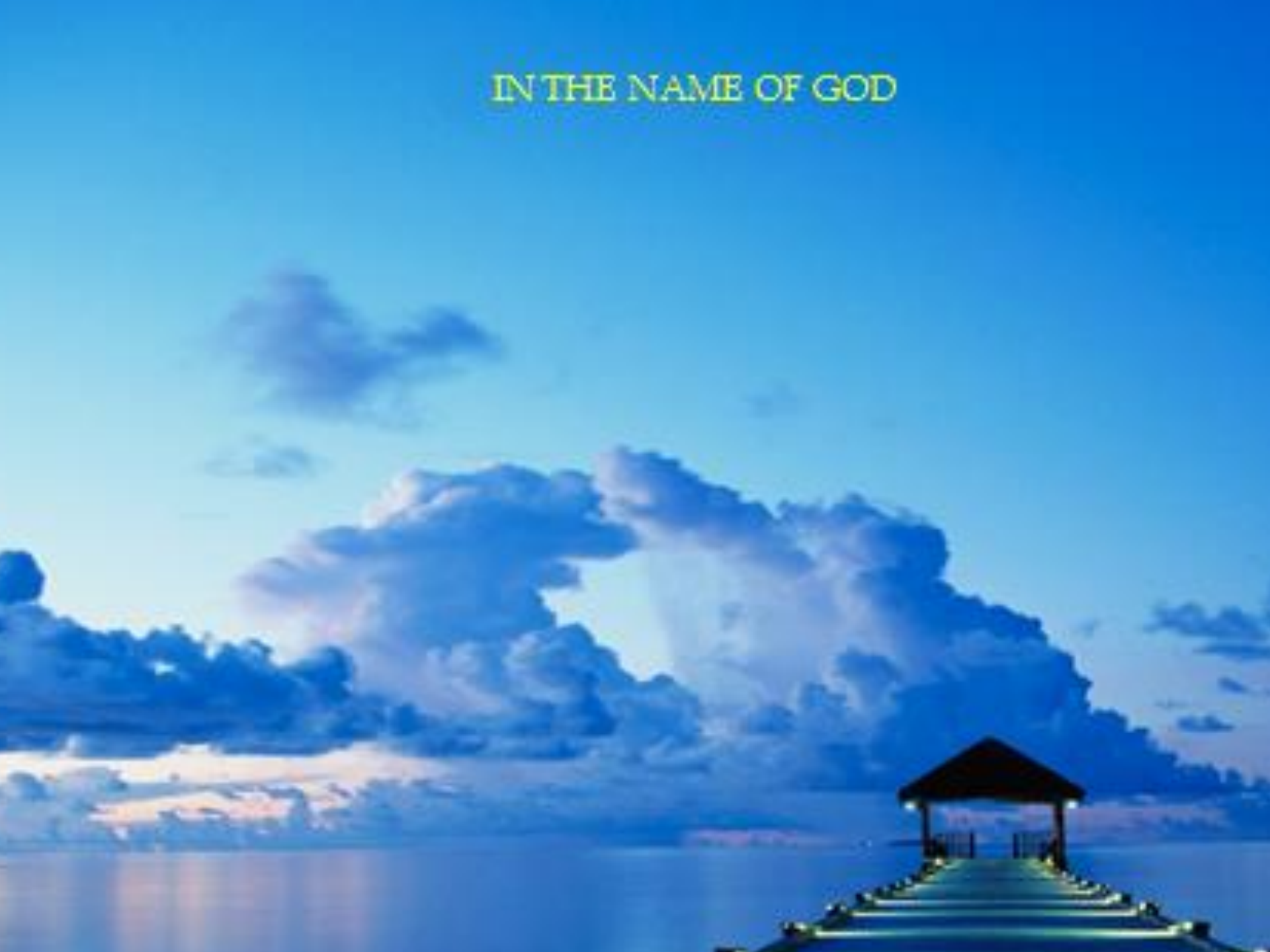
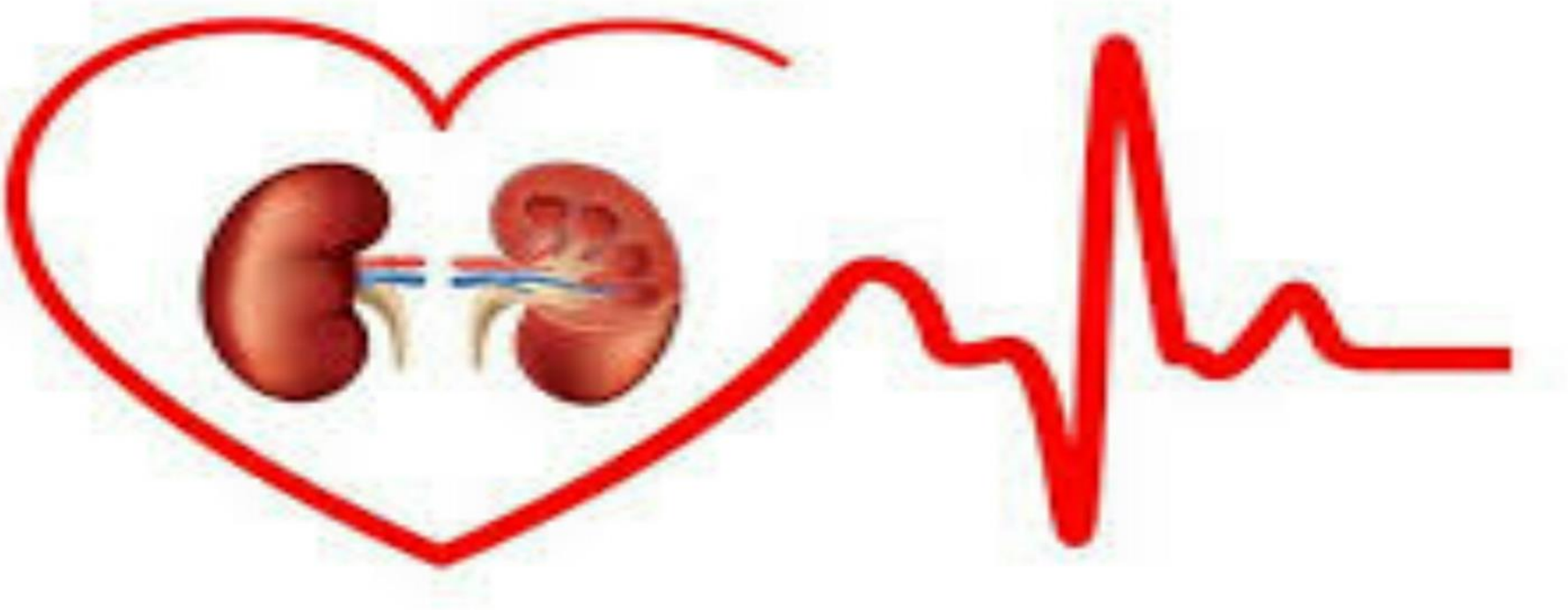
IN THE NAME OF GOD



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=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- 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.

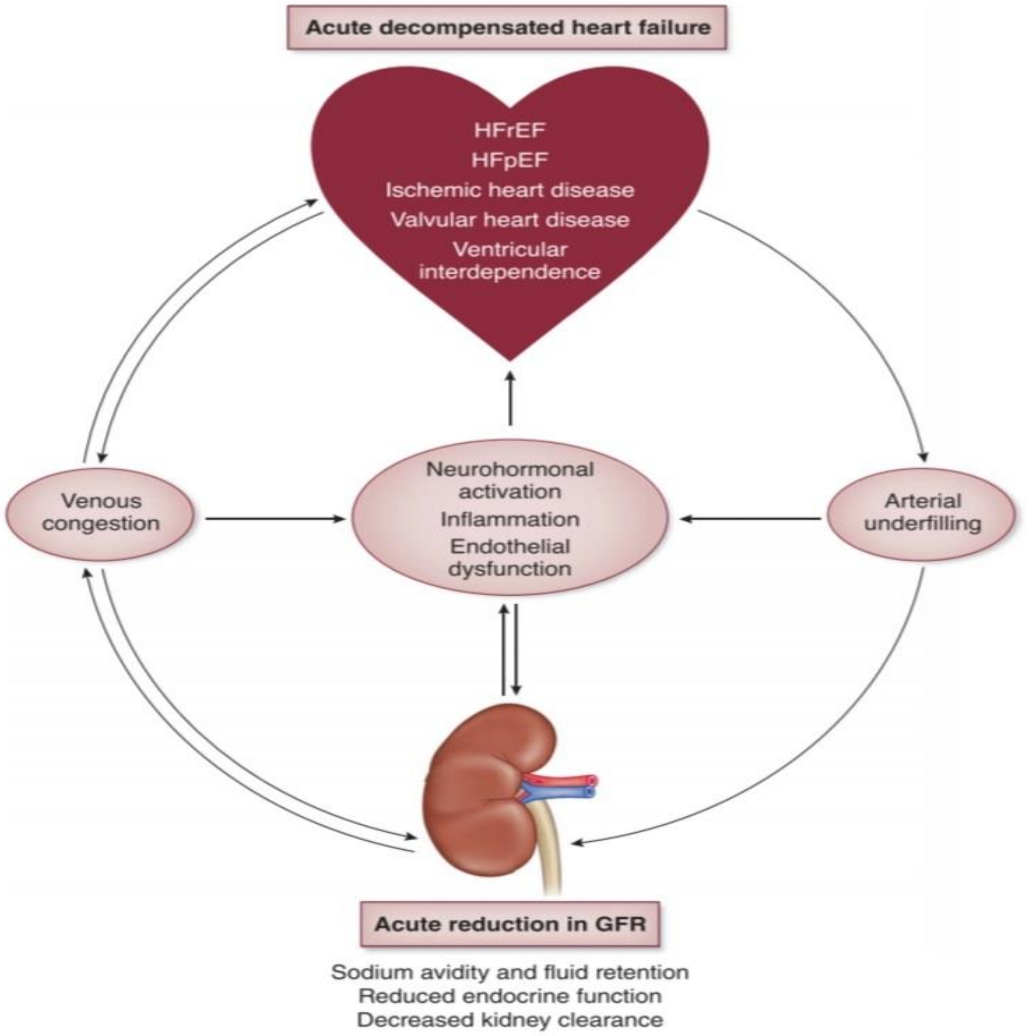


Figure 1. Proposed pathophysiological pathways leading to the cardiorenal syndrome and its complications. The inciting event is usually an acute decompensation of heart failure. This may lead to either arterial underfilling or venous congestion as mediators that promote neurohormonal activity, inflammation,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

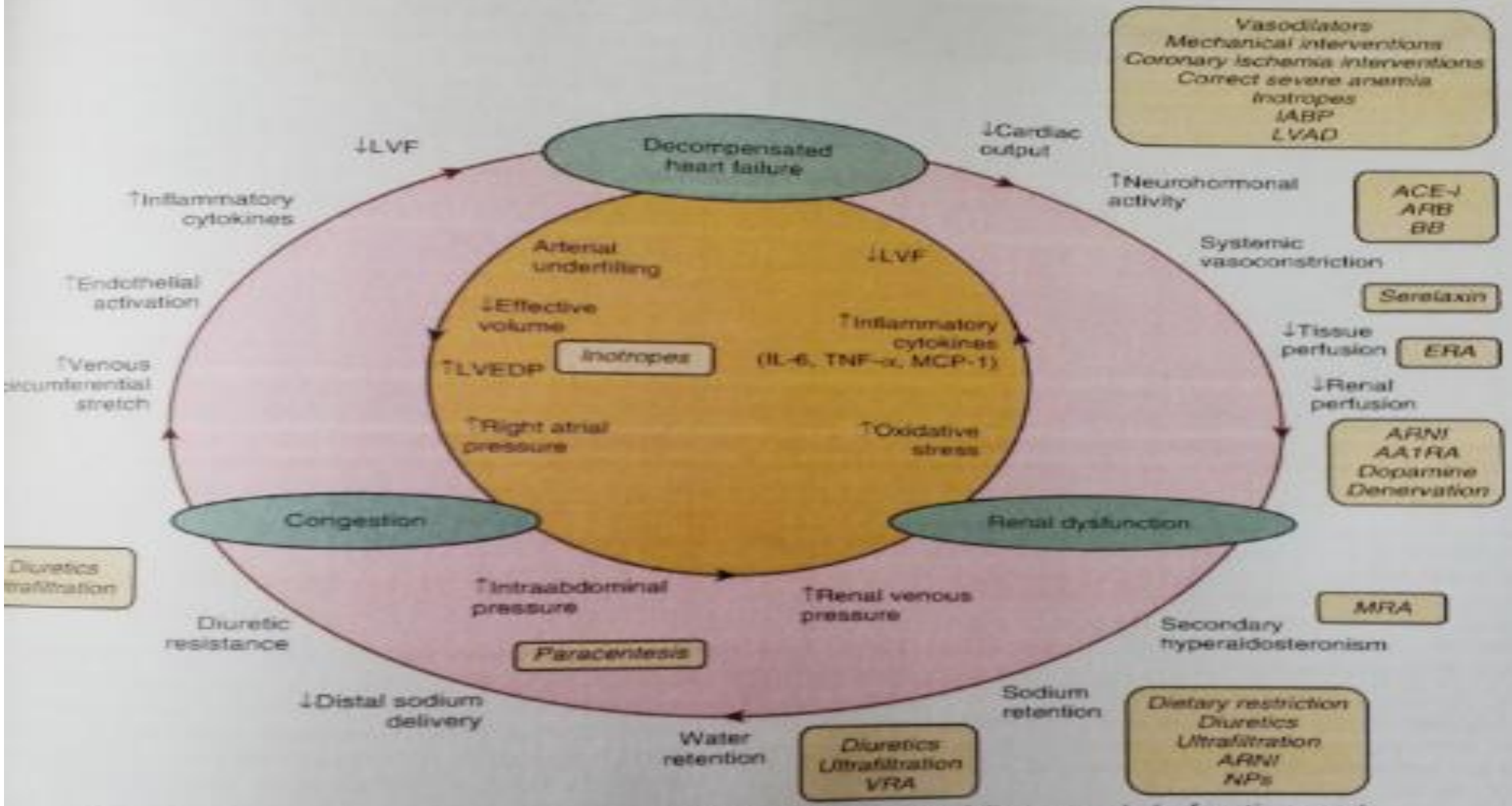


Fig. 72.1 Reciprocal pathophysiologic pathways linking heart failure, renal dysfunction, and congestion in cardiorenal syndrome. Decompensation of heart failure can lead to deterioration in renal function via exacerbated neurohormonal activity (i.e., low forward flow) or through fluid overload and renal venous congestion (i.e., high backward pressure). The impact of various pharmacologic and nonpharmacologic therapeutic options on the underlying pathophysiologic mechanisms is illustrated. *AA1RA*, Adenosine A1 receptor antagonist; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor neprilysin inhibitor; *BB*, β-blocker; *ERA*, endothelin receptor antagonist; *IABP*, intraaortic balloon pump; *IL-6*, interleukin-6; *LVAD*, left ventricular assist device; *LVEDP*, left ventricular end-diastolic pressure; *LVF*, left ventricular function; *MCP-1*, monocyte chemoattractant protein-1; *MRA*, mineralocorticoid receptor antagonist; *NPs*, natriuretic peptides; *TNF-α*, tumor necrosis factor-α; *VRA*, vasopressin receptor antagonist.

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].

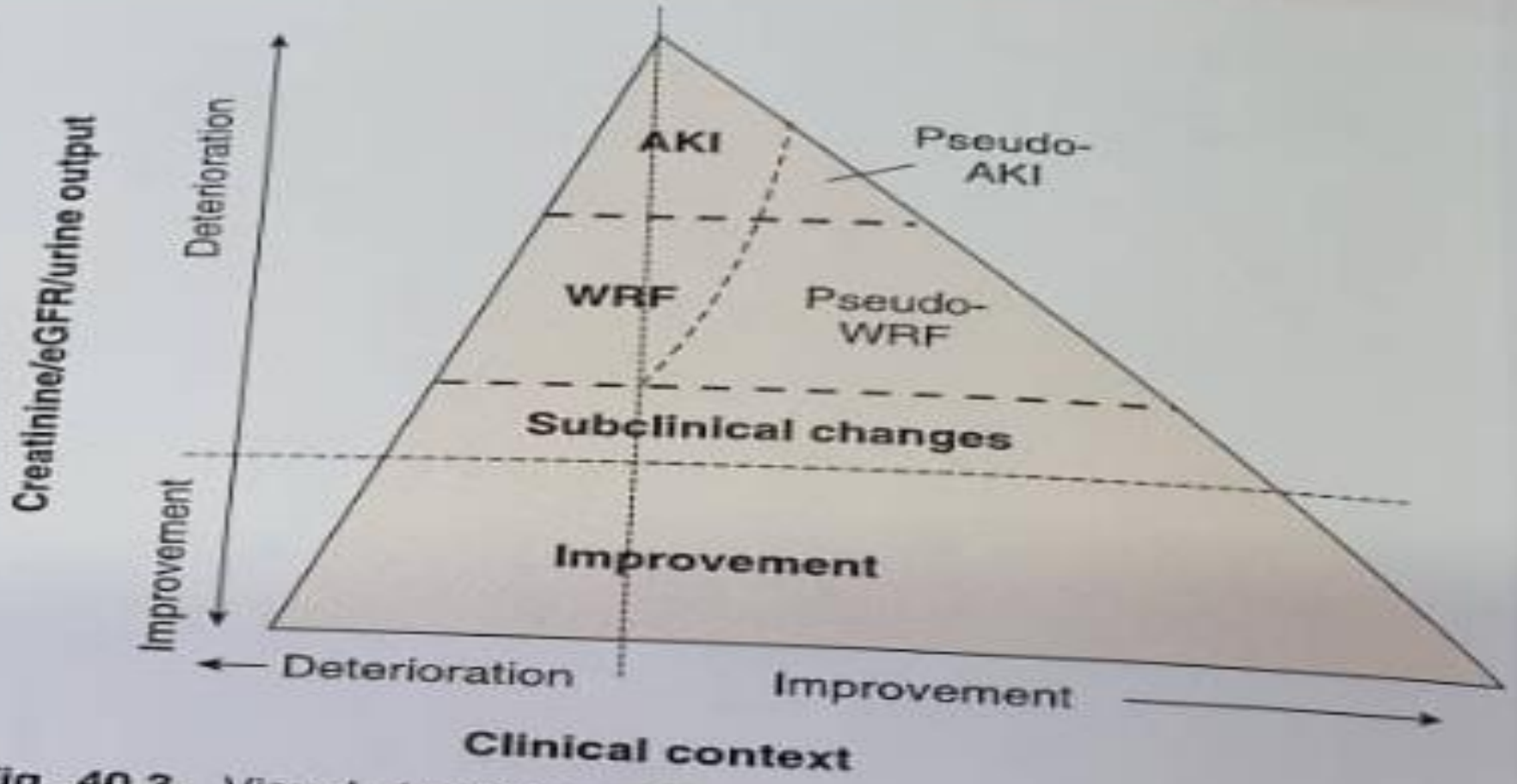


Fig. 40.3 Visual depiction of association among changes in renal function, clinical condition, and mortality risk. Only when both deterioration in clinical status and increase in the serum creatinine level (or decrease in renal function) track together is this associated with worse clinical outcomes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

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

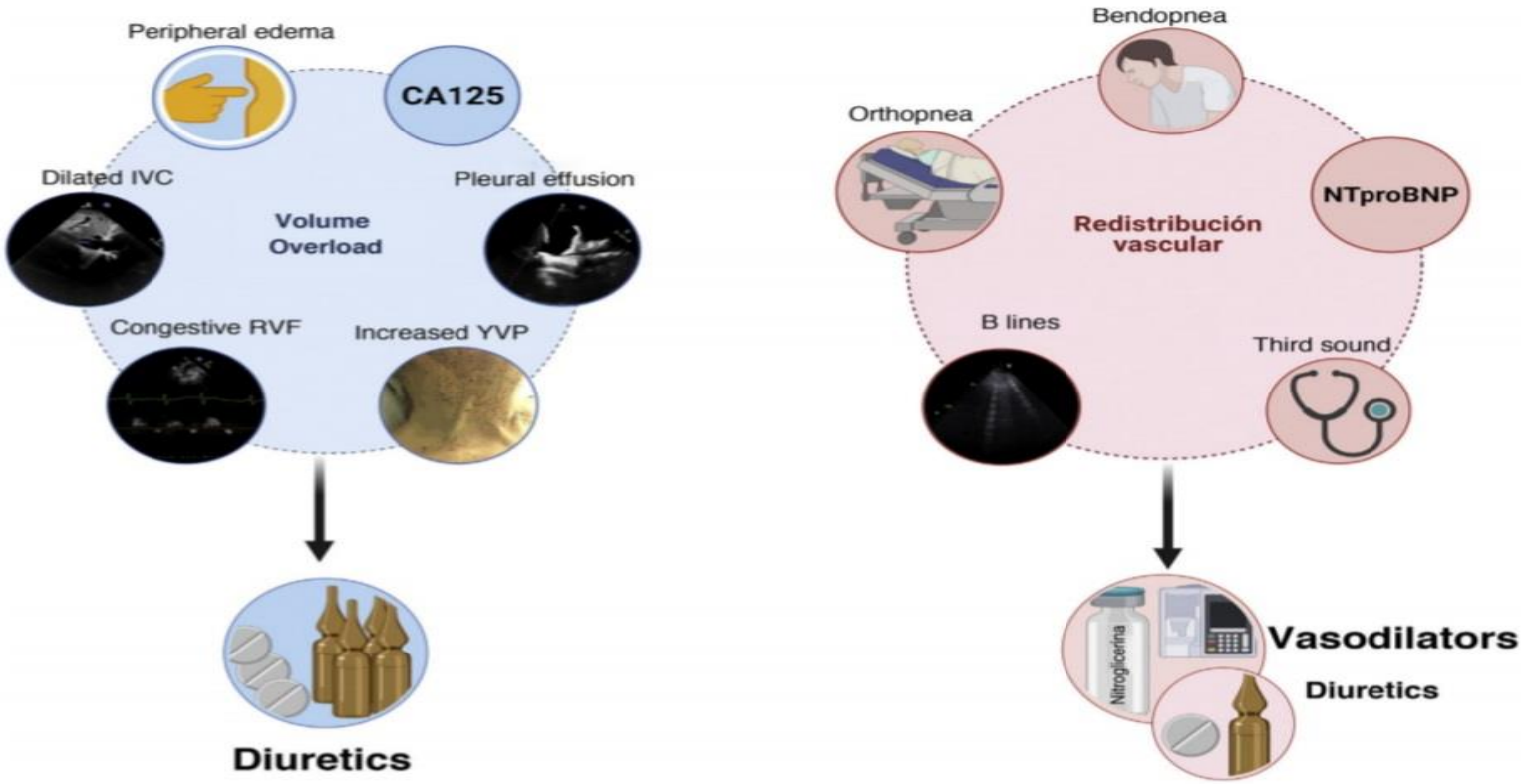


Figure 1 – Integration of clinical methods, biomarkers and imaging techniques to distinguish between congestion due to volume overload vs. vascular redistribution.
CA125: carbohydrate antigen 125; RVF: renal venous flow; NTproBNP: N-terminal fragment of B-type natriuretic peptide; JVP: jugular venous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

Na and water retention:

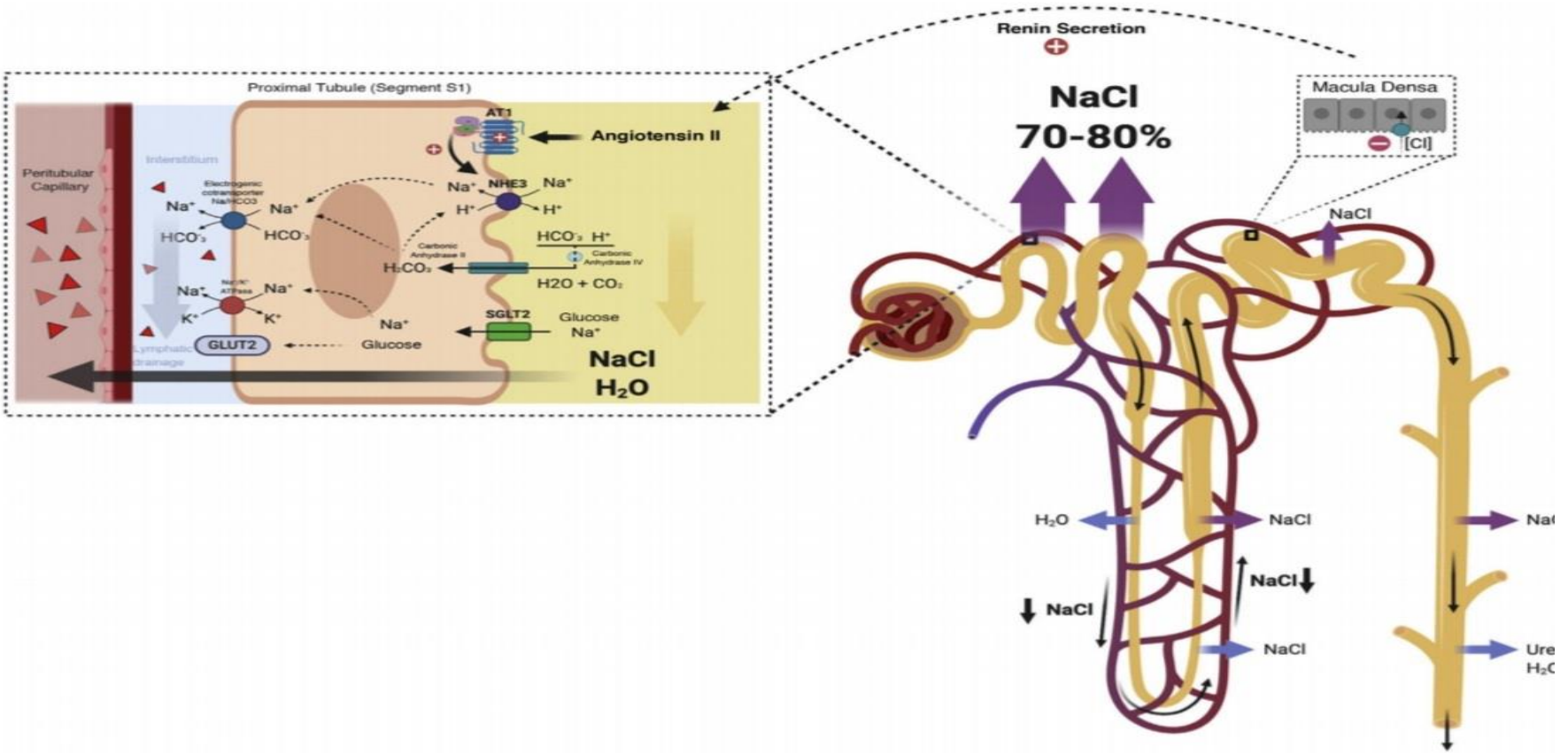
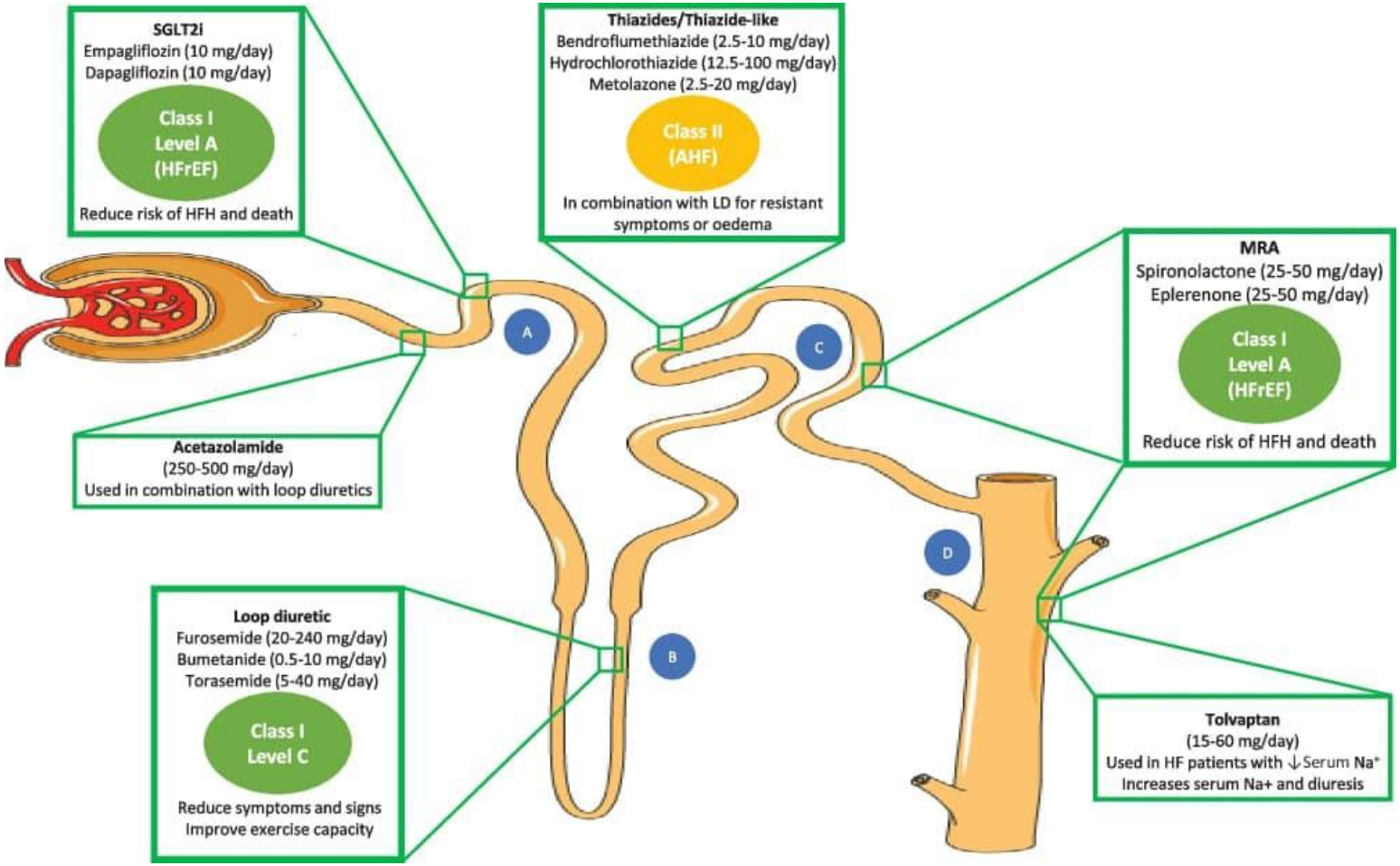
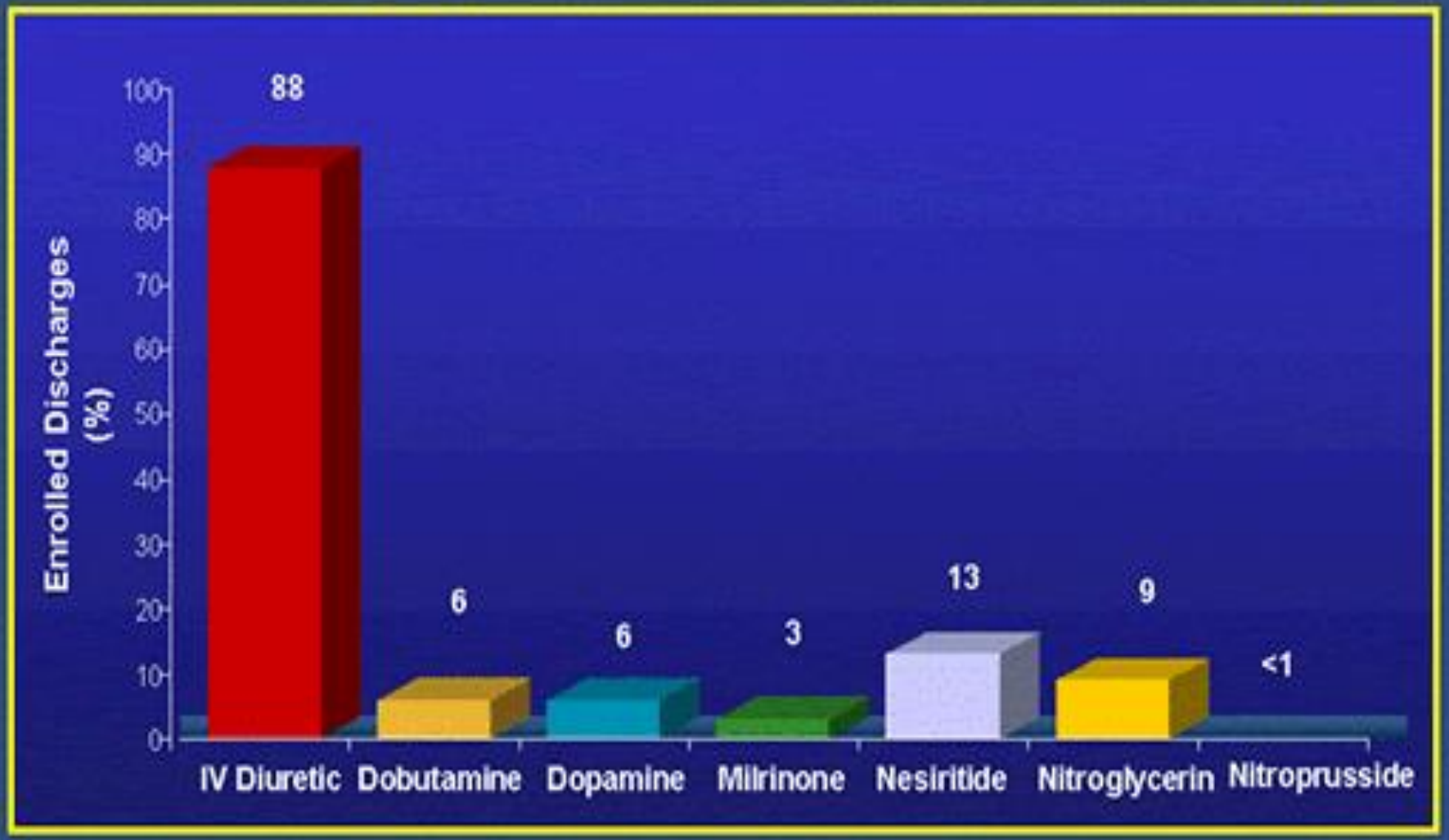


Figure 3 – Proximal tubule. Neurohormonal activation and intraglomerular and peritubular hemodynamic changes facilit Na and water reabsorption in the proximal tubule. Additionally, increased lymphatic flow washes out interstitial protein and decreases oncotic pressure in the renal interstitium, further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

Diuretics: comparison of site of action



ADHERE: Loop Diuretics Most Common IV Therapy, Often Used as Monotherapy



ADHERETM Registry Data. All Enrolled Discharges (n =150,745); October 2001 to December 2004

Review

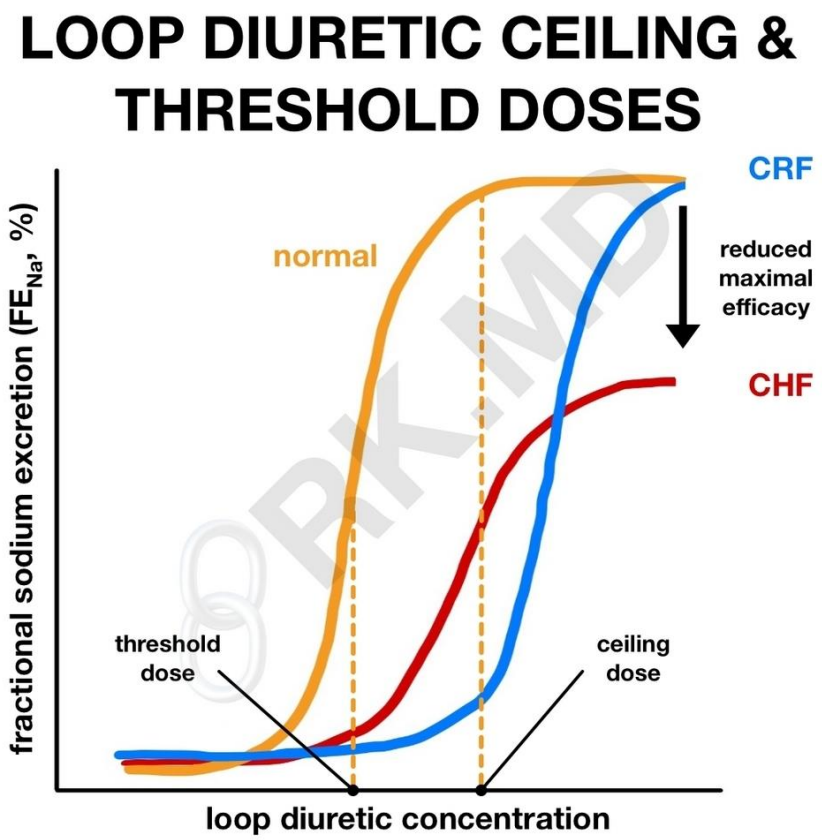
Continuous Infusion Versus Bolus Injection of Loop Diuretics for Patients With Congestive Heart Failure: A Meta-Analysis

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

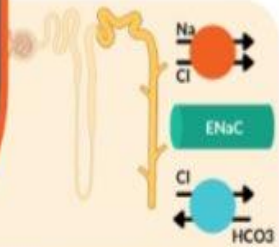
NSAIDs

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.

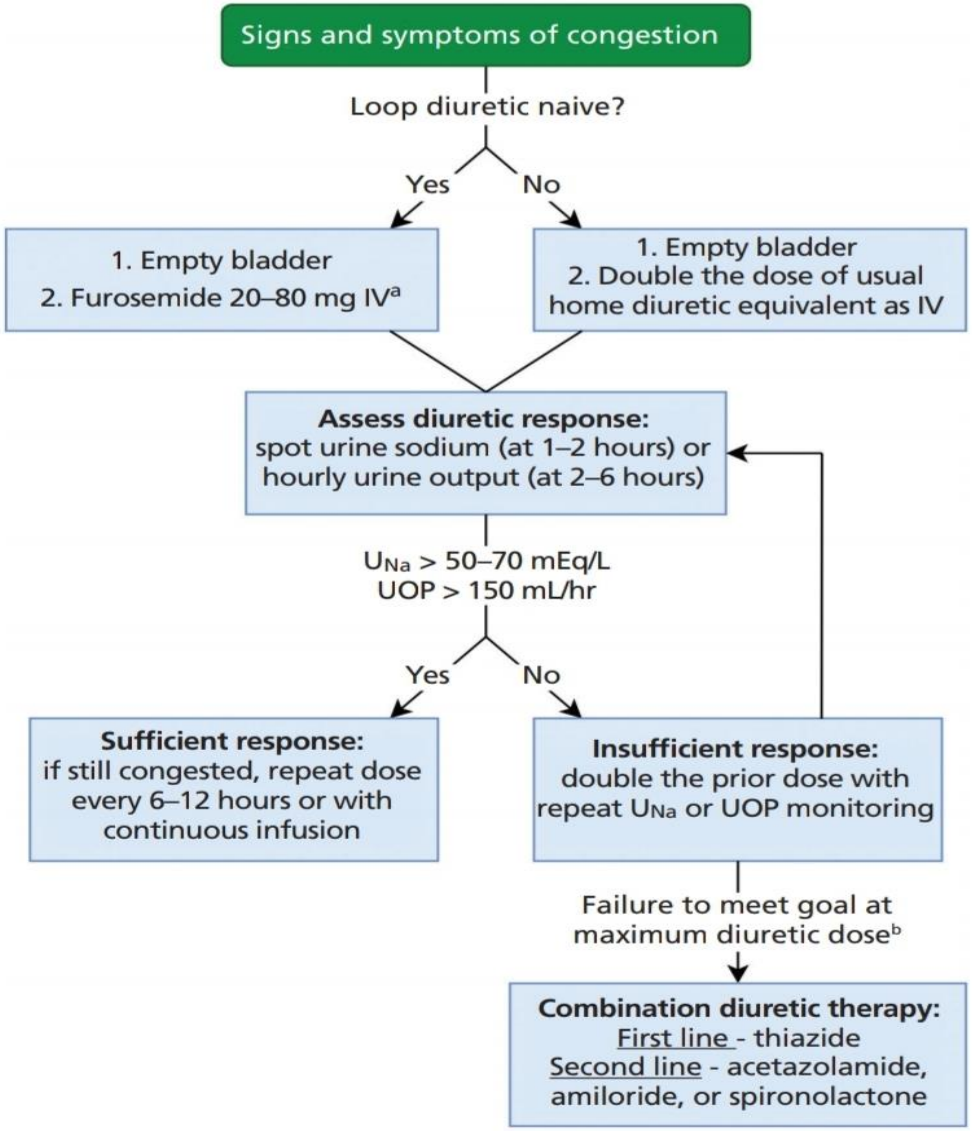


FIGURE 2. Algorithm for initiation (day 1) of diuretic titration in patients with acute decompensated heart failure.

[a]Higher dose for reduced glomerular filtration rate.

[b]See Table 1 for maximum recommended total daily dosing.

IV = intravenous; U_{Na} = urine sodium; UOP = urine output

Based on data from references 1 and 2.

Diuretics combination:

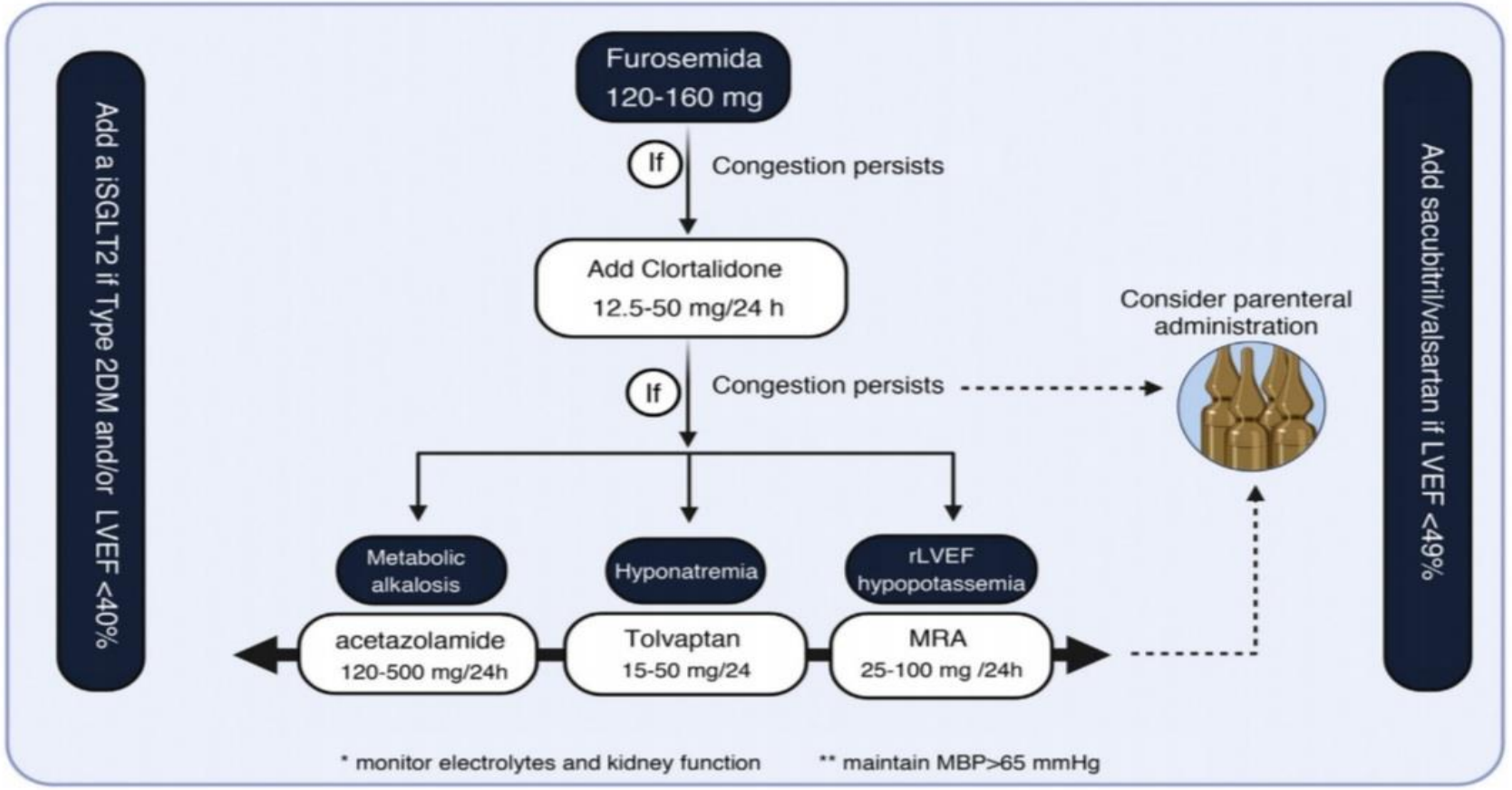


Figure 7 – Proposal of therapeutic algorithm.

Diuretic therapy

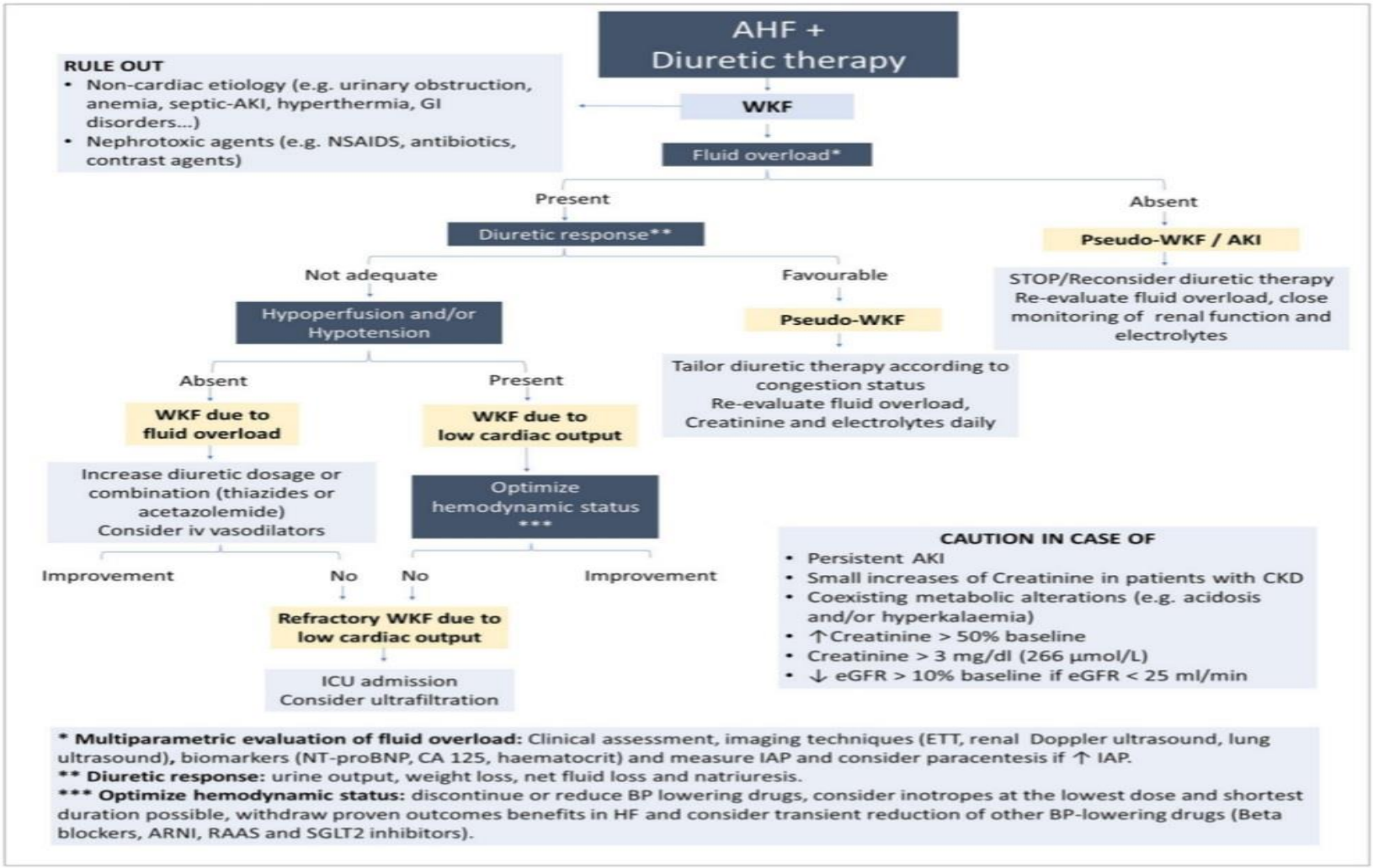


Figure 4: Approach to worsening kidney function in AHF.

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

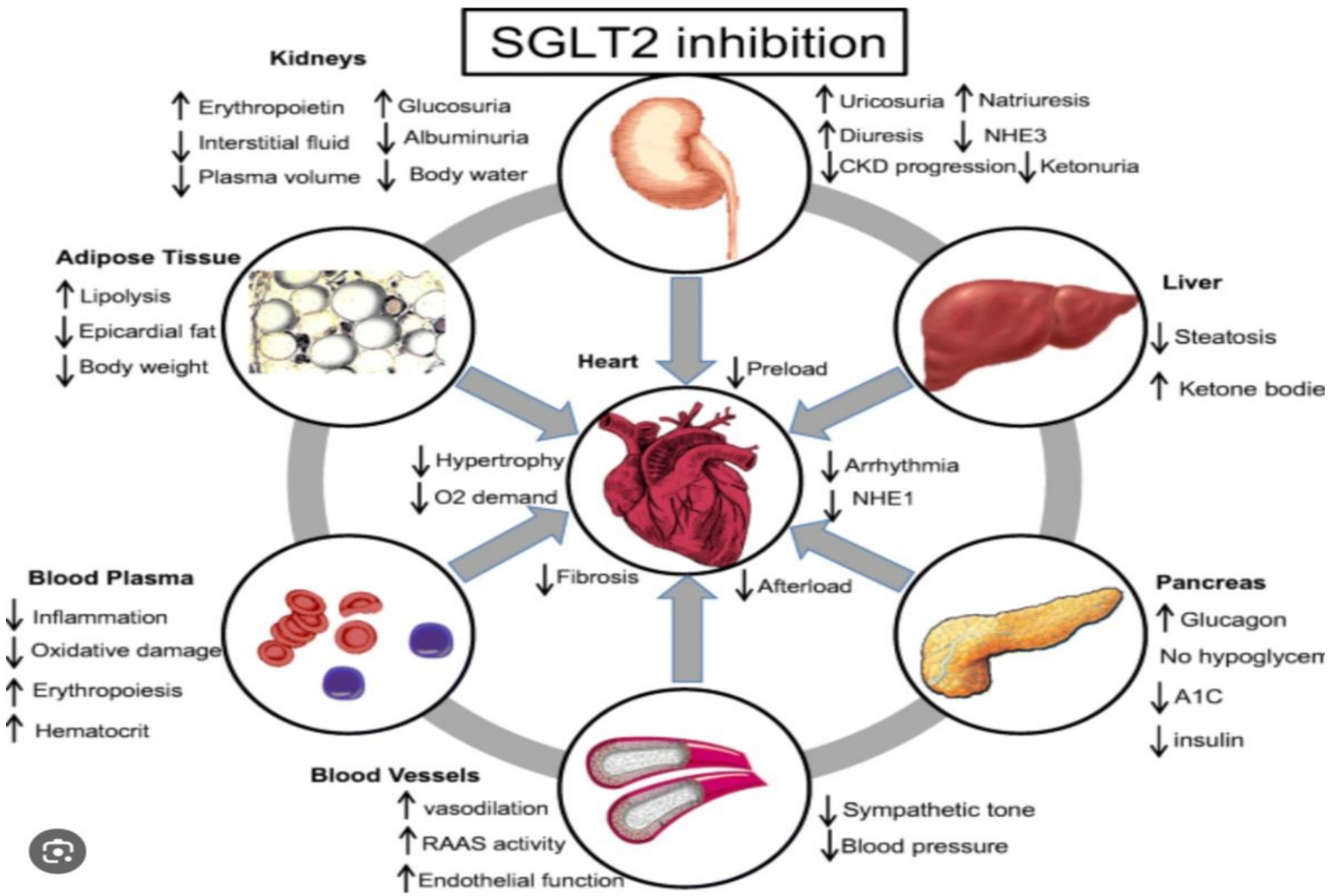
Adults ≥18 years with clinical signs of volume overload (edema, pleural effusion, ascites); NT-proBNP >1000 pg/mL or BNP >250 pg/mL; Oral maintenance therapy with 40 mg of furosemide, 20 mg of torsemide, 1 mg of bumetanide or more for ≥1 month prior to randomization

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

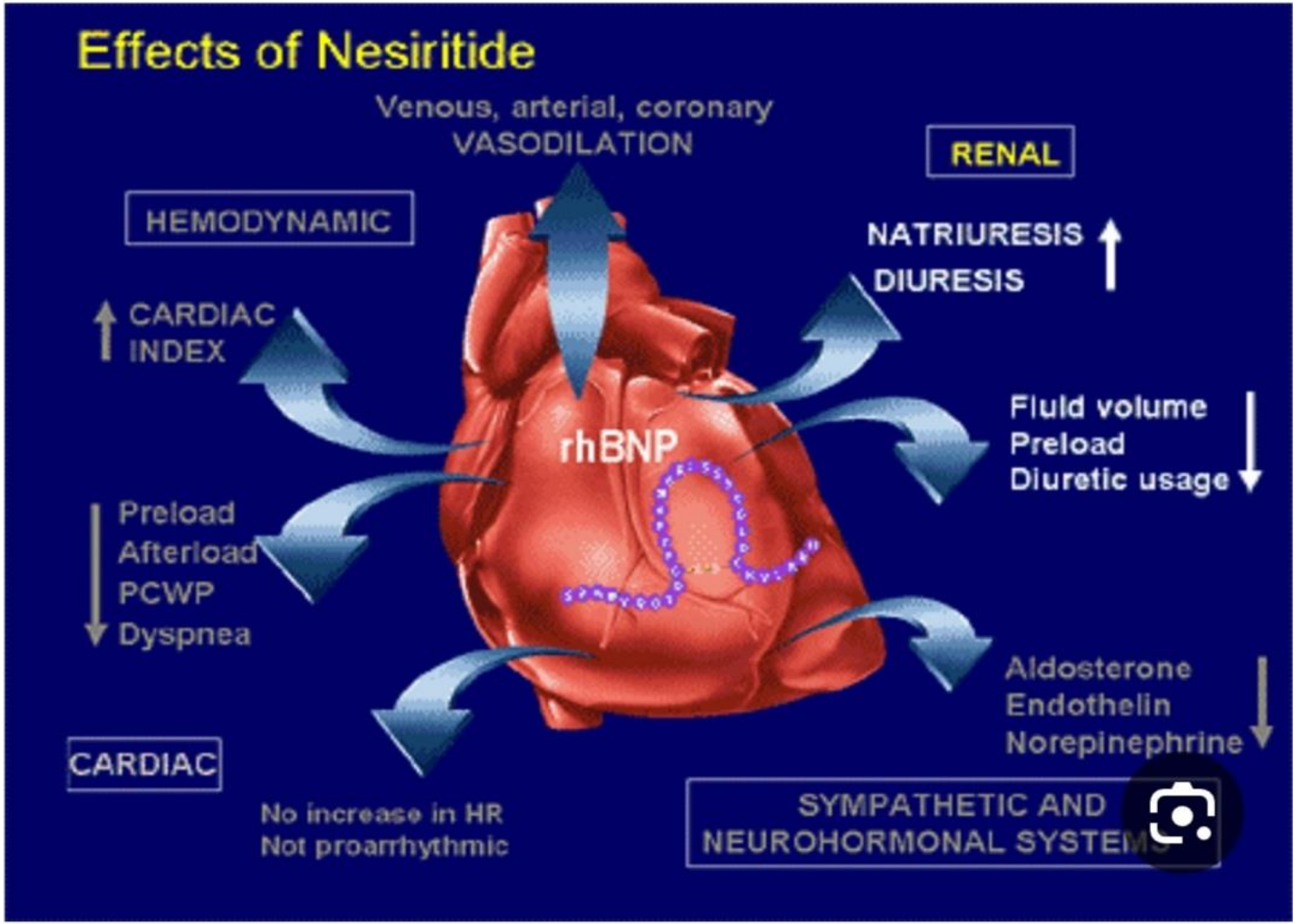


Mechanisms and Evidence for Heart Failure Benefits from SGLT2 ...

Visit >

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‡


Effects of Nesiritide
Venous, arterial, coronary
VASODILATION
HEMODYNAMIC
CARDIAC
INDEX
Preload
Afterload
PCWP
Dyspnea
CARDIAC
No increase in HR
Not proarrhythmic
RENAL
NATRIURESIS
DIURESIS
Fluid volume
Preload
Diuretic usage
Aldosterone
Endothelin
Norepinephrine
SYMPATHETIC AND
NEUROHORMONAL SYSTEMS
rhBNP

Review article

First published online January 17, 2020

Nesiritide in patients with acute myocardial infarction and heart failure: a meta-analysis

Xuecheng Zhao, Da-Qi Zhang, [...], and Guoqiang Zhang    View all authors and affiliations

Conclusions

Nesiritide appears to be safe for patients with AMI and heart failure, and it improves global cardiac and systemic function.

Nesiritide considerations

- Consider the risks (e.g., worsening renal function, mortality) and benefits to the patient before initiating therapy.
- Use nesiritide only in hospitalized patients with acutely decompensated congestive heart failure with dyspnea at rest.
- Avoid using nesiritide in place of diuretic therapy.
- Avoid regular repetitive use of nesiritide.
- Avoid use for off-label indications, including enhancing renal function or augmenting diuresis.

to conventional treatment. The recommended dose of nesiritide is an intravenous bolus of 2 µg/kg followed by a continuous infusion of 0.01 µg/kg/min.

Ultrafiltration for refractory Volume overload in Acute heart failure

- CRRT/ SCUF(Slow continues ultrafiltration)
- Acute PD (CAPD, APD)
- Isolated UF (conventional HD)

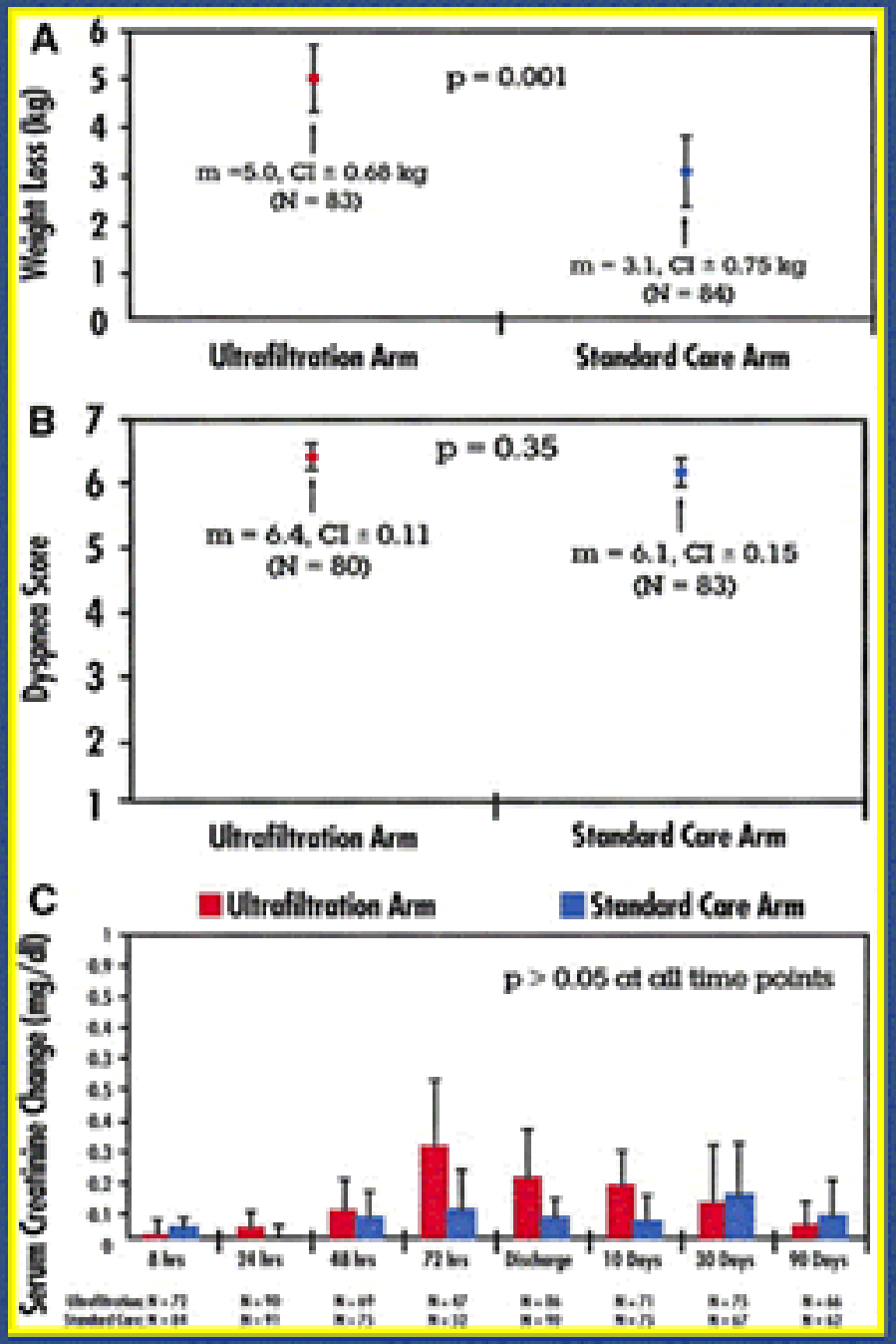
UF vs Diuretics for CHF: Theoretical Advantages

- 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

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

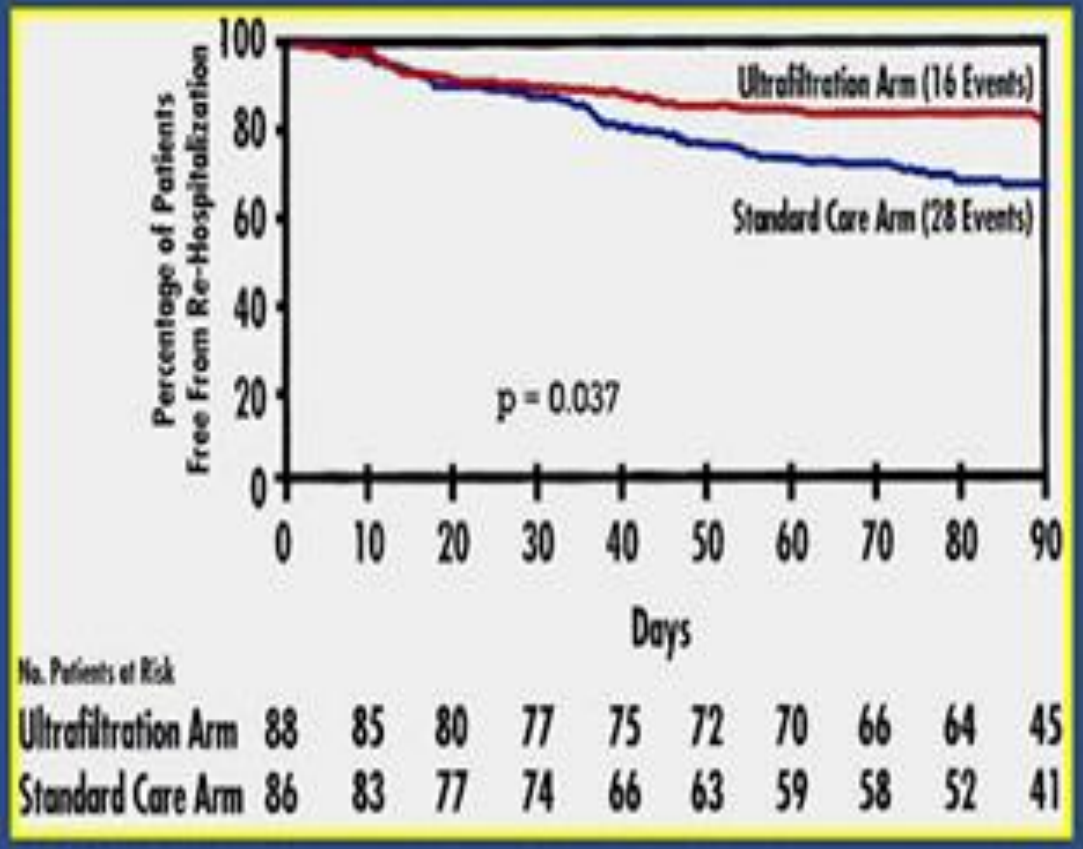
<or>

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.

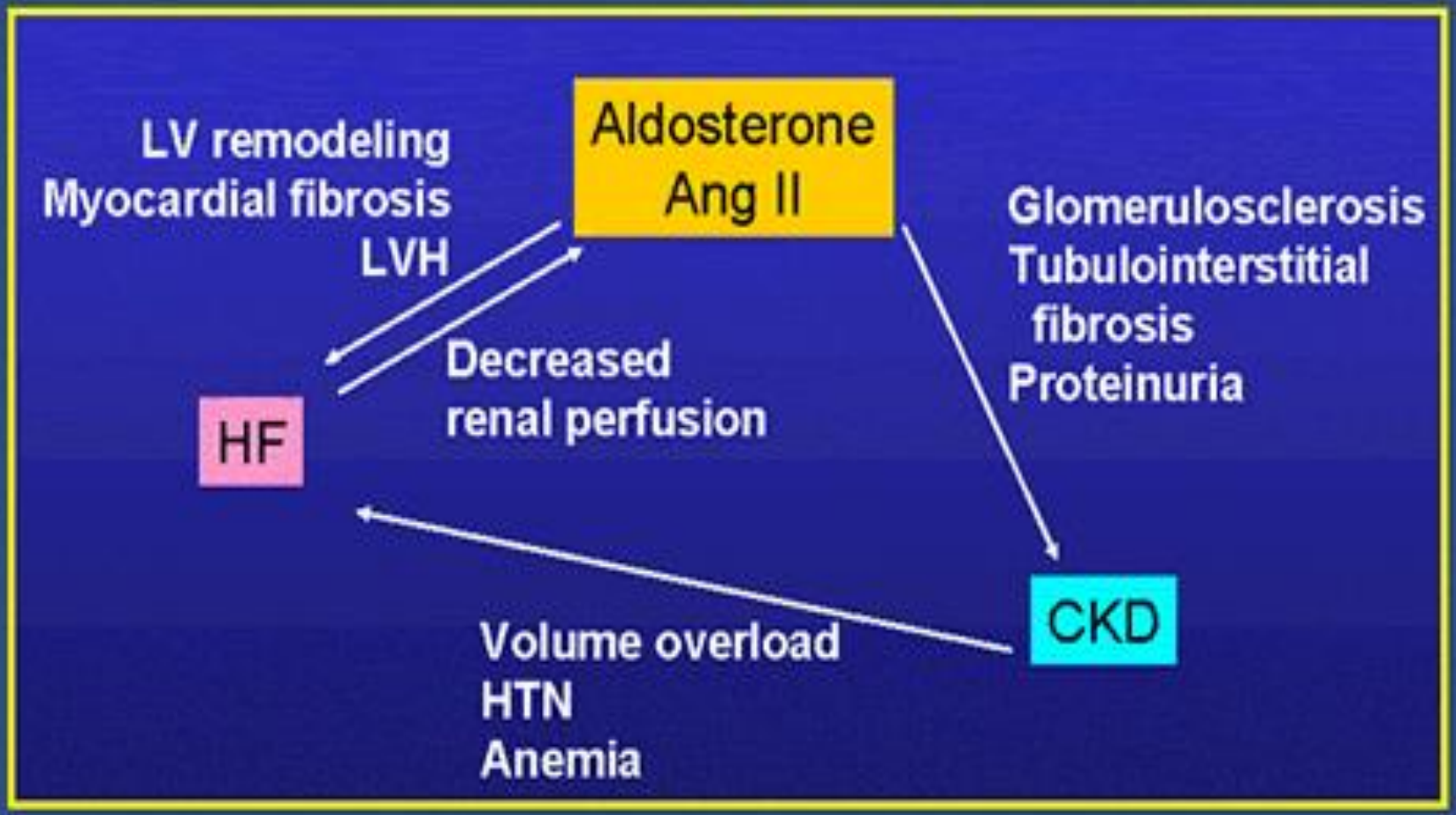
Author Information and Affiliations

Last Update: April 7, 2023.

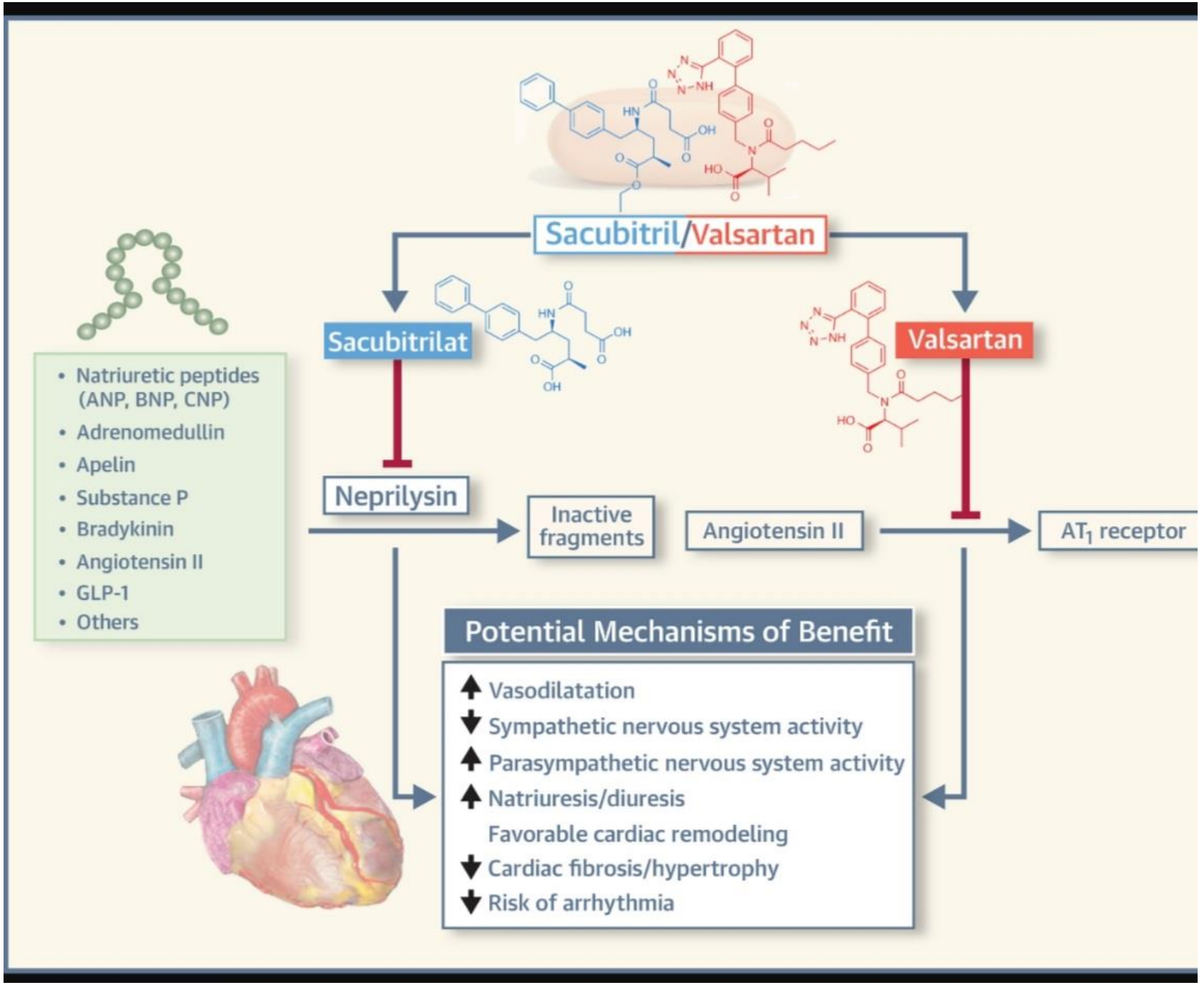
Case problems:

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

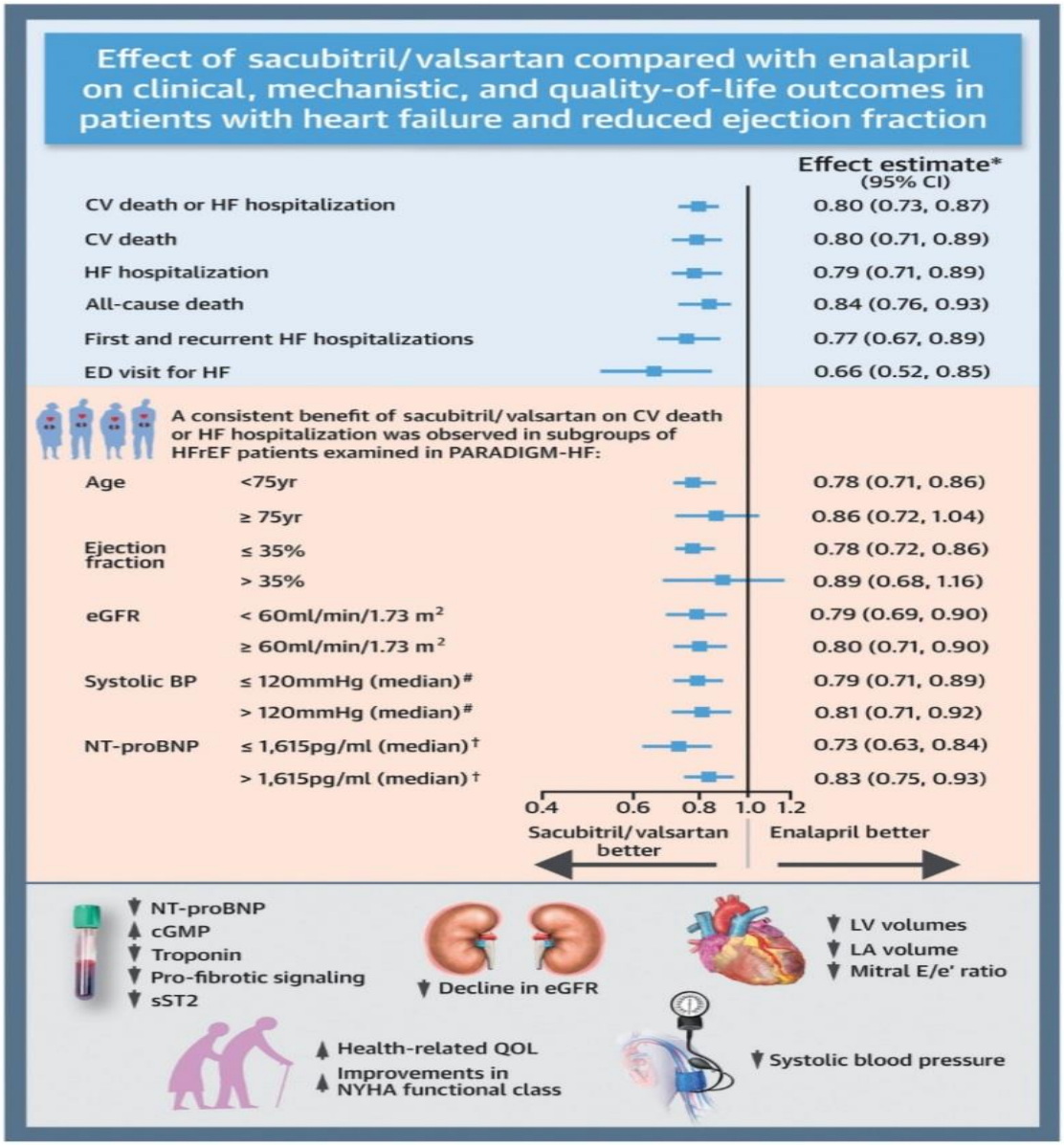
Central Role of RAAS in Progressive CKD and Cardiomyopathy



Volpe M et al. J Am Soc Nephrol. 2002; 13 (suppl 3): S173
Brewster UC et. al. Am J Med Sci. 2003;326:15
Hirsch AT et al. Am J Cardiol. 1990; 66:22D


Sacubitril/Valsartan
Sacubitrilat
Valsartan
Neprilysin
Inactive fragments
Angiotensin II
AT1 receptor
• Natriuretic peptides (ANP, BNP, CNP)
• Adrenomedullin
• Apelin
• Substance P
• Bradykinin
• Angiotensin II
• GLP-1
• Others
Potential Mechanisms of Benefit
Vasodilatation
Sympathetic nervous system activity
Parasympathetic nervous system activity
Natriuresis/diuresis
Favorable cardiac remodeling
Cardiac fibrosis/hypertrophy
Risk of arrhythmia

CENTRAL ILLUSTRATION: Effect of Sacubitril/Valsartan Compared With Enalapril on Clinical, Mechanistic, and Quality-of-Life Outcomes in Patients With Heart Failure With Reduced Ejection Fraction



Docherty, K.F. et al. J Am Coll Cardiol HF. 2020;8(10):800–10.

Table 40.3 Characteristics of Different Treatment in HFREF Patients With Chronic Kidney Disease

Therapy	Incidence of Worsening Renal Function and Adverse Events	Incidence of Hyperkalemia	Effectiveness in HFREF Patients*		Cautions and Remarks
			CKD Stage 1–3	CKD Stage 4 or 5	
ACE inhibitor	1.5%–13.7% (35% in NYHA IV)	1.1%–6.4% (7% in NYHA IV)	Yes	Unclear; possible	Induces early decline in eGFR; some increase in serum creatinine should be accepted. Very large increases should prompt further investigation and (temporary) stopping of drug.
ARB	5.5%–17% (24% with high-dose losartan)	1%–3% (10% with high-dose losartan)	Yes	Unclear	
MRA	1.9%–17%	2%–8%	Yes	Unclear; possible	
ARNI	2.2%	4.3% (potassium > 6 mmol/L)	Yes	Unclear; possible	Sacubitril/valsartan was superior to enalapril in reducing renal events and also slowing progression of decline in eGFR; increases urinary albumin excretion to some extent. Large increases should prompt further investigation.
Beta-blocker	7%–10.1%	NA	Yes	Probable	Effect on renal function negligible compared with placebo; should be continued if possible.
Loop diuretics	NA	Probably low	NA	NA	Use and dose associated with worsening renal function. Long-term effects on renal function unknown. Dose should be higher in patients with CKD stage 3–5.
CRT	NA	NA	Yes	Unclear; possible	Improvement in renal function in parallel—improvement in clinical symptoms can be expected.
LVAD	NA	NA	Yes	Unclear; possible	LVAD therapy improves renal function in the long term. However, risk of AKI is peri- and postoperatively higher in patients with CKD stage 3-5 at baseline. Risk contrast nephropathy at ti of implantation.

*Improvement in clinical outcome.

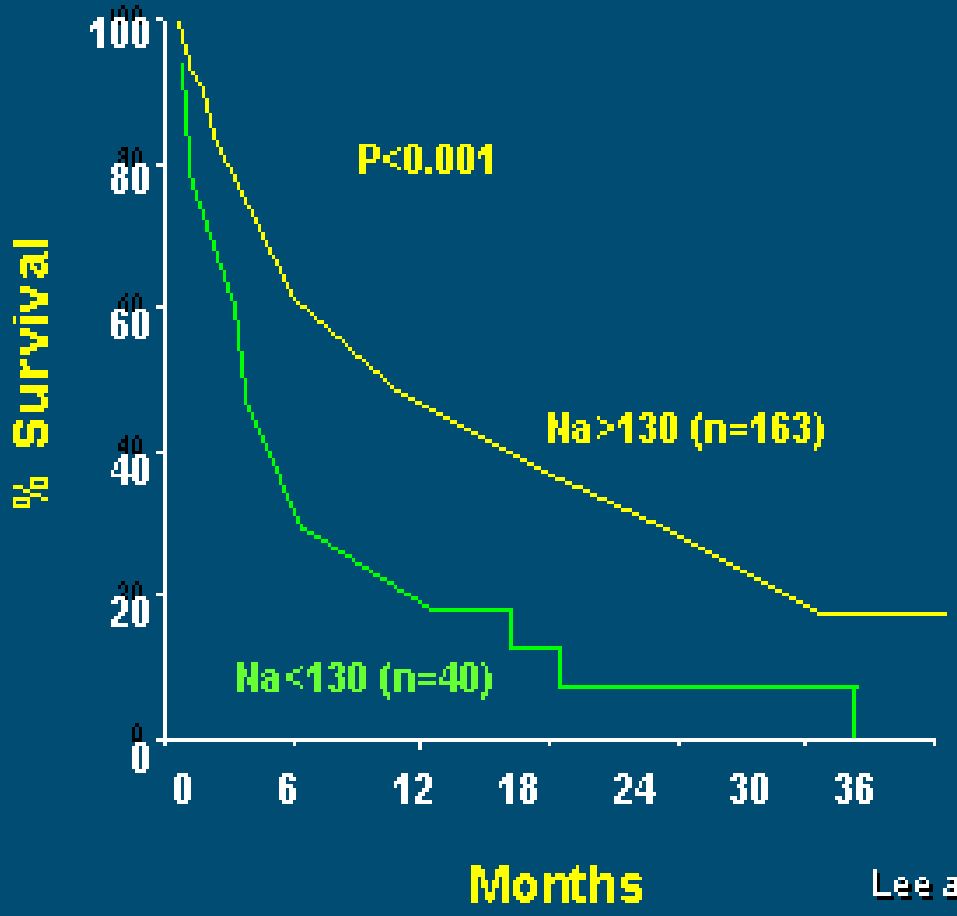
ARB, Angiotensin II receptor blocker; *ACE*, angiotensin-converting enzyme; *ARNI*, angiotensin receptor blocker neprilysin inhibitor; *CKD*, chronic kidney disease; *CRT*, cardiac resynchronization therapy; *eGFR*, estimated glomerular filtration rate; *HFREF*, heart failure reduced ejection fraction; *LVAD*, left ventricular assist device; *NYHA*, New York Heart Association.

Adapted from Damman K, Tang WH, Felker GM, et al. Current evidence on treat

Case problems:

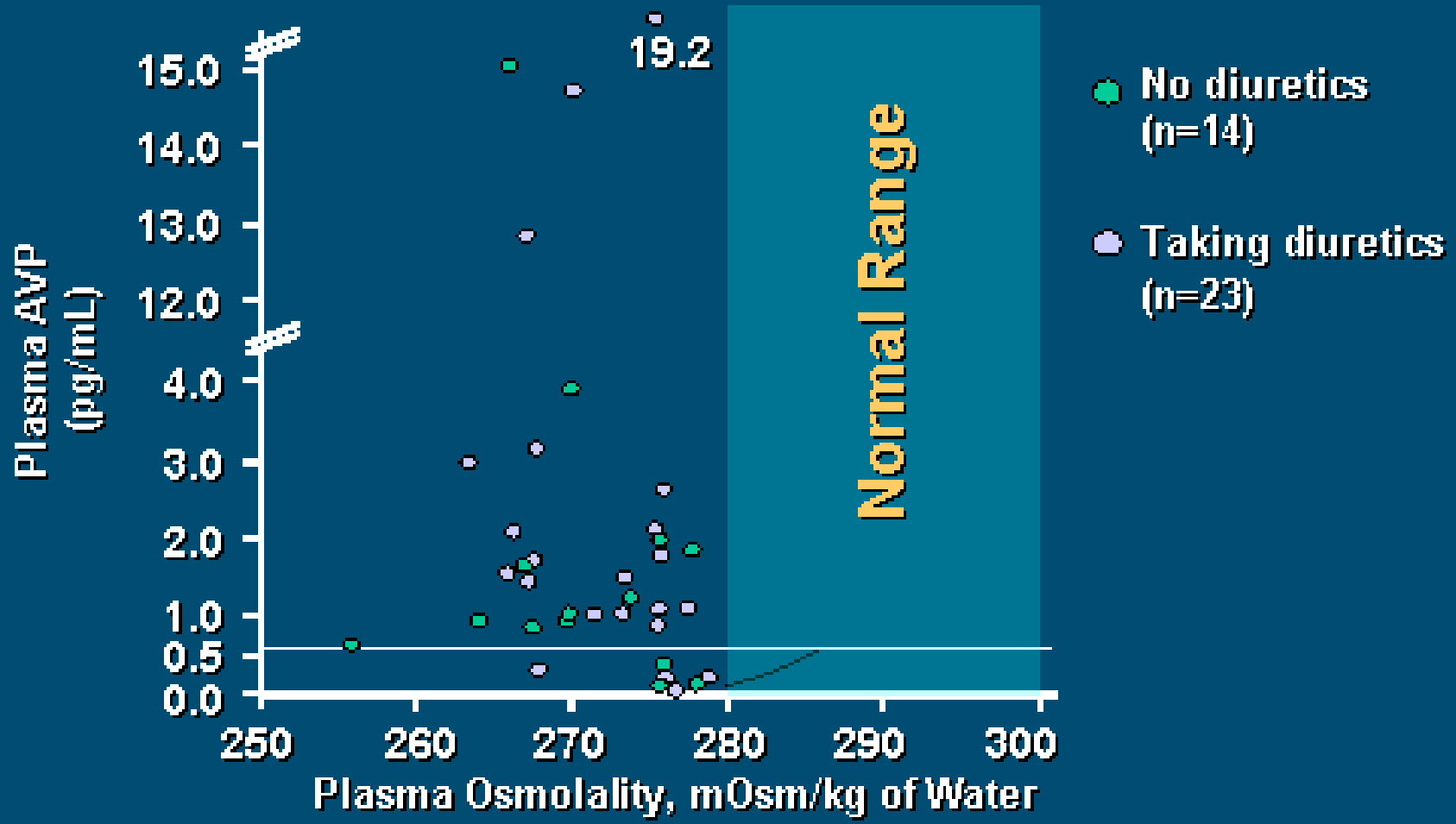
- 1 -Volume overload (Diuretic therapy vs UF) ?
- 2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?
- **3-Hyponatremia management (Vaptan)?**
- 4-Hyperurecemia management (Allopurinol)?
- 5- Anemia Management (CRAIDS and EPO)?
- 6-Mineral receptor antagonist?
- 7-Contrast nephropathy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

Pretreatment Hyponatremia Predicts an Unfavorable Prognosis in Patients with Heart Failure



Lee and Packer, Circulation, 73: 257-67, 1986

AVP Levels are also Elevated in Patients with CHF



Szatalowicz et al, N Engl J Med 305:263, 1981

Szatalowicz VL et al. *N Engl J Med. 1981 Jul 30;305(5):263-6.*

Vasopressin (AVP, ADH)

- Nonapeptide hormone synthesized in the hypothalamus
- Released into the circulation by the posterior pituitary
- V_1 vascular receptor:
  - vasoconstriction => increased peripheral vascular resistance, afterload
- V_2 renal tubular receptor:
  - water retention => increased intra- and extracellular volume overload
- Indirect mechanisms:
  - both AVP and AG II stimulate ET synthesis

Goldsmith and Gheorghiade JACC 2005;46:1785-91

Effects of Tolvaptan on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Edema, and KCCQ Overall Summary Score

Table 3. Effects of Tolvaptan on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Edema, and KCCQ Overall Summary Score

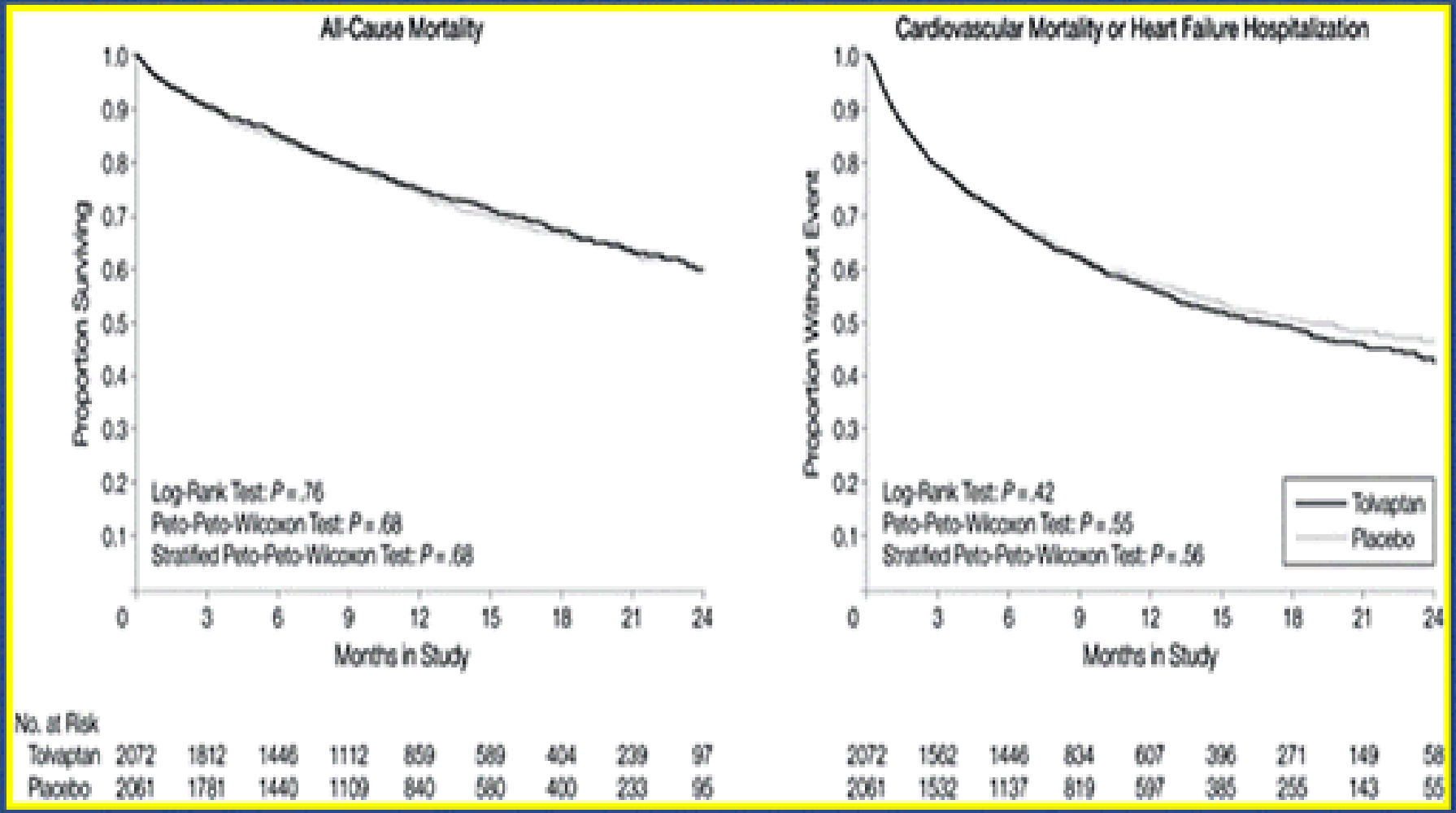
	Tolvaptan	Placebo	*P* Value
Change in body weight at 1 day, mean (SD), kg	−1.76 (1.91) [n = 1999]	−0.97 (1.84) [n = 1999]	<.001*
Change in dyspnea at 1 day, % showing improvement in dyspnea score†	74.3 [n = 1835]	68.0 [n = 1829]	<.001‡
Change in serum sodium at 7 days (or discharge if earlier), mean (SD), mEq/L§	5.49 (5.77) [n = 162]	1.85 (5.10) [n = 161]	<.001*
Change in edema at 7 days (or discharge), % showing at least a 2-grade improvement†	73.8 [n = 1600]	70.5 [n = 1595]	.003‡
Change in KCCQ overall summary score at postdischarge week 1, mean (SD)	19.90 (18.71) [n = 872]	18.52 (18.83) [n = 856]	.39*

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire.
*Based on analysis of covariance model.
†Among patients with symptoms at baseline.
‡Based on van Elteren test.[28]
§Among participants with baseline sodium levels of less than 134 mEq/L.

JAMA

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

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



No. at Risk									
Tolvaptan	2072	1812	1446	1112	859	589	404	239	97
Placebo	2061	1781	1440	1109	840	580	400	233	95

2072	1562	1446	804	607	396	271	149	58
2061	1532	1137	819	597	385	255	143	55

JAMA

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

Case problems:

- 1 -Volume overload (Diuretic therapy vs UF) ?
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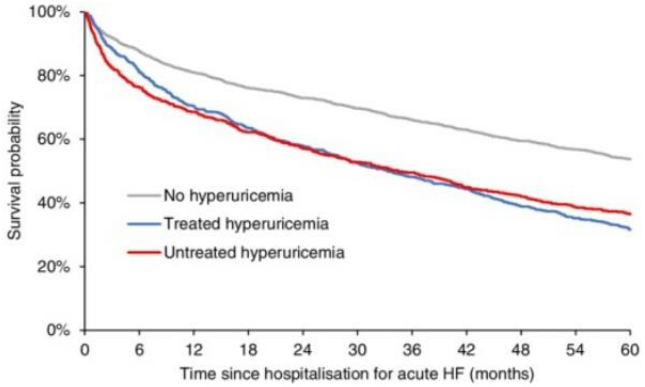
- 6-Mineral receptor antagonist?
- 7-Contrast nephropathy risk and prophylaxy?

Clinical Cardiology
Wiley-Blackwell

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	68.6% (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

ORIGINAL ARTICLE

Effects of Allopurinol on the Progression of Chronic Kidney Disease

Sunil V. Badve, Ph.D., Elaine M. Pascoe, M.Biostat., Anushree Tiku, M.B., B.S., Neil Boudville, D.Med., et al. for the CKD-FIX Study Investigators*

June 25, 2020

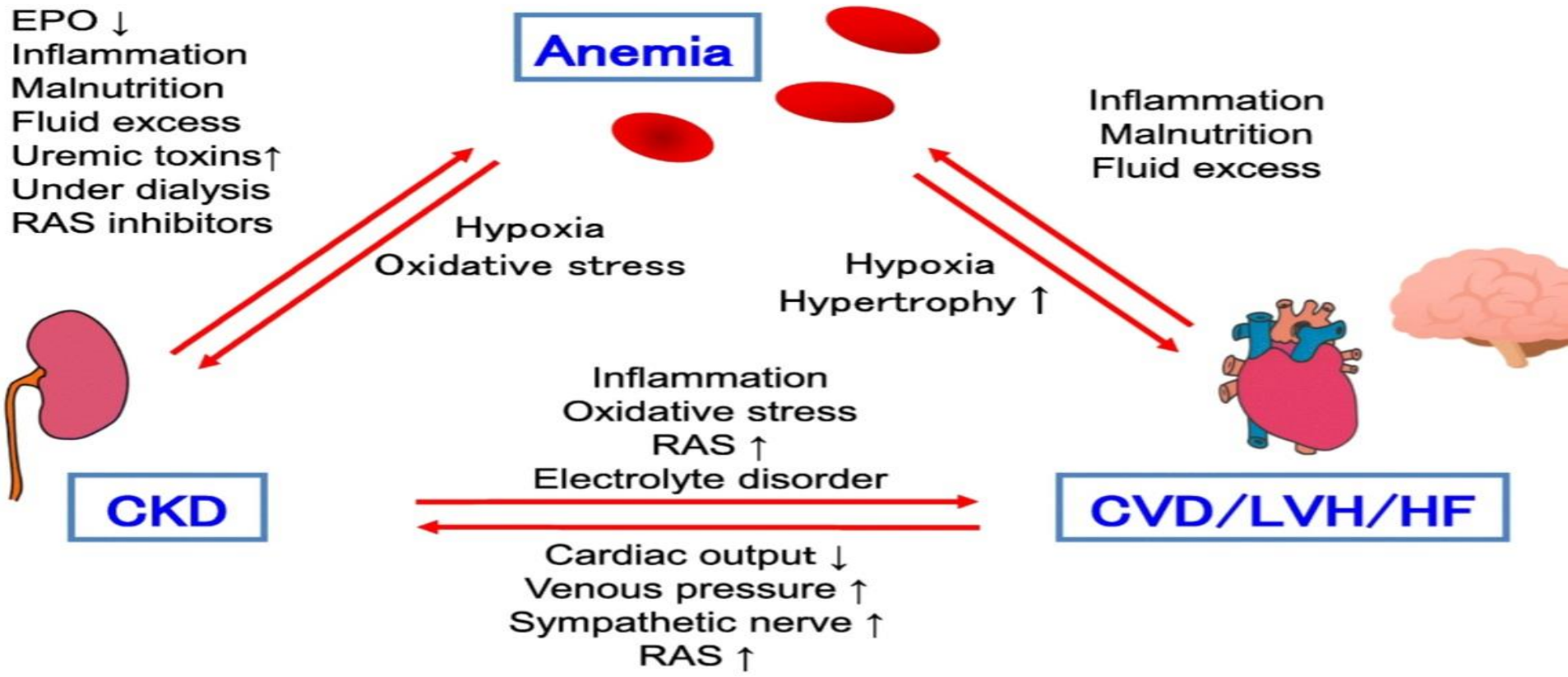
N Engl J Med 2020; 382:2504-2513

CONCLUSIONS In patients with chronic kidney disease and a high risk of progression, urate-lowering treatment with allopurinol did not slow the decline in eGFR as compared with placebo. (Funded by

Case problems:

- 1 -Volume overload (Diuretic 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,HIF)?**
- 6-Mineral receptor antagonist?
- 7-Contrast nephropathy risk and prophylaxy?
-

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 in 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

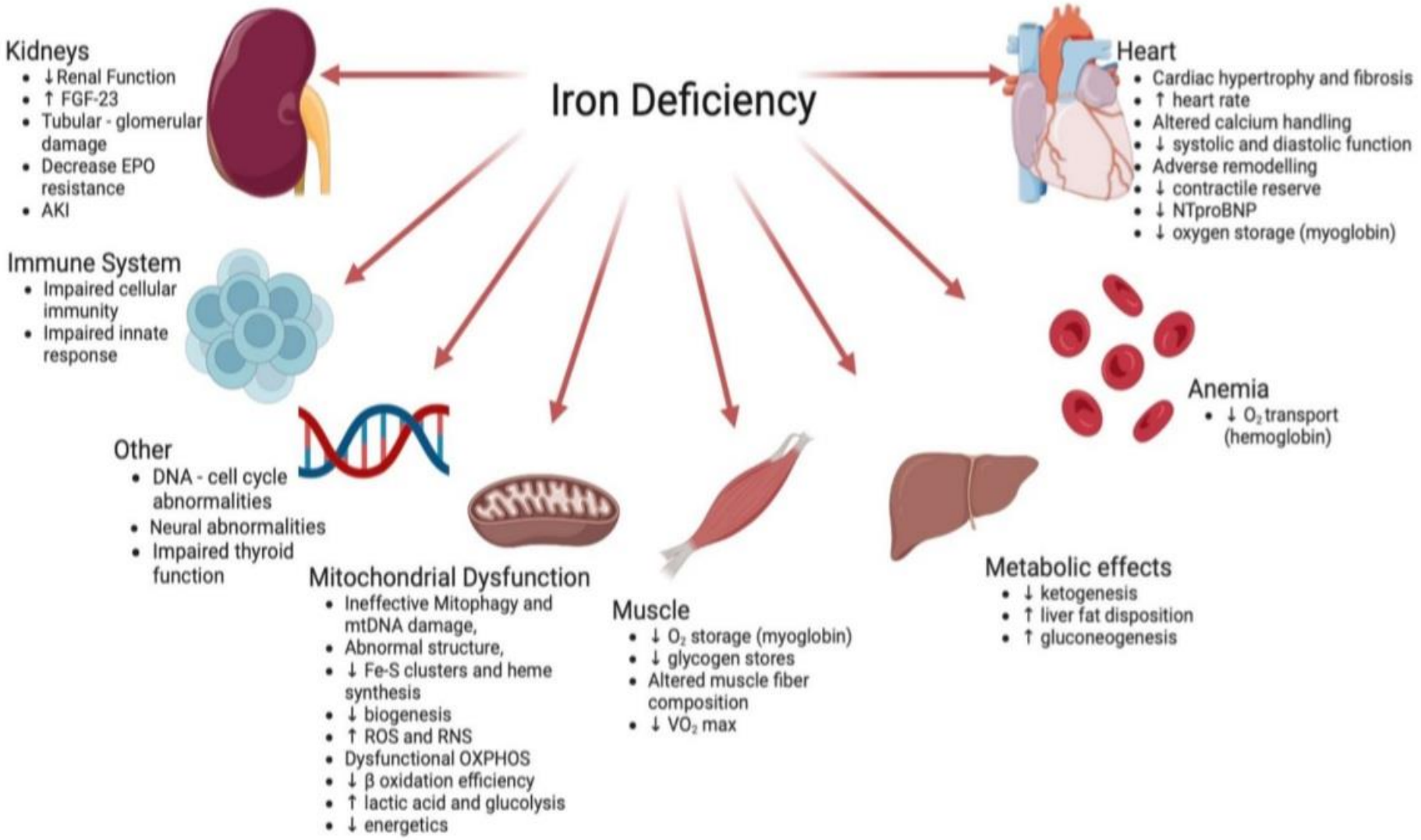
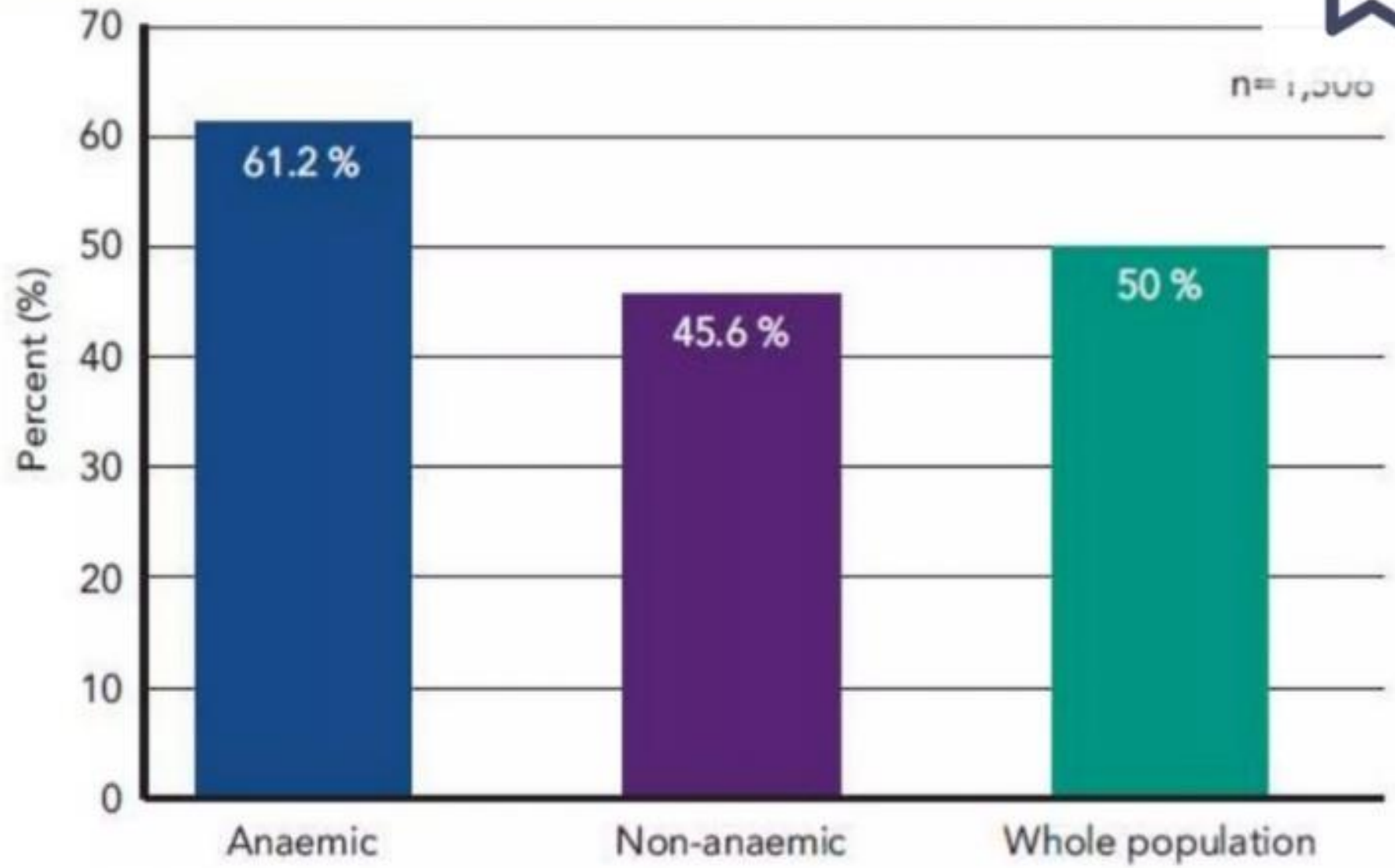


Fig. 2 An overview of the potential biological implications of iron deficiency. *FGF23* fibroblast growth factor-23, *EPO* erythropoietin, *AKI* acute kidney injury, *DNA* deoxyribonucleic acid, *mtDNA* mitochondrial DNA, *ROS* reactive oxygen species, *RNS* reactive nitrogen species, *OXPHOS* oxidative phosphorylation, *NTproBNP* N-terminal pro-b-type natriuretic peptide. Adapted from Alnuwaysir et al. 2021 [30]

Figure 1: Prevalence of Iron Deficiency in Chronic Heart Fa



Source: Klip et al., 2013.[3]

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)

Table 1 Clinical trials with intravenous iron administration in patients with heart failure

	No of patients/follow-up	Intervention	Dose	HF status	Reported results	Results in patients with low eGFR
FERRIC-HF	35/16 weeks	Iron sucrose vs placebo	200 mg/week iron sucrose for 4 weeks, followed by a maintenance dose every 4 weeks	Symptomatic CHF patients with NYHA class II or III (LVEF ≤ 45%)	Treatment with IV iron sucrose associated with significant improvements in maximal exercise capacity and symptoms of HF, no change in Hb levels. Benefit more evident in patients who were anemic at baseline	No clear data
FAIR-HF	459/24 weeks	FCM: placebo	200 mg/week FCM until normal ferritin, TSAT (correction phase) 200 mg FCM per 4 weeks (maintenance phase)	CHF patients with NYHA class II or III, LVEF ≤ 40% for patients with NYHA class II, or ≤ 45 for NYHA class III	FCM for 24 weeks in patients with CHF and iron deficiency with or without anemia improved symptoms, functional capacity, and quality of life	No clear data
CONFIRM-HF	304/52 weeks	FCM: placebo	500–1000 mg FCM (at baseline and week 6) (correction phase) 500 mg FCM (at weeks 12, 24, and 36, if ID was still present) (maintenance phase)	Symptomatic HF patients with LVEF ≤ 45%	In symptomatic, iron-deficient HF patients with and without anaemia i.v. FCM results in sustainable improvement in functional capacity (6-MWT), in NYHA functional class, health-related quality of life, and fatigue score FCM was also associated with a significant reduction in the risk of hospitalizations for worsening HF	Beneficial impact on the 6-min walk test distance in the subgroup of 105 patients with HF and an eGFR below 60 ml/min/1.73 m^2
AFFIRM-AHF	1132/ 52 weeks	FCM: placebo	500–1000 mg FCM (at baseline—before discharge) and week 6) (correction phase) 500 mg FCM (at weeks 12 and 24, if ID was still present) (maintenance phase)	Patients hospitalized due to acute HF with elevated natriuretic peptide levels, and had a LVEF < 50%	Significant treatment benefits of FCM compared with placebo were seen for the time to first HF hospitalization or CV death, and for days lost due to HF hospitalization and cardiovascular death	FCM administration to stabilized patients with eGFR below 42.69 ml/min/1.73 m^2 after an episode of acute heart failure and concomitant ID did not result in statistically significant reductions in the composite endpoint of hospitalizations for HF and cardiovascular death when compared to placebo

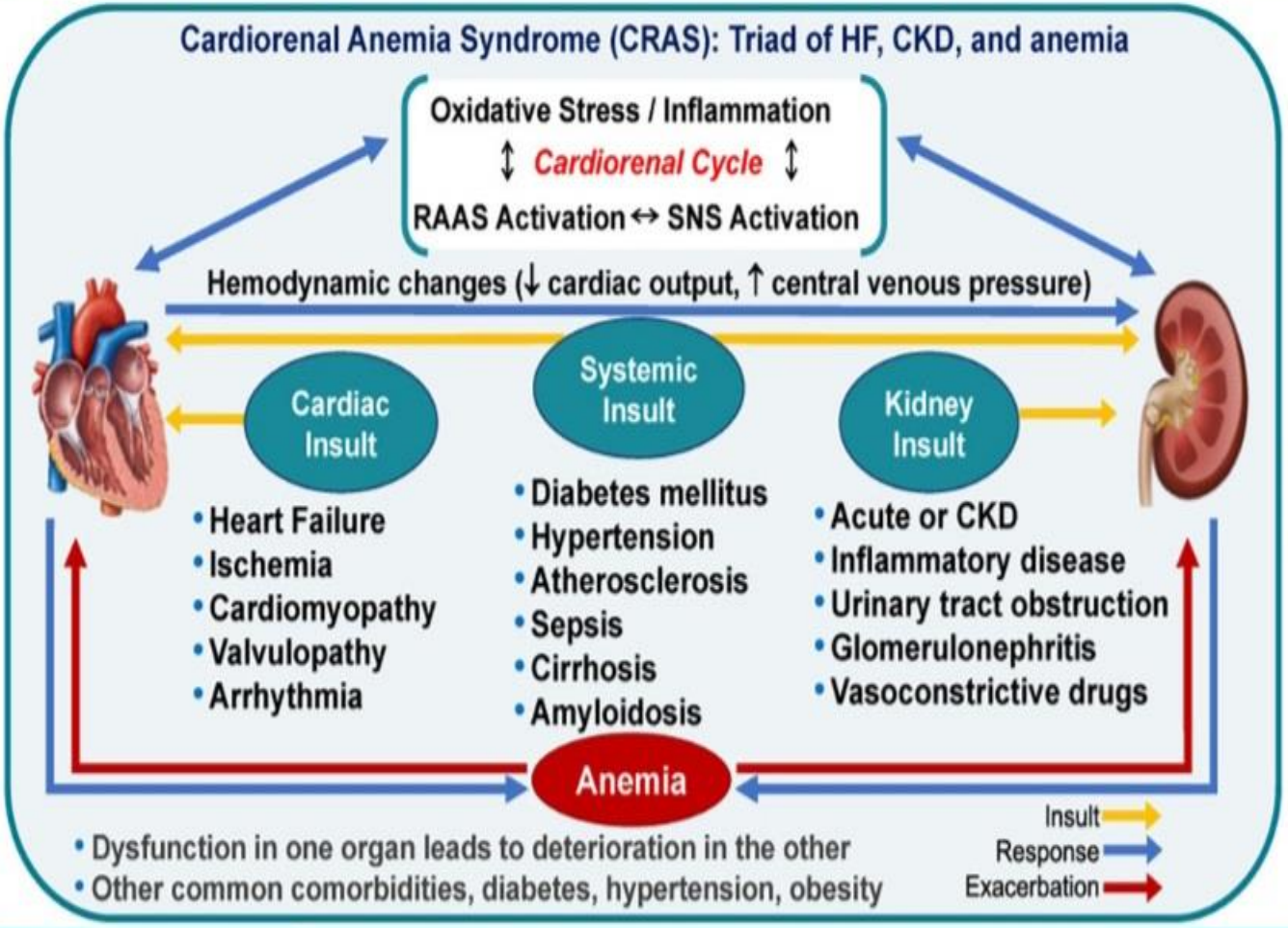
MINT: Liberal vs. Restrictive Transfusion Strategies in Patients With AMI and Anemia

Nov 11, 2023

Contribution To Literature:

The MINT trial showed that in patients with acute MI and anemia (Hgb <10 g/dL), a liberal transfusion goal (Hgb ≥10 g/dL) was not superior to a restrictive strategy (Hgb 7-8 g/dL) with respect to 30-day all-cause death and recurrent MI.

Anemia of Cardiorenal Syndrome



Anemia Management Challenges in CRAS

- No GDMT; limited options
- ESAs not recommended in HF
- ESAs ↑ Hb, may also ↑ CV risk
- Multiple comorbidities

HIF-PHIs:

↑ Endogenous EPO production
↑ Hb

Improve iron absorption & utilization

Function regardless of inflammatory status

CONCLUSIONS:

- Multifactorial treatment approaches and GDMT are needed for CRAS
- HIF-PHIs may offer benefits in this complex patient population with heightened inflammatory status

kidney INTERNATIONAL supplements

McCullough, 2021

CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agent; GDMT: guideline-directed medical therapy; Hb: hemoglobin; HF: heart failure; HIF-PHI: hypoxia-inducible factor-prolyl hydroxylase inhibitor; RAAS: renin-angiotensin-aldosterone system inhibitor; SNS: sympathetic nervous system.

SGLT-2 Inh and Anemia correction

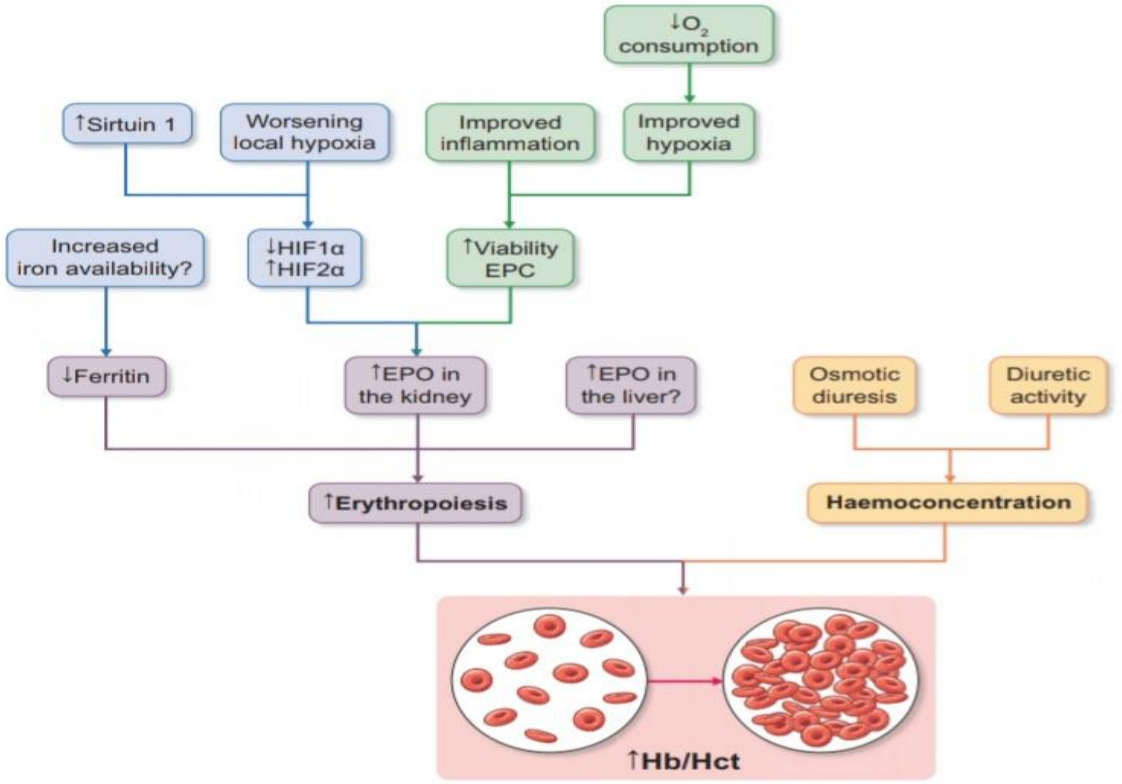


Figure 1: Possible mechanisms explaining increased erythropoiesis following therapy with SGLT2 inhibitors. The observed increase in Hb/Hct levels is due to the combination of increased erythropoiesis and haemoconcentration. Increased erythropoiesis can be sustained by increased iron availability, increased 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.

Case problems:

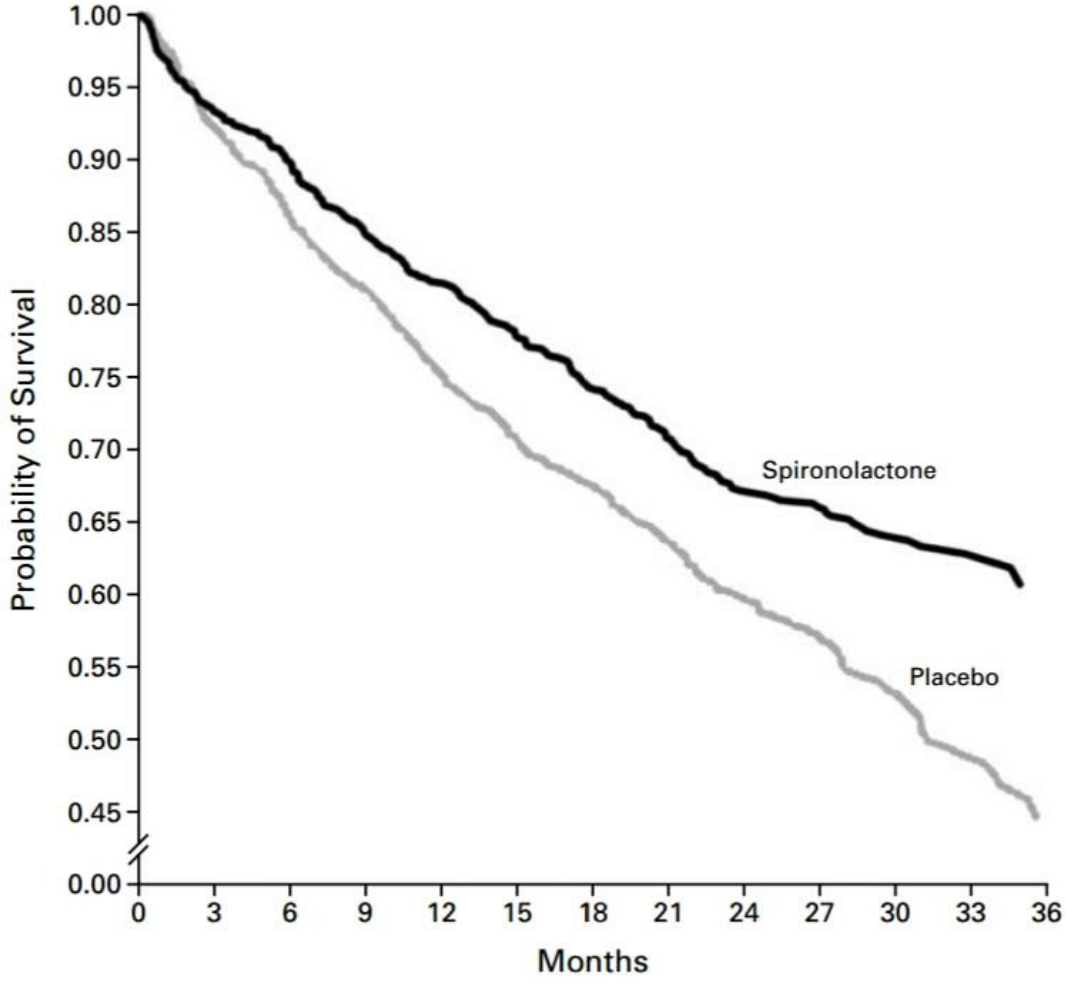
- 1 -Volume overload (Diuretic therapy vs UF) ?
- 2- RAAS blockade and Neprylisin inhibitor (Worsening of renal function)?
- 3-Hyponatremia management (Vaptan)?
- 4-Hyperurecemia management (Allopurinol)?
- 5- Anemia Management (CRAIDS and EPO)?
- **6-Mineral receptor antagonist?**
- 7-Contrast nephropathy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

The New England
Journal of Medicine

VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*



No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Figure 1. Kaplan–Meier Analysis of the Probability of Survival among Patients in the Placebo Group and Patients in the Spironolactone Group.

The risk of death was 30 percent lower among patients in the spironolactone group than among patients in the placebo group ($P<0.001$).

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Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

Bertram Pitt, M.D., Willem Remme, M.D., Faiez Zannad, M.D., James Neaton, Ph.D., Felipe Martinez, M.D., Barbara Roniker, M.D., Richard Bittman, Ph.D., Steve Hurley, B.S., Jay Kleiman, M.D., and Marjorie Gatlin, M.D., for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators*

ABSTRACT

BACKGROUND

Aldosterone blockade reduces mortality and morbidity among patients with severe heart failure. We conducted a double-blind, placebo-controlled study evaluating the effect of eplerenone, a selective aldosterone blocker, on morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

METHODS

Patients were randomly assigned to eplerenone (25 mg per day initially, titrated to a maximum of 50 mg per day; 3313 patients) or placebo (3319 patients) in addition to optimal medical therapy. The study continued until 1012 deaths occurred. The primary-end points were death from any cause and death from cardiovascular causes or hospitalization for heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia.

RESULTS

During a mean follow-up of 16 months, there were 478 deaths in the eplerenone group and 554 deaths in the placebo group (relative risk, 0.85; 95 percent confidence interval, 0.75 to 0.96; P=0.008). Of these deaths, 407 in the eplerenone group and 483 in the placebo group were attributed to cardiovascular causes (relative risk, 0.83; 95 percent confidence interval, 0.72 to 0.94; P=0.005). The rate of the other primary-end point, death from cardiovascular causes or hospitalization for cardiovascular events, was reduced by eplerenone (relative risk, 0.87; 95 percent confidence interval, 0.79 to 0.95; P=0.002). As was the secondary end point of death from any cause or any hospitalization (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.98; P=0.02). There was also a reduction in the rate of sudden death from cardiac causes (relative risk, 0.79; 95 percent confidence interval, 0.64 to 0.97; P=0.03). The rate of serious hyperkalemia was 5.5 percent in the eplerenone group and 3.9 percent in the placebo group (P=0.002), whereas the rate of hypokalemia was 8.4 percent in the eplerenone group and 13.3 percent in the placebo group (P<0.001).

CONCLUSIONS

The addition of eplerenone to optimal medical therapy reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

From the University of Michigan, Ann Arbor (B.P.); STEMBRIO, Cardiovascular Research Foundation, Rotterdam, the Netherlands (W.R.); the Centre of Investigation Clinique de Nancy, Nancy, France (F.Z.); the University of Minnesota, Minneapolis (J.N.); the Fundacion Favaloro, Cordoba, Argentina (F.M.); and Pharmacia, Skokie, IL (B.R., R.B., S.H., J.K., M.G.). Address reprint requests to Dr. Pitt at the Department of Internal Medicine, Division of Cardiology, University of Michigan Medical Center, 9220 Taubman, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0364, or at bpitt@umich.edu.

*Members of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Group are listed in the Appendix.

N Engl J Med 2003;348:1309-21.

Eplerenone vs Placebo

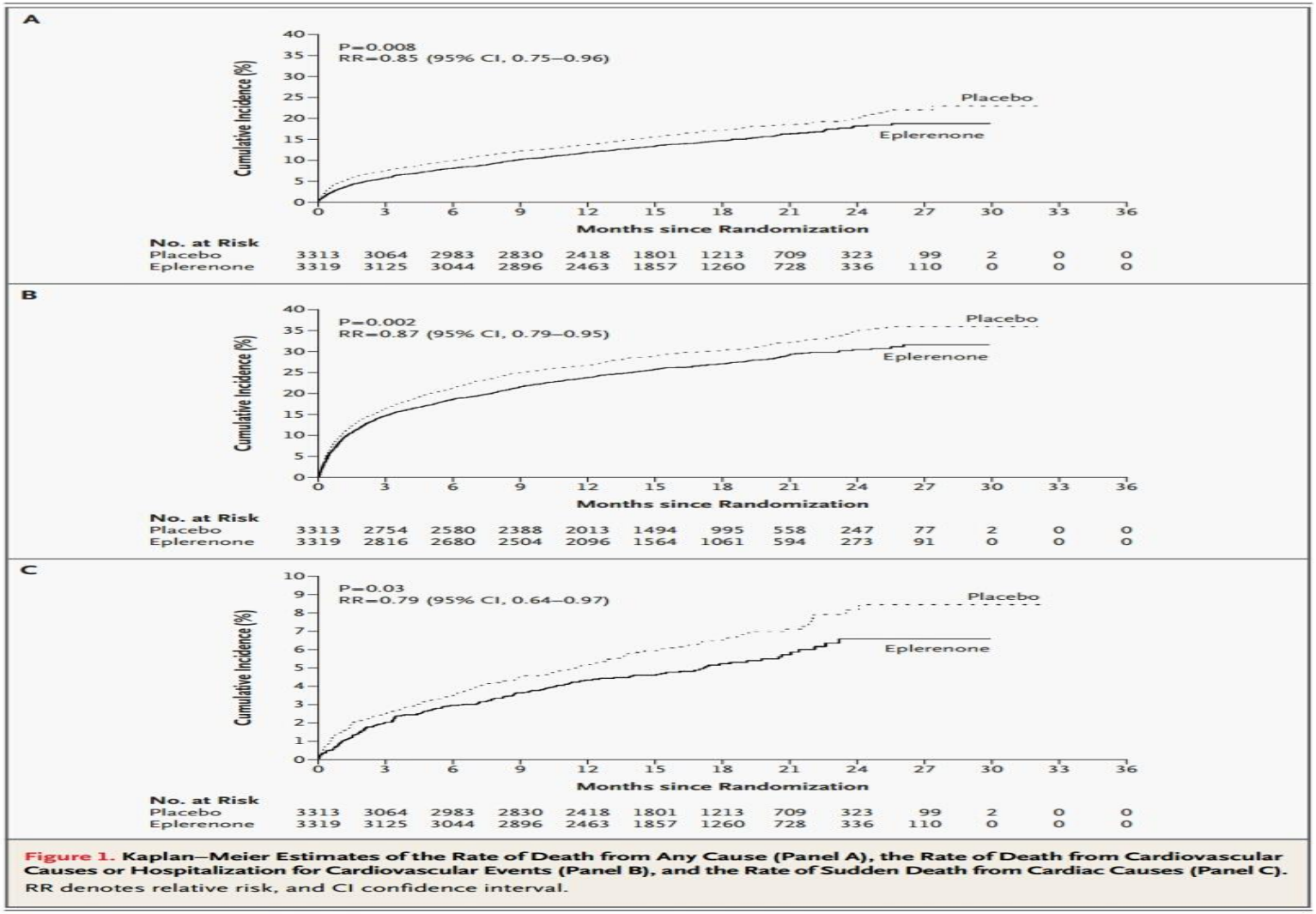
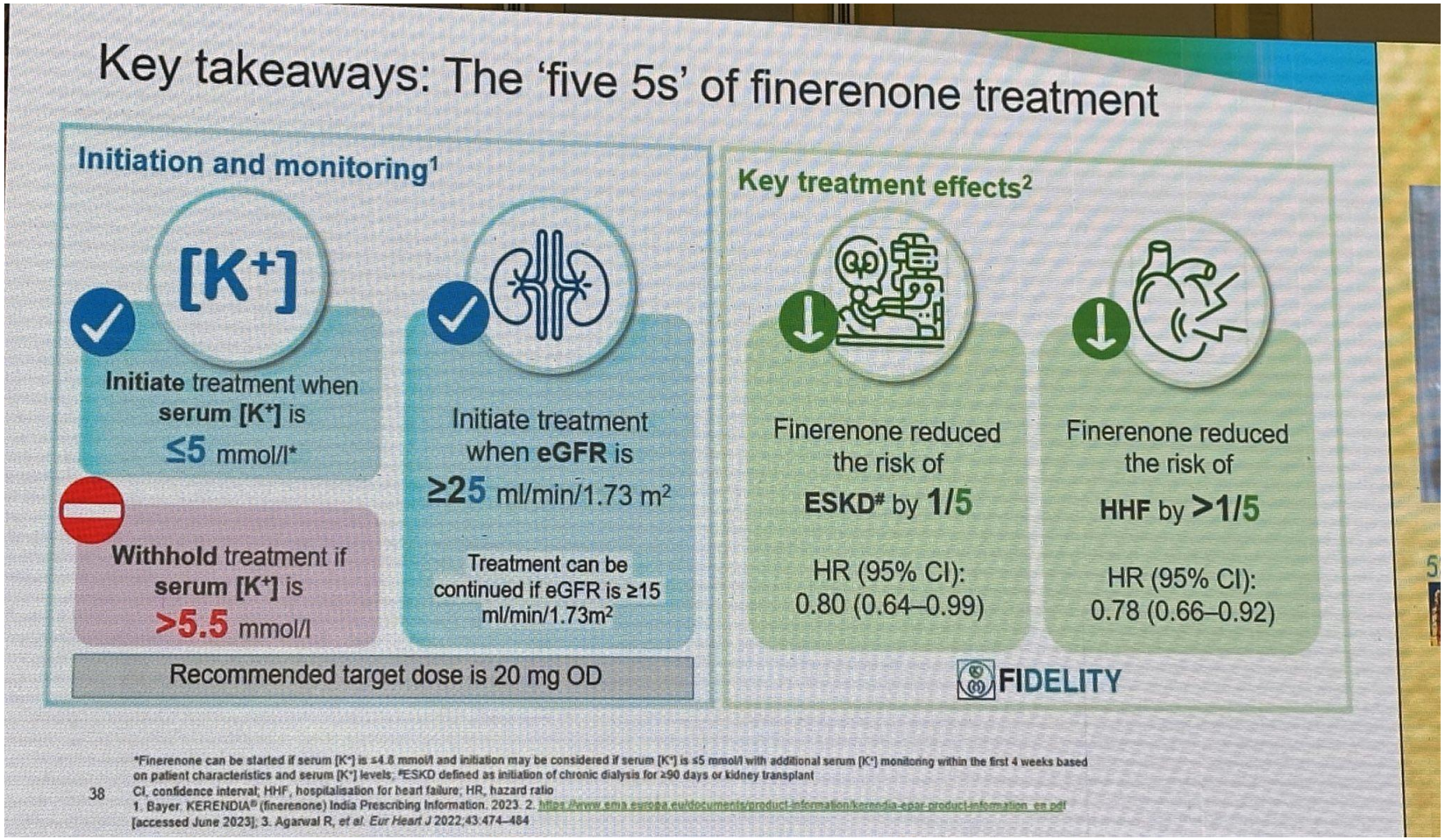


Figure 1. Kaplan–Meier Estimates of the Rate of Death from Any Cause (Panel A), the Rate of Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events (Panel B), and the Rate of Sudden Death from Cardiac Causes (Panel C). RR denotes relative risk, and CI confidence interval.

Finerenone

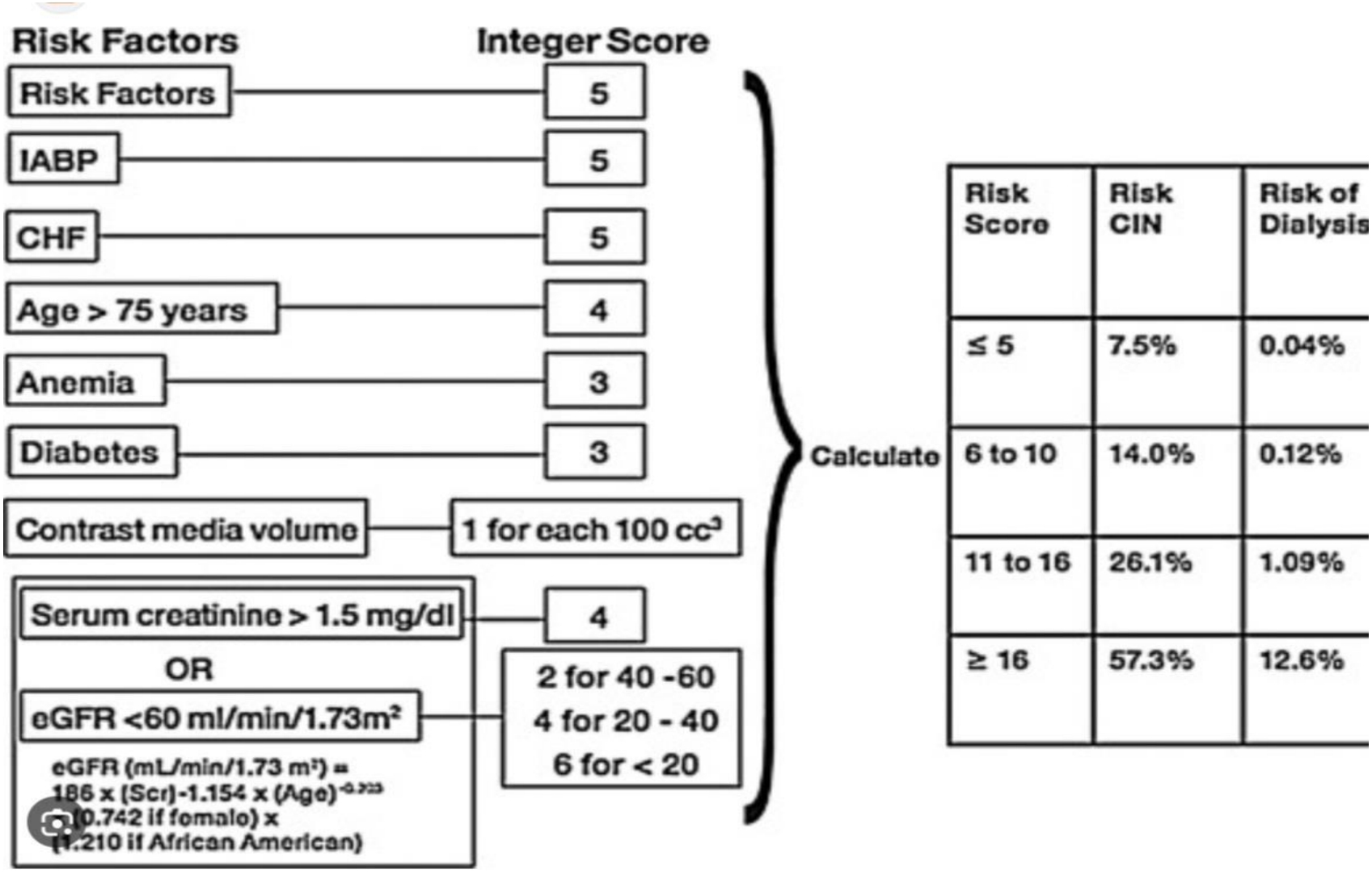

Key takeaways: The 'five 5s' of finerenone treatment
Initiation and monitoring[1]
[K+]
Initiate treatment when serum [K+] is ≤5 mmol/l*
Withhold treatment if serum [K+] is >5.5 mmol/l
Initiate treatment when eGFR is ≥25 ml/min/1.73 m²
Treatment can be continued if eGFR is ≥15 ml/min/1.73m²
Recommended target dose is 20 mg OD
Key treatment effects[2]
Finerenone reduced the risk of ESKD# by 1/5
HR (95% CI): 0.80 (0.64–0.99)
Finerenone reduced the risk of HHF by >1/5
HR (95% CI): 0.78 (0.66–0.92)
FIDELITY
*Finerenone can be started if serum [K+] is ≤4.8 mmol/l and initiation may be considered if serum [K+] is ≤5 mmol/l with additional serum [K+] monitoring within the first 4 weeks based on patient characteristics and serum [K+] levels; #ESKD defined as initiation of chronic dialysis for ≥90 days or kidney transplant
CI, confidence interval; HHF, hospitalisation for heart failure; HR, hazard ratio
1. Bayer. KERENDIA® (finerenone) India Prescribing Information. 2023. 2. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed June 2023]; 3. Agarwal R, et al. Eur Heart J 2022;43:474–484
38

	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	+++	++	+

Case problems:

- 1 -Volume overload (Diuretic 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 EPO)?
- 6-Mineral receptor antagonist?
- **7-Contrast nephropathy risk and prophylaxy?**

Mehran contrast nephropathy Risk score



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

Visit >

Evidence of drugs for mortality reduction in heart failure

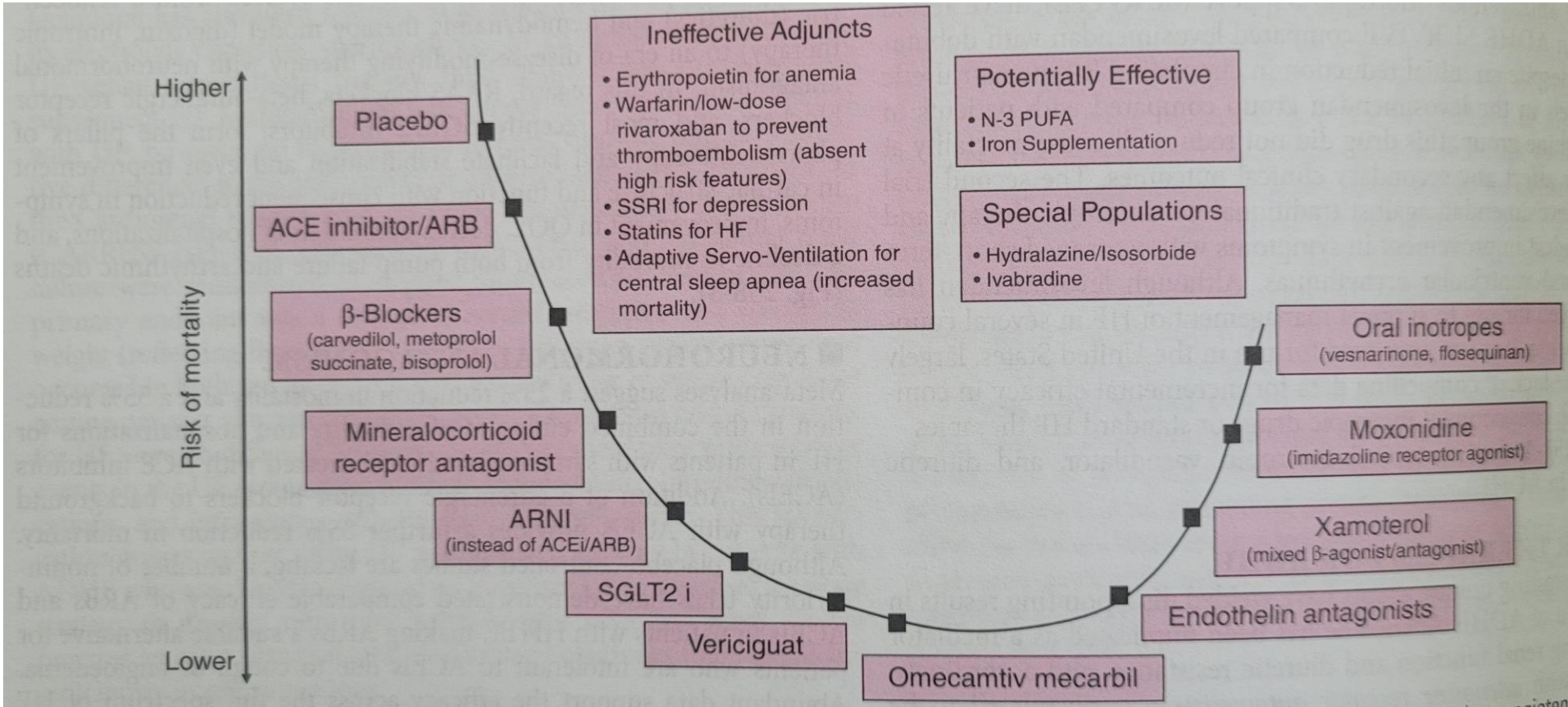
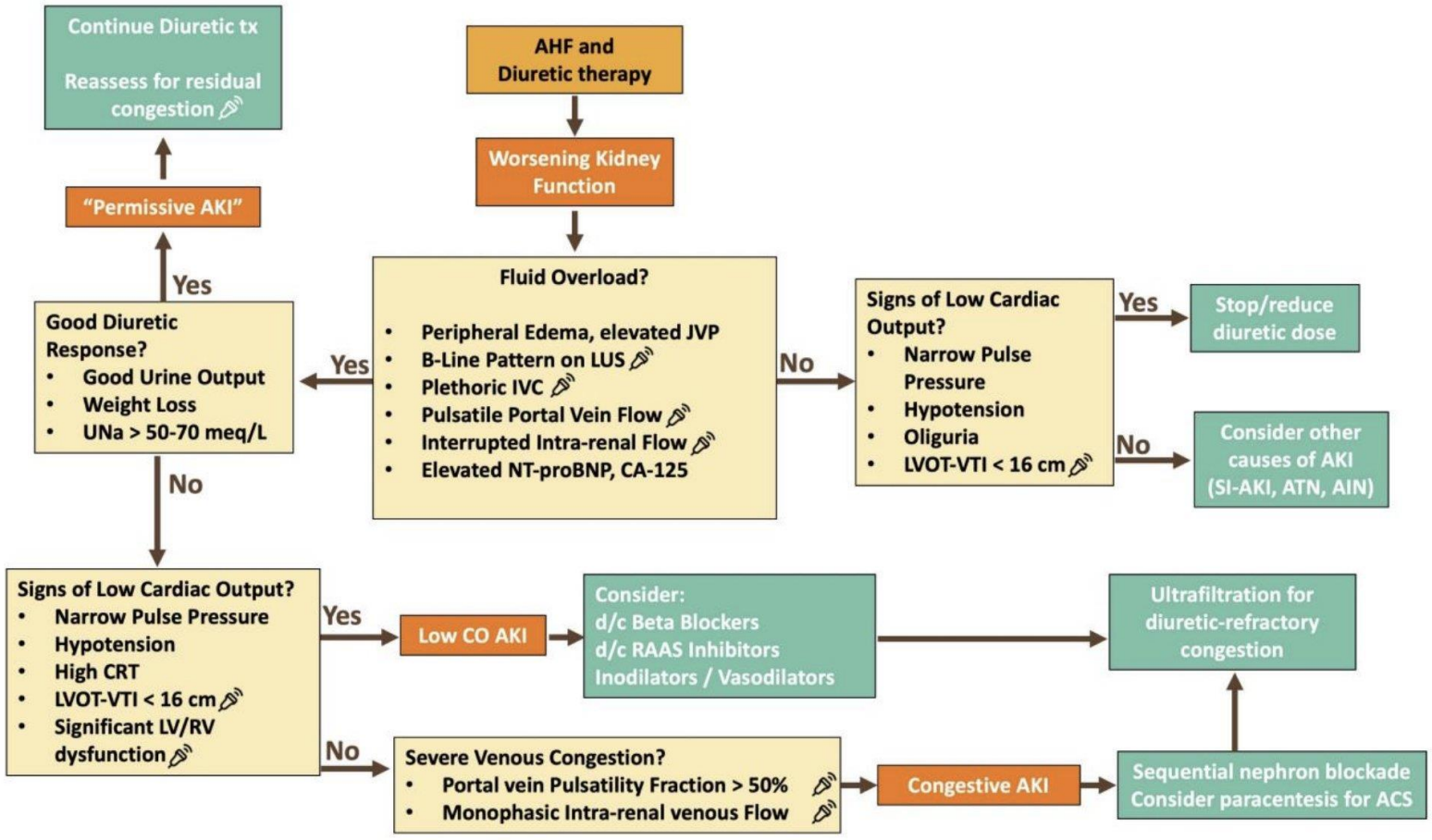


FIGURE 258-3 Progressive decline in mortality with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) or angioten neprilysin inhibitors (ARNIs), beta blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and balanced (*selected populations such as African Americans); addition of selected therapies (ivabradine, vericiguat) may further reduce heart failure (HF) hospitalization substantially impact mortality; further stack-on neurohormonal therapy is ineffective or results in worse outcome; management of comorbidity (e.g., iron defi apnea) is of unproven efficacy. HFrEF, heart failure with reduced ejection fraction; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibi

Conclusion


AHF and Diuretic therapy
Worsening Kidney Function
Fluid Overload?
• Peripheral Edema, elevated JVP
• B-Line Pattern on LUS
• Plethoric IVC
• Pulsatile Portal Vein Flow
• Interrupted Intra-renal Flow
• Elevated NT-proBNP, CA-125
Yes
Good Diuretic Response?
• Good Urine Output
• Weight Loss
• UNa > 50-70 meq/L
Yes
"Permissive AKI"
Continue Diuretic tx
Reassess for residual congestion
No
Signs of Low Cardiac Output?
• Narrow Pulse Pressure
• Hypotension
• High CRT
• LVOT-VTI < 16 cm
• Significant LV/RV dysfunction
Yes
Low CO AKI
Consider:
d/c Beta Blockers
d/c RAAS Inhibitors
Inodilators / Vasodilators
Ultrafiltration for diuretic-refractory congestion
No
Severe Venous Congestion?
• Portal vein Pulsatility Fraction > 50%
• Monophasic Intra-renal venous Flow
Congestive AKI
Sequential nephron blockade
Consider paracentesis for ACS
No
Signs of Low Cardiac Output?
• Narrow Pulse Pressure
• Hypotension
• Oliguria
• LVOT-VTI < 16 cm
Yes
Stop/reduce diuretic dose
No
Consider other causes of AKI (SI-AKI, ATN, AIN)

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,Neprylisin inhibitor, nesiritide) is required.
- 4. Only **SGLT-2 inh,MRA,BB , ACEinh/ ARB and ARNI** have good evidences for mortality reduction in heart failure.
- 5 . In diuretic resistant cases or unstable hemodynamics with volume overload **UF therapy may be useful (CRRT/SCUF/HD/PD).**