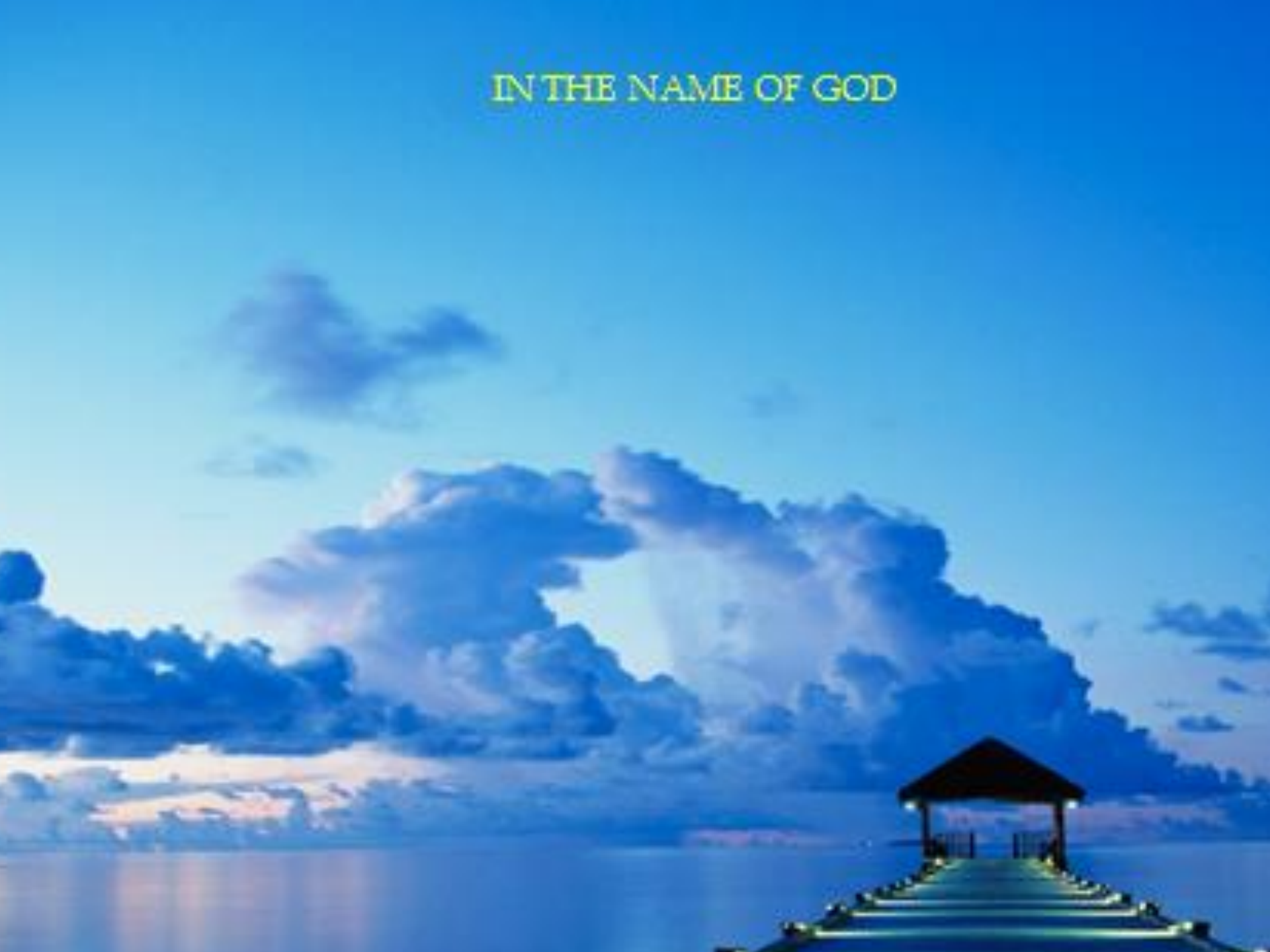
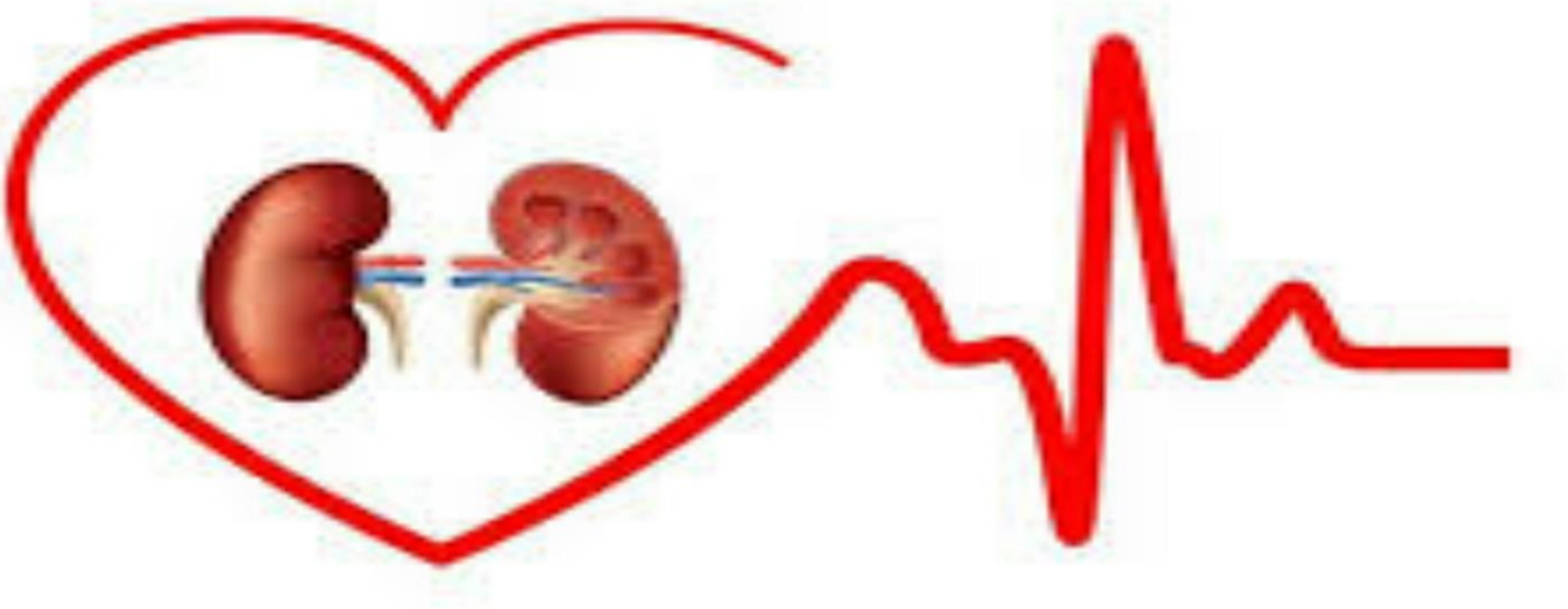
IN THE NAME OF GOD



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 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=١١cm H2O**
- **Lab: BUN=100 mg/dl, Cr =٣/٥**
- **Hb= 9.5 g/dl**, Na =135 meq/l, K= 5 meq/l, **Cl= 90 meq/ l**
- FBS=١٣٠ 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- RAAS blockade and Neprylisin inhibitor (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.

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].

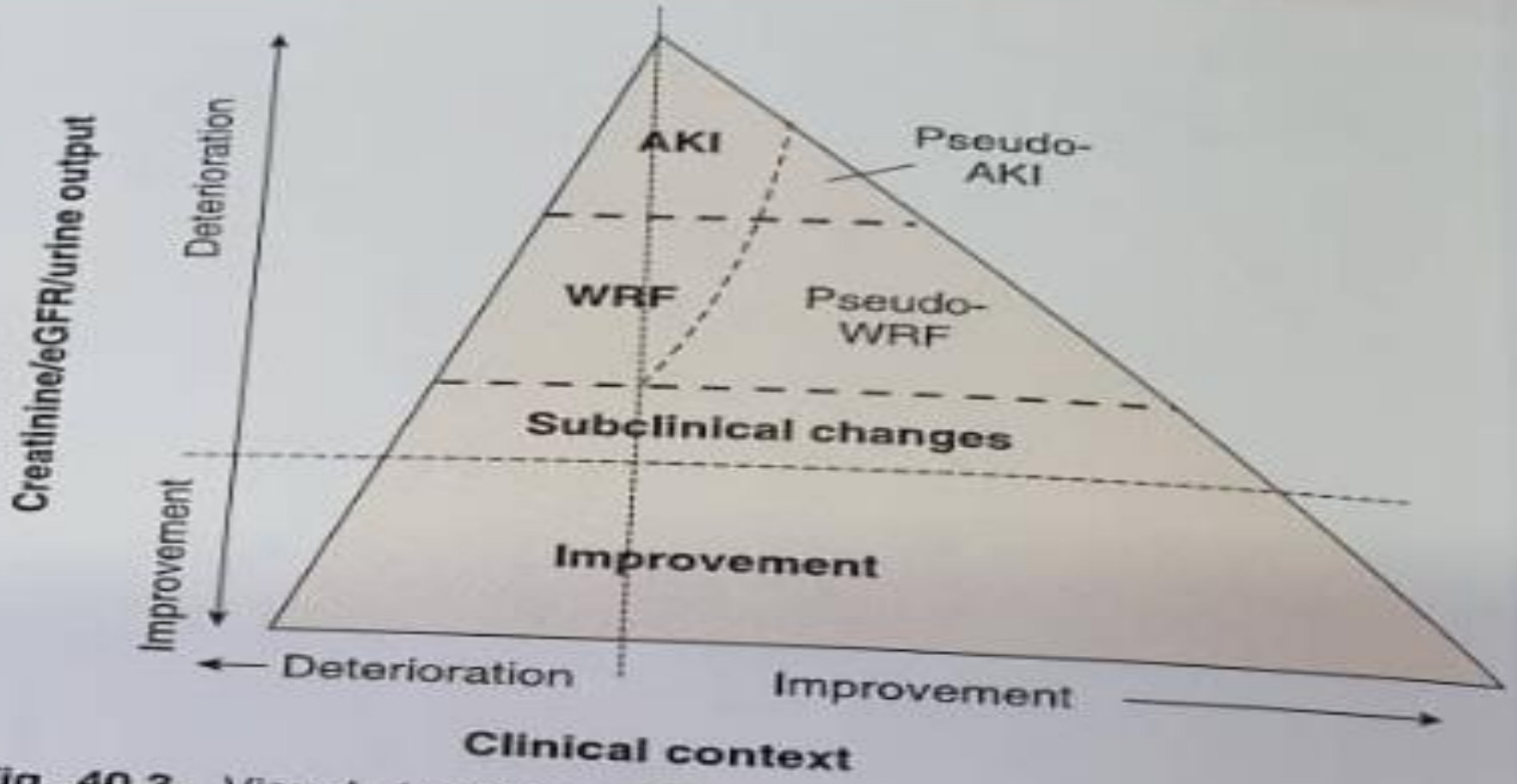


Fig. 40.3 Visual depiction of association among changes in renal function, clinical condition, and mortality risk. Only when both deterioration in clinical status and increase in the serum creatinine level (or decrease in renal function) track together is this associated with worse clinical outcomes 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.)

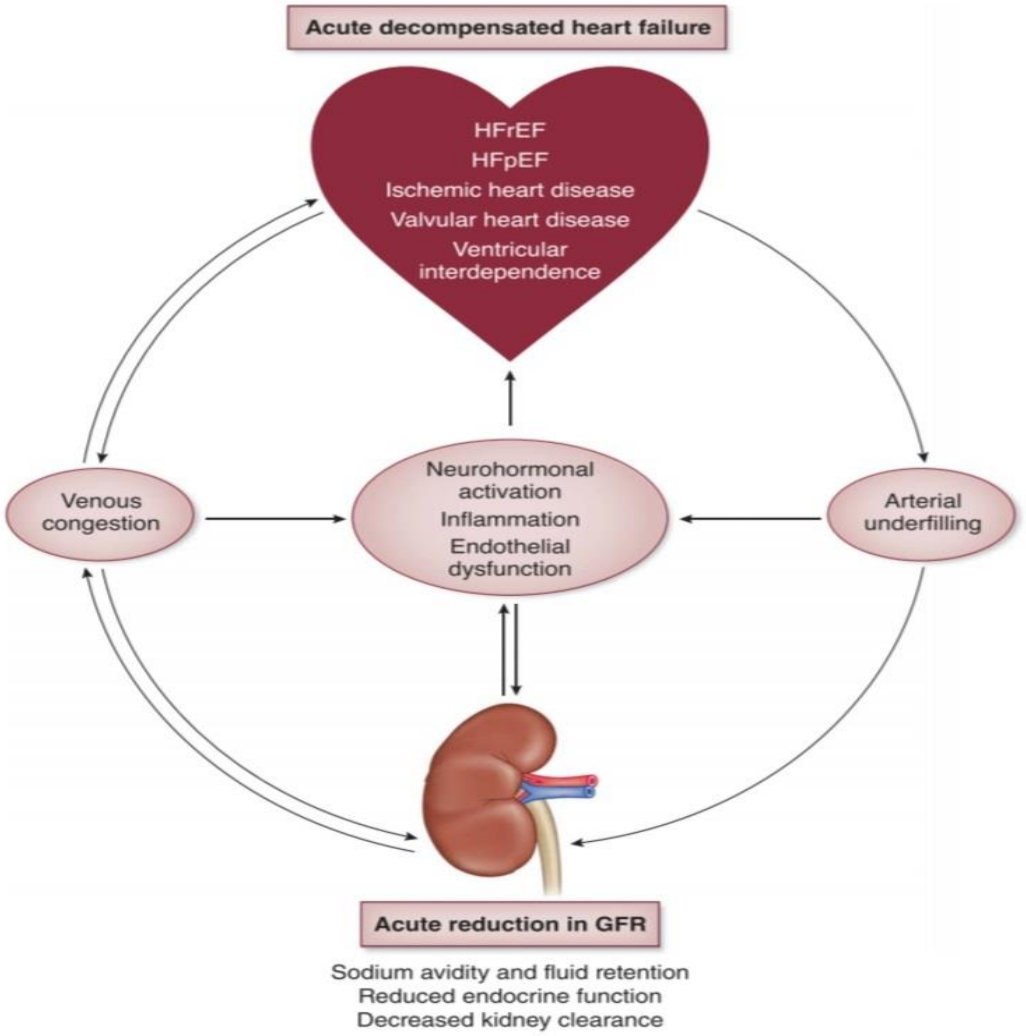


Figure 1. Proposed pathophysiological pathways leading to the cardiorenal syndrome and its complications. The inciting event is usually an acute decompensation of heart failure. This may lead to either arterial underfilling or venous congestion as mediators that promote neurohormonal activity, inflammation, 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.

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?**

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

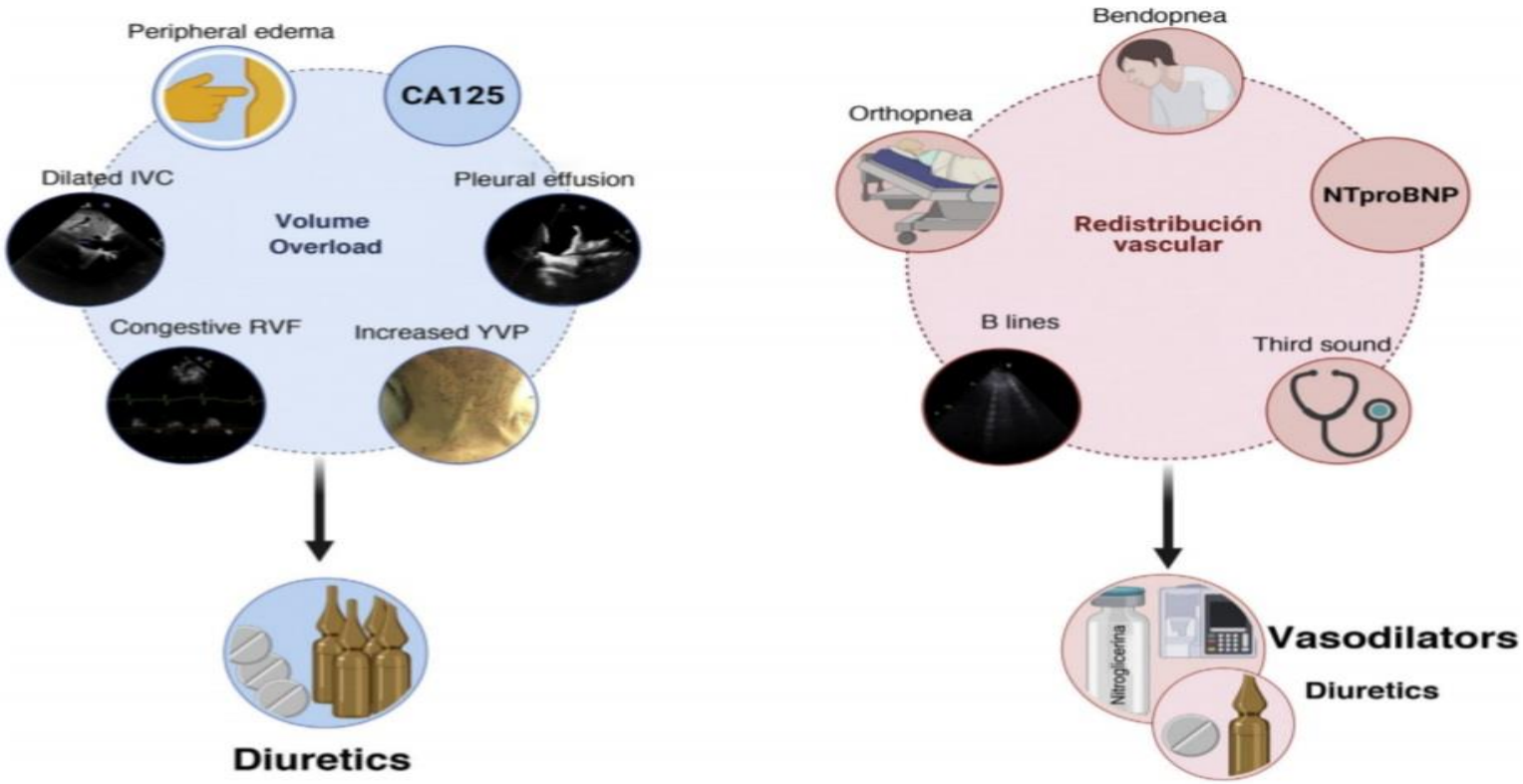


Figure 1 – Integration of clinical methods, biomarkers and imaging techniques to distinguish between congestion due to volume overload vs. vascular redistribution.
CA125: carbohydrate antigen 125; RVF: renal venous flow; NTproBNP: N-terminal fragment of B-type natriuretic peptide; JVP: jugular venous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

Renal sodium avidity

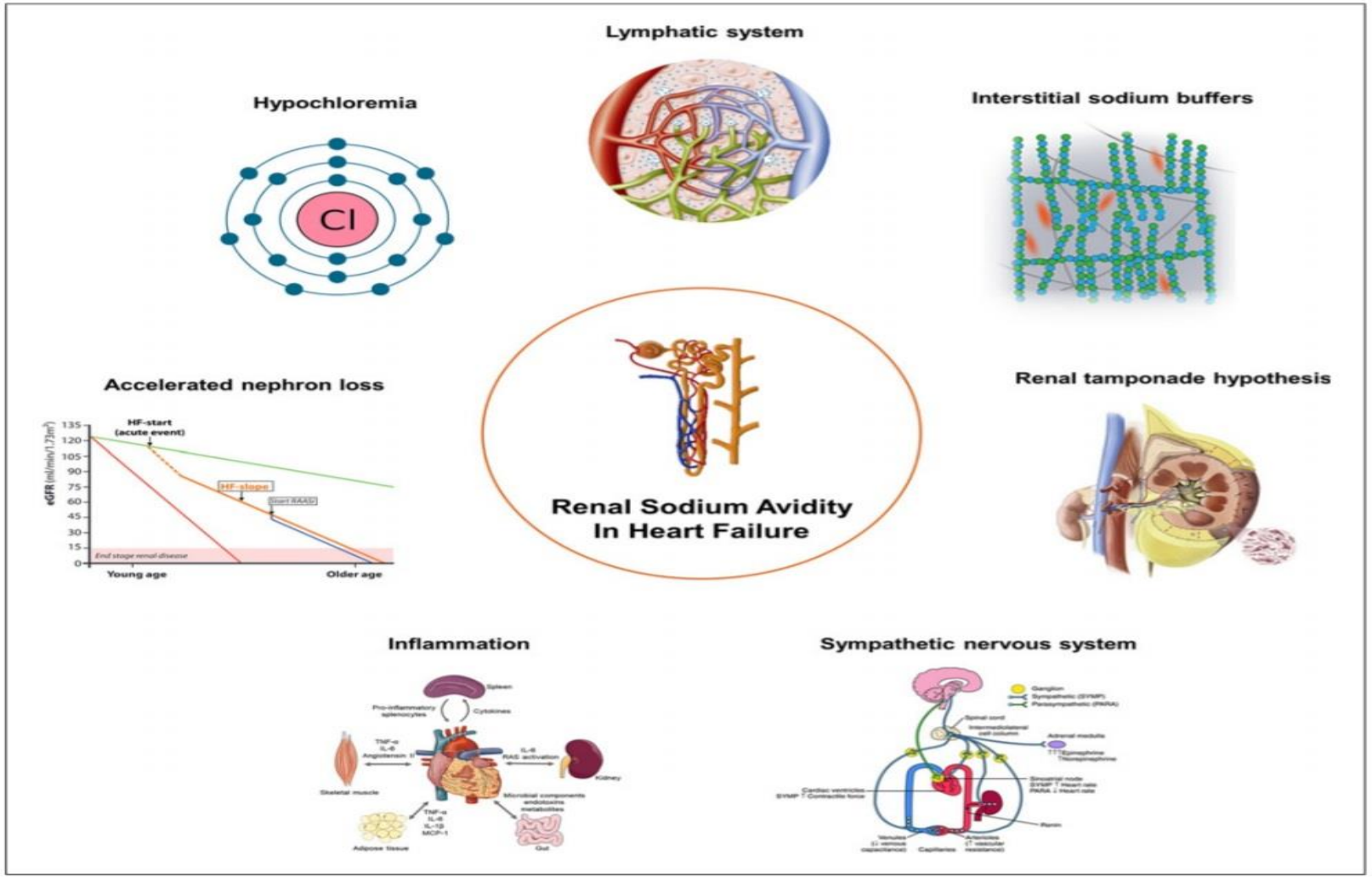


Fig. 1. Novel concepts in the pathophysiology of renal sodium avidity in HF.

Na and water retention:

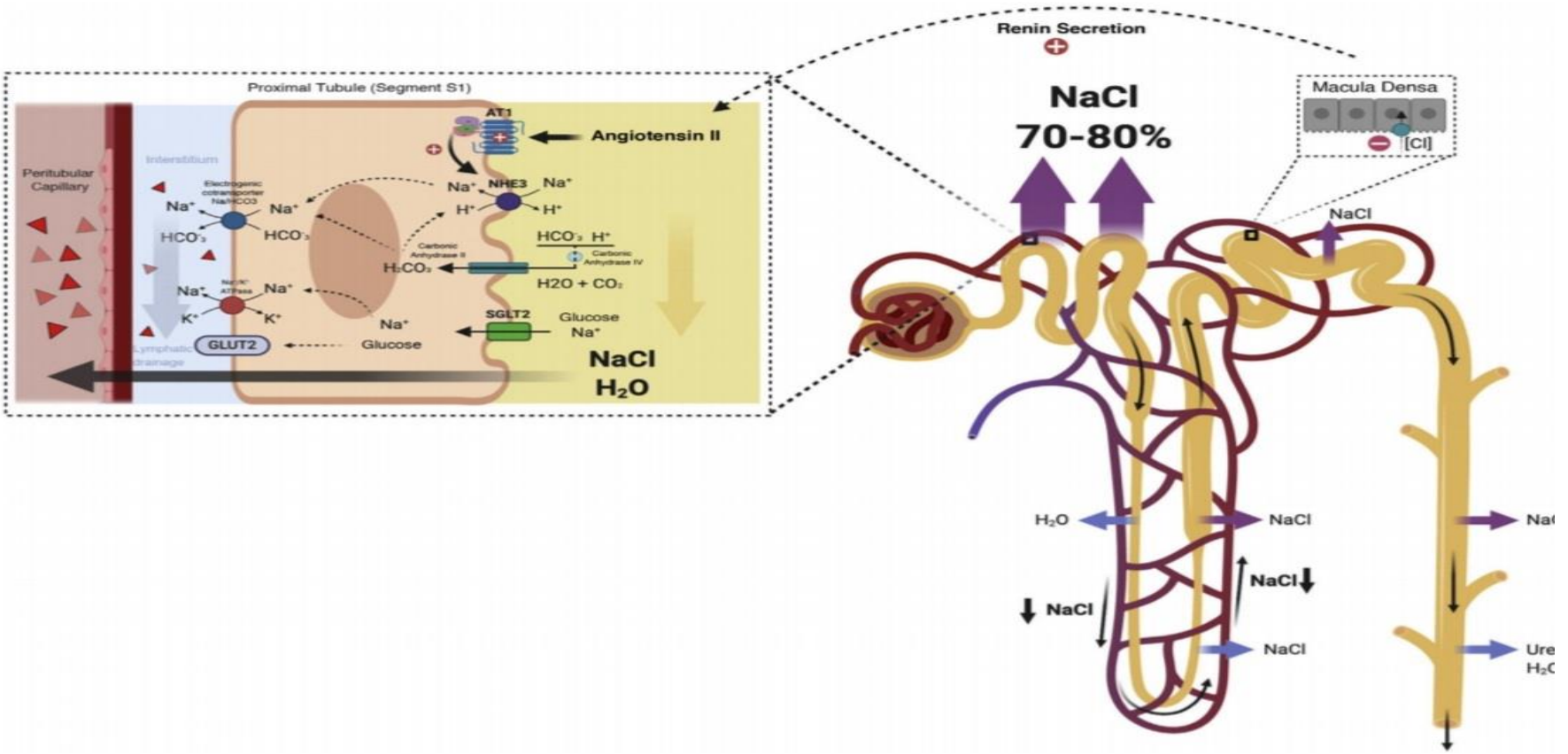


Figure 3 – Proximal tubule. Neurohormonal activation and intraglomerular and peritubular hemodynamic changes facilit Na and water reabsorption in the proximal tubule. Additionally, increased lymphatic flow washes out interstitial protein and decreases oncotic pressure in the renal interstitium, further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

Sodium avidity

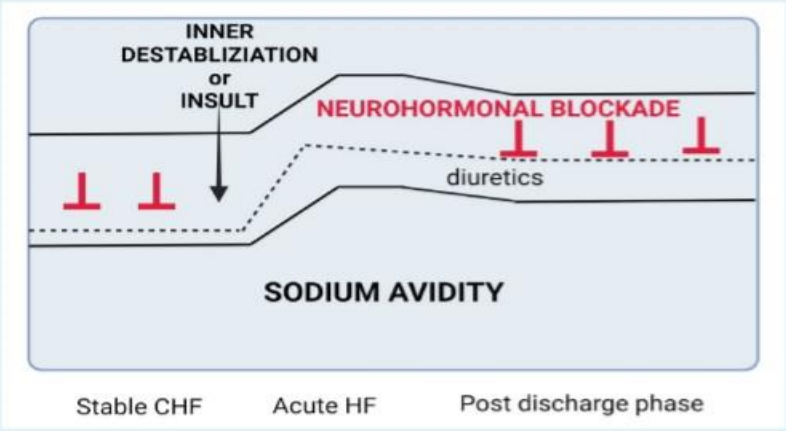


Figure 3 The classic 'diuretic centric' approach for decongestion. Neurohormonal blockade and diuretics counteract sodium avidity at a steady state (stable chronic heart failure [CHF]). Sodium avidity increases days/weeks before an episode of decompensation (inner destabilization of the sodium/water 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.

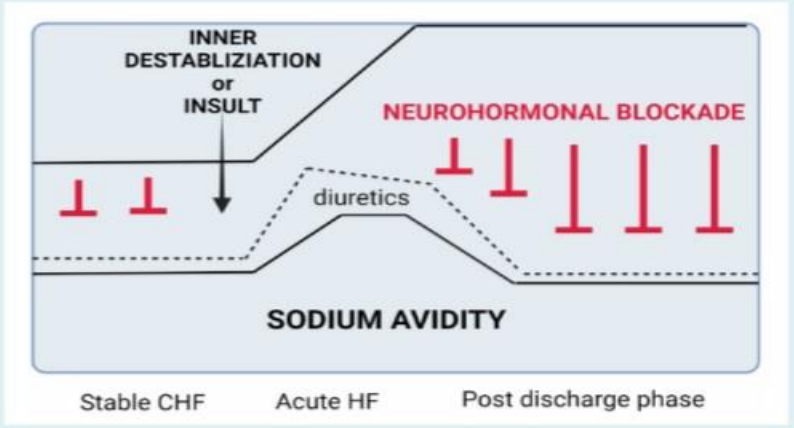


Figure 4 The new neurohormonal centric approach for sustained decongestion. The neurohormonal centric decongestion approach assumes that in the long run, sodium avidity should be mainly counterbalanced by neurohormonal blockade (guideline-directed medical therapy) with the lowest possible dose of diuretics. 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.

Pathophysiology of congestion

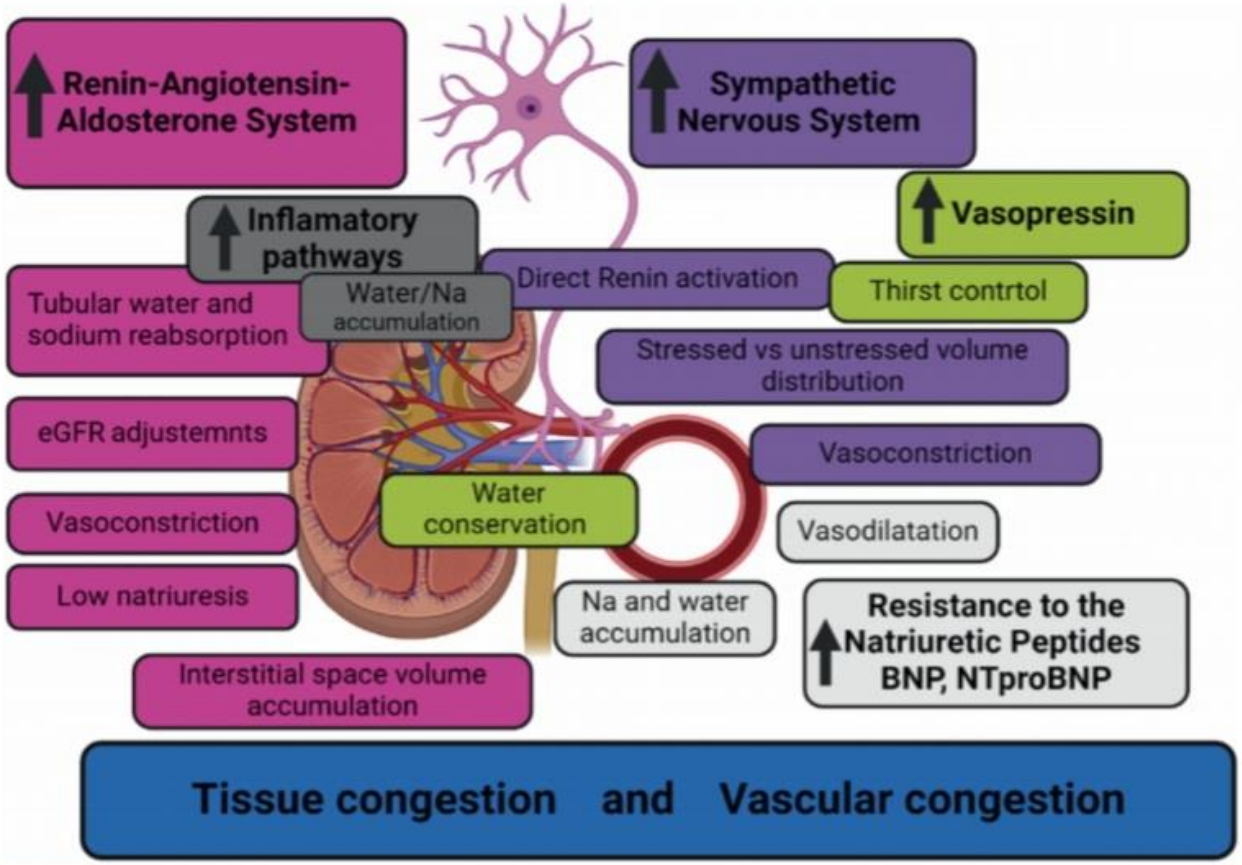


Figure 1 The simplified pathophysiological pathways that contribute to the development of congestion in heart failure. BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Treatment strategies in CRS

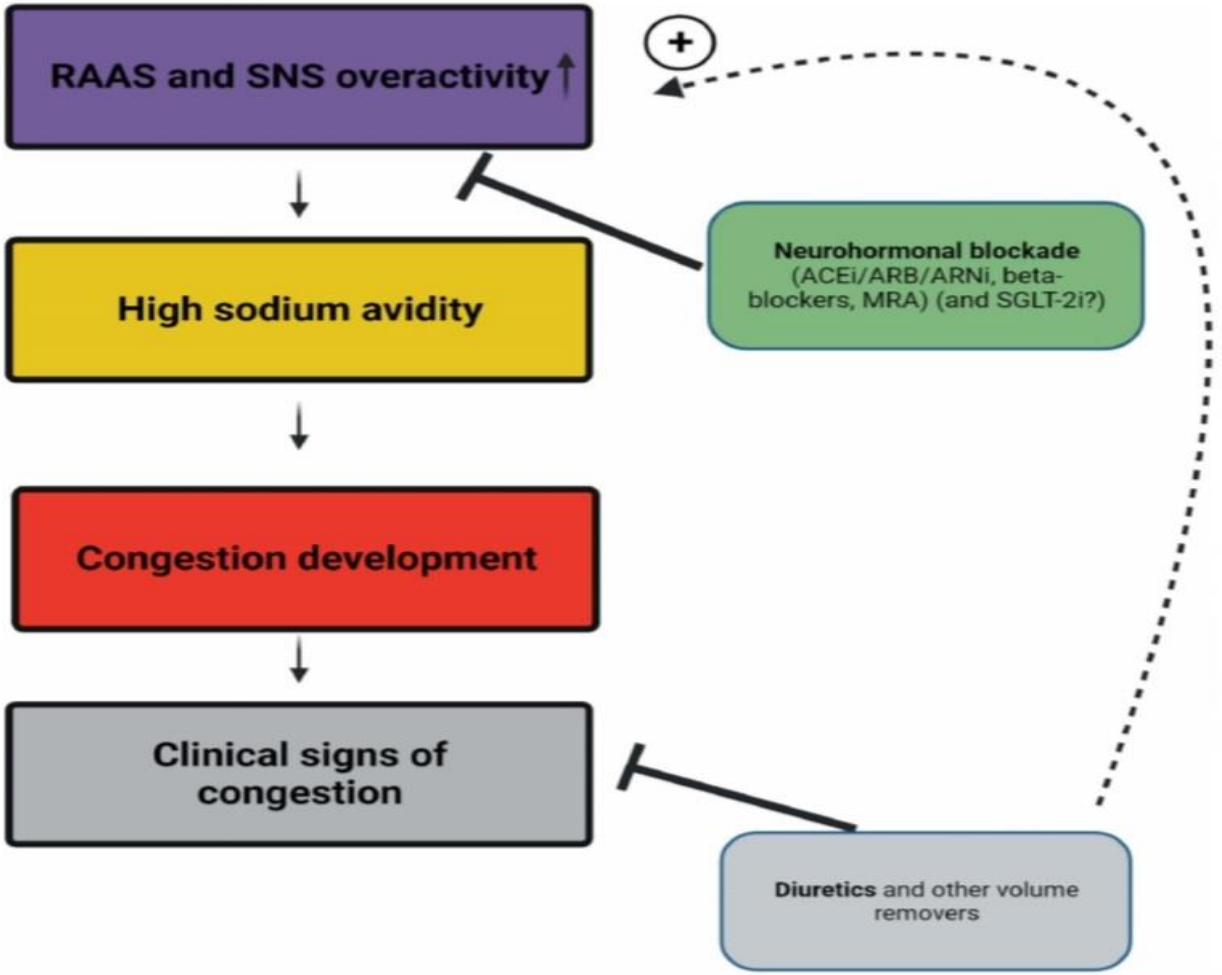
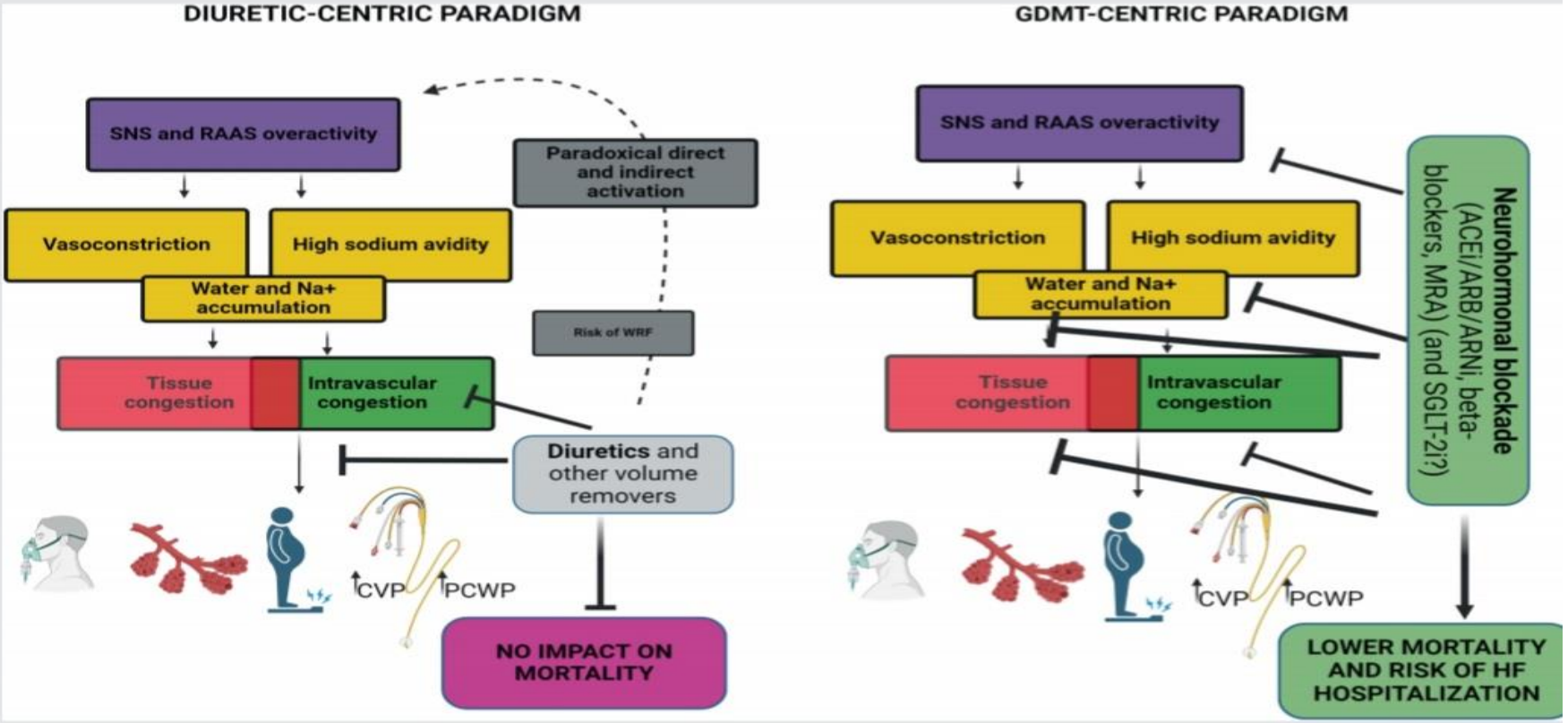


Figure 2 Differences in mechanisms of action between direct sodium/water removers versus neurohormonal blockade and sodium–glucose cotransporter 2 inhibitors (SGLT-2i). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA,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

Treatment strategies in CRS

Graphical Abstract



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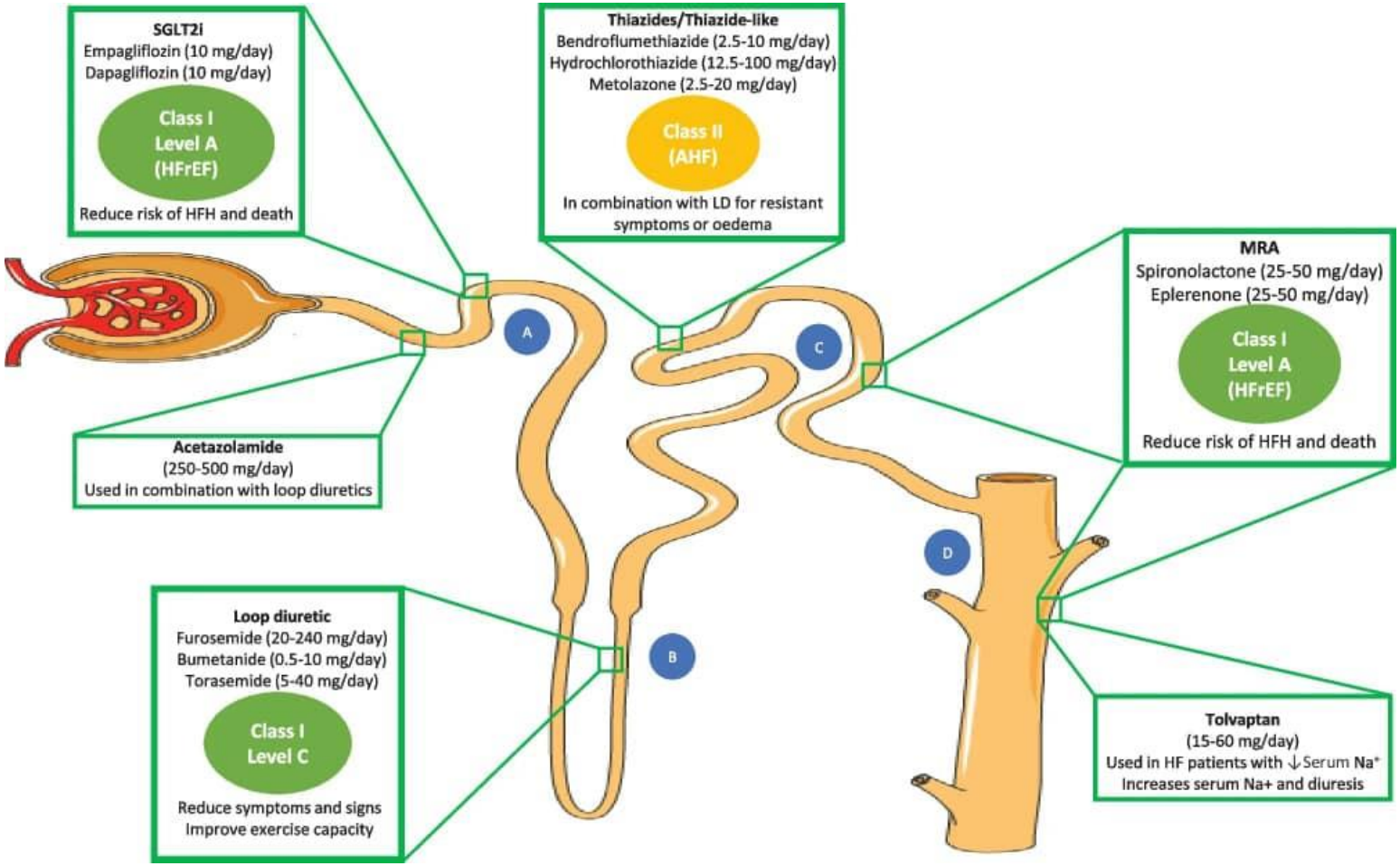
Diuretics: comparison of site of action



Review

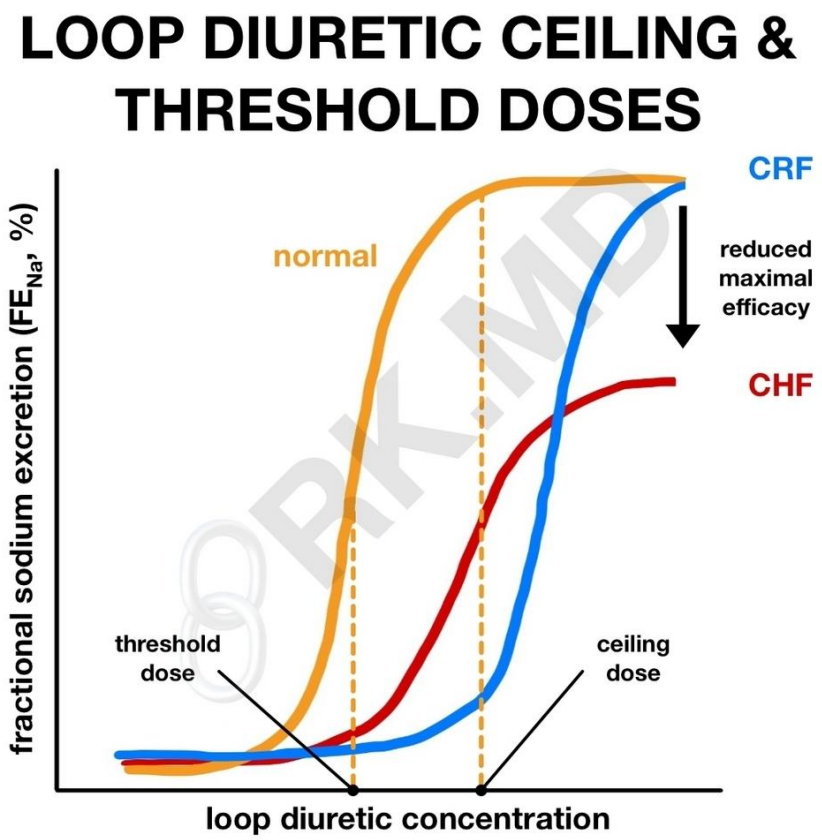
Continuous Infusion Versus Bolus Injection of Loop Diuretics for Patients With Congestive Heart Failure: A Meta-Analysis

Jithin Karedath et al. Cureus. 2023.

Free PMC article

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

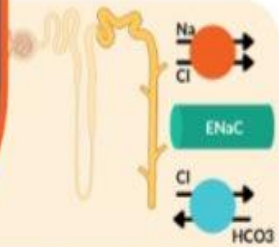
NSAIDs

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.

Diuretics:

TABLE 1
Commonly used diuretics and doses in chronic heart failure

Drug	Starting daily dose	Maximum recommended total daily dose	Duration of action
Loop diuretics			
Bumetanide	PO/IV: 0.5–1.0 mg once or twice	PO/IV: 10 mg	4–6 hr
Furosemide	PO/IV: 20–40 mg once or twice	PO/IV: 600 mg	6–8 hr
Torsemide	PO: 10–20 mg once	PO/IV: 200 mg	12–16 hr
Thiazide diuretics[a]			
Chlorothiazide	PO: 250–500 mg once or twice	PO: 1,000 mg	6–12 hr
Chlorthalidone	PO: 12.5–25 mg once	PO: 100 mg	24–2 hr
Hydrochlorothiazide	PO: 25 mg once or twice	PO: 200 mg	6–12 hr
Indapamide	PO: 2.5 mg once	PO: 5 mg	36 hr
Metolazone	PO: 2.5 mg once	PO: 20 mg	12–24 hr
Carbonic anhydrase inhibitors			
Acetazolamide	PO: 250–375 mg once IV: 500 mg once	PO/IV: 1,500 mg	PO: 18–24 hr IV: 4–5 hr
Potassium-sparing diuretics			
Amiloride	PO: 5 mg once	PO: 20 mg	24 hr
Triamterene	PO: 50–75 mg twice	PO: 200 mg	7–9 hr
Spironolactone	PO: 12.5–25 mg once	PO: 100 mg	24 hr[b]

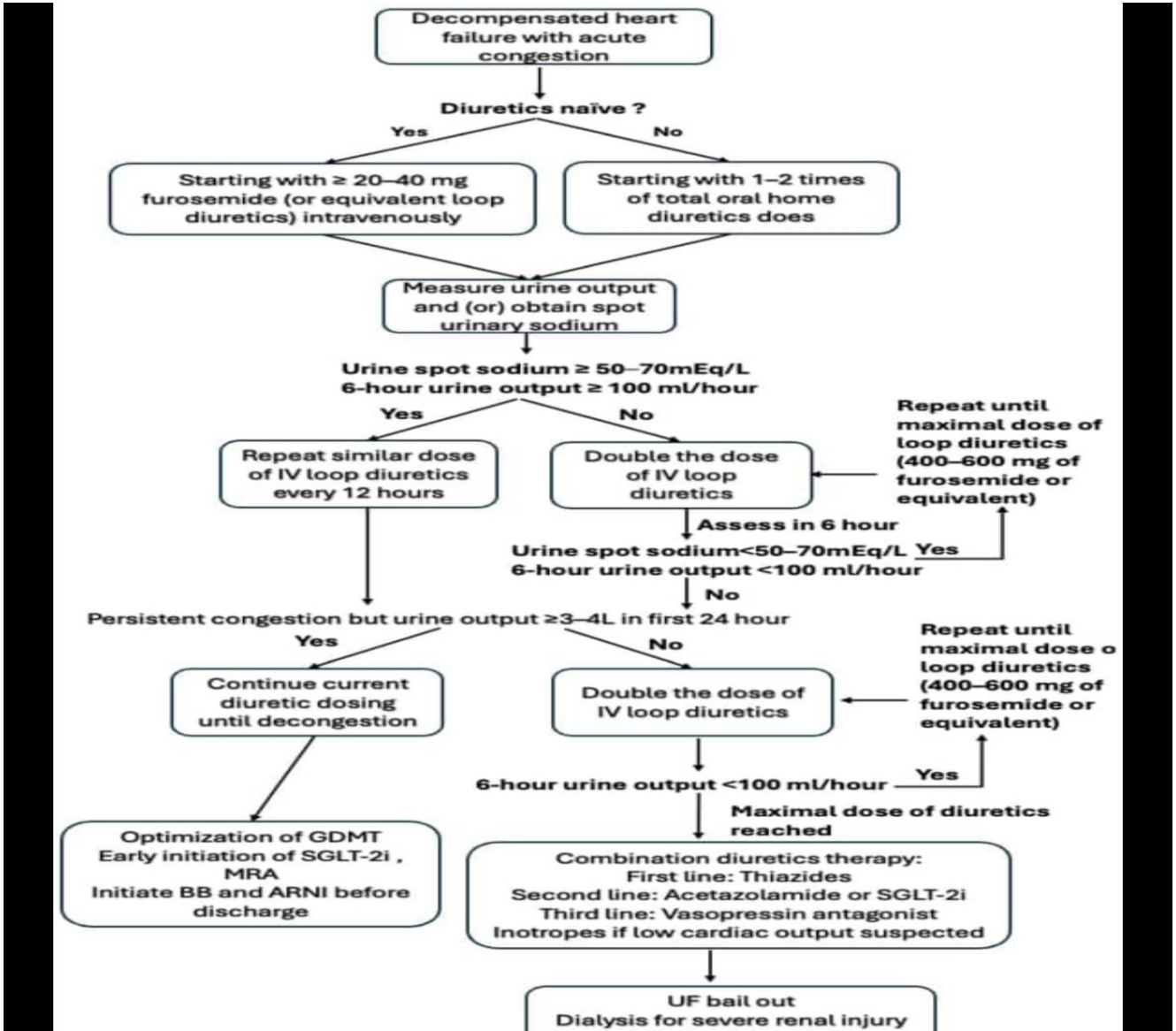
[a]Sequential nephron blockade dose of metolazone is 2.5 to 10 mg once daily (PO), hydrochlorothiazide 25 to 100 mg once or twice daily (PO), and chlorothiazide 500 to 1,000 mg once daily (IV), all 30 minutes before loop diuretics.

[b]Duration of action based on half-life of canrenone, the active metabolite of spironolactone.

IV = intravenous; PO = oral

Based on data from references 1, 4, and 5.

Stepwise diuretic therapy



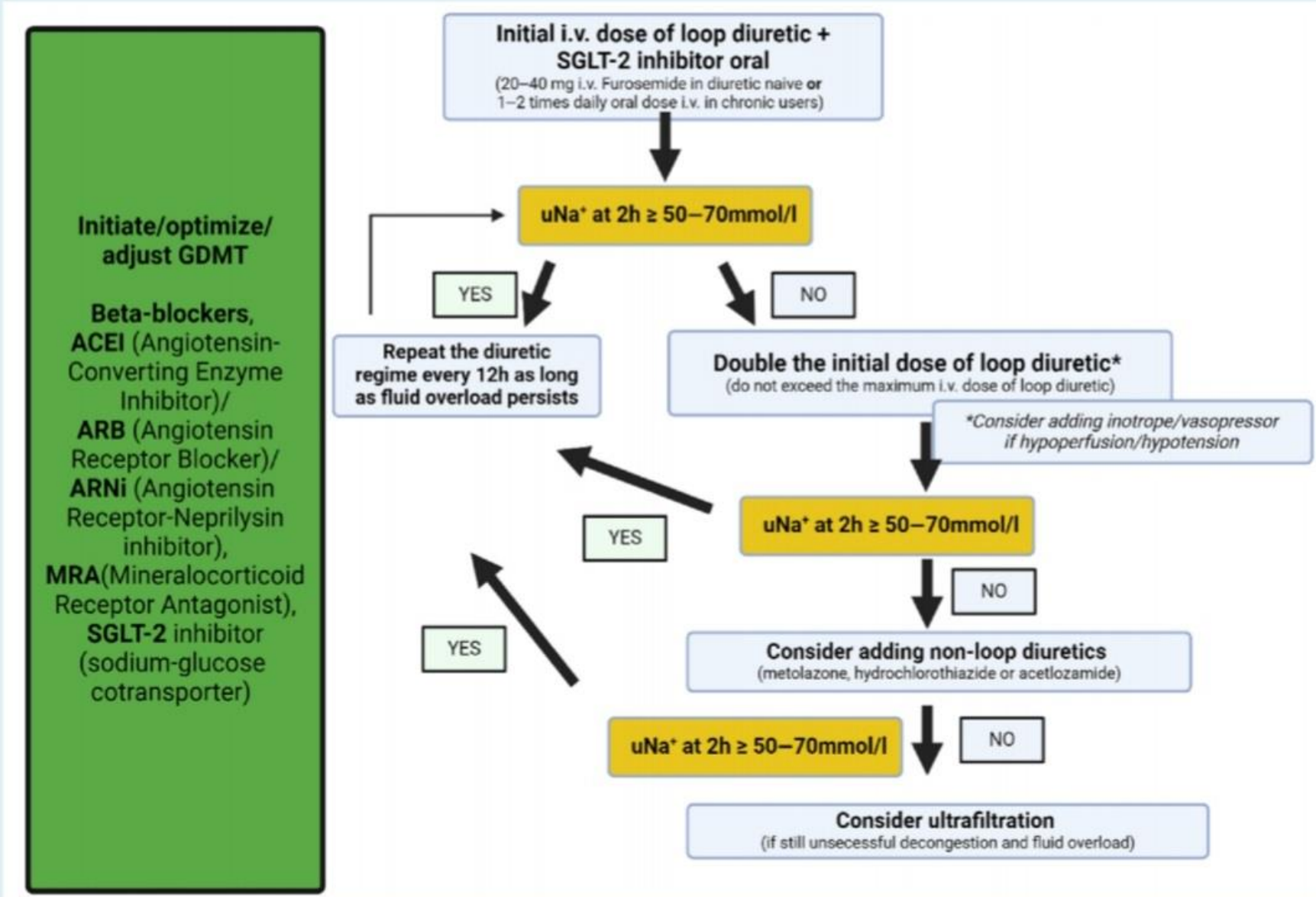


Figure 5 Algorithm to optimize decongestion in decompensated heart failure. GDMT, guideline-directed medical therapy; uNa^+, urine sodium.

Diuretics combination:

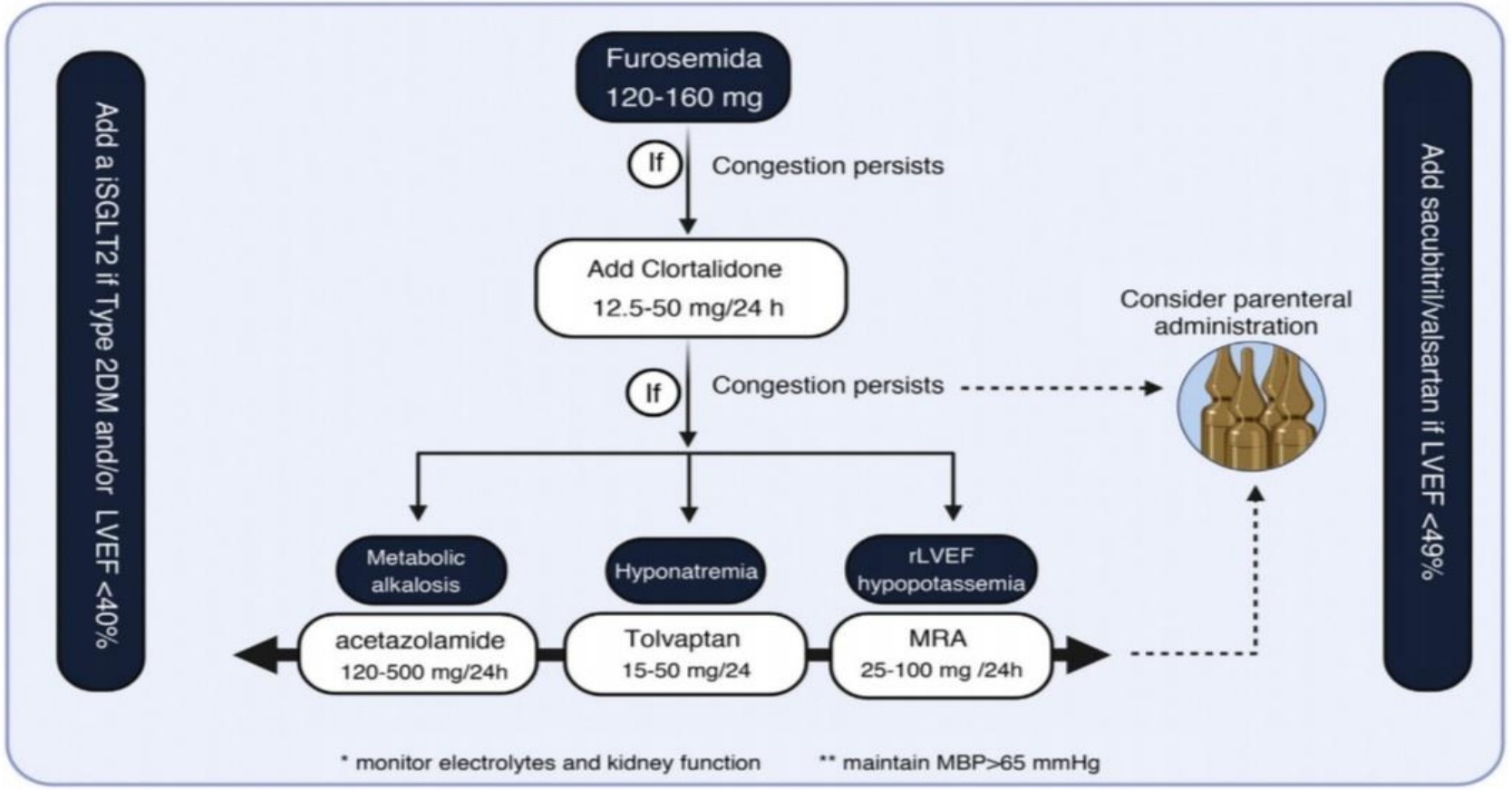


Figure 7 – Proposal of therapeutic algorithm.

AKI during Diuretic therapy

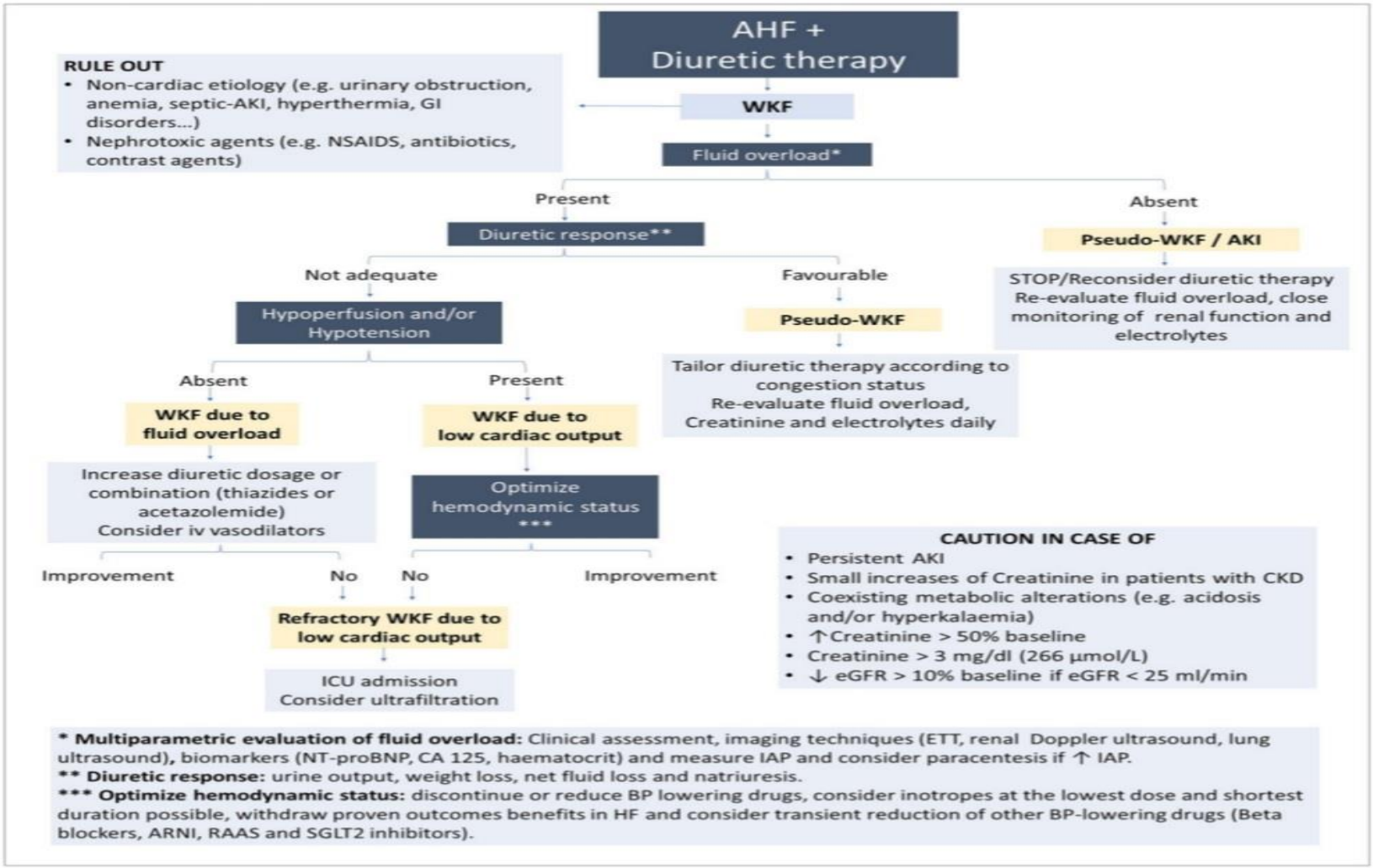


Figure 4: Approach to worsening kidney function in AHF.

2022

ADVOR STUDY

Acetazolamide in acute decompensated heart failure with volume overload

multicenter, parallel-group, double-blind, randomized, placebo-controlled trial

Objective: To compare the incidence of successful decongestion with addition of acetazolamide vs placebo to loop diuretic therapy in patients with acute decompensated heart failure

519 Patients

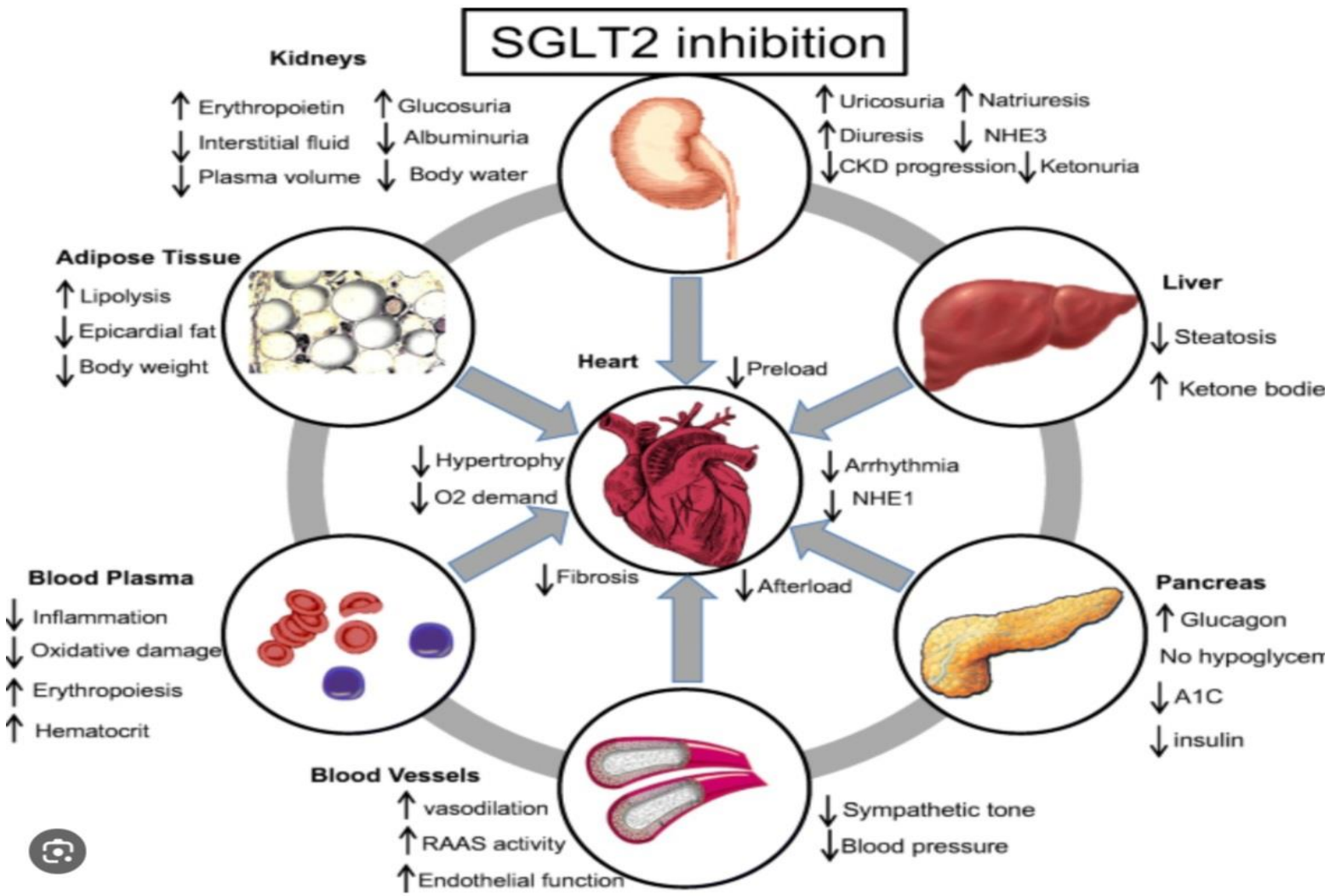
Adults ≥18 years with clinical signs of volume overload (edema, pleural effusion, ascites); NT-proBNP >1000 pg/mL or BNP >250 pg/mL; Oral maintenance therapy with 40 mg of furosemide, 20 mg of torsemide, 1 mg of bumetanide or more for ≥1 month prior to randomization

Acetazolamide [n=259]		Placebo [n=260]
	PRIMARY OUTCOME	
42.2	Successful decongestion within 3 days after randomization % HR 1.07; 95% CI, 0.78 to 1.48; P < 0.001	30.5
	SECONDARY OUTCOMES	
29.7	All-cause mortality or rehospitalization for HF during 3 months of follow-up %	27.8
8.8	Duration of hospital stay (in days) % P=0.016	9.9
2.7	Combined renal safety endpoint % P=0.10	0.8

Conclusion: The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure resulted in a greater incidence of successful decongestion.

W Mullens et al. DOI: 10.1056/NEJMoa2203094 | Summary by Dr.Shreyash Bhoyar, MBBS

SGLT-2 inhibitor



Mechanisms and Evidence for Heart Failure Benefits from SGLT2 ...

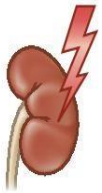
Visit >

Clinical Kidney Journal

Effects of SGLT2 inhibitors on parameters of renal venous congestion in intrarenal Doppler ultrasonography

Renal venous congestion (VC) plays an important role in cardiorenal syndrome.
This study investigated the effects of SGLT2i therapy on intrarenal Doppler sonography parameters of renal VC.

Methods

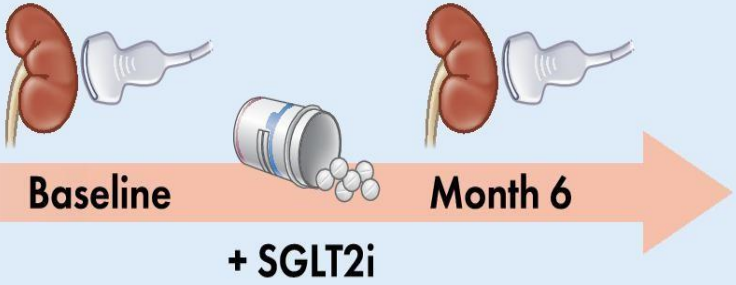


CKD

± Diabetes mellitus type 2

± HFrEF

Results



Venous impedance index: 0.51 → 0.38 ($p < 0.01$)

Intrarenal venous flow pattern

Conclusion: SGLT2i therapy resulted in a reduction in renal venous congestion. These findings underscore the potential hemodynamic benefits of SGLT2i in cardiorenal syndrome.

Wallbach, M.
Clinical Kidney Journal (2024)
@CKJsocial

SGLT-۲ 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‡

Ultrafiltration in CRS

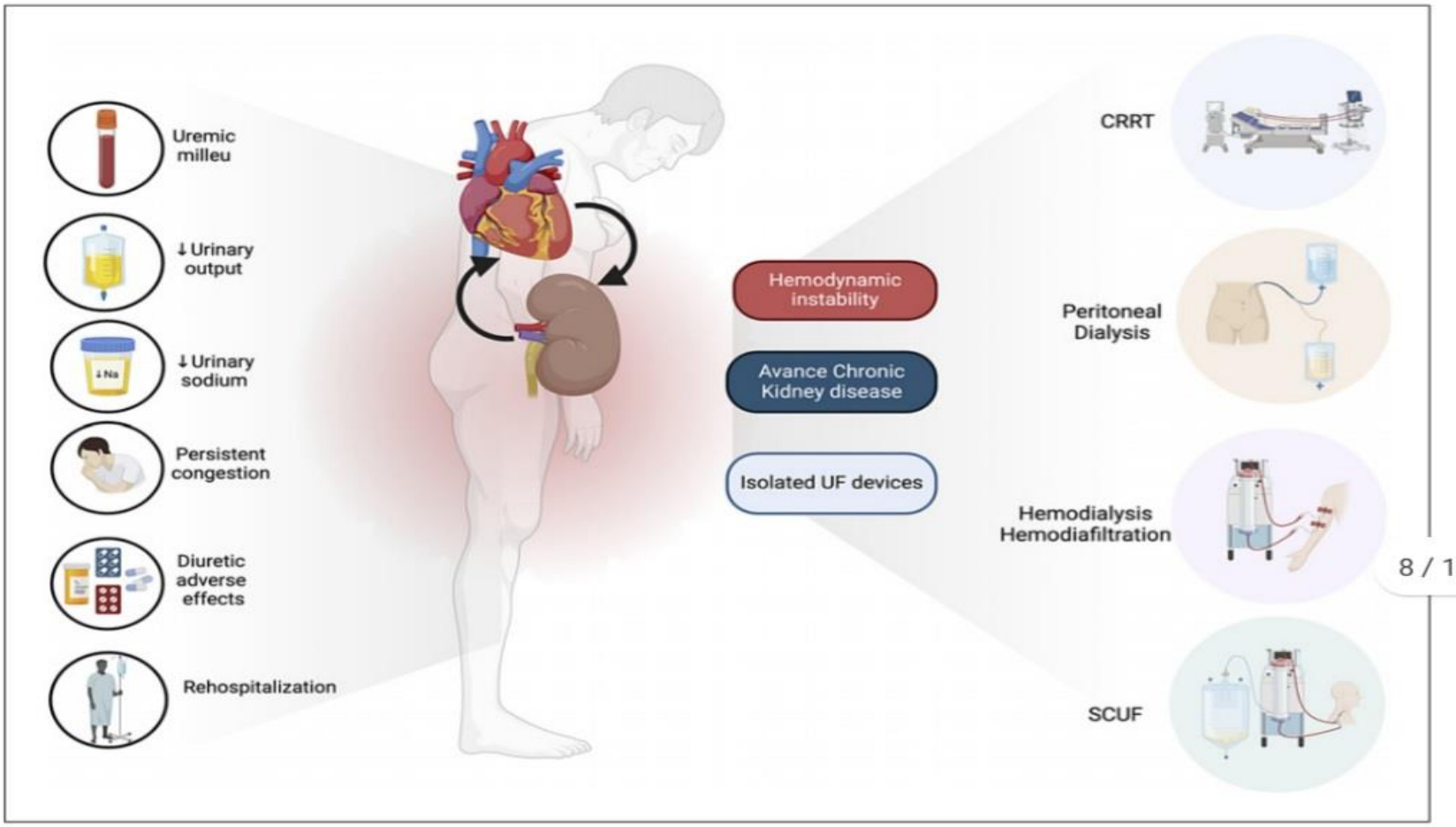


Fig. 1. Clinical scenarios for initiation of KRT in people with CRS. In patients with CRS, clinical scenarios may arise where the initiation of KRT should be considered, such as a uremic milieu, ineffective urinary volume for the predicted decongestion goals, or when adverse events occur from the use of diuretics and limit their continuity such as hypokalemia, metabolic alkalosis, or hypochloremia. In these cases, the choice of KRT will depend on the hemodynamic stability, predilection of the patient and their family, hospital logistics, and the realistic objectives set by the cardiorenal team. CRRT, continuous renal replacement therapy; KRT, kidney replacement therapy; SCUF, slow continuous ultrafiltration.

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

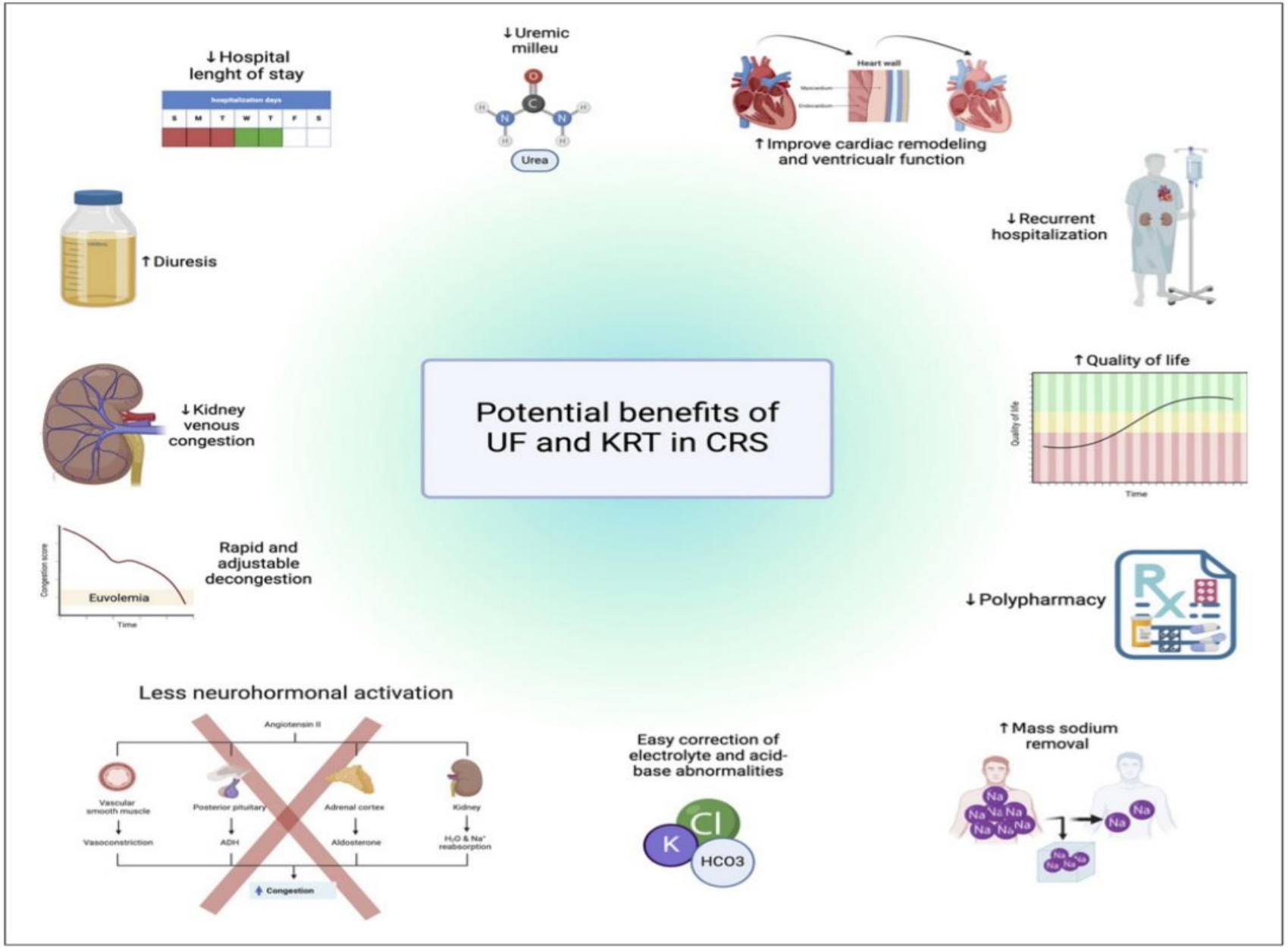


Fig. 3. Potential benefits of KRT or UF in patients with CRS. The use of KRT or UF in patients with CRS has demonstrated multiple benefits, which may be sufficient arguments to consider its use, especially in patients where diuretics have been insufficient for acceptably satisfactory management. ADH,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

Ultrafiltration in CRS assessment

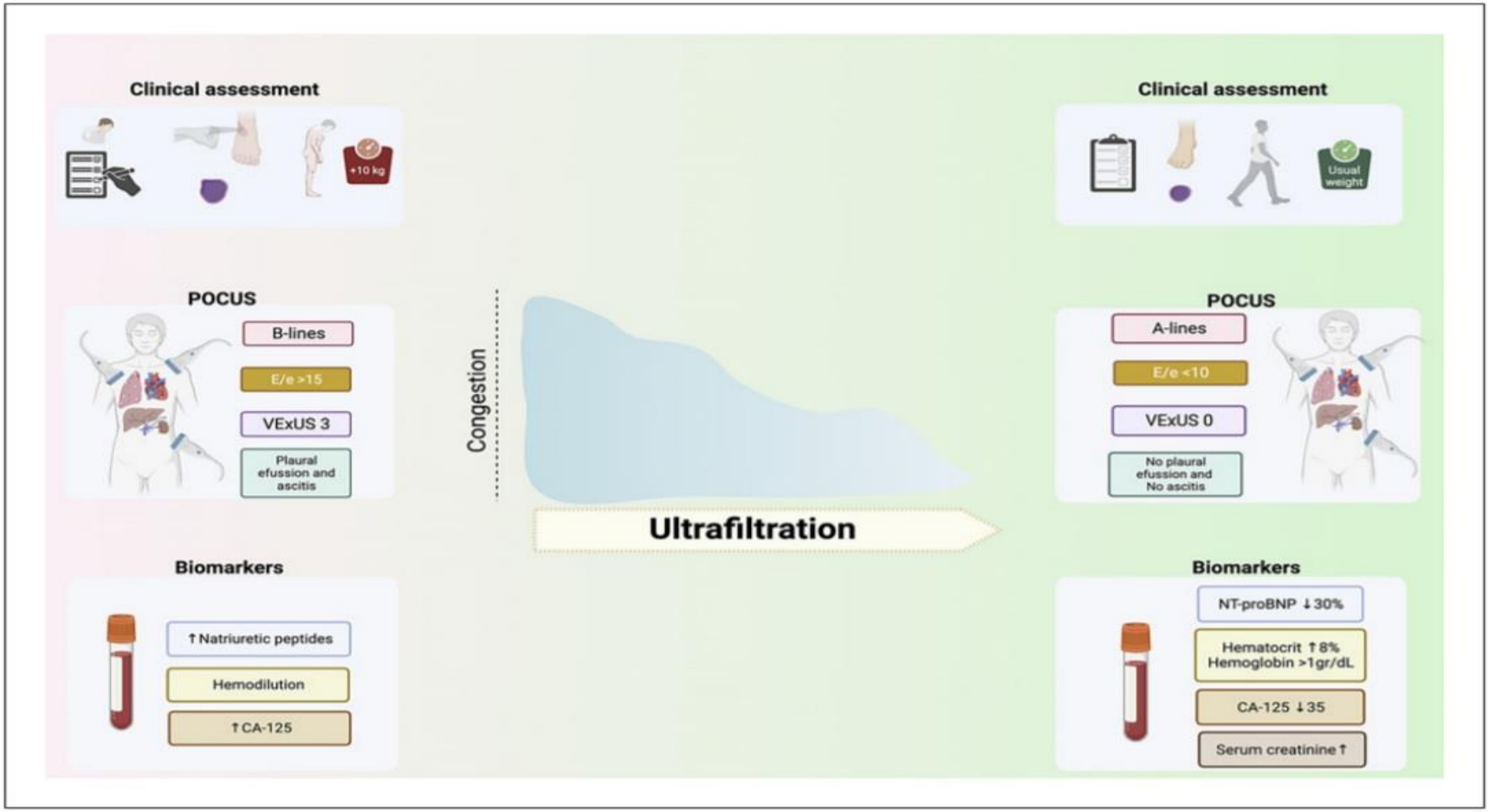


Fig. 2. Multimodality assessment of decongestion during UF in CRS. During decongestion with extracorporeal therapies, UF must be continuously evaluated and modulated through multimodality assessment, and it is the set of measurements that range from the clinical evaluation of symptoms, body weight, POCUS viewing central vein morphology, echocardiography, and the trajectory of laboratory variables that suggest decongestion, such as the reduction of natriuretic peptides, CA-125, increases in hematocrit, hemoglobin, and serum creatinine. POCUS, point-of-care ultrasound.

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

Table 2 (continued)

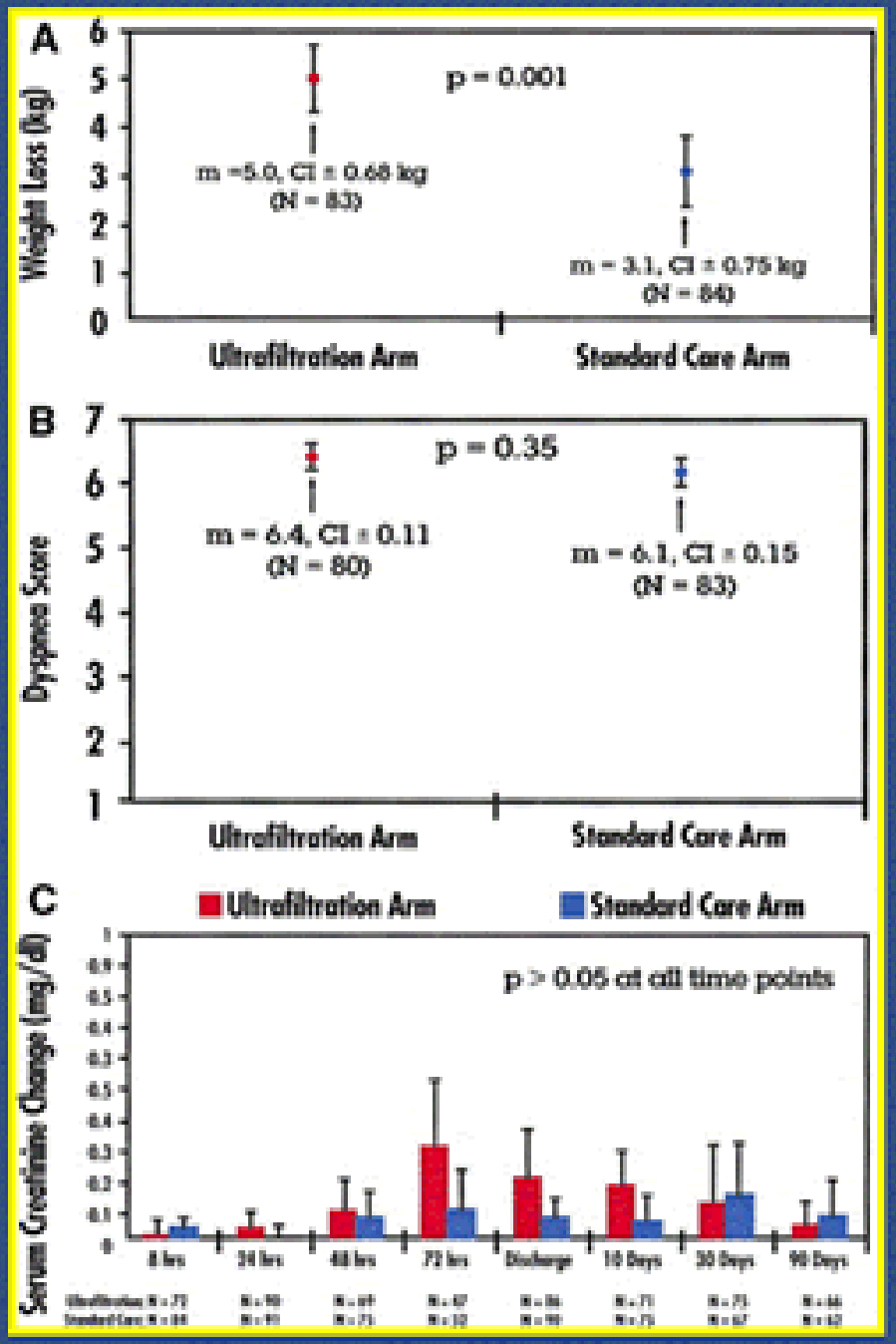
Study	Modality	Description	Objective	KRT	Results	Comments
UNLOAD [64]	UF versus intravenous diuretics	200 patients hospitalized for congestive ADHF	Weight loss and dyspnea in 48 h	UF rate up to 500 mL/h	Weight loss 5.0 + 3.1 kg versus 3.1 + 3.5 kg, and fluid loss 4.6 versus 3.3 L were higher in the UF 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.

UNLOAD Trial

- 200 patient RCT: UF vs. Diuretic Rx for ADHF
- Mean serum creatinine in both groups was 1.5±0.5mg/dl (exclusion > 3mg/dl)
- ULTRAFILTRATION:
- Rx: UF with BFR 10-40ml/min, heparinization, UF ≤500ml/hour
- → Fluid removal rate averaged 241ml/hr for 12.3±12 hours
- DIURETICS:
- Rx: Intravenous route, minimum dosing of ≥ 2 double the prehospitalization oral diuretic dose for at least 48 hrs post-randomization
- → Received 181±121mg of furosemide (or equivalent bumetanide or torsemide doses), the majority by intermittent boluses

UNLOAD Trial: Efficacy



Primary Endpoint:

(A) Weight Loss

&

(B) Dyspnea Scores at 48 hours

Safety: no difference in AKI rates

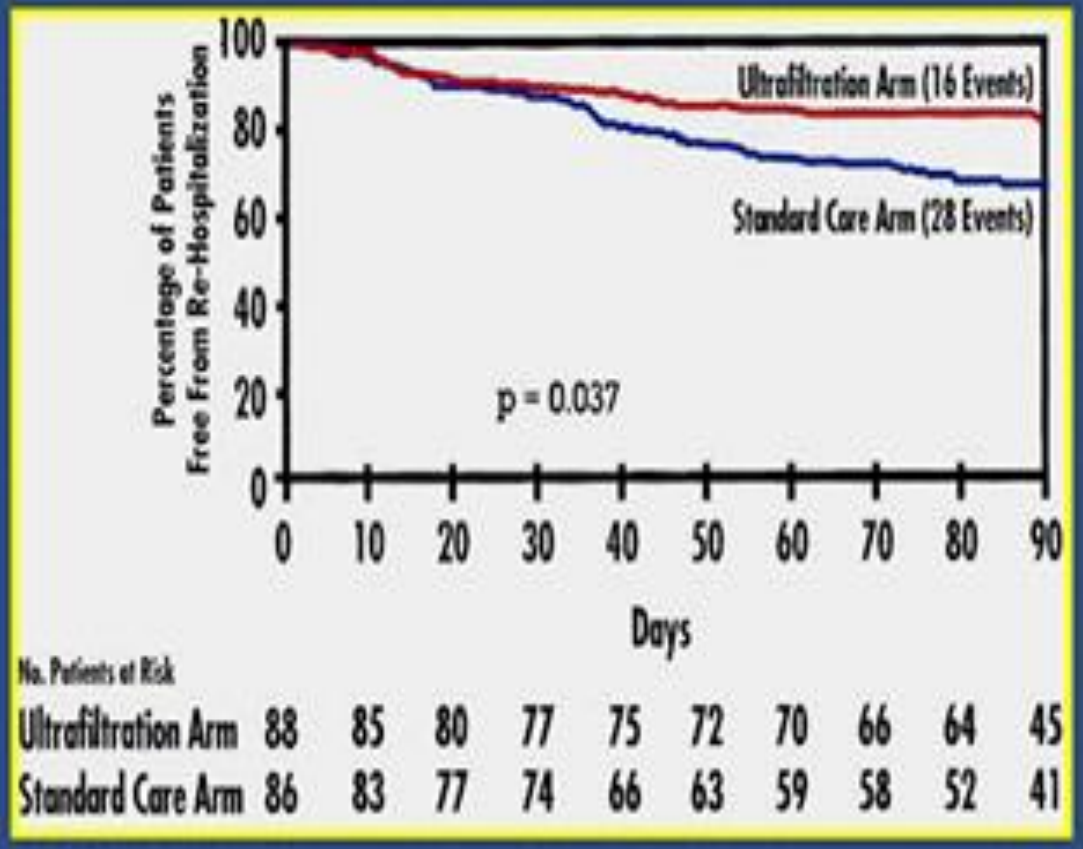
<or>

Hypotension rates

More hypokalemia in diuretic group

Constanzo MR, et al: JACC 2007;49:675-83

UNLOAD Trial: Outcomes



Lengths of index hospitalization did not differ between the ultrafiltration group (6.3±4.9 days) vs. diuretic group (5.8±3.8 days, p=0.979)

90 day rehospitalizations with heart failure were significantly more common in the diuretic group (32%) than the ultrafiltration group (18%, p=0.037)

Mortality rates were not significantly different

Constanzo MR, et al: JACC 2007;49:675-83

Table 2. Examples of trials of decongestion strategies for acute decompensated heart failure

Class of Drug or Diuretic Strategy	Trial	Year	No. of Patients	Intervention	Kidney-Related Exclusion Criteria	Summary of Key Findings
Loop diuretic dosing strategy[50]	DOSE	2011	308	Bolus versus continuous loop diuretic strategy; low (same as home) versus high dose (2.5× home dose)	Creatinine >3 mg/dl	No significant difference in dyspnea with bolus versus continuous dosing. Trend toward improvement with high dose over low dose. Higher rates of creatinine >0.3 mg/dl in the high dose (23%) versus low dose (14%) at 72 h
Thiazide plus loop[53]	CLOROTIC	2022	230	Hydrochlorothiazide (25, 50, or 100 mg) plus loop diuretic versus placebo plus loop diuretic	Kidney failure requiring dialysis Sodium ≤125 mmol/L	Weight loss was greater in the thiazide versus placebo arm (−2.3 versus −1.5 kg) at 72 h. Higher rates of rise in creatinine by >0.3 mg/dl in thiazide arm (46.5%) versus placebo (17.2%)
SGLT2 inhibitor[57]	EMPULSE	2022	530	Empaglifozin 10 mg once daily versus placebo for patients no longer requiring escalation of IV diuretic dosing or use of IV vasodilators or inotropes	eGFR <20 ml/min per 1.73 m^2	Empagliflozin showed a greater win ratio of 1.36 over placebo for components of the primary outcome of time to death and frequency of heart failure exacerbations. Greater diuretic response (−2.31 [−3.77 to −0.85] kg more in weight loss per mean daily loop diuretic dose) in the empagliflozin versus placebo arm
Mineralocorticoid receptor antagonist[60]	ATHENA	2017	360	Spironolactone 100 mg or 25 mg versus placebo (plus standard therapy) for 4 d	eGFR <30 ml/min per 1.73 m^2 K >5.0 mmol/L	No significant difference in the primary outcome of change in NT-proBNP levels. No difference in cumulative net urine output or weight change
Nesiritide[64]	ASCEND-HF	2011	7141	Nesiritide bolus of 2 μg/kg followed by 0.01 μg/kg per min versus placebo (plus standard therapy) for 1–7 d	Kidney failure requiring dialysis	No significant difference in rates of all-cause mortality (3.6% versus 4%) or rates of eGFR decline by >25% (31.4% versus 29.5%) in nesiritide or placebo arms, respectively
Nesiritide or dopamine[65]	ROSE	2013	360	Nesiritide 0.005 μg/kg per min versus dopamine 2 μg/kg per min versus placebo (plus standard therapy) for 3 d	eGFR <15 or >60 ml/min per 1.73 m^2	No significant difference in cumulative urine output or changes in cystatin C at 72 h

Table 2. (Continued)

Class of Drug or Diuretic Strategy	Trial	Year	No. of Patients	Intervention	Kidney-Related Exclusion Criteria	Summary of Key Findings
Carbonic anhydrase inhibitor[59]	ADVOR	2022	519	Acetazolamide 500 mg IV daily versus placebo (plus standard therapy) for 3 d for patients not receiving thiazides or SGLT2i therapy	eGFR <20 ml/min per 1.73 m^2	Greater rates of decongestion (no edema, pleural effusion, or ascites) in the acetazolamide arm (42.2%) versus the placebo arm (30.5%) at 3 d. No significant difference in secondary outcome of mortality or heart failure rehospitalization. No significant difference in rates of a combined kidney safety end point[a]
Vasopressin V2 antagonist[63]	ACTIV in CHF	2007	319	Tolvaptan 30 mg, 60 mg, 90 mg daily versus placebo (plus standard therapy)	Creatinine >3.5 mg/dl	Greater weight loss in tolvaptan arm that was sustained after hospitalization. No significant difference in the secondary outcome of heart failure hospitalization. No differences in serum creatinine at the time of discharge
Hypertonic saline[68]	HHS	2005	94	150 ml IV of hypertonic saline (1.4%–4.6% NaCl) twice daily plus furosemide versus furosemide alone for patients unresponsive to furosemide 250–500 mg/d	Creatinine >2 mg/dl	Faster reduction in BNP levels and greater amount of urine output in the hypertonic saline plus furosemide arm (2.2±0.5) versus furosemide alone arm (1.5±0.4) L/d
Hypertonic saline[67]	SMAC-HF	2011	1771	150 ml IV of hypertonic saline (1.4%–4.6% NaCl) twice daily versus no hypertonic saline (plus standard therapy with furosemide)	Creatinine >2.5 mg/dl	Lower rates of cardiovascular mortality in the hypertonic saline arm (12.9%) versus the diuretic-only arm (23.8%)
UF[69]	UNLOAD	2007	100	UF (variable rate, average of 241 ml/h) versus pharmacological therapy	Creatinine >3 mg/dl	Net fluid loss was greater in the UF arm (4.6±2.6 L) versus pharmacological arm (3.3±2.6 L) at 48 h. No difference in rates of creatinine rise by ≥0.3 mg/dl (26.5% versus 20.5%) in the UF versus pharmacological arms, respectively
UF[70]	CARRESS	2012	188	UF (fixed at 200 ml/h) versus stepped diuretic protocol for those demonstrating creatinine rise of ≥0.3 mg/dl	Creatinine >3.5 mg/dl	No significant difference in weight loss at 96 h. Significantly different change in creatinine at 96 h, with mean increase of 0.23±0.7 mg/dl in the UF arm versus −0.04±0.5 mg/dl in the pharmacological arm

Table 2. (Continued)

Class of Drug or Diuretic Strategy	Trial	Year	No. of Patients	Intervention	Kidney-Related Exclusion Criteria	Summary of Key Findings
UF[71]	AVOID-HF	2016	224	UF (variable rate, average of 138 ml/h) versus stepped diuretic protocol	Creatinine >3 mg/dl	No significant difference in the primary outcome of time to a heart failure rehospitalization or unscheduled visit for heart failure. No difference in changes in creatinine at 90 d or rates of kidney failure requiring dialysis (0.9% versus 0.9% in each arm)

DOSE, Diuretic Optimization Strategies Evaluation; CLOROTIC, Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure; SGLT2, sodium-glucose cotransporter 2; EMPULSE, EMPagliflozin 10 mg compared with placebo, initiated in patients hospitalized for acUte heart faiLure who have been StabilizEd; ATHENA, Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure; ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; ROSE, Renal Optimization Strategies Evaluation; ADVOR, Acetazolamide in Decompensated Heart Failure with Volume Overload; ACTIV in CHF, Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure; HHS, hypertonic saline solution; SMAC-HF, Self-Management and Care of Heart Failure; SGLT2i, SGLT2 inhibitor; NaCl, sodium chloride; UF, ultrafiltration; UNLOAD, Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure; CARRESS, Cardiorenal Rescue Study in Acute Decompensated Heart Failure; AVOID-HF, Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure.

[a]Combined safety end point of doubling of serum creatinine, ≥50% sustained decrease in eGFR, or need for KRT during hospitalization.

Acute PD for refractory Acute heart failure

RESEARCH ARTICLES | JULY 27 2021

Outcomes after Acute Peritoneal Dialysis for Critical Cardiorenal Syndrome Type

0.01). ***Conclusions:*** PD is a viable dialysis option in CRS1, especially in a resource-limited setting. PD can save up to 27% of lives among patients with critically ill CRS1.

Introduction: The aim of the study was to demonstrate the outcomes of peritoneal dialysis (PD) in critically ill cardiorenal syndrome type 1 (CRS1).
Methods: A cohort of 147 patients with CRS1 who received PD from 2011 to 2019 in a referral hospita in Thailand was analyzed. The primary outcome was 30-day in-hospital mortality. Ultrafiltration and net fluid balance among survivors and nonsurvivors in the first 5 PD sessions were compared. ***Results:*** The 30-day mortality rate was 73.4%. Most patients were critically ill CRS1 (al patients had a respiratory failure of which 68% had cardiogenic shock). Blood urea nitrogen and creatinine at the commencement of PD were 60.1 and 4.05 mg/dL. In multivariable analysis, increasing age, unstable hemodynamics, and positive fluid balance in the first 5 PD sessions were associated with the risk of in-hospital mortality. The change of fluid balance per day during the first 5 dialysis days was significantly different among survivor and nonsurvivor groups (−353 vs. 175 mL per day, p =

Isolated UF (conventional HD) for refractory Acute heart failure

- Contraindications:
- 1. Unstable hemodynamic/acute MI
- 2. Coagulopathy
- 3. Hyperkalemia

Ultrafiltration in Acute Decompensated Heart Failure

Luay Sarsam; Muhammad B. Malik; Khalid Bashir.

Author Information and Affiliations

Last Update: April 7, 2023.

Case problems:

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

- 1 -Volume overload (stepped 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 and blood transfusion, EPO, iron,SGLT-2 inh effect)?
- 6-Mineral receptor antagonist?(finerenon)
- 7-Contrast nephropathy risk and prophylaxy?

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.
- 5 . In diuretic resistant cases or unstable hemodynamics with volume overload **UF therapy may be useful (CRRT/SCUF/HD/PD).**