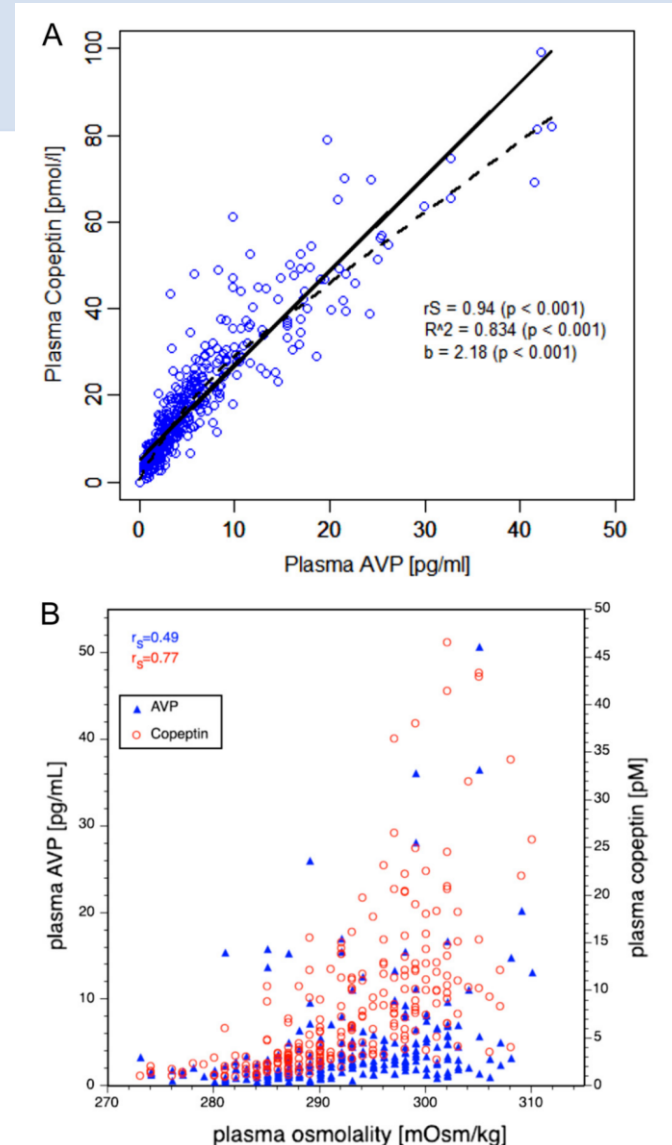
AVP and Copeptin Release in Hypothalamus and Pituitary and its Effects



## 1

## PHYSIOLOGY AND FUNCTION

- Stimuli
  - Decrease plasma osmolality
  - Decrease extracellular fluid
  - Stress
- PK/PD
  - Equimolar synthesis AVP
  - $T_{1/2}$ : 30-100 min
  - (Partial) Renal elimination



# 1

## PHYSIOLOGY AND FUNCTION

- Stimuli
  - Decrease plasma osmolality
  - Decrease extracellular fluid
  - Stress
- PK/PD
  - Equimolar synthesis AVP
  - $T_{1/2}$ : 30-100 min
  - (Partial) Renal elimination
- Function
  - Prolactine-releasing factor?
  - AVP chaperone?
  - Peripheral function?



Surrogate biomarker of ADH

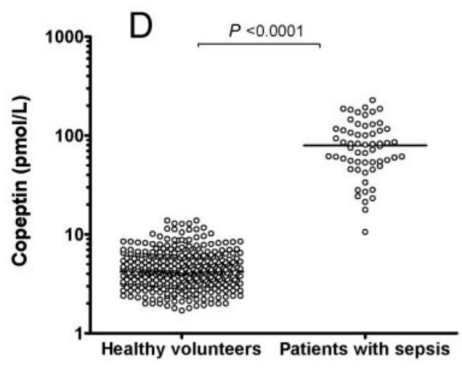
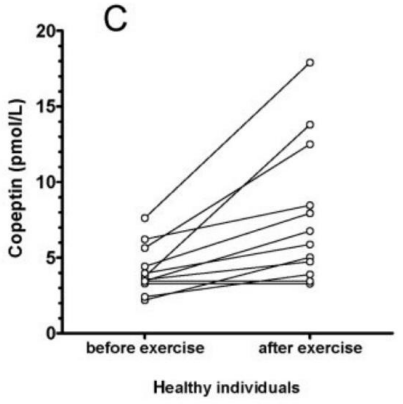
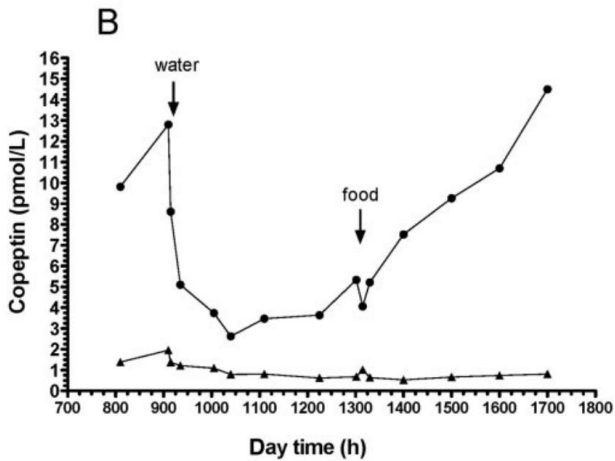
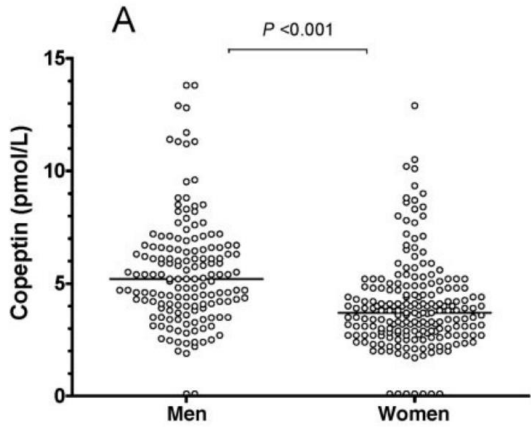
# 1

# NORMAL VALUE

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

# 1

# NORMAL VALUE



# 2

## CLINICAL SETTINGS

### Fluid balance

- Diabetes insipidus
- Hyponatremia

### Stress

- Sepsis
- Cardiovascular disease
- Stroke – Traumatic Brain Injury
- Diabetes mellitus
- CKD
- Stress of the newborn

# 2

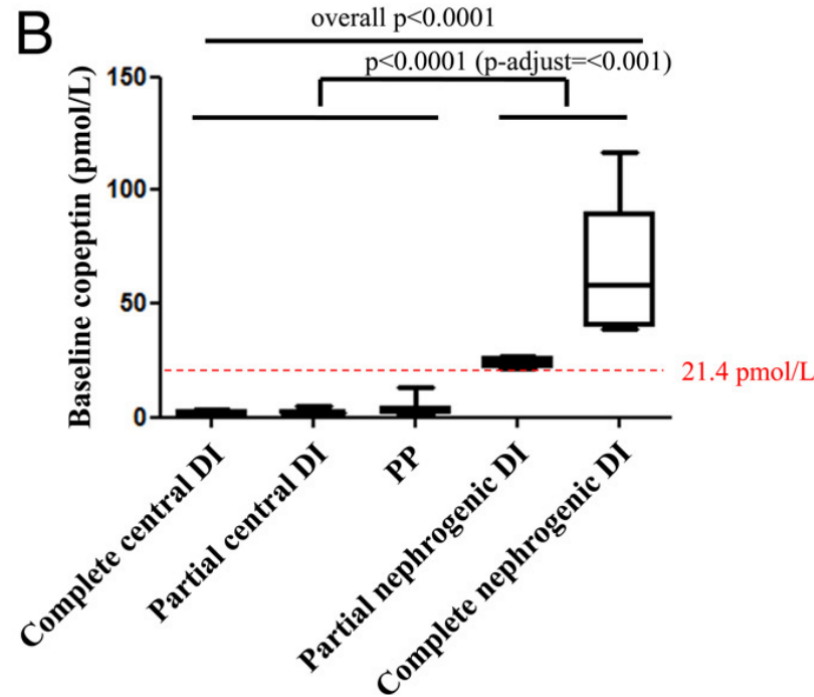
# DIABETES INSIPIDUS - DIRECT COPEPTIN MEASUREMENT

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



# 2

## DIABETES INSIPIDUS - DIRECT COPEPTIN MEASUREMENT

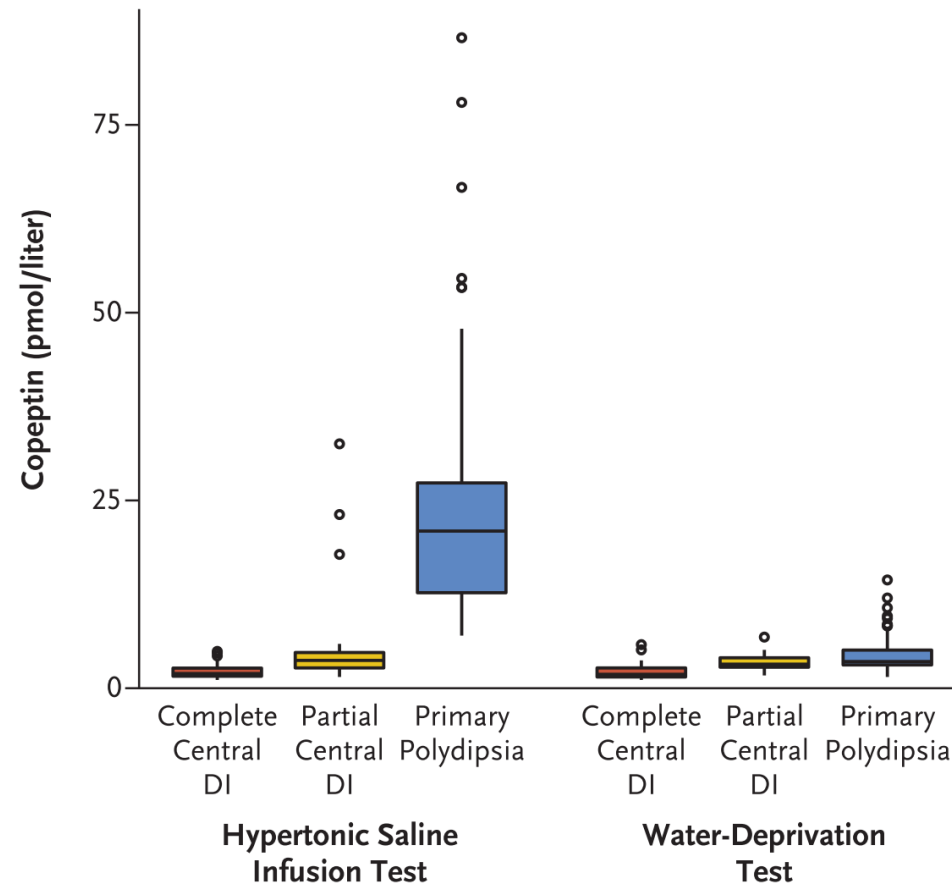


Sensitivity 100%  
Specificity 100%

# 2

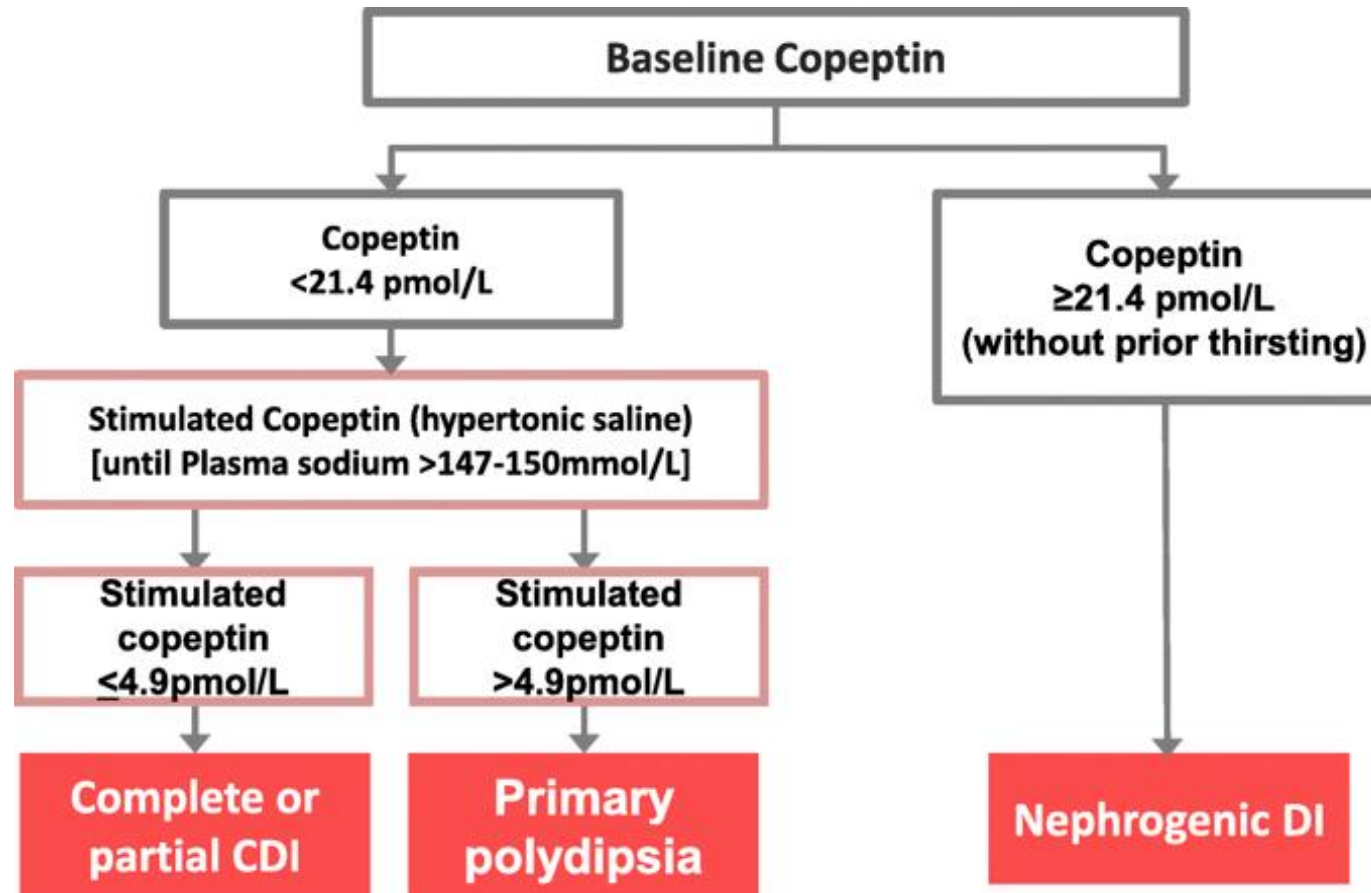
## DIABETES INSIPIDUS - DIRECT COPEPTIN MEASUREMENT

B Complete or Partial Central Diabetes Insipidus vs. Primary Polydipsia



## 2

## DIABETES INSIPIDUS - DIRECT COPEPTIN MEASUREMENT



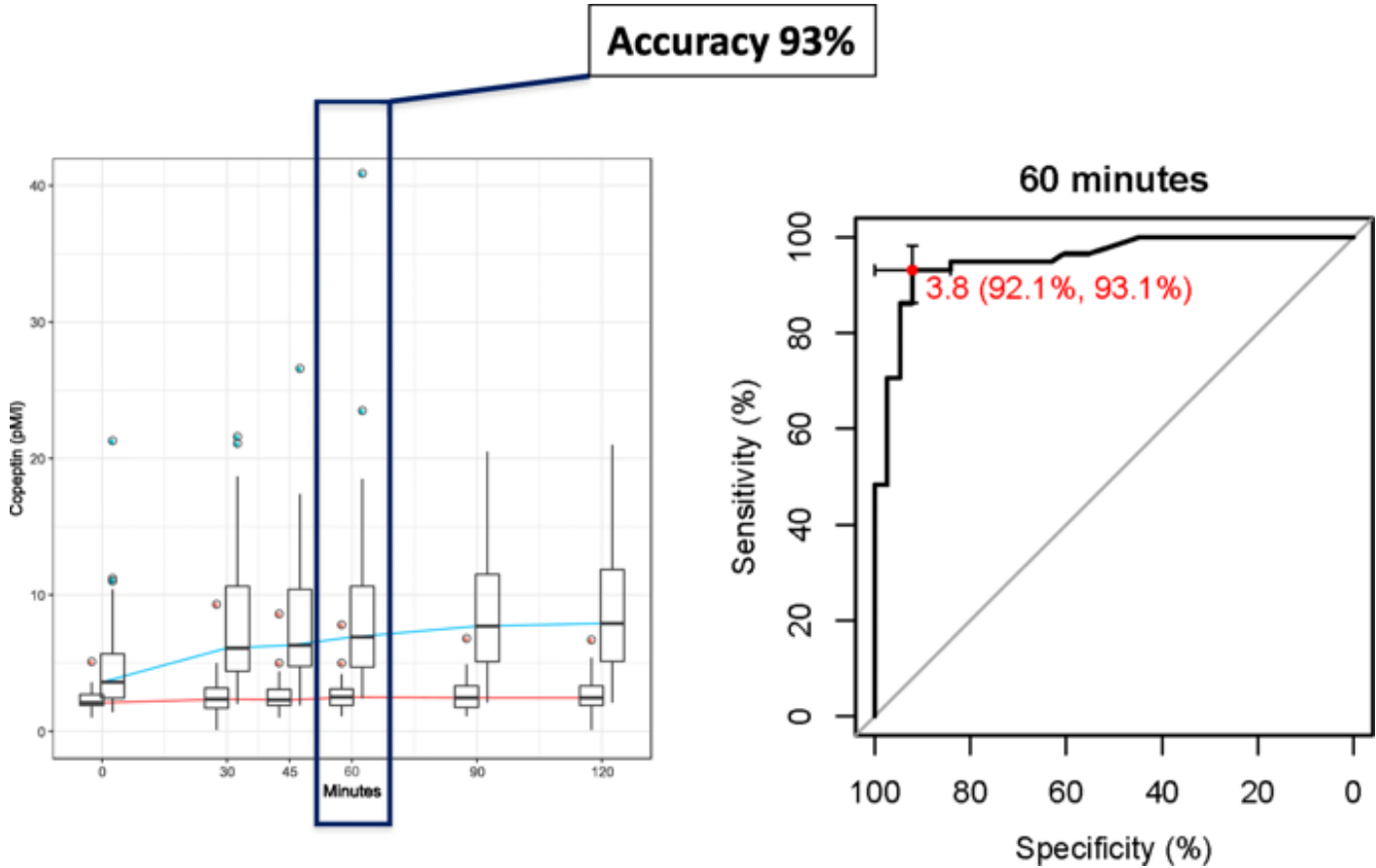
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## 2

# HYPONATREMIA

No diagnostic utility of copeptin in the differentiation of hyponatremia

Wide overlap between different etiologies of hyponatremia

Large variability especially in SIAD

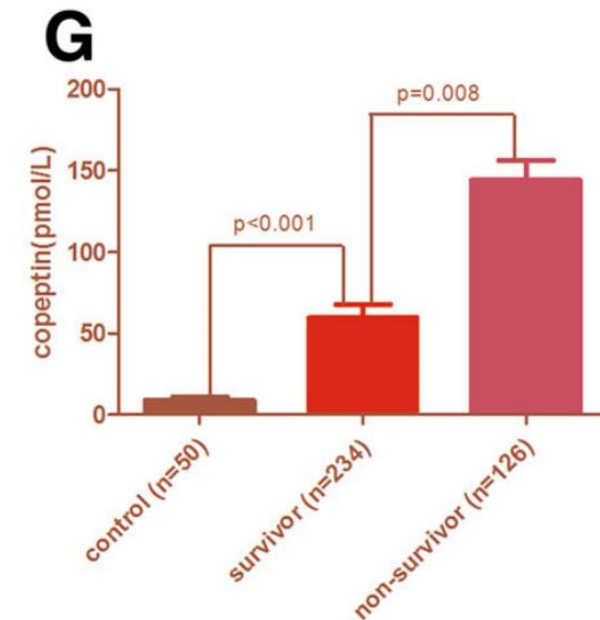
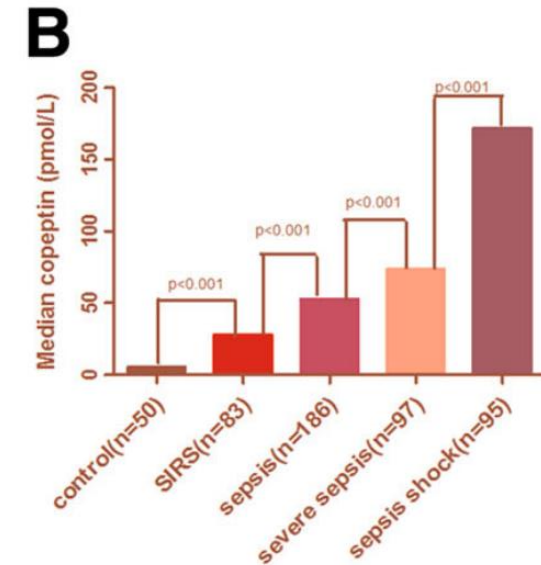


Non-osmotic stress-related copeptin stimulus in acute hospitalized hyponatremic patients may confound the osmotic or paraneoplastic impulse

## 2

## SEPSIS

- Stepwise increase healthy – septic shock
  - Median value 79,5 pmol/L (10,6-228;  $p < 0.001$ )
- Non-survivor: higher value on admission
- Predictor for development of septic shock
  - 96,5 pmol/L
- Superior accuracy for 28-day mortality when compared to the CRB-65 score and CRP and procalcitonin.

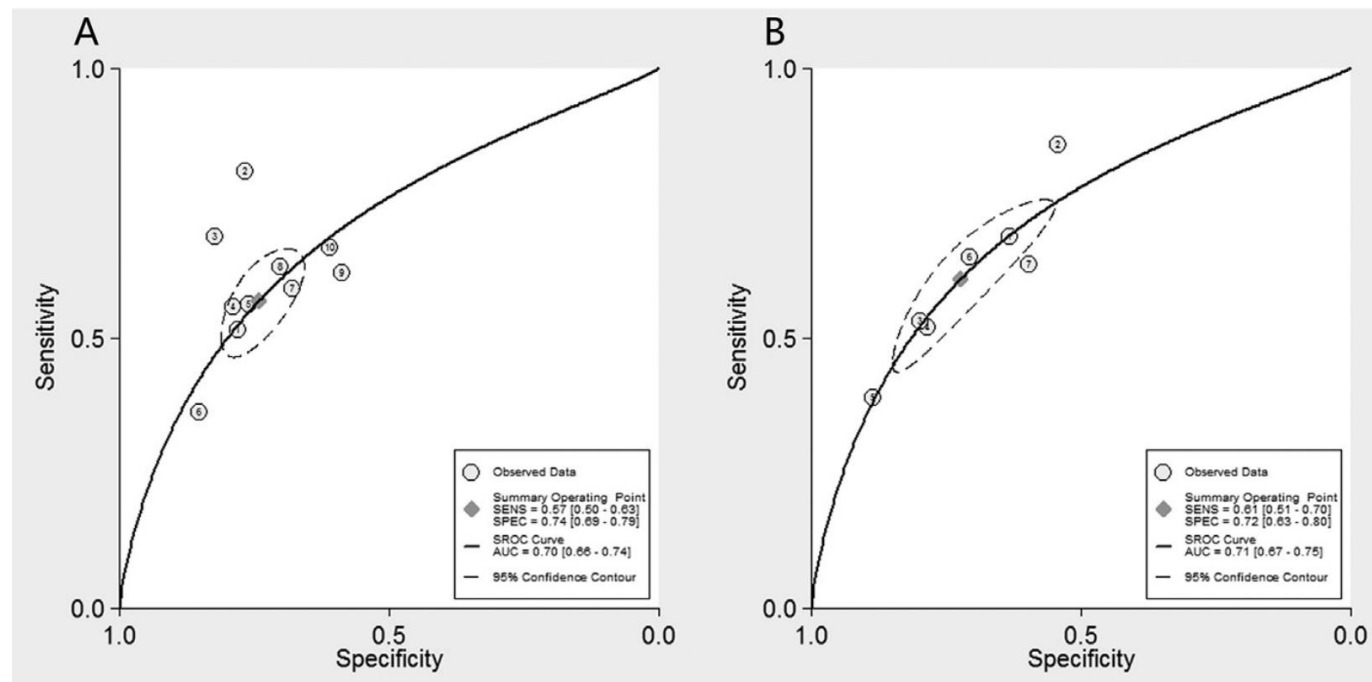




## 2

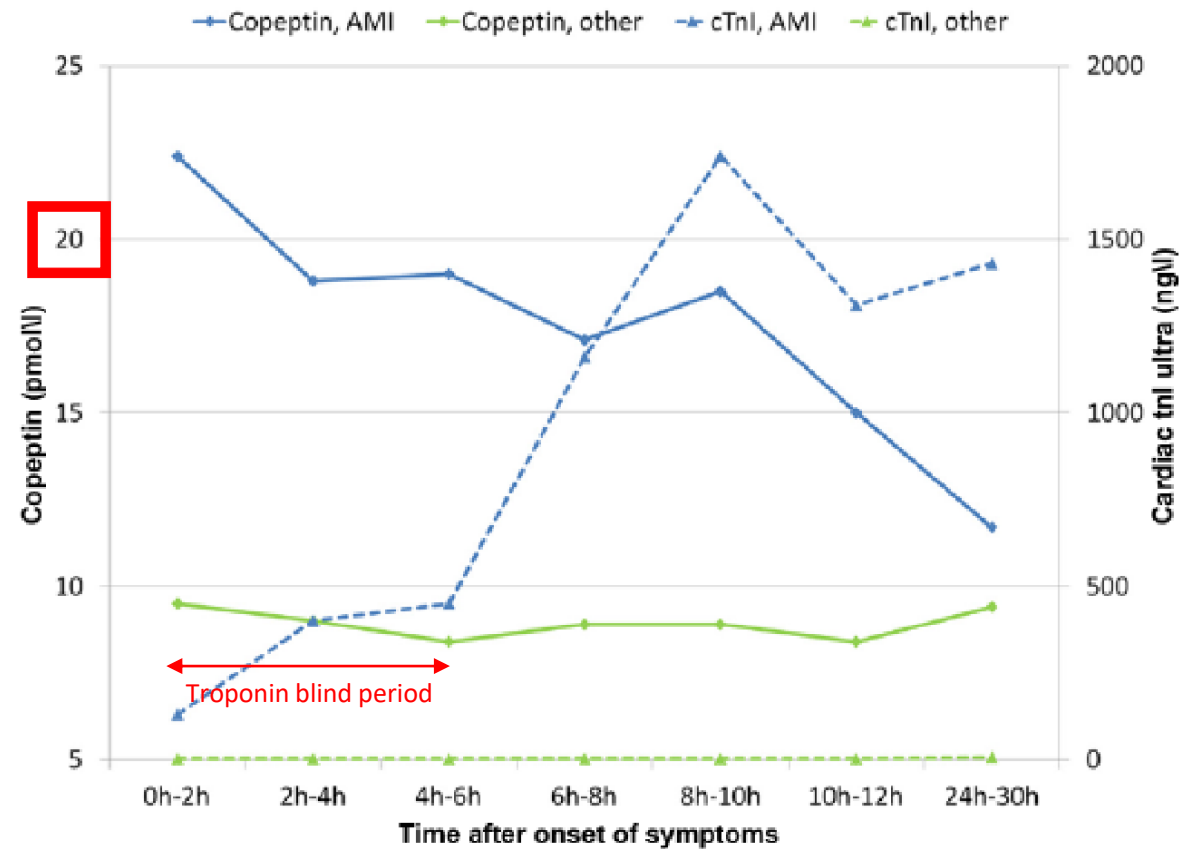
## CARDIOVASCULAR DISEASE – HF

- Associated with increased risk and severity of HF and all-cause mortality
  - Median value 22 pmol/L
- Similar prognostic value as compared to NT-proBNP for all-cause mortality in patients with HF



# 2

## CARDIOVASCULAR DISEASE – AMI



## 2

## CARDIOVASCULAR DISEASE – AMI

**Table 2.** Diagnostic accuracy of troponin (Tn) and copeptin.

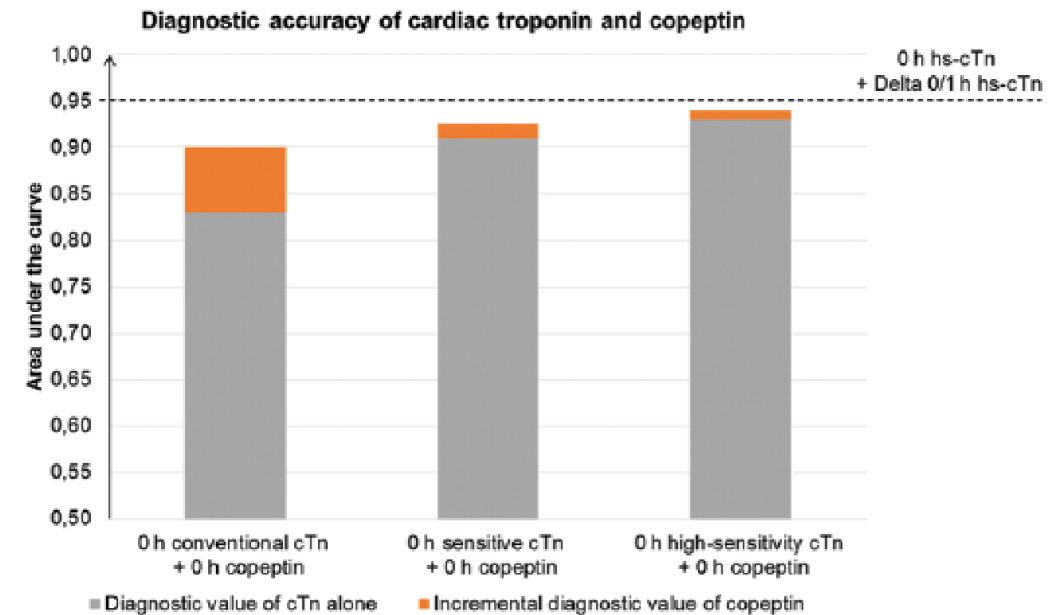
Methods	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
<b><i>Copeptin</i></b>	0.62 (0.4–0.8)	0.72 (0.6–0.8)	2.22 (1.88–2.6)	0.52 (0.33–0.81)
<b><i>Early hs-TnT</i></b>	0.89 (0.79–0.94)	0.84 (0.74–0.9)	5.62 (3.38–9.34)	0.12 (0.7–0.24)
<b><i>Late hs-TnT</i></b>	0.89 (0.78–0.94)	0.83 (0.70–0.92)	5.56 (2.87–1.77)	0.12 (0.07–0.24)
<b><i>Tn and copeptin</i></b>	0.91 (0.85–0.95)	0.65 (0.58–0.71)	2.63 (2.22–3.12)	0.14 (0.08–0.22)

CI: confidence interval; hs-TnT: high sensitivity troponin T; LR–: negative likelihood ratio; LR+: positive likelihood ratio.

## 2

## CARDIOVASCULAR DISEASE – AMI

- Dual-marker strategy:
  - Conventional cTn:
    - Recommended for the rapid rule-out of AMI (ESC-guidelines)
    - Increases the diagnostic accuracy and negative predictive value
  - High sensitive cTn:
    - Small increment in sensitivity, at the expense of specificity
    - Diagnostic accuracy increased not or only marginally
    - Insignificant when hs-TnT only protocol is used



## 2

# STROKE – TRAUMATIC BRAIN INJURY

- Pathophysiology: brain edema
- No difference between stroke and other patients
  - Median value 20 pmol/L
- Elevated concentrations are positively associated:
  - Higher risk of death and adverse outcomes
  - Recurrence of a stroke
- In combination with outcome tools:
  - NIHSS-score improved predictive power
  - CoRisk score:
    - Numeric increase in AUC curves (0,816 vs. 0,819  $p < 0,001$ )
    - Net reclassification index (NRI) of 46%

# 3

## IMPLEMENTATION

### DIAGNOSIS DIABETES INSIPIDUS

- More stable surrogate biomarker of AVP release
- More accurate than indirect water-deprivation test
- Simplified test protocol
- Preferred by majority of patients
- Expert consultation

### CARDIOVASCULAR

- Dual-marker strategy: cTn
- Limited use with hs-TnT
- Cost-effective?

### FUNCTIONAL OUTCOME AND SHORT TERM MORTALITY?

## 3

## AVAILABLE KITS

- Immunoluminometric assay (LIA) or automated chemiluminescence sandwich immunoassay
  - BRAHMS Copeptin proAVP Kryptor by ThermoFischer Scientific

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

- ELISA

# 3

## ESTIMATED COST

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



# 3

## ESTIMATED COST

MONTHLY		
<b>Estimated request rate</b>	2-3	
<b>Calibration rate</b>	Semimonthly	15 days stability 1-point
<b>Control</b>	Each patient sample 1 level after calibration	
<b>Reagent cost</b>	€ 108-152	VAT incl.
<b>Added personnel cost</b>	€ 240-314	VAT incl.



## TO DO/ACTIONS

- Consideration and review of the feasibility of implementing the copeptin assay in UZ Leuven.
- Reimbursement for copeptin test in polyuria polydipsia syndrome.

Questions?