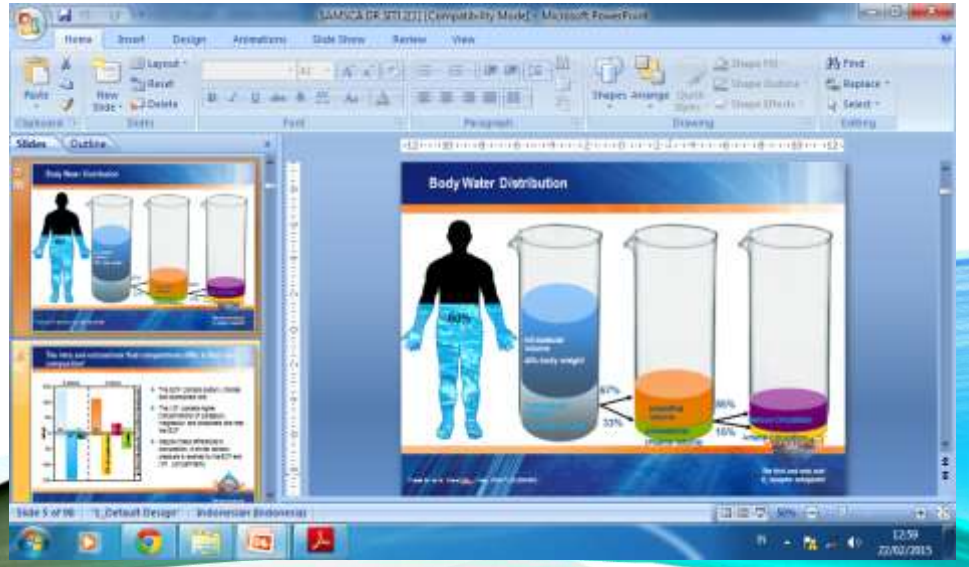
HYPONATREMIA IN HEART FAILURE
&
DIURETIC RESISTANCE



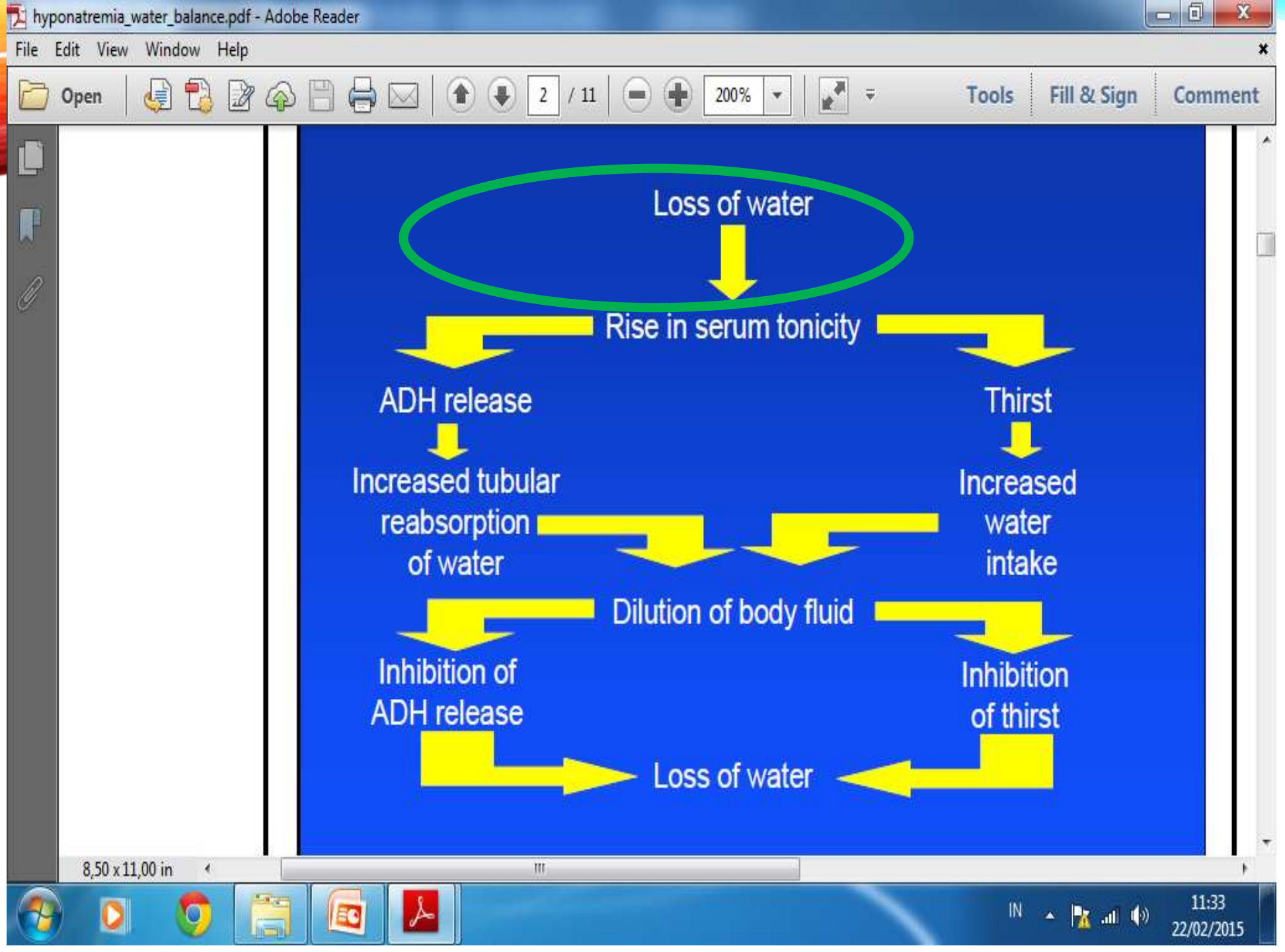
Siti Elkana

DEFINITION

Plasma sodium level < 135 mEq/L

SODIUM HOMEOSTASIS

- Antidiuretic hormone /ADH
  -osmoreceptor and baroreceptor
  -regulate water excretion
- Renin Angiotensin System
  -baroreceptor
  -regulate sodium excretion
- Atrial Natriuretic Peptide
  -baroreceptor
  -regulate sodium and water excretion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Loss of water
Rise in serum tonicity
ADH release
Thirst
Increased tubular reabsorption of water
Increased water intake
Dilution of body fluid
Inhibition of ADH release
Inhibition of thirst
Loss of water
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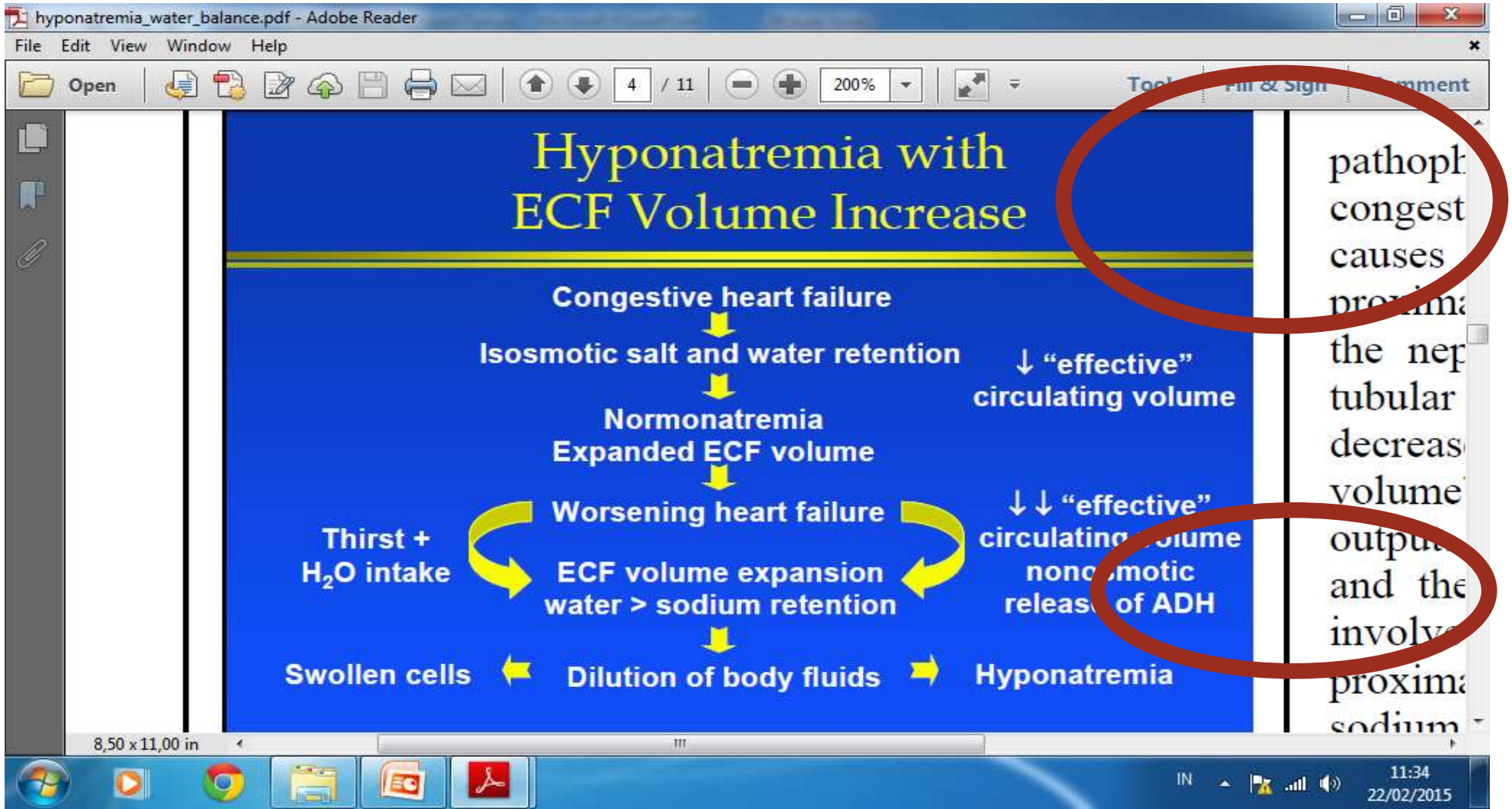
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Hyponatremia with ECF Volume Increase
Congestive heart failure
Isosmotic salt and water retention
↓ "effective" circulating volume
Normonatremia
Expanded ECF volume
Worsening heart failure
↓↓ "effective" circulating volume
Thirst + H_2O intake
ECF volume expansion
water > sodium retention
non osmotic release of ADH
Swollen cells
Dilution of body fluids
Hyponatremia
pathophl
congest
causes
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HYPONATREMIA IN HF

Decreased renal perfusion

Nonosmotic release of AVP

Sympathetic activation

SODIUM AND WATER IMBALANCE

Medications	Comorbid (DM, hypothoroid)

MANAGEMENT

A 73 yo male admitted with weakness and fatigued for approximately one month

- Ramipril 5mg BID
  50mg BID, Furose
  Warfarin 6mg dai
- T 37.5, BP 128/68
  (irregular), RR 16, SaO2 95%
- RESP no crackles or wheezes
- CVS: JVP 6
- S1/S2 present, no S3/S4
- 3+ pitting edema bilaterally to sacrum

A. **GIVE 3% SALINE**
B. **IV DIURETICS**
C. **Others?**

A 47 yo male admitted with pain in suprapubic area approximately one month. Pts with history of treated with
0 mg and Bisporolol

30 RR 12, SaO2 99%

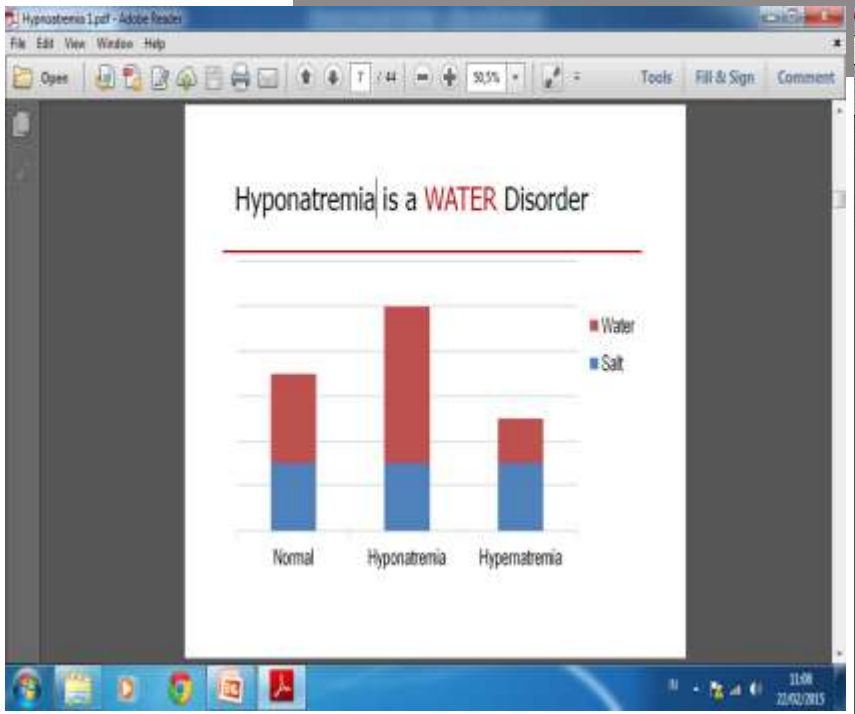
RESP no crackles or wheezes

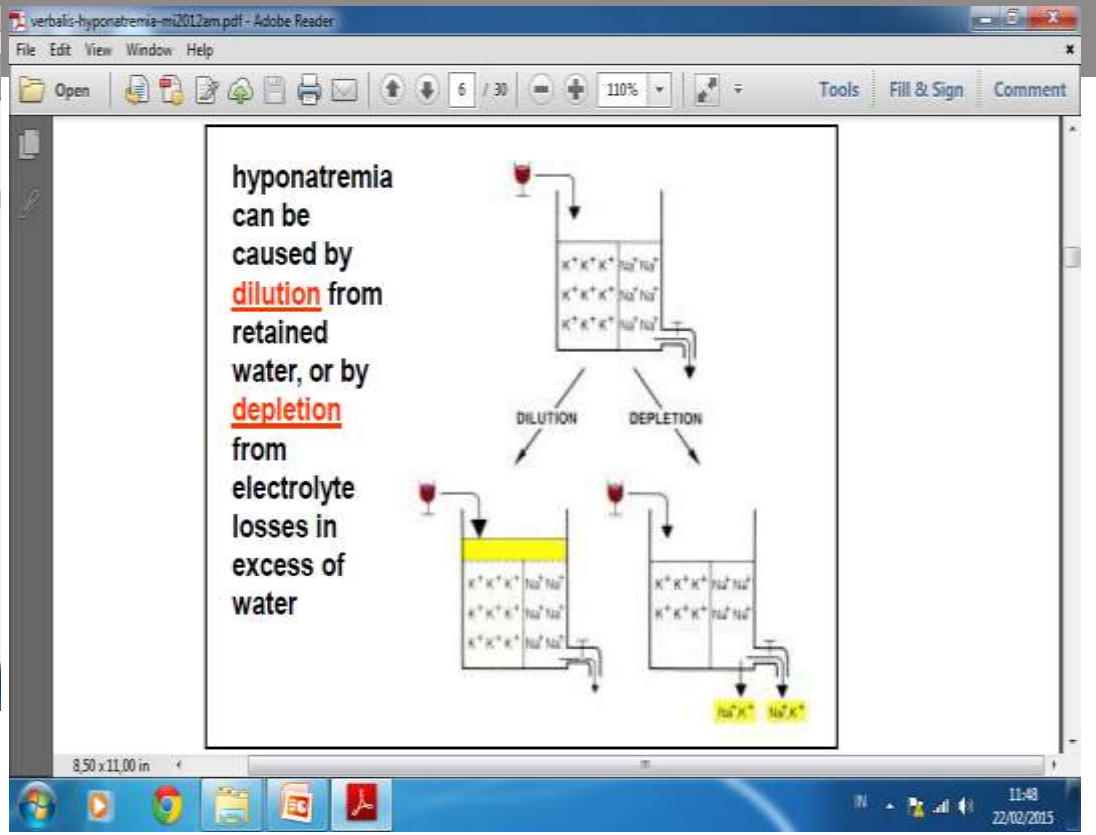
S1/S2 present, no S3/S4

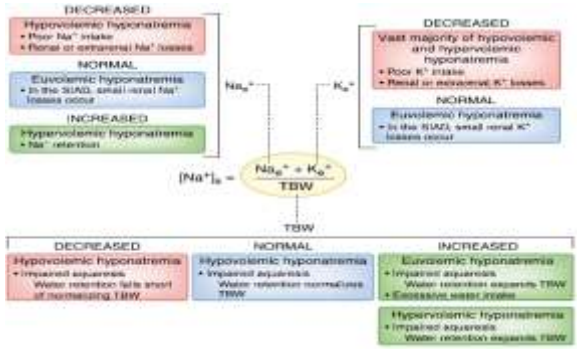
No edema

Renal panel: Na 104 mmol/L, K 4,6 mmol/L, Cr 69 umol/L, Cr 5,9, Urea 197

HYPONATREMIA PRINCIPLE





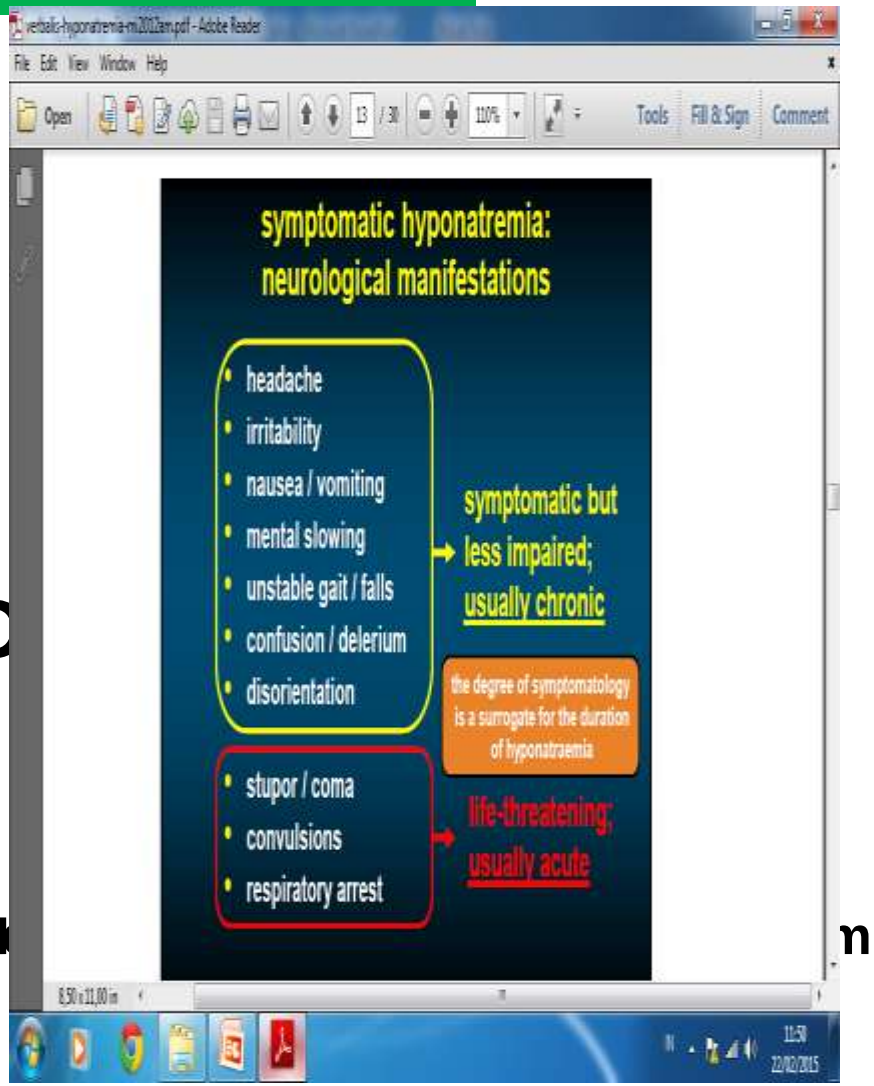


CLASSIFICATION

Chronic > 48 hrs

Symptoms Sodium leveD

Moderate-severe Mild (130 s/d135 nmol/l)



CLASSIFICATION

Hypovolemic

Euvolemic

Hypervolemic

Serum osmolality

Volume status

Hypotonic (<280 mOsm/kgH2O)

Isotonic (280-295 mOsm/kgH2O)

Hypertonic (> 295 mOsm/kgH2O)

HOW TO ASSESS

1.

1.

-

HOW TO ASSESS

1. Assess volume status

Physcogenic, SIADH

CKD, CHF, Cirrhosis, Nephrotic

HYPERVOLEMIC | HYPOVOLEMIC | EUVOLEMIC

Renal/ extrarenal sodium loss

WHAT DOES THE HEART FAILURE GUIDELINE SAYS.....

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: Addenda

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

PROBLEM SOLVING

Asymptomatic low blood pressure
- Dose may be reduced if no symptoms or signs of congestion

Symptomatic hypotension
- Causing dizziness/light headedness–reduce dose if no symptoms or signs of congestion
- Reconsider need for nitrates, CCBs,[d] and other vasodilators
- If these measures do not solve problem, seek specialist advice

Hypokalaemia/hypomagnaesaemia
- Increase ACE inhibitor/ARB dose, add MRA, potassium supplements; magnesium supplements

Hyponatraemia
- *Volume depleted:* stop thiazide or switch to loop diuretic, if possible; reduce dose/stop loop diuretics if possible; *volume overloaded:* fluid restriction; increase dose of loop diuretic; consider AVP antagonist (e.g. tolvaptan if available); i.v. inotropic support; consider ultrafiltration

Hyperuricaemia/gout
- Consider allopurinol prophylaxis; for symptomatic gout use colchicine for pain relief; avoid NSAIDs

Hypovolaemia/dehydration
- Assess volume status; consider diuretic dosage reduction

Insufficient diuretic response/diuretic resistance
- Check compliance and fluid intake; increase dose of diuretic; consider switching from furosemide to bumetanide or torasemide; add MRA/increase dose of MRA; combine loop diuretic and thiazide/metolazone[e]; administer loop diuretic twice (or more times) daily or on empty stomach/consider short-term i.v. infusion of loop diuretic; consider ultrafiltration

Renal impairment (rising creatinine/BUN–urea)
- Check for hypovolaemia/dehydration; exclude use of other nephrotoxic agents, e.g. NSAIDs, trimethoprim; withhold MRA; if using concomitant loop and thiazide diuretic stop thiazide diuretic; consider reducing dose of ACE inhibitor/ARB; consider haemofiltration/dialysis

Table 4. Practical Therapeutic Approach to Hyponatremia in HF

Establish the diagnosis of HF-related hypervolemic hyponatremia via history, physical exam, and laboratory studies; rule out noncardiac causes (eg, hyperglycemia, medications, and diarrhea).

Limit Na-free fluid intake (replace IV medication carriers to isotonic Na-containing solution in the inpatient setting).

Prescribe IV loop diuretics with close monitoring of serum Na (can be accompanied by simultaneous administration of hypertonic or isotonic saline solution in selected patients under supervision of an experienced physician).

Prescribe oral or IV VRA with close monitoring of serum Na to avoid rapid increase in serum Na and overcorrection.

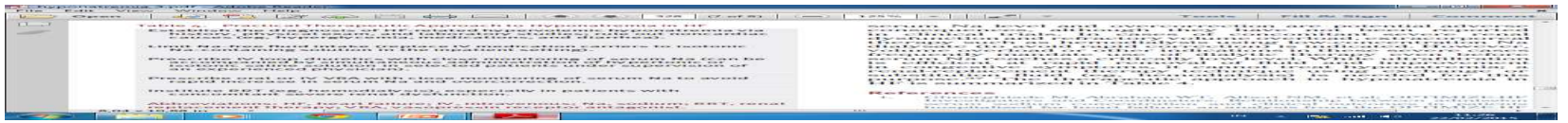
Institute RRT (eg, hemodialysis), especially in patients with concomitant severe renal dysfunction.

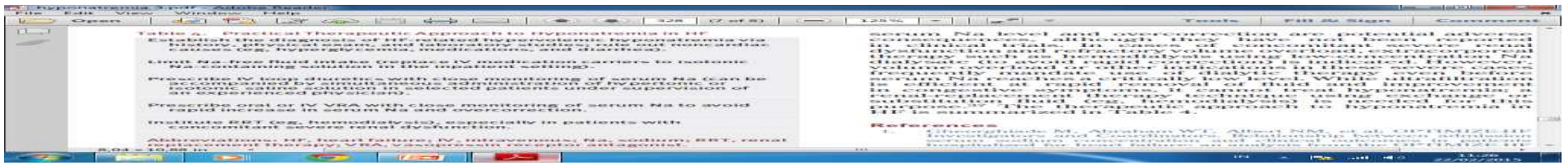
Abbreviations: HF, heart failure; IV, intravenous; Na, sodium; RRT, renal replacement therapy; VRA, vasopressin receptor antagonist.

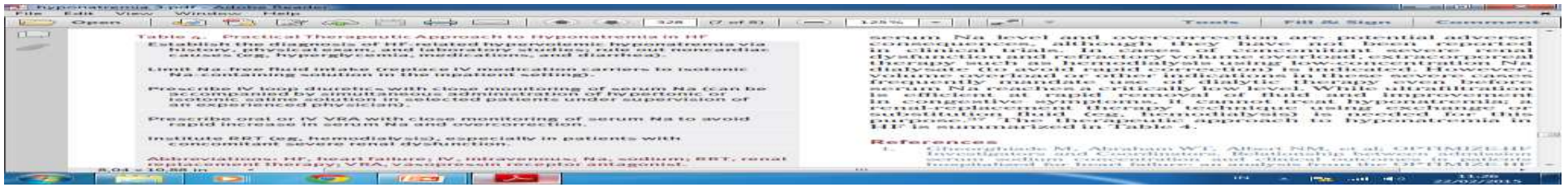
serum Na level and overcorrection are potential adverse consequences, although they have not been reported in clinical trials. In cases of concomitant severe renal dysfunction and refractory volume overload, extracorporeal therapy such as hemodialysis using low-concentration Na dialysate (to avoid rapid correction) is indicated. However, volume overload or other indications in these severe cases frequently mandate use of dialytic therapy even before serum Na reaches a critically low level. While ultrafiltration is efficient at rapid removal of fluid and improvement in congestive symptoms, it cannot treat hyponatremia; a renal-replacement therapy technique using exchanger or substitution fluid (eg, hemodialysis) is needed for this purpose.[87] The therapeutic approach to hyponatremia in HF is summarized in Table 4.

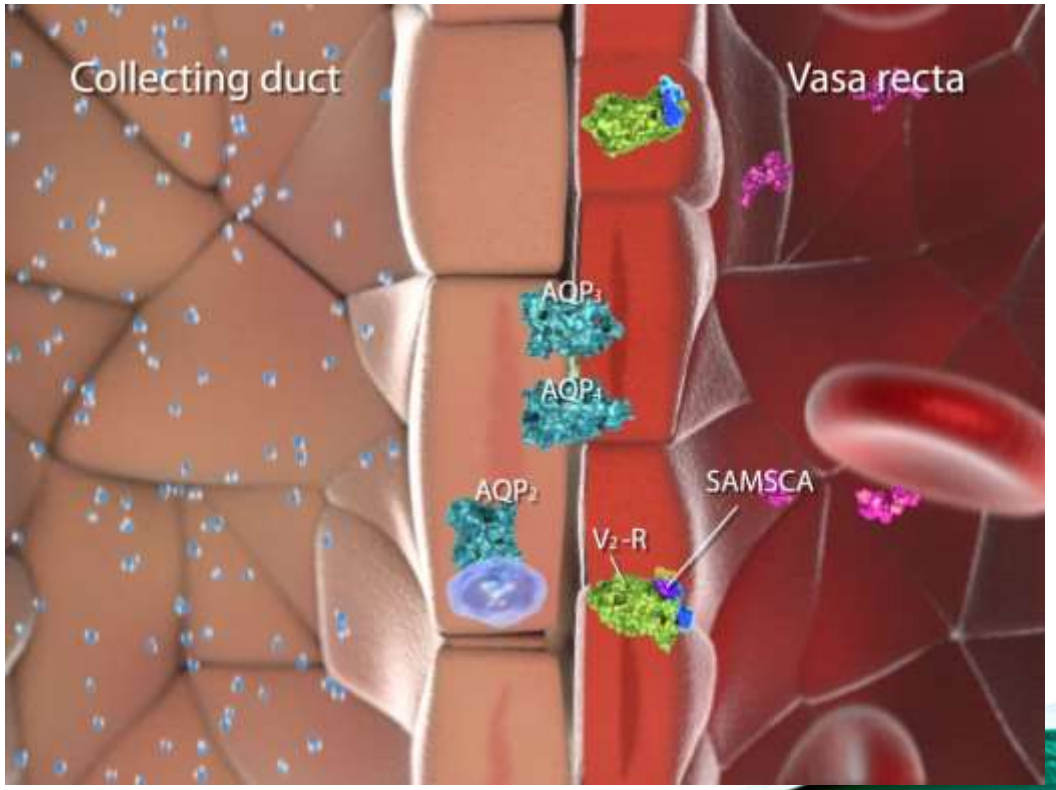
References

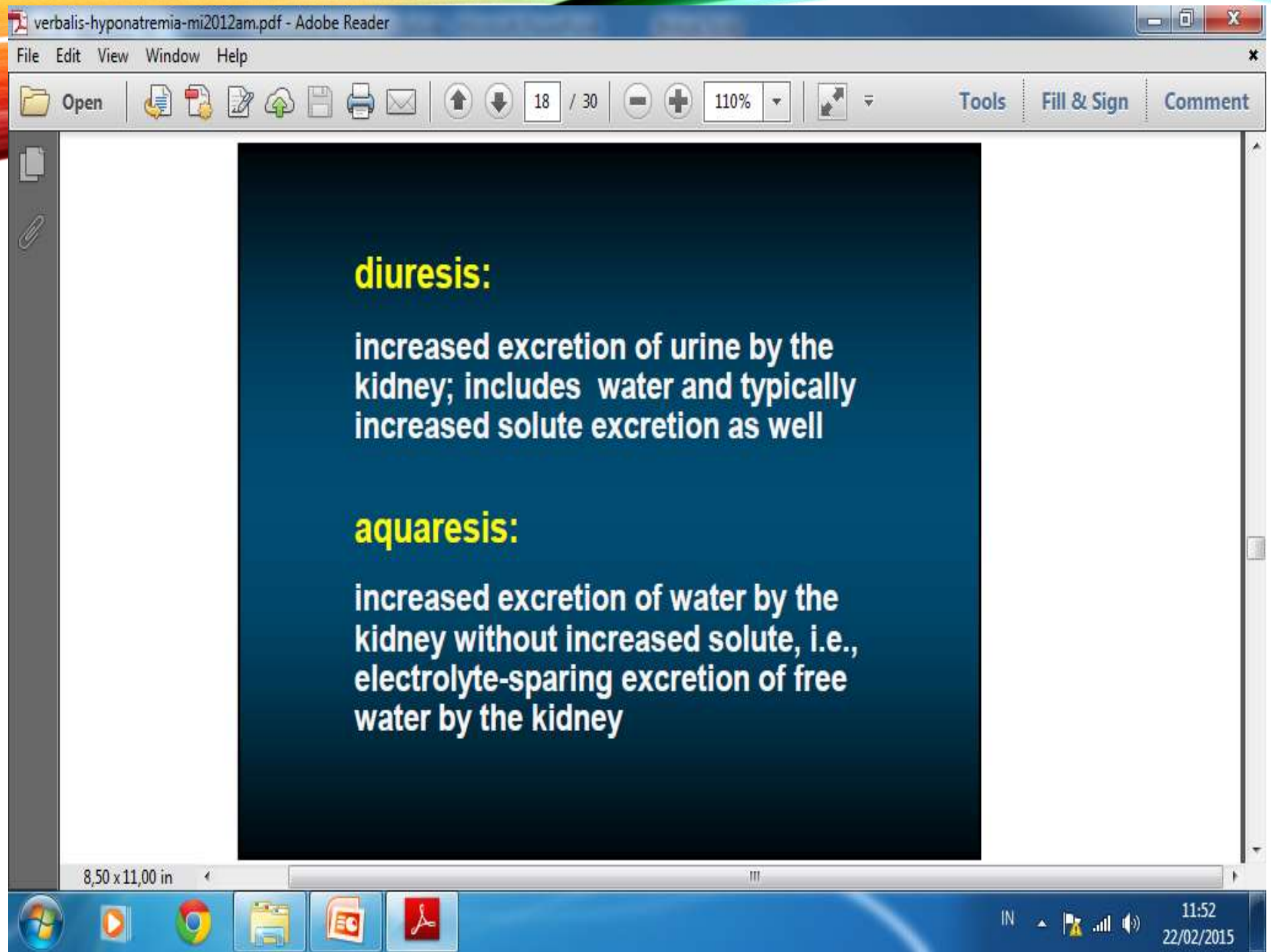
1. Gheorghiade M, Abraham WT, Albert NM, et al; OPTIMIZE-HF Investigators and Coordinators. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF








Collecting duct
Vasa recta
AQP3
AQP4
AQP2
SAMSCA
V2-R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diuresis:
increased excretion of urine by the kidney; includes water and typically increased solute excretion as well
aquaresis:
increased excretion of water by the kidney without increased solute, i.e., electrolyte-sparing excretion of free water by the kidney
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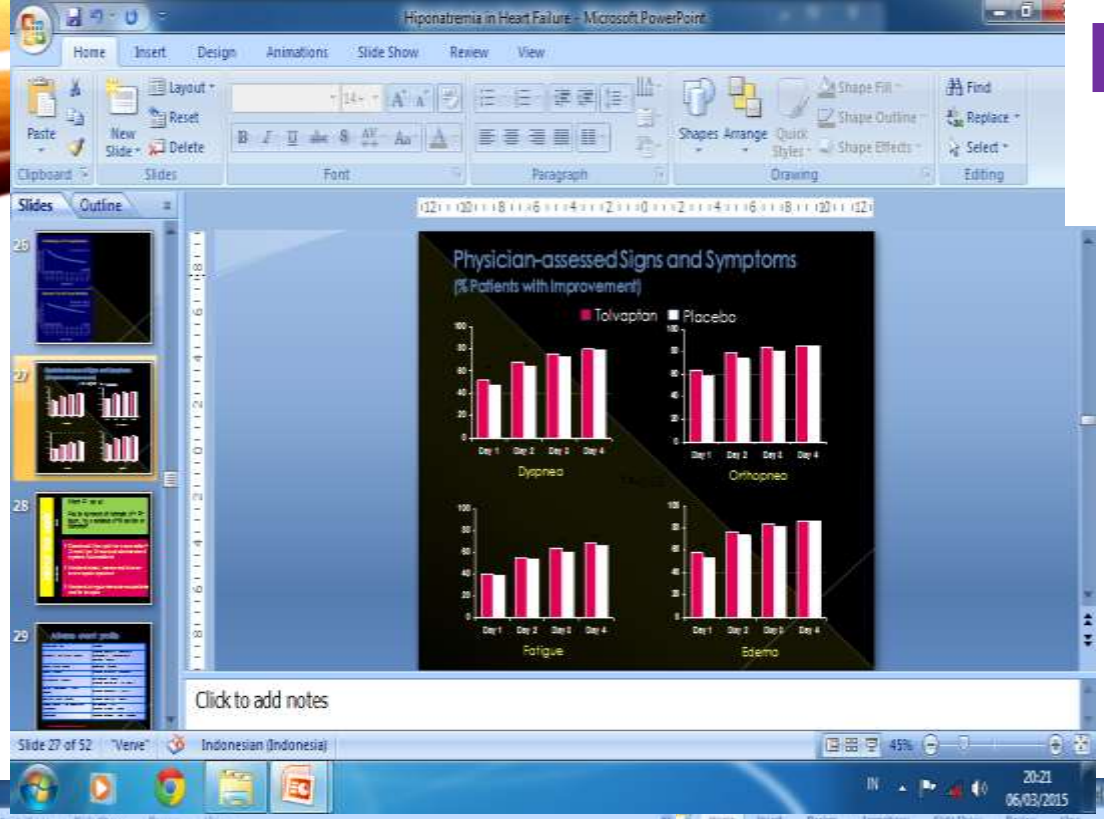
INDICATION

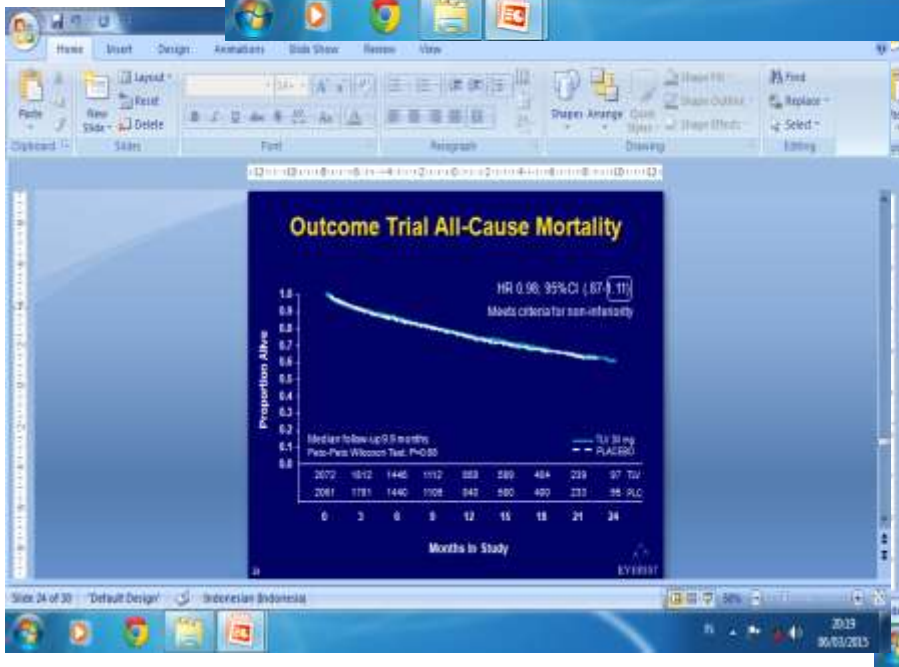
Indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

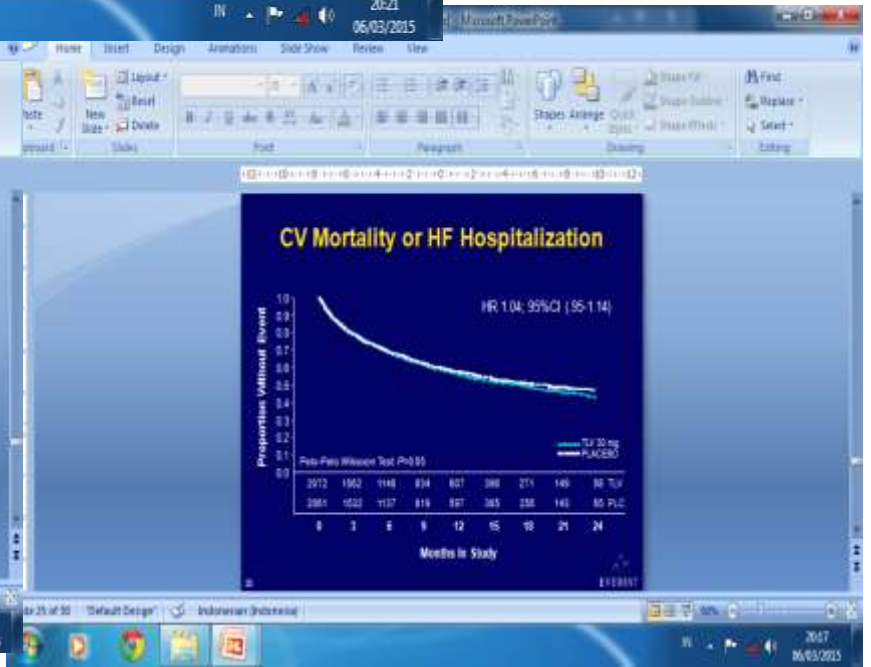
Indicated for volume overload in heart failure when adequate response is not obtained with other diuretics (e.g., loop diuretics)

Indicated for the treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)

EVEREST


Hiponatremia in Heart Failure - Microsoft PowerPoint
Physician-assessed Signs and Symptoms
(% Patients with Improvement)
Tolvaptan
Placebo
Dyspnea
Orthopnea
Fatigue
Edema
Click to add notes


Outcome Trial All-Cause Mortality
Proportion Alive
Months in Study


CV Mortality or HF Hospitalization
Proportion Without Event
Months in Study

HOW TO USE

- **Start 15 mg od**
- **Can be increased at intervals of ≥ 24 hours, to a maximum of 60 mg/day as tolerated1**

- Discontinued if too rapid rise in serum sodium (> 12 mmol/l per 24 hours) and administration of hypotonic fluid considered
- Monitored closely, in severe renal failure or severe hepatic impairment

Adverse event profile

System organ class	Frequency
Metabolism and nutrition disorders	Common: polydipsia, dehydration, hyperkalaemia, hyperglycaemia, decreased appetite
Nervous system disorders	Uncommon: dysgeusia
Vascular disorders	Common: orthostatic hypotension
Gastrointestinal disorders	Very common: nausea Common: constipation, dry mouth
Skin and subcutaneous tissue disorders	Common: ecchymosis, pruritus
Renal and urinary disorders	Common: pollakiuria, polyuria
General disorders and administration site conditions	Very common: thirst Common: asthenia, pyrexia
Investigations	Common: increased blood creatinine

1. Samsca Summary of Product Characteristics. 2009.

CONTRAINDICATIONS

- Hypersensitivity
- Anuria
- Volume depletion
- Hypovolaemic hyponatraemia
- Hypernatraemia
- Patients who cannot perceive thirst
- Pregnancy
- Breastfeeding

WARNINGS

Urgent need to raise serum [Na+] acutely

Urinary outflow obstruction

Diabetes mellitus

1. Samsca Summary of Product Characteristics. 2009.

A 73 yo male admitted with weakness and fatigued for approximately one month

Diuretics
Fluid restriction
Tolvaptan

- T 37.5, BP 128/68 HR 80 (irregular), RR 16, SaO2 95%
- RESP no crackles or wheezes
- CVS: JVP 6
- S1/S2 present, no S3/S4
- 3+ pitting edema bilaterally to sacrum

A 47 yo male admitted with pain in suprapubic area approximately one month. Pts with history of

Dialysis
Remove the stone

BP 140/90 HR 80 RR 12, SaO2 99%

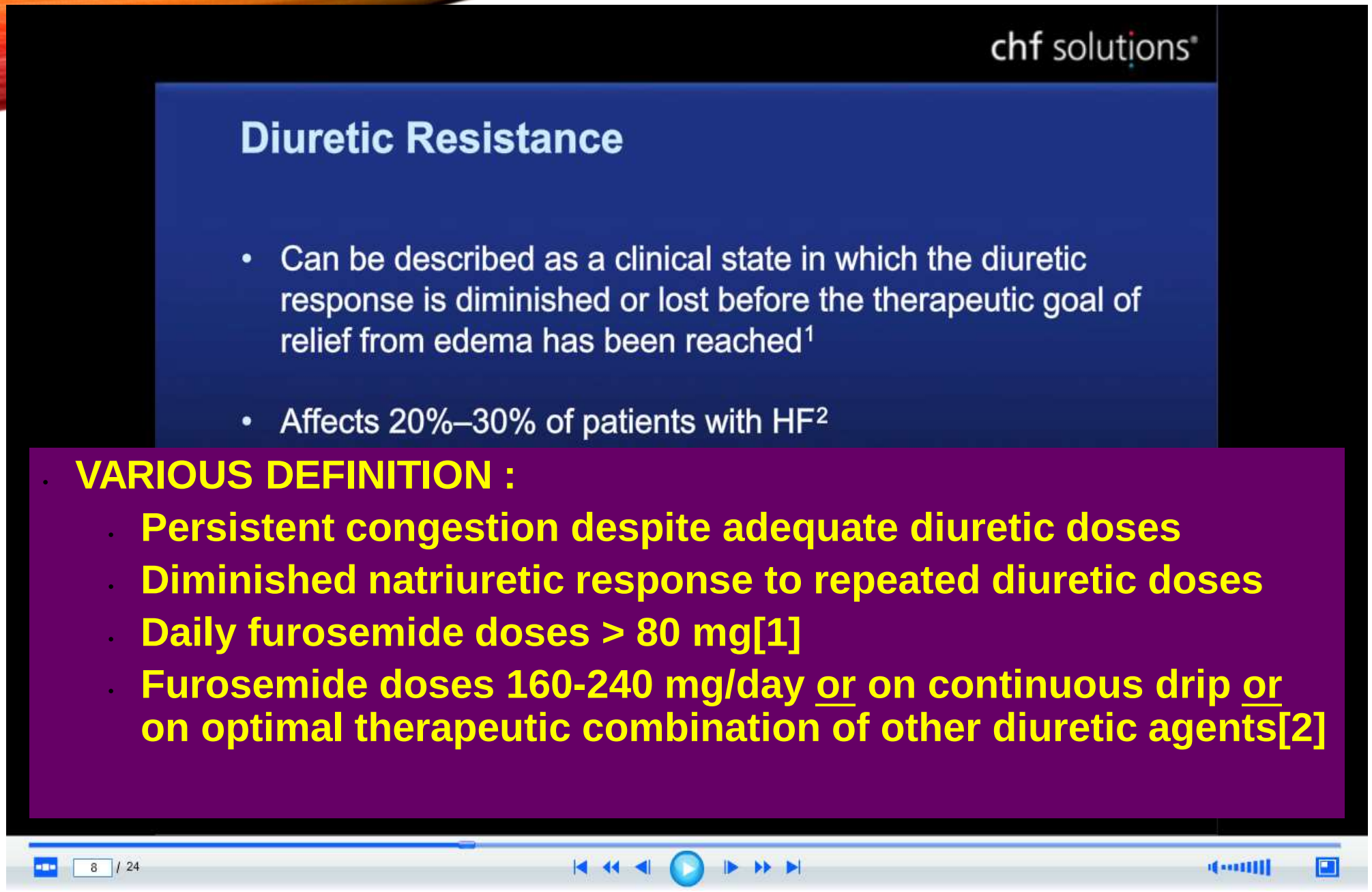
RESP no crackles or wheezes

S1/S2 present, no S3/S4

No edema

Renal panel: Na 104 mmol/L, K 4,6 mmol/L, Cr 69 umol/L, Cr 5,9, Urea 197

Problems	Suggested action
Hypokalaemia/hypomagnesaemia	▪ Increase ACEI/ARB dosage ▪ Add aldosterone antagonist ▪ Potassium supplements ▪ Magnesium supplements
Hyponatraemia	▪ Fluid restriction ▪ Stop thiazide diuretic or switch to loop diuretic, if possible ▪ Reduce dose/stop loop diuretics if possible ▪ Consider AVP antagonist, e.g. tolvaptan if available ▪ I.v. inotropic support ▪ Consider ultrafiltration
Hyperuricaemia/gout	▪ Consider allopurinol ▪ For symptomatic gout use colchicine for pain relief ▪ Avoid NSAIDs
Hypervolaemia/dehydration	▪ Assess volume status ▪ Consider diuretic dosage reduction
Insufficient response or diuretic resistance	▪ Check compliance and fluid intake ▪ Increase dose of diuretic ▪ Consider switching from furosemide to bumetanide or torasemide ▪ Add aldosterone antagonist ▪ Combine loop diuretic and thiazide/metolazone ▪ Administer loop diuretic twice daily or on empty stomach ▪ Consider short-term i.v. infusion of loop diuretic
Renal failure (excessive rise in urea/BUN and/or creatinine)	▪ Check for hypervolaemia/dehydration ▪ Exclude use of other nephrotoxic agents, e.g. NSAIDs, trimethoprim ▪ Withhold aldosterone antagonist ▪ If using concomitant loop and thiazide diuretic stop thiazide diuretic ▪ Consider reducing dose of ACEI/ARB ▪ Consider ultrafiltration



- **VARIOUS DEFINITION :**
  - **Persistent congestion despite adequate diuretic doses**
  - **Diminished natriuretic response to repeated diuretic doses**
  - **Daily furosemide doses > 80 mg[1]**
  - **Furosemide doses 160-240 mg/day or on continuous drip or on optimal therapeutic combination of other diuretic agents[2]**

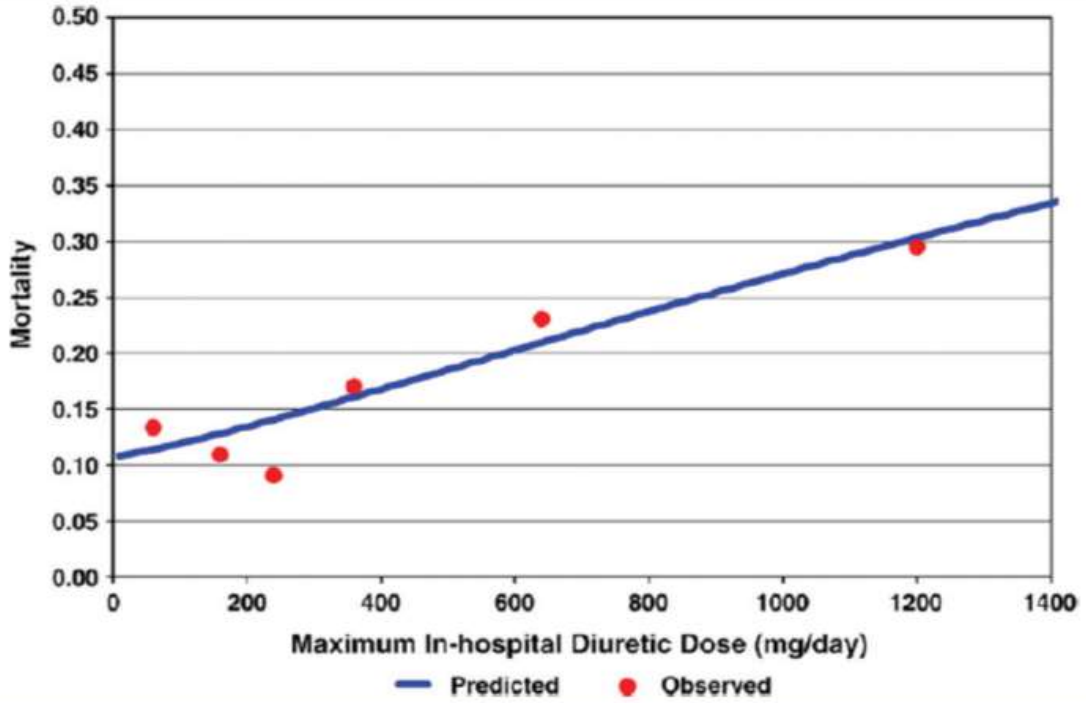


Figure 2 Relationship between maximum daily dose of loop diuretic, expressed in furosemide equivalents, and mortality at 180 days in 395 patients admitted to the hospital with decompensated heart failure. $P = 0.003$. Reprinted with permission from Hasselblad V, Stough WG, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail* 2007;**9**:1064–1069.

MECHANISM

Strategy for t

Reduce RAS & SNS activity

Reduce RAS & SNS activation

Continuous infusion

Change to intravenous

Higher doses of loop diuretic

1. Check compliance and fluid intal
2. Increase dose
3. Long acting loop diuretics
4. Empty stomach

Prevent post diuretic so	Reduce side effects	Ototoxicity

Thiazide (50-100 mg/day) or thiazide like (metolazone 10 mg/day))

Acetazolamide (250 mg/day)

AVP antagonist

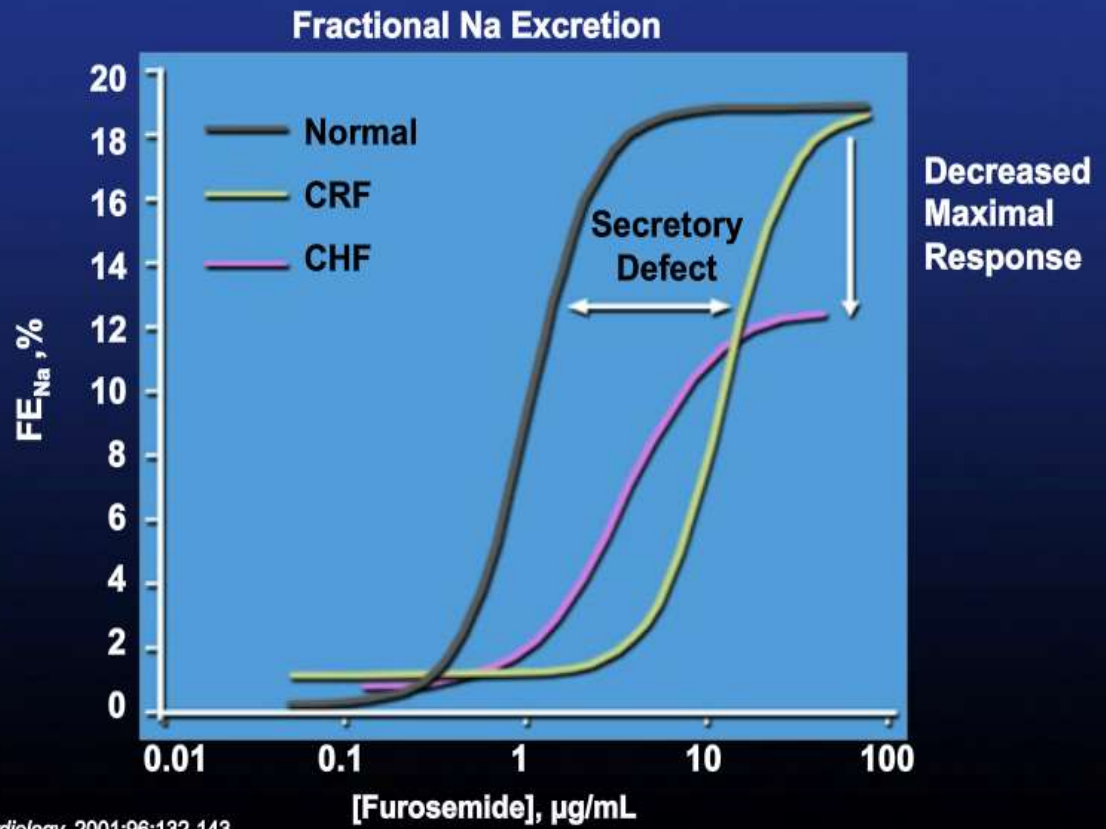
Renal dose dopamin

Ultrafiltration

Combination with other diur

chf solutions®

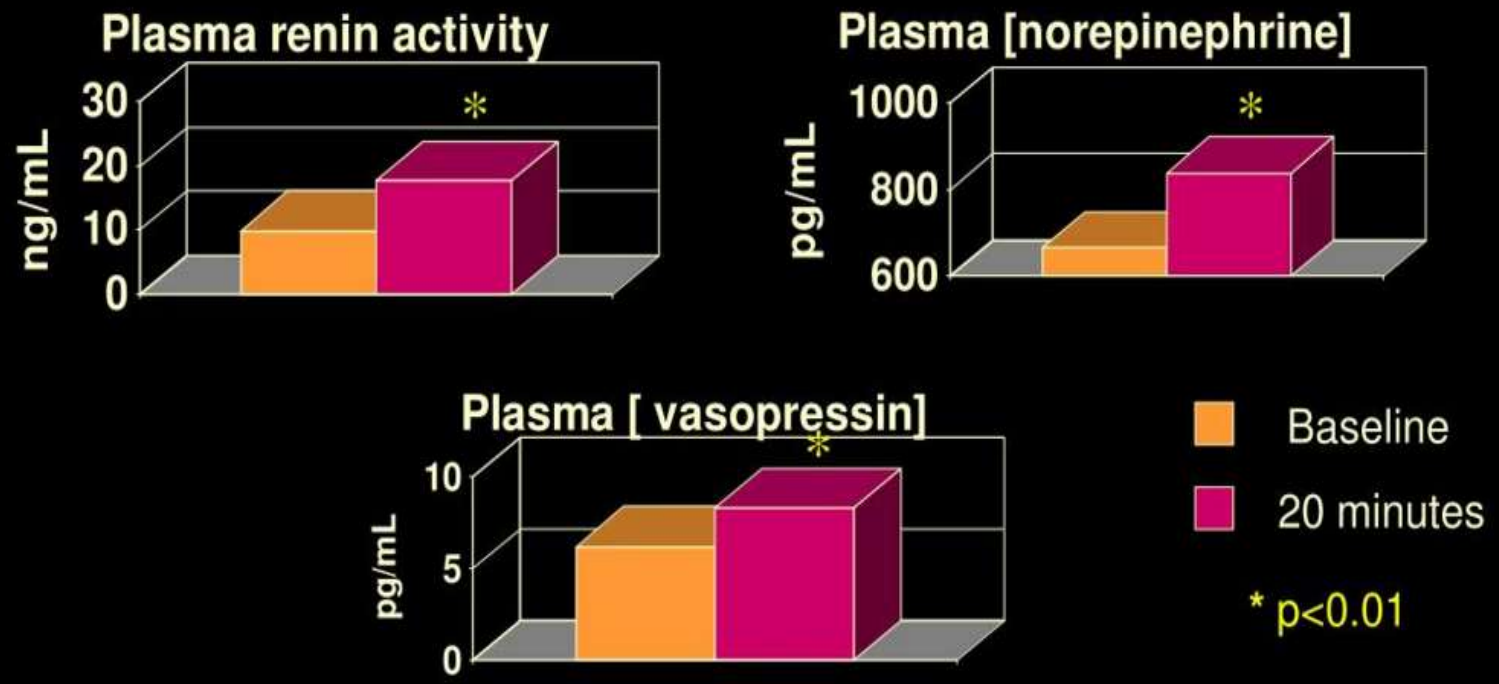
Dose Response Curves for Loop Diuretics in ADHF Are Altered



Ellison. *Cardiology*. 2001;96:132-143.

13

Diuretic Resistance
Neurohormonal Stimulation



Francis GS, et al. Ann Intern Med 1985;103:1-6.

Treatment of Diuretic Resistance

IV Bolus vs Continuous Infusion

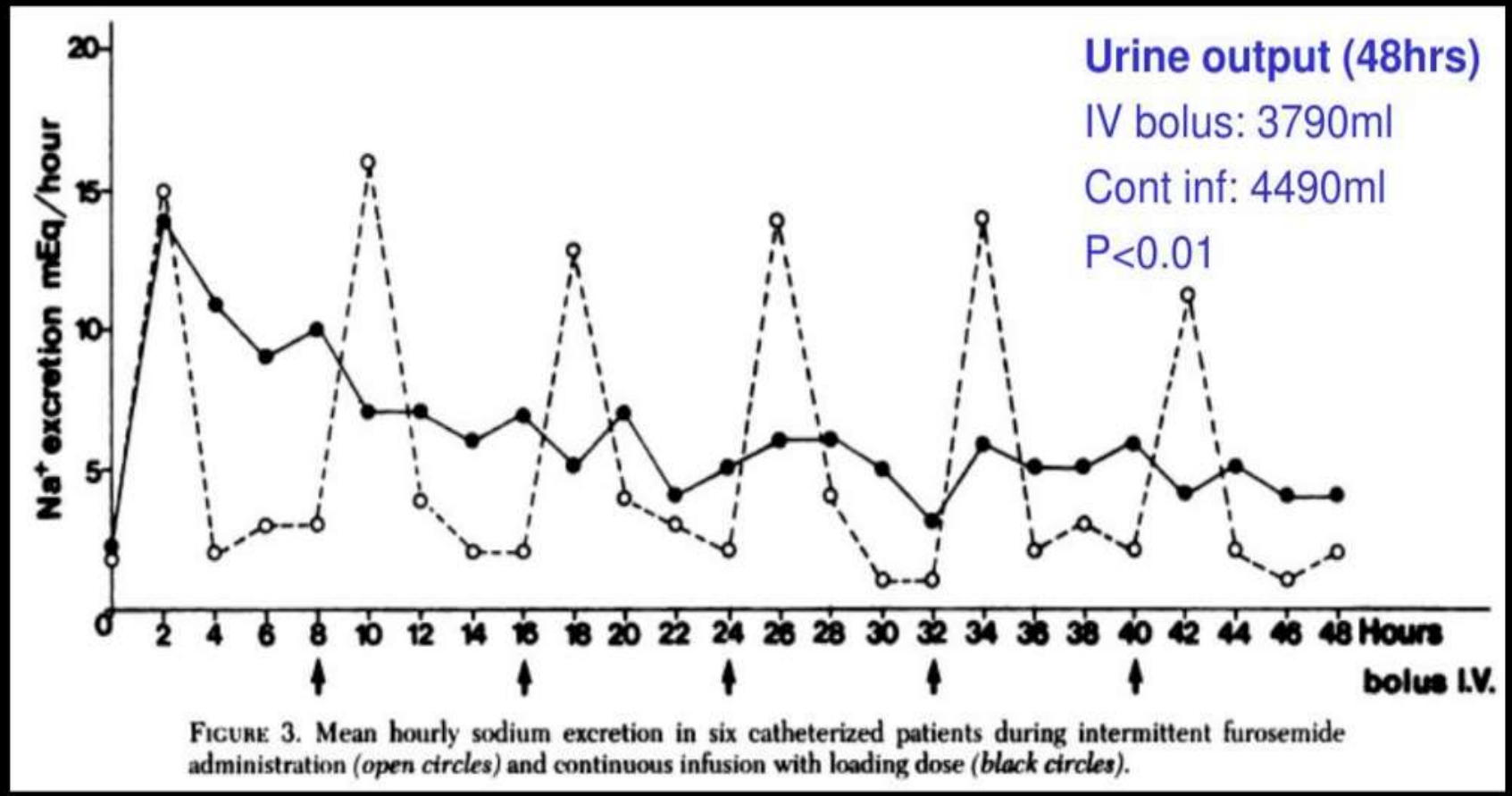


FIGURE 3. Mean hourly sodium excretion in six catheterized patients during intermittent furosemide administration *(open circles)* and continuous infusion with loading dose *(black circles)*.

Lahav M, et al. Chest 1992;102:725-31.

IV Vasoactive Therapy in ADHF

ADHERE Mortality Analysis

Table 4. Mortality Odds Ratios in Pair-Wise Treatment Comparisons

Analysis*	NTG (n = 6,055) vs. MIL (n = 1,660)	NTG (n = 5,713) vs. DOB (n = 3,478)	NES (n = 4,663) vs. MIL (n = 1,534)	NES (n = 4,270) vs. DOB (n = 3,301)	NES (n = 4,402) vs. NTG (n = 5,668)	DOB (n = 3,656) vs. MIL (n = 1,496)
Unadjusted	0.34 (0.28–0.41)†	0.24 (0.20–0.28)†	0.53 (0.44–0.64)†	0.37 (0.32–0.44)†	1.64 (1.38–1.94)†	1.39 (1.15–1.68)†
Adjusted for covariates‖	0.69 (0.54–0.88)†	0.46 (0.38–0.57)†	0.59 (0.48–0.73)†	0.47 (0.39–0.56)†	0.95 (0.78–1.16)‡	1.27 (1.04–1.56)§
Adjusted for covariates and propensity score¶	0.69 (0.53–0.89)†	0.46 (0.37–0.57)†	0.59 (0.48–0.73)†	0.47 (0.39–0.56)†	0.94 (0.77–1.16)‡	1.24 (1.03–1.55)§

Hosmer-Lemeshow goodness-of-fit test not significant at 5% levels for the models adjusted for risk factors and/or propensity, except for covariate-adjusted NTG vs. DOB comparison, where p = 0.04. Area under the receiver operator curve = 0.70 or higher. Because of multiple pair-wise comparisons, only p values <0.008 were considered significant using Bonferroni correction. *Patients taking both medications were excluded from each pair-wise analysis. †p < 0.005. ‡p = 0.58. §p = 0.021 for covariate adjustment and 0.027 for covariate and propensity score adjustment. ‖Covariates include age, gender, SBP, DBP, BUN, creatinine, sodium, heart rate, and dyspnea. ¶Covariates included in the propensity score by treatment comparison are: NES vs. DOB: SBP, sodium, BUN, creatinine, age, weight, LVEF, edema; NES vs. MIL: SBP, age, LVEF, dyspnea, weight; NTG vs. DOB: SBP, sodium, BUN, heart rate, LVEF, symptom duration; NTG vs. MIL: SBP, BUN, LVEF, symptom duration, dyspnea, QRS >120 ms, previous revascularization; NES vs. NTG: SBP, BUN, creatinine, LVEF, symptom duration, edema, previous HF, QRS >120 ms; DOB vs. MIL: SBP, age, hemoglobin, heart rate, dyspnea, VTF.

DOB = dobutamine; HF = heart failure; LVEF = left ventricular ejection fraction; MIL = milrinone; NES = nesiritide; NTG = nitroglycerin; OR = odds ratio; VTF = ventricular tachycardia/fibrillation; other abbreviations as in Table 1.

Abraham WT, et al. JACC 2005;46:57-64.

Diuretic Resistance

1. Compensatory Mechanisms
2. Failure to reach tubular site of action

1. Interference by other drugs
2. Tubular adaptation

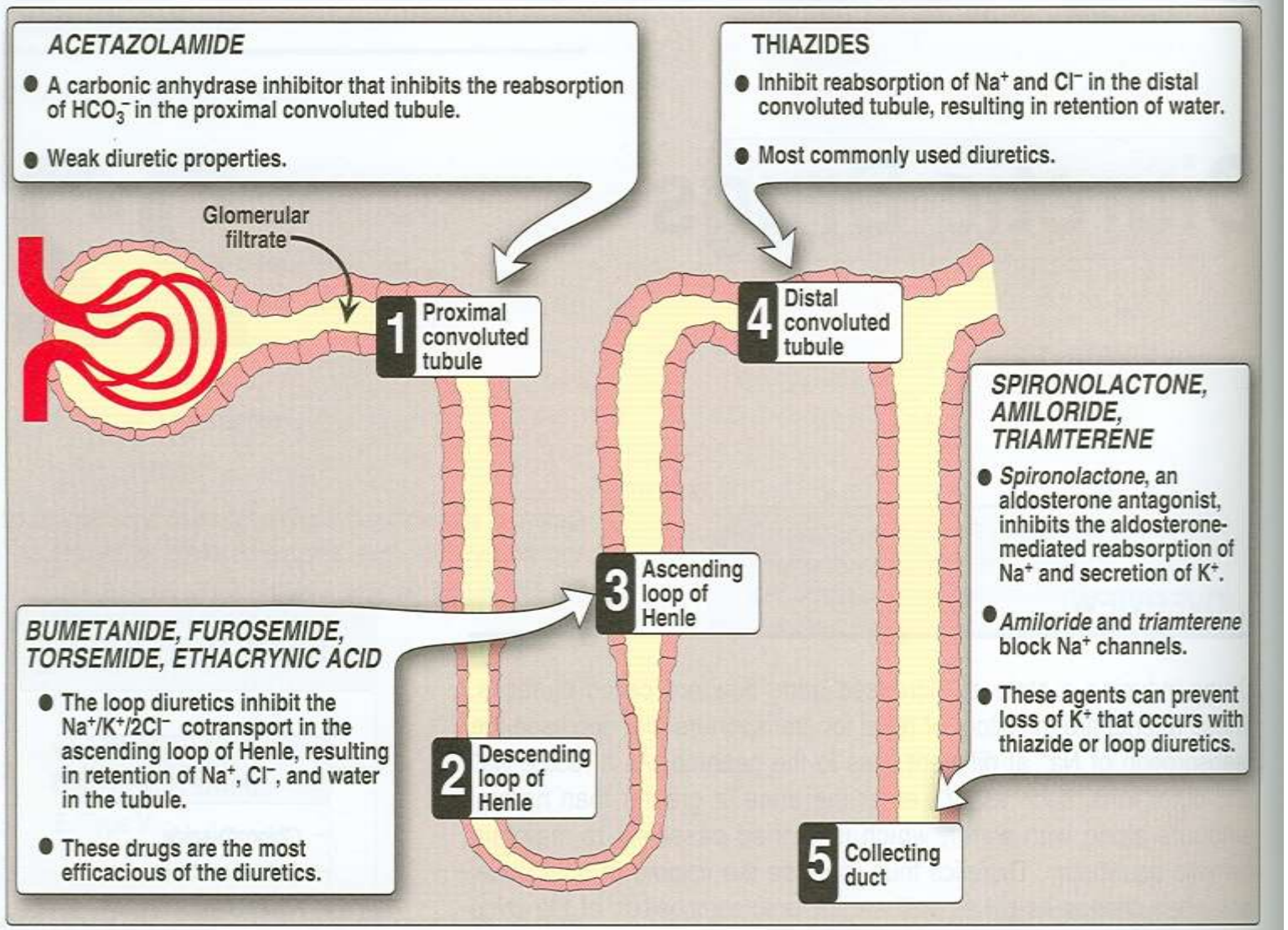


Figure 22.2
Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

ESC GUIDELINES DESK REFERENCE
ESC Committee for Practice Guidelines
To improve the quality of clinical practice and patient care in Europe
CARDIOVASCULAR MEDICINE
COMPENDIUM OF
ABRIDGED ESC GUIDELINES
2011

Fluid re			
Modera			ymptoms response - Monitor K,
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Refracto to loop diuretic and thiazides			failure

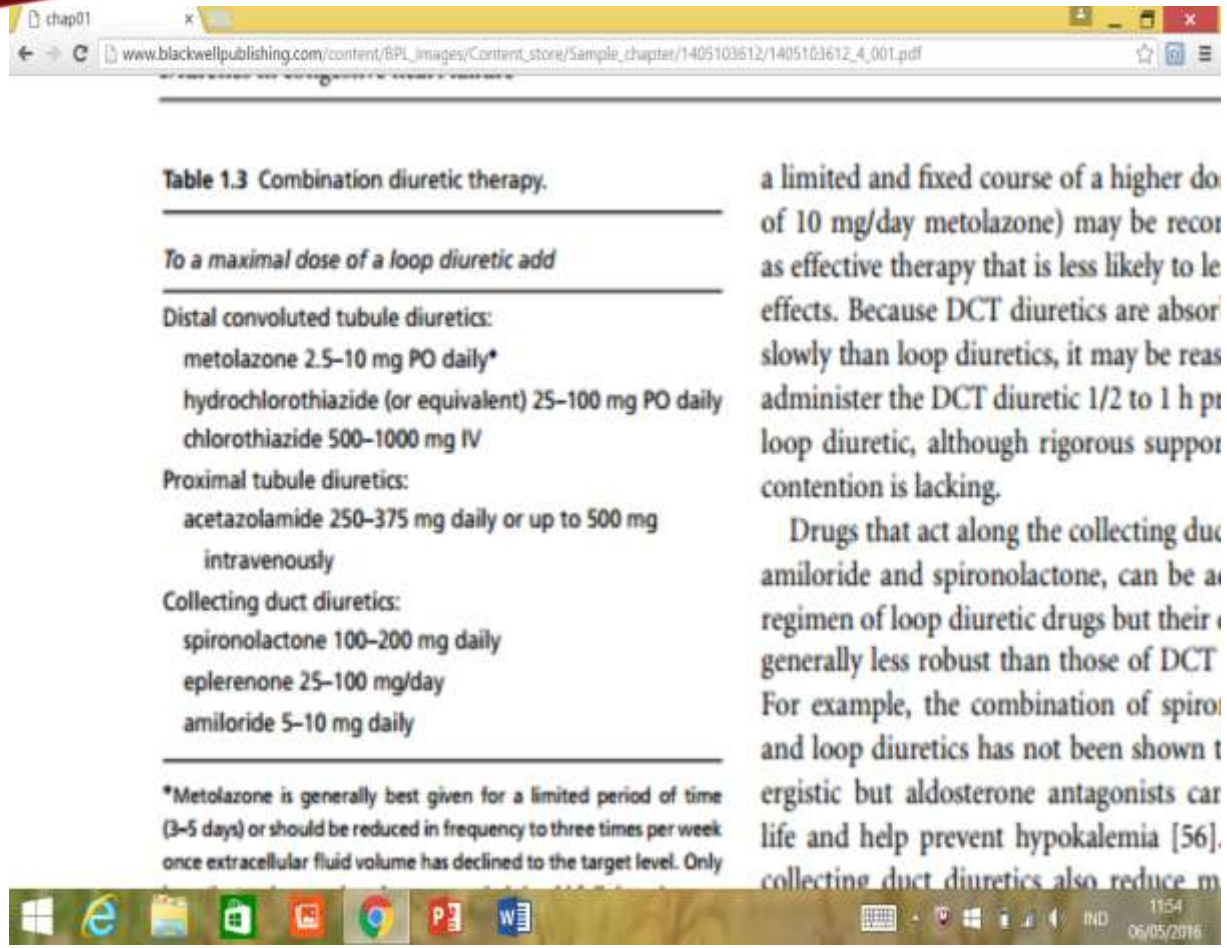

Table 1.3 Combination diuretic therapy.

To a maximal dose of a loop diuretic add
Distal convoluted tubule diuretics:
metolazone 2.5–10 mg PO daily*
hydrochlorothiazide (or equivalent) 25–100 mg PO daily
chlorothiazide 500–1000 mg IV
Proximal tubule diuretics:
acetazolamide 250–375 mg daily or up to 500 mg intravenously
Collecting duct diuretics:
spironolactone 100–200 mg daily
eplerenone 25–100 mg/day
amiloride 5–10 mg daily

*Metolazone is generally best given for a limited period of time (3–5 days) or should be reduced in frequency to three times per week once extracellular fluid volume has declined to the target level. Only

a limited and fixed course of a higher do
of 10 mg/day metolazone) may be recor
as effective therapy that is less likely to le
effects. Because DCT diuretics are absor
slowly than loop diuretics, it may be reas
administer the DCT diuretic 1/2 to 1 h pr
loop diuretic, although rigorous suppor
contention is lacking.

Drugs that act along the collecting duc
amiloride and spironolactone, can be a
regimen of loop diuretic drugs but their
generally less robust than those of DCT
For example, the combination of spiro
and loop diuretics has not been shown t
ergistic but aldosterone antagonists car
life and help prevent hypokalemia [56].
collecting duct diuretics also reduce m

SUMMARY

- Hyponatremia in heart failure is a hypervolemia hyponatremia (dilutional hyponatremia)
- Hypertonic saline and isotonic saline are contraindicatd in heart failure setting
- AVP antagonist is effective in reducing lasma overload Penggunaan antagonis AVP yang bersifat aquareik terbukti efektif meningkatkan diuresis tanpa kehilangan narium


Thank You