Iranian Society of Heart Failure

Diuretic Resistance in Acute Heart Failure

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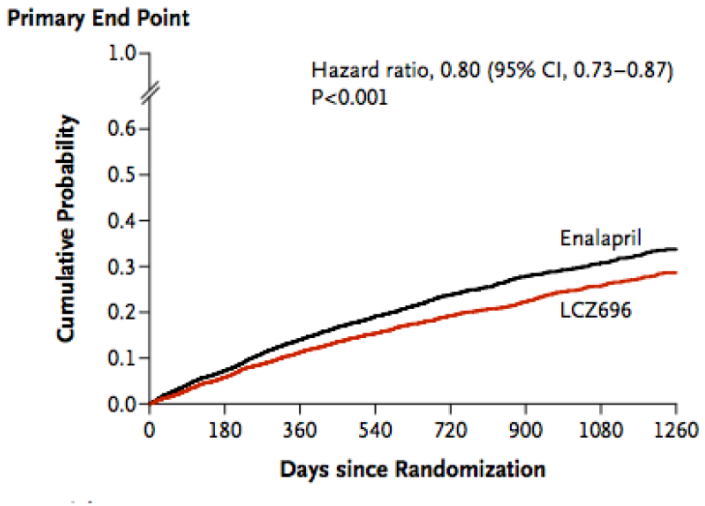
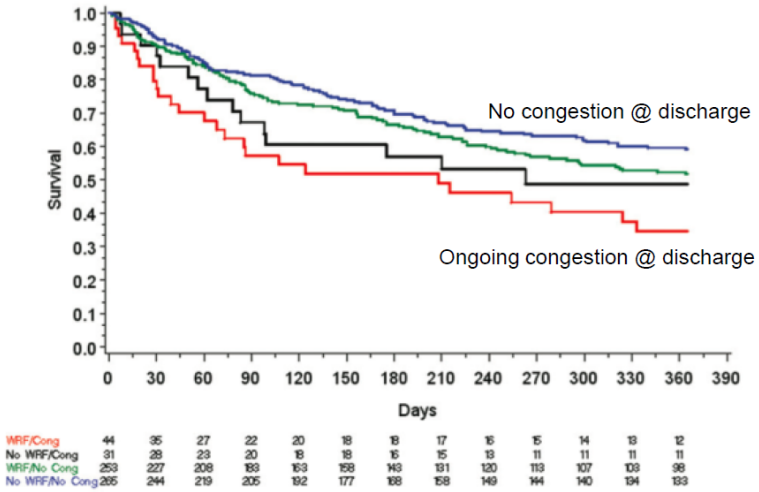
Tehran-Iran

Underappreciated risk for hospitalization / death linked to residual congestion in HFpnts

Ambulatory: 20% risk at 2 years

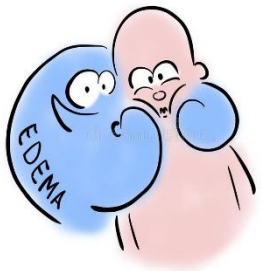
Recently Hospitalized: 60% risk at 1 year

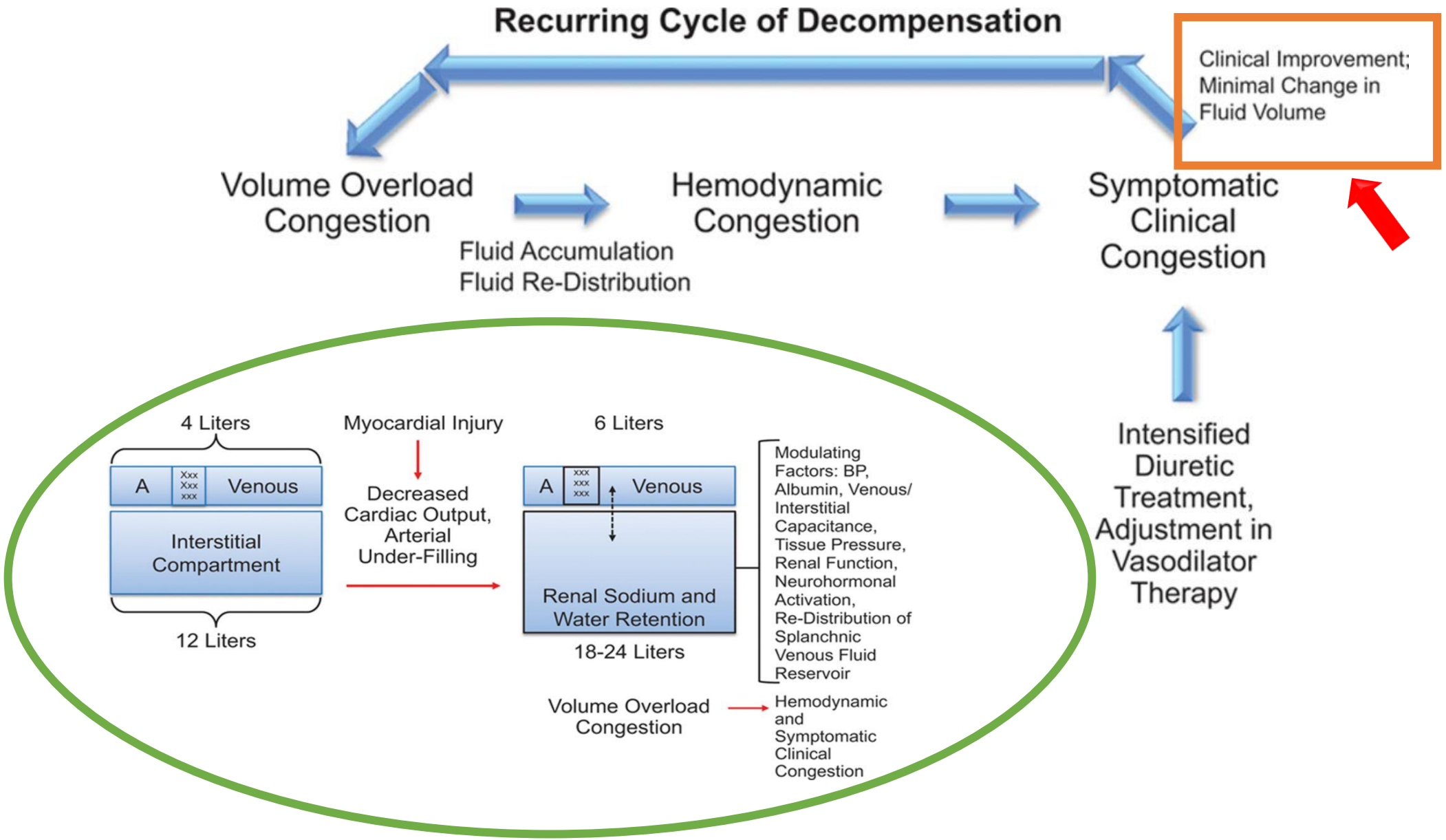




McMurray, Packer et al NEJM 2014
Metra M et al. Circ Heart Fail. 2012;5:54-62

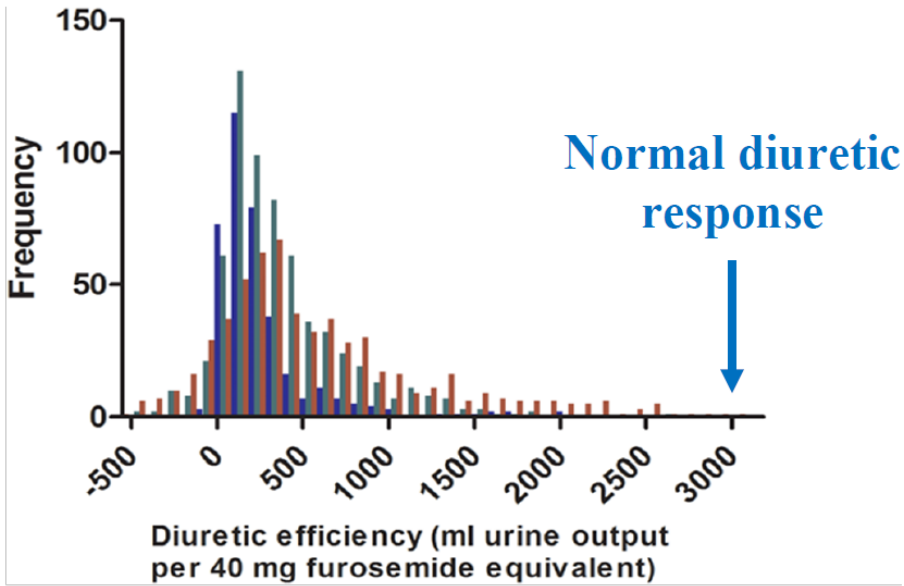
31% of acute heart failure patients leave hospital with residual congestion, having a higher risk of 1-year mortality compared with those discharged with no congestion



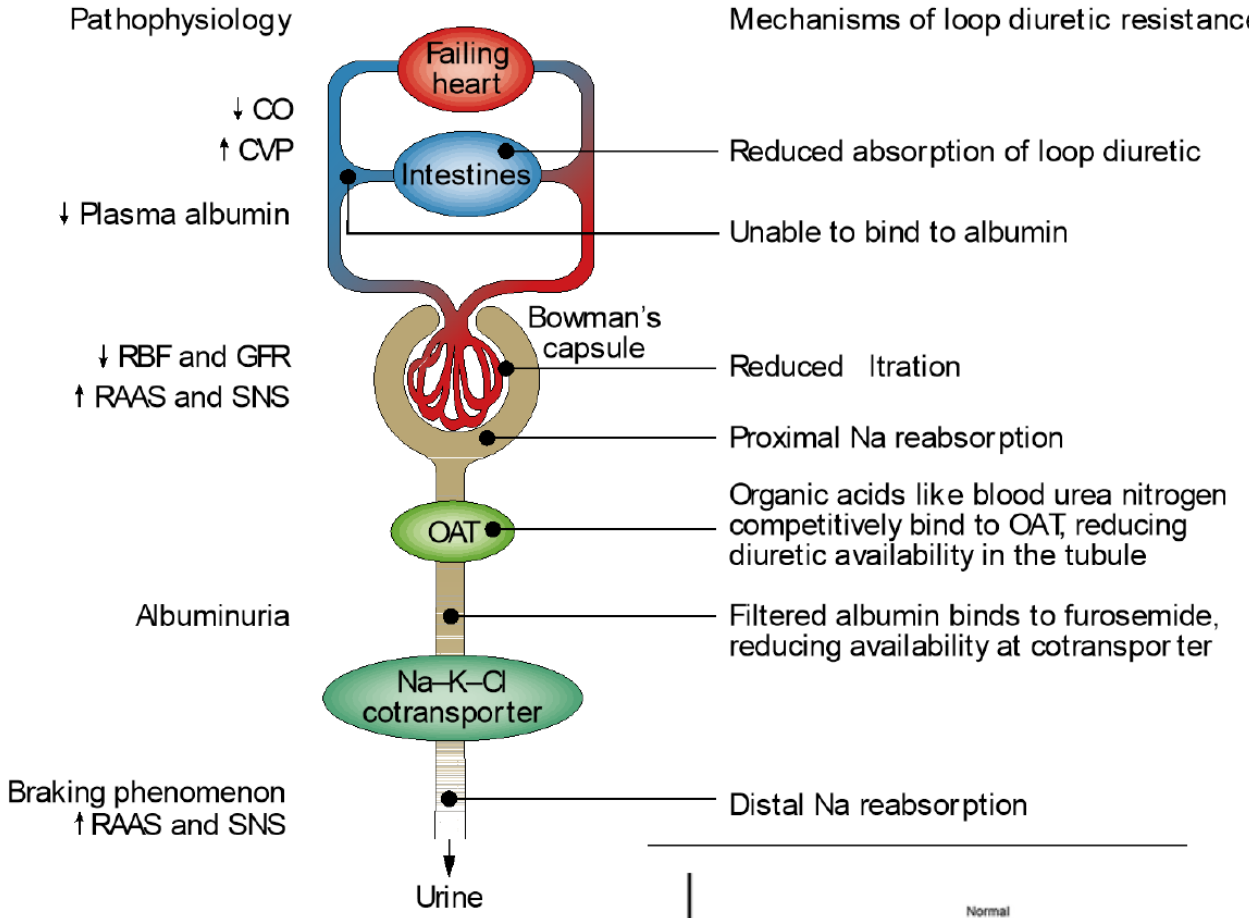


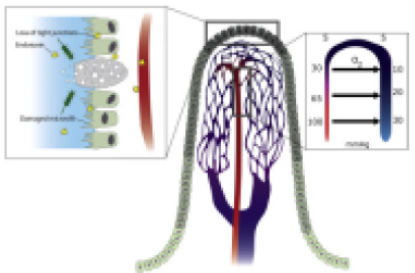
Wayne L. Miller. Circulation: Heart Failure. Fluid Volume Overload and Congestion in Heart Failure DOI: (10.1161/CIRCHEARTFAILURE.115.002922)

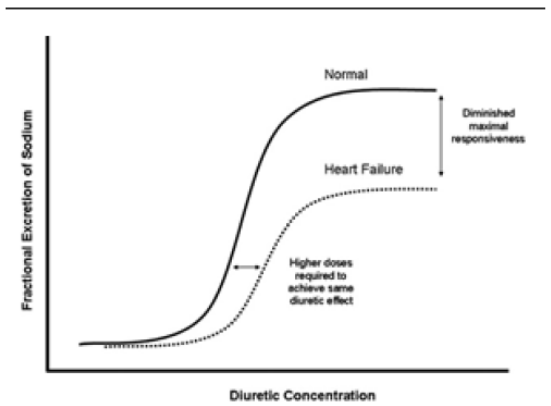
"Diuretic resistance" is omnipresent in HF patients



Diuretic resistance is defined as an impaired sensitivity to diuretics resulting in reduced natriuresis and diuresis limiting the possibility to achieve euvolaemia



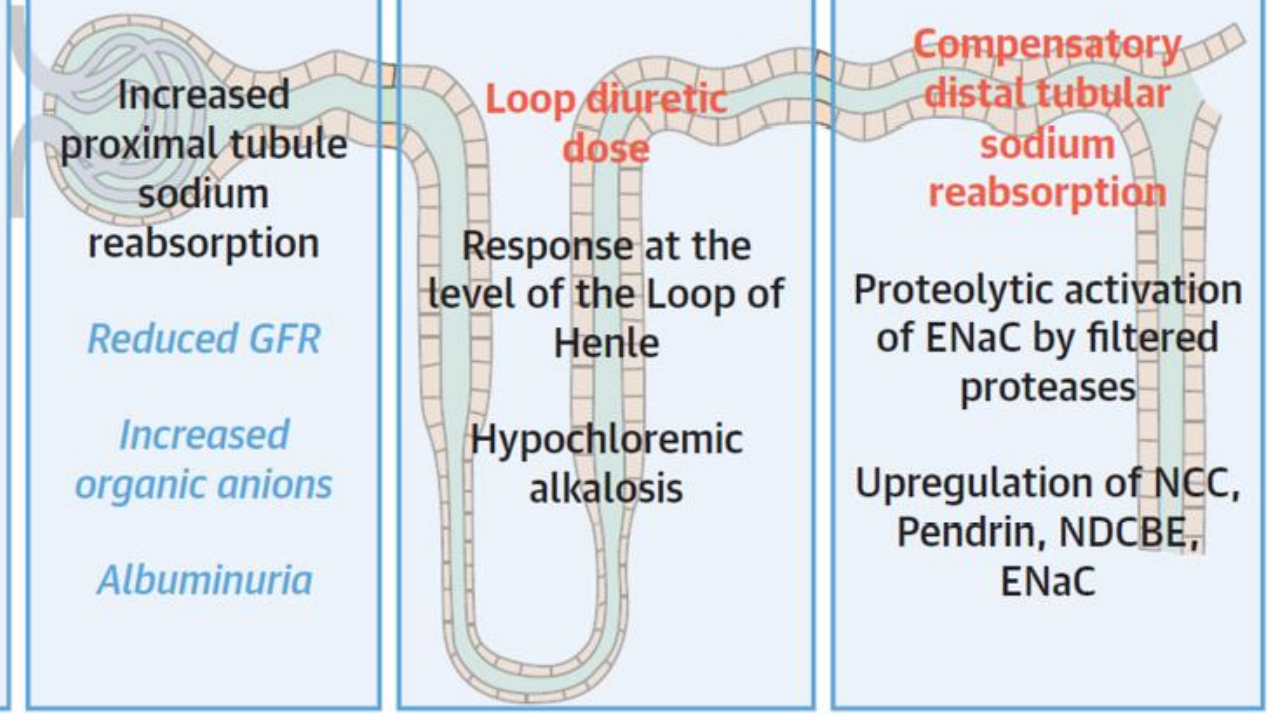




Heart Failure & World Congress on Acute Heart Failure 2021

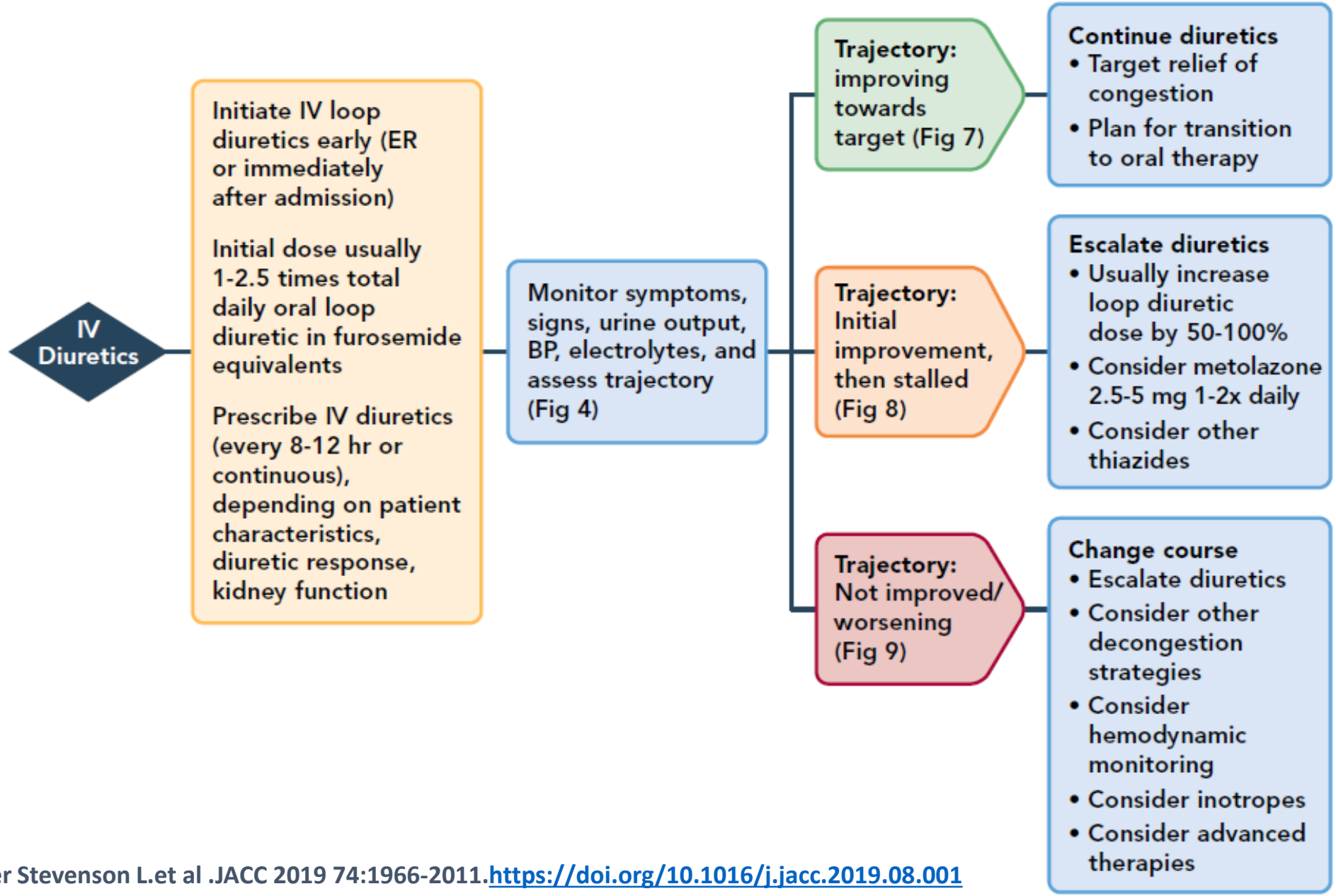
Testani J et al. Circ Heart Fail 2014
ter Maaten, J. M. et al. Nat. Rev. Cardiol. 2015

Importance of specific cause/mechanism on diuretic resistance	Diuretic Resistance Categorization			
	Pre-Renal	Intra-Renal		
		Pre-Loop of Henle	Loop of Henle	Post-Loop of Henle
Significant Unknown but hypothesized to be significant *Not significant with the mild to moderate derangement found in the average HF patient*	Venous congestion Increased intra-abdominal pressure *Reduced cardiac output* *Hypoalbuminemia* *High sodium intake*	Increased proximal tubule sodium reabsorption *Reduced GFR* *Increased organic anions* *Albuminuria*	**Loop diuretic dose** Response at the level of the Loop of Henle Hypochloremic alkalosis	**Compensatory distal tubular sodium reabsorption** Proteolytic activation of ENaC by filtered proteases Upregulation of NCC, Pendrin, NDCBE, ENaC



Cox ZL, Testani JM. Loop diuretic resistance in a patient with acute heart failure. In: Tang WHW, Verbrugge FH, Mullens W, editors. Cardiorenal Syndrome in Heart Failure. London, UK: Springer Nature, 2019:153–73.

FIGURE 6 Diuretic Therapy in Different Clinical Trajectories



Hollenberg SM, Warner Stevenson L.et al .JACC 2019 74:1966-2011.https://doi.org/10.1016/j.jacc.2019.08.001

ESC European Society of Cardiology

European Journal of Heart Failure (2019) **21**, 137–155
doi:10.1002/ejhf.1369

POSITION PAPER

The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology

Wilfried Mullens[1,2]*, Kevin Damman[3], Veli-Pekka Harjola[4], Alexandre Mebazaa[5], Hans-Peter Brunner-La Rocca[6], Pieter Martens[1,2], Jeffrey M. Testani[7], W.H. Wilson Tang[8], Francesco Orso[9], Patrick Rossignol[10], Marco Metra[11], Gerasimos Filippatos[12,13], Petar M. Seferovic[14], Frank Ruschitzka[15], and Andrew J. Coats[16]

[1]Ziekenhuis Oost Limburg, Genk, Belgium; [2]University of Hasselt, Hasselt, Belgium; [3]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [4]Emergency Medicine, University of Helsinki, Helsinki University Hospital, Helsinki, Finland; [5]University of Paris Diderot, Hôpitaux Universitaires Saint Louis Lariboisière, APHP, U 942 Inserm, F-CRIN INI-CRCT, Paris, France; [6]Maastricht University Medical Center, Maastricht, The Netherlands; [7]Yale University, New Haven, CT, USA; [8]Cleveland Clinic, Cleveland, OH, USA; [9]University of Florence, Florence, Italy; [10]Université de Lorraine, Inserm, Centre d'Investigations Clinique 1433 and Inserm U1116; CHRU Nancy; F-CRIN INI-CRCT, Nancy, France; [11]University of Brescia, Brescia, Italy; [12]National and Kapodistrian University of Athens, Athens, Greece; [13]University of Cyprus, Nicosia, Cyprus; [14]University of Belgrade, Faculty of Medicine, Belgrade, Serbia; [15]UniversitätsSpital Zürich, Zürich, Switzerland; and [16]IRCCS, San Raffaele Pisana, Rome, Italy

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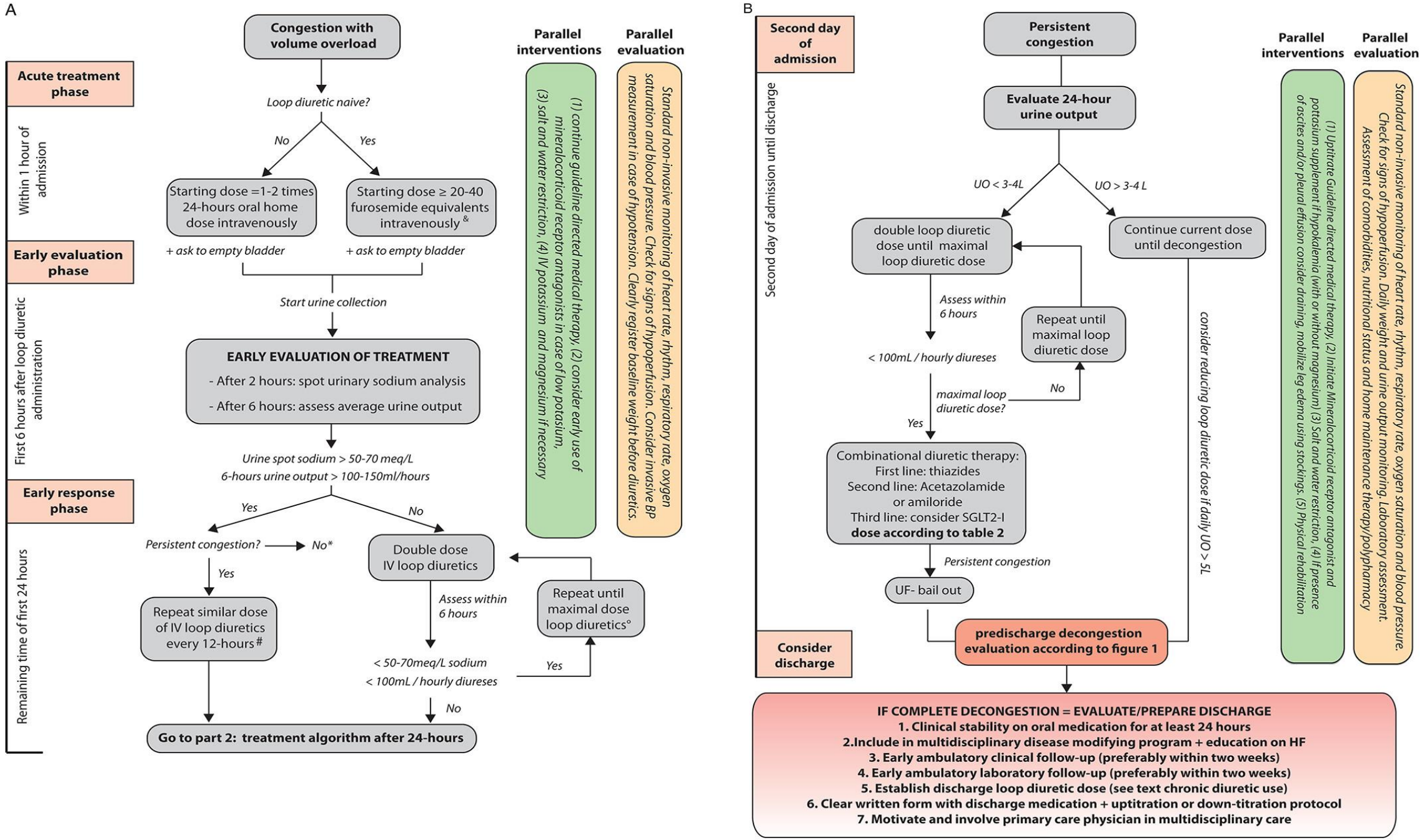
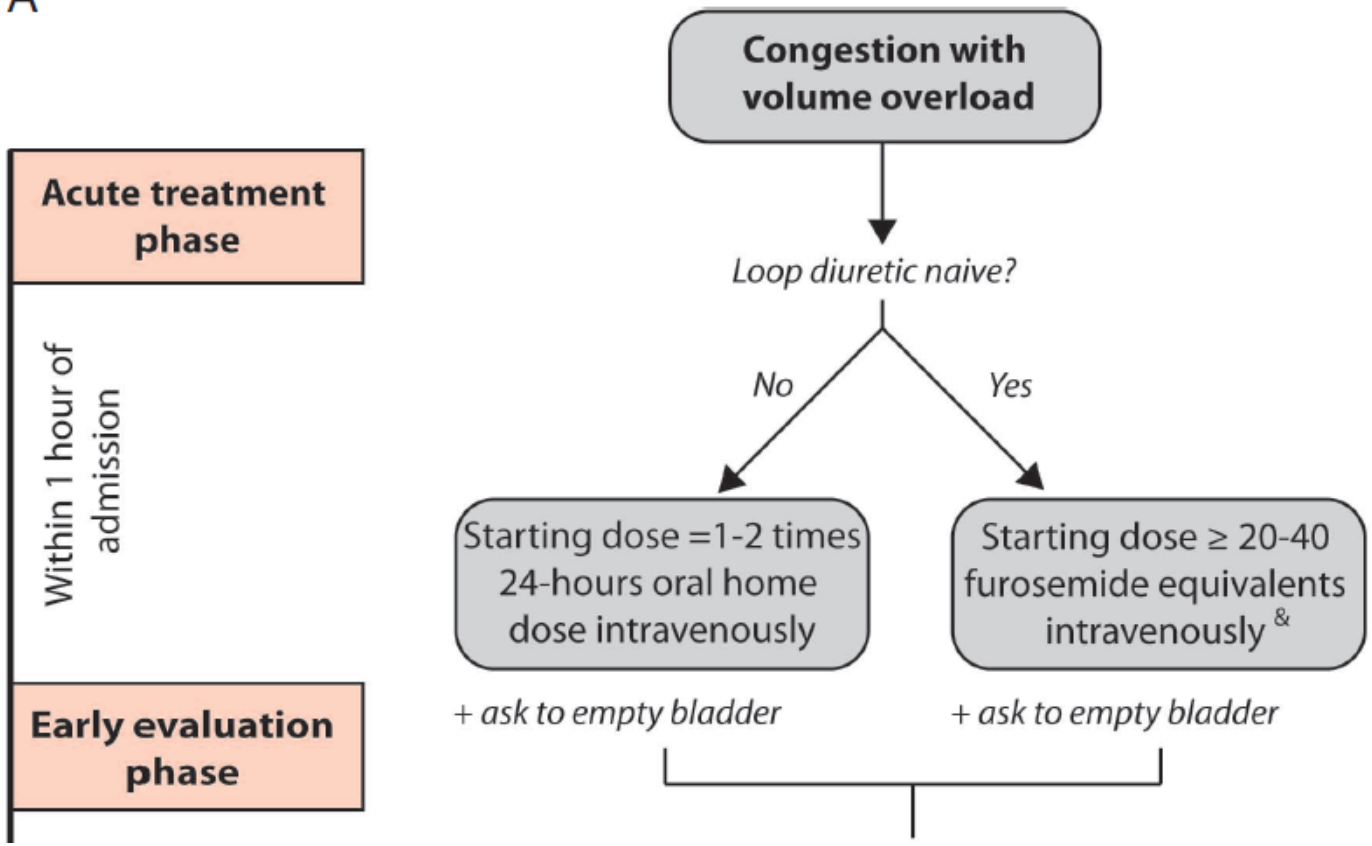

A
Acute treatment phase
Within 1 hour of admission
Early evaluation phase
First 6 hours after loop diuretic administration
Early response phase
Remaining time of first 24 hours
Congestion with volume overload
Loop diuretic naive?
No
Yes
Starting dose =1-2 times 24-hours oral home dose intravenously
Starting dose ≥ 20-40 furosemide equivalents intravenously &
+ ask to empty bladder
+ ask to empty bladder
Start urine collection
EARLY EVALUATION OF TREATMENT
- After 2 hours: spot urinary sodium analysis
- After 6 hours: assess average urine output
Urine spot sodium > 50-70 meq/L
6-hours urine output > 100-150ml/hours
Yes
No
Persistent congestion?
No*
Yes
Repeat similar dose of IV loop diuretics every 12-hours #
Double dose IV loop diuretics
Assess within 6 hours
< 50-70meq/L sodium
< 100mL / hourly diureses
No
Yes
Repeat until maximal dose loop diuretics°
Go to part 2: treatment algorithm after 24-hours
Parallel interventions
(1) continue guideline directed medical therapy, (2) consider early use of mineralocorticoid receptor antagonists in case of low potasium, (3) salt and water restriction, (4) IV potassium and magnesium if necessary
Parallel evaluation
Standard non-invasive monitoring of heart rate, rhythm, respiratory rate, oxygen saturation and blood pressure. Check for signs of hypoperfusion. Consider invasive BP measurement in case of hypotension. Clearly register baseline weight before diuretics.
B
Second day of admission
Second day of admission until discharge
Persistent congestion
Evaluate 24-hour urine output
UO < 3-4L
UO > 3-4 L
double loop diuretic dose until maximal loop diuretic dose
Continue current dose until decongestion
Assess within 6 hours
< 100mL / hourly diureses
Repeat until maximal loop diuretic dose
No
maximal loop diuretic dose?
Yes
Combinational diuretic therapy:
First line: thiazides
Second line: Acetazolamide or amiloride
Third line: consider SGLT2-I
dose according to table 2
Persistent congestion
UF- bail out
predischarge decongestion evaluation according to figure 1
consider reducing loop diuretic dose if daily UO > 5L
Consider discharge
Parallel interventions
(1) Uptitrate Guideline directed medical therapy, (2) Initiate Mineralocorticoid receptor antagonist and pottasium supplement if hypokalemia (with or without magnesium) (3) Salt and water restriction, (4) If presence of ascites and/or pleural effusion consider draining, mobilize leg edema using stockings. (5) Physical rehabilitation
Parallel evaluation
Standard non-invasive monitoring of heart rate, rhythm, respiratory rate, oxygen saturation and blood pressure. Check for signs of hypoperfusion. Daily weight and urine output monitoring. Laboratory assessment. Assessment of comorbidities, nutritional status and home maintenance therapy/polypharmacy
IF COMPLETE DECONGESTION = EVALUATE/PREPARE DISCHARGE
1. Clinical stability on oral medication for at least 24 hours
2.Include in multidisciplinary disease modifying program + education on HF
3. Early ambulatory clinical follow-up (preferably within two weeks)
4. Early ambulatory laboratory follow-up (preferably within two weeks)
5. Establish discharge loop diuretic dose (see text chronic diuretic use)
6. Clear written form with discharge medication + uptitration or down-titration protocol
7. Motivate and involve primary care physician in multidisciplinary care

A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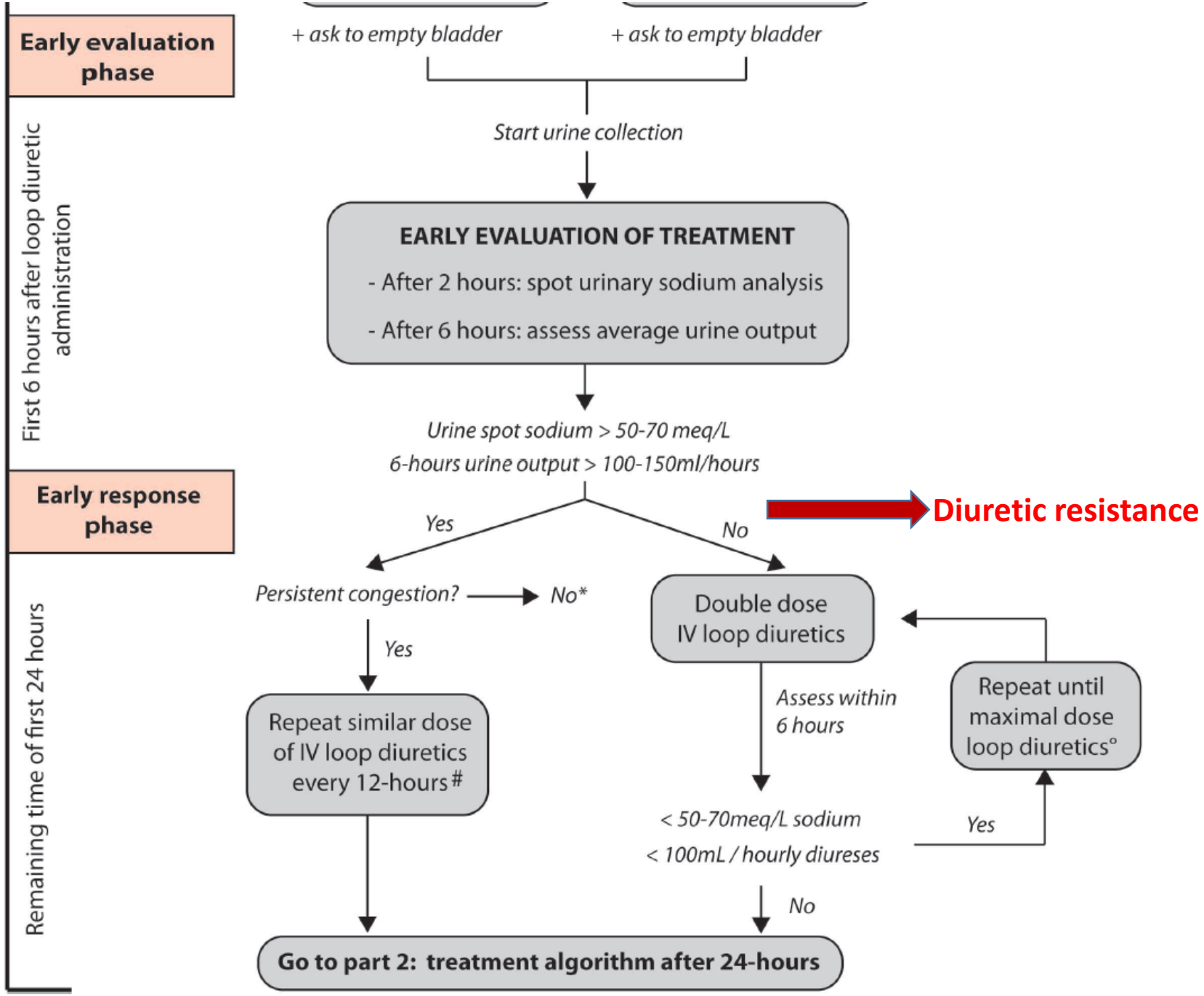
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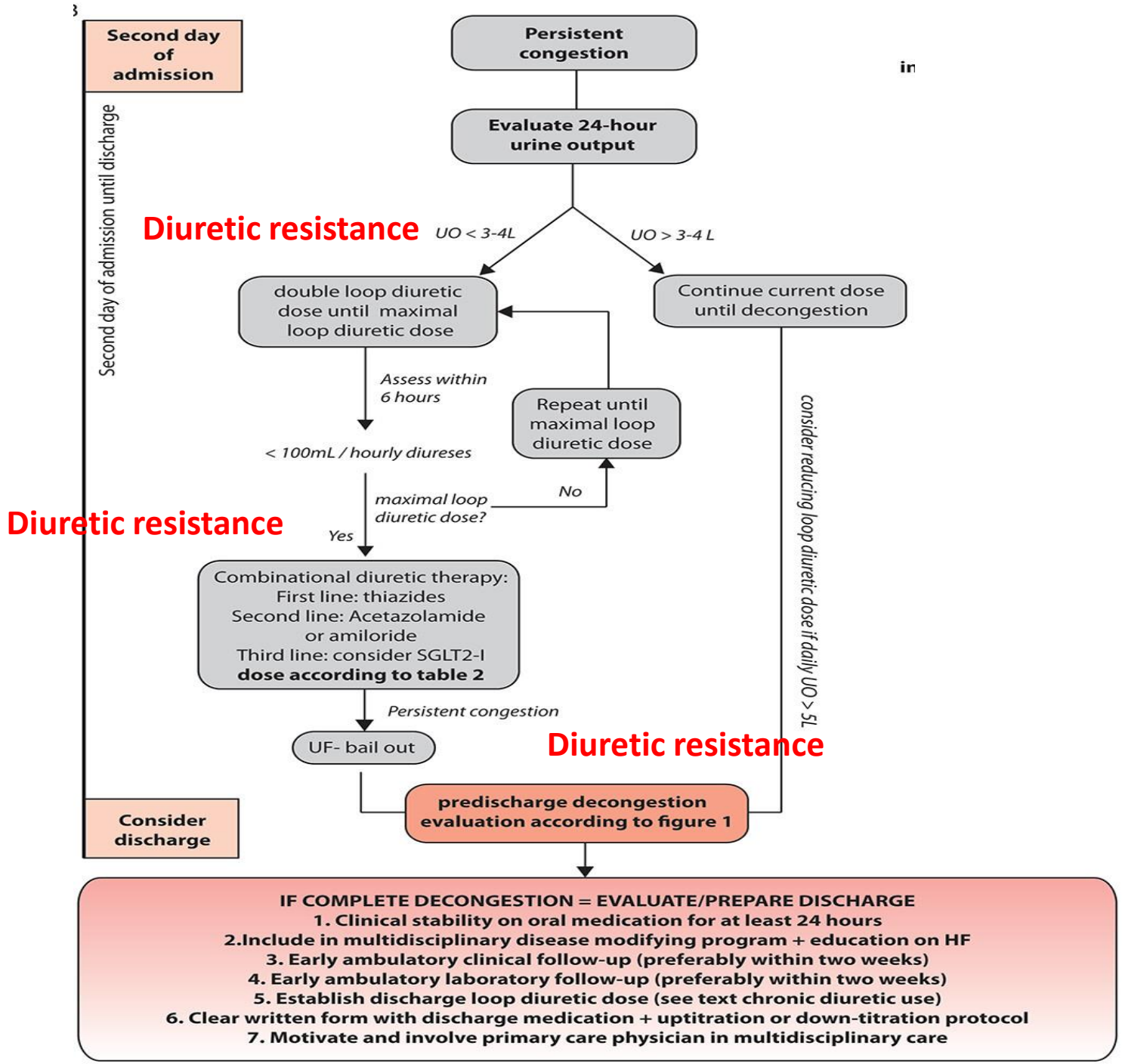
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Combinational diuretic therapy:
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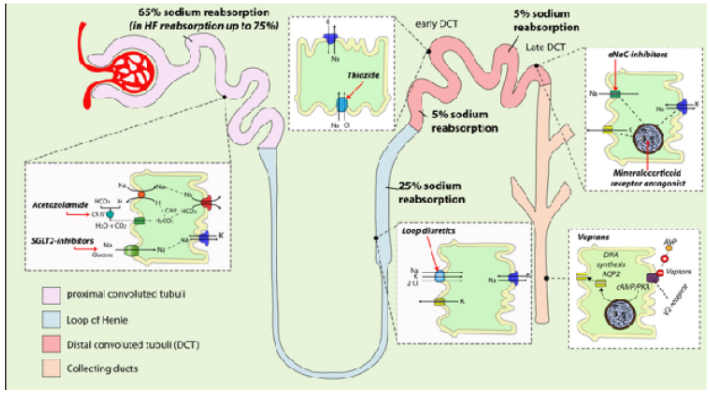
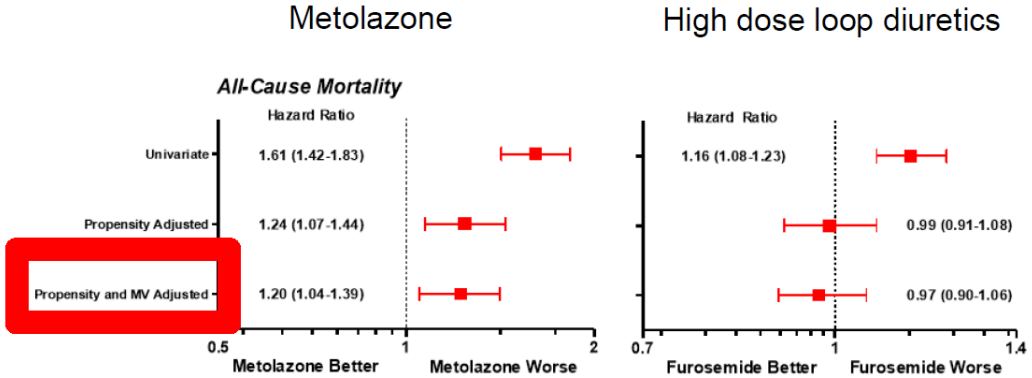
Thiazides, know how to use them

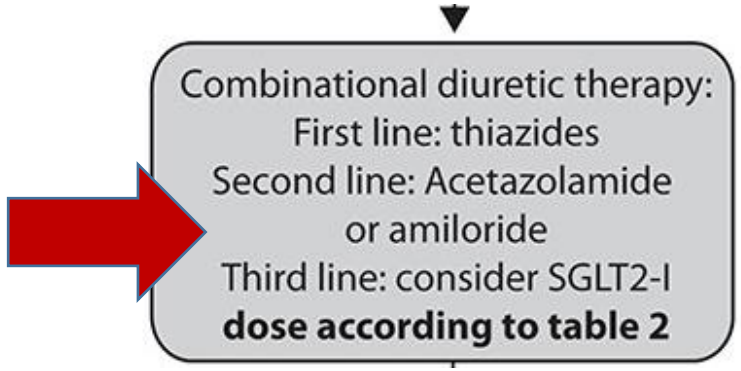




- Work distal in nephron (poor diuretic effect)
- Might counterbalance distal hypertrophy with chronic use of high dose LD
- Also work in low eGFR states
- Slow GI absorption (need to be given hours before LD)
- Protein bound like loop diuretics
- Long half life

Mullens W, Eur J Heart Fail 2019; 21:137-155.

Brisco-Bacik, J Card Fail 2017 abstract supplement S56.



Recent positive trials on acute heart failure

- ADVOR (acetazolamide in decompensated heart failure with volume overload)
- EMPULSE (empagliflozin in patients hospitalized for acute heart failure
- DELIVER (Dapaglifozin Evaluation to Improve the LIVEs of Patients with preserved ejection fraction heart failure)

Heart Failure 2023

DAPAgliflozin versus metolazone in patients with heart failure and diuretic RESISTance: DAPA RESIST

ESC European Society of Cardiology

European Heart Journal (2023) **44**, 2966–2977
https://doi.org/10.1093/eurheartj/ehad341

FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics

Su Ern Yeoh[1†], Joanna Osmanska[1†], Mark C. Petrie [1], Katriona J. M. Brooksbank [1], Andrew L. Clark [2], Kieran F. Docherty [1], Paul W. X. Foley [3], Kaushik Guha[4], Crawford A. Halliday[5], Pardeep S. Jhund [1], Paul R. Kalra[4,6], Gemma McKinley[7], Ninian N. Lang [1], Matthew M. Y. Lee [1], Alex McConnachie [7], James J. McDermott[8], Elke Platz [9], Peter Sartipy[10], Alison Seed[11], Bethany Stanley [7], Robin A.P. Weir [12], Paul Welsh [1], John J. V. McMurray [1], and Ross T. Campbell [1]*

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n=61 hospitalized HF + diuretics resistance

1:1 randomization

Dapagliflozin 10 mg

Metolazone 5-10 mg

3 consecutive treatment days

Baseline characteristics

79 years-old

44% HFrEF

54% women

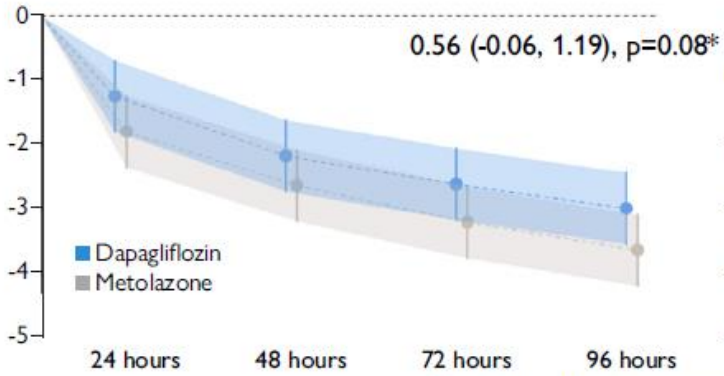
26% eGFR <30

98% peripheral oedema

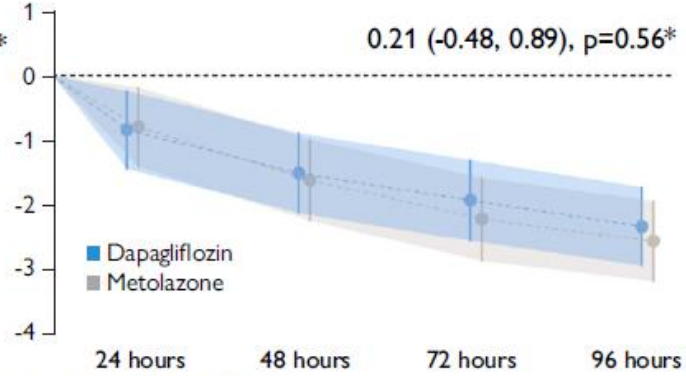
244 mg IV furosemide daily

Efficacy

Change in weight (kg) from baseline to 96 hours



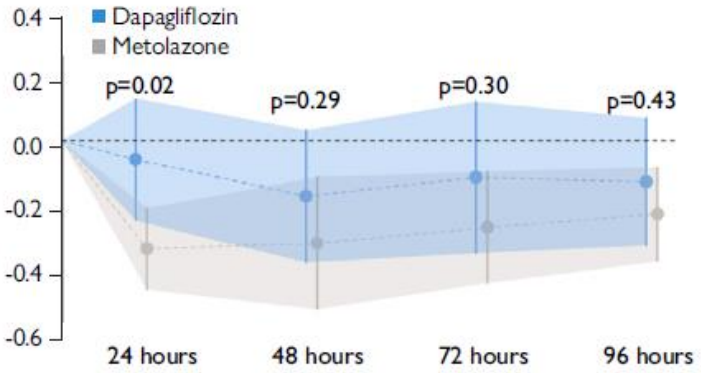
Change in modified ADVOR congestion score from baseline to 96 hours



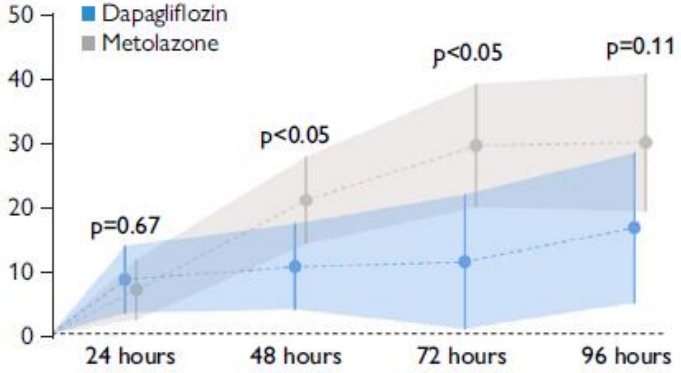
*Combined estimate of effect from 48-96 hours

Safety

Change in serum potassium (mmol/L) from baseline to 96 hours



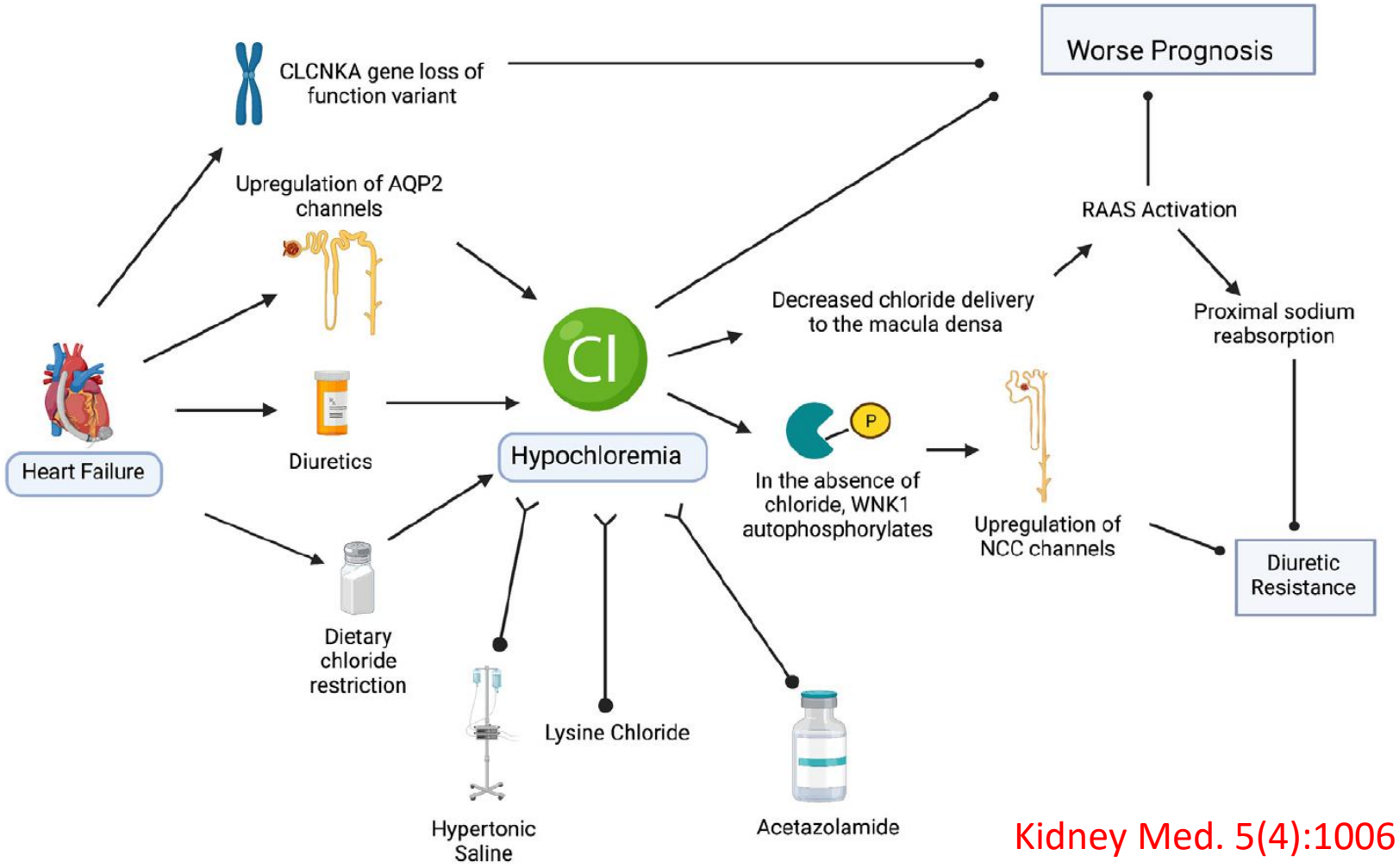
Change in serum creatinine (mmol/L) from baseline to 96 hours



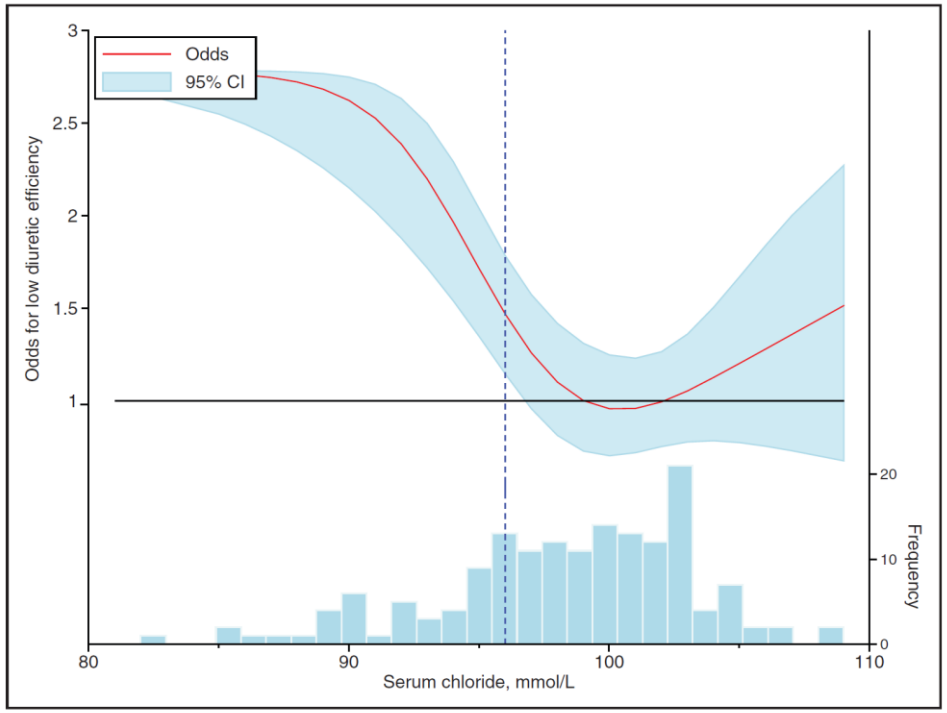
Take home message

- Both dapagliflozin and metolazone are similarly effective at relieving congestion when added to intravenous furosemide in patients with diuretic resistance.
- Treatment with an SGLT2i is well tolerated and associated with a better biochemical profile.

Hypochloremia and Diuretic Resistance



Kidney Med. 5(4):100614.



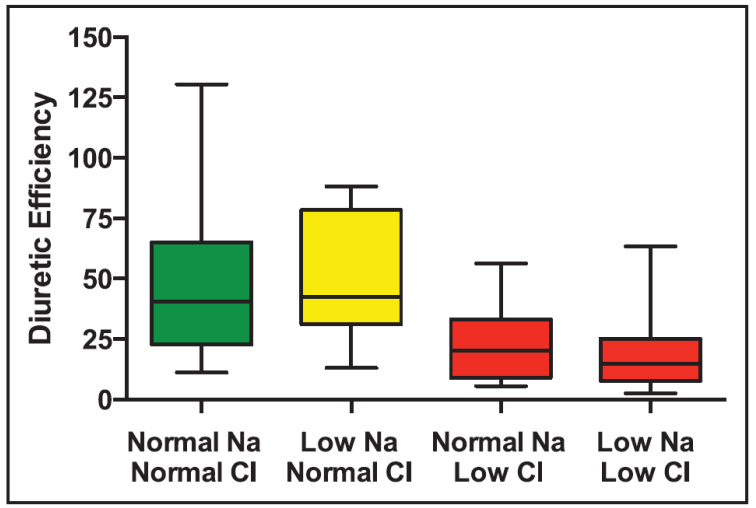
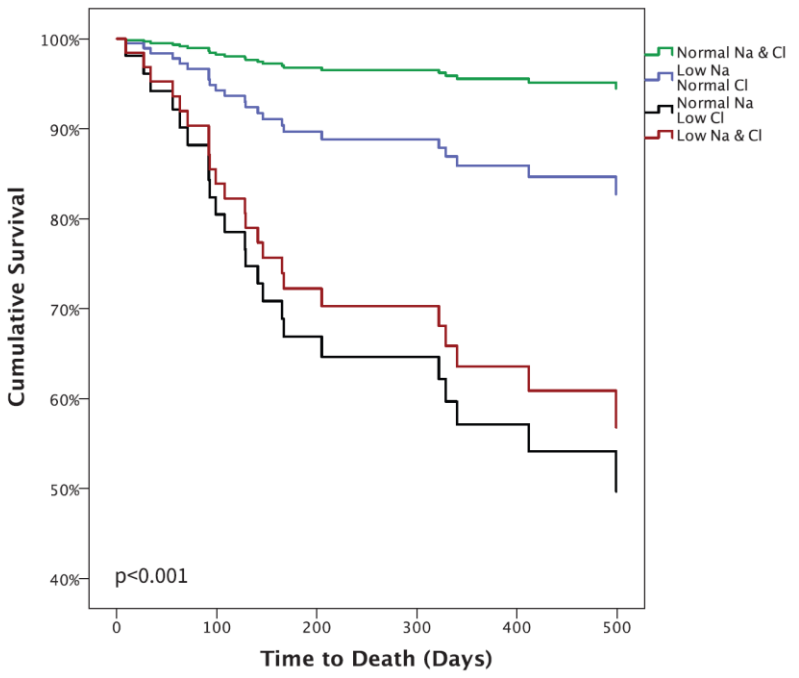
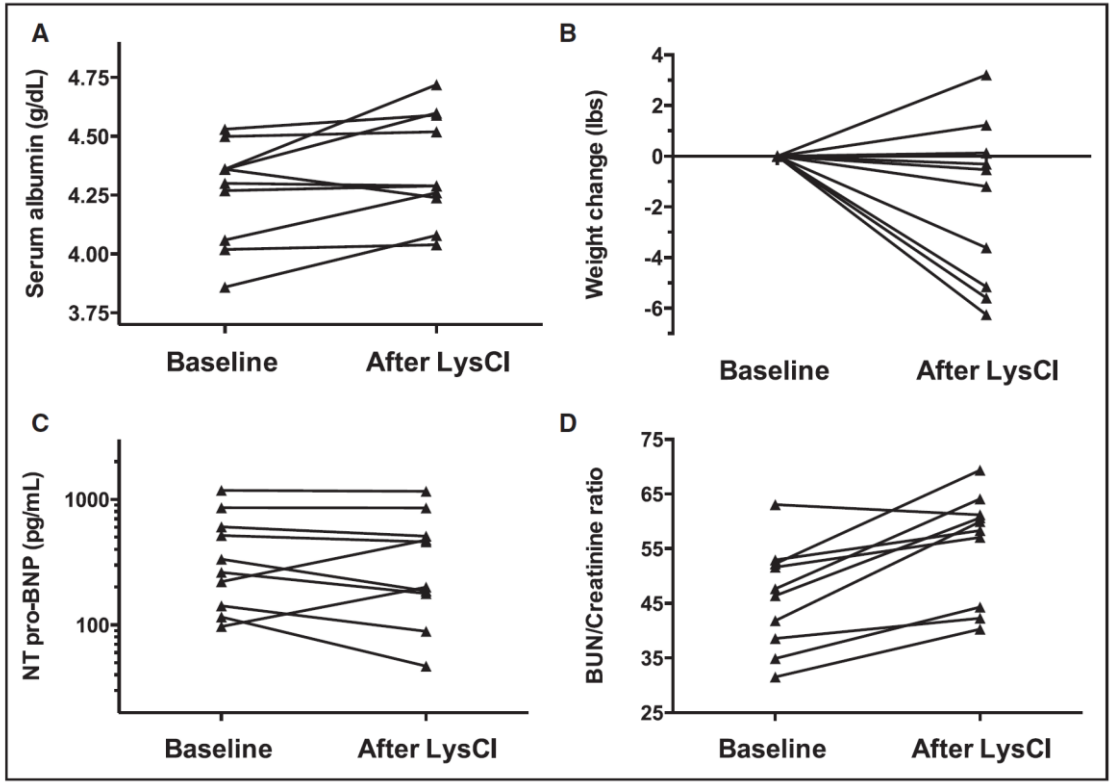
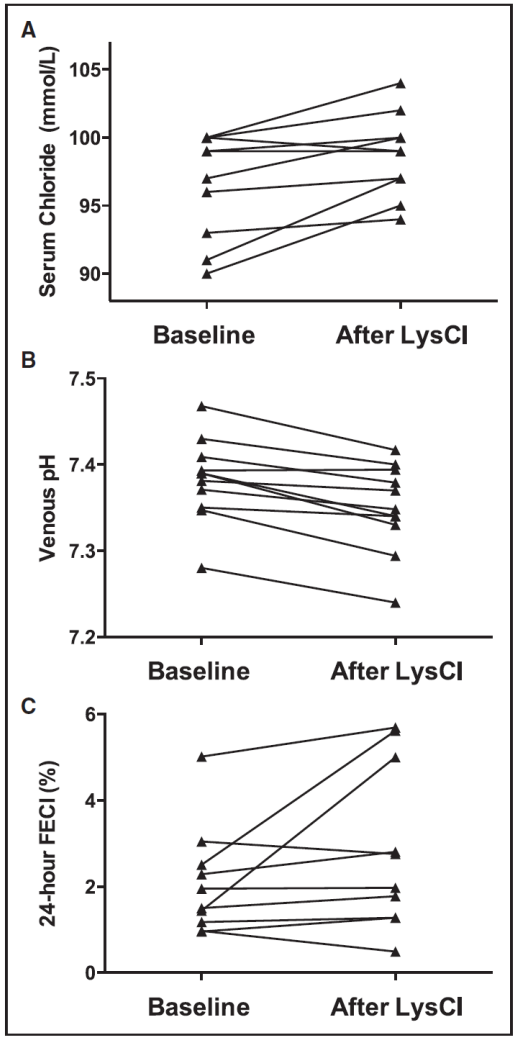


Figure 2. Diuretic efficiency in groups defined by presence or absence of hyponatremia and hypochloremia. Diuretic efficiency is expressed in mmol of sodium excreted per doubling of loop diuretic dose. Whiskers extend from 10th to 90th percentile.



Circ Heart Fail. 2016;9:e003180. DOI: 10.1161/CIRCHEARTFAILURE.116.003180





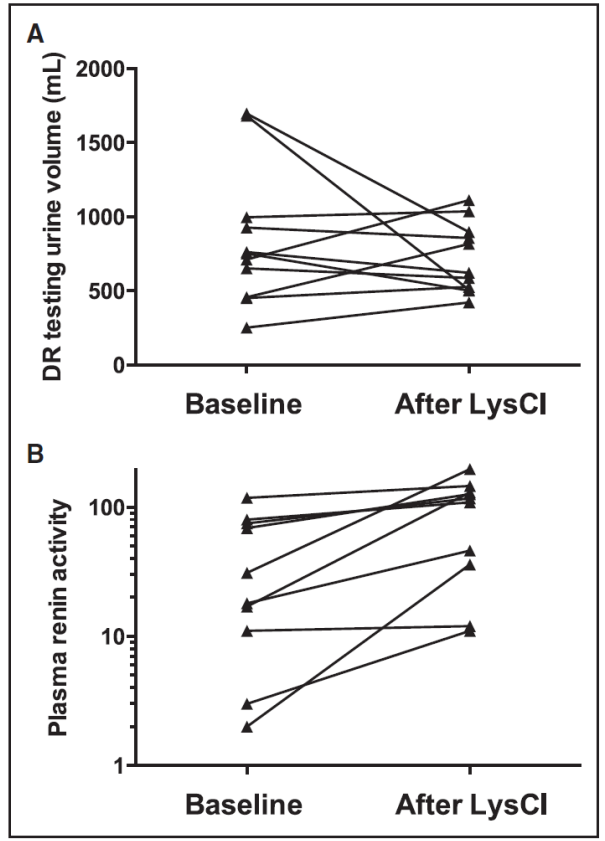


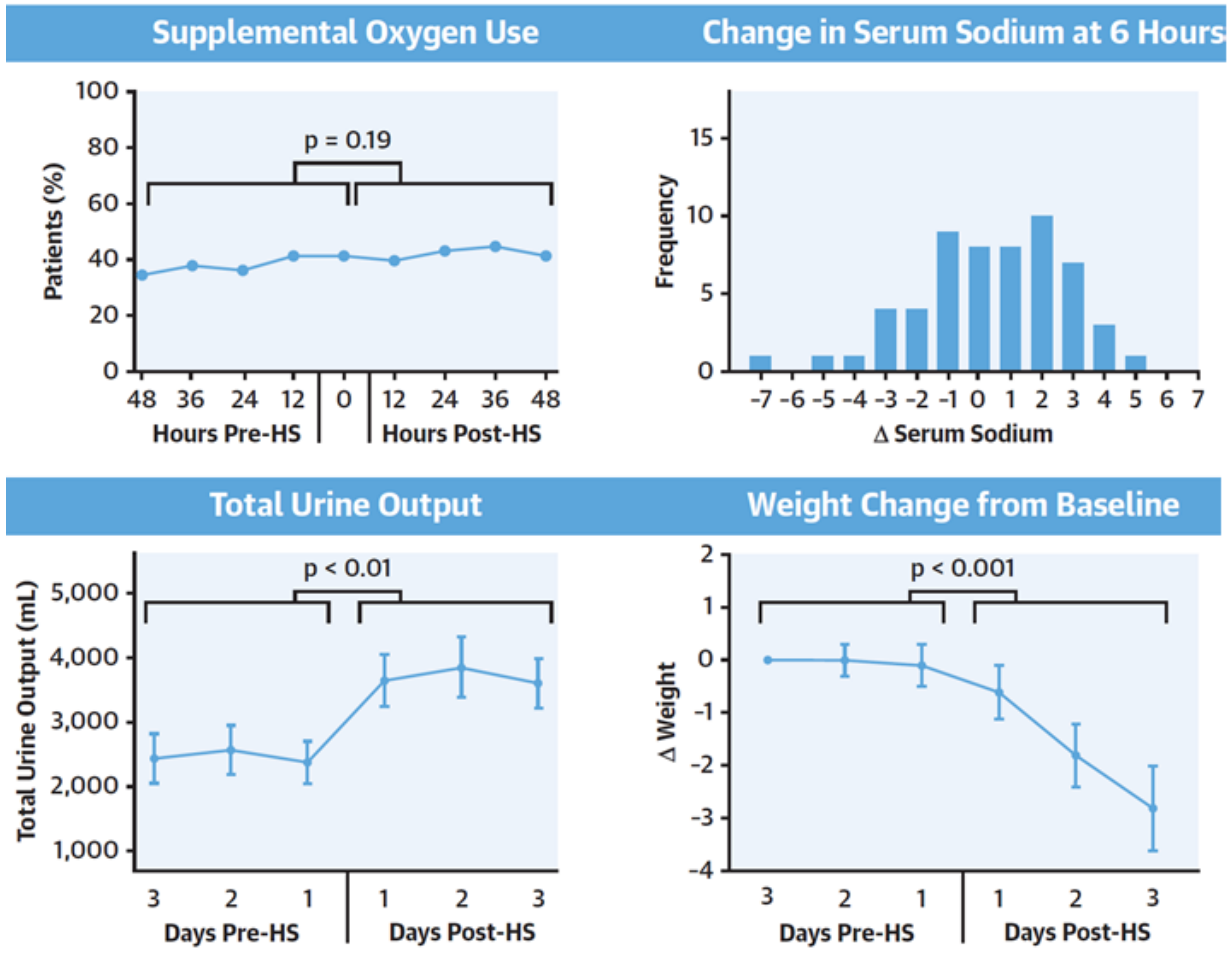
Figure 5. Diuretic induced urine volume and plasma renin activity

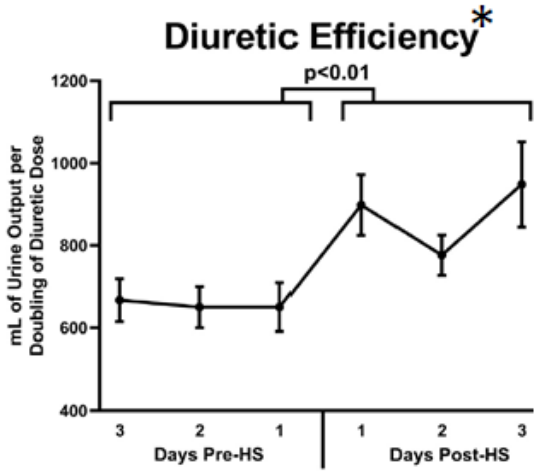
Circ Heart Fail. 2016;9:e003180. DOI: 10.1161/CIRCHEARTFAILURE.116.003180

What About Hypertonic Saline?

TABLE 1 Baseline Characteristics of the Cohort (N = 58)

Age, yrs	60 ± 11
Females	45
Medical history, %	
Hypertension	55
Diabetes mellitus	36
Coronary artery disease	45
Implantable cardioverter-defibrillator	60
Moderate to severe valvular disease	62
Left ventricular assist device	25
Ejection fraction	35 ± 22
Ejection fraction ≤40%	65
Vital signs	
Heart rate, beats/min	85 ± 17
Systolic blood pressure, mm Hg	103 ± 14
Diastolic blood pressure, mm Hg	60 ± 13
Mean Arterial Pressure, mm Hg	72 ± 11
Estimated FiO_2, %	28 (21-33)
Laboratory values	
Sodium, mmol/l	131 (125-134)
Chloride, mmol/l	88 (83-93)
BUN, mg/dl	64 (40-83)
Creatinine, mg/dl	1.8 (1.5-2.8)
eGFR, ml/min/m^2	36 ± 20
Hemoglobin, g/dl	9.9 ± 1.9
Inotropes/vasopressors, %	64
Milrinone	36
Dopamine	33
Dobutamine	10
Norepinephrine	2
Multiple	17
Length of stay and outcomes	
Length of stay, days	29 (17-76)
Rehospitalized within 30 days of discharge, %	17 (10/58)
Deaths within 30 days of discharge, %	33 (13/40)
Discharged to hospice, %	21 (12/58)
Deaths, discharge to hospice, or readmissions within 30 days, %	47 (27/58)
Baseline diuretics	
Loop diuretic dose, mg of furosemide equivalents	400 (200-875)
Thiazide diuretic	35 (59)*
Thiazide diuretic dose, mg of metolazone equivalents	10 (10-20)
Acetazolamide, %	3 (5)
Acetazolamide dose, mg	500 (500-2,000)
Tolvaptan	5 (8)

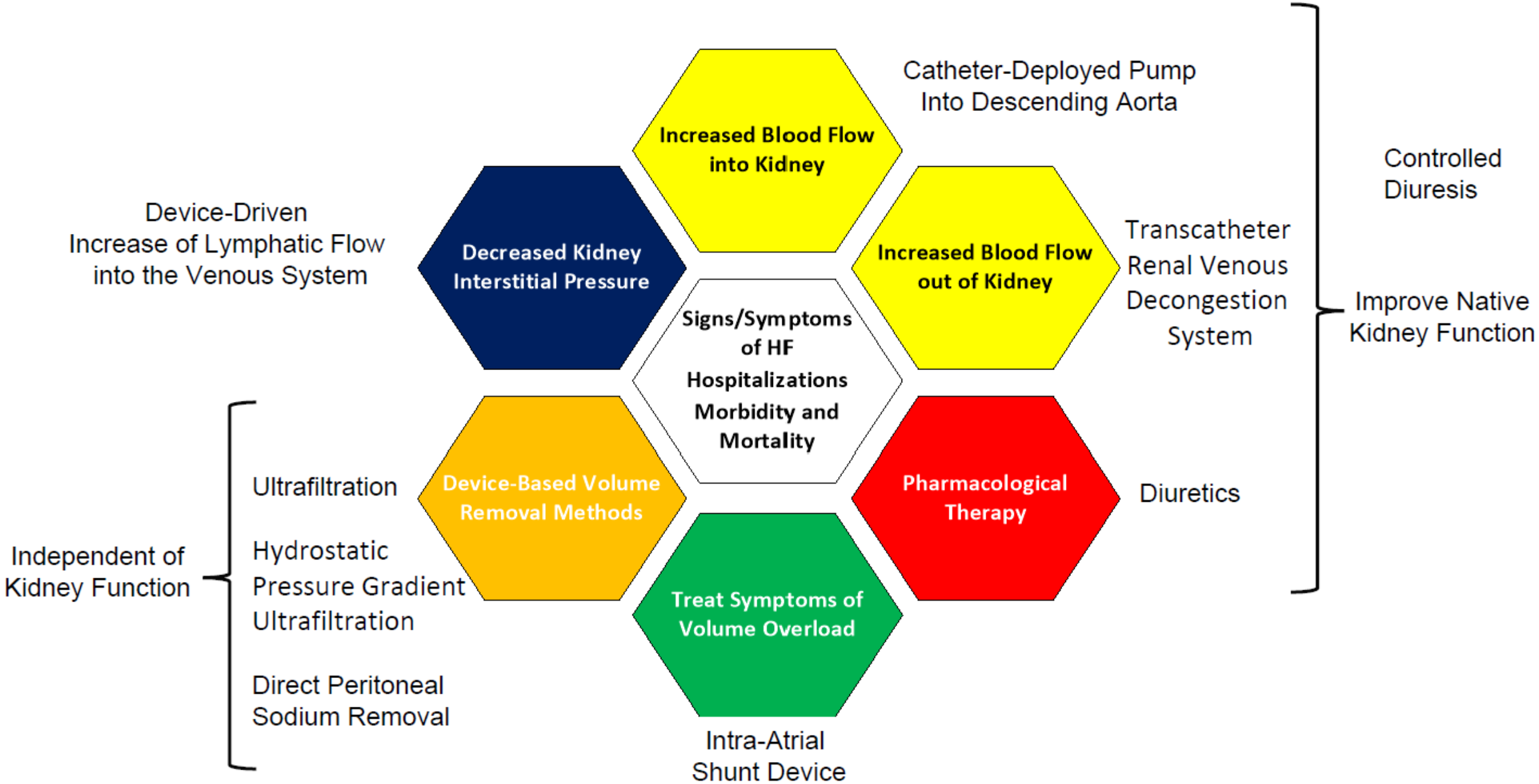




*Diuretic Efficiency Defined as Increase in UO per Doubling of LD Dose

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

Novel Decongestive Therapies



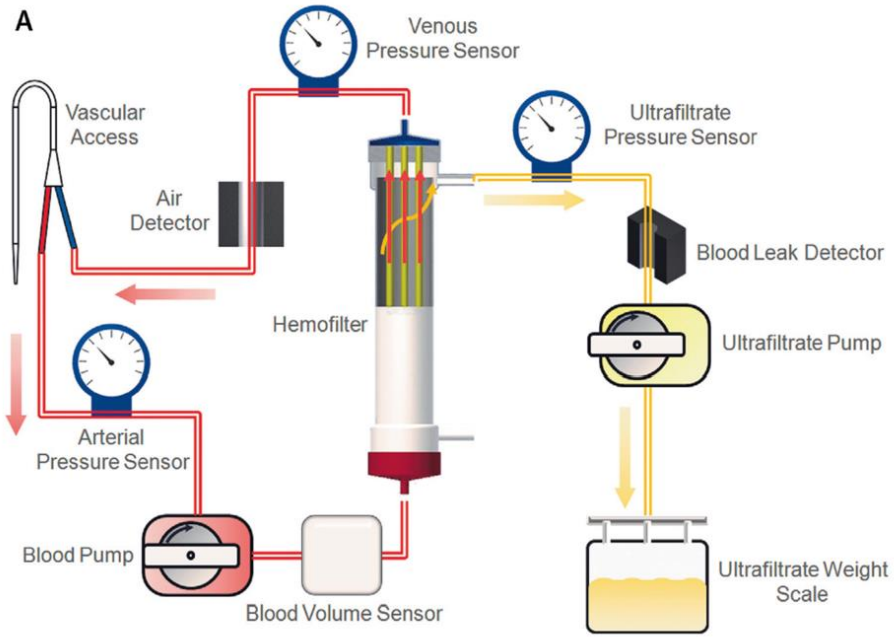
Combinational diuretic therapy:
First line: thiazides
Second line: Acetazolamide
or amiloride
Third line: consider SGLT2-I
dose according to table 2

Persistent congestion

UF- bail out

I

Peripheral Isolated Veno-Venous Ultrafiltration



Differences between diuretics and ultrafiltration

- The most important attributes of ultrafiltration are

➢The predictable removal of sodium,

➢Restoration of diuretic responsiveness,

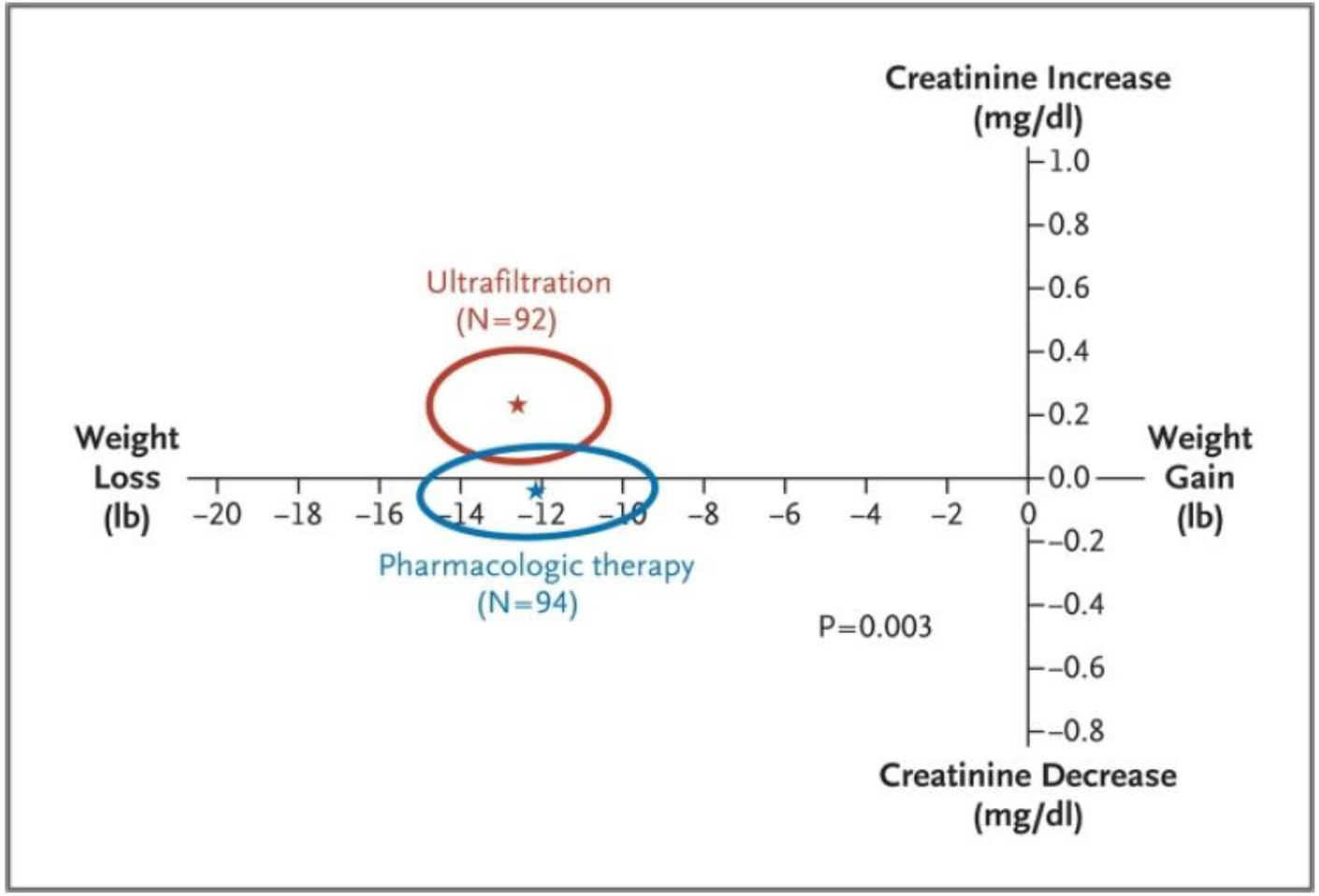
➢An unaltered electrolyte,

➢More effective decongestion,

➢Improve in glomerular filtration

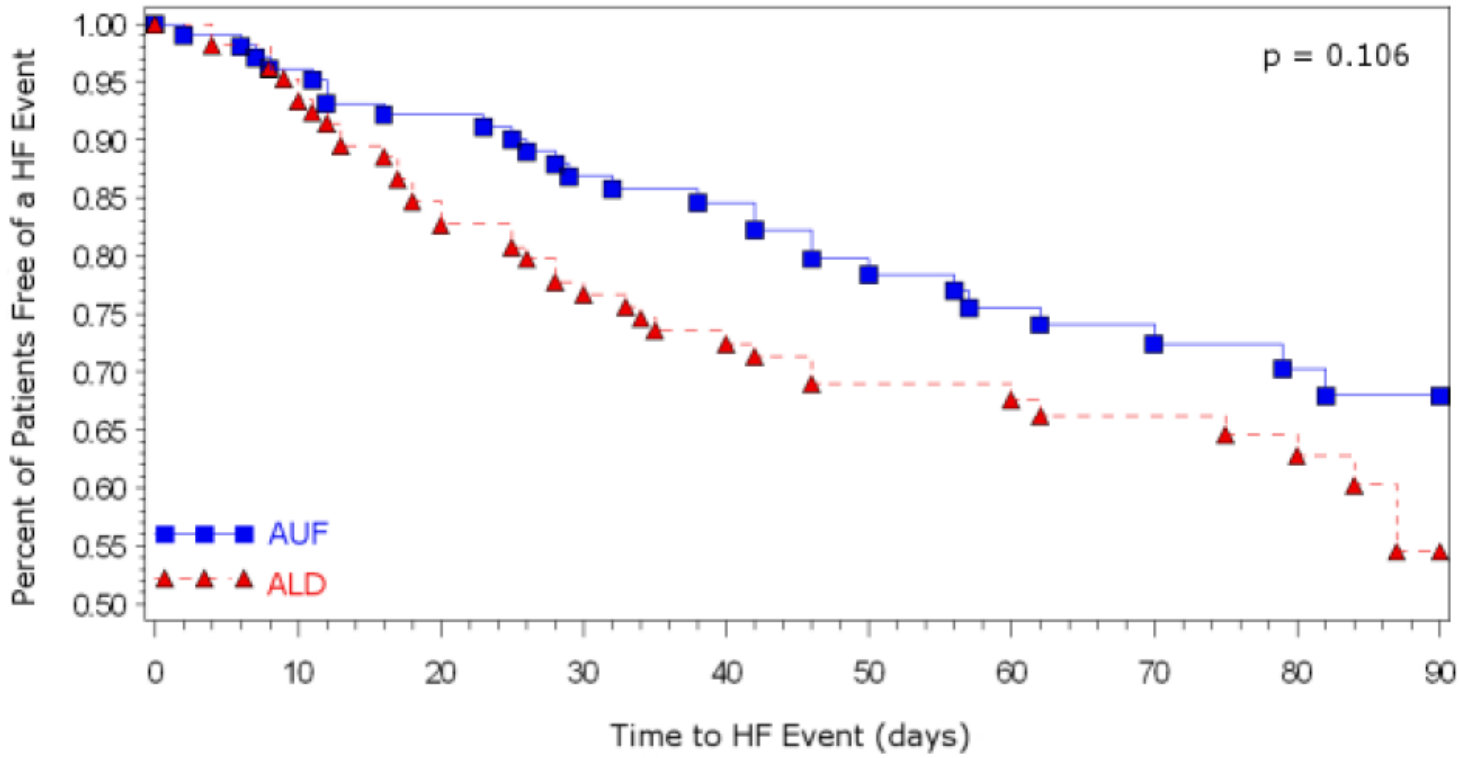
CARRESS

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



Bart BA et al. N Engl J Med 2012: 367: 2296–304.

Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF)
Primary End-Point: Time to HF Event After Discharge



	Baseline	30 Days	60 Days	90 Days
AUF	105	80	52	19
ALD	108	74	49	15

Costanzo MR et al. J Am Coll Cardiol HF 2016;4:95–105

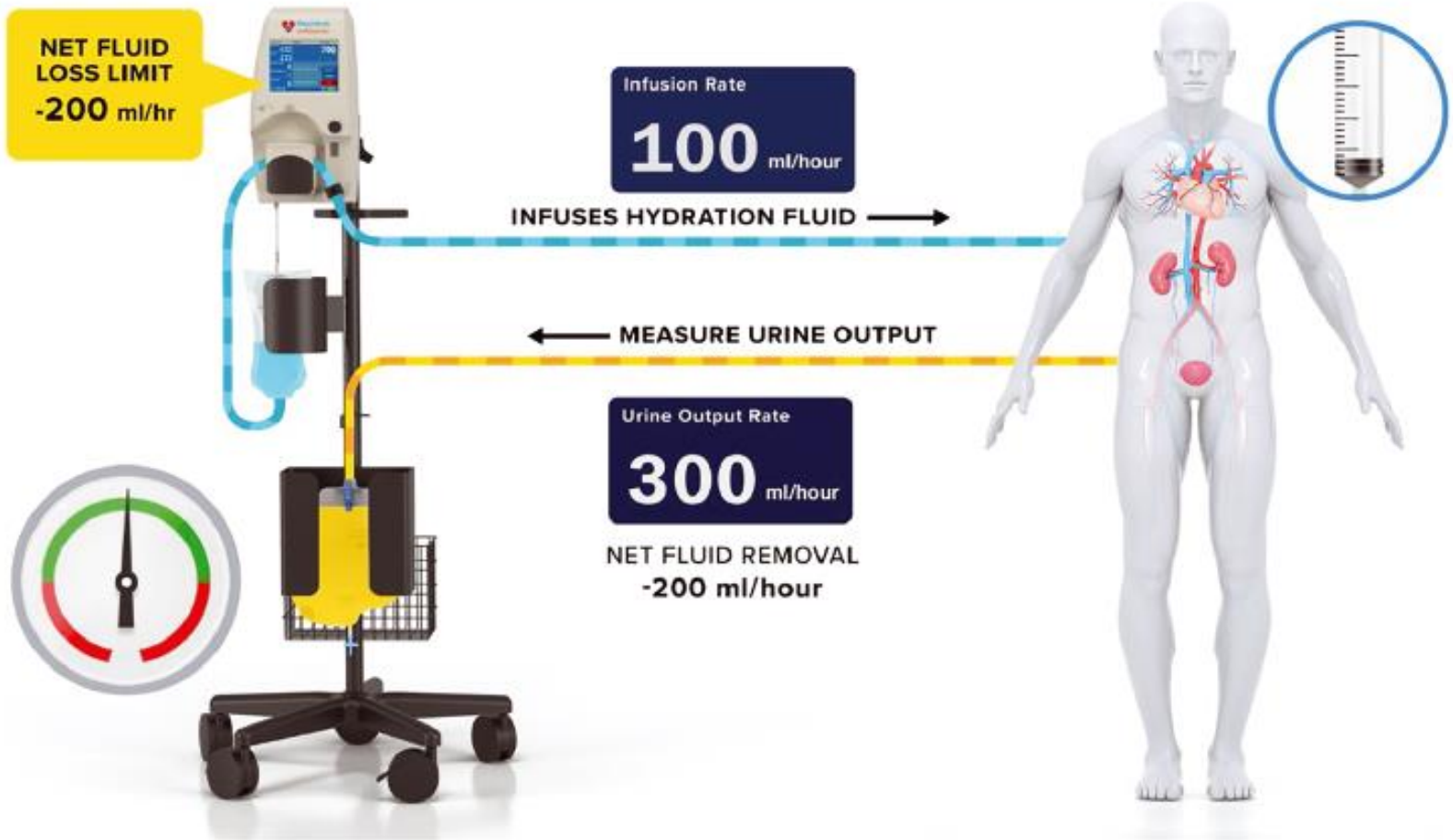
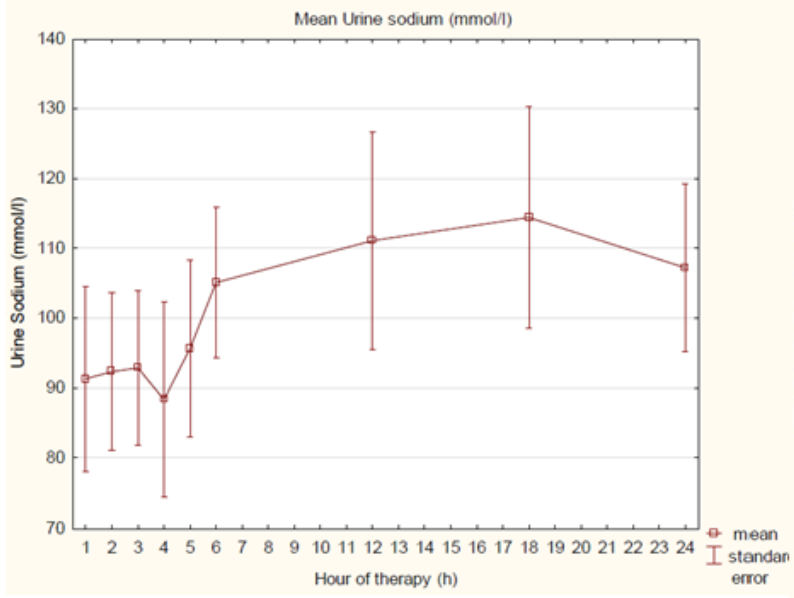
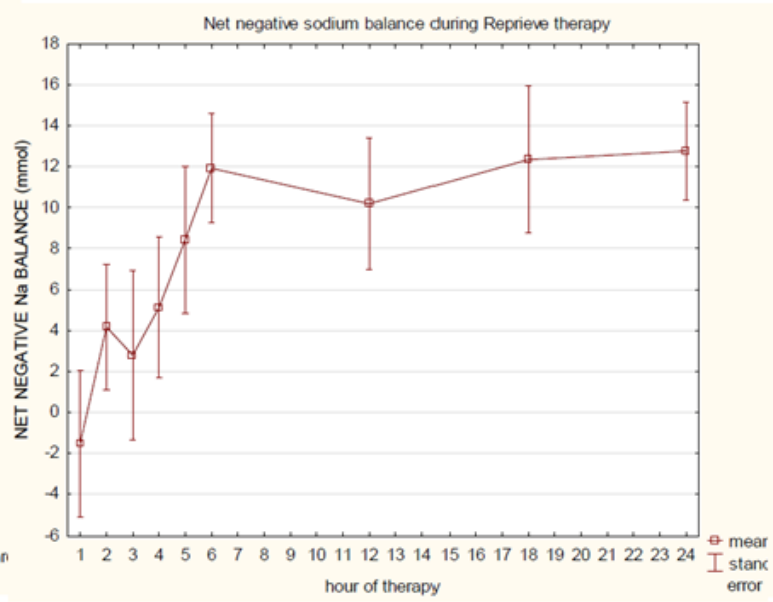


Figure 1 Scheme of the Reprieve-based therapy.

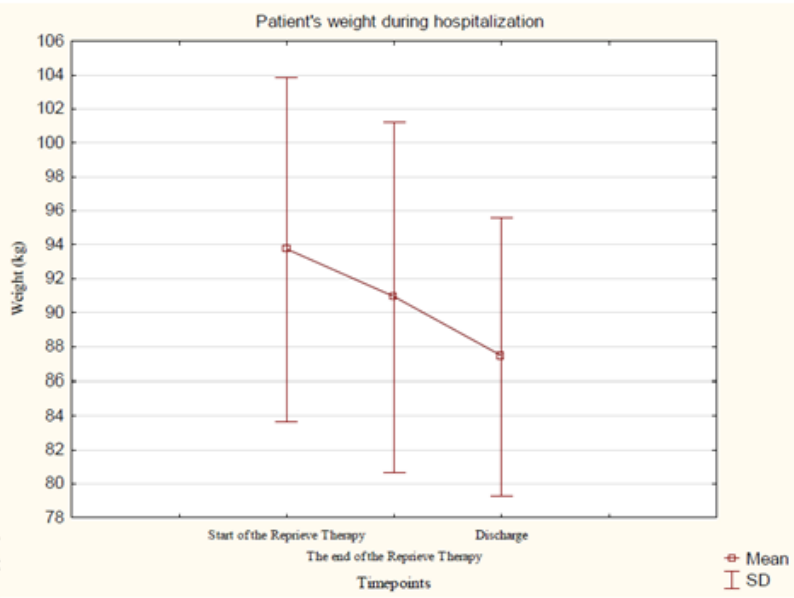
Urinary Sodium



Net Negative Sodium Balance



Weight



Controlled Decongestion by Reprieve Therapy™ in Acute Heart Failure: the Results of the TARGET-1 and TARGET-2 Studies

Biegus J et al. Eur J Heart Fail doi: 10.1002/ejhf.1533

Circulation

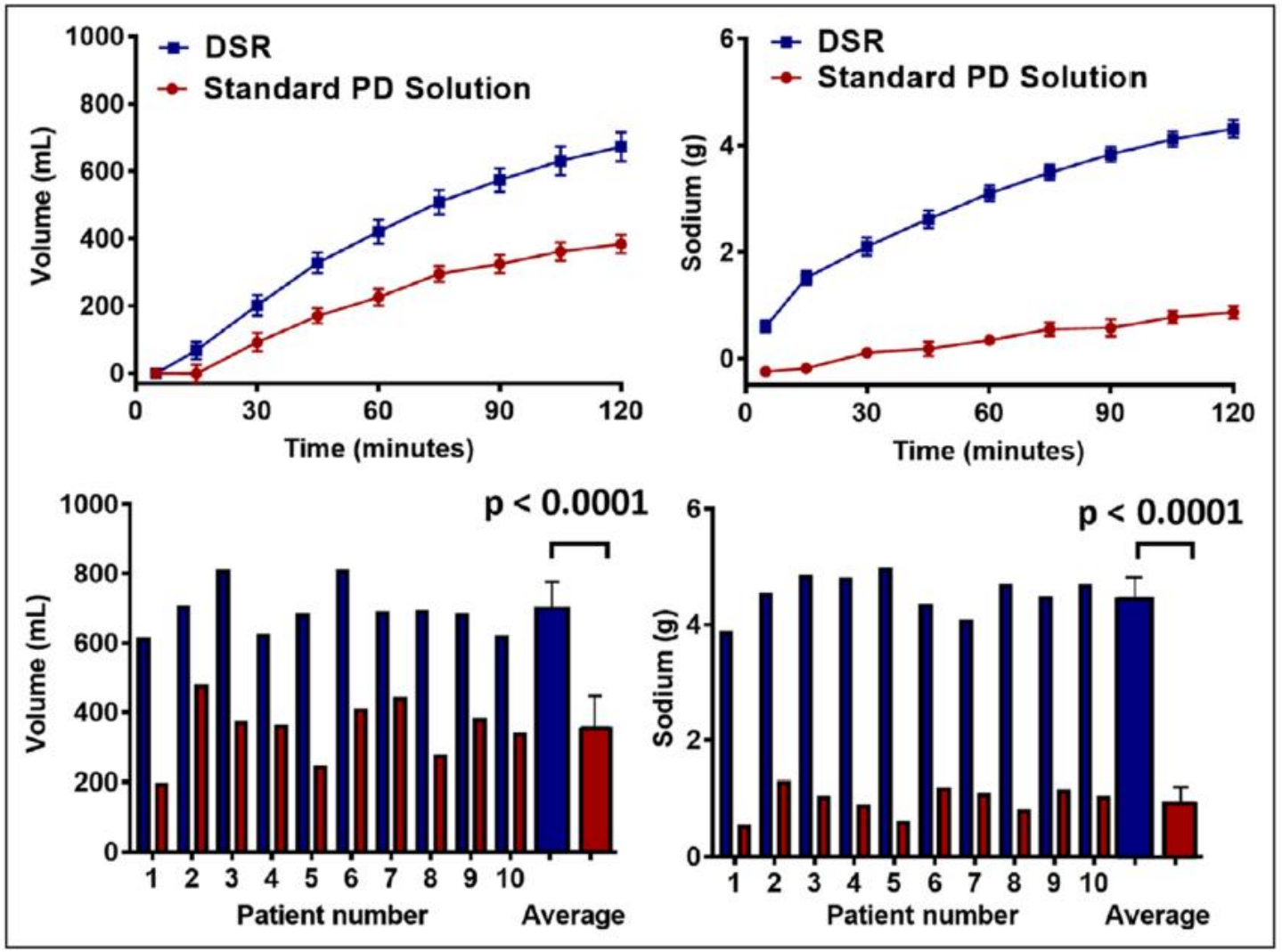
ORIGINAL RESEARCH ARTICLE

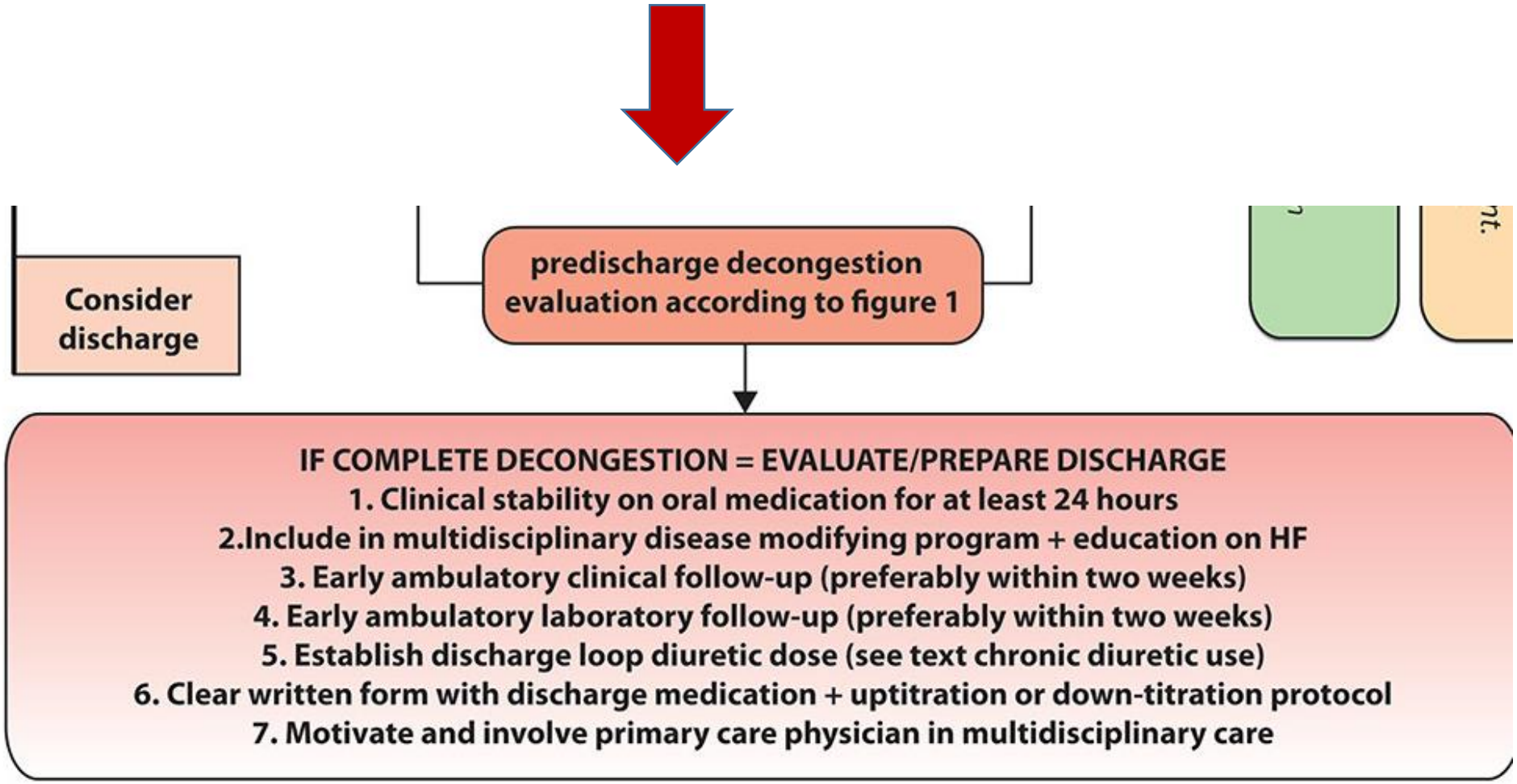
First-in-Human Experience With Peritoneal Direct Sodium Removal Using a Zero-Sodium Solution

A New Candidate Therapy for Volume Overload

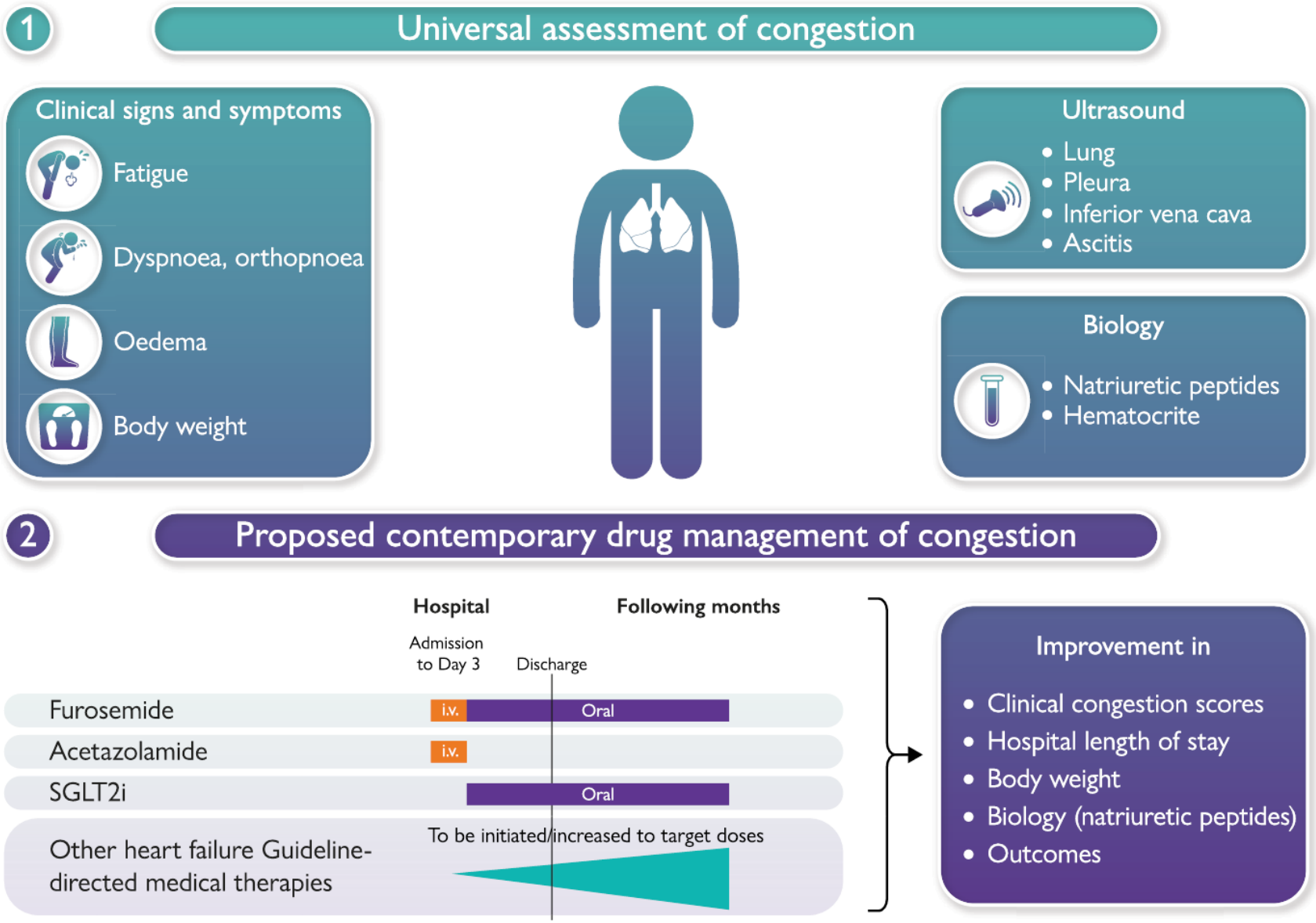
First in Human Experience with Peritoneal Direct Sodium Removal Using a Zero Sodium Solution: A New Candidate Therapy for Volume Overload

Rao V et al. Circulation 2020; 141:1043-53




Consider discharge
predischarge decongestion evaluation according to figure 1
IF COMPLETE DECONGESTION = EVALUATE/PREPARE DISCHARGE
1. Clinical stability on oral medication for at least 24 hours
2.Include in multidisciplinary disease modifying program + education on HF
3. Early ambulatory clinical follow-up (preferably within two weeks)
4. Early ambulatory laboratory follow-up (preferably within two weeks)
5. Establish discharge loop diuretic dose (see text chronic diuretic use)
6. Clear written form with discharge medication + uptitration or down-titration protocol
7. Motivate and involve primary care physician in multidisciplinary care

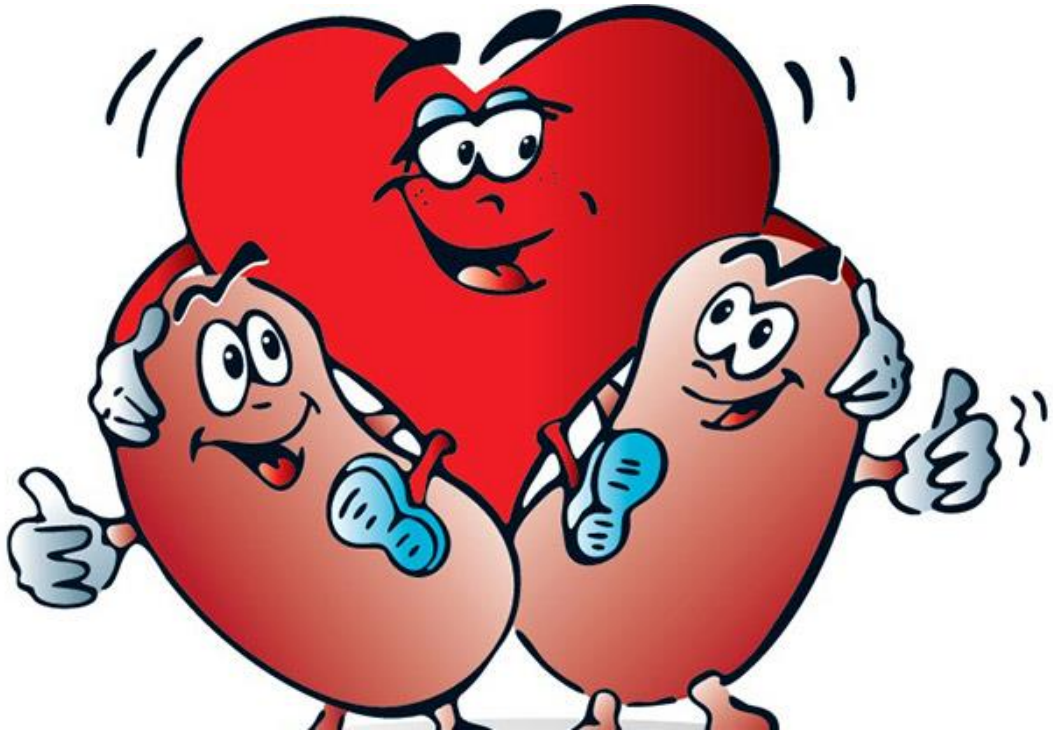
Graphical Abstract



Management of congestion in acute heart failure **European Heart Journal (2023) 44, 51–53**

Conclusions

- Incomplete decongestion is major determinant of HF rehospitalization and adverse outcome
- A timely stepped diuretic approach **(Door to Diuretics + Correct dose of diuretic+Combination diuretic therapy)** have potential for improve decongestion efficiacy
- There is increased attention toward avoidance of intravascular volume depletion and consequent renal hypoperfusion
- Novel decongestive methods range from the requirement of a peripheral venous access and urinary catheter to that for intraperitoneal implant procedures



GOOD LUCK