HEART FAILURE UPDATE 2021 VIRTUAL

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Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

Treatment of the Diuretic Resistant Patient with Acute Heart Failure

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Conflict of Interest Disclosures

- **Grants/research support**: Boehringer-Ingelheim
- **Consulting fees**: Boehringer-Ingelheim, Novartis, Servier
- **Speaker fees**: Astra Zeneca
- **Other**:

Objectives

- 1. Understand the contributors to diuretic resistance in patients with volume overload.
- 2. Describe a stepped approach to diuretic management in the resistant patient.
- 3. Describe potential alternatives to traditional diuretic treatment for volume overload.

OBJECTIVE 1:

CONTRIBUTORS TO DIURETIC RESISTANCE IN PATIENTS WITH ACUTE HEART FAILURE

Case: Ms. Anne Uric

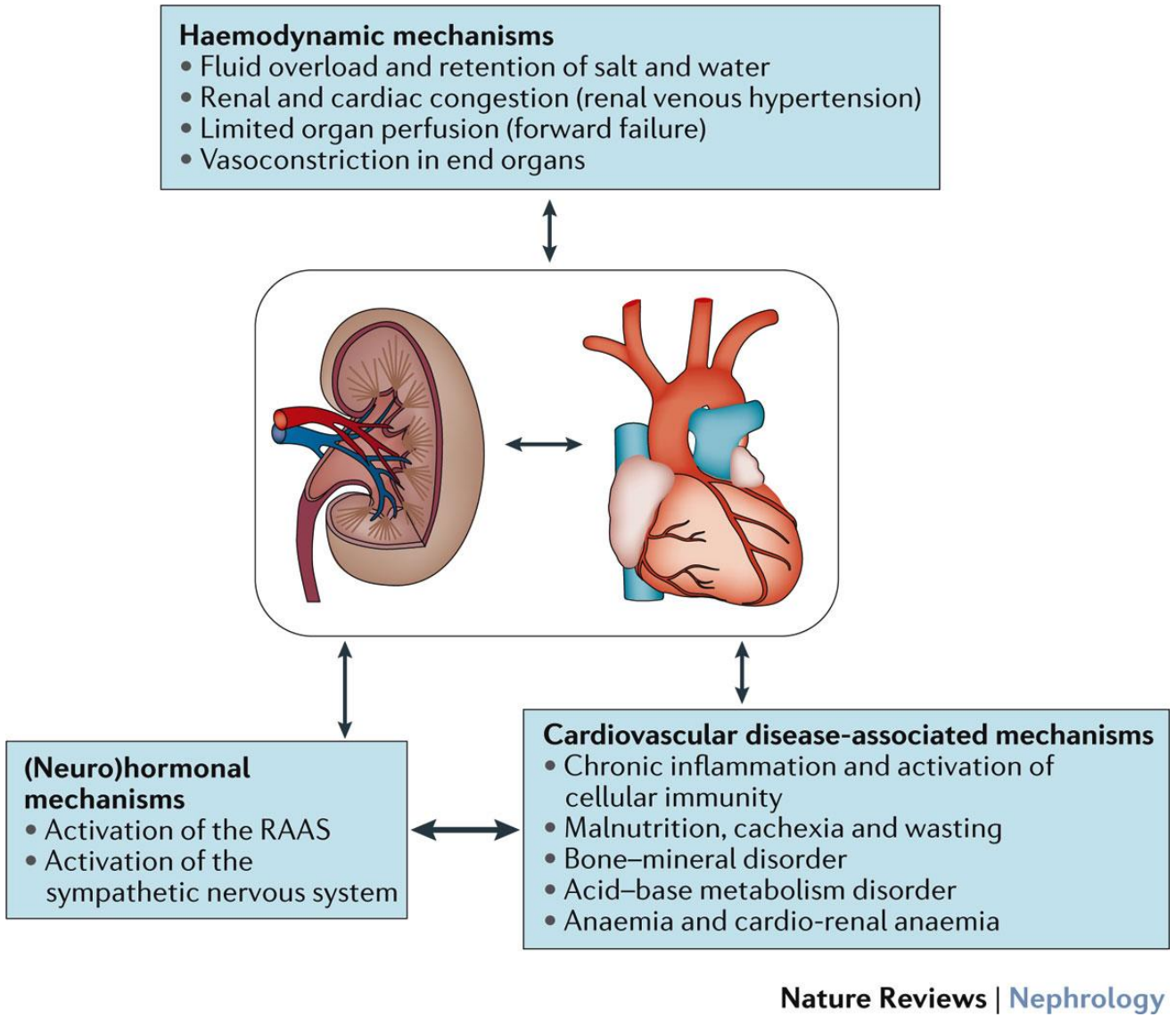
- 33 year old woman
- Past medical history:
  - Bioprosthetic tricuspid and mitral valve replacements (2018) for infective endocarditis, complicated by embolic events including anterior MI requiring PCI to LAD
  - Now has severe biventricular dysfunction (LVEF 27%) with failing bioprosthetic valves as a result of recurrent endocarditis due to ongoing iv drug use (IVDU)
  - Not a candidate for advanced therapies due to medication non-adherence and IVDU
- To ER with increasing dyspnea, worsening lower limb edema and 1 episode of vomiting
- Had been taking ibuprofen for generalized “muscle aches” and furosemide 80 mg BID at home
- On examination: 109/80 mmHg, 86 beats/min, 98% on 3L nasal prongs, JVP 5 cm above the sternal angle, moderate pitting edema to mid-shins
- Labs: hemoglobin 101 (stable), wbc 5.1, platelets 270, sodium 137, potassium 2.5, creatinine 166 (baseline), lactate 1.5

- Admitted to GIM ward with decompensated heart failure (HF)
- Given furosemide 80 mg iv in ER and ibuprofen stopped
- Next day, creatinine increased to 214
- Furosemide held, since patient appeared euvolemic and hemodynamically still stable
- Two days later: creatinine up to 355, potassium 6.8, lactate 4.1
- Transferred to ICU, Cardiology and Nephrology consulted

Ms. Anne Uric: ICU

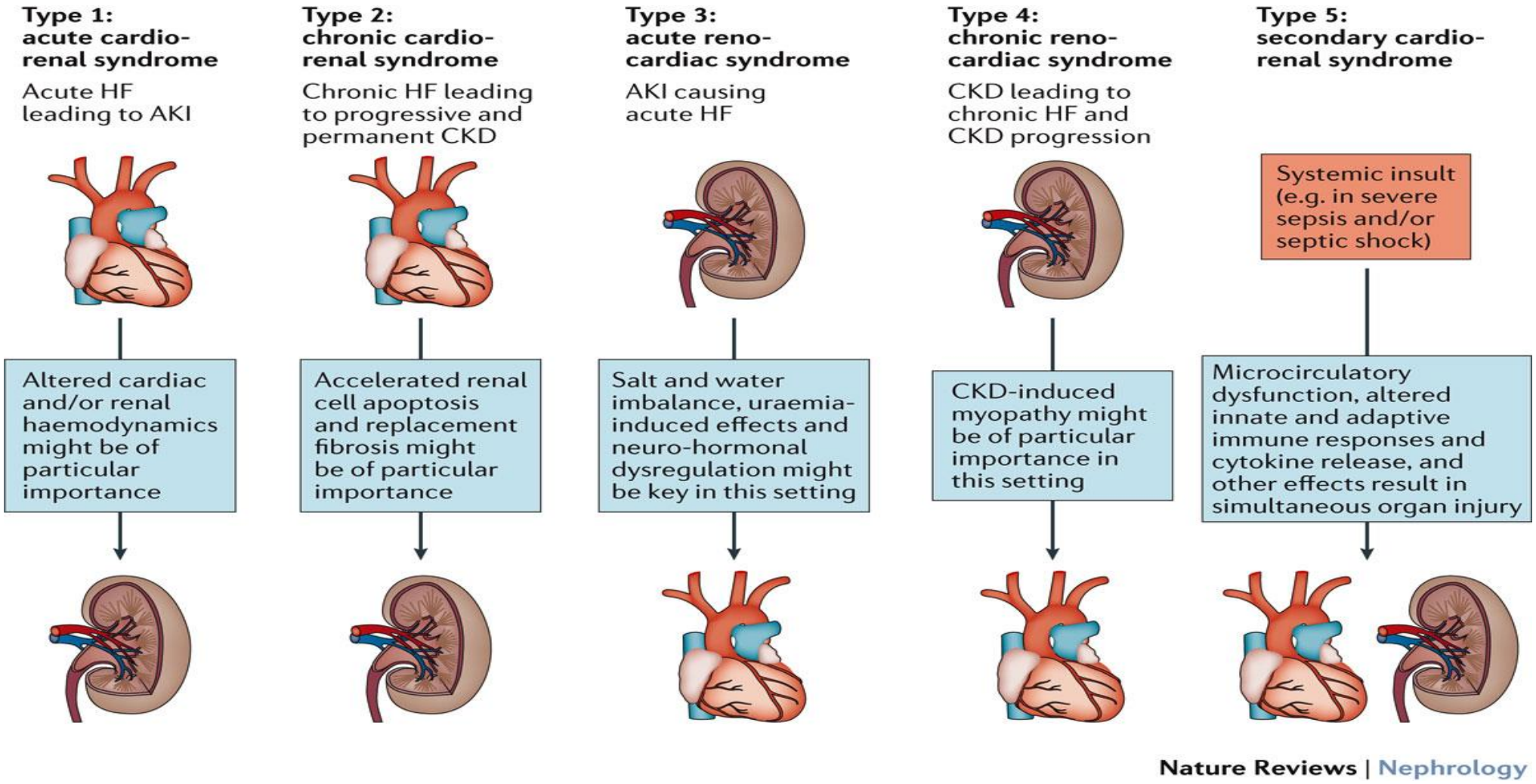
- Potassium shifted by ICU team
- Patient given furosemide 80 mg iv and started on furosemide infusion at 20 mg/h
- On examination: 108/71 mmHg, 85 beats/min, 95% 2L NP
- Urine output only 20-30 cc/h and fluid balance positive 750 cc for past 24 hours
- Labs: sodium 135, potassium 5.7, creatinine 344, lactate 2.1
- **What should we do next?**

Overview of Key Cardio-Renal Interactions



Schefold, J. C. *et al.* (2016) Heart failure and kidney dysfunction: epidemiology, mechanisms and management *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2016.113

Definitions of Cardio-renal Syndromes (CRS)



Schefold, J. C. *et al.* (2016) Heart failure and kidney dysfunction: epidemiology, mechanisms and management
Nat. Rev. Nephrol. doi:10.1038/nrneph.2016.113

Reasons for Worsening Kidney Function in CRS

- Patients with heart failure (HF) may be unable to generate forward blood flow, resulting in kidney hypoperfusion and activation of the renin-angiotensin-aldosterone system (RAAS)
- Activation of the RAAS leads to further salt and water retention, increased preload, and worsening pump failure.
- Conversely, medications used in the treatment of HF, such as diuretics and RAAS inhibitors, can also worsen kidney function
- Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic

Auguste BL et al. *Can J Kidney Health Dis*. 2020;7:2054358120979239.
Hoorn EJ and Ellison DH. *Am J Kidney Dis*. 2017;69:136-42.

Common Causes of Diuretic Resistance

- **Nonadherence to recommended sodium and/or fluid restriction**
- **Drug not reaching the kidney**
  - Nonadherence
  - Dose too low or too infrequent
  - Poor absorption
- **Reduced diuretic secretion**
  - Tubular uptake of diuretic impaired by uremic toxins
  - Decreased kidney blood flow
  - Decreased functional kidney mass
- **Insufficient kidney response to drug**
  - Low glomerular filtration rate
  - Decreased effective intravascular volume despite elevated total extracellular fluid volume
  - Activation of the renin-angiotensin system
  - Nephron adaptation
  - Use of nonsteroidal anti-inflammatory drugs

Hoorn EJ and Ellison DH. *Am J Kidney Dis*. 2017;69:136-42.

OBJECTIVE 2:

MEDICAL MANAGEMENT OF AKI AND CRS

Basic Principles of Medical Management for AKI and CRS

- 1. Optimize hemodynamics and fluid balance
- 2. Avoid or discontinue potential nephrotoxins (ex. aminoglycosides, NSAIDs, iodinated radiocontrast).
- 3. Consider holding RAAS inhibitors during severe AKI, since they can reduce GFR
  - However, RAAS inhibitors have beneficial effects in patients with cardiovascular disease, so continuing these medications initially may be reasonable during mild AKI and CRS
- 4. Avoid excessive fluid administration to prevent harmful volume overload.

CARRESS-HF: Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

- 188 patients with acute decompensated heart failure, worsened renal function, and persistent congestion.
- Stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients).
- Primary endpoint: bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after random assignment.
- Patients were followed for 60 days.

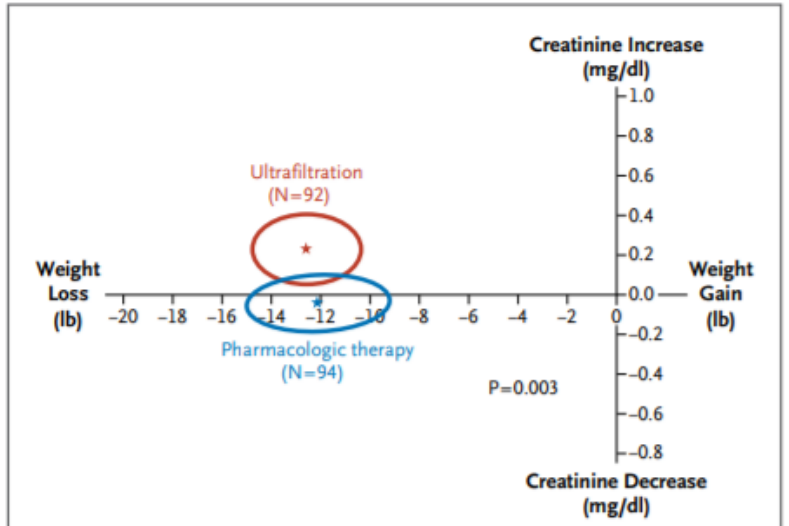


Figure 1. Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).

The ellipses represent the 95% confidence regions and the stars the exact values for the mean changes in the serum creatinine level and weight at 96 hours in the ultrafiltration group and the pharmacologic-therapy group. Data from two patients who had been randomly assigned to the ultrafiltration group were excluded from the analysis: baseline creatinine measurements were missing for one patient, and all post-baseline creatinine measurements were missing for the other patient. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for weight to kilograms, multiply by 0.45.

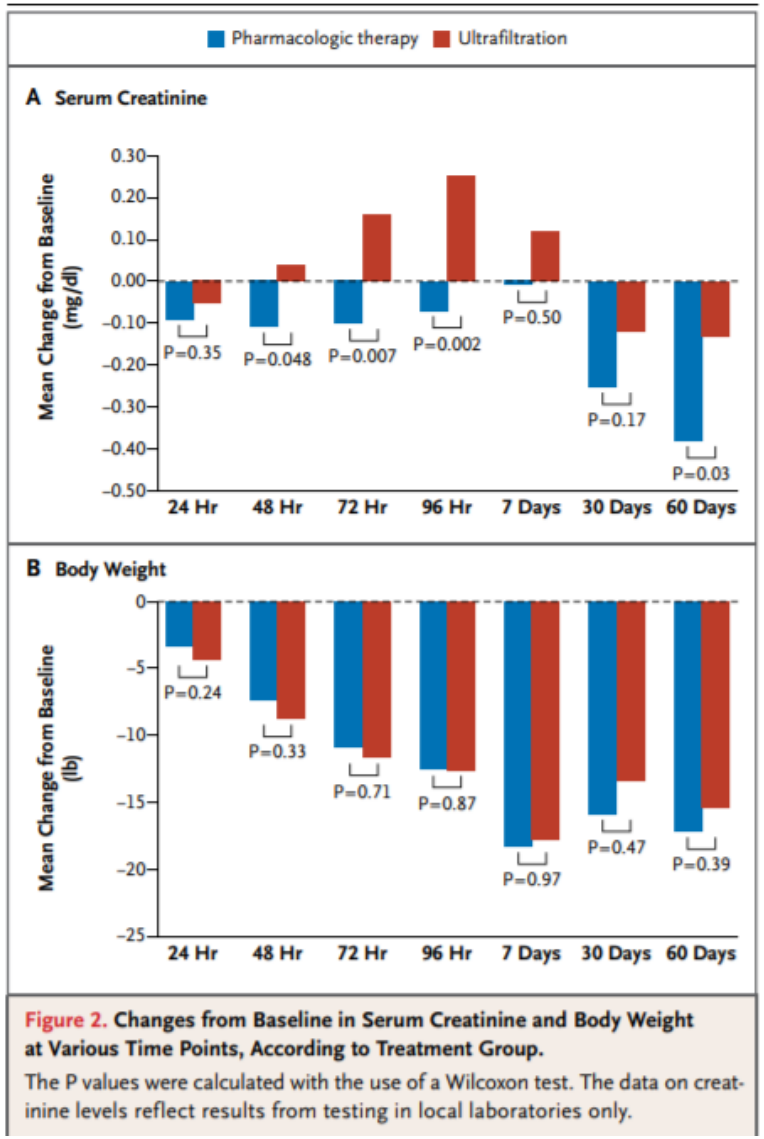
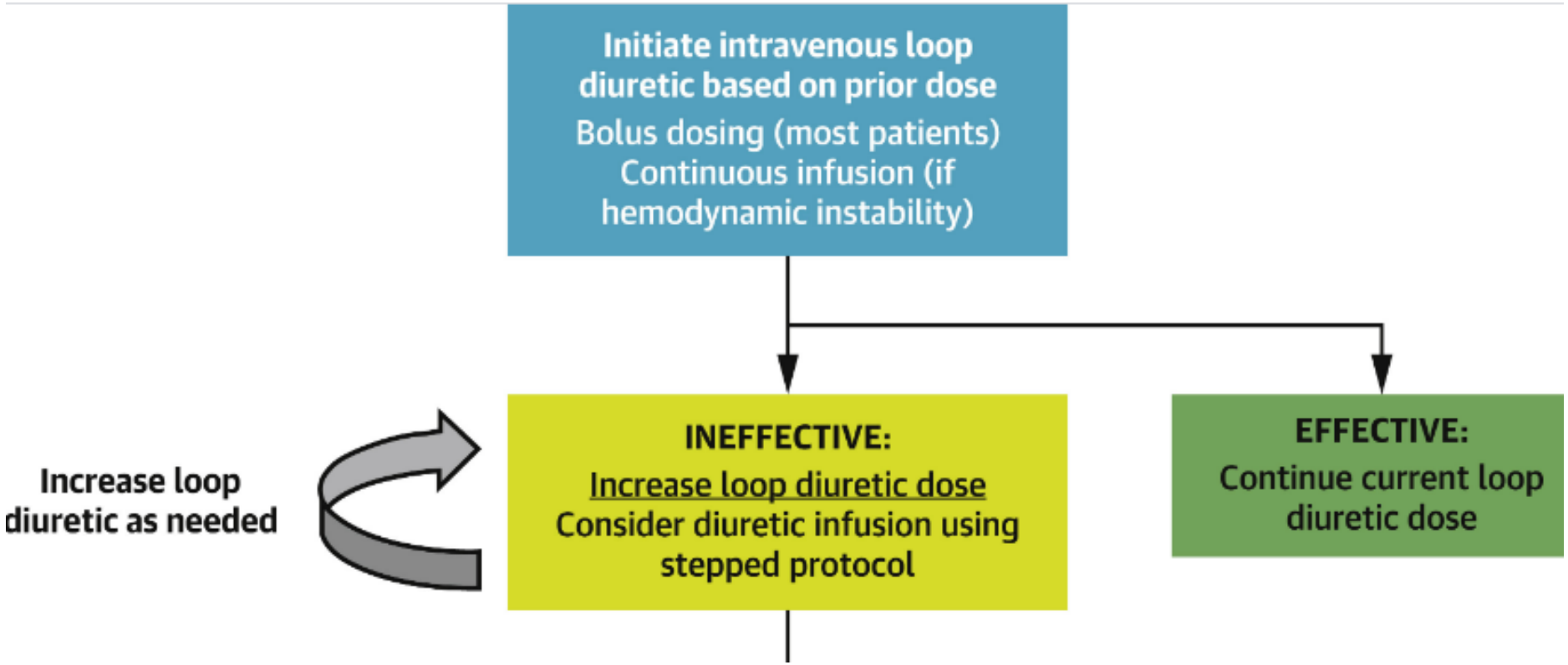


Figure 2. Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group.

The P values were calculated with the use of a Wilcoxon test. The data on creatinine levels reflect results from testing in local laboratories only.

[1]Bart BA et al. *N Engl J Med* 2012;367:2296-304

Volume Management in Patients with Acute HF and CRS



Jentzer JC et al. *J Am Coll Cardiol* 2020;76(9):1084-101.

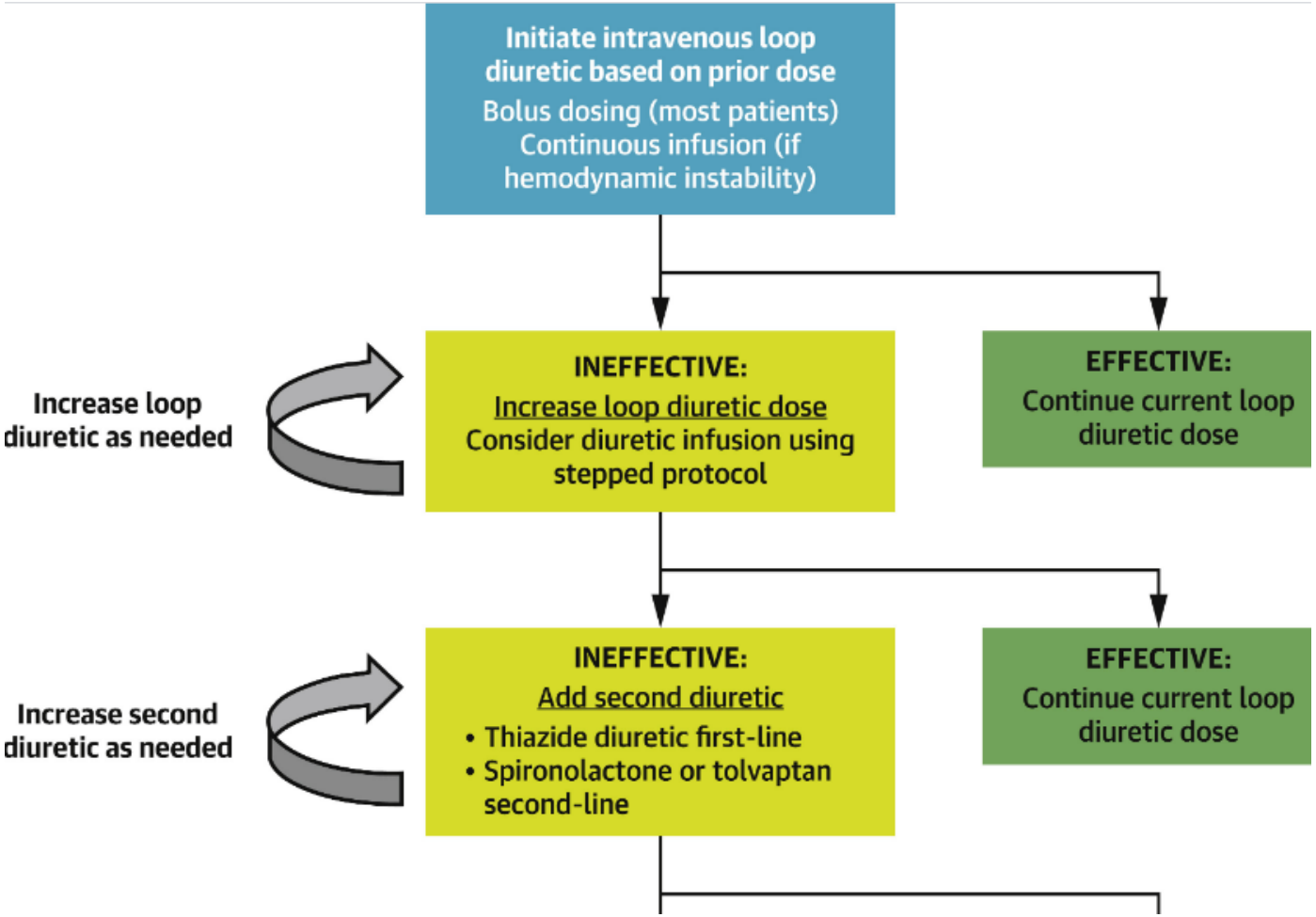
Stepped Diuretic Algorithm Used in CARRESS-HF[1]

Step	Current Diuretic Regimen		Suggested Diuretic Regimen	
	Furosemide Dose (PO)	Thiazide	Furosemide Dose (IV)	Metolazone
1	≤ 80 mg/day	+/-	40 mg + 5 mg/h	0
2	81-160 mg/day	+/-	80 mg + 10 mg/h	5 mg OD
3	161-240 mg /day	+/-	80 mg + 20 mg/h	5 mg BID
4	>240 mg/day	+/-	80 mg + 30 mg/h	5 mg BID

- The starting diuretic dose is determined by the outpatient or current inpatient diuretic dose
- Patient is moved to a higher diuretic dose if urine output is < 3L/day on current dose
- All loop diuretic doses are given in furosemide equivalents, although alternative could be used
- Vasodilator or inotrope can be added for patients who have urine output < 3L/day on Step 4

[1]Bart BA et al. *N Engl J Med* 2012;367:2296-304

Volume Management in Patients with Acute HF and CRS



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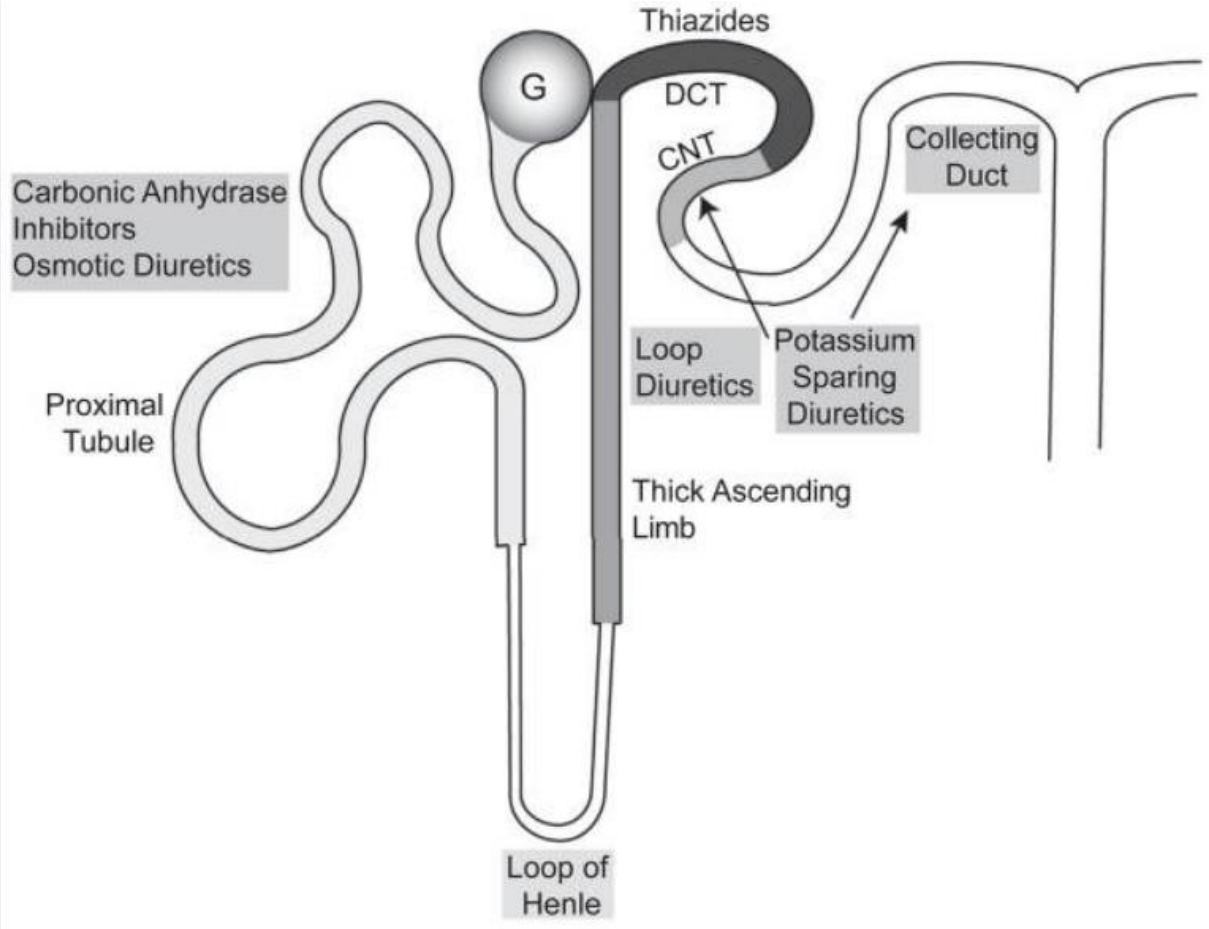
General Principles of Managing Diuretic Resistance



Schematic of a nephron shows sites of action of diuretics along the various segments. Abbreviations: CNT, connecting tubule; DCT, distal convoluted tubule; G, glomerulus.

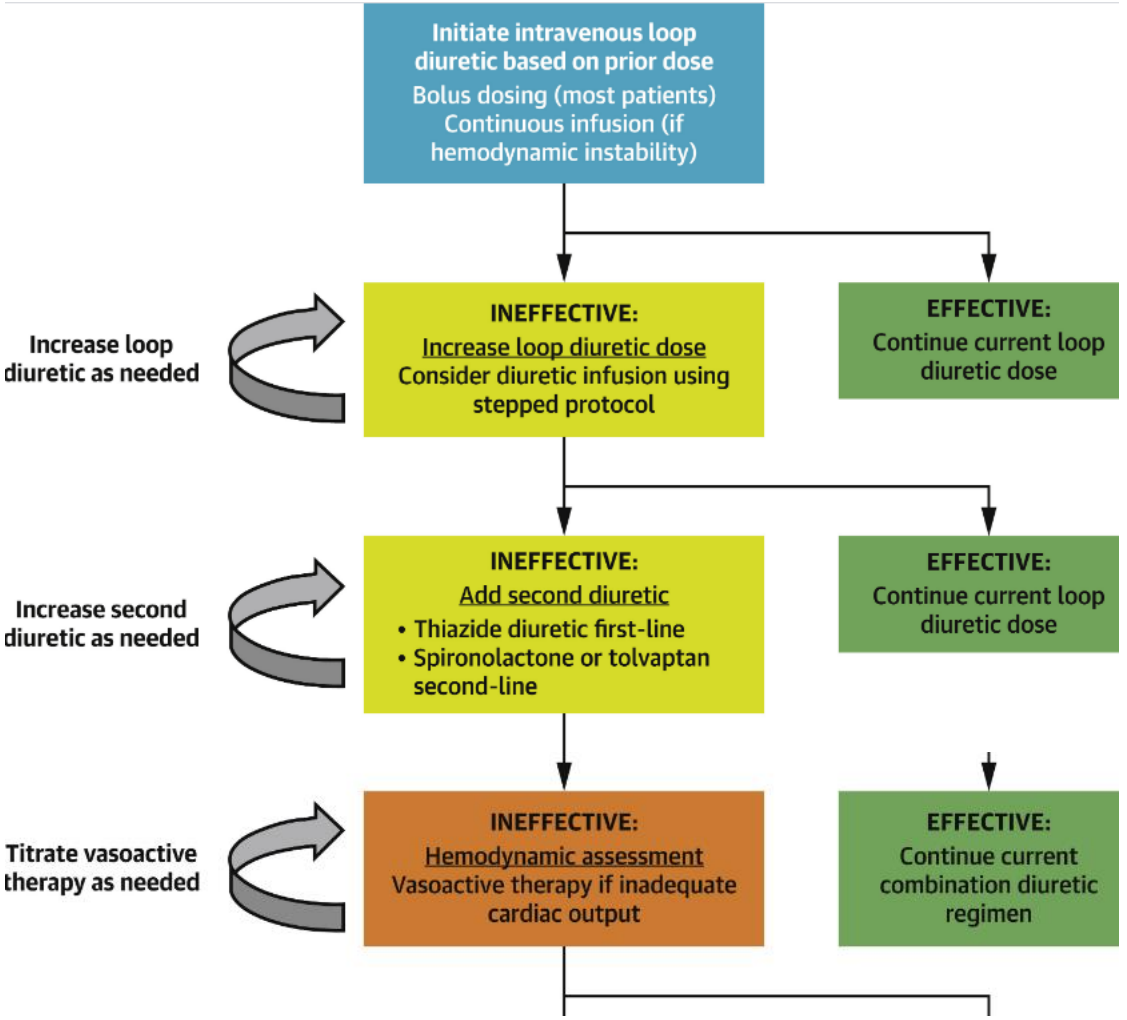
- A key strategy to overcome diuretic resistance frequently relies on combining 2 types of diuretic (diuretic synergism)
- There are several classes of diuretics, dictated by their site of action in the nephron
- Because loop diuretics are the first drug of choice in edematous disorders, this implies adding a diuretic that targets another tubular segment.
- Especially for patients with liver cirrhosis and ascites, the specific combination of furosemide and spironolactone is supported by data[2].
- For the other edematous disorders, the evidence for specific combinations of diuretics is less obvious, and usually a thiazide diuretic is recommended as a second diuretic[1].

[1]Hoorn EJ and Ellison DH. *Am J Kidney Dis*. 2017;69:136-42.
[2]Moore KP et al. *Hepatology.* 2003;38:258–266.

OBJECTIVE 3:

ALTERNATIVES TO DIURETIC TREATMENT FOR VOLUME OVERLOAD

Volume Management in Patients with Acute HF and CRS



Jentzer JC et al. *J Am Coll Cardiol* 2020;76(9):1084-101.

Use of Inotropes and Vasodilators in Treatment of AKI or CRS

- Inotropic therapy is most likely to be effective in patients with CRS who are also hypotensive and/or have objective evidence of reduced cardiac output
- Empirical use of inotropes should be avoided due to their potential toxicity
- No specific vasoactive drug has been shown to prevent or treat AKI or CRS, including inotropes or vasodilators[1, 2]

Canadian Journal of Cardiology 29 (2013) 168–181

Society Guidelines

The 2012 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Acute and Chronic Heart Failure

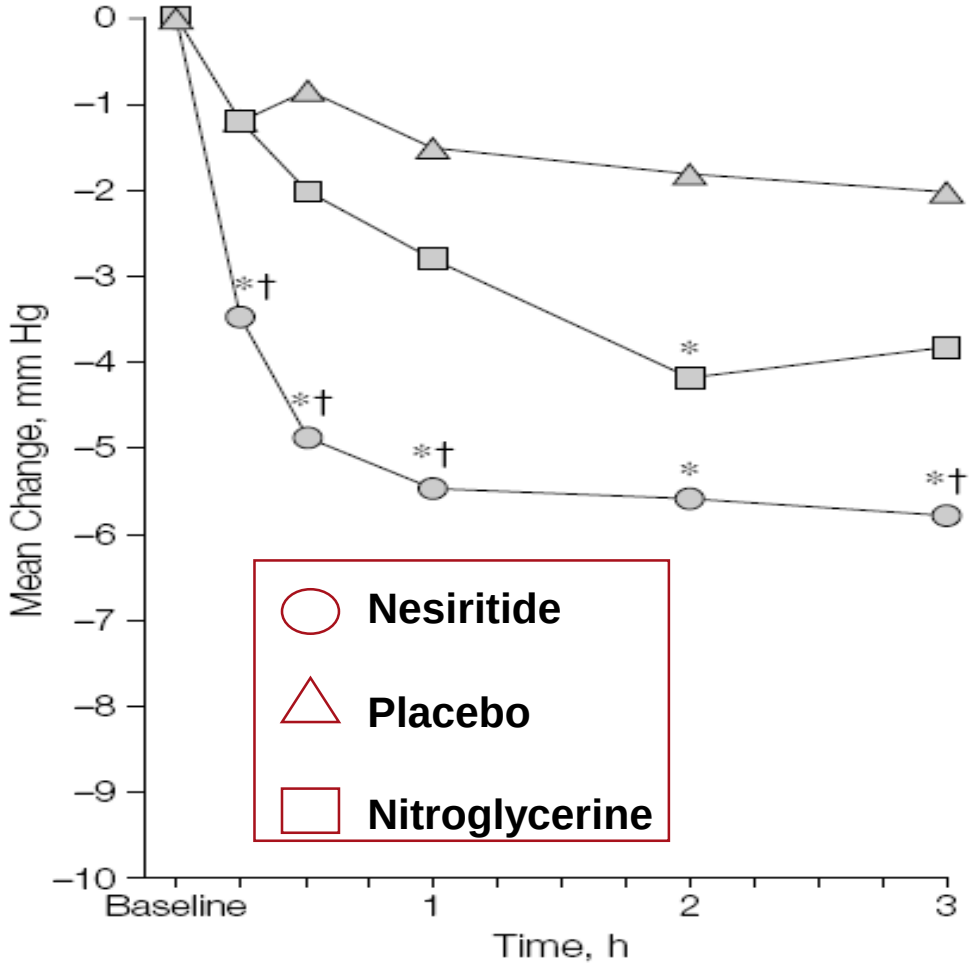
- Recommend the following intravenous vasodilators, titrated to a systolic blood pressure (sBP) over 100 mm Hg, for relief of dyspnea in hemodynamically stable patients (sBP over 100 mm Hg):
  - Nitroglycerine (Strong Recommendation, Moderate-Quality Evidence);
  - Nesiritide (Weak Recommendation, High-Quality Evidence);
  - Nitroprusside (Weak Recommendation, Low-Quality Evidence).

[1]Jentzer JC, Chawla LS. *Crit Care Clin* 2015;31:685-703
[2]Rangaswami J et al. *Circulation* 2019;139:e840-78.

Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure

A Randomized Controlled Trial

- VMAC trial compared nesiritide (n=204), nitroglycerine (n=143), or placebo (n=142) to standard therapy for 3 h, followed by nesiritide (n=278) or NTG (n=216) added to standard treatment for 24 h in acute HF patients with dyspnea at rest



- At 3 hours, the mean (SD) decrease in PCWP from baseline was -5.8 mmHg for nesiritide, -3.8 mmHg for NTG, and -2 mmHg for placebo

VMAC Investigators *JAMA* 2002;287:1531-40

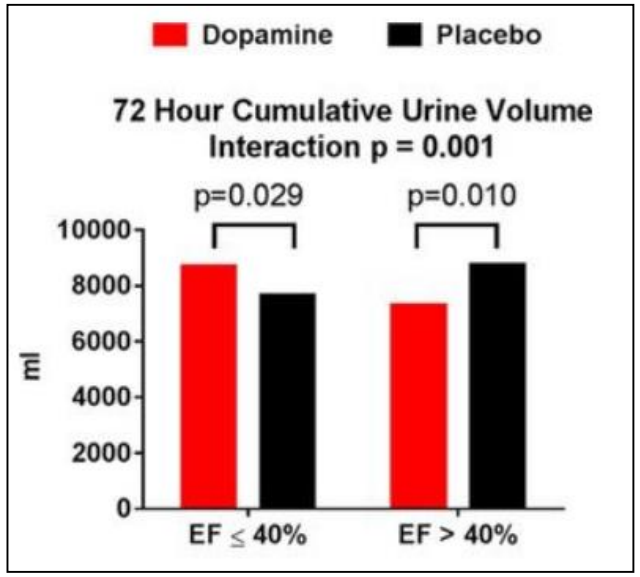
Circulation: Heart Failure
Volume 9, Issue 8, August 2016
https://doi.org/10.1161/CIRCHEARTFAILURE.115.002593

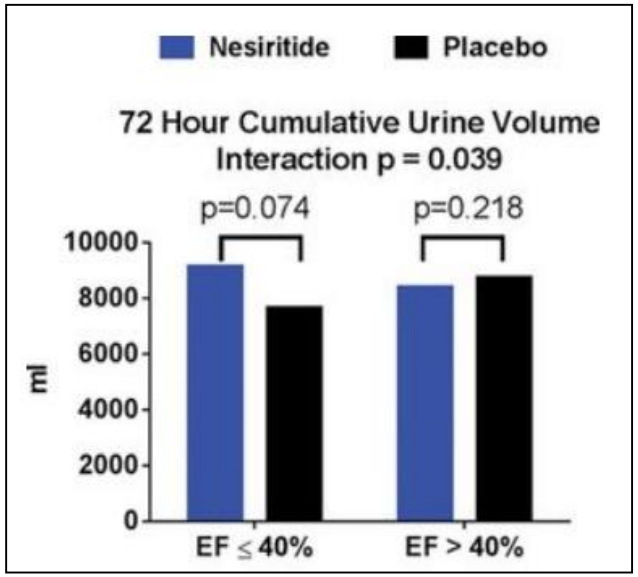
ORIGINAL ARTICLE

Differential Response to Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Reduced or Preserved Ejection Fraction

Results From the ROSE AHF Trial (Renal Optimization Strategies Evaluation in Acute Heart Failure)

Siu-Hin Wan, MD, Susanna R. Stevens, MS, Barry A. Borlaug, MD, Kevin J. Anstrom, PhD, Anita Deswal, MD, G. Michael Felker, MD, Michael M. Givertz, MD, Bradley A. Bart, MD, W.H. Wilson Tang, MD, Margaret M. Redfield, MD, and Horng H. Chen, MBBCh



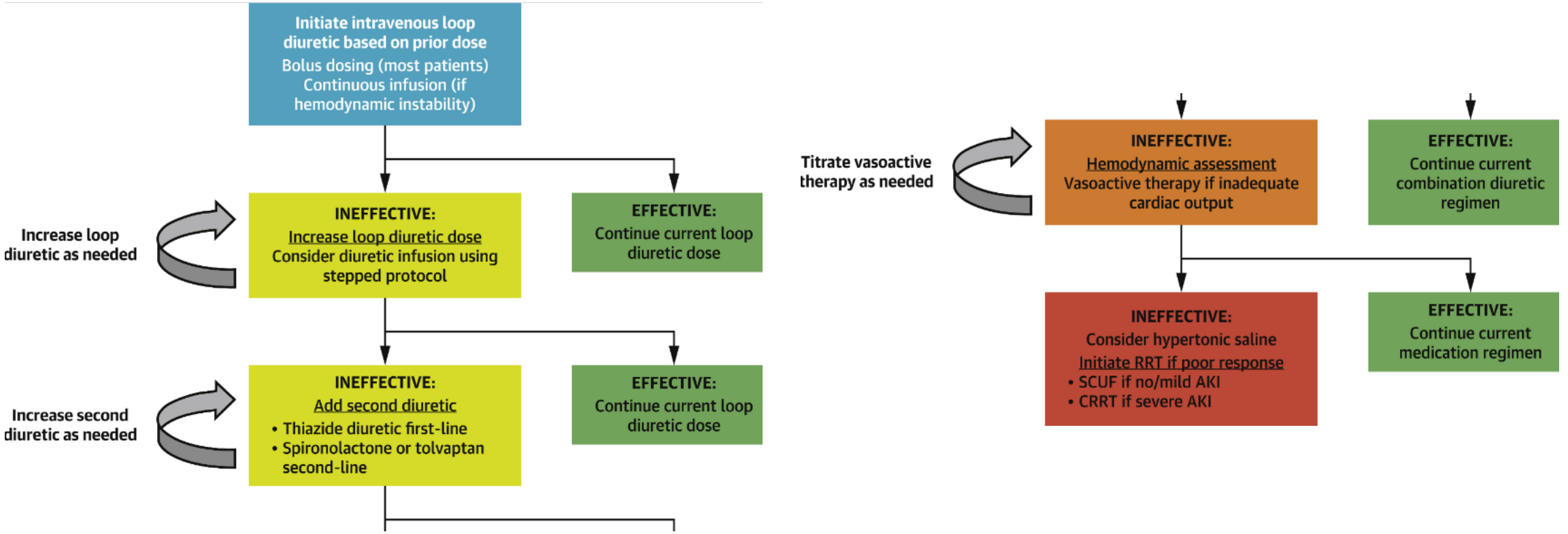


- Dopamine has cardiac inotropic effects and can enhance kidney function as well as diuresis in some patients
- However, dopamine has not consistently improved kidney function, diuresis, or clinical outcomes in patients with CRS[1]
- There is a possible beneficial effect of low-dose dopamine (2 mcg/kg/min) in patients who have CRS and HFrEF[2]

• ROSE AHF enrolled AHF patients (n=360; any EF) with renal dysfunction
• The effect of dopamine (interaction *P*=0.001) and nesiritide (interaction *P*=0.039) on urine volume varied by EF group.
• In HFrEF, urine volume was higher with active treatment versus placebo.

[1]Jentzer JC et al. *J Am Coll Cardiol* 2020;76:1084-101
[2]Wan SH et al. Circ Heart Fail 2016;9(8):10.1161/CIRCHEARTFAILURE.115.002593 e002593.

Volume Management in Patients with Acute HF and CRS



Jentzer JC et al. *J Am Coll Cardiol* 2020;76(9):1084-101.

Direct Modulation of Sodium Avidity with Hypertonic Saline to Promote Excretion

- Use of hypertonic saline solution (HSS) in combination with high-dose furosemide has long been considered a controversial treatment strategy for acute CRS in advanced HF
- HSS increases intracellular NaCl concentration, resulting in instantaneous mobilization of extravascular fluid into the intravascular space through osmotic action[1]
- Through the baroreceptor reflex, plasma volume expansion leads to a reduction in systemic vascular resistance[2]
- This small increase in preload and significant decrease in afterload translates into increased cardiac output, renal blood flow and enhanced organ perfusion
- Meta-analysis showed small-volume HSS may improve diuretic responsiveness and renal function in patients with CRS[3]

[1] Paterna S et al. *Adv Ther* 1999;16:219-228
[2] Liszkowski M and Nohria A. *Curr Heart Fail Rep* 2010;7:134-139
[3] Gandhi S et al. *Int J Cardiol* 2014;173:139-45

Real World Use of Hypertonic Saline in Refractory Acute Decompensated Heart Failure

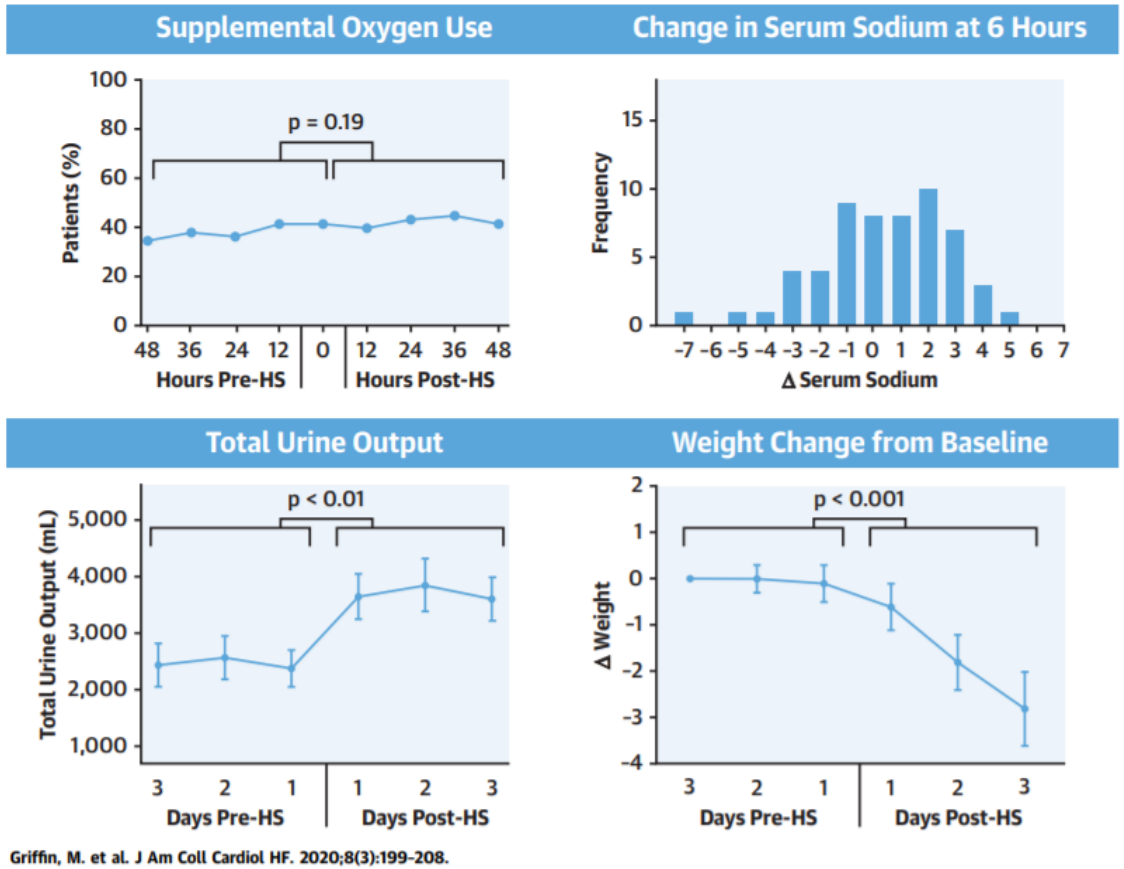
A U.S. Center's Experience

Matthew Griffin, MD,[a,*] Aaron Soufer, MD,[a,*] Erden Goljo, MD,[b] Matthew Colna, MD,[c] Veena S. Rao, PhD,[a] Sangchoon Jeon, PhD,[d] Parinita Raghavendra, BS,[a] Julie D'Ambrosi, PharmD,[e] Ralph Riello, PharmD,[e] Steven G. Coca, DO, MS,[f] Devin Mahoney, BS,[a] Daniel Jacoby, MD,[a] Tariq Ahmad, MD, MPH,[a] Michael Chen, MD,[a] W.H. Wilson Tang, MD,[g] Jeffrey Turner, MD,[h] Wilfried Mullens, MD, PhD,[i,j] Francis P. Wilson, MD, MSCE,[h] Jeffrey M. Testani, MD, MTR[a]

- Retrospective analysis of 58 hypertonic saline episodes were identified across 40 patients with diuretic-therapy refractory ADHF at Yale University
- Received 150 ml of 3% NaCl to be given over 30 min (300 ml/h), administered simultaneously with high doses of loop diuretic agents:

Day	Admissions (n)	Diuretic Dose (Average ± SD), furosemide equivalents	Diuretic Efficiency (change in UOP per doubling of loop diuretic dose)
-3	45	568 ± 489mg	656±362 mL
-2	54	586 ± 525mg	657±364mL
-1	58	606 ± 594mg	627±427mL
1	58	749 ± 655mg	841±496mL
2	58	667 ± 634mg	909±470mL
3	58	517 ± 487mg	878±542mL

Online Table 1. Dose of loop diuretic and diuretic efficiency by day.

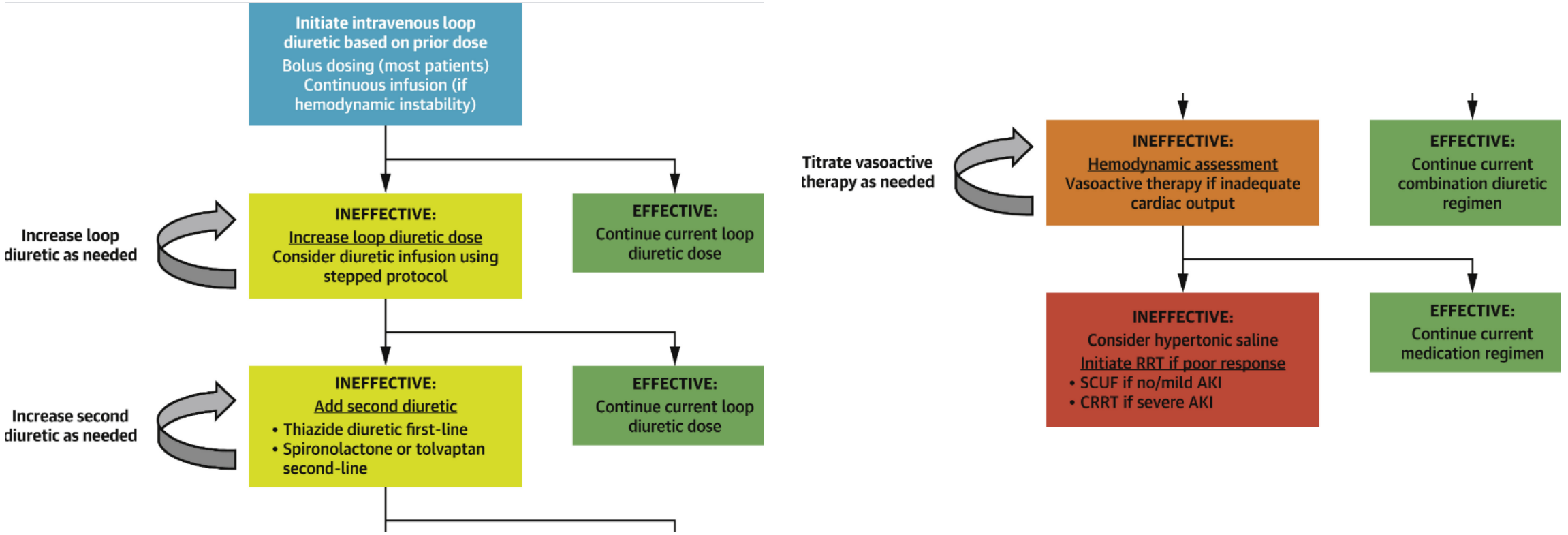


Griffin, M. et al. J Am Coll Cardiol HF. 2020;8(3):199-208.

- Both total urine output and weight loss significantly improved with hypertonic saline
- No significant changes in respiratory status or overcorrection of serum sodium with the intervention
- Additional study of hypertonic saline as a diuretic adjuvant is warranted.

Griffin M et al. *JACC Heart Fail.* 2020;8:199-208.

Volume Management in Patients with Acute HF and CRS



Jentzer JC et al. *J Am Coll Cardiol* 2020;76(9):1084-101.

Potential General and CICU-Specific CRRT Indications

General Acute RRT Indications	Proposed CICU-Specific CRRT Indications
A: Severe metabolic acidosis (i.e. Severe lactic acidosis with refractory shock and multiorgan failure)	Patients with severe cardiac and/or valvular dysfunction and borderline blood pressure with AKI and volume overload
E: Severe electrolyte disturbances, most commonly hyperkalemia	Cardiogenic shock or HF with pulmonary edema on mechanical ventilation and high FiO_2 (>80-90%) despite diuretic therapy
I: Intoxication with dialyzable drugs or toxins	Refractory cardiorenal syndrome with progressive AKI (e.g. Stage 2-3 AKI plus volume overload with inadequate diuretic response)
O: Medically refractory volume overload	Pre-cardiac surgical volume removal to improve likelihood of chest closure and prevent post-operative right ventricular failure
U: Severe azotemia or symptoms of uremia	

Jentzer JC et al. *J Am Coll Cardiol.* 2020;76:1084-1101.

Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

Maria Rosa Costanzo, MD, FACC,* Maya E. Guglin, MD, FACC,†
Mitchell T. Saltzberg, MD, FACC,* Mariell L. Jessup, MD, FACC,‡ Bradley A. Bart, MD, FACC,§
John R. Teerlink, MD, FACC,‖ Brian E. Jaski, MD, FACC,¶ James C. Fang, MD, FACC,#
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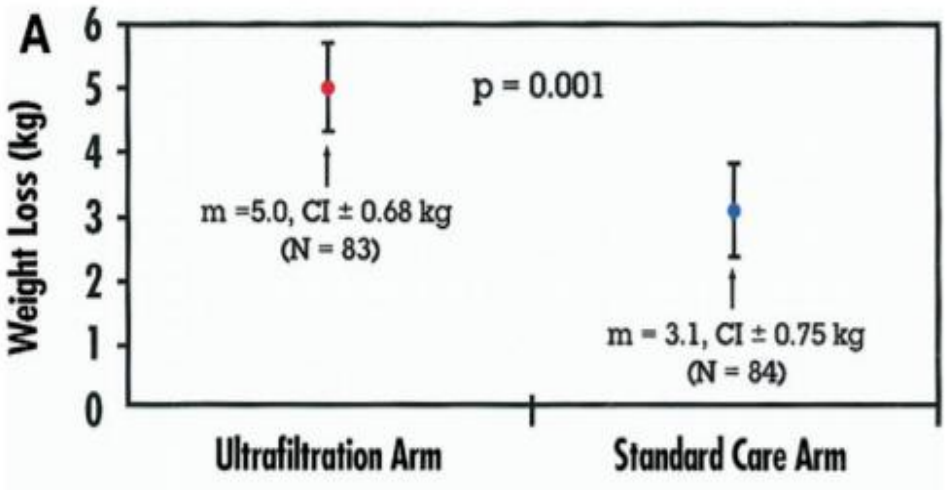
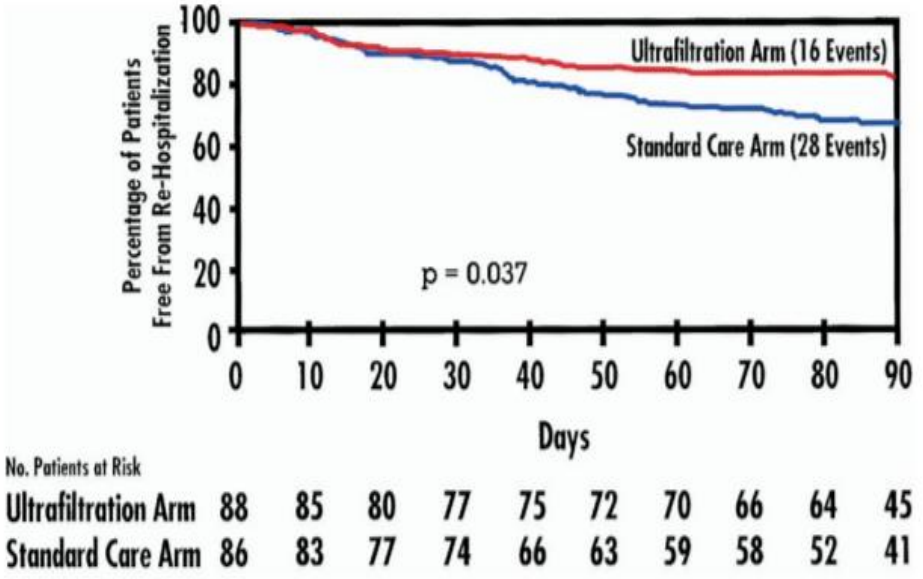
Michael P. Schollmeyer, DVM,§§ Paul A. Sobotka, MD, FACC,§§ for the UNLOAD Trial Investigators

Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio



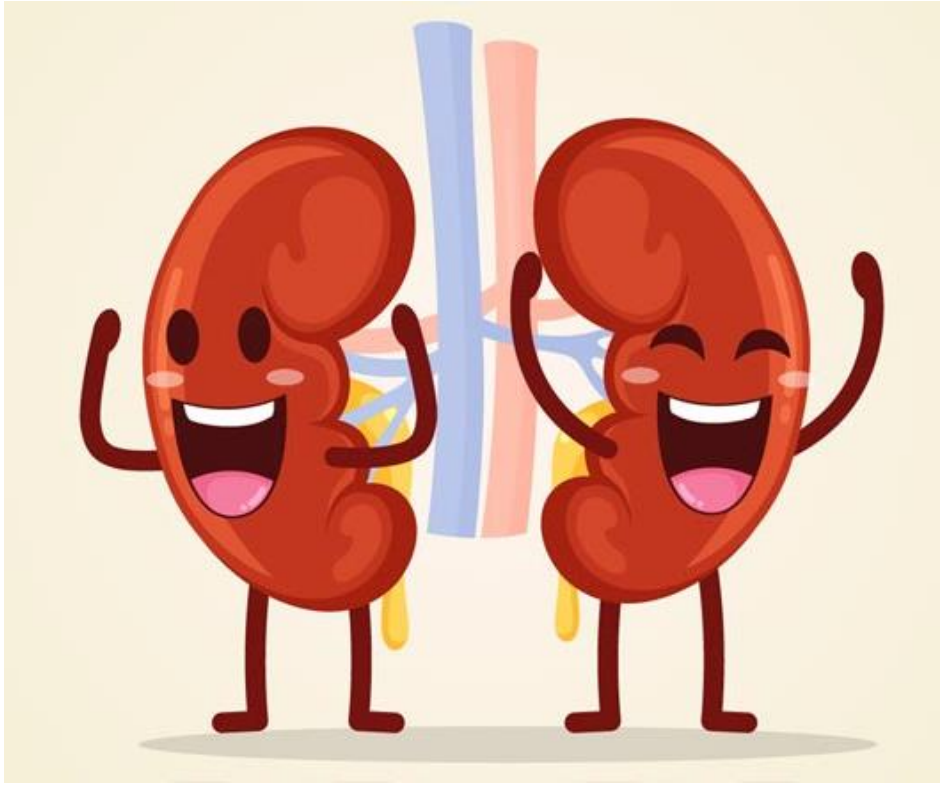
- This study was designed to compare the safety and efficacy of veno-venous ultrafiltration and standard intravenous diuretic therapy for hypervolemic HF patients.
- Two hundred patients (63±15 years, 69% men, 71% LVEF ≤ 40%) were randomized to ultrafiltration or intravenous diuretics.
- Conclusion: in decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternative therapy.



Costanzo MR et al. *J Am Coll Cardiol.* 2007;49:675-83.

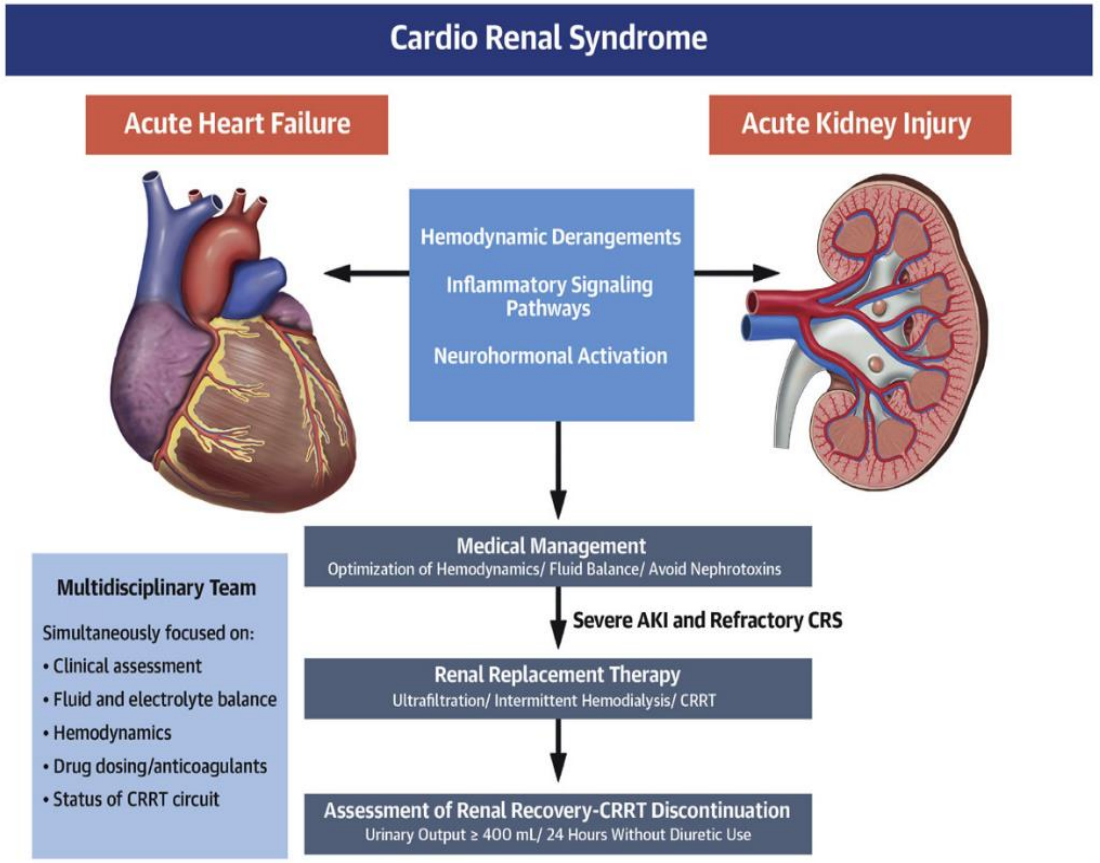
Back to Case: Ms. Anne Uric

- Nephrology on standby for possible initiation of CRRT since urine output 30 cc/h
- Patient transferred to Cardiology, under CICU team
- Diuretics escalated stepwise to furosemide 120 mg iv BID with metolazone 5 mg BID and furosemide 30 mg/h
- Following this, urine output increased to 200 cc/h
- Potassium 3.0, so lasix decreased and patient started on spironolactone.
- Creatinine decreased from 355 back down to 188, lactate normalized
- Patient now transitioned to and stable on bumetanide 4 mg BID with spironolactone 50 mg OD and intermittent use of metolazone



Summary: Treatment of the Diuretic Resistant Patient with Acute Heart Failure

- Cardiorenal syndrome (CRS) involves the interplay between hemodynamic, inflammatory, and neurohumoral abnormalities to produce worsening heart and kidney function.
- Management of patients with CRS involves multidisciplinary care, starting with medical management and avoidance of further acute kidney injury (AKI).
- Initial therapy of CRS and diuretic resistance involves a stepped diuretic regimen, vasoactive therapies if appropriate, and possible consideration of hypertonic saline solution.
- For medically refractory CRS and severe AKI, renal replacement therapy may be necessary.



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