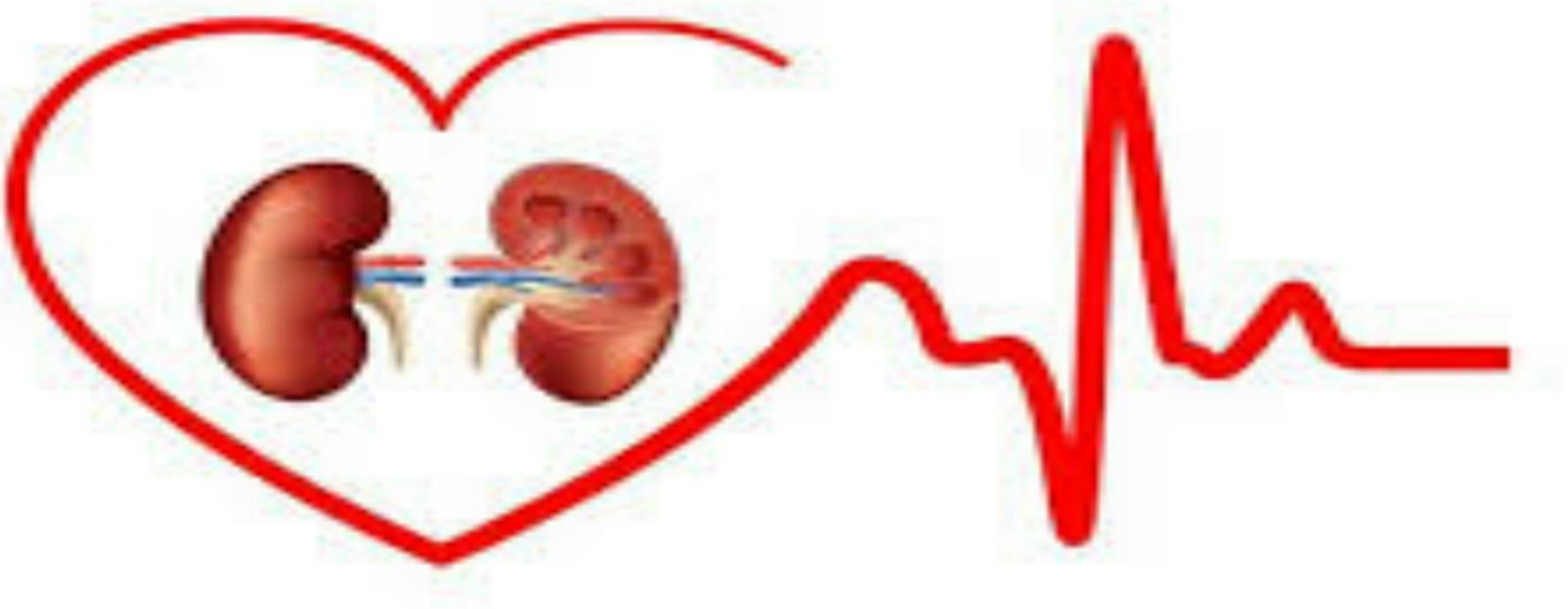
Update on Treatment of cardiorenal syndrome 1; Nephrologist view



- **Dr.F.Haghverdi MD**

CASE:

- 65-year- old man with history of HTN,DM and congestive heart failure presented with Acute STEMI and dyspnea and admitted in CCU. Also he was known case of CKD 3b (DM nephropathy) ,(Cr= 2 mg/dl three month ago, eGFR= 40 cc/ min ,CKD EPI).
- 2 days after admission in CCU, his cardiologist noticed oliguria and creatinin rising.(Cr on admission day was 2 and now is 3.5 mg/dl).
- **Cardiologist requested nephrology consult for AKI on CKD and urgent coronary angiography.**

CASE:

- **Ph Exam:** BP=110/60 ,RR=30/min ,T=37 , PR=100/min , O2 sat=90% (3lit O2nasal), W=70 kg
- **fine Rales in 1/3 of both lungs**
- **S3 sound, 2+ edema on legs, JVP=11cm H2O**
- **Lab: BUN=100 mg/dl, Cr =3.5**
- **Hb= 9.5 g/dl**, Na =135 meq/l, K= 5 meq/l, **Cl= 90 meq/ l**
- FBS=130 mg/dl, **Uric acid= 12 mg/dl, Alb=2.5 g/ dl**
- ABG: PH =7.34 , PCO2 =27 , HCO3 =15
- Urine analysis :+ +protein , **Urine output= 400 cc / day**
- SONO : RK=110 mm, LK =115 mm, EF= 30% ,**pro BNP= 500pg/ml**
- **POXUS: Lung ultrasound 5 B _ line in at least two zone, , IVC diameter = 3 cm and less than 50% collapsibility in spiration.**

CASE:

- **Drugs**: ASA 80/d, valsartan 80 mg Bd, Amp lasix 5mg/h , TNG 5 mic/min , plavix75/d, atorvastatin 40mg/d , Heparin 1000 u/ h ,Insulin glargin 10 u/ day

- **As a Consultant nephrologist , What is your diagnosis and treatment plan?**

Case problems:

CRS1, true AKI or Pseudo AKI(permissive AKI)?

- 1 -Volume overload (stepped Diuretics therapy vs UF) ?
- 2- Four pillars treatment (ARNI,SGLT2 INH, MRA,GLP_1 agonist and Worsening of renal function)?
- 3-Hyponatremia management (Vaptan)?
- 4-Hyperurecemia management (Allopurinol)?
- 5- Anemia Management (CRAIDS and blood transfusion, EPO, iron,SGLT-2 inh effect)?
- 6-Mineral receptor antagonist?(finerenon)
- 7-Contrast nephropathy risk and prophylaxy?

Cardiorenal syndrome classification

Type	Definition
CRS type 1 (acute cardiorenal syndrome)	Abrupt worsening of cardiac function (e.g. acute cardiogenic shock, acute decompensation of chronic heart failure or acute coronary syndrome) leading to acute kidney injury.
CRS type II (chronic cardiorenal syndrome)	Chronic abnormalities in cardiac function (e.g. chronic heart failure) causing progressive chronic kidney disease.
CRS type III (acute renocardiac syndrome)	Abrupt worsening of renal function (e.g. acute kidney failure due to volume depletion or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, pulmonary edema).
CRS type IV (chronic renocardiac syndrome)	Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and / or increased risk of adverse cardiovascular events.
CRS type V (secondary cardiorenal syndrome)	Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction.

CRS classification (nephrologist view)

Table 1 | Proposed CRS classification based on putative pathophysiology and clinical applicability at time of patient evaluation

CRS category	Definition	Comments
1) Haemodynamic	Haemodynamic compromise is the major clinical manifestation	Can be subclassified as acute (1a) or chronic (1b)
2) Uraemic	Uraemic manifestations are the most prominent clinical appearances	Can be subclassified as acute (2a) or chronic (2b)
3) Vascular	Cardiovascular and/or renovascular manifestations are the most prominent clinical findings	Can be subclassified as acute (3a) or chronic (3b) and as atherosclerotic (as), thromboembolic (te) or endothelial dysfunction (ed)
4) Neurohumoral	Electrolyte disorders, acid–base disorders or dysautonomia is the most prominent finding	Can be subcategorized into acute (4a) or chronic (4b) and into electrolyte (el), acid–base (ab) or autonomic dysregulation (ad)
5) Anaemia and/or iron metabolism	Anaemia and/or iron metabolism dysregulation are the most prominent clinical manifestations	Can be subcategorized into acute (5a) or chronic (5b)
6) Mineral metabolism	Dysregulation of calcium and phosphorus and their regulators including vitamin D and FGF23 are the most prominent clinical manifestations	This category is mostly chronic by nature
7) Malnutrition–inflammation–cachexia	Malnutrition, cachexia and inflammatory state is the most prominent clinical manifestation	This category is mostly chronic by nature

Each category shows the most prominent clinical manifestation of the patient that needs to be addressed first. The category of any given patient may vary with time and depends on the current clinical evaluation. The category at any point in time guides the clinician to the main focus of management. Abbreviations: CRS, cardiorenal syndrome; FGF23, fibroblast growth factor 23.

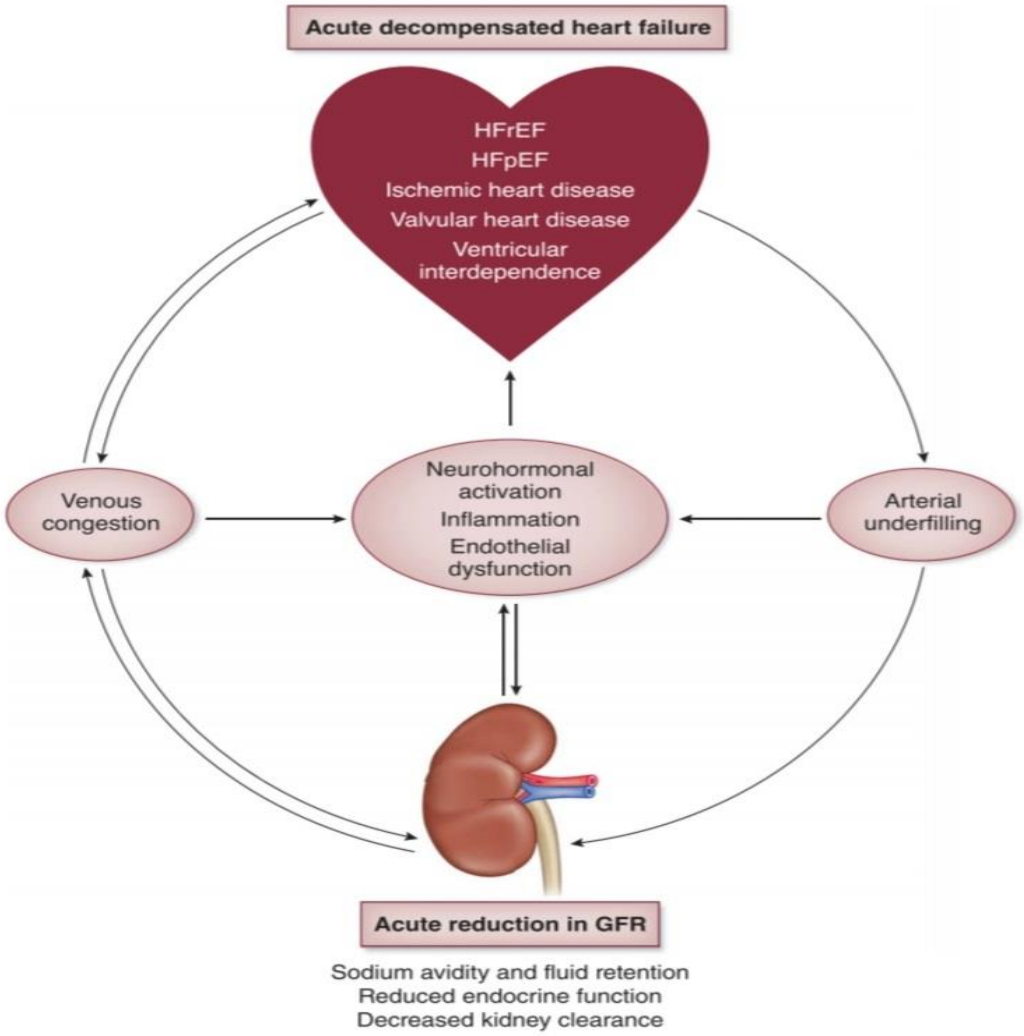


Figure 1. Proposed pathophysiological pathways leading to the cardiorenal syndrome and its complications. The inciting event is usually an acute decompensation of heart failure. This may lead to either arterial underfilling or venous congestion as mediators that promote neurohormonal activity, inflammation, and endothelial dysfunction. In combination, these pathways lead to reductions in glomerular filtration rate. Complications include sodium avidity and fluid retention, reduced kidney clearance, and endocrine function, all of which further perpetuate the pathophysiology. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Na and water retention:

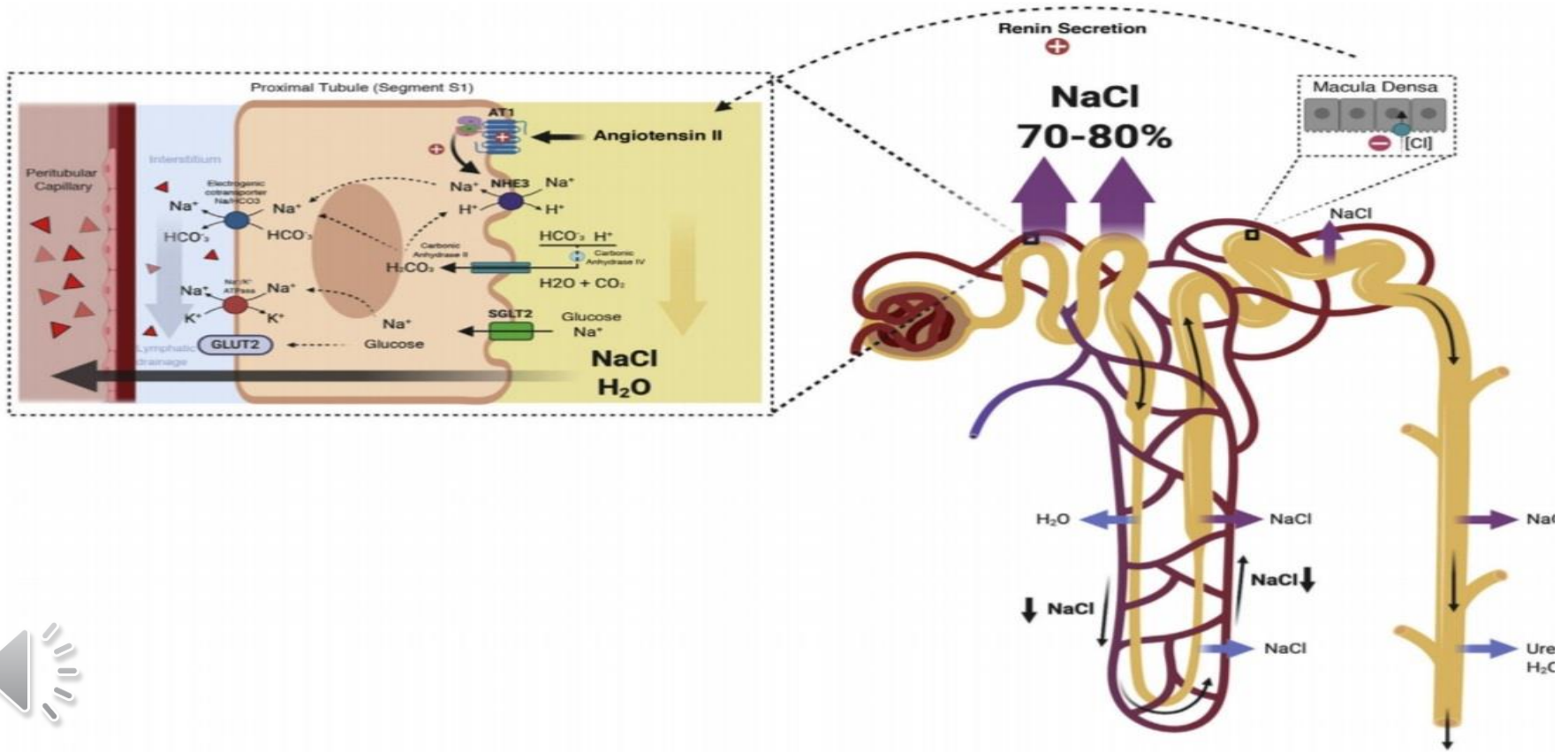


Figure 3 – Proximal tubule. Neurohormonal activation and intraglomerular and peritubular hemodynamic changes facilit Na and water reabsorption in the proximal tubule. Additionally, increased lymphatic flow washes out interstitial protein and decreases oncotic pressure in the renal interstitium, further promoting passive Na reabsorption.

Renal sodium avidity

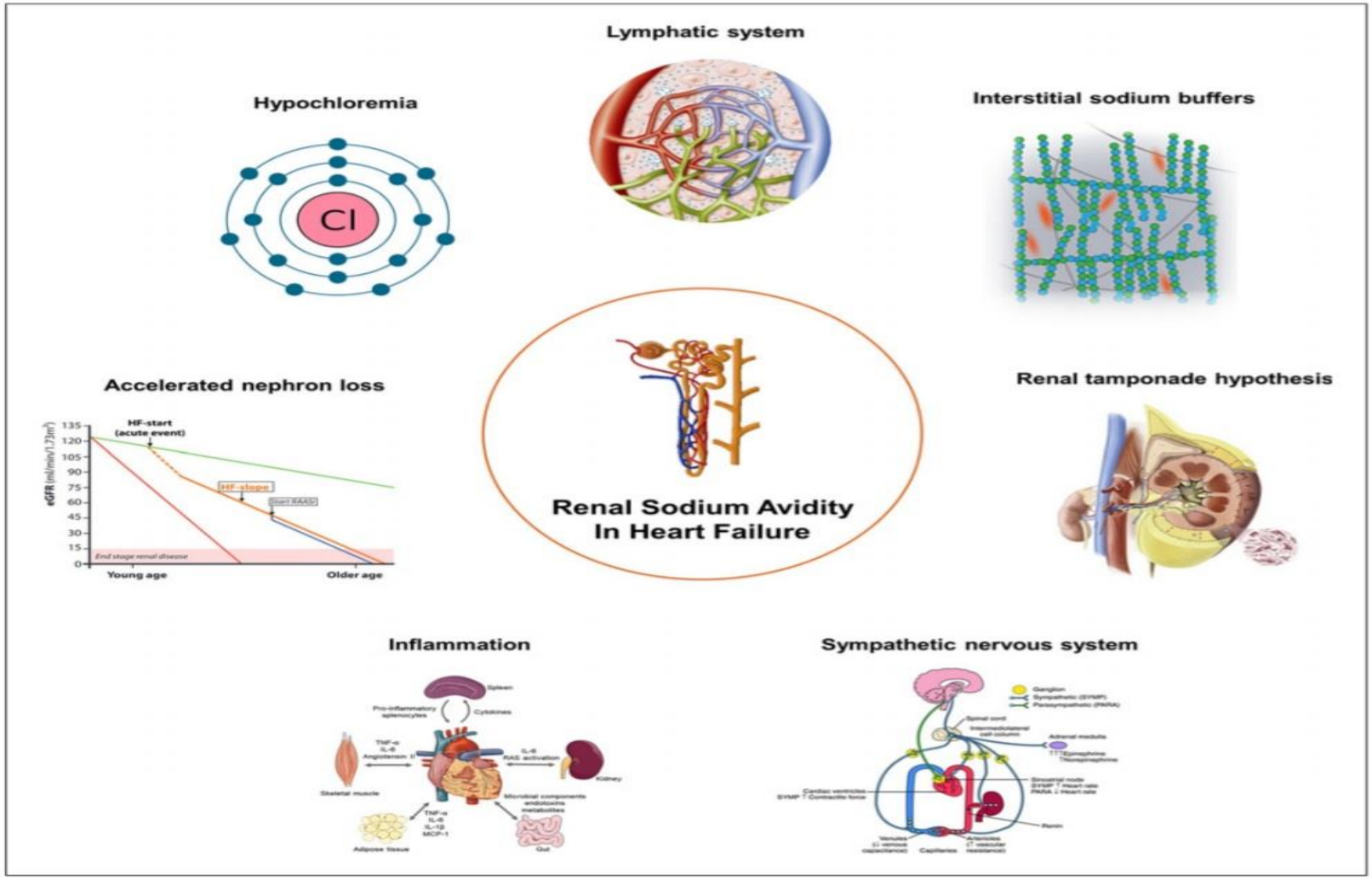


Fig. 1. Novel concepts in the pathophysiology of renal sodium avidity in HF.

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Sodium avidity

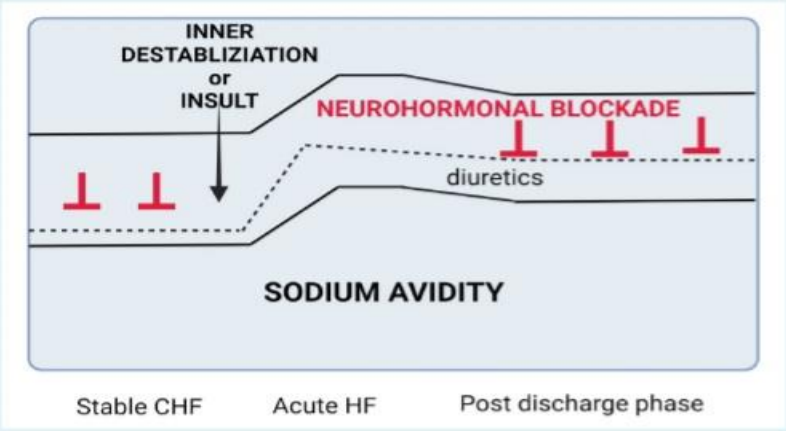


Figure 3 The classic 'diuretic centric' approach for decongestion. Neurohormonal blockade and diuretics counteract sodium avidity at a steady state (stable chronic heart failure [CHF]). Sodium avidity increases days/weeks before an episode of decompensation (inner destabilization of the sodium/water homeostasis control). Once the patient is admitted to the hospital (acute heart failure [HF]), the dose of diuretics is usually increased to counterbalance the elevated sodium avidity and excrete accumulated water and sodium. In the 'diuretic-centric' decongestion approach, once the excess water and sodium are excreted, the patient is discharged home with a dosage of loop diuretics, usually the same as or higher than before hospitalization. Neurohormonal blockade is usually not up-titrated adequately to counteract the increased sodium avidity, and the potential excess of sodium avidity is counterbalanced solely by adding diuretics. This approach only targets symptoms and does not effectively protect patients from subsequent decompensations or death.

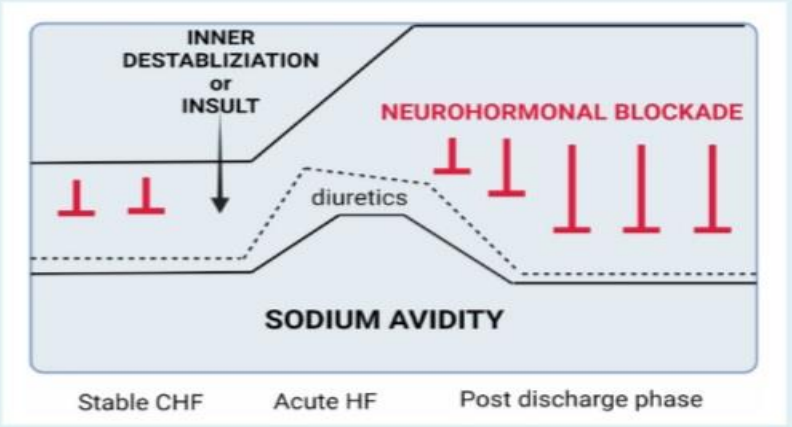


Figure 4 The new neurohormonal centric approach for sustained decongestion. The neurohormonal centric decongestion approach assumes that in the long run, sodium avidity should be mainly counterbalanced by neurohormonal blockade (guideline-directed medical therapy) with the lowest possible dose of diuretics. Sodium avidity increases days/weeks before an episode of decompensation. Once the patient is admitted to the hospital (acute heart failure [HF]), the dose of diuretics is usually increased to counterbalance the high sodium avidity and excrete accumulated water and sodium. However, in the neurohormonal centric approach, once the patient does not present overt fluid overload, the major goal is to initiate/up-titrate neurohormonal blockade to counterbalance sodium avidity, so the dose of diuretics usually does not need to be increased (it can be even decreased in some cases). This approach targets the core mechanisms of congestion development, allows to maintain decongestion for a longer time, and provides not only symptomatic relief but also reduces the risk of subsequent HF hospitalizations and death. CHF, chronic heart failure.

Volume overload: multiparametric evaluation (Clincal Findings, biomarkers,imaging Techniques)

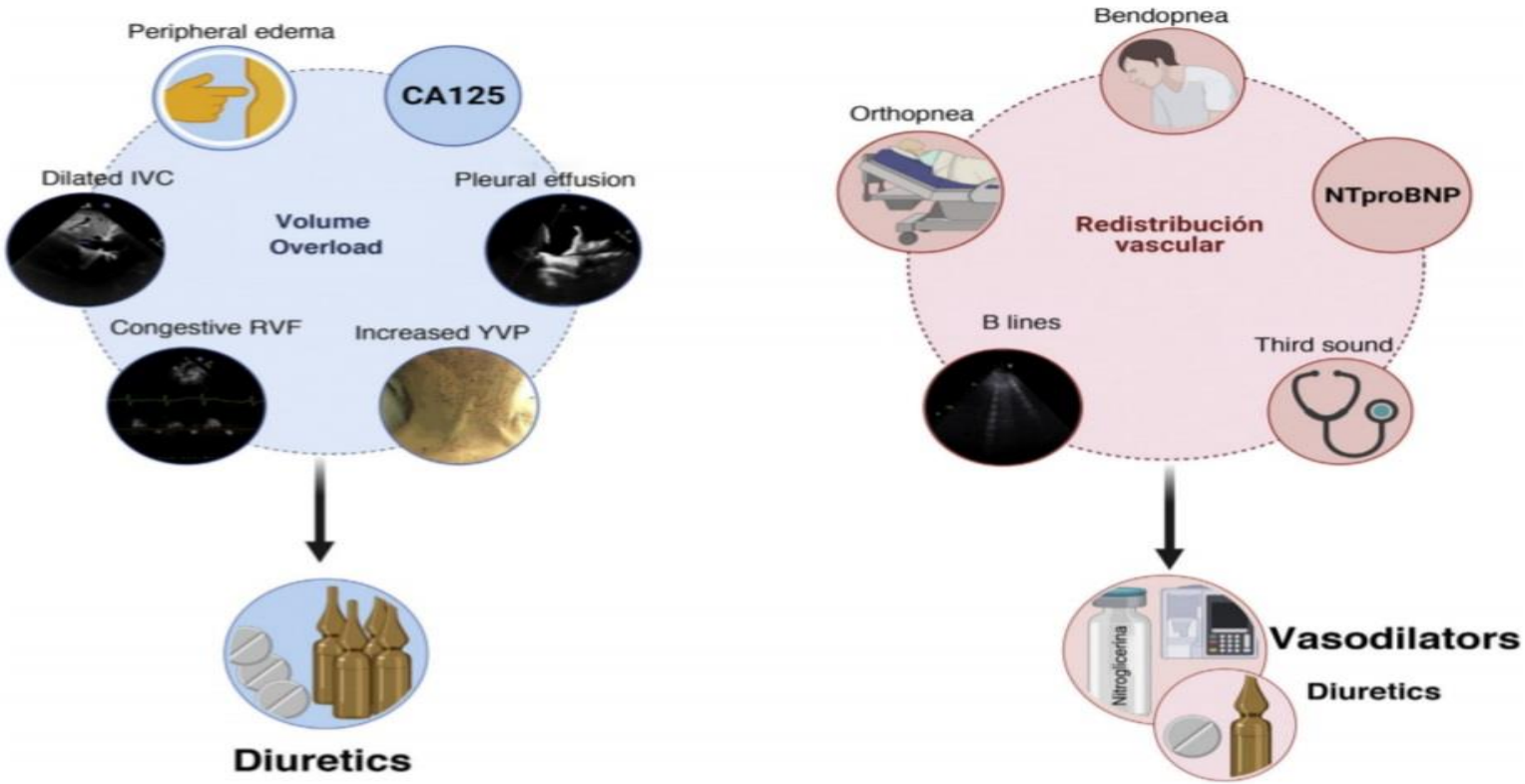
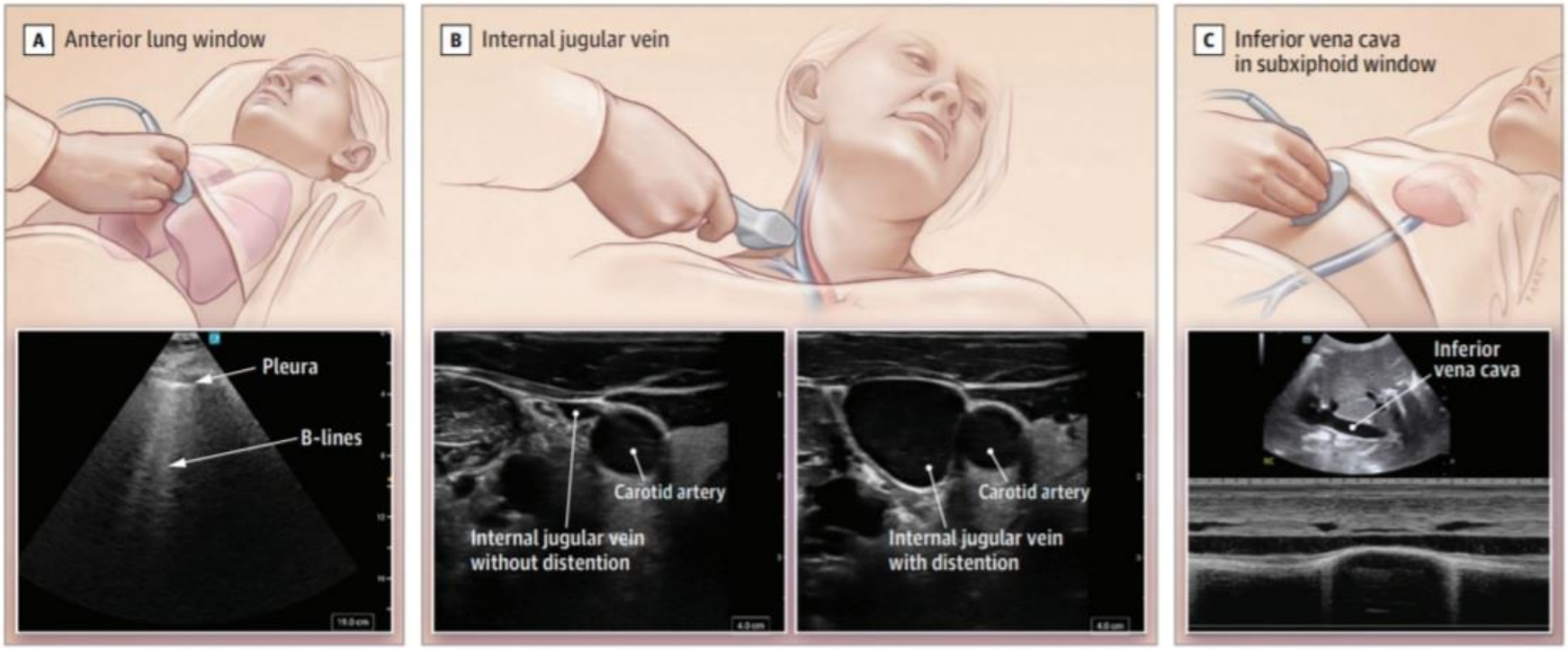


Figure 1 – Integration of clinical methods, biomarkers and imaging techniques to distinguish between congestion due to volume overload vs. vascular redistribution.
CA125: carbohydrate antigen 125; RVF: renal venous flow; NTproBNP: N-terminal fragment of B-type natriuretic peptide; JVP: jugular venous pressure; IVC: inferior vena cava.

POCUS

Figure 2. Ultrasonographic Images to Determine Volume Status

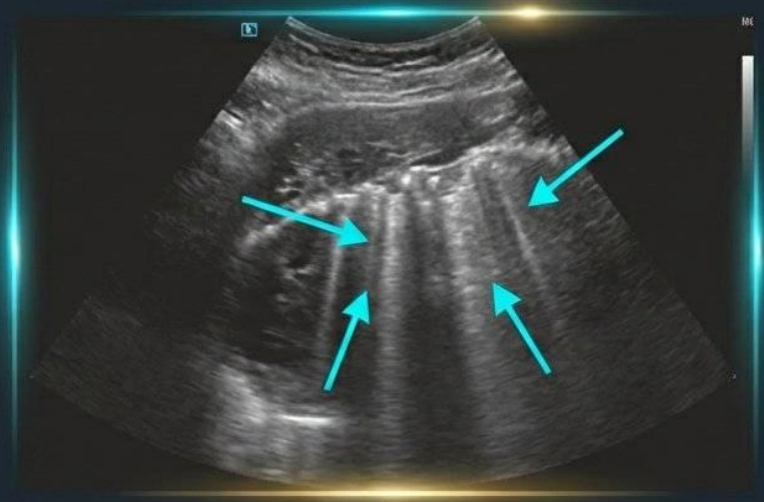


A, Hyperechoic B-lines extend perpendicularly and deeply to the pleura in an anterior lung window. The top panel shows probe placement.

B, A cross-sectional view of the internal jugular vein. The top panel shows probe placement.

C, Longitudinal view of the inferior vena cava in the subxiphoid window with M-mode applied 2 cm from the right atrium to assess respiratory variation. The top panel shows probe placement.

POCUS: Pulmonary B-Lines



Finding: >2 B-lines in 2 zones bilaterally.

Rule In Power: **LR 4.0.**

Rule Out Power (The Hero Stat): **LR 0.09.**

Key Insight: The most powerful tool for **EXCLUDING** volume overload. No B-lines = No Overload.

True AKI vs Pseudo AKI (Permissive AKI)

Table 2: Differential diagnosis of worsening kidney function in AHF.

Characteristic	True WKF	Pseudo-WKF
Fluid overload	Mild congestion/fluid redistribution, hypoperfusion	Severe congestion (based on a multiparan evaluation)
Clinical course and decongestion	Persistent or worsening congestion	Resolution of congestion (multiparametri evaluation)
Baseline renal function and magnitude of changes	Large increase in creatinine or decrease in GFR, especially in subjects with baseline renal dysfunction. Caution if increasing creatinine >50% of baseline or >3 mg/dl and decreasing GFR >10% of baseline if eGFR is <25 ml/min	Small changes in patients with normal or impaired renal function
Onset and time course	≥5 days after admission, persistent	≤4 days after admission, transient
Aetiology	Hypoperfusion, nephrotoxic agents	Venous congestion, diuretic therapy, RAAS inhibitor, ARNI, SGLT2i initiation or up-tit
Prognosis	Worse	Does not necessarily mean a worse progn adequate decongestion is attained

Permissive AKI

- Congestive AKI....
- Hemodynamicaly AKI...
- Functional AKI...
- Induced AKI...
- psudo- WKF...

tion with SGLT2i). As a result, the 2021 European HF guidelines consider an increase in SCr of <50% above baseline (as long as it is <3 mg/dl or 266 µmol/L) or a decrease in eGFR of <10% from baseline (as long as eGFR is >25 ml/min/1.73 m^2) as acceptable and expected changes after initiation of RAAS inhibitors, ARNIs or SGLT2is [6].

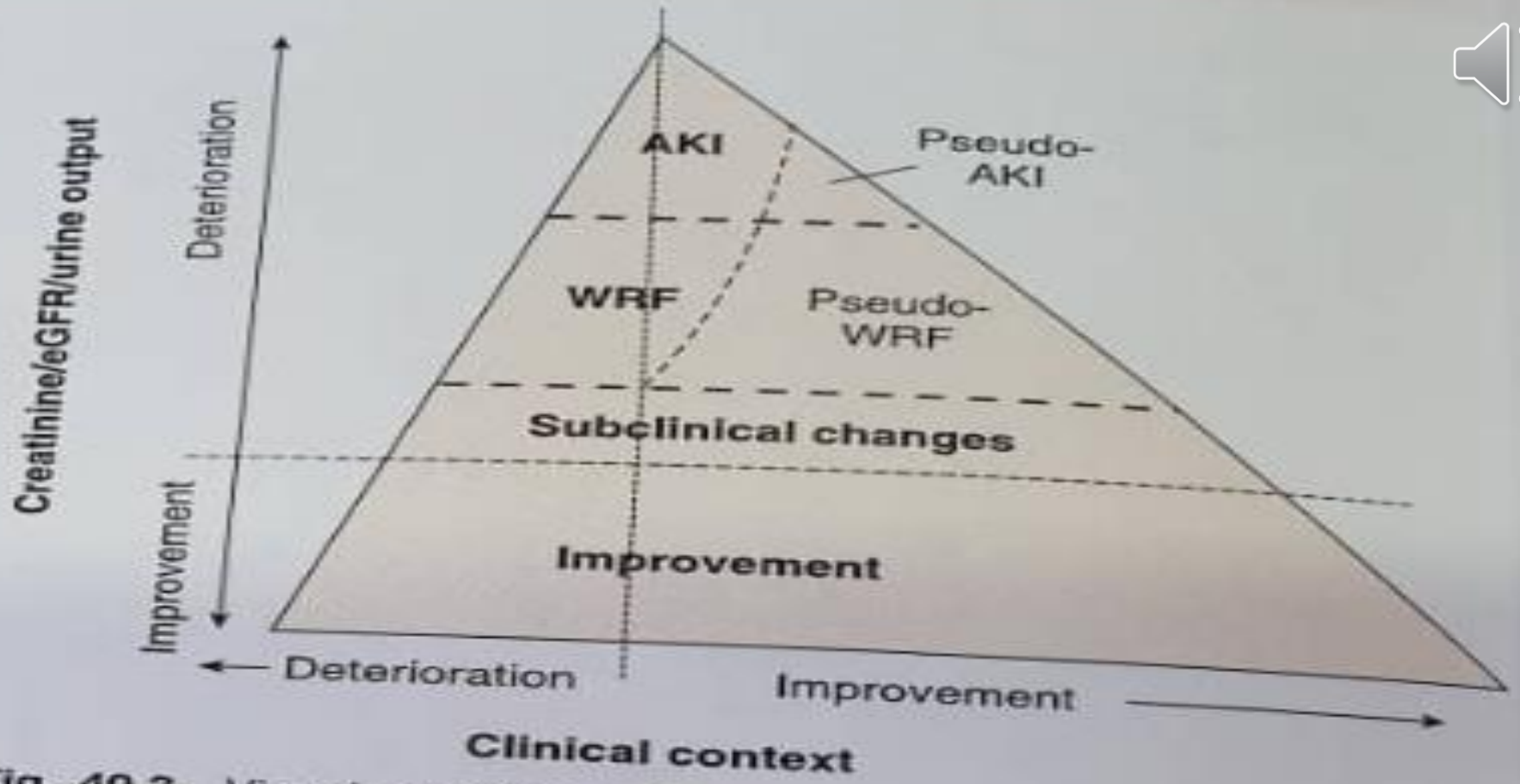
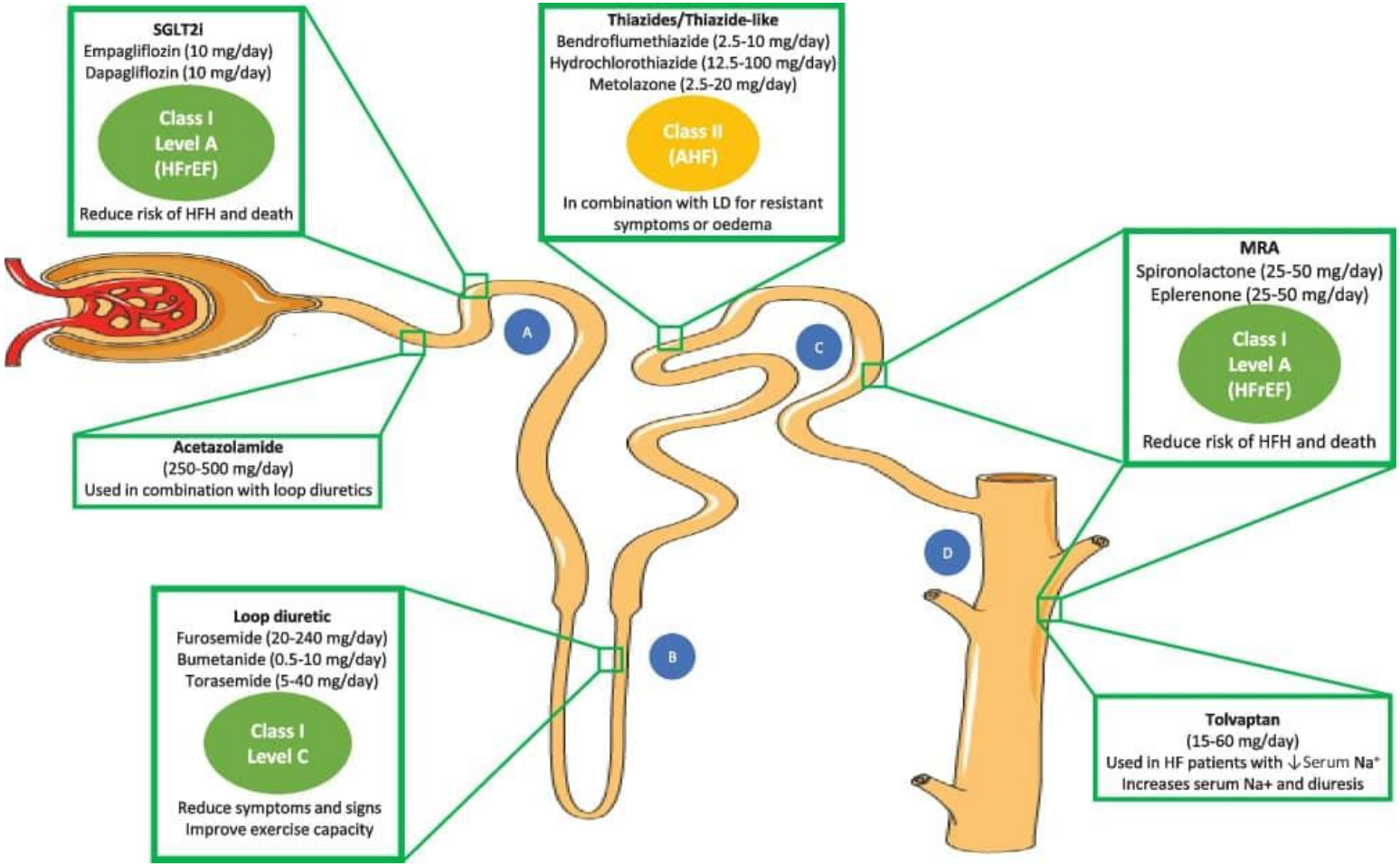


Fig. 40.3 Visual depiction of association among changes in renal function, clinical condition, and mortality risk. Only when both deterioration in clinical status and increase in the serum creatinine level (or decrease in renal function) track together is this associated with worse clinical outcomes in heart failure. *AKI*, Acute kidney injury; *GFR*, glomerular filtration rate; *WRF*, worsening renal function. *Darker colors* indicate higher mortality risk. (From Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J.* 2015;36:1437–1444. Reprinted with permission from Oxford University Press.)

Case problems:
This patient has true AKI.

- **1 -Volume overload (Diuretics therapy vs UF)?**
- **2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?**
- **3-Hyponatremia management (Vaptan)?**
- **4-Hyperurecemia management (Allopurinol)?**
- **5- Anemia Management (CRAIDS , EPO)?**
- **6-Mineral receptor antagonist?**
- **7-Contrast nephropathy risk and prophylaxy?**

Diuretics: comparison of site of action



Treatment strategies in CRS1

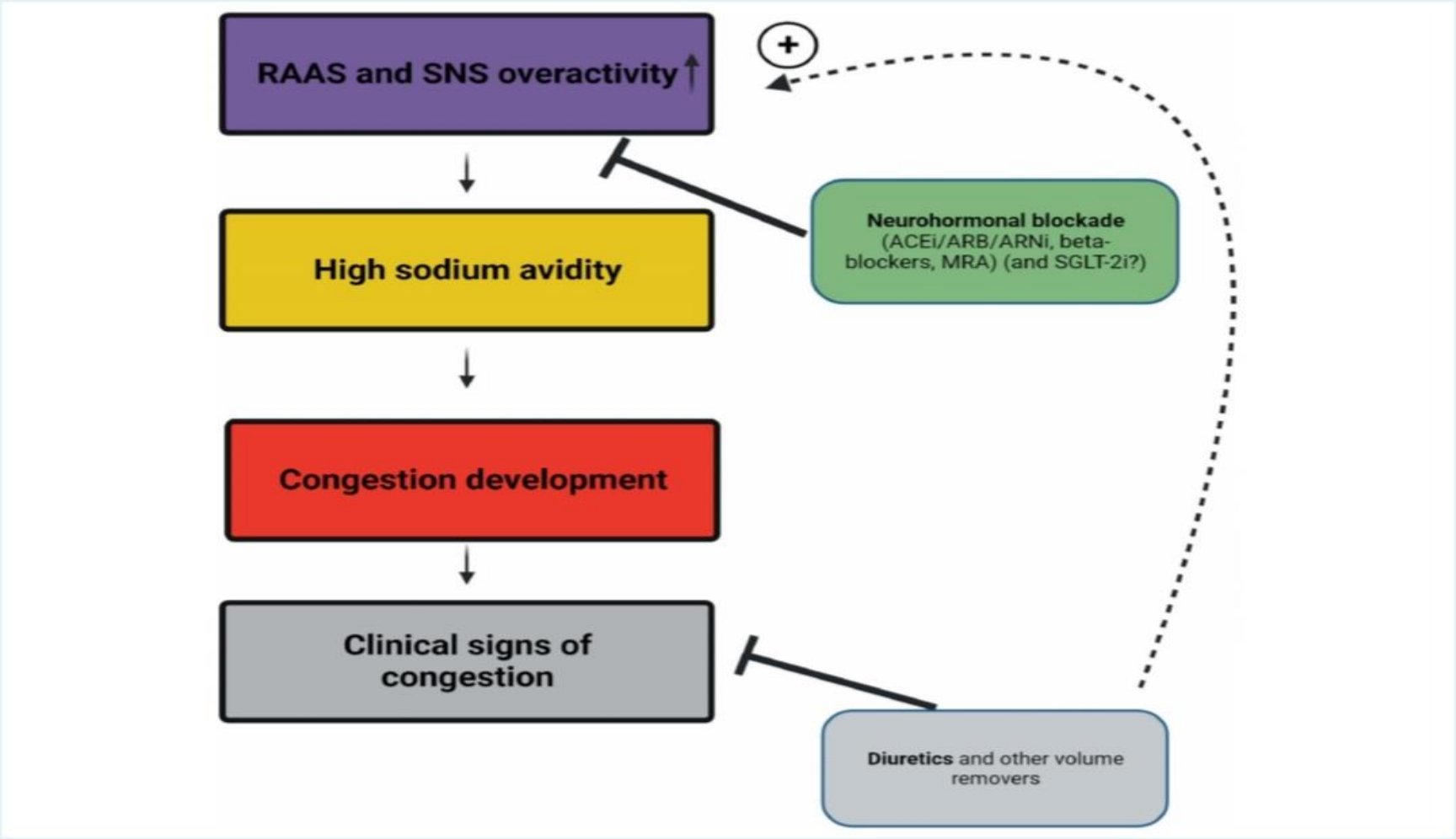
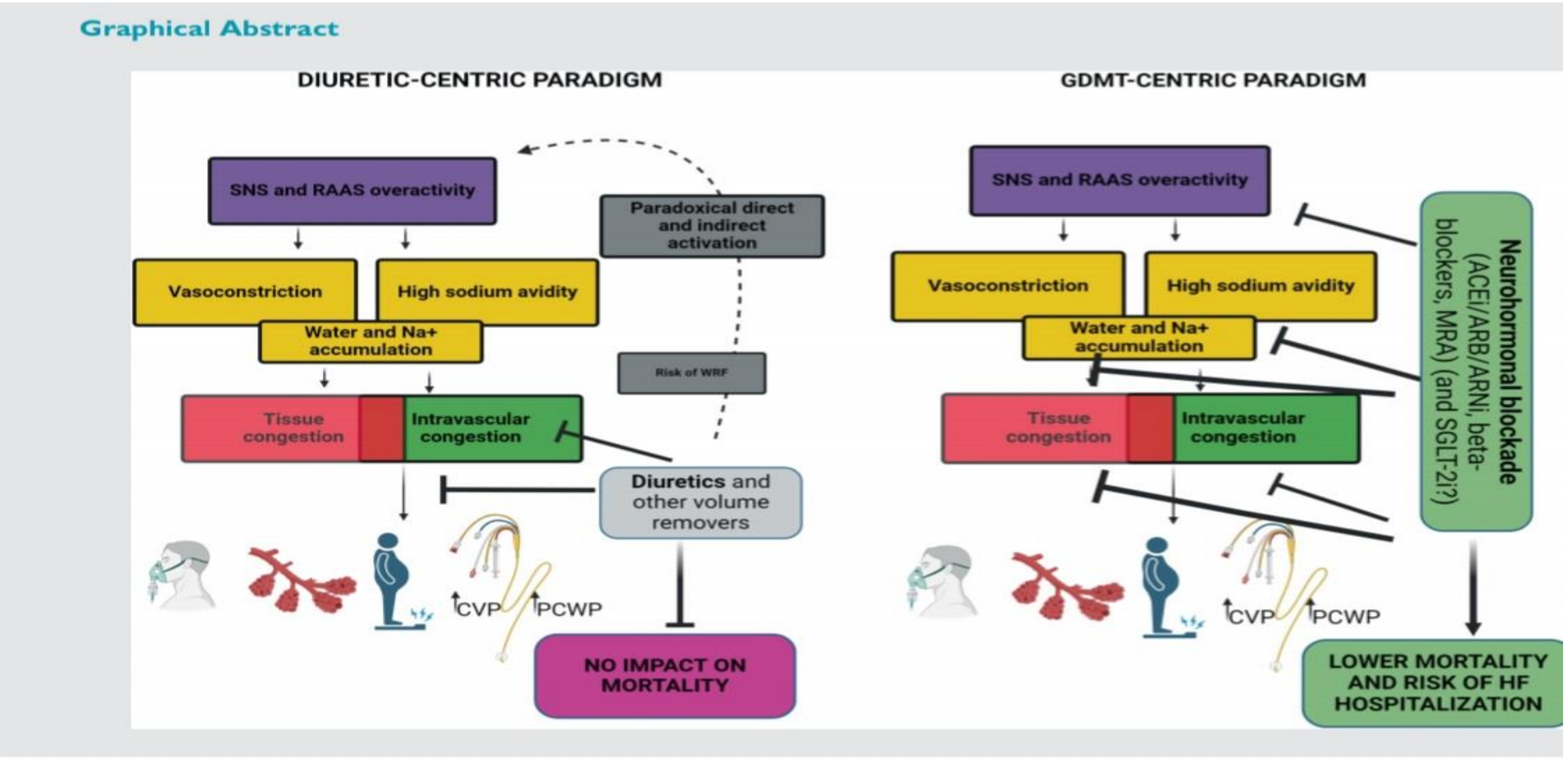


Figure 2 Differences in mechanisms of action between direct sodium/water removers versus neurohormonal blockade and sodium–glucose cotransporter 2 inhibitors (SGLT-2i). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

Treatment strategies in CRS 1



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Review

Continuous Infusion Versus Bolus Injection of Loop Diuretics for Patients With Congestive Heart Failure: A Meta-Analysis

Jithin Karedath et al. Cureus. 2023.

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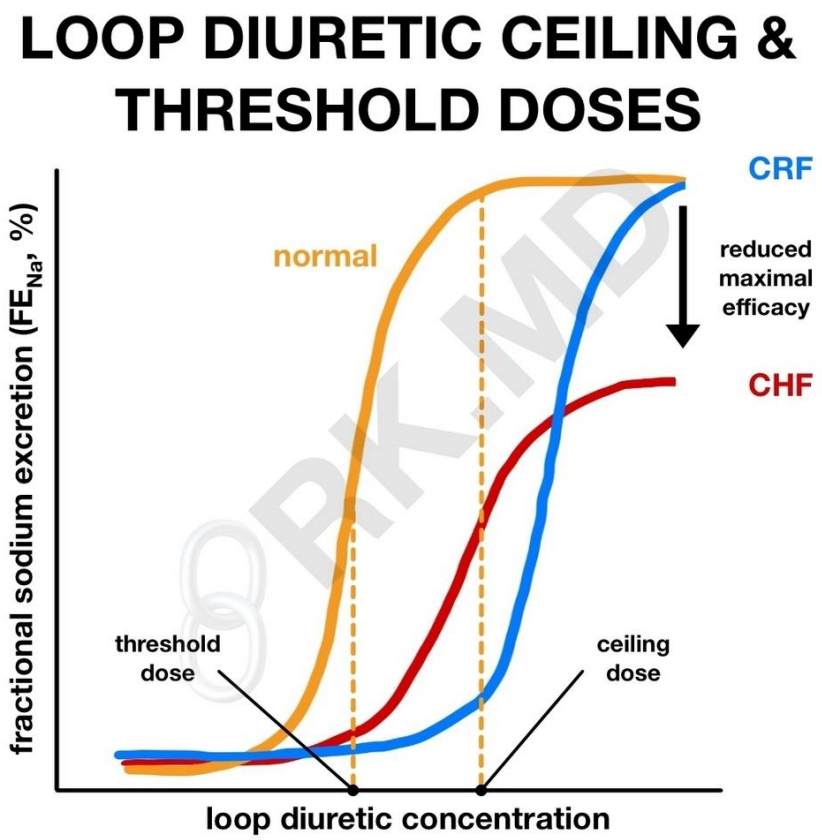
administration. In conclusion, in the current meta-analysis of nine randomized controlled trials (RCTs), continuous infusion of furosemide seemed to have a greater reduction of body weight. However, no significant difference was there in 24-hrs urine output. However, we cannot conclude that intravenous continuous infusion has a better diuretic effect compared to bolus administration.

Loop diuretic response



Roadblocks to Diuresis: Mechanisms of Diuretic Resistance

A. Insufficient delivery of loop diuretics to the tubule

1 Variable GI Absorption

Furosemide bioavailability at 10-100%

Influenced by food intake and gut edema

2 Hypoalbuminemia

Alb

Less delivery of diuretic to the kidney

Free drug molecules diffuse in tissues

Alb

Albuminuria bind to intratubular loop diuretics

3 Decreased Kidney Perfusion

e.g. heart failure

Low MAP limits the secretion of loop diuretics into proximal tubular fluid and glomerular filtration of water and sodium.

4 Competition for Transport Channels

Alb — Diuretic bound to albumin

Urea

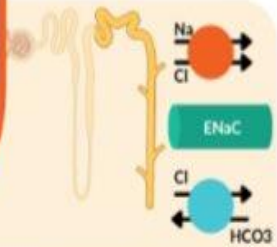
NSAIDs

Competitors like urea use same transport channels and decrease diuretic entry into the tubular lumen

5 Reduced Kidney Function

Decreased functional nephron mass means less sites for loop diuretics to act on

B. Heightened Sodium Avidity



Compensatory sodium reabsorption at distal sites drive diuretic resistance

Conclusion: Diuretic resistance is the failure to decongest despite adequate and escalating doses of diuretics. Major mechanisms leading to diuretic resistance include insufficient delivery of diuretic to the proximal tubule (affected by absorption, hypoalbuminemia, renal function and perfusion and competing molecules) and compensatory distal sodium reabsorption.

Reference: Gupta et al. *Diuretic Resistance in Heart Failure*. 2019 10.1007/s11897-019-0424-1

Visual Abstract by Carlo Trinidad, MD

@hellokidneyMD

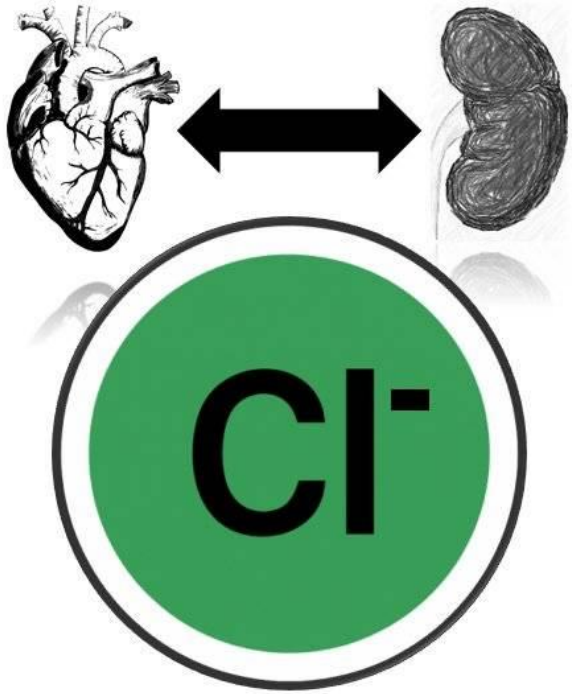
Visual abstract by @hellokidneyMD on Gupta et al

Diuretic resistance :

Box 1. Causes of Diuretic Resistance, With Examples

- No volume overload (wrong diagnosis)
  - Venous stasis
  - Lymphedema, lipedema
- Nonadherence
  - Excess salt intake
  - Nonadherence to medication
- Decreased drug delivery
  - Decreased absorption (gut edema)
  - Inadequate dose/frequency
  - Hypoalbuminemia
- Decreased drug secretion
  - Decreased kidney blood flow: AKI/CKD, decreased EABV
  - Tubule transport inhibition: FFAs, bile acids, organic acids, NSAIDs, indoxyl sulfate, *p*-cresyl sulfate
  - Decreased kidney mass
- Decreased kidney response
  - Distal tubule hypertrophy
  - Renin-angiotensin-aldosterone activation

Based on information in Hoorn and Ellison, 2017(*Am J Kidney Dis.* https://doi.org/10.1053/j.ajkd.2016.08.027). Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; EABV, effective arterial blood volume; FFA, free fatty acid; NSAID, nonsteroidal anti-inflammatory drug.



Neurohormonal activation:

Cl^- sensed at macula densa

↓ RAAS modulation

↓ $[Cl^-]$ → ↑ Renin + AT II levels

Cl^- repletion → ⊖ Neurohormonal drive

Volume and Fluid Balance:

ECF and Osmolarity regulation

"Dilutional" vs "Depletional" hypochloremia

Urine $[Cl^-]$ assessment for volume status classification

Diuretic responsiveness:

↓ [Ser Cl^-] → ⊕ WNK kinases

↓

↑ NCC/NKCC2

↓ Diuretic efficiency ↓ Natriuresis

Acid-Base regulation:

Chloride-bicarbonate exchange

↑ $[Cl^-]$ → metabolic acidosis (renal/ GI tract loss)

Worse prognosis

Cardiac arrhythmias:

Membrane potential modulation

Intracellular K+ regulation

pH buffering impairment

Hypochloremia management:

IV Furosemide or Combination diuretic therapy (+ACTZ)

Sodium-free Cl^- repletion in "depletional" states

SGLT2i/MRAs

Fluid restriction in dilutional states

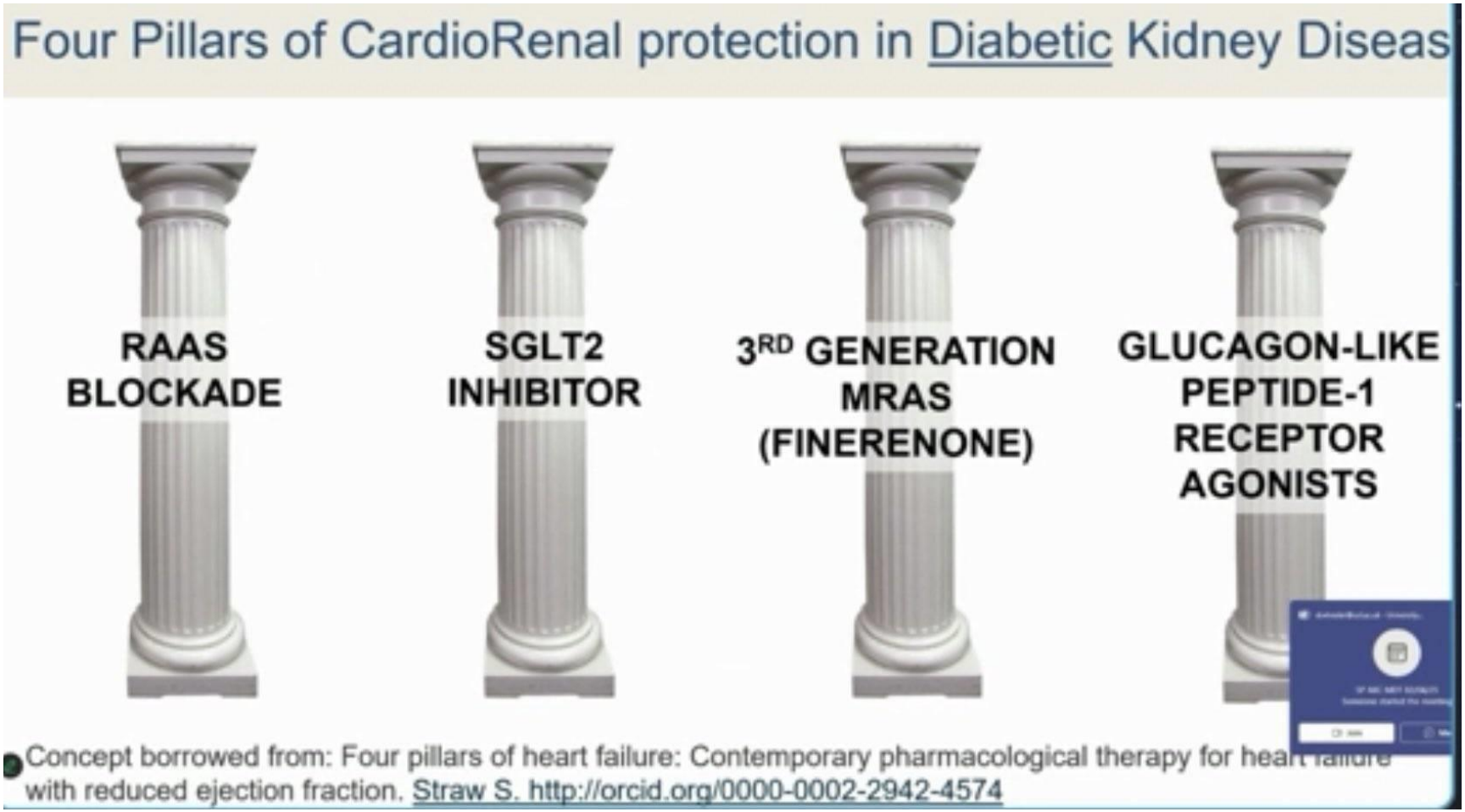
Future perspectives:

- ❑ Prognostic value of Cl^- dynamics
- ❑ Inclusion in HF risk models
- ❑ Diuretic resistance management

SGLT-2 inhibitor

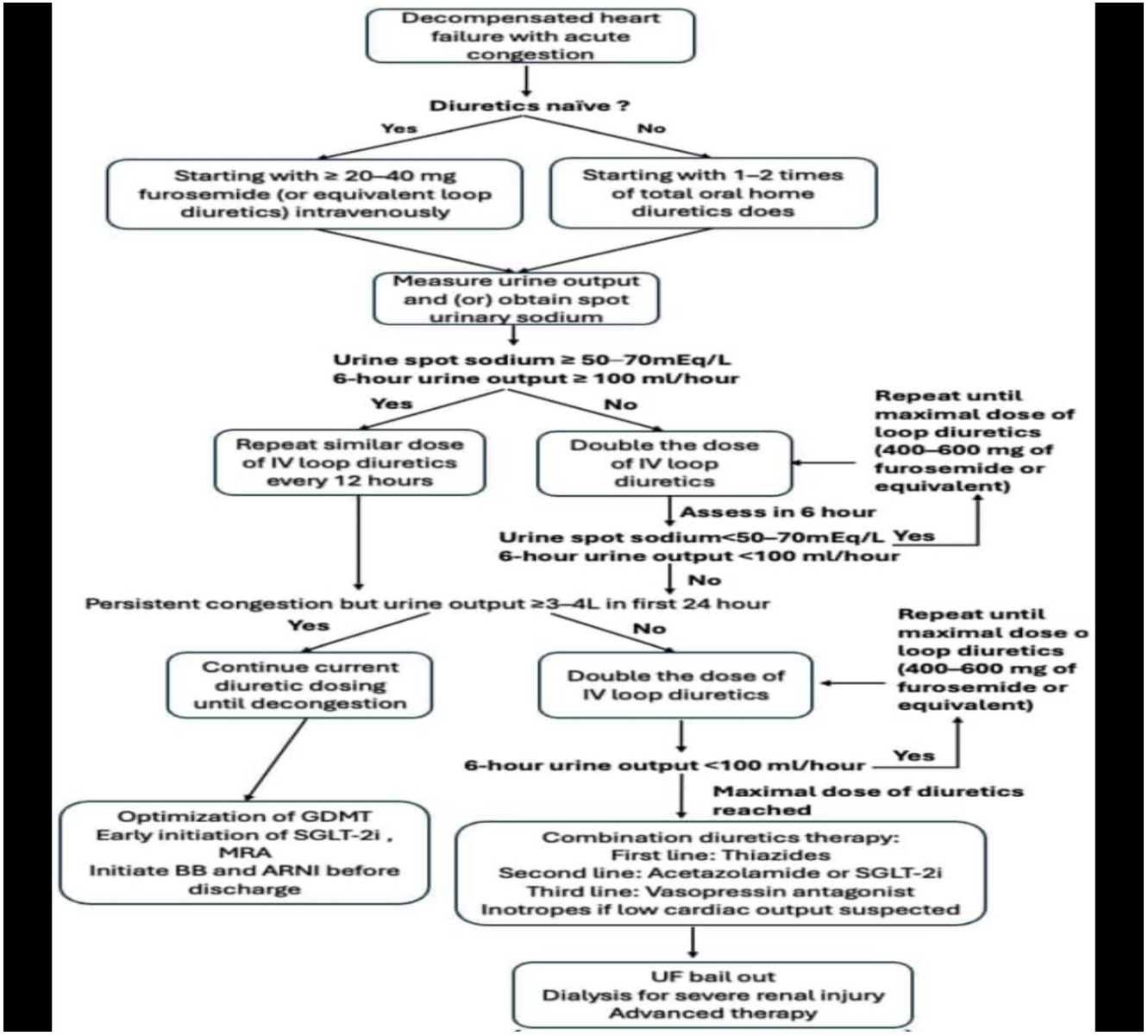
SGLT-2 inhibition to reduce risk of kidney disease and cardiovascular outcomes*		Urinary Albumin-to-creatinine ratio (mg/mmol)	
		<25	≥25
eGFR (mL/min/1.73m^2)	≥60	†	Recommended
	≥45 <60	Suggested (in type 2 diabetes)	Recommended
	≥20 <45	Recommended	Recommended
	<20	Suggested	Suggested
	Dialysis	Not recommended‡	Not recommended‡

Four Pillars of CardioRenal protection in Diabetic Kidney Diseas



Concept borrowed from: Four pillars of heart failure: Contemporary pharmacological therapy for heart failure with reduced ejection fraction. Straw S. http://orcid.org/0000-0002-2942-4574

Stepwise diuretic therapy



Diuretics combination:

NEFROLOGIA. 2022;42(2):145–162

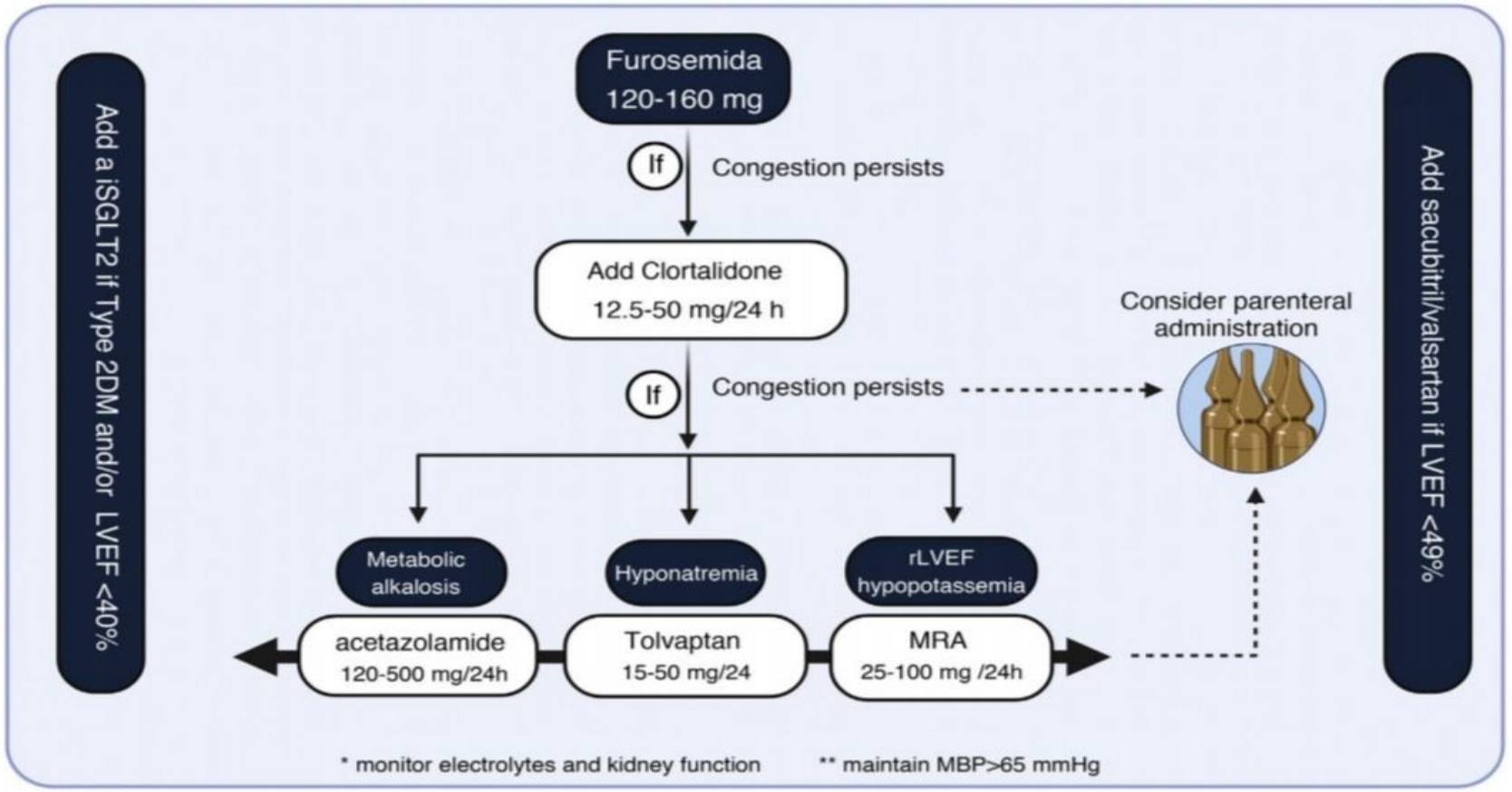


Figure 7 – Proposal of therapeutic algorithm.

UF vs Diuretics for CHF: Theoretical Advantages

- More rapid and predictable fluid removal and negative fluid balance
- Greater loss of sodium and ECF per ml of ultrafiltrate
- Less potassium, magnesium loss per ml of ultrafiltrate
- Less activation of TG feedback, possibly better preservation of residual RBF and GFR
- Possible acute improvement in cardiac function by unloading LV/RV and moving on Starling curve
  - Secondary improvement in response to vasoactive drugs and diuretics
- Possible acute improvement in GFR by relieving elevated CVP, renal venous hypertension
  - Secondary improvement in response to diuretics

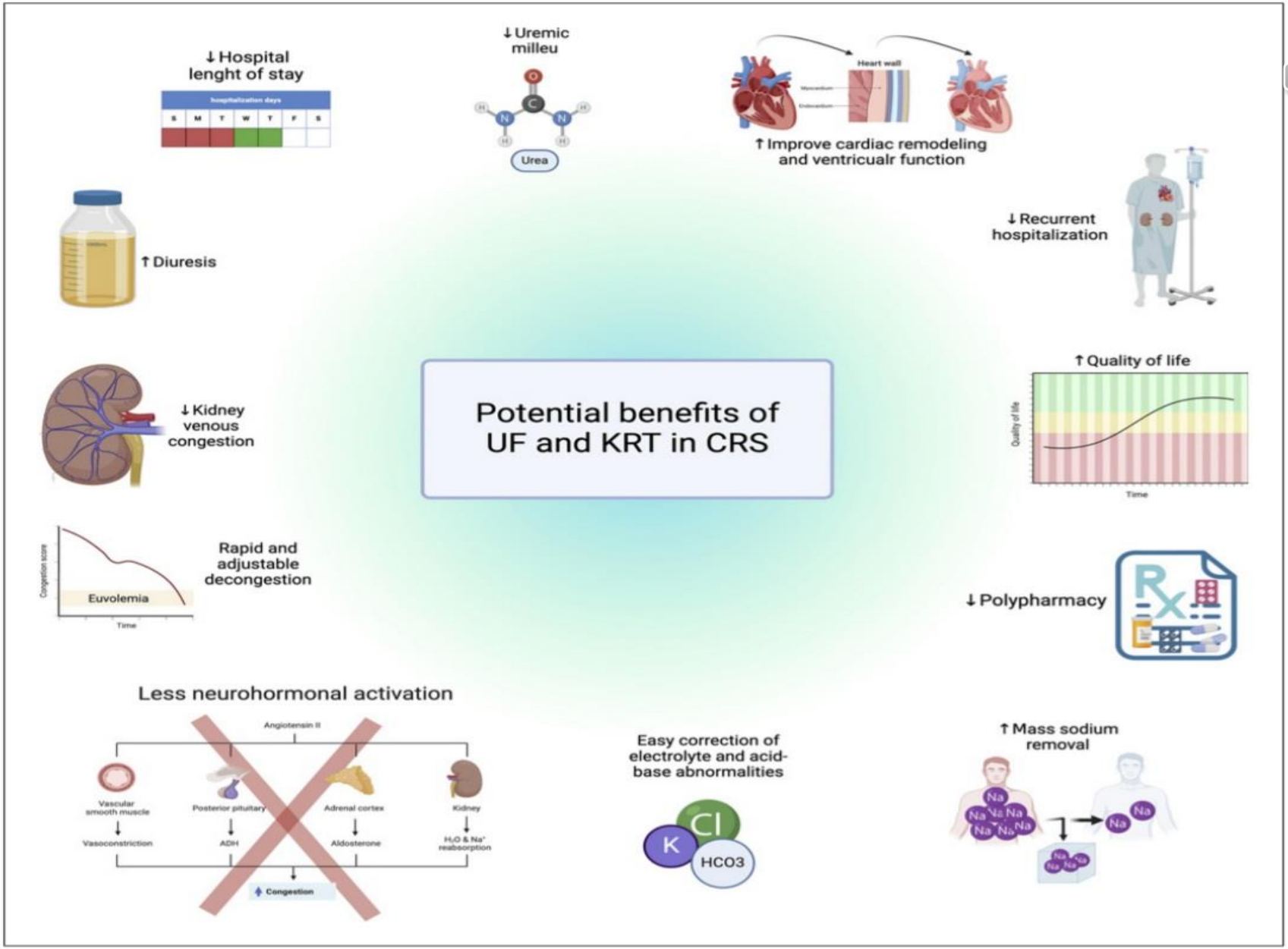


Fig. 3. Potential benefits of KRT or UF in patients with CRS. The use of KRT or UF in patients with CRS has demonstrated multiple benefits, which may be sufficient arguments to consider its use, especially in patients where diuretics have been insufficient for acceptably satisfactory management. ADH, antidiuretic hormone; K, potassium; Cl, chloride; CRS, cardiorenal syndrome; HCO3, bicarbonate; Na, sodium; KRT, kidney replacement therapy; UF, ultrafiltration.

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Ultrufiltration in CRS1 studies

Table 2 (continued)

Study	Modality	Description	Objective	KRT	Results	Comments
UNLOAD [64]	UF versus intravenous diuretics	200 patients hospitalized for congestive ADHF	Weight loss and dyspnea in 48 h	UF rate up to 500 mL/h	Weight loss 5.0 + 3.1 kg versus 3.1 + 3.5 kg, and fluid loss 4.6 versus 3.3 L were higher in the UF group	In ADHF, UF produces greater weight and fluid loss compared to diuretics
RAPID-CHF [65]	Single UF session versus usual care	40 patients with ADHF	Weight loss after 24 h	8-h session with UF rate 500 mL/h	Fluid removal in 24 h of 4,650 mL in UF and 2,838 mL for usual care Weight loss of 2.5 kg and 1.86 kg in the UF and usual care, respectively	Early UF is well tolerated and allows weight and fluid loss
Apparent Paradox of Neurohumoral Axis Inhibition after Body Fluid Volume Depletion in Patients with Chronic Congestive Heart Failure and Water Retention [66]	UF	22 patients with CHF	Determine whether an intravascular volume deficit explains patterns that exceed the limits of a homeostatic response	UF 500 mL/h until right atrial pressure is reduced to 50% of the initial value	In UF, with a 20% reduction in plasma volume, there was a moderate decrease in cardiac output, norepinephrine levels, plasma renin activity, and aldosterone	UF improves cardiac indices and decreases neurohormonal activity

ADHF, acute decompensated heart failure; BUN, blood urea nitrogen; CAPD, continuous ambulatory peritoneal dialysis; CRS1, cardiorenal syndrome 1; CHF, chronic heart failure; GFR, glomerular filtration rate; KRT, kidney replacement therapy; LVEF, left ventricular ejection fraction; PD, peritoneal dialysis; PDT, peritoneal dialysis tidal; UF, ultrafiltration.

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Ultrufiltration in CRS1 studies

Table 2. Some studies of KRT in CRS

Study	Modality	Description	Objective	KRT	Results	Comments
PD						
Peritoneal and Urinary Sodium Removal in Refractory Congestive Heart Failure Patients [53]	DPCA	66 patients with CHF	Mortality and ADHF episodes through urinary and peritoneal Na removal	1–4 exchanges per day with 1.36 and 2.27% PD glucose solution or icodextrin based on kidney function	CAPD increased Na excretion and was associated with lower mortality and ADHF episodes	High Na removal identifies patients with lower cardiovascular risk. PD optimizes decongestion
Tidal PD versus UF in CRS1: A Prospective Randomized Study [58]	PDT versus UF	88 patients with SCR1, randomized to PDT or UF	Change in serum creatinine from baseline and LVEF at 72 and 120 h. Followed for 90 days after hospital discharge	DPT group: 20–25 L/day, filling volume of 1.5–2 L for 90–120 min dwell time 12–14 cycles/day UF group: blood flow rate 100–170 mL/min and UF rate 75–120 mL/h	UF was inferior to DPT with respect to changes in serum creatine and LVEF Net UF was greater in DPT Greater adverse events in the UF group DPT had fewer rehospitalizations for ADHF (14.2% vs. 32.5%)	The use of PDT was superior to UF for the preservation of renal function and improvement of cardiac function
Outcomes after Acute PD for Critical CRS1 [59]	PD	147 patients with CRS1, creatinine 4.0 mg/dL, and BUN 60 mg/dL	In-hospital and 30-day mortality UF and net water balance in the first 5 PD sessions	Filling volume of 1.5 L, 36 or 18 L volume/day, adjusted to cycles of 3–6 h depending on volume and metabolic profiles	30-day mortality of 73.4% The change in water balance in the first 5 days was different between survivors and non-survivors	PD was associated with better survival, especial if negative balances in the first days
PD in Patients with Refractory Congestive Heart Failure: A Systematic Review [60]	DP	Meta-analysis of 21 cohorts with 673 patients	Describe the risk-benefit ratio on PD use in CHF	PD techniques were not reported for all studies Glucose, icodextrin, and glucose + icodextrin were used	DP reduced weight (−3.6 kg) and reduced risk of loss of 5 mL/min in eGFR, and LVEF increased by 4%	The deterioration of functional class could be prevented, and 5 days of hospitalization per year could be saved
Extracorporeal techniques						
AVOID-HF [61]	UF adjustable versus diuretics	224 congestive patients	Time to first ADHF event 90 days after hospital discharge	Adjusted during fluid removal	UF rate 138 mL/h for 70 h	At 30 days, the UF group had fewer cardiovascular and ADHF events Changes in kidney function and mortality at 90 days were similar in both groups
CUORE [62]	UF versus standard therapy	56 patients with CHF	Rehospitalization for ADHF	UF until fluid removal greater than 2 L	UF reduces the risk of rehospitalization for ADHF by 86%	No differences in mortality
CARRES-HF [63]	UF versus stepped diuretic	188 patients with CRS1	Change in creatinine and body weight at 96 h	UF started 8 h after randomization, with an average duration of 40 h UF rate 200 mL/h with a negative balance of 3.4 L	Creatinine UF versus diuretic: increase of 0.23 + 0.70 mg/dL versus decrease of 0.04 + 0.53 mg/dL, respectively Change in body weight: 5.5 + 5.1 kg versus 5.7 + 3.9 kg	UF was associated with an increase in creatinine without improvement in fluid removal or clinical improvement compared with step diuretic therapy

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Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
- 2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?
- **3-Hyponatremia management (Vaptan)?**
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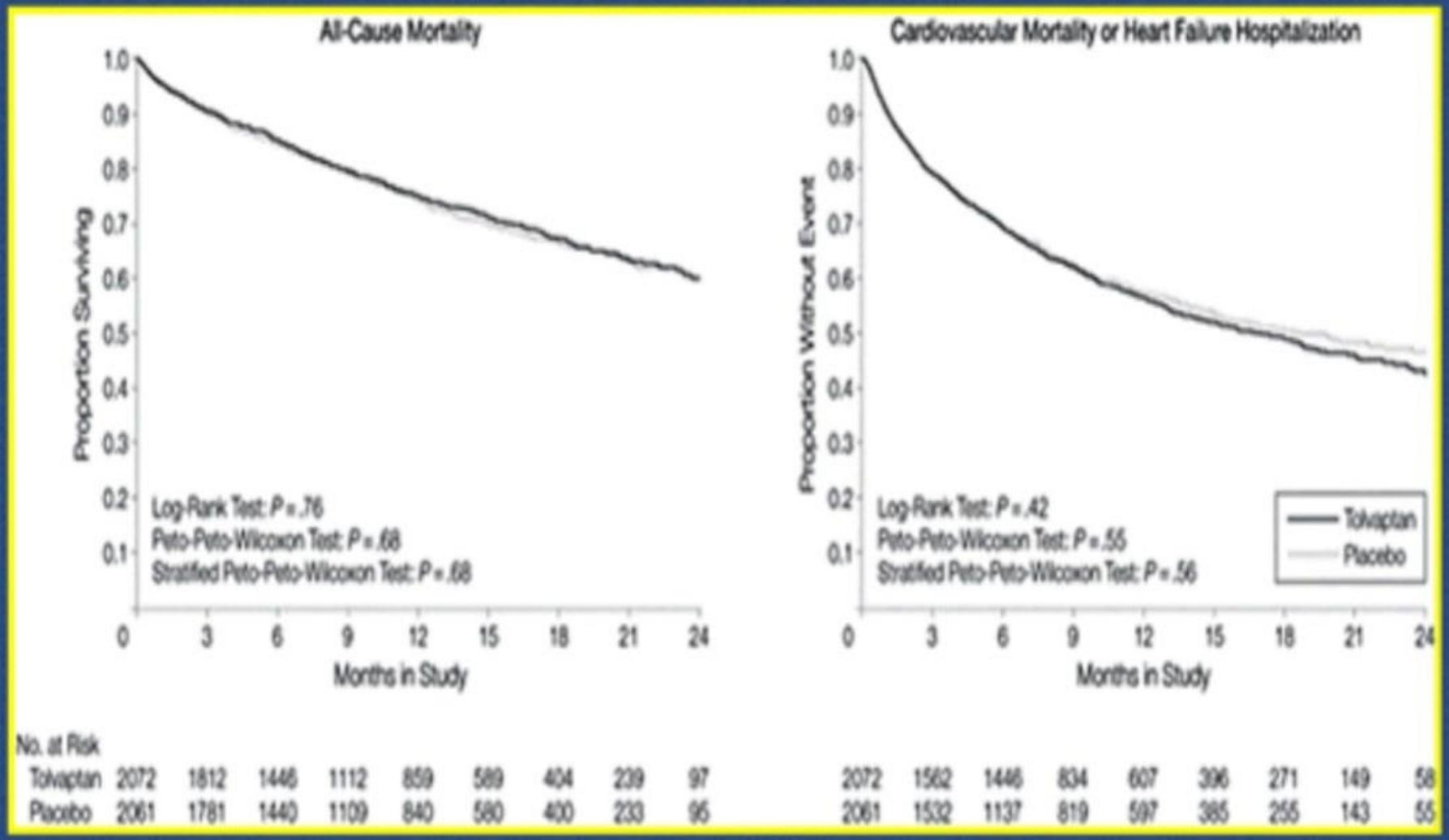
- 6-Mineral receptor antagonist?
- 7-Contrast nephropathy risk and prophylaxy?

EVEREST Trial: Tolvaptan, All-Cause Mortality and Cardiovascular Mortality or Hospitalization for Heart Failure



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JAMA

Konstam, M. A. et al. JAMA 2007;297:1319-1331.

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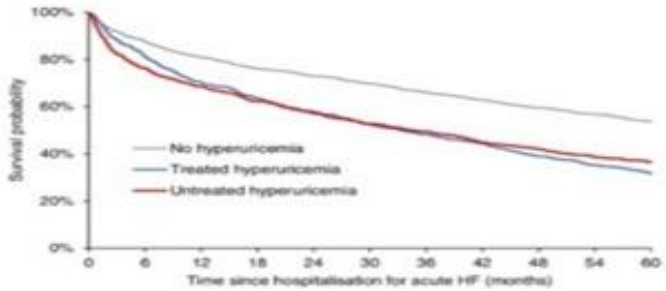
Clinical Cardiology
Wiley-Blackwell

- Dou

Hyperuricemia treatment in acute heart failure patients does not improve their long-term prognosis: A propensity score matched analysis from the AHEAD registry

Marie Pavlusova, Jiri Jarkovsky, [...], and Jiri Parenica



No. at risk:											
No hyperuricemia	1,786	1,564	1,444	1,359	1,302	1,244	1,179	1,124	1,062	1,013	959
Treated hyperuricemia	793	643	558	504	460	416	382	352	309	279	251
Untreated hyperuricemia	583	444	399	362	332	307	288	261	245	225	212

	Overall survival (95% CI)		
	1-year	2-year	5-year
No hyperuricemia	80.9% (82.7%; 0.8%)	72.9% (75.0%; 0.7%)	53.7% (56.0%; 0.5%)
Treated hyperuricemia	70.4% (73.5%; 0.7%)	58.0% (61.4%; 0.5%)	31.7% (34.9%; 0.3%)
Untreated hyperuricemia	66.6% (72.3%; 0.6%)	57.0% (61.1%; 0.5%)	36.4% (40.3%; 0.3%)

Log-rank test: **p < 0.001**
Post-hoc comparison at 5 years: no hyperuricemia vs treated hyperuricemia **p < 0.001**, no hyperuricemia vs untreated hyperuricemia **p < 0.001**, treated hyperuricemia vs untreated hyperuricemia p = 0.370

Kaplan – Meier estimate of 5 – year overall survival in patients with acute heart failure according to hyperuricemia and its treatment (before propensity

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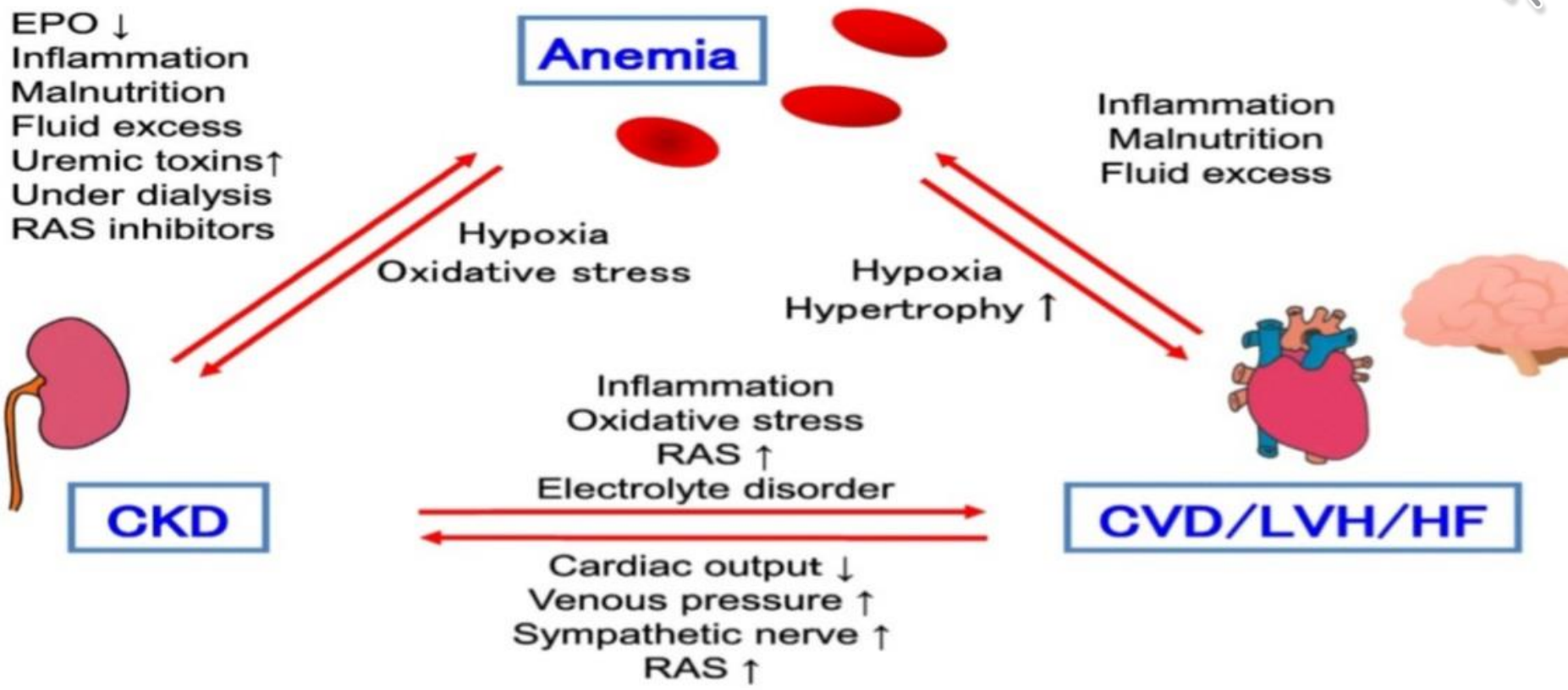
Cardio–Renal Anemia (CRA) Syndrome



Cardio-renal-anemia (CRA) syndrome. CKD-induced anemia produces hypoxic condition which leads to an increase in oxidative stress. CKD also facilitates chronic inflammation and hypoxia in renal tissue, activating systemic, and local RAS. These changes trigger to aggravate cardiac hypertrophy and reduce cardiac output, which i turn decreases organ perfusion including the kidney. With such a mechanism, renal anemia in CKD creates a vicious circle in conjunction with CVD/HF, so-called the CRA syndrome, which may eventually result in poor patients' prognosis. CVD cerebrovascular disease, LVH left ventricular hypertrophy, HF heart failure. Quoted from reference # 23,24

Ferritin (iron stores) 100-299 µg/L
Transferrin saturation (bioavailable iron) <20%

Causes of iron deficiency in heart failure

Reduced iron storage: Absolute iron deficiency

Malnutrition

- Loss of appetite: <50% intake

Malabsorption:

- GI mucosal oedema
- Delayed gastric emptying, altered intestinal motility
- PPI, PO_4 binders
- Reduced iron transport in duodenum. Altered villous blood flow

GI blood losses

- Gastritis/peptic ulcer
- Medications - Anti-coagulants, NSAIDs, antiplatelet
- Mucosal integrity

Blood Loss menstrual, blood sampling

Reduced iron mobilization: Functional iron deficiency

Inflammation

Cytokines, IL-6, IL-1, TNF-α

- Blunted responses to EPO
- Apoptosis of erythroid progenitors
- Hepcidin-mediated malabsorption and RES pooling

(Jankowska et al. Eur Heart J 2013)

SGLT-2 Inh and Anemia correction

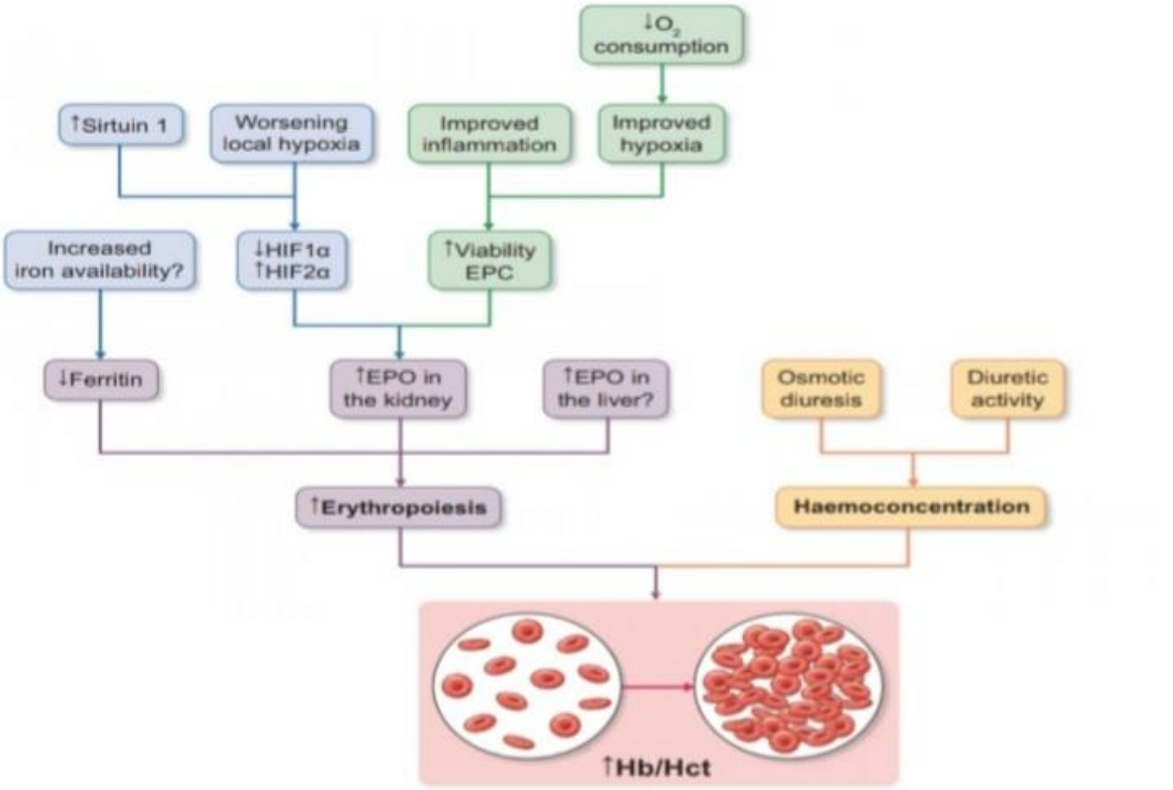


Figure 1: Possible mechanisms explaining increased erythropoiesis following therapy with SGLT2 inhibitors. The observed increase in Hb/Hct levels is due to the combination of increased erythropoiesis and haemoconcentration. Increased erythropoiesis can be sustained by increased iron availability, increased production of erythropoietin from the kidney and possibly by the liver. Among possible mechanisms explaining the increased erythropoietin production, either improved hypoxia following reduced oxygen consumption or activation of the HIF system because of local hypoxia could be considered. HIF activation from sirtuin 1 has also been suggested. Finally, decreased inflammation could also have a role in improving the viability of erythropoietin-producing cells in the kidney and thus increase erythropoietin synthesis. EPC, erythropoietin-producing cells; EPO, erythropoietin.

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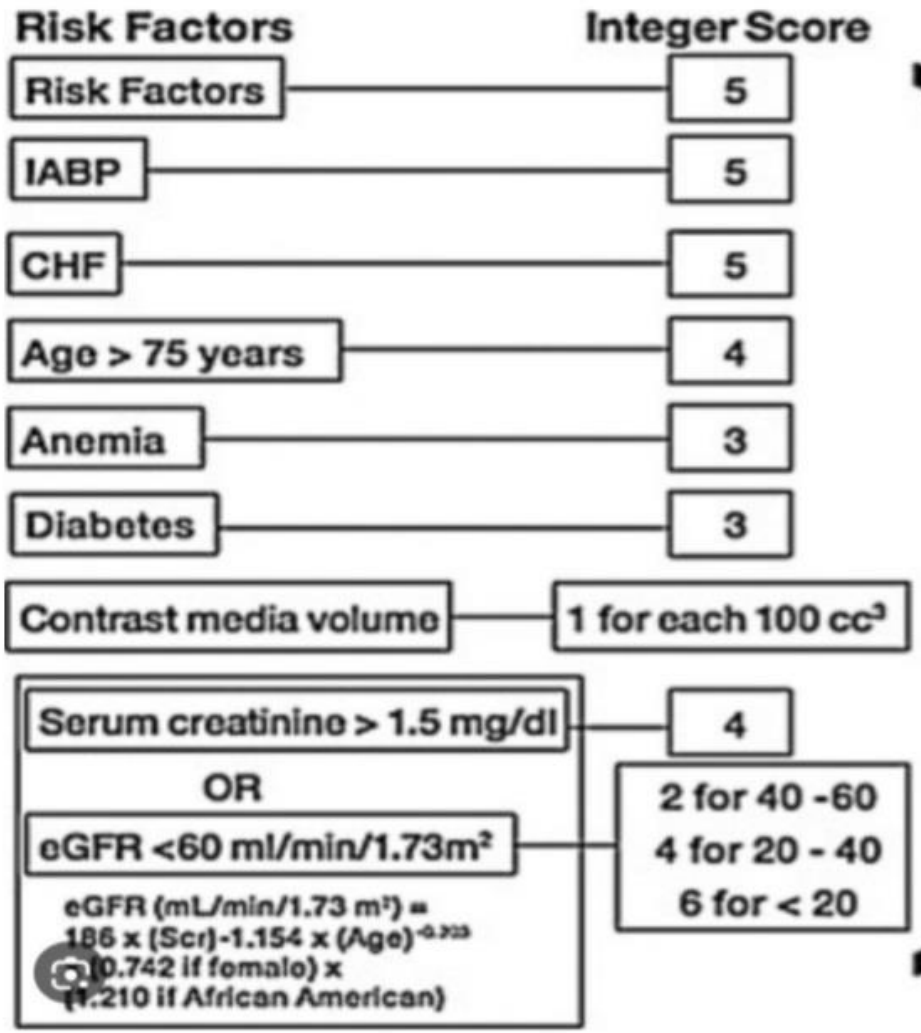
	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	-
Sexual side effects	++	+	-
Half-life	>20h	4-6h	2-3h
Active metabolites	++	-	-
Effect on BP	+++	++	+

Mehran contrast nephropathy Risk score



Risk Score	Risk CIN	Risk of Dialysis
≤ 5	7.5%	0.04%
6 to 10	14.0%	0.12%
11 to 16	26.1%	1.09%
≥ 16	57.3%	12.6%

Mehran contrast nephropathy risk score: Is it still useful 10 ...

Visit >

Conclusion

- 1. It's important to differentiate **True AKI** from **Permissive AKI** in CRS1.
- 2. We need multiparametric evaluation (clinical findings, biomarkers and POCUS) for early and better detection of **volume overload** in CRS1.
- 3. Treatment of congestion with **loop diuretic** is corner stone and usually combination of diuretics (Thiazids ,MRA , acetazolamid, SGL2-inh,vaptans) is required.
- 4. Only **SGLT-2 inh,MRA,BB , ACEinh/ ARB and ARNI** have good evidences for **mortality reduction i**n heart failure and we recommend use of these treatments as soon as possible in hospital before discharge of patients and reduction in dose of loop diuretics
- 5 . In diuretic resistant cases or unstable hemodynamics with volume overload **UF therapy may be useful (CRRT/SCUF/HD/PD).**