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Jointly Provided by
UC San Diego SCHOOL OF MEDICINE
and
CRRT, INC.

Symposium B - Deresuscitation in the ICU:
How to use Diuretics, Ultrafiltration and Dialysis

Ultrafiltration and Diuretic Therapy in Acute Heart Failure

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Disclosures

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Outline

- Congestion and Natriuresis in AHF
- Diuretic Therapy in AHF
- Sequential Nephron Blockade
- Ultrafiltration for AHF

Case

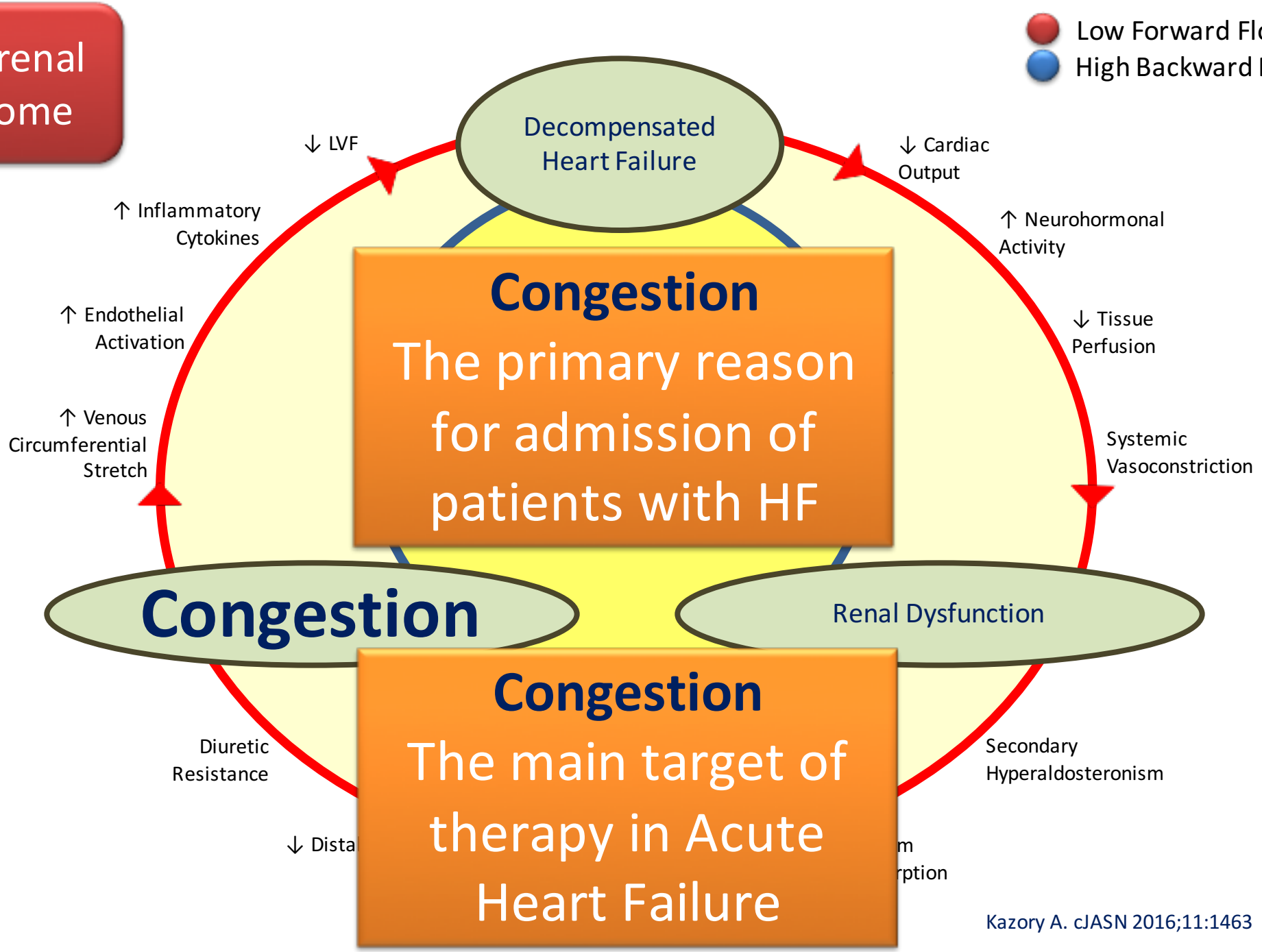
A 65-year-old man with a history of CAD, HTN, HFrEF (EF 35%) is admitted to the Cardiac ICU for progressive dyspnea and a weight gain of 15 lbs over the last 1 month. His BP is 121/56, PR 14, RR 59, T 98.5. His home meds include lisinopril 40 mg/day, furosemide 40 mg BID, and Metorolol XL 50 mg/day. CXR shows pulmonary edema.

He is started on IV furosemide 80 mg BID. The next day, his urine output is 450 ml and the labs show the following: Na 136, K 4.1, Cl 96, Bicarb 29, BUN 22, Creatinine 1.2

<u>Which of the following is the best next step?</u>

1) Check urine sodium
2) Add IV acetazolamide 500 mg once daily
3) Add Empagliflozin 10 mg once daily
4) Start HCTZ 25 mg once daily
5) Start ultrafiltration

Cardiorenal Syndrome

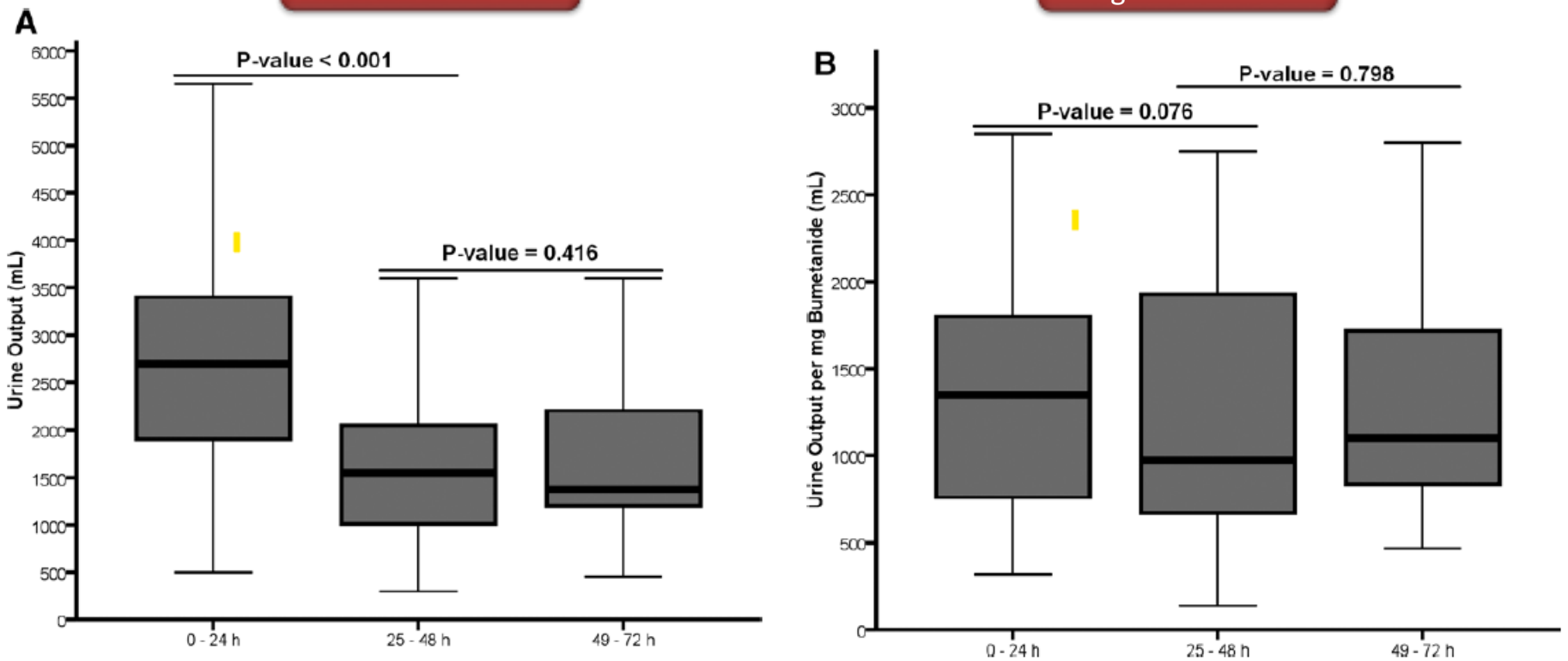


Kazory A. cJASN 2016;11:1463

Natriuresis Declines Rapidly During Decongestion

Urine Output (ml)

Urine Output (ml)/ mg Bumetanide

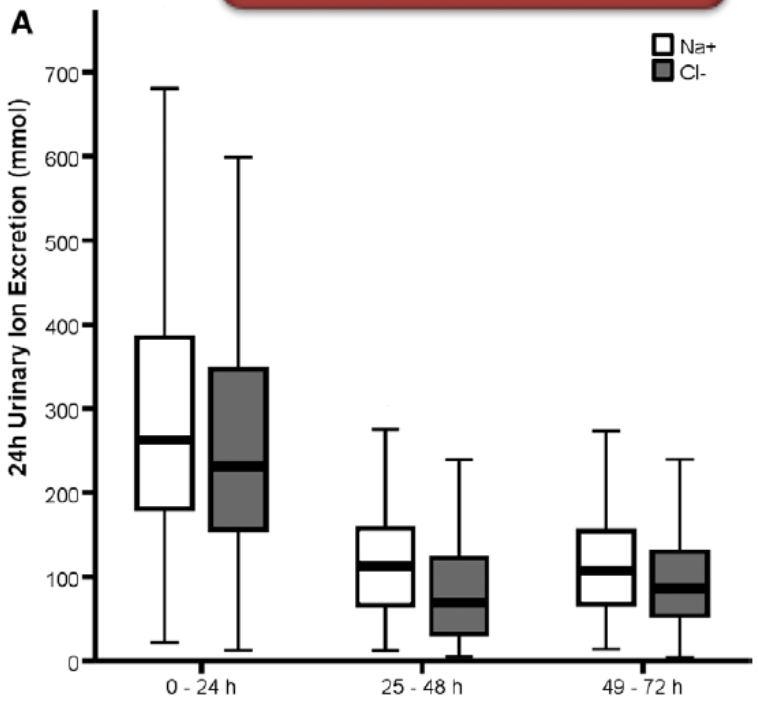


Urine volume does not decline when adjusted for diuretic dose
Urine output/mg of bumetanide: 900-1300 ml

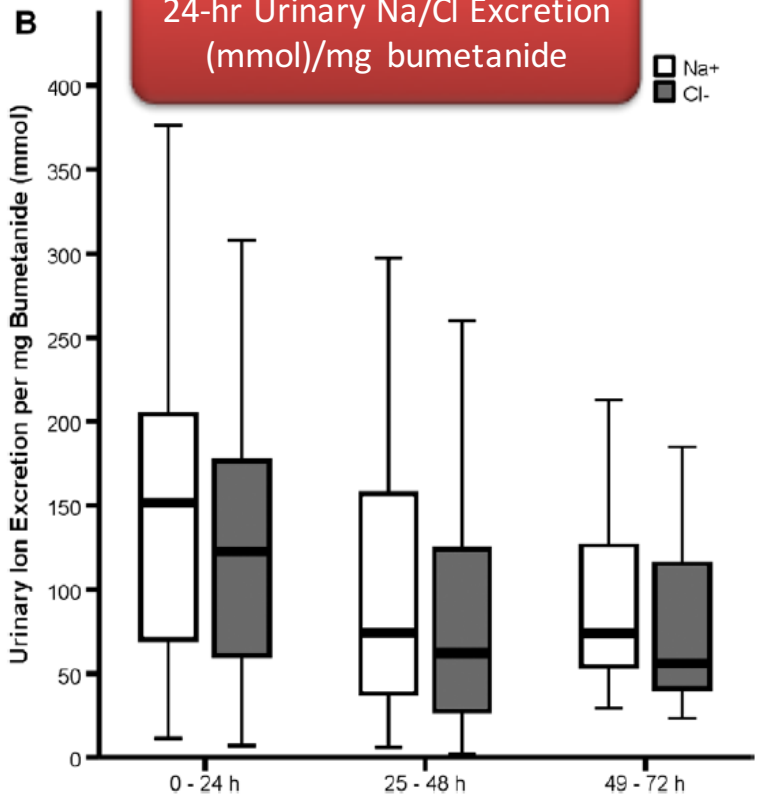
Verbrugge FH. Circ Heart Fail 2014;7:766

Natriuresis Declines Rapidly During Decongestion

24-hr Urinary Na/Cl Excretion (mmol)



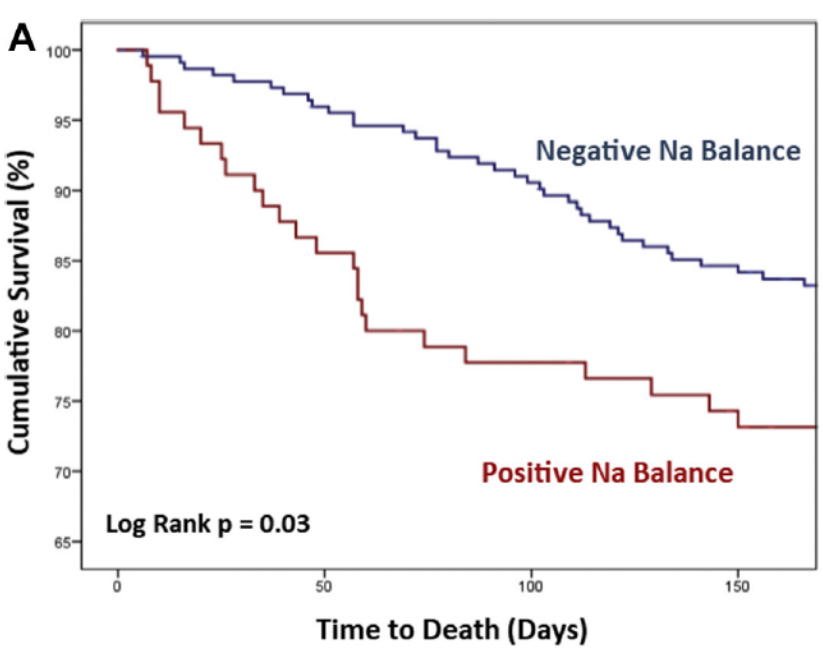
24-hr Urinary Na/Cl Excretion (mmol)/mg bumetanide

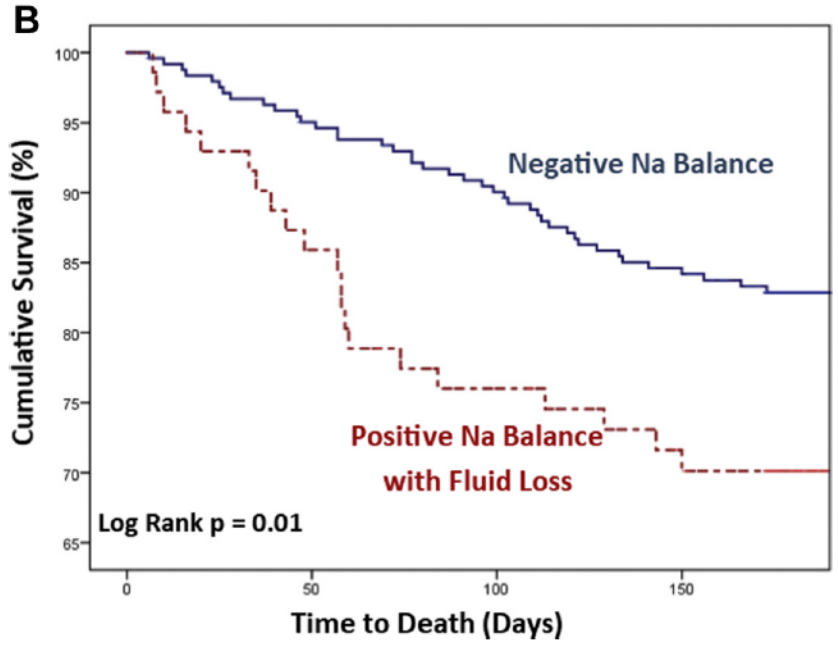


Natriuresis does decline even after adjustment for diuretic dose
Urine sodium/mg of bumetanide: 75-150 mmol

Verbrugge FH. Circ Heart Fail 2014;7:766

Natriuretic Response and Survival



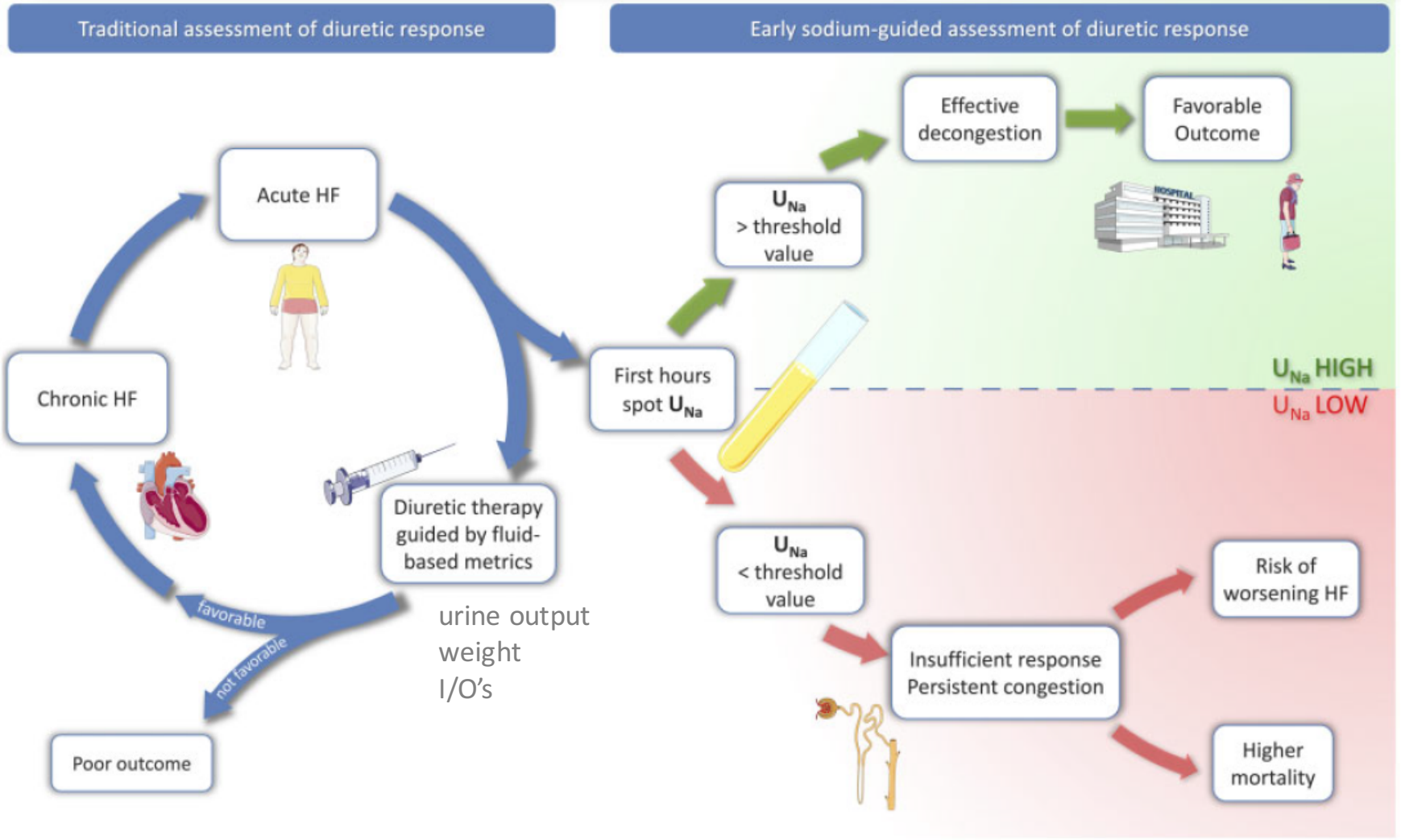


2 g/day sodium diet

A positive sodium balance is associated with an increased risk of death, even in the presence of negative fluid balance

Hodson DZ. JACC HF 2019; 7: 383

Natriuresis-Guided Therapy in AHF



Tersalvi G. Eur Heart J 2021; 10: 216

Natriuresis-Guided Therapy in AHF

Name	Clinical Trial Identifier	Expected Number of Patients	Design	Intervention arm	Control arm	Primary Endpoint
PUSH-HF	NCT04606927	310	RCT	Natriuresis-guided treatment	Standard of care	Total natriuresis after 24 hours, first occurrence of all-cause mortality or heart failure rehospitalization
DECONGEST	NCT05411991	104	RCT	Natriuresis-guided treatment	Standard of care	Mortality, days in hospital, and decongestion
ENACT-HF	NR	454	Multi-national Pragmatic	Natriuresis-guided treatment	Standard of care	Total natriuresis after 24 hours
Collins S.	NCT04481919	484	RCT	Natriuresis-guided treatment	Guideline-based care	Days of clinical benefit (global clinical status, hospital days, and death)

Kazory A. Cardiorenal Med 2023

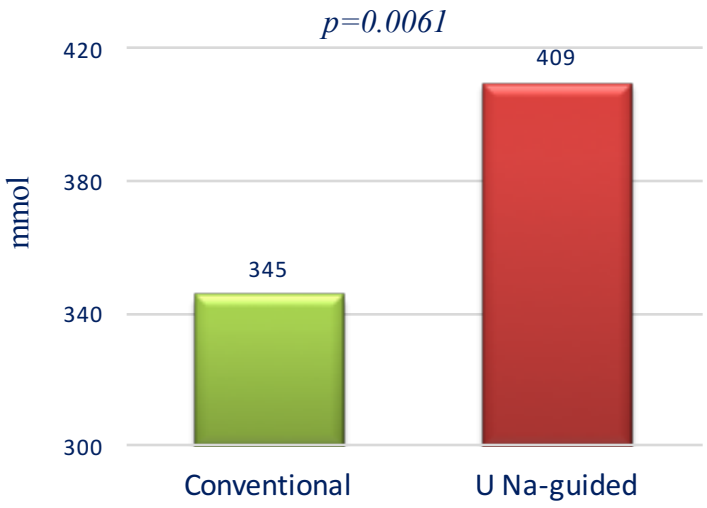
PUSH-AHF Trial

European Society of Cardiology – Amsterdam (Aug 28, 2023)

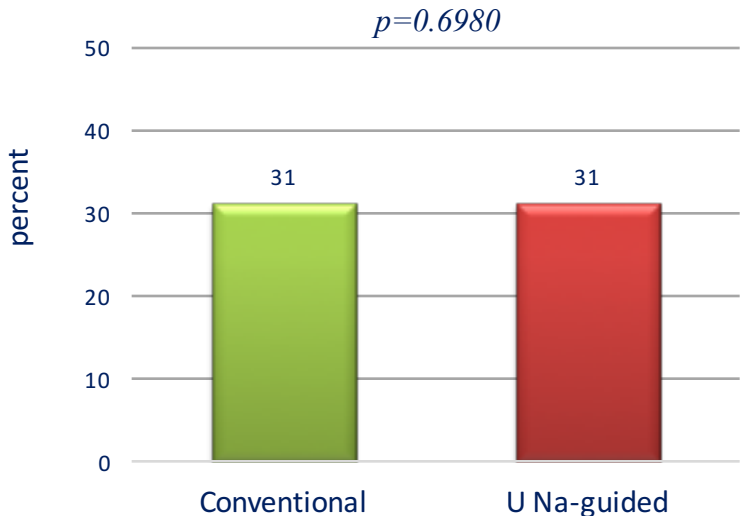
Urinary Sodium-based treatment algoritHm in Acute Heart Failure

310 patients

24-hour U sodium excretion



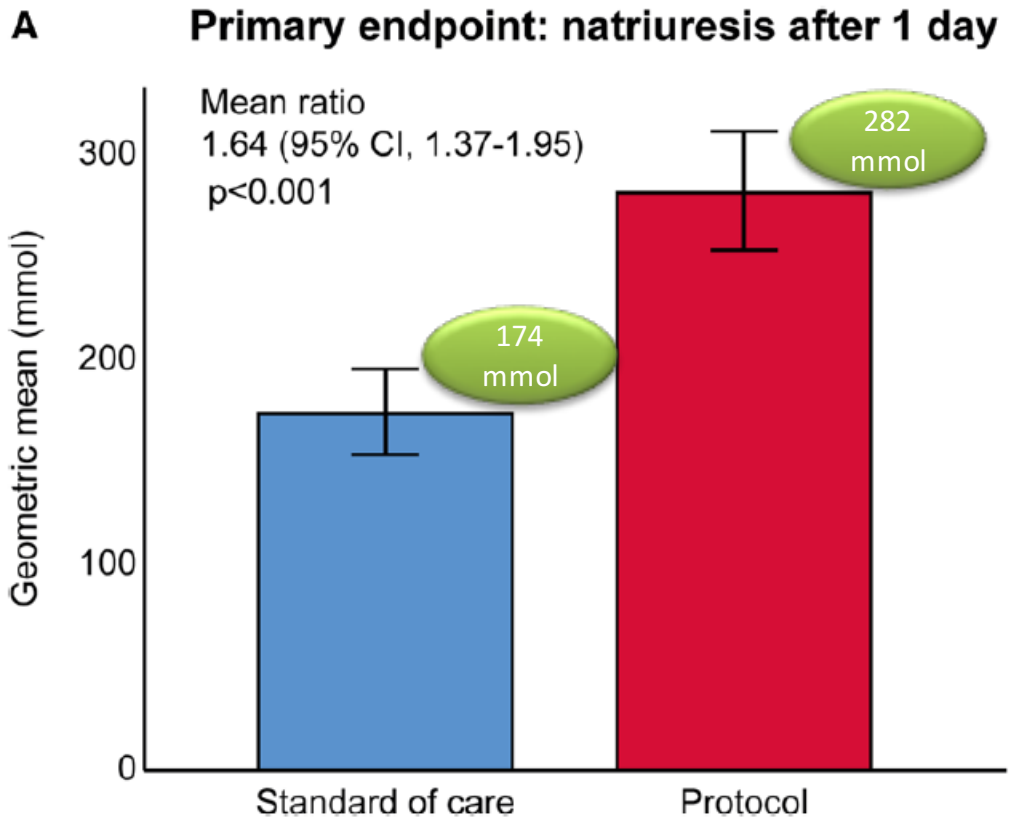
Mortality or AHF in 180 days

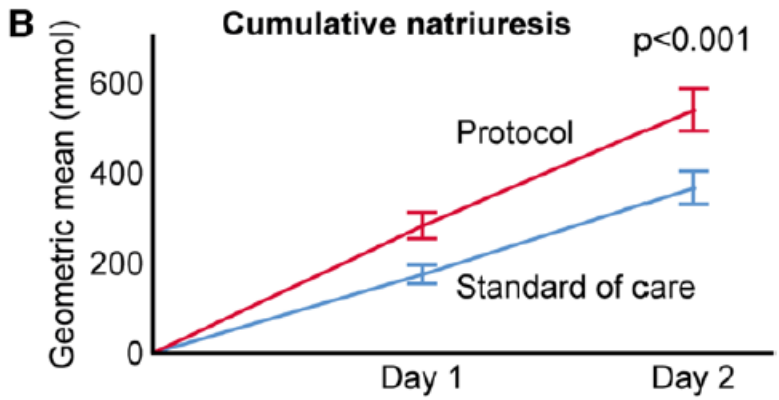


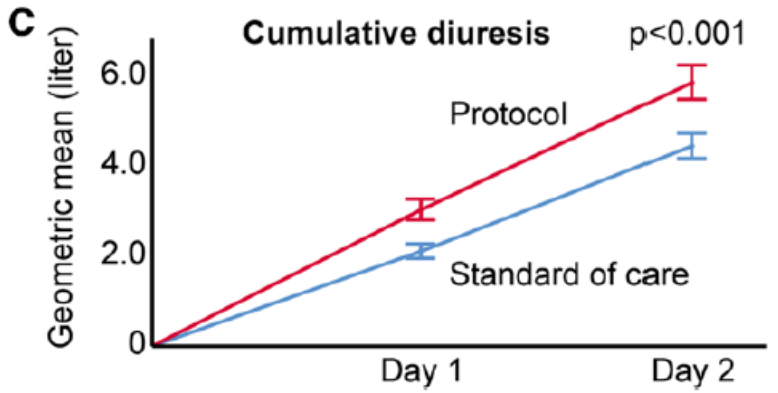
Natriuresis during the first 24 hours was significantly higher in the natriuresis guided group, but the combined endpoint of time to all-cause mortality or first HF rehospitalization at 180 d was the same.

Adapted-Ter Maaten J. Nature Med 2023:29;2625

ENACT-HF Trial







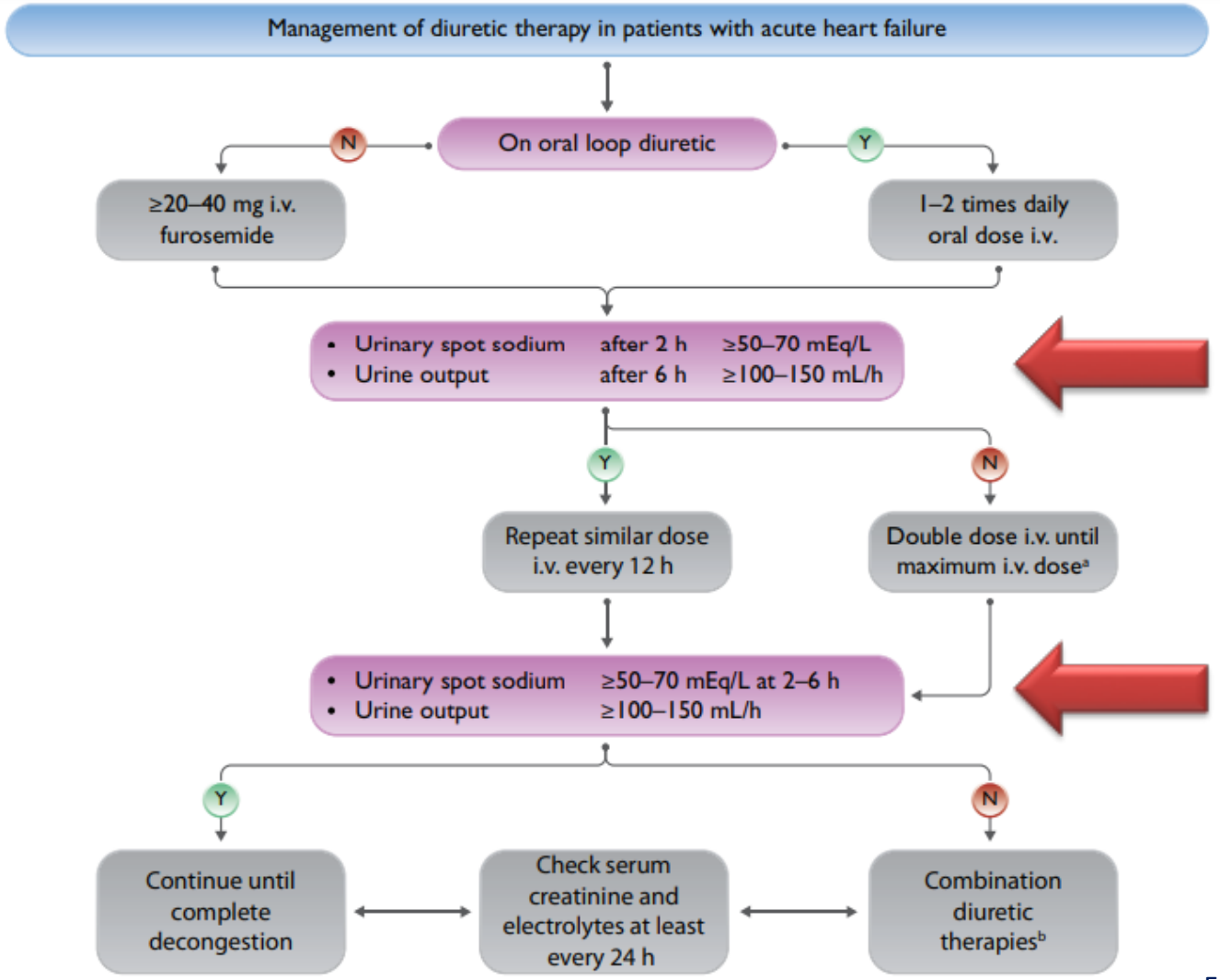
401 patients

Natriuresis and diuresis were significantly higher in the natriuresis guided group, with shorter length of stay

Dauw J. Circulation HF 2024:17

Treatment Algorithm for AHF

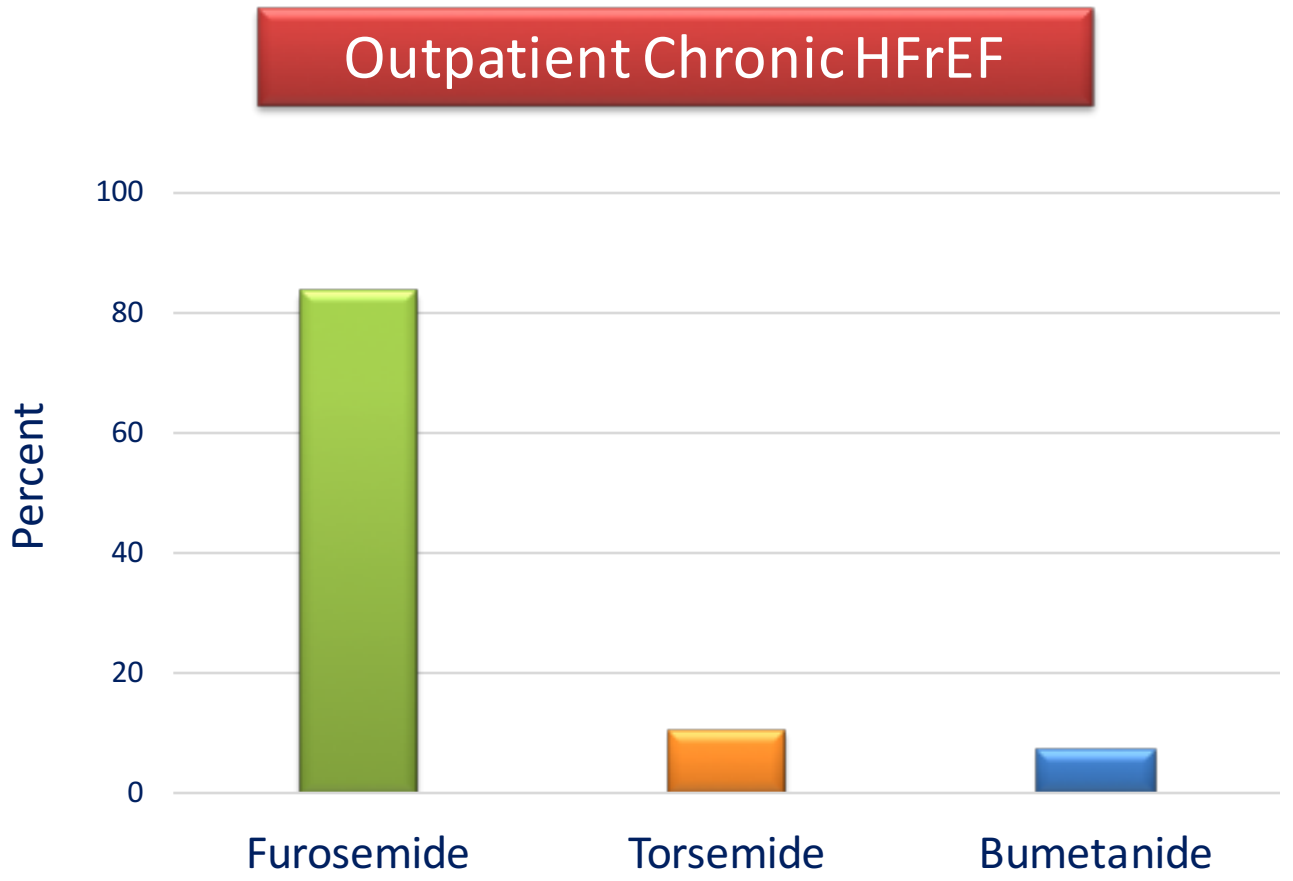
European Society of Cardiology



The maximal daily dose for i.v. loop diuretics is generally considered **furosemide 400-600 mg**, though up to 1000 mg may be considered in patients with severely impaired kidney function.

ESC Guidelines. Europ Heart J. 2021;42: 3599

Furosemide or Torsemide?



Adapted-Khan MS. Circ Heart Fail 2021;14:e008351

Furosemide or Torsemide?

Potential Advantages of Torsemide over Furosemide

Preclinical data	Clinical data
• Improved diuresis • Decreased kaliuresis • Decreased aldosterone secretion • Inhibition of aldosterone receptor* • Inhibition of Ang II effects • Improved LV function • Decreased myocardial collagen • Increased survival rate	• Improved diuresis and weight reduction • Decreased transcardiac aldosterone extraction • Less RAAS activation • Decreased myocardial collagen • Decreased levels of PICP† and PIIINP (collagen surrogates)Decreased PCP activity • Decreased levels of plasma BNP • Improved LV function • Improved NYHA class† • Improved subjective quality of life • Decreased all-cause‡ and cardiac-associated mortality • Decreased rates of hospitalization‡ • Decreased length of hospital stay related to HF

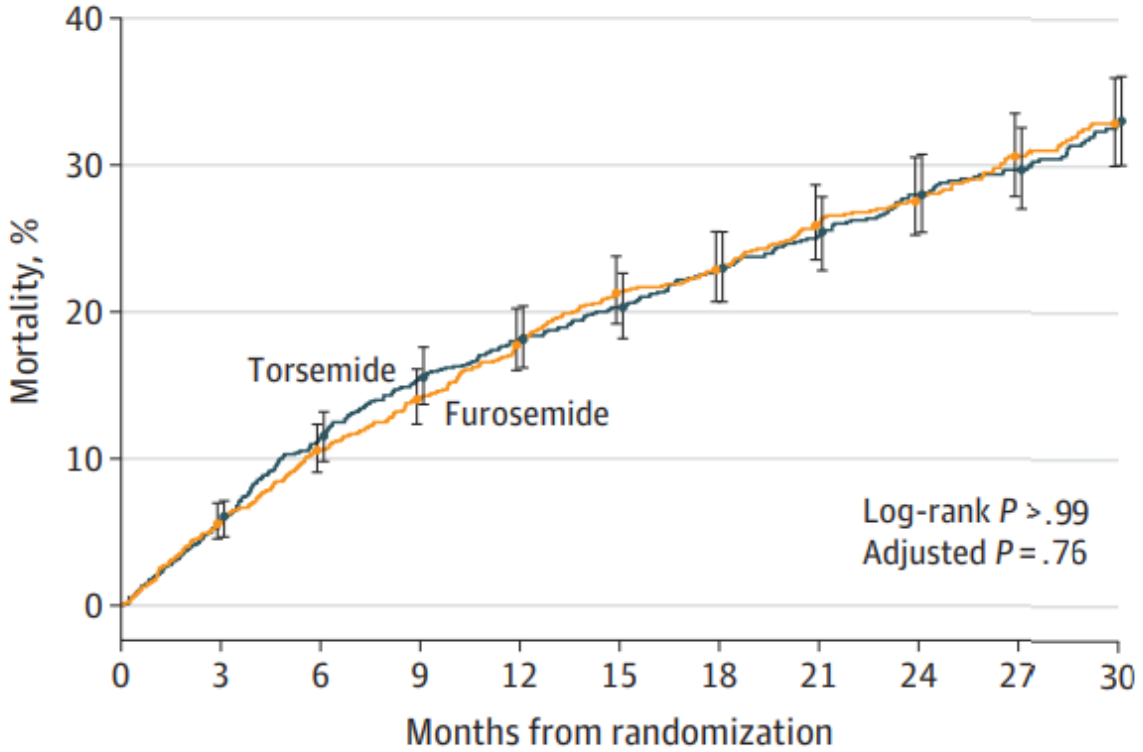
Buggey J. Am Heart J 2015;169:323

Furosemide or Torsemide?

TRANSFORM-HF trial

Primary Outcome of All-Cause Mortality

2859 patients



No. at risk											
Torsemide	1431	1301	1135	1027	904	787	689	661	543	434	317
Furosemide	1428	1295	1151	1036	897	782	707	658	542	428	317

Patients discharged after HF hospitalization
Open-label, pragmatic RCT
participants hospitalized with HF
60 hospitals in US
median follow-up of 17.4 months

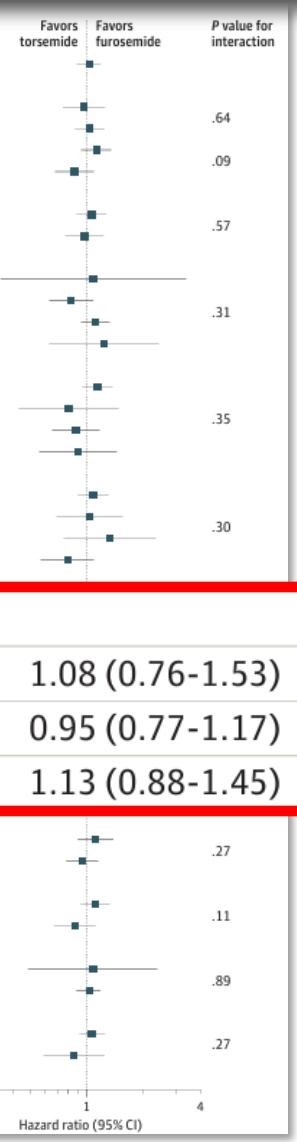
Mentz RJ. JAMA 2023;329:214

Furosemide or Torsemide?

TRANSFORM-HF trial

2859 patients

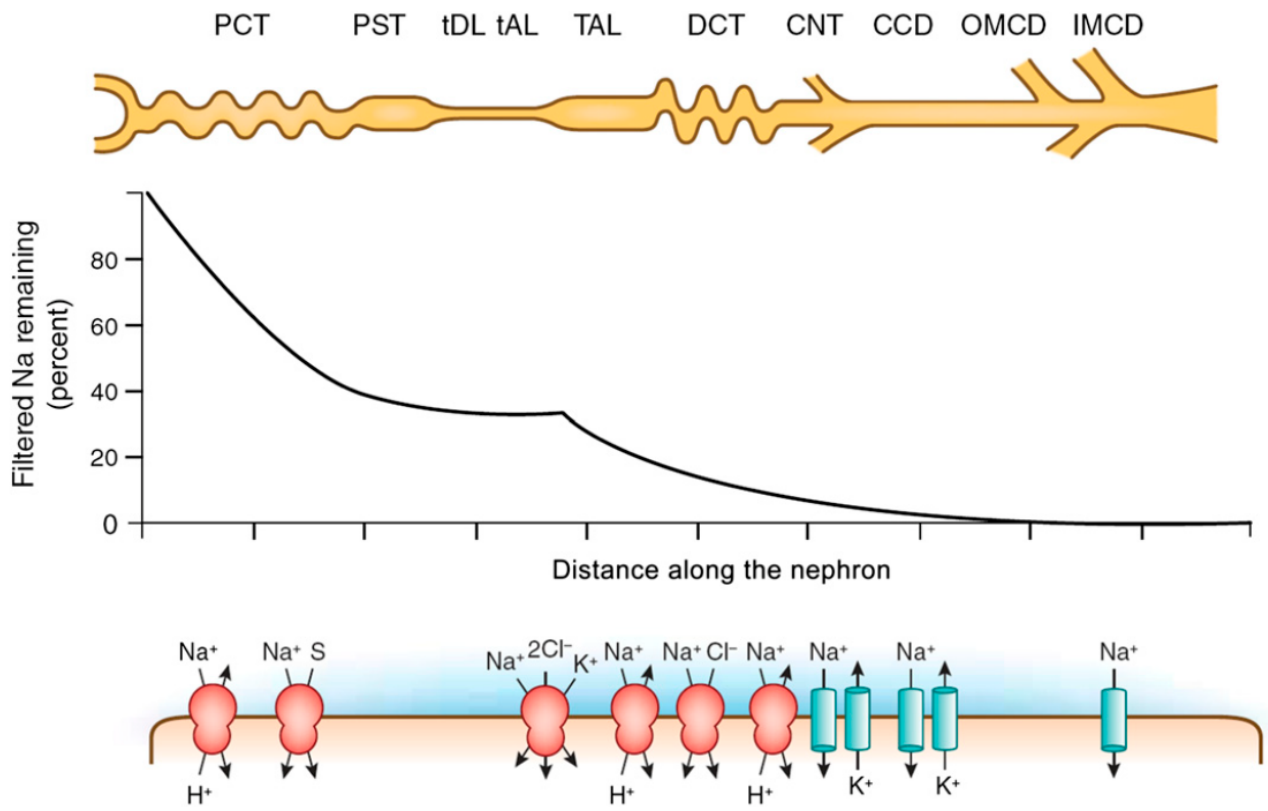
Subgroup	Deaths, No./total (%) Torsemide	Furosemide	Hazard ratio (95% CI)	P value for interaction
Overall	373/1431 (26.1)	374/1428 (26.2)	1.02 (0.89-1.18)	
Age, y				
<65	119/680 (17.5)	121/663 (18.3)	0.96 (0.75-1.24)	.64
≥65	254/751 (33.8)	253/765 (33.1)	1.04 (0.87-1.23)	
<75	249/1083 (23.0)	219/1049 (20.9)	1.12 (0.93-1.34)	.09
≥75	124/348 (35.6)	155/379 (40.9)	0.86 (0.68-1.09)	
Sex				
Male	244/933 (26.2)	221/871 (25.4)	1.06 (0.88-1.27)	.57
Female	129/498 (25.9)	153/557 (27.5)	0.97 (0.77-1.22)	
Race and ethnicity[a]				
Asian	6/37 (16.2)	6/26 (23.1)	1.08 (0.35-3.36)	
Black	98/474 (20.7)	119/494 (24.1)	0.82 (0.63-1.08)	.31
White	248/831 (29.8)	234/837 (28.0)	1.11 (0.93-1.33)	
Other	21/87 (24.1)	15/68 (22.1)	1.23 (0.63-2.39)	
Left ventricular ejection fraction, %				
≤40	239/935 (25.6)	212/901 (23.5)	1.14 (0.94-1.37)	
41-49	20/81 (24.7)	21/70 (30.0)	0.80 (0.43-1.48)	.35
≥50	84/318 (26.4)	101/330 (30.6)	0.88 (0.66-1.17)	
Unknown	30/97 (30.9)	40/127 (31.5)	0.90 (0.56-1.44)	
Loop diuretic prior to index hospitalization				
Furosemide	229/754 (30.4)	227/778 (29.2)	1.08 (0.90-1.30)	
Torsemide	53/146 (36.3)	42/113 (37.2)	1.03 (0.69-1.55)	.30
Bumetanide/ethacrynic acid	26/64 (40.6)	23/65 (35.4)	1.32 (0.75-2.32)	
None/unknown	65/467 (13.9)	82/472 (17.4)	0.78 (0.57-1.09)	
NYHA class at randomization				
eGFR categories, mL/min/1.73 m^2				
<30	58/144 (40.3)	68/165 (41.2)	1.08 (0.76-1.53)	
≥30 to <60	181/641 (28.2)	188/607 (31.0)	0.95 (0.77-1.17)	.55
≥60	134/644 (20.8)	118/653 (18.1)	1.13 (0.88-1.45)	
Diabetes				
No	167/743 (22.5)	165/752 (21.9)	1.11 (0.89-1.38)	.27
Yes	206/688 (29.9)	209/676 (30.9)	0.94 (0.78-1.14)	
Mineralocorticoid receptor antagonist use at randomization				
No	258/907 (28.4)	245/930 (26.3)	1.11 (0.93-1.32)	.11
Yes	115/524 (21.9)	129/498 (25.9)	0.86 (0.67-1.11)	
Enrolled at an academic/teaching hospital				
No	12/30 (40.0)	13/31 (41.9)	1.08 (0.49-2.37)	.89
Yes	361/1401 (25.8)	361/1397 (25.8)	1.02 (0.88-1.18)	
Duration of heart failure				
Worsening of chronic heart failure	319/1002 (31.8)	313/1018 (30.7)	1.06 (0.91-1.24)	.27
Newly diagnosed	54/428 (12.6)	61/410 (14.9)	0.85 (0.59-1.23)	



Mentz RJ. JAMA 2023;329:214

Sodium Transport along the Nephron

(Healthy Individuals)



In healthy individuals, the majority of sodium absorption takes place within proximal tubule and thick ascending limb of loop of Henle

Palmer LG. Clin J Am Soc Nephrol 2015: 676

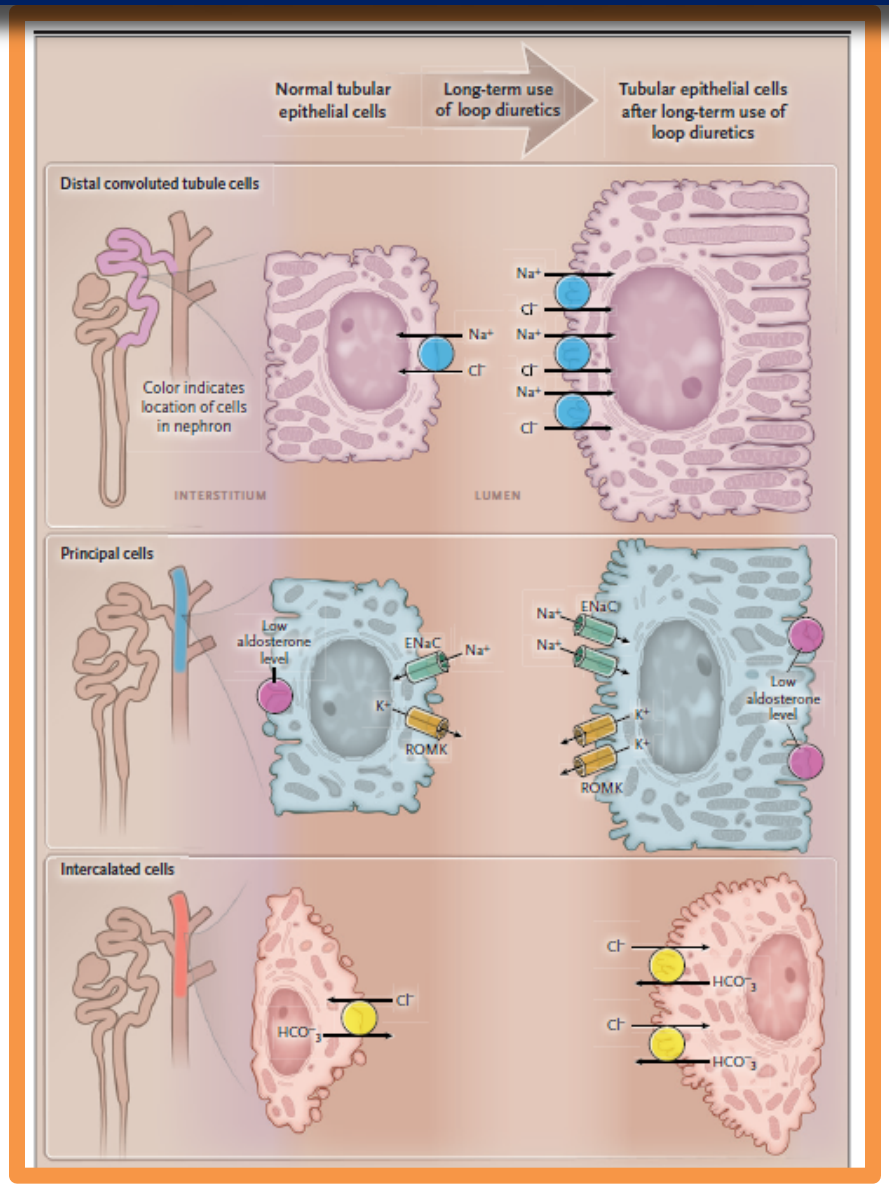
Distal Nephron Remodeling

long-term use of loop diuretics

NCC

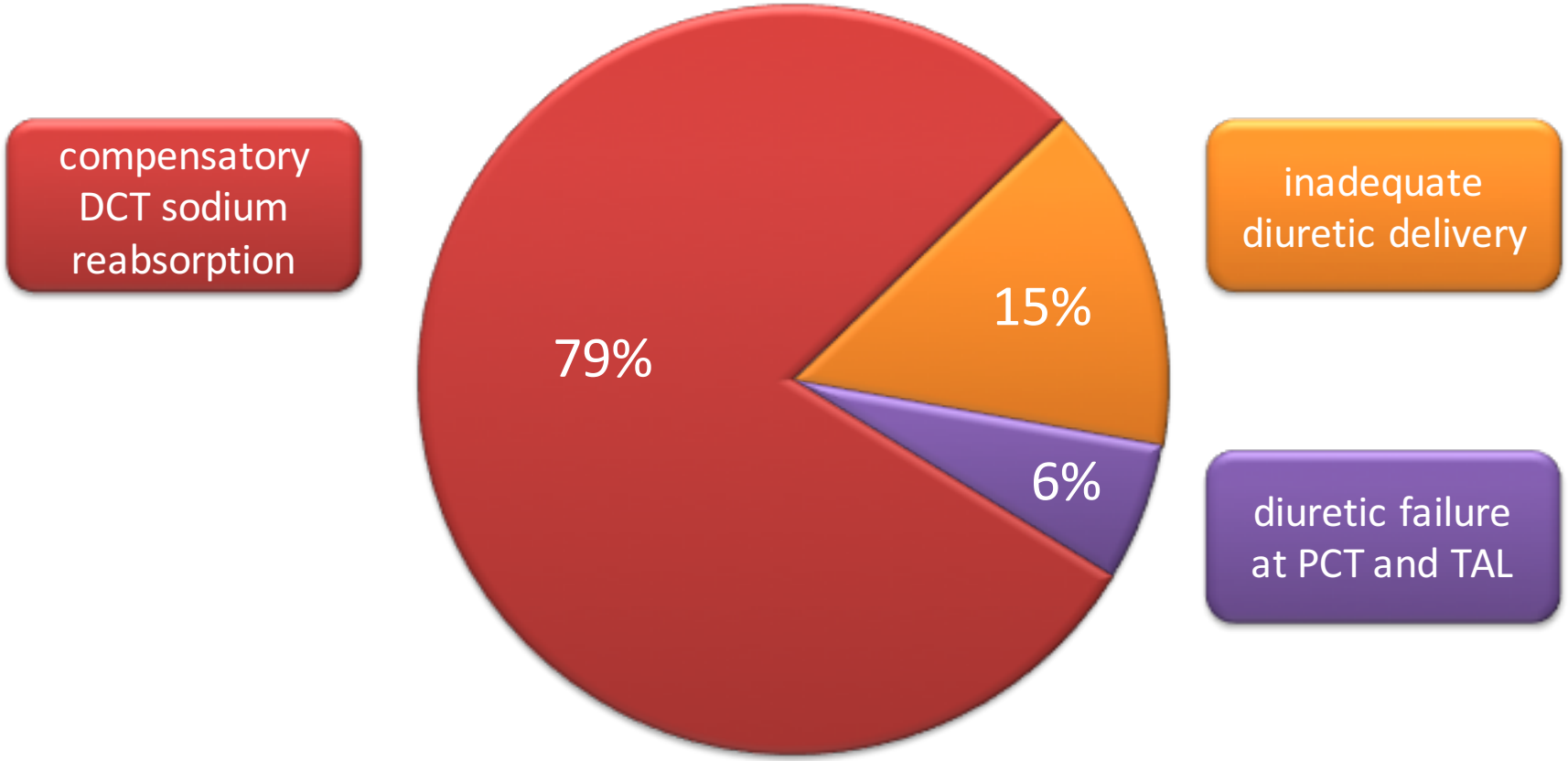
ENaC

Pendrin



Ellison D. Engl J Med 2017;377:1964

Diuretic Resistance is Driven by DCT



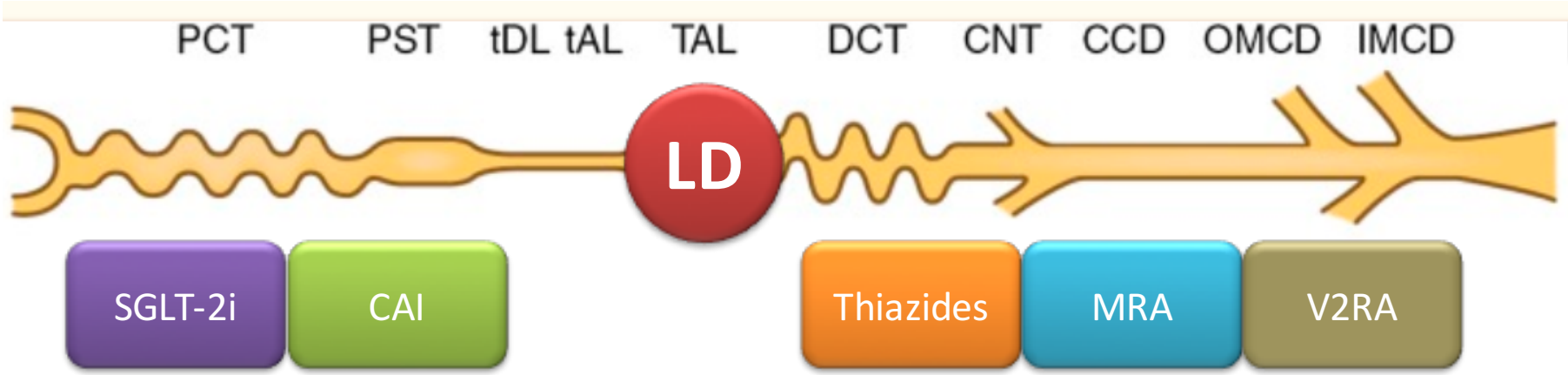
In humans, similar to rodents, distal tubular compensatory sodium reabsorption is a primary driver of DR

Adapted-Rao VS. Am Soc Nephrol 28: 3414–3424, 2017

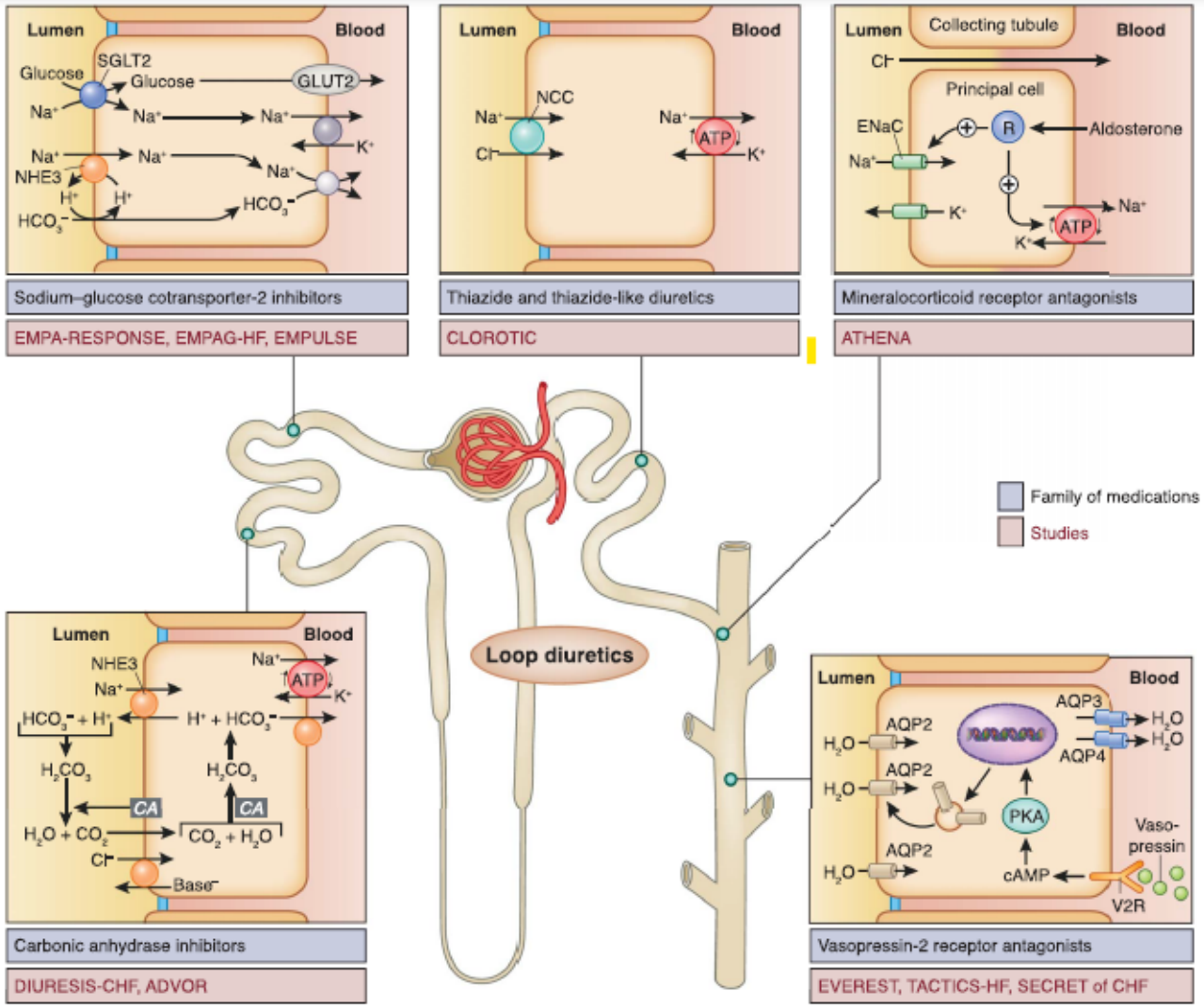
What to do when diuresis/natriuresis is suboptimal?

Nesiritide	X
Dopamine	X
Hypertonic Saline	?
Sequential Nephron Blockade	+
Extracorporeal Ultrafiltration	+

Sequential Nephron Blockade

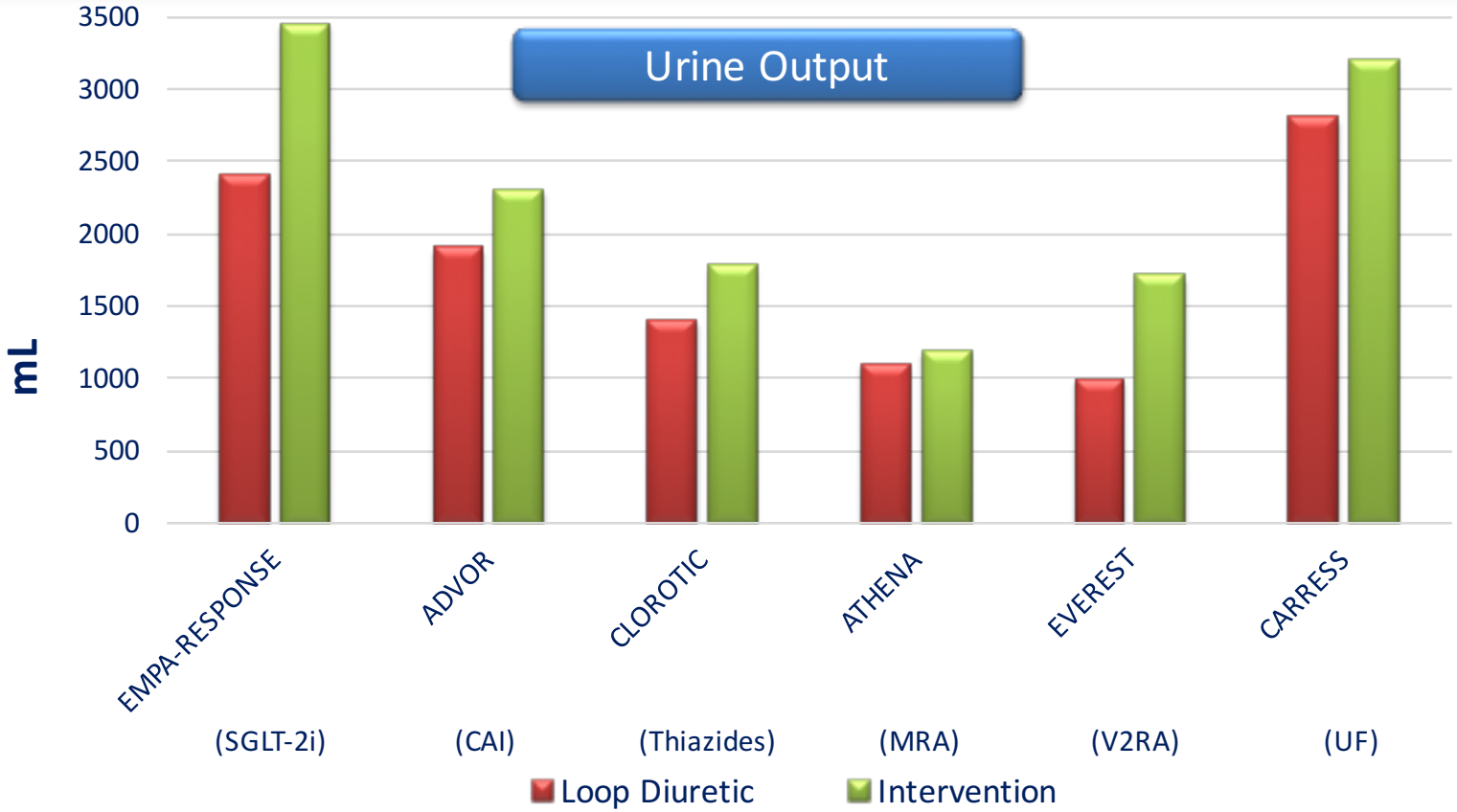


Sequential Sodium Blockade in 2024



Kazory A. Clin J Am Soc Nephrol 2023;18:1372

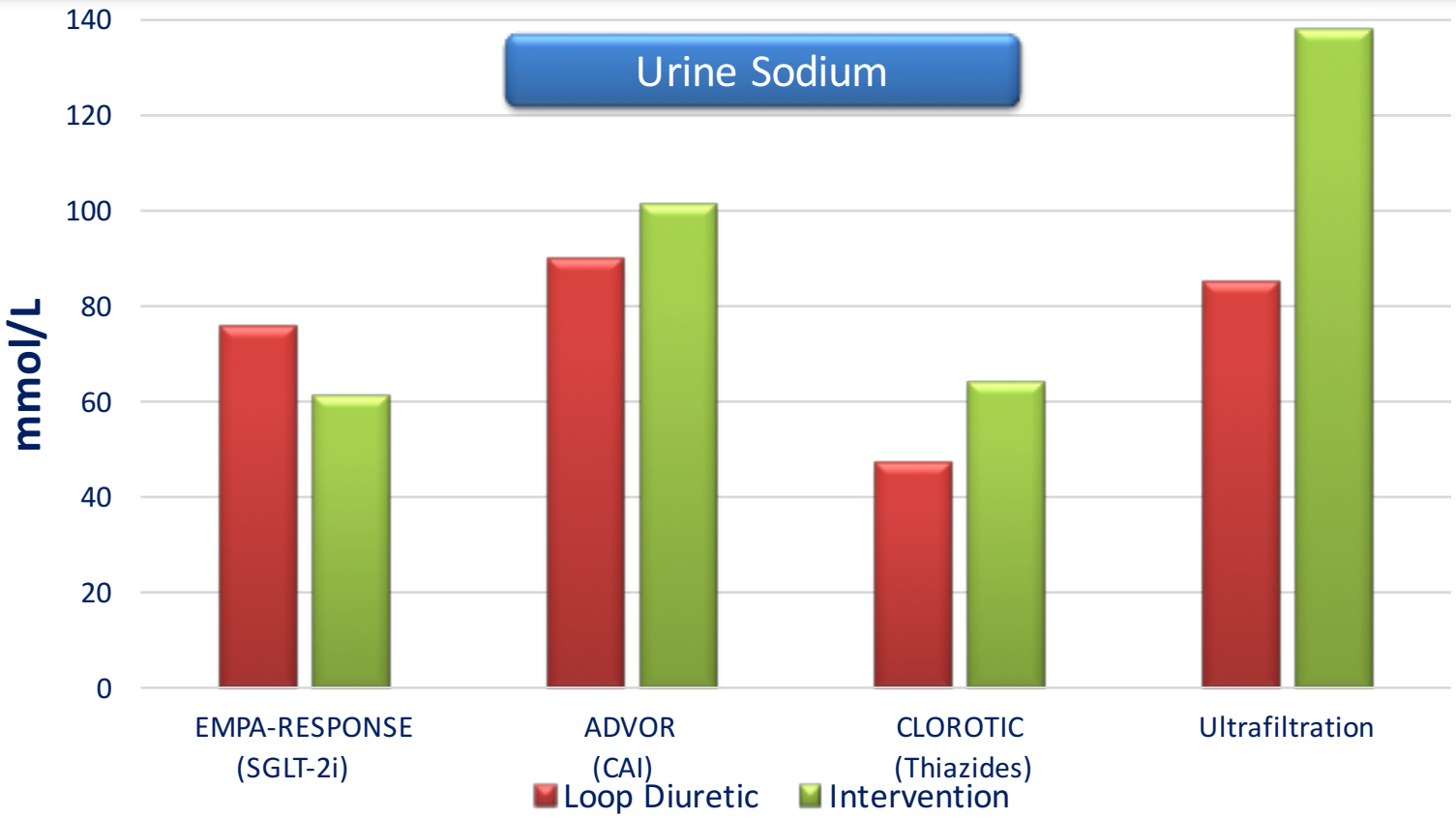
CDT and Urine Volume



The difference in UOP is more pronounced for SGLT-2i and V2RA

Kazory A. cJASN 2023

CDT and Urine Sodium



The difference in sodium concentration is more pronounced for Thiazides and ultrafiltration

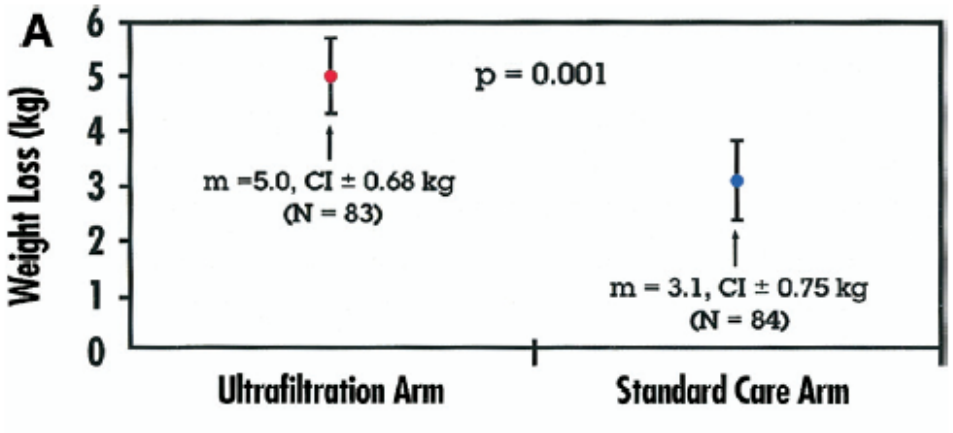
Kazory A. cJASN 2023

ULTRAFILTRATION

“Practice of UF Therapy”: What did Landmark Clinical Trials Show?

UNLOAD	CARRESS-HF
ADHF – 200 patients	CRS – 186 patients
Randomized within 24 hours of admission	RSC 90 days before to 10 days after admission
Baseline Creatinine 1.5 mg/dl	Baseline Creatinine 2.0 mg/dl
Primary Endpoint: changes in weight	Primary Endpoint: changes in weight and serum creatinine
Flexible UF (up to 500 ml/hr)	Fixed UFR (200 ml/hr)

UNLOAD



Decongestion: UF > DR
RSC (WRF): UF = DR

CARRESS-HF

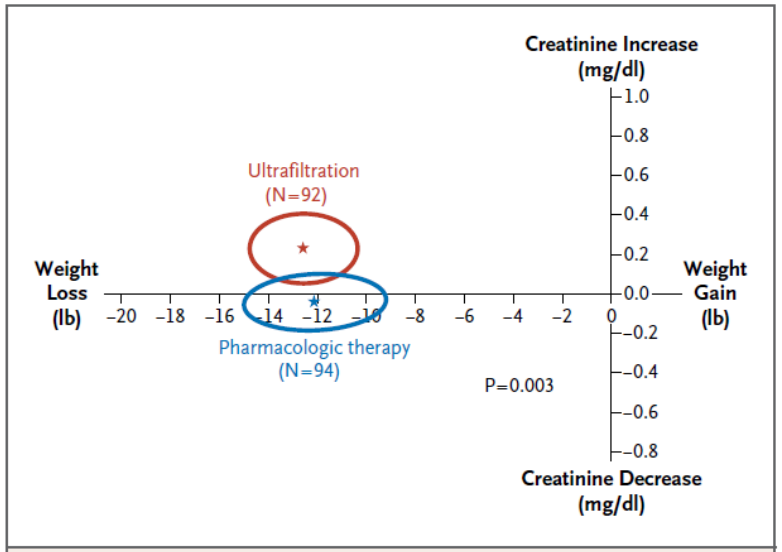
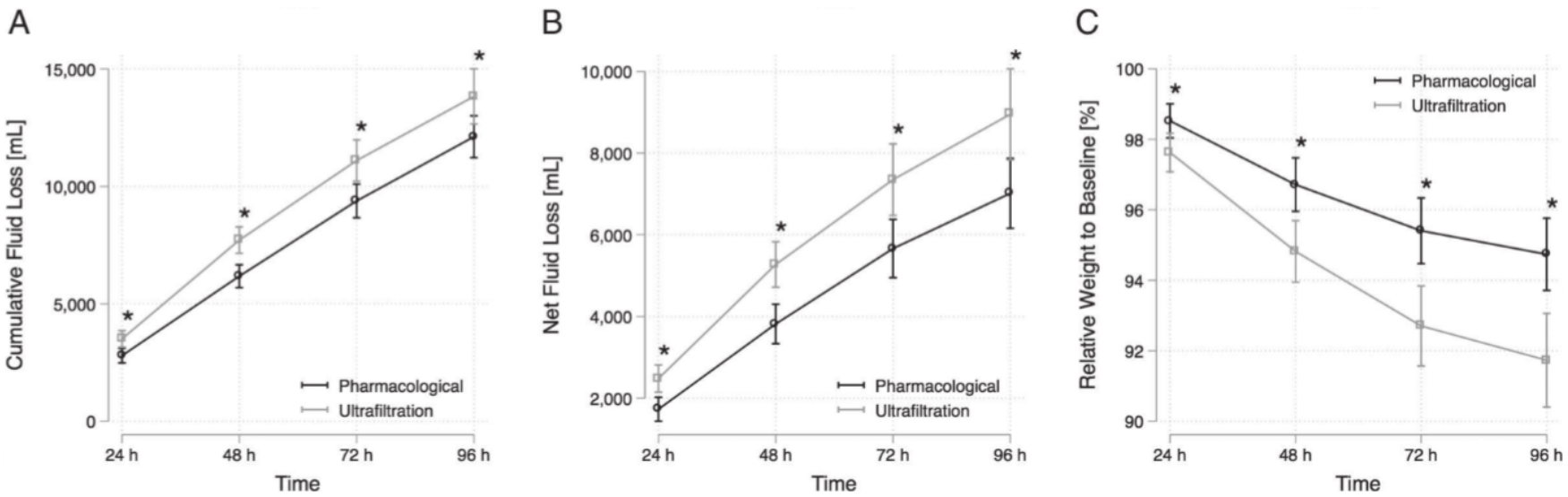


Figure 1. Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response).

Decongestion: UF = DR
RSC (WRF): UF > DR

CARRESS-HF

per-protocol analysis



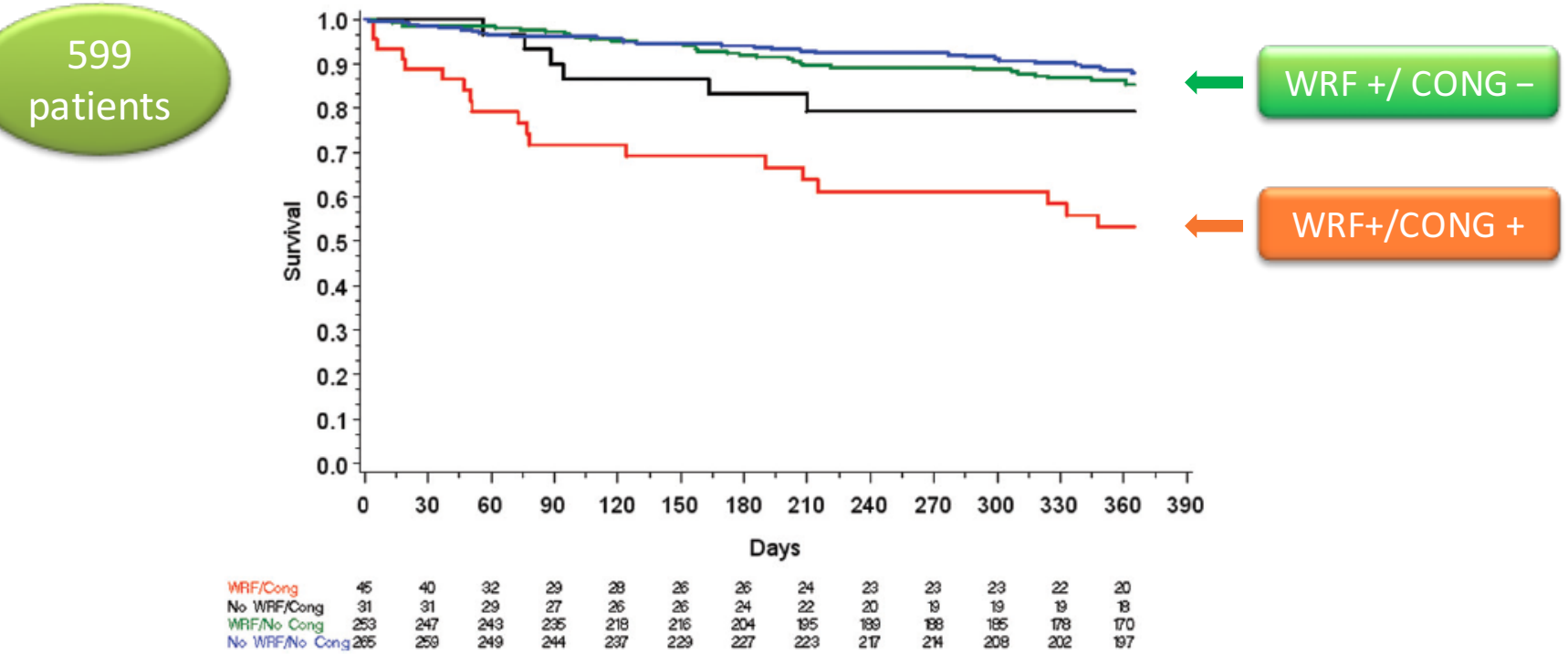
In contrast to the original trial (intention-to-treat), UF was associated with significantly more fluid loss and weight reduction

Decongestion: UF > DR

[Grodin JL, Europ J Heart Fail 2018doi:10.1002/ejhf.1158]

Interplay of RSC (WRF)-De(Congestion)

599 patients



WRF +/ CONG –

WRF+/CONG +

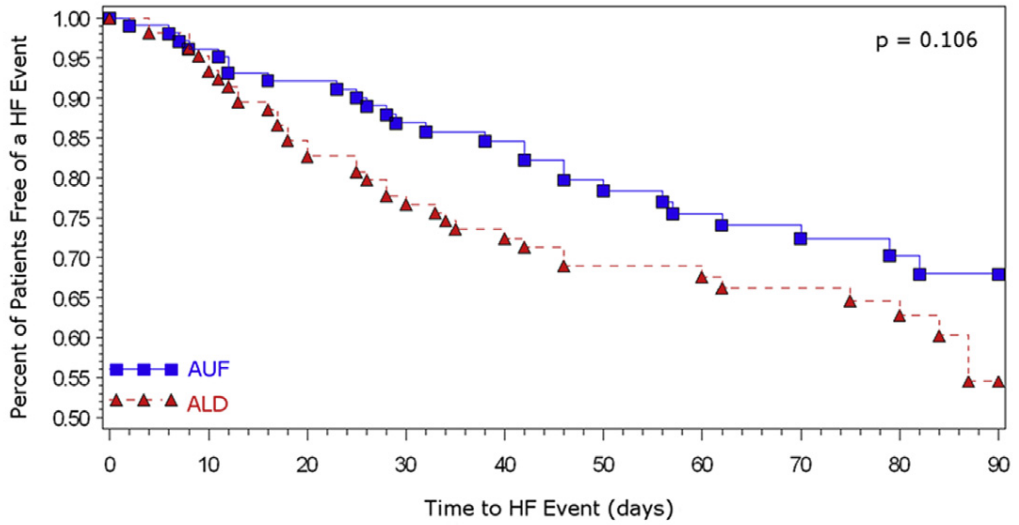
Endpoints: 1 year death or urgent transplantation

[Metra M. Circ Heart Fail 2012; 5: 54]

AVOID-HF

- ADHF – 224 patients
- Randomized within 24 hours of admission
- Baseline Creatinine 1.5 mg/dl
- Time to first HF event within 90 days: Primary Endpoint
- Adjustable UF

FIGURE 2 Primary Endpoint: Time to Heart Failure Event after Discharge



Fluid Removal: UF > DR
HF Event: UF < DR
RSC (WRF): UF = DR

[Costanzo MR, JACC Heart Fail 2016; 4: 95-105*]*

Table IV. Treatment guidelines for the aquapheresis arm

General comments:
1. Once an initial UF rate is chosen, avoid increasing the UF rate unless there are clear indications to do so.
2. Because patients' plasma refill rate usually declines as fluid is removed, it should be expected that UF rate will need to be decreased during the course of therapy.

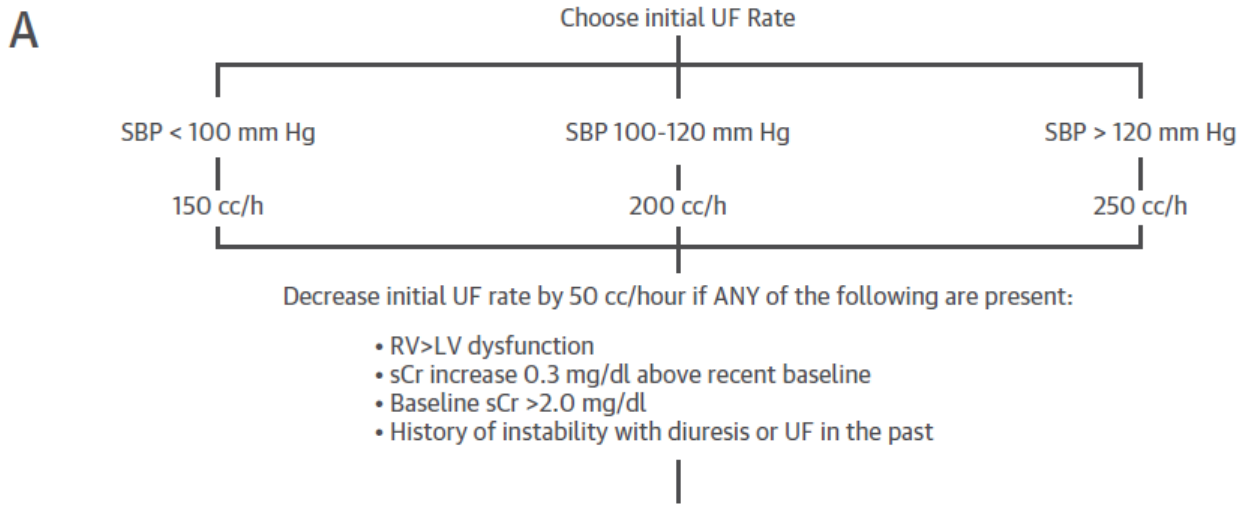
A. Choose initial UF rate:
SBP <100 mm Hg: 150 cc/h
SBP 100-120 mm Hg: 200 cc/h
SBP >120 mm Hg: 250 cc/h

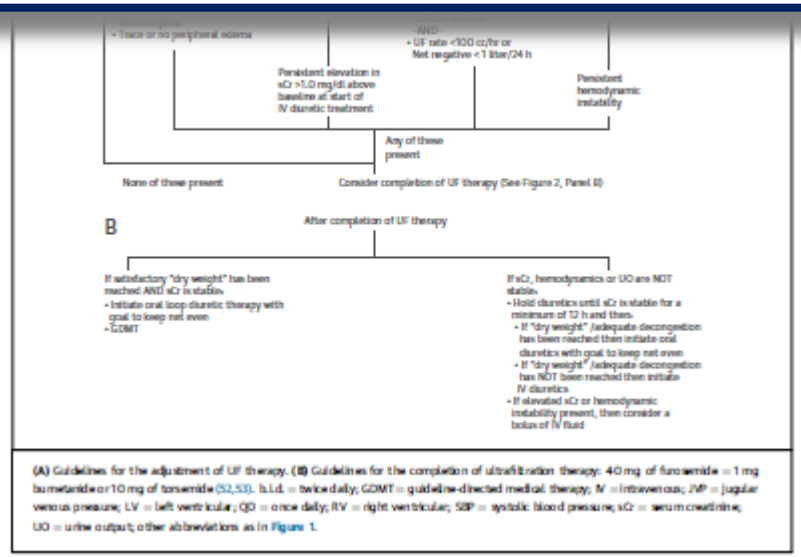
General comments:
1. Once an initial UF rate is chosen, avoid increasing the UF rate unless there are clear indications to do so.
2. Because patients' plasma refill rate usually declines as fluid is removed, it should be expected that UF rate will need to be decreased during the course of therapy.
A. Choose initial UF rate:
SBP <100 mm Hg: 150 cc/h
SBP 100-120 mm Hg: 200 cc/h
SBP >120 mm Hg: 250 cc/h
B. Decrease starting UF rate by 50 cc/h if any of the following are present:
a. RV > LV systolic dysfunction
b. sCr increase 0.3 mg/dL above recent baseline
c. Baseline sCr > 2.0 mg/dL
d. History of instability with diuresis or UF in the past
C. Reevaluate UF rate every 6 h:
1. Evaluate recent BP, HR, UO, net intake/output, sCr
2. Consider decreasing Aq. by 50 cc/h and checking STAT sCr (unless sent in past 2 h) if:
D. Consider completion of UF therapy if one of the following occurs:
1. Resolution of congestion (all of following):
a. Jugular venous pressure <8 cm H_2O
b. No orthopnea
c. Trace or no peripheral edema
2. Best achievable dry weight has been reached
a. Evidence of poor tolerance of fluid removal
AND
b. UF rate <100 cc/h or net negative <1 L/24 h
3. Persistent elevation in sCr >1.0 mg/dL above baseline at start of UF treatment
4. Persistent hemodynamic instability
E. After completion of UF Therapy:
1. If satisfactory dry weight has been reached AND sCr is stable:
a. Initiate oral loop diuretics with goal to keep net even (new dose of loop diuretics may be less than baseline dose in some patients)
b. GDMT
2. If sCr, hemodynamics, or UO are NOT stable:
a. Hold diuretics until sCr is stable for minimum of 12 h, then:
i. If dry weight/adequate decongestion has been reached then initiate oral diuretics as above
ii. If dry weight/adequate decongestion has NOT been reached then initiate IV diuretics
b. If elevated sCr or hemodynamic instability persist, then consider bolus of IV fluids

Abbreviations: *SBP*, Systolic blood pressure; *RV*, right ventricle; *LV*, left ventricle; *BP*, blood pressure; *HR*, heart rate; *UO*, urine output; HFpEF, Heart Failure with preserved ejection fraction.

[Costanzo MR, JACC Heart Fail 2016; 4: 95-105]

FIGURE 2 Adjustable UF Guidelines Used by the AVOID-HF Investigators





(A) Guidelines for the adjustment of UF therapy. (B) Guidelines for the completion of ultrafiltration therapy: 40 mg of furosemide = 1 mg bumetanide or 10 mg of torsemide (52,53). b.i.d. = twice daily; GDMT = guideline-directed medical therapy; IV = intravenous; JVP = jugular venous pressure; LV = left ventricular; QD = once daily; RV = right ventricular; SBP = systolic blood pressure; sCr = serum creatinine; UO = urine output; other abbreviations as in Figure 1.

Average
UFR: 138 ml/h
For 80 hours

[Costanzo et al. J Am Coll Cardiol 2017; 69:2428]

Optimal Ultrafiltration Protocol for ADHF and Fluid Overload

1) Patients selection (recurrent admissions)
2) Early initiation of UF
3) Withhold Diuretics during UF therapy
4) Use low UFR
5) Customize UF therapy on initiation
6) Revisit UFR frequently during therapy
7) Objectively monitor decongestion

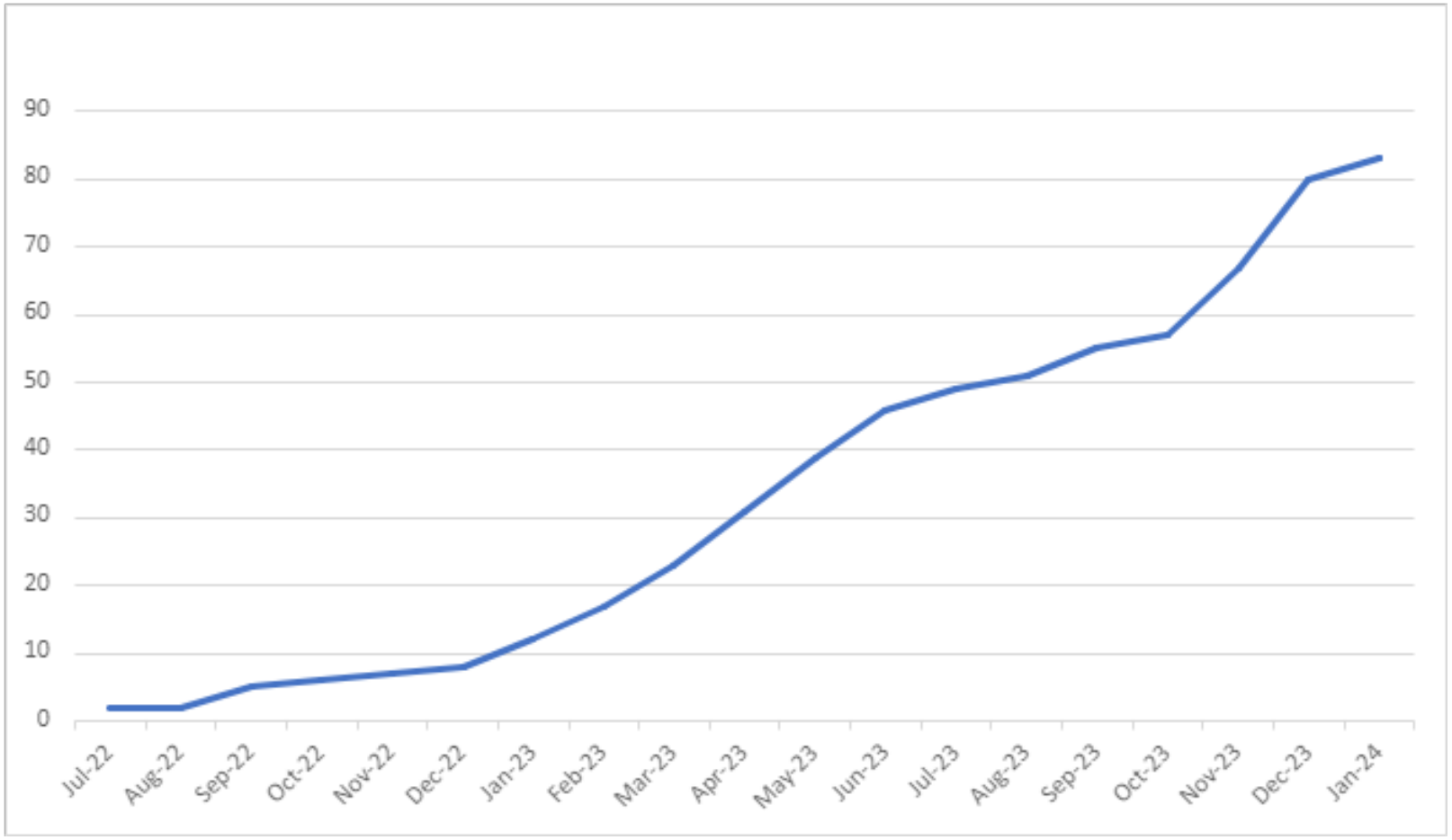
In the Pipeline: 2024

Ultrafiltration versus IV Diuretics in Worsening Heart Failure (REVERSE-HF)

- Multicenter, Open Label, RCT USA
- Aquadex Smartflow® System
- Adjustable UF vs. Adjustable Diuretics
- ADHF – 372 patients
- 6 months follow up
- Endpoints: Time to first HF event (90 d), Mortality (90 d), HF event (30 d)

In the Pipeline: 2024

REVERSE-HF Subjects Enrolled



Case

A 65-year-old man with a history of CAD, HTN, HFrEF (EF 35%) is admitted to the Cardiac ICU for progressive dyspnea and a weight gain of 15 lbs over the last 1 month. His BP is 121/56, PR 14, RR 59, T 98.5. His home meds include lisinopril 40 mg/day, furosemide 40 mg BID, and Metoprolol XL 50 mg/day. CXR shows pulmonary edema.

He is started on IV furosemide 80 mg BID. The next day, his urine output is 450 ml and the labs show the following: Na 136, K 4.1, Cl 96, Bicarb 29, BUN 22, Creatinine 1.2

<u>Which of the following is the best next step?</u>

1) Check urine sodium
2) Add IV acetazolamide 500 mg once daily
3) Add Empagliflozin 10 mg once daily
4) Start HCTZ 25 mg once daily
5) Start ultrafiltration

Case

A 65-year-old man with a history of CAD, HTN, HFrEF (EF 35%) is admitted to the Cardiac ICU for progressive dyspnea and a weight gain of 15 lbs over the last 1 month. His BP is 121/56, PR 14, RR 59, T 98.5. His home meds include lisinopril 40 mg/day, furosemide 40 mg BID, and Metoprolol XL 50 mg/day. CXR shows pulmonary edema.

He is started on IV furosemide 80 mg BID. The next day, his urine output is 450 ml and the labs show the following: Na 136, K 4.1, Cl 96, Bicarb 29, BUN 22, Creatinine 1.2

Which of the following is the best next step?

1) Check urine sodium **[PUSH-HF]**
2) Add IV acetazolamide 500 mg once daily **[ADVOR]**
3) Add Empagliflozin 10 mg once daily **[EMPA-RESPONSE]**
4) Start HCTZ 25 mg once daily **[CLOROTIC]**
5) Start ultrafiltration **[ADVOR]**

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CRRT, INC.

Thank You...

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