

Managing fluid, salt, K⁺ and creatinine in heart failure or cardiorenal syndrome

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Conflict of Interest Disclosures - Serge Lepage, MD, FRCPC, CSPQ

- **Consulting Fees/Honoraria:**

- Novartis, AstraZeneca, Janssen, Servier, Amgen, Sanofi

- **Clinical Trials:**

- Novartis, Amgen

Learning objectives

Following this session, participants will be better able to:

- Understand the interaction of diabetes, kidney disease and HF
- Review the management of potassium, the "forgotten ion"
- Understand established & new modalities for the treatment of potassium disorders

Electrolyte and Fluid Disturbances in Congestive Heart Failure

New topic?

MEDICAL PROGRESS

FREE PREVIEW

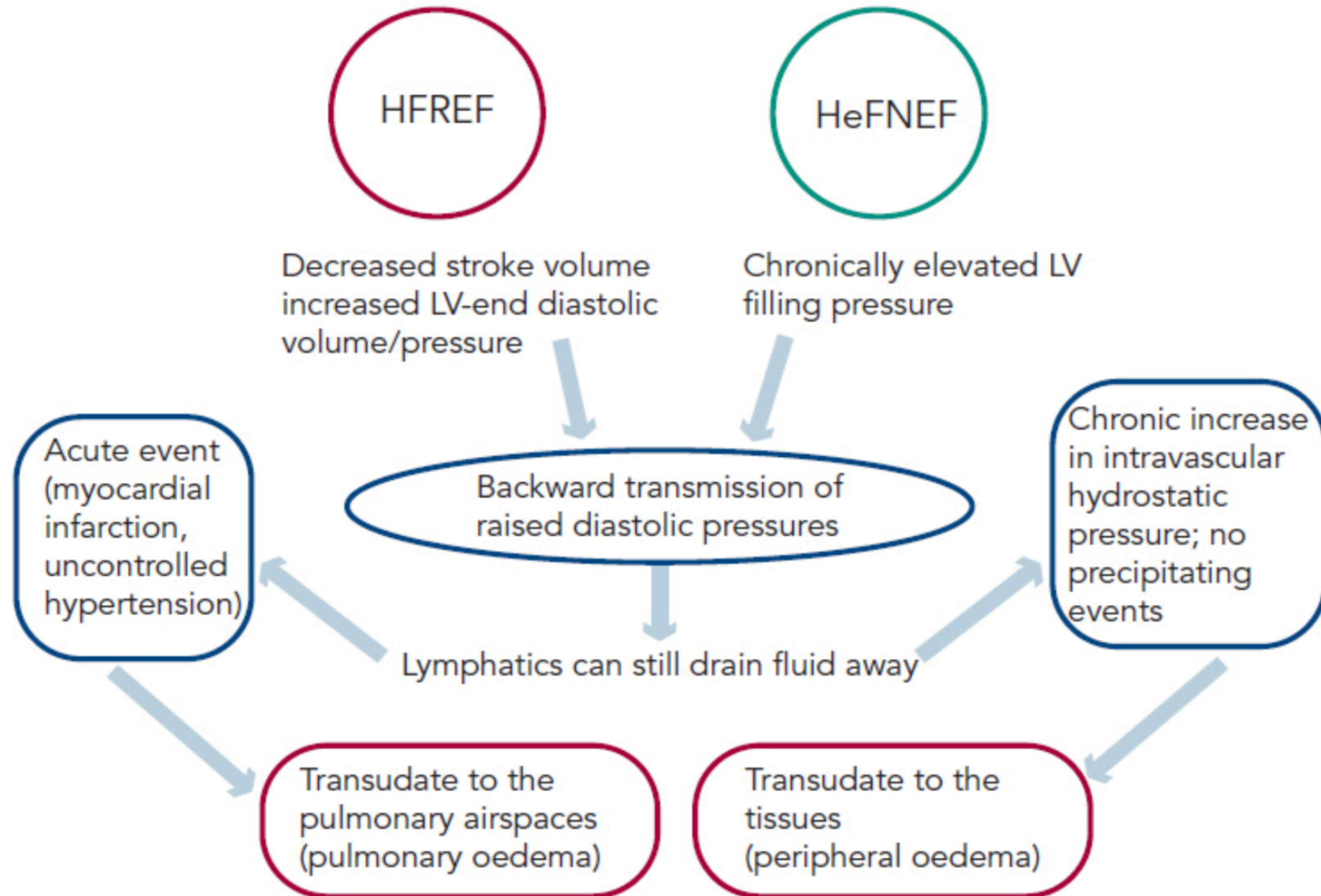
ARCHIVE

Electrolyte and Fluid Disturbances in Congestive Heart Failure

Charles K. Friedberg, M.D.[†]

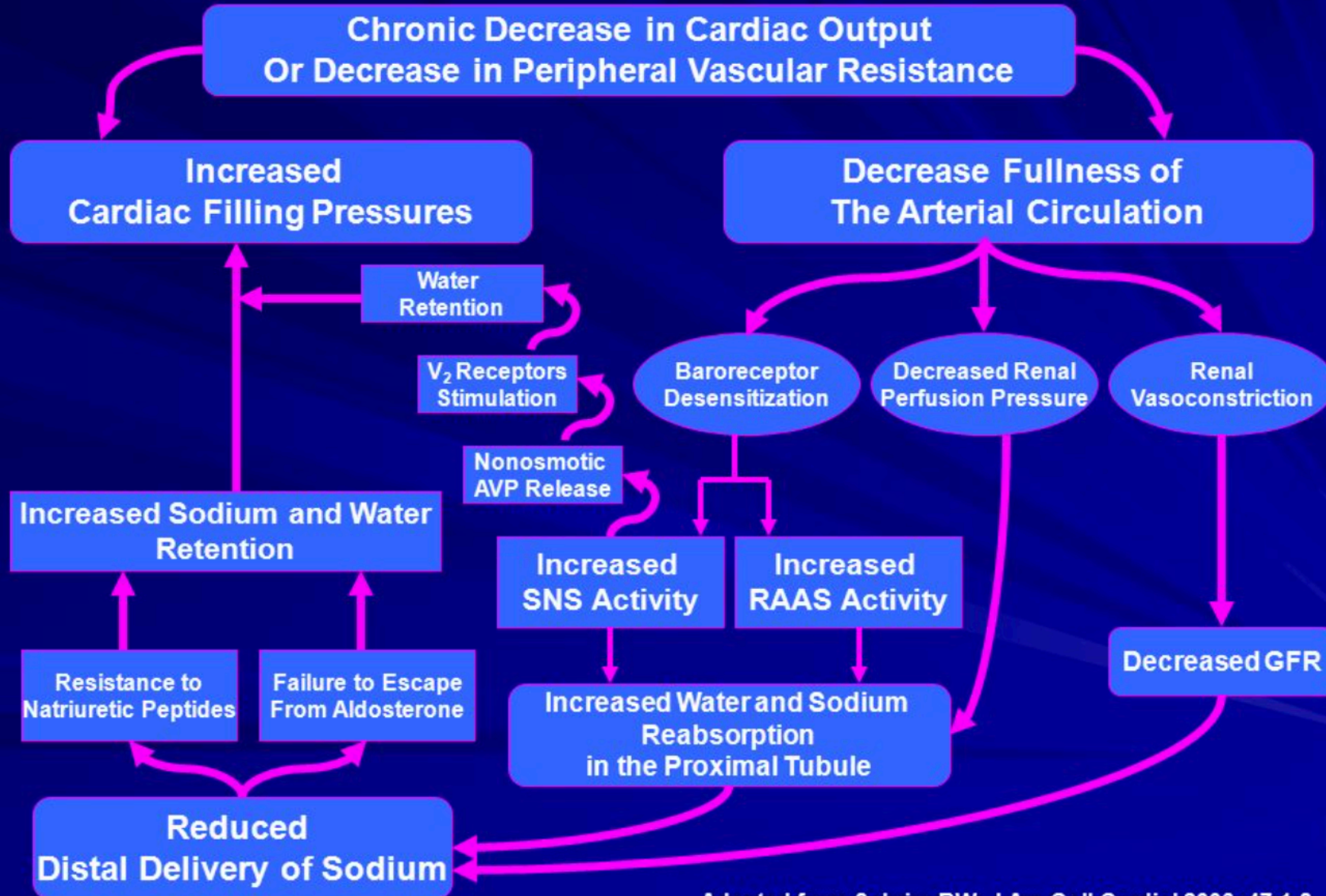
[November 22, 1951](#)

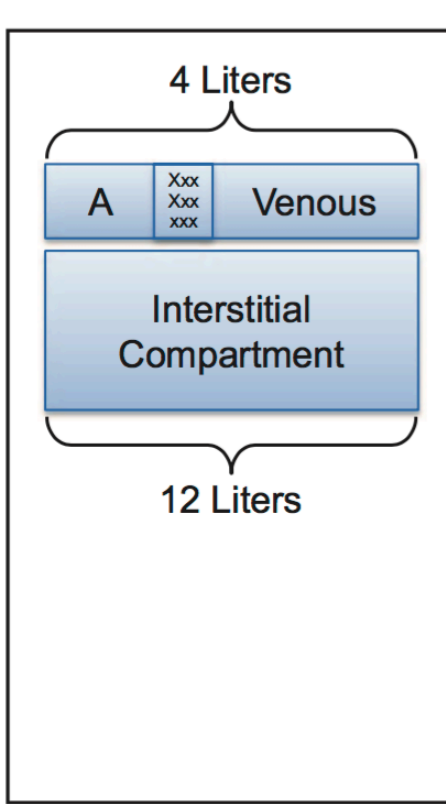
N Engl J Med 1951; 245:812-821



HeFNEF = heart failure with normal ejection fraction; HFREF = heart failure with reduced ejection fraction; LV= left ventricular.

Mechanisms of Sodium and Water Retention in Heart Failure





Normal Physiology



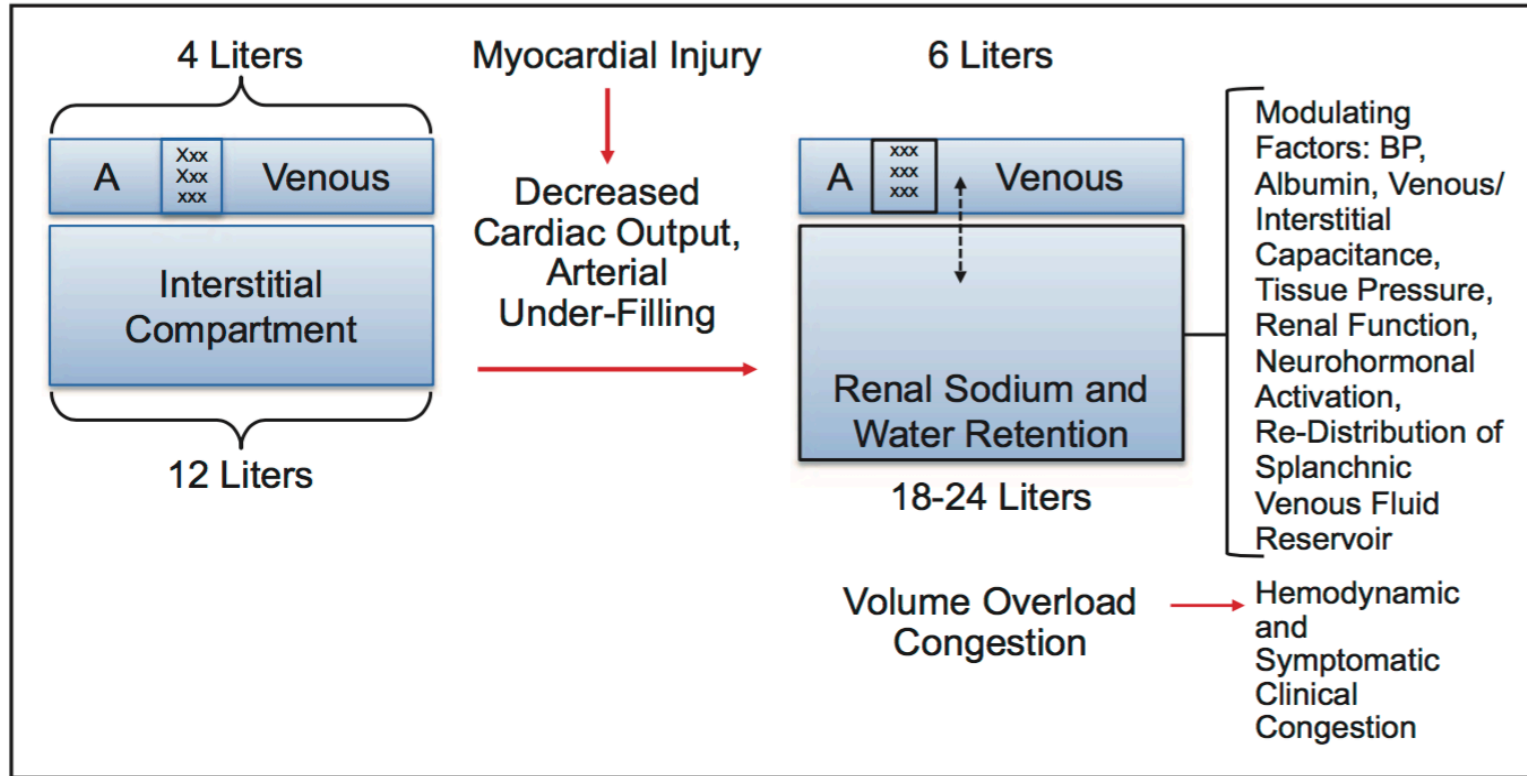


Figure 4. Paradigm of interstitial and intravascular volume expansion in chronic heart failure. BP indicates blood pressure; and CO, cardiac output.

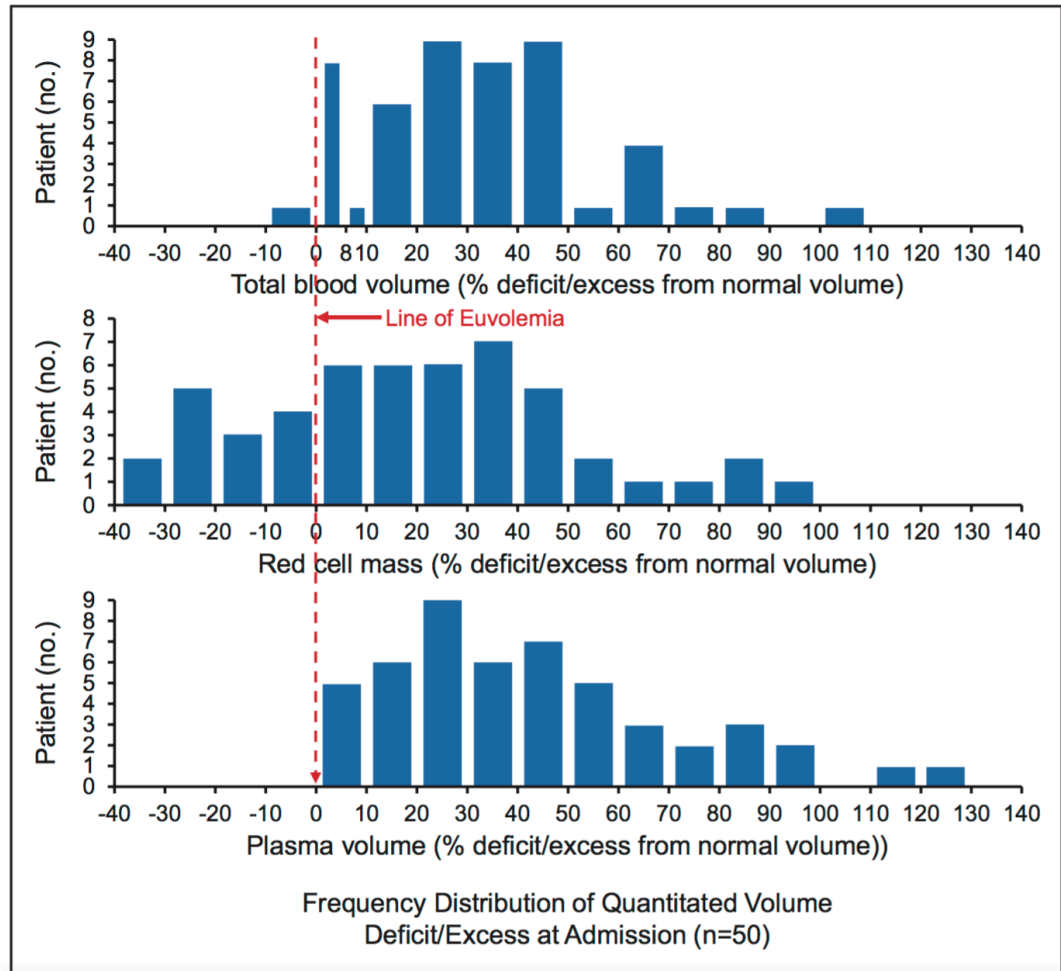


Figure 3. Frequency distribution of measured total blood volume, red blood cell mass, and plasma volume at hospital admission in patients with decompensated chronic heart failure. Percent deviation from normal expected volumes.

Clinical Evaluation of HF

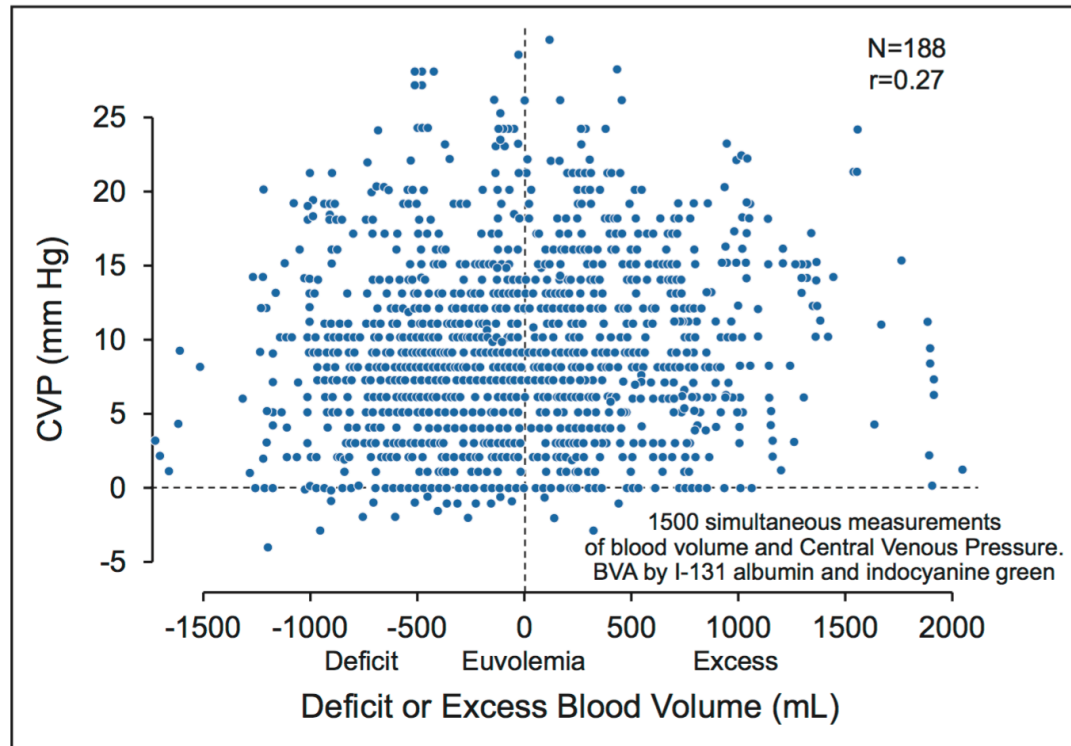
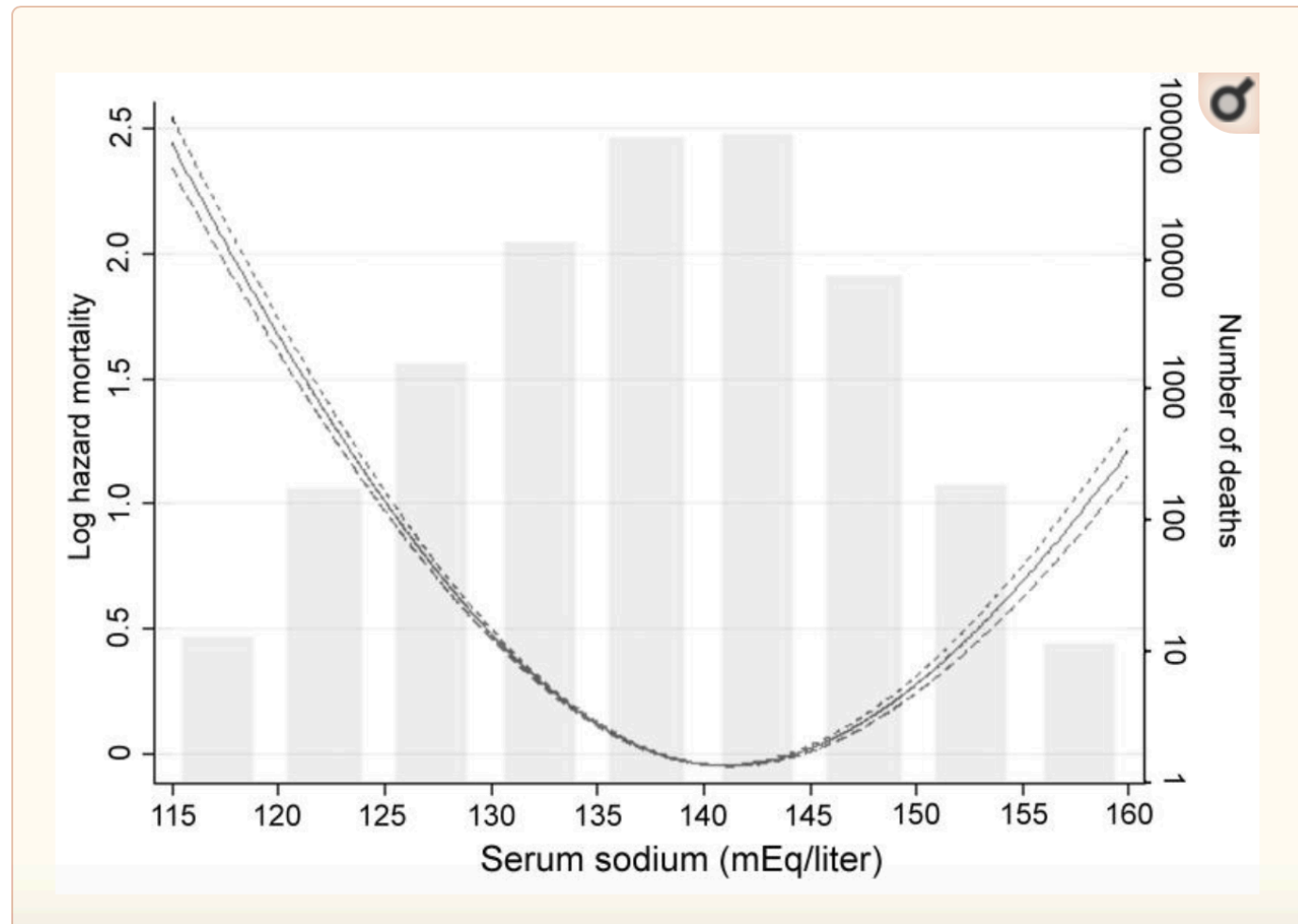
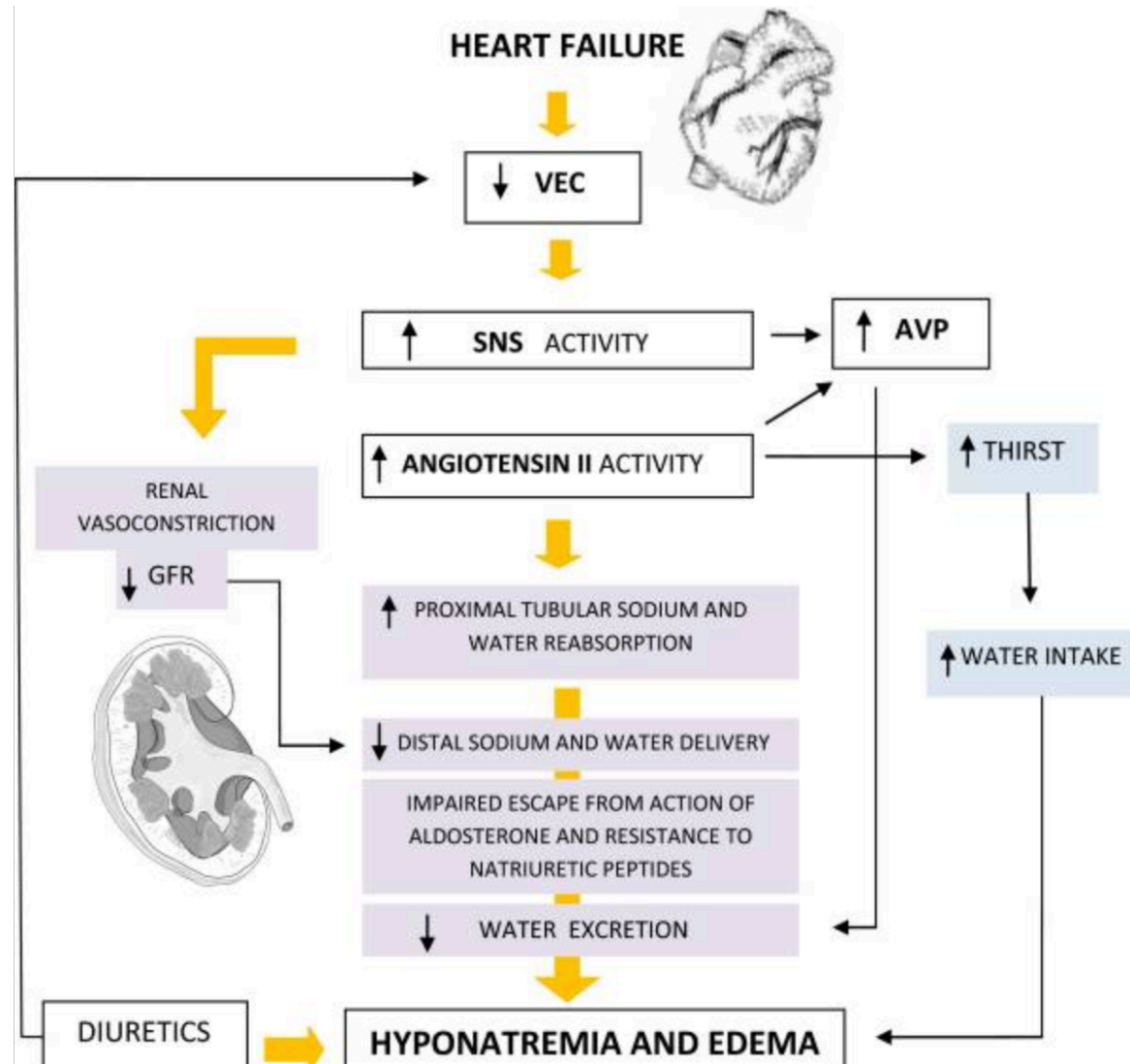


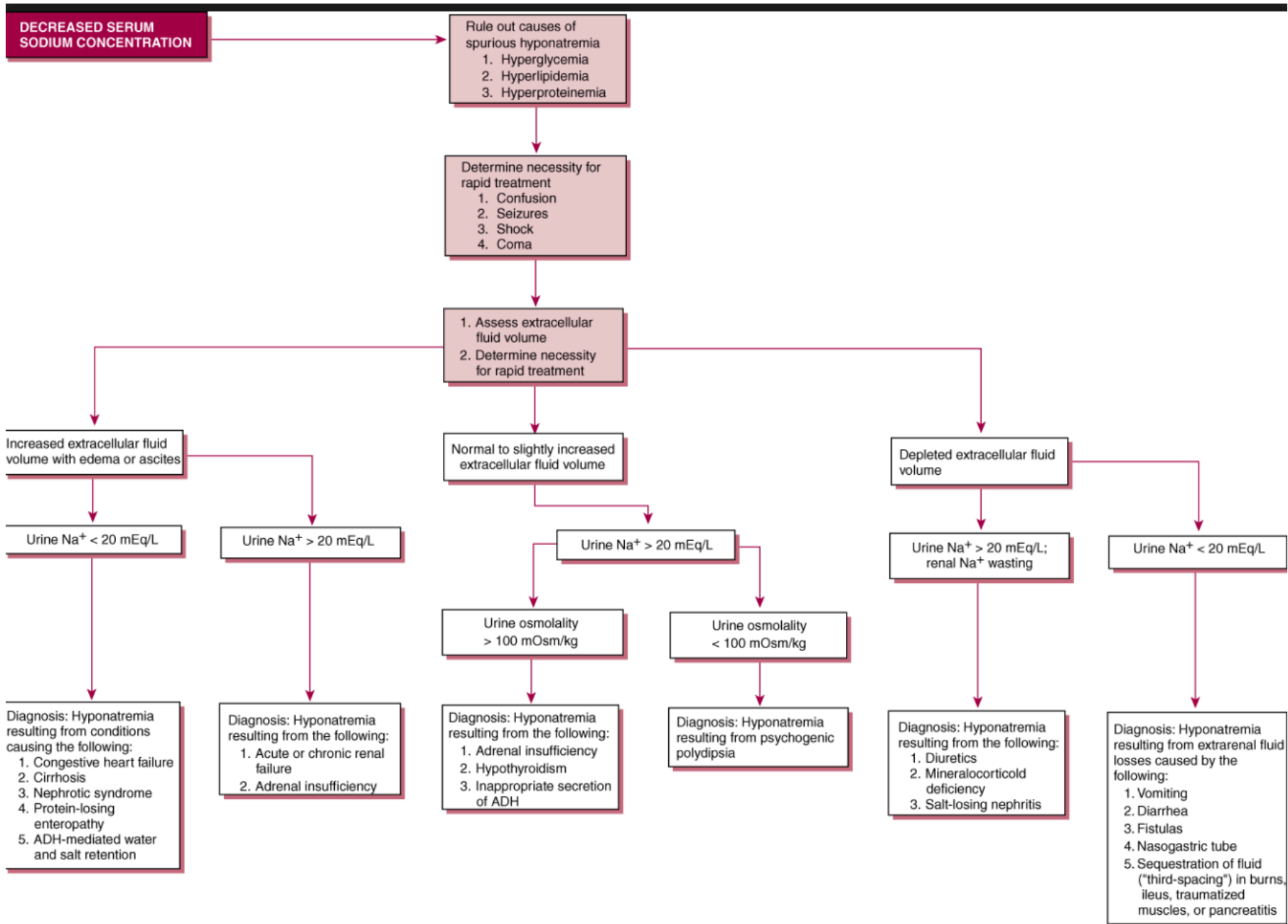
Figure 7. Lack of correlation between central venous pressure and measured total blood volume. Pressure is not volume. Reprinted from Shippy et al³³ with permission of the publisher. Copyright ©1984, Wolters Kluwer Health.

Sodium and HF



Edema and Sodium





Hyponatremia signs and symptoms may include:

- Nausea and vomiting
- Headache
- Confusion
- Loss of energy, drowsiness and fatigue
- Restlessness and irritability
- Muscle weakness, spasms or cramps
- Seizures
- Coma

Correction of hyponatremia



Correction of Hyponatremia

Hyponatremia Type	Treatment Regimen	Comments
Acute symptomatic	Serum sodium concentration should be increased by 2 mmol/L per hr until symptoms subside; may be used with or without loop diuretics such as furosemide	Correction should be limited to 8 mmol/L per 24 hr to avoid the risk of adverse neurologic outcomes
Chronic symptomatic	Rate of correction should be 0.5 to 1 mmol/L. Therapy should be discontinued when serum sodium concentrations are raised by 10% or when symptoms subside; may be used with or without loop diuretics such as furosemide	Correction should be limited to 25 mmol/L per 48 hr to avoid the risk of adverse neurologic outcomes
Chronic asymptomatic	Restrict fluid intake; use other pharmacologic agents	Loop diuretics may exacerbate hyponatremia

Therapeutic Options for Hyponatremia Due to Congestive Heart Failure

Treatment	Mechanism	Limitations
Fluid restriction	Decreases total body water volume, increasing ratio of sodium to water	Treatment adherence issues
Hypertonic saline	Increase ratio of sodium to water; may be used with furosemide to avoid fluid overload	Careful monitoring required; rapid correction can lead to neurologic damage
Loop diuretics	Increase rate of urine flow	Promote excretion of sodium, exacerbating hyponatremia
Aldosterone antagonists	Inhibit aldosterone-mediated water retention	Promote excretion of sodium, exacerbating hyponatremia
Demeclocycline	Inhibits antidiuretic actions of AVP by inducing nephrogenic diabetes insipidus	Potential for nephrotoxicity
Lithium	Reduces antidiuretic activity of AVP by reducing V ₂ -receptor-mediated stimulation of adenylyl cyclase	Slow onset of action; CNS side effects, cardiotoxicity, and GI disturbances
Urea	Increases the osmolality of the plasma and tubular fluid	Nonpalatable; contraindicated in impaired renal function, intracranial bleeding, and liver failure

AVP = arginine vasopressin; CNS = central nervous system; GI = gastrointestinal.

Symptoms of hypernatremia

- • Non-specific,
- • Restlessness,
- • Irritability,
- • Muscular twitching,
- • Hyperreflexia,
- • Spasticity, and
- • Seizures
- • With hypotonic losses - signs of volume loss
- • Tachycardia,
- • Hypotension,
- • Decreased JVP,
- • Dry mucosa,
- • Reduced skin turgor and
- • Thick doughy skin

Treatment recommendations for symptomatic hypernatremia

Recommendations are as follows:

- Establish documented onset (acute, < 24 h; chronic, >24h)
- In acute hypernatremia, correct the serum sodium at an initial rate of 2-3 mEq/L/h (for 2-3 h) (maximum total, 12 mEq/L/d).
- Measure serum and urine electrolytes every 1-2 hours
- Perform serial neurologic examinations and decrease the rate of correction with improvement in symptoms
- Chronic hypernatremia with no or mild symptoms should be corrected at a rate not to exceed 0.5 mEq/L/h and a total of 8-10 mEq/d (eg, 160 mEq/L to 152 mEq/L in 24 h).
- If a volume deficit and hypernatremia are present, intravascular volume should be restored with isotonic sodium chloride prior to free-water administration.

Distribution of Total Body K⁺

Intracellular fluid

3,500 mEq (140-150 mEq/L)

Muscle: 2,700 mEq

Liver: 250 mEq

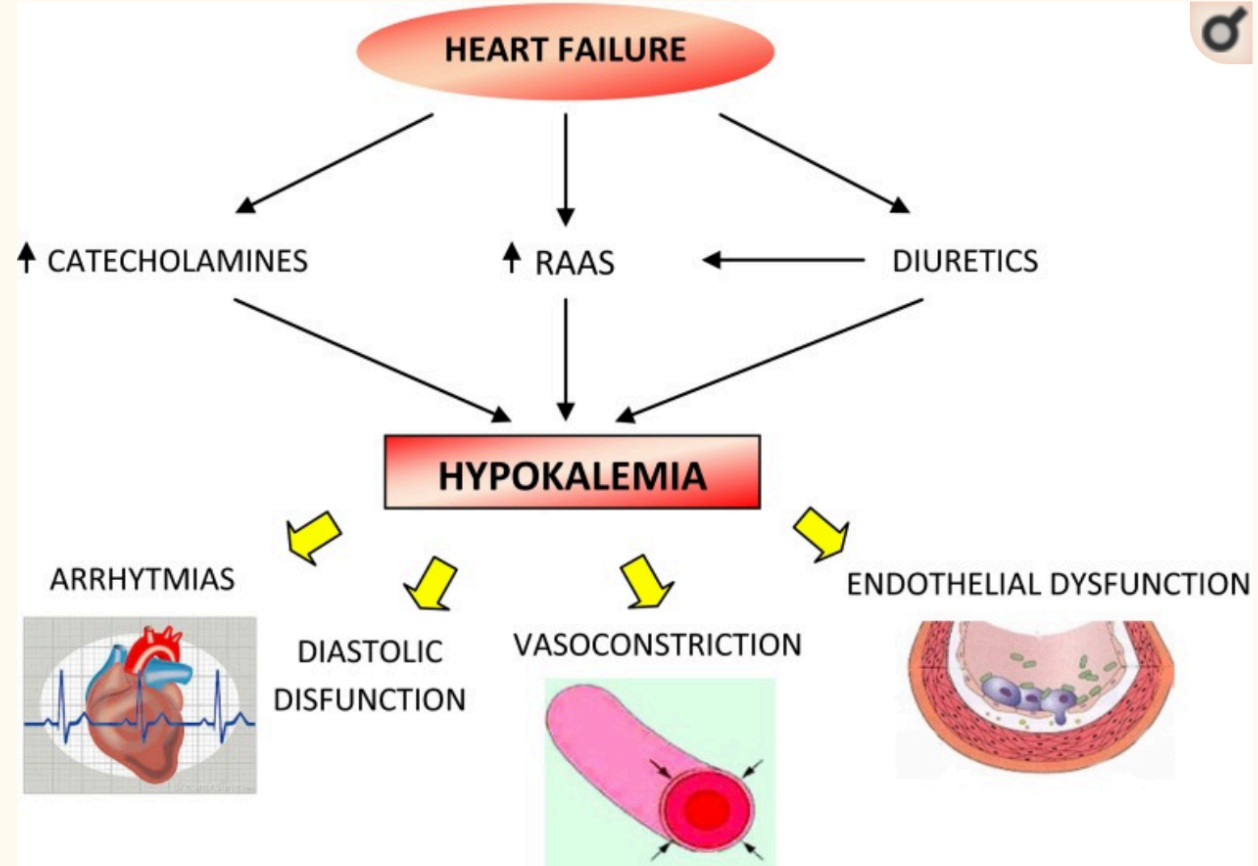
Erythrocytes: 250 mEq

Bone: 300 mEq

Extracellular fluid

70 mEq (3.5-5.5 mEq/L)

Heart Failure and Potassium



[Fig. 2](#)

Hypokalemia in heart failure. *RAAS* renin–angiotensin–aldosterone system

Homeostasis- controlled by EXCRETION

Kidney plays the most important role

- 90% of K^+ is resorbed before the distal tubule and collecting duct-
 - In distal tubule and collecting duct- K^+ absorbed and secreted
 - Tubular secretion that regulates the amount of K^+ in the urine
 - Regulating hormone- aldosterone (\uparrow in hyperkalemia)
 - Acts on cortical collecting duct
 - Moves sodium into cells
 - Creates a negative charge in the lumen $\rightarrow K^+$ excretion.
 - \uparrow intracellular Na^+ stimulates the basolateral Na^+ , K^+ -ATPase
 - Moves K^+ into cells lining the cortical collecting duct from blood side.
- Glucocorticoids, ADH, high urine flow, and high Na^+ delivery to the distal nephron also \uparrow urine K^+ .
- Alkalosis - \uparrow urine K^+ .
- Acidosis \downarrow urine K^+ .
- Excretion is decreased by insulin, catecholamines, and urine ammonia

Hypokalemia in CHF

Causes:

- Medication
- Increased losses: extrarenal and renal
- Transcellular shifts
- Decreased intake
- *Lab error- spurious

Treatment- Hypokalemia

Severe, symptomatic hypokalemia requires aggressive treatment

Because of the risk of hyperkalemia, use IV potassium cautiously

0.5–1 mEq/kg, usually given over 1 hr. The adult maximum dose is 40 mEq.

Oral potassium is safer.

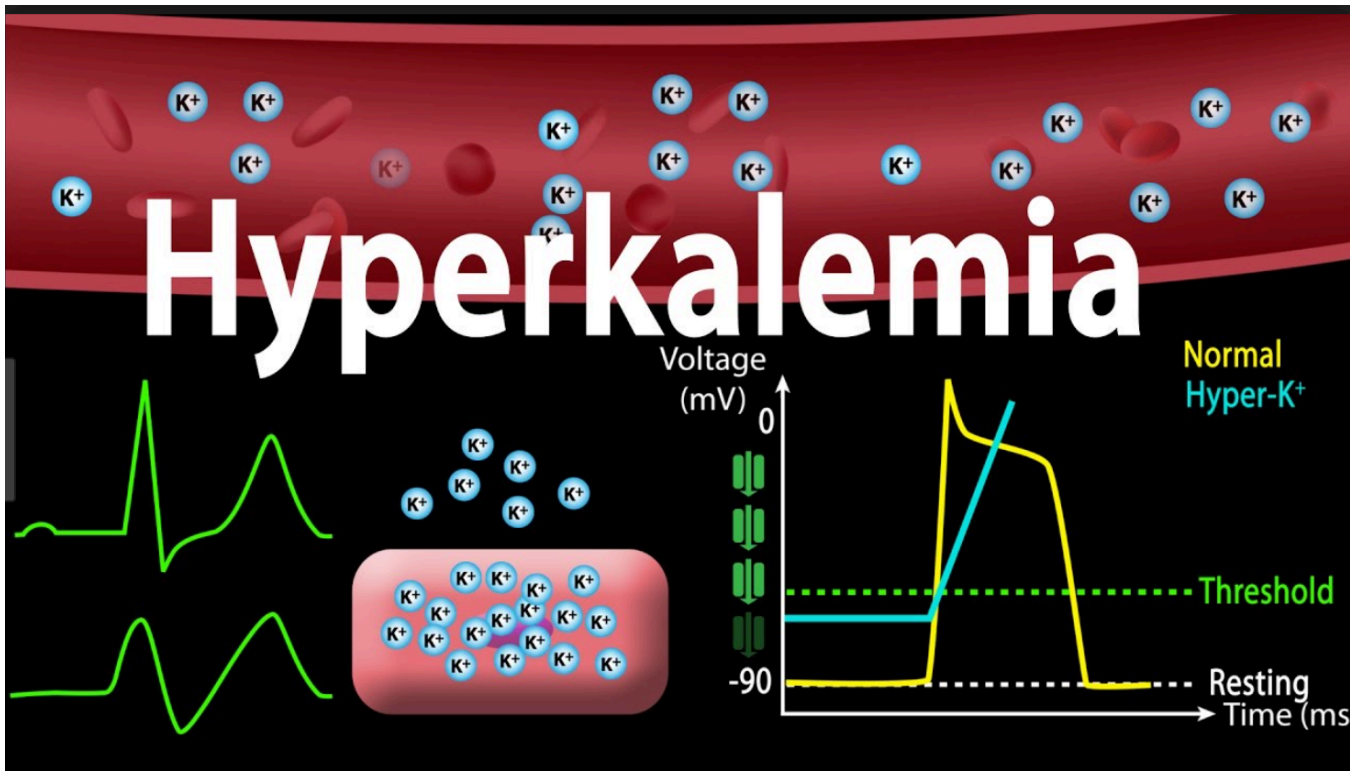
Potassium chloride is the usual choice for supplementation.

Potassium acetate or potassium citrate for patients with acidosis and hypokalemia

Potassium phosphate if hypophosphatemia is present

Potassium-sparing diuretics-

ACE – Inhibitors/ARB



Hyperkalemia is routinely defined as a serum potassium level >5 mmol/L

The PARADIGM-HF trial suggest the incidence of hyperkalemia was $\approx 16\%$ over a median follow-up time of 27 months, despite a highly selected and carefully monitored clinical trial population.

Hyperkalemia in CHF

“One of the few things one can die from without any symptoms...”

Causes

Medications

Spurious

Increased Intake

Decreased Excretion

Transcellular shifts

RASi (i.e. ACE-I and ARB)
in heart failure patients

Initiate with caution in patients with: Renal dysfunction (creatinine >3mg/dl), high potassium >5.0 mmol/L or bilateral renal artery stenosis.

Check potassium and renal function

1-2
weeks

Every 3-6
months



Discontinue or dose decrease for potassium >5.5mmol/L. Carefully reintroduce as soon as possible.

MRA in heart failure patients

Initiate with caution in patients with: Renal dysfunction (creatinine ≥ 2.5 mg/dL or GFR <30 mL/min/1.73 m²), high potassium >5.0mmol/L.

Check potassium and renal function

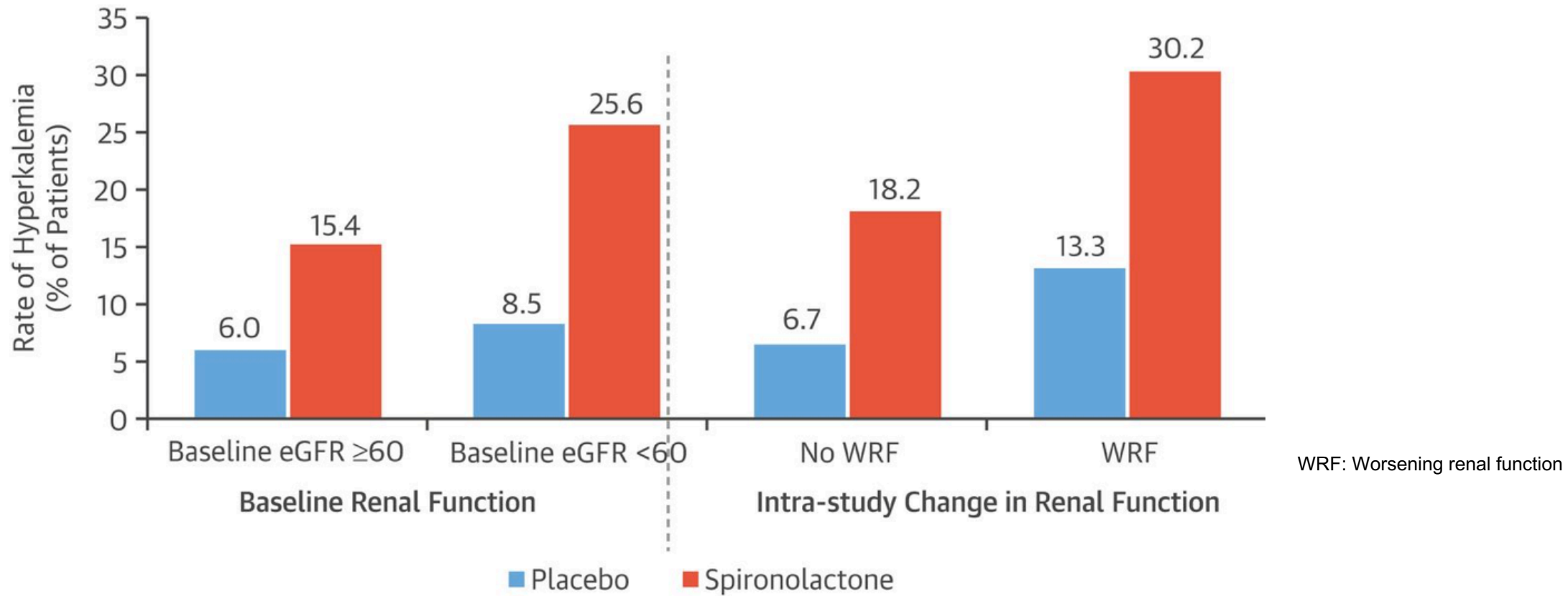
1
week

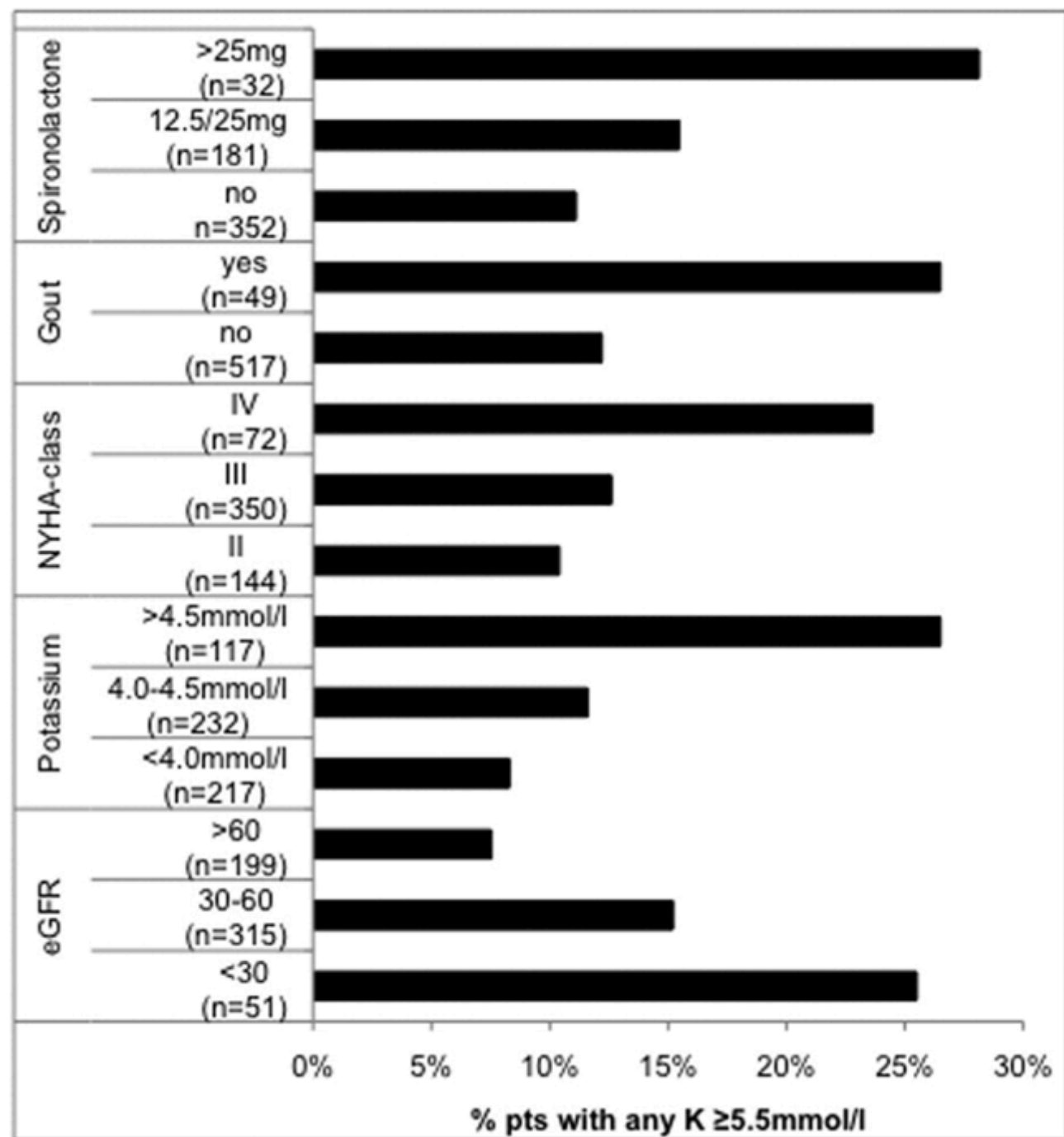
4
weeks

Every 3-6
months



Discontinue or dose decrease for potassium >5.5mmol/L. Carefully reintroduce as soon as possible.



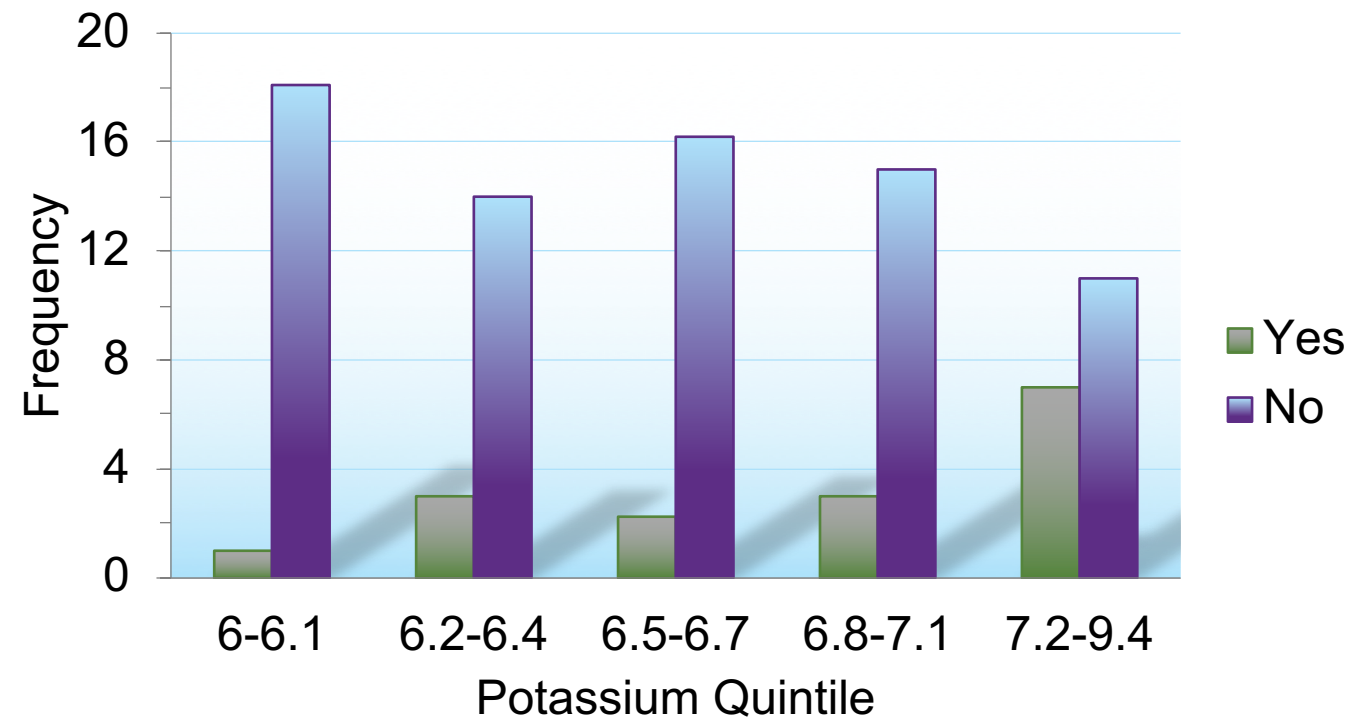


Poor Sensitivity and Specificity of ECG as Diagnostic Test for Hyperkalemia

- In 127 patients with serum K⁺ between 6-9.3 mEq/L, only 46% of ECGs noted to have changes¹
- In 90 cases, only 24 noted to have characteristic T-wave changes as read by a cardiologist²
- Only 1/14 who presented with arrhythmias or arrest had strict criteria²

ECG, electrocardiogram.

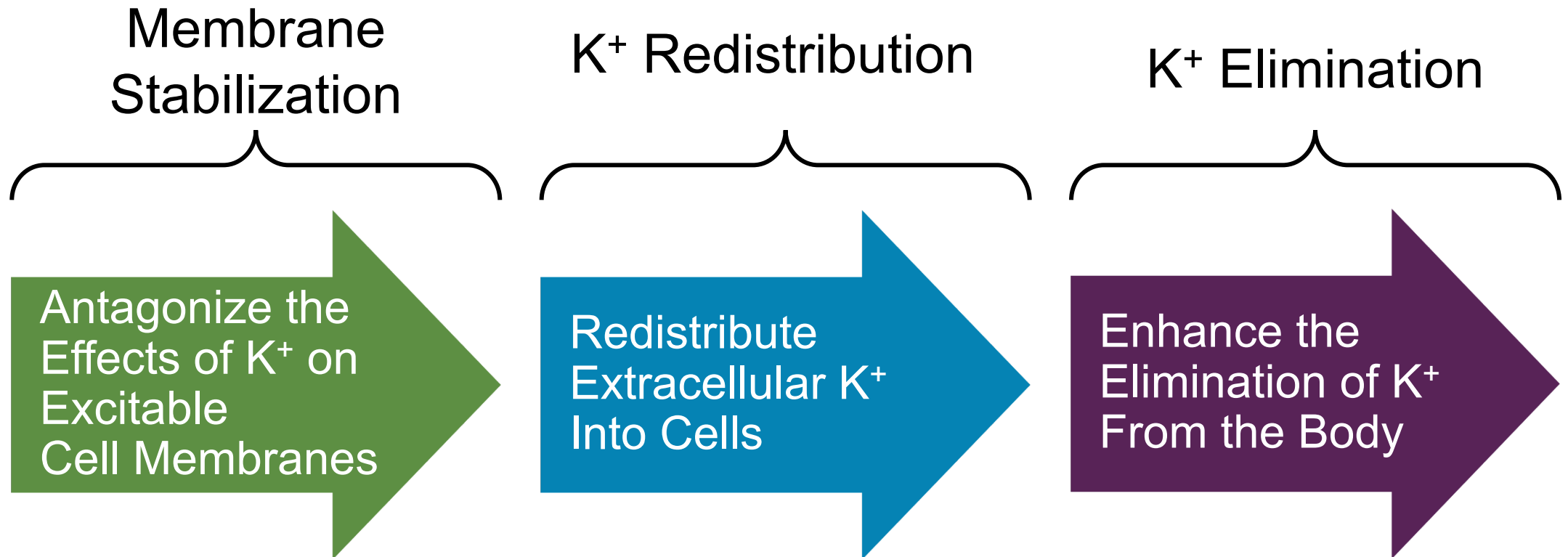
Potassium quintiles by presence of strict criteria for ECG changes



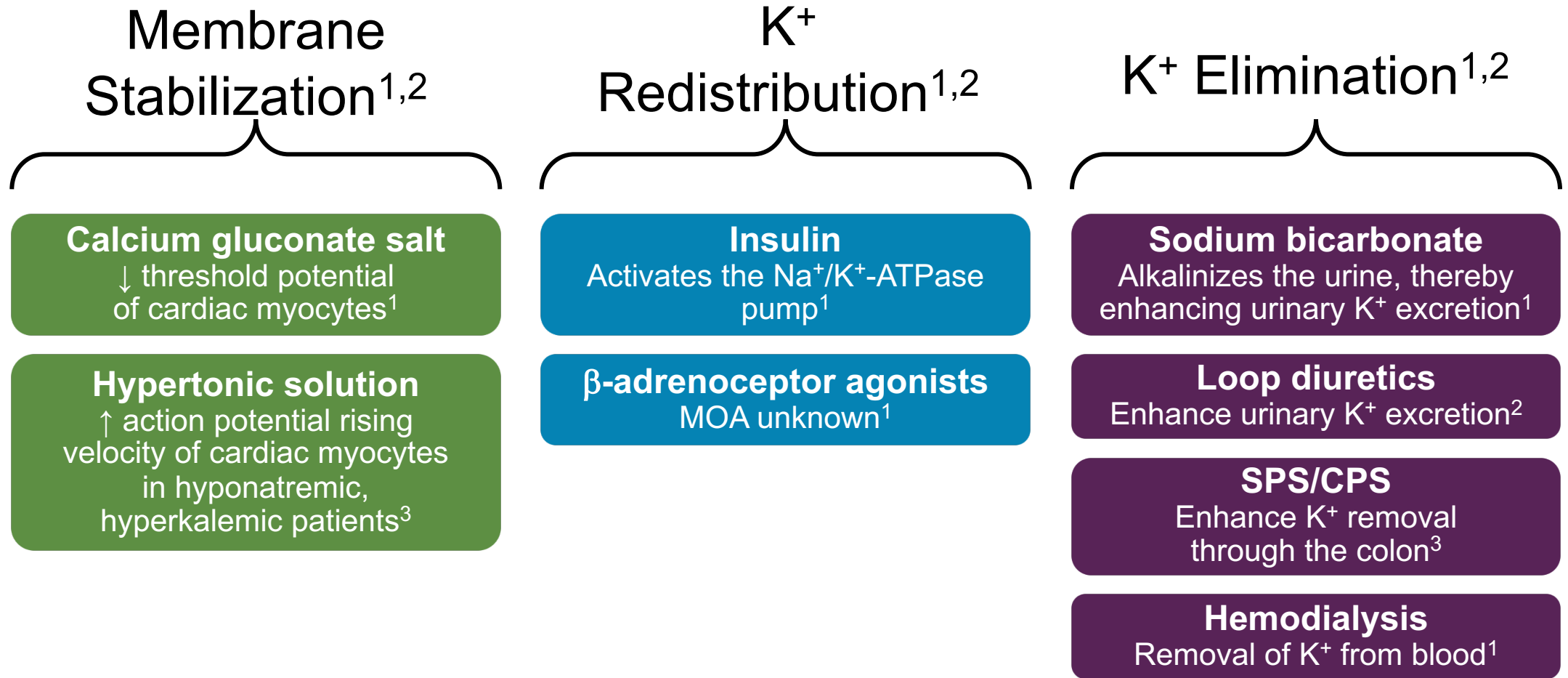
1. Acker CG, et al. *Arch Intern Med.* 1998;158:917-924.

2. Montague BT, et al. *Clin J Am Soc Nephrol.* 2008;3:324-330.

Goals of Therapy to Treat Acute Hyperkalemia



Therapies to Treat Acute Hyperkalemia



CPS, calcium polystyrene sulfonate; MOA, mechanism of action; SPS, sodium polystyrene sulfonate.

1. Modified from Weisberg LS. *Crit Care Med.* 2008;36(12):3246-3251.

2. Modified from Floege J, Johnson RJ, Feehally J, eds. *Comprehensive Clinical Nephrology.* St. Louis, MO: Mosby; 2010.

3. Ballantyne F 3rd, Davis LD, Reynolds EW Jr. *Am J Physiol.* 1975;229(4):935-940.

Characteristic	Sodium Polystyrene Sulfonate	Patiromersorbitex Calcium	Sodium Zirconium Cyclosilicate	
FDA approval	Approved as Kayexalate	Approved as Veltassa	Under review Lokelma	? CADTH
Structure	Benzene, diethenyl-polymer, with ethenylbenzene, sulfonated, sodium salt, organic polymer	100-µm bead, organic polymer	Octahedral, micropore ring 3Å diameter, inorganic crystal	
Administration	15-60 g, up to 4 times daily (85)	8.4 g once daily and can be advanced to 16.8 g to 25.2 g at weekly intervals	5–15 g, once daily, oral (71)	
Normalize serum K ⁺	Variable and not known	48 to 72 h (60) Vifor Innomar	2.2 h (mean) AstraZeneca	



NEW TREATMENTS FOR HYPERKALEMIA: Patiromer (RLY5016) and Sodium zirconium cyclosilicate (ZS-9)

Positive effects:

- Normalizes and maintains potassium levels
- Efficacy in heart failure
- Reduces aldosterone levels and blood pressure

Side Effects:

- Drug-drug interactions
- Edema (at high doses of ZS-9)
- Constipation, diarrhea, flatulence, nausea
- Hypomagnesemia
- Hypokalemia

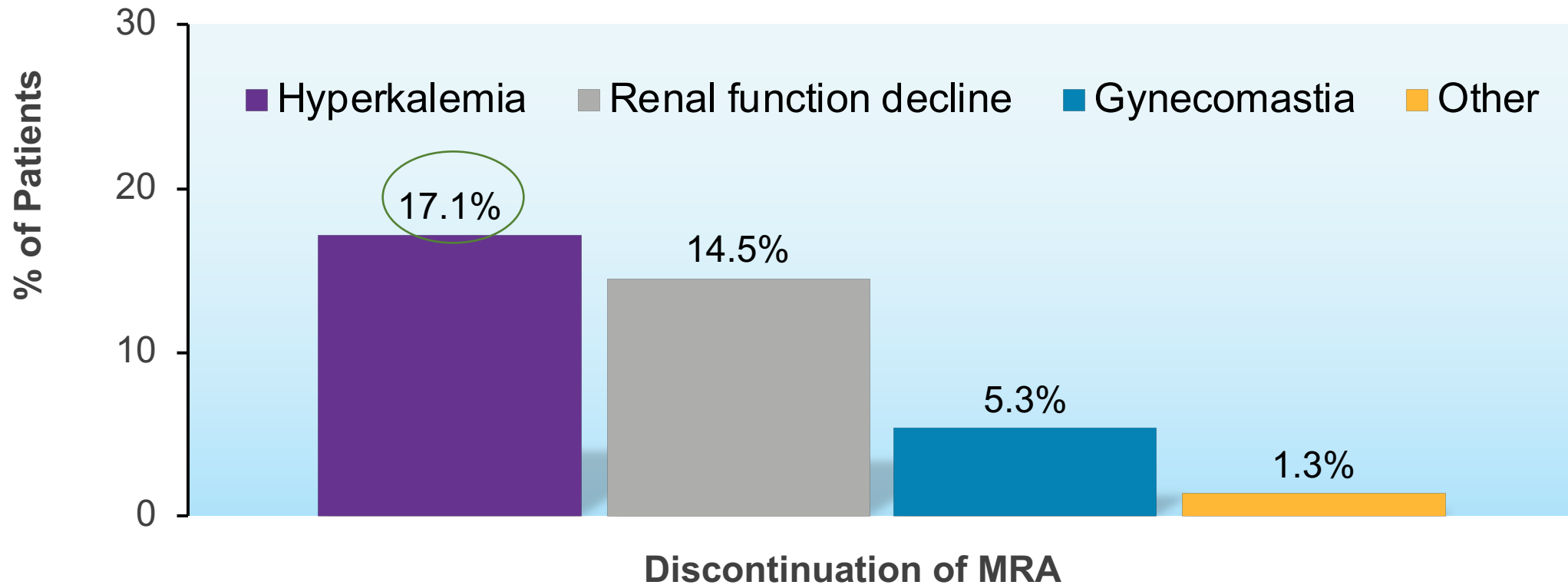
Evidence gaps:

- *Prevention* of hyperkalemia
- Limitation of RAASi optimization due to hypotension or worsening renal function
- Safety and efficacy of RAASi optimization in patients excluded from previous trials
- Safety and efficacy of RAASi use at higher doses than used in previous trials

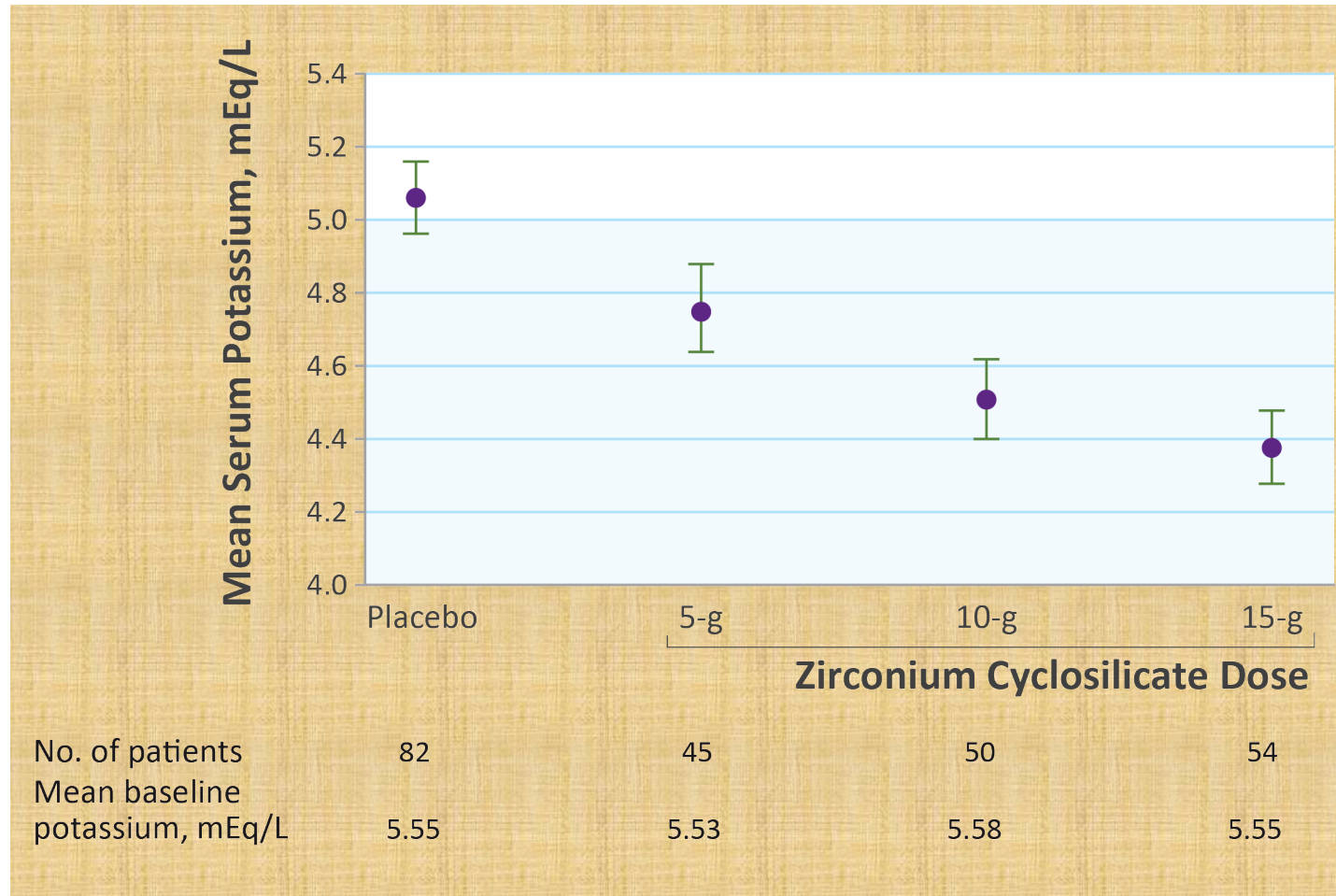
Hyperkalemia Is a Major Reason for Discontinuation of MRA

- 134 HF patients followed in a Portuguese HF clinic
- Spironolactone use in patients with SCr ≤ 2.5 mg/dL and K⁺ ≤ 5 mEq/L
- 25% of patients withdrew from spironolactone therapy (19/76)

Reason for spironolactone suspension (%)

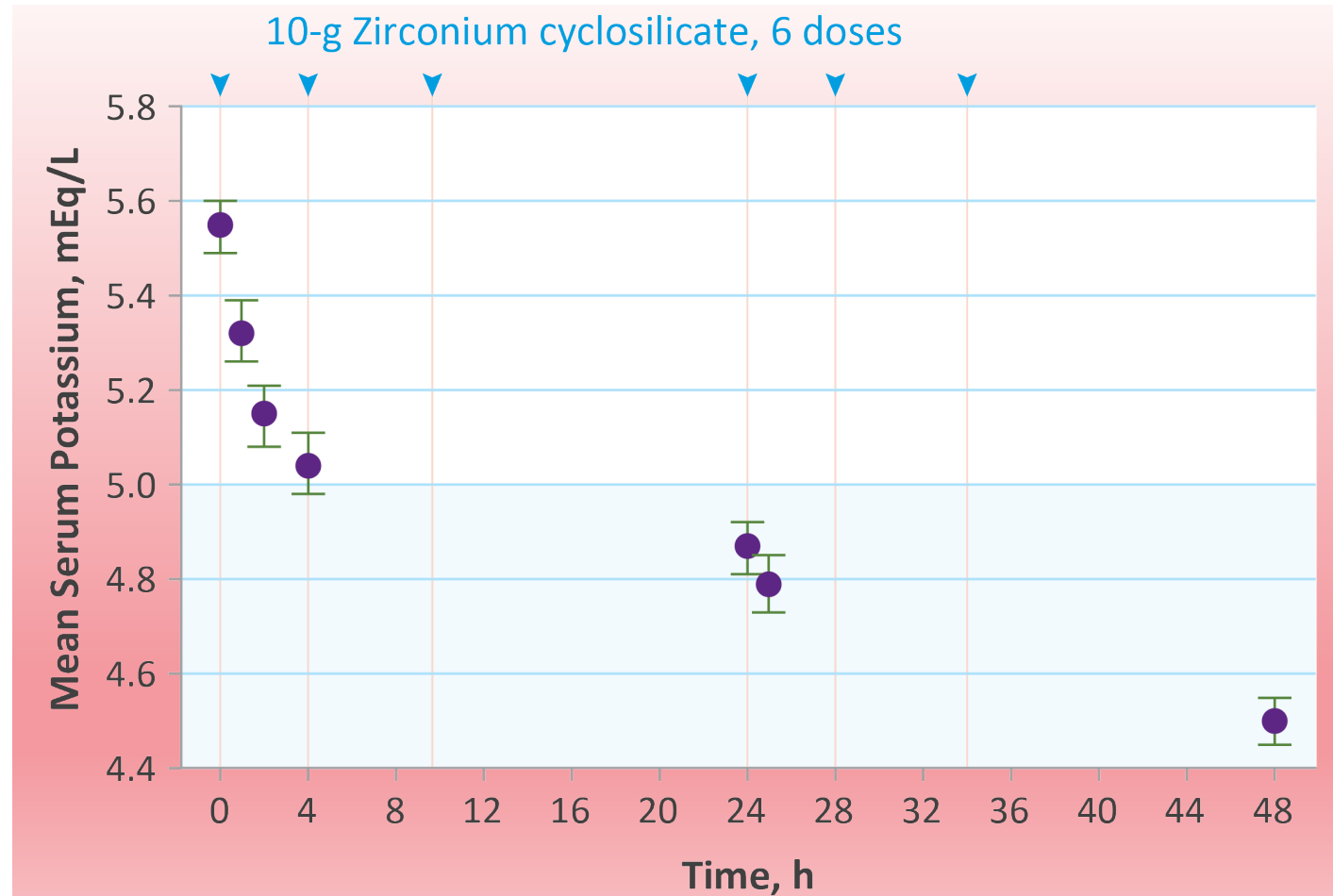


Serum Potassium Levels During the Randomized Phase (Days 8–29) According to Study Group

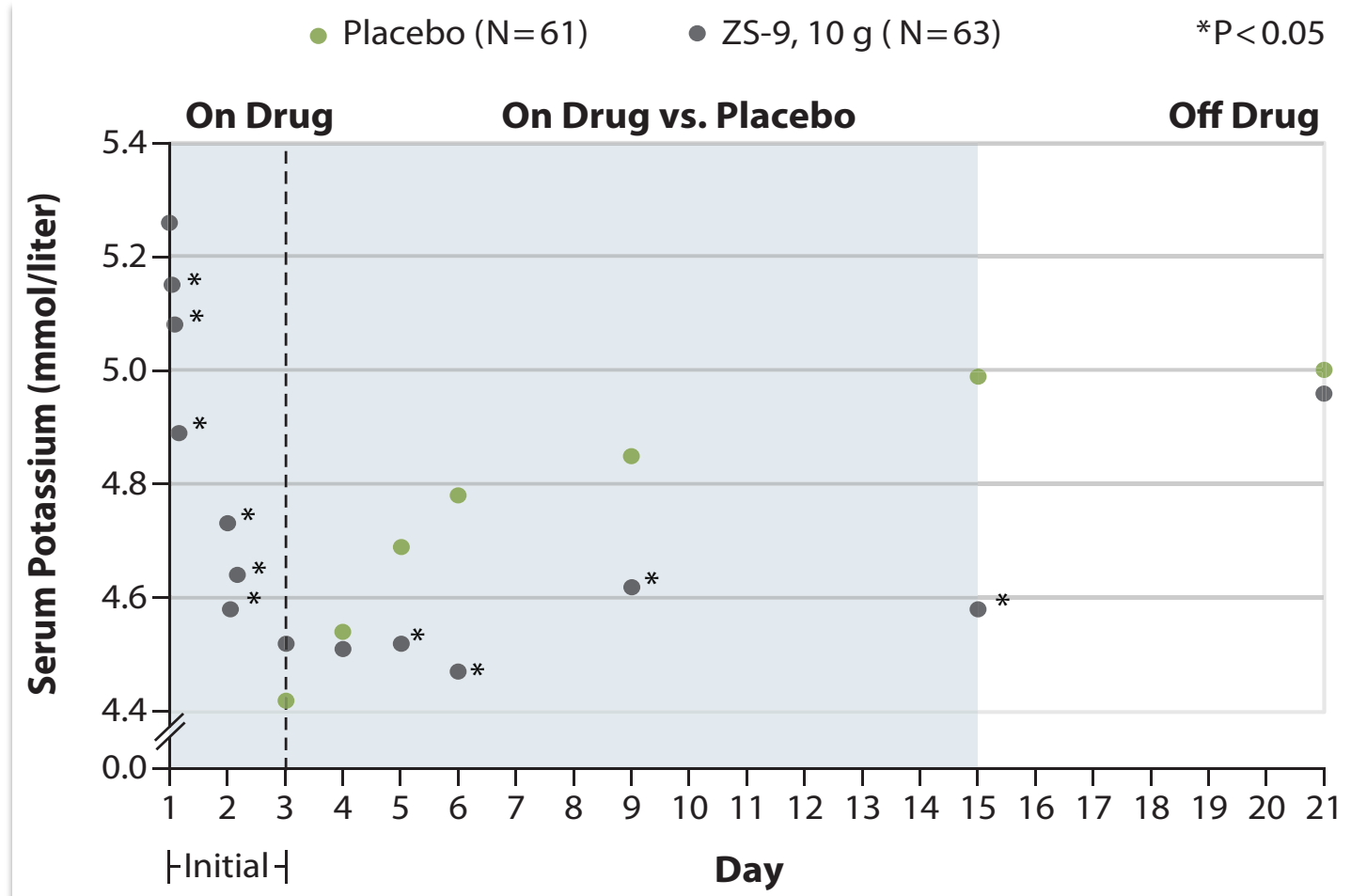


Kosiborod M, et al. *JAMA*. 2014;312(21):2223-2233.

Serum Potassium Levels During the Open-Label Phase (48 hours)



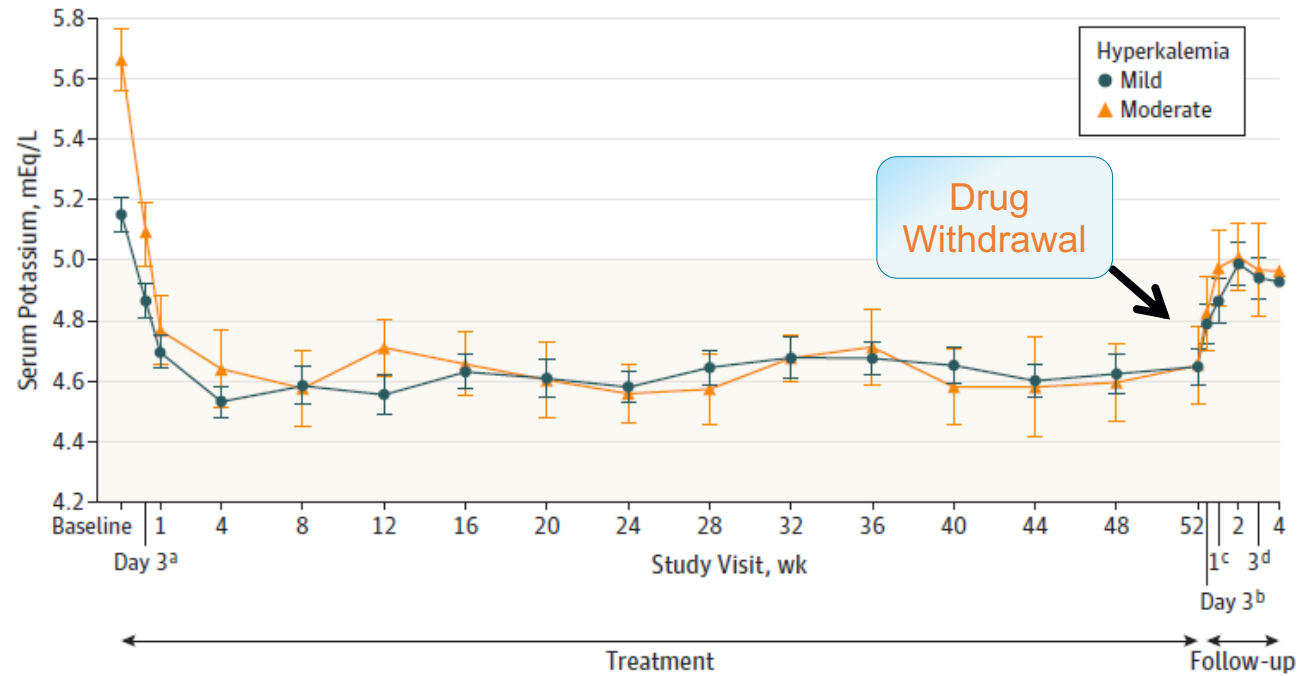
Potassium Levels with Sodium Zirconium Cyclosilicate 10 g Once-Daily During Phase 2



From "Sodium Zirconium Cyclosilicate in Hyperkalemia",
David K. Packham, 352, 3, 222-231 copyright © NEJM, Reprinted with permission from Massachusetts Medical Society

Effect of Patiromer on Serum Potassium Level: AMETHYST-DN (52 weeks)

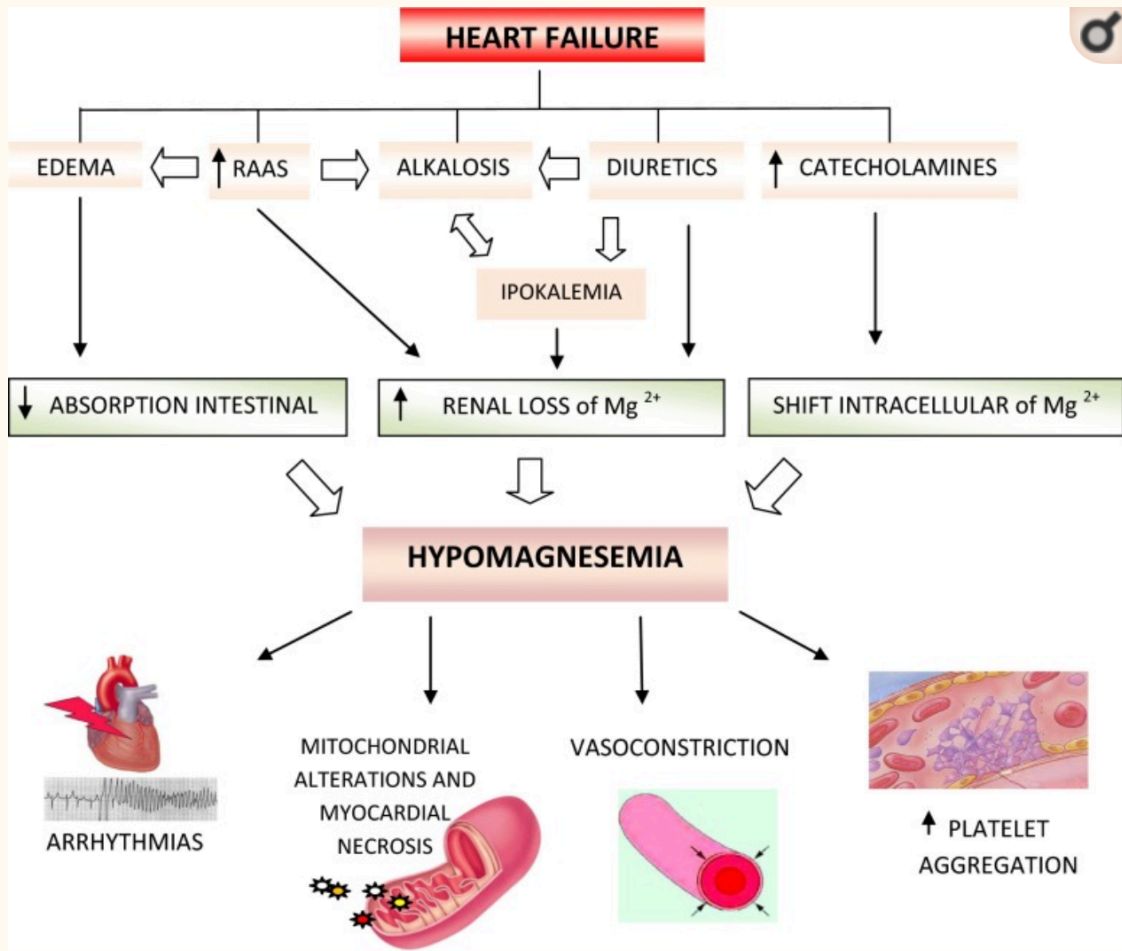
Figure 3. Least Squares Mean (95% CI) Serum Potassium Levels Over 52 Weeks and During Posttreatment Follow-up in Patients With Mild or Moderate Hyperkalemia (Post Hoc Mixed-Effects Models for Repeated-Measures Analysis)



No. of patients																	
Hyperkalemia																	
Mild	218	204	199	192	175	168	161	161	163	158	156	151	148	149	145	131	126
Moderate	83	83	73	70	65	62	62	62	61	53	53	53	52	49	49	48	47

Strategies to Overcome Cardiorenal Syndrome

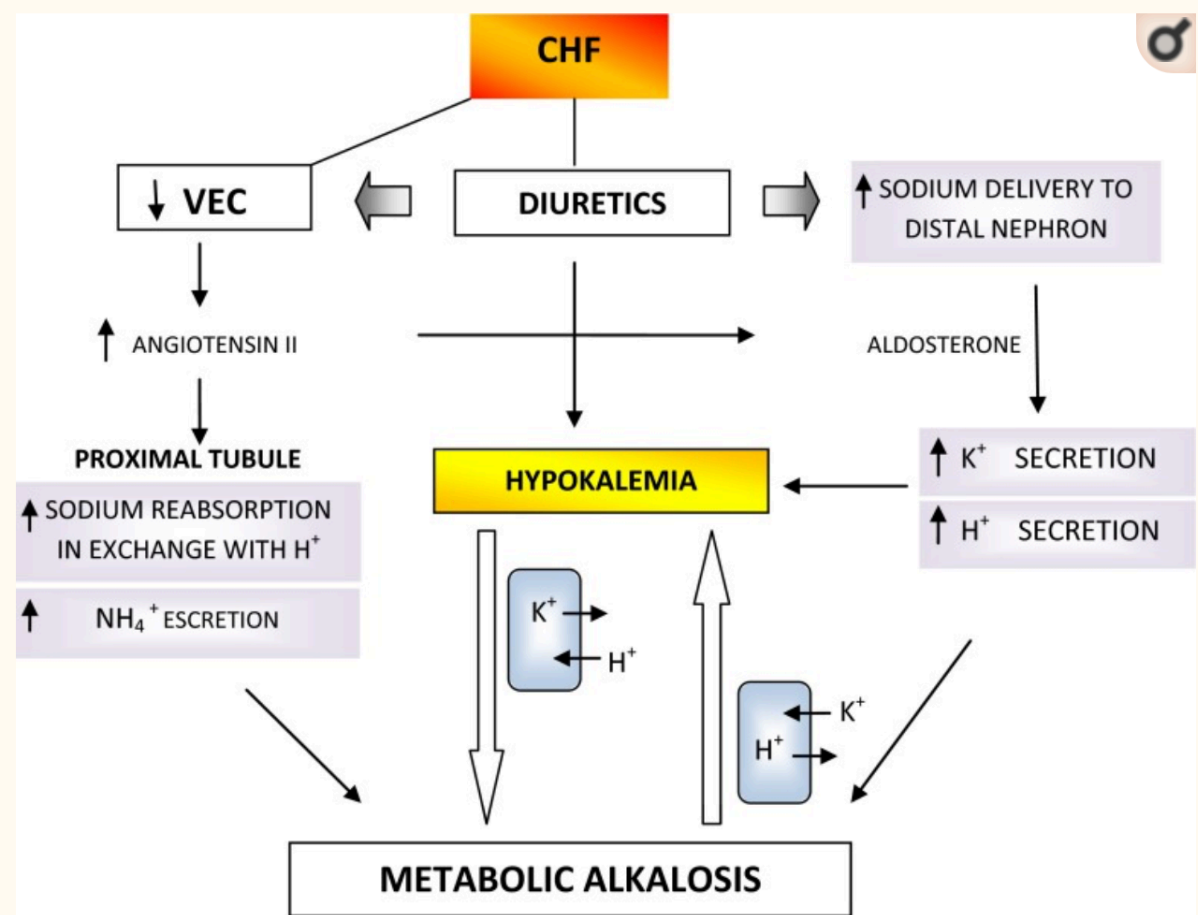
- Avoid Hypotension
- Avoid “over diuresis” and allow adequate time for circulatory “refill”
- Addition of thiazide-type diuretics should be considered when a progressive decrease in loop diuretic efficacy is observed; Add to block distal tubule
- Reduce CVP and TR
- Improve RV function when possible: reduce PVR, support RV function
- MRA: use natriuretic dose (> 25 mg spironolactone). Peak effect 48 hours; use with loop diuretic
- Reduce Intra abdominal pressure: paracentesis



[Open in a separate window](#)

Fig. 3

Pathogenesis and effects of hypomagnesemia in CHF. RAAS renin–angiotensin–aldosterone system



Prognosis

- Hyponatremia is an independent predictor of morbidity and mortality in CHF
- Hypokalemia is an independent predictor of sudden cardiac death
- Hyperkalemia is more prevalent than usually thought and often associated with disease modifying drug withdrawal
- Serum magnesium is not an independent risk factor of death in patients with moderate to severe CHF

Thank you !