Iranian Society of Heart Failure

Cardiorenal syndrome

Cardiologist perspective

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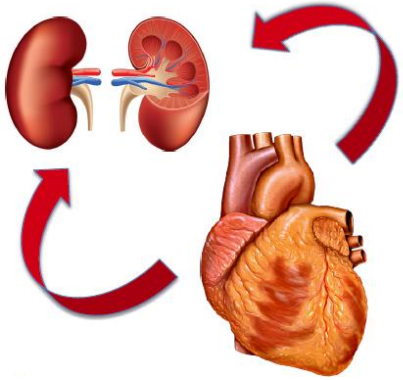


- **Which of the following applies to you?**

A) I **regularly** use the term ‘Cardiorenal Syndrome’ in my clinical practice

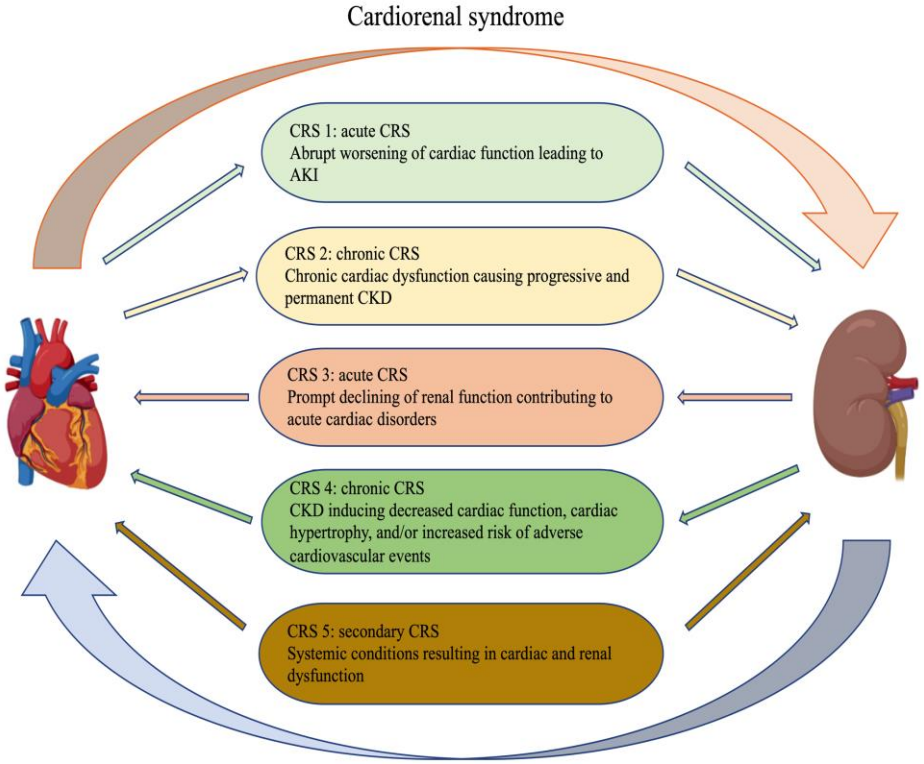
B) I **never** use the term ‘Cardiorenal Syndrome’ in my clinical practice

C) I **have no idea** what ‘Cardiorenal Syndrome’ means

Cardiorenal Syndrome

- Classification based on epidemiology
- Do not use it in clinical practice

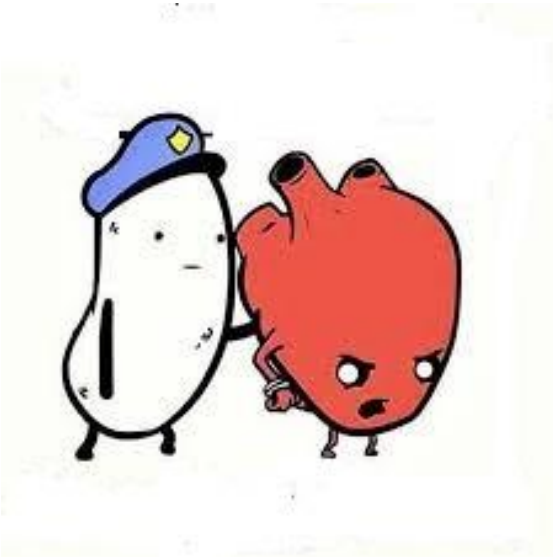
- **Great for:**
  - Creating Awareness
  - Popular term / Hype
- **However:**
  - Does not help to select the right treatment
  - “CRS type I” very diverse
  - Not every renal dysfunction in heart failure is equal (and vise versa)



- **(All) Heart Failure = (a) Cardiorenal Syndrome**

What is True? Renal impairment in Heart failure case is most likely caused by:

A)Low Cardiac Output
B)Venous Congestion
C)A combination of both A and B
D)Pre-existent due to unknown renal disease



Pathophysiology of Renal Failure in HF

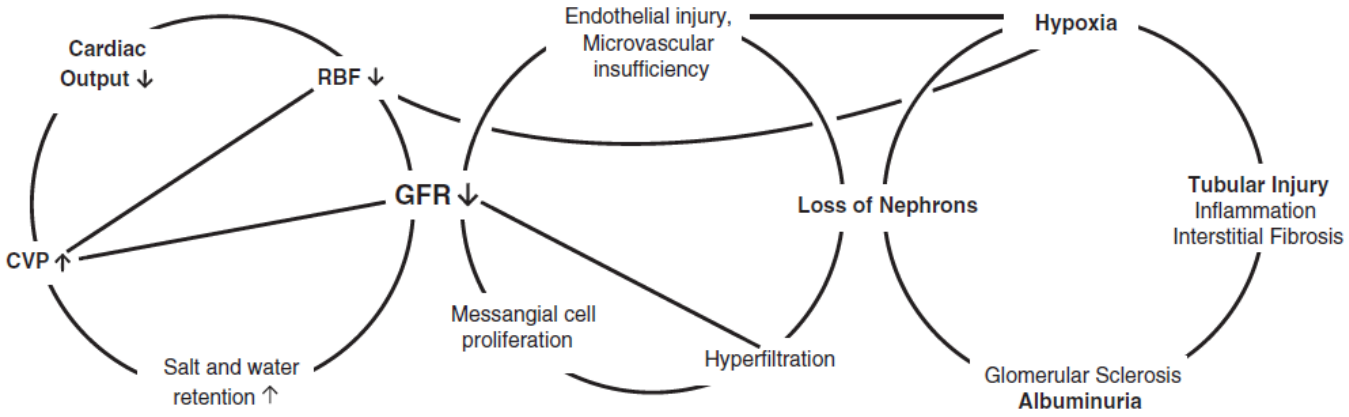


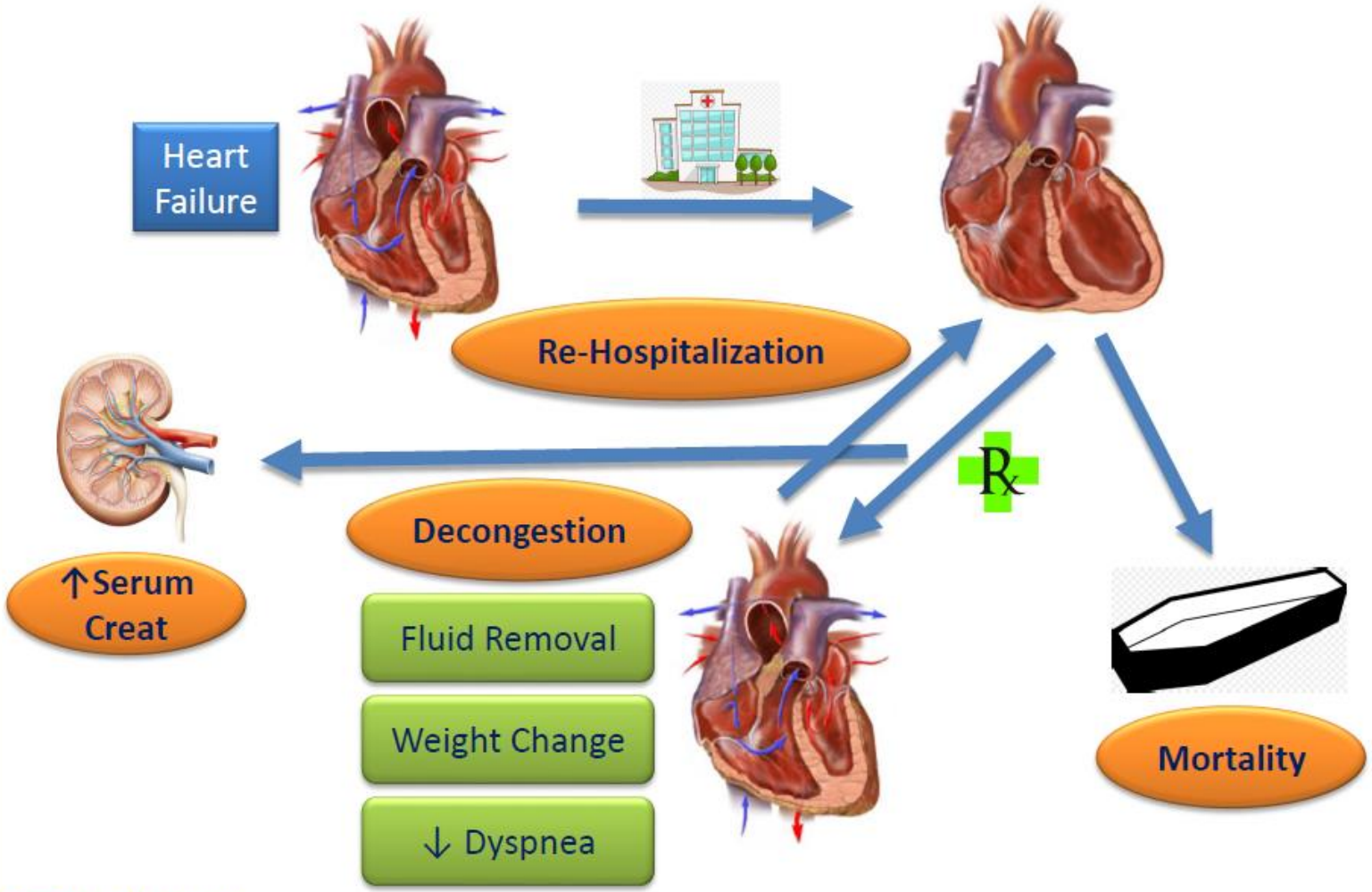
Fig 6. Integrated pathways of the cardiorenal syndrome in HF.

- **Interplay** between:

- Comorbid organ dysfunction **(Susceptibility):**
  - Hypertension
  - Diabetes
  - CKD
  - Peripheral artery disease
- **Hemodynamics (Direct cause):**
  - Reduced Cardiac Output
  - Reduced Renal Blood Flow
  - Increased Renal/Central Venous Pressure
- Intra-abdominal pressure **(Direct cause):**
- Therapy **(Modulation):**
  - Inotropes / Vasodilators / Diuretics
  - RAASi

Damman et al Progr Cardiovasc Dis 2011

Identifying the Right CardioRenal Endpoints



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Identifying the Right CardioRenal Endpoints

- Efficacy
  - Fluid Removal
  - Change in Weight
  - Improvement of Dyspnea

  - Jugular venous distention of < 8 cm
  - Orthopnea
  - Peripheral edema at hospital discharge

  Changes in B-type natriuretic peptide

  - Lung ultrasound, Bioimpedance Cardiography

- Safety
  - Renal Function

  - Serum creatinine (sCr)
  - Blood urea nitrogen (BUN)
  - BUN/sCr
  - Glomerular filtration rate (eGFR)
  - Renal biomarkers

- Re-Hospitalization
  - Unscheduled clinic visit
  - ED visit

  - Length of stay during the index hospitalization
  - Total number of days re-hospitalized for HF at 30 and 90 days
  - IV therapy for HF , including diuretics and/or positive inotropic agents and/or vasodilators at 30 and 90 days after discharge
  - Total number of HF re-hospitalizations at 30 and 90 days after discharge

  -Total number of cardiovascular re-hospitalizations at 30 and 90 days after discharge

  - Total number of days for CV re-hospitalizations at 30 and 90 days after discharge

- Mortality
  - Heart Failure
  - All Cause-


Intervention
↑ SCr
?
validated
Adverse Outcomes

WRF is associated with increased mortality in ADHF

1681 patients

Outcomes	Total	WRF Absent	WRF Present	Adjusted Estimate*
In-hospital mortality	68 (4%)	36 (3%)	32 (7%)	2.72 (1.62–4.58)
30-d mortality	123 (7%)	76 (6%)	47 (10%)	1.87 (1.25–2.80)
30-d readmission, all-cause	296 (18%)	201 (17%)	95 (20%)	1.29 (0.98–1.71)
30-d readmission, heart failure related	118 (7%)	80 (7%)	38 (8%)	1.17 (0.77–1.77)
6-month mortality	354 (21%)	235 (19%)	119 (25%)	1.56 (1.19–2.05)
6-month readmission, all-cause	790 (47%)	555 (46%)	235 (50%)	1.16 (0.93–1.44)
6-month readmission, heart failure related	380 (23%)	264 (22%)	116 (25%)	1.07 (0.82–1.39)
Length of hospital stay, mean (SD) (d)	7.55 (4.70)	6.93 (3.92)	9.14 (6.01)	2.28 (0.25)†
Hospital cost, mean (SD)	$6,823 ($5,175)	$6,327 ($4,874)	$8,085 ($5,665)	$1,758 ($287.2)†

Estimates were odds ratios and 95% confidence intervals for mortality and readmission outcomes, and regression coefficients and their standard errors for length of hospital stay and hospital cost outcomes; estimates adjusted for sex, age, diabetes, hypertension, rales, pulse, baseline creatinine, systolic blood pressure, and left ventricular ejection fraction.

†$p < 0.0001$.

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[Krumholz HM. Am J Cardiol 2000; 85: 1110-1113]

Increase in S creat *("WRF")*: Impact on Survival

412 patients

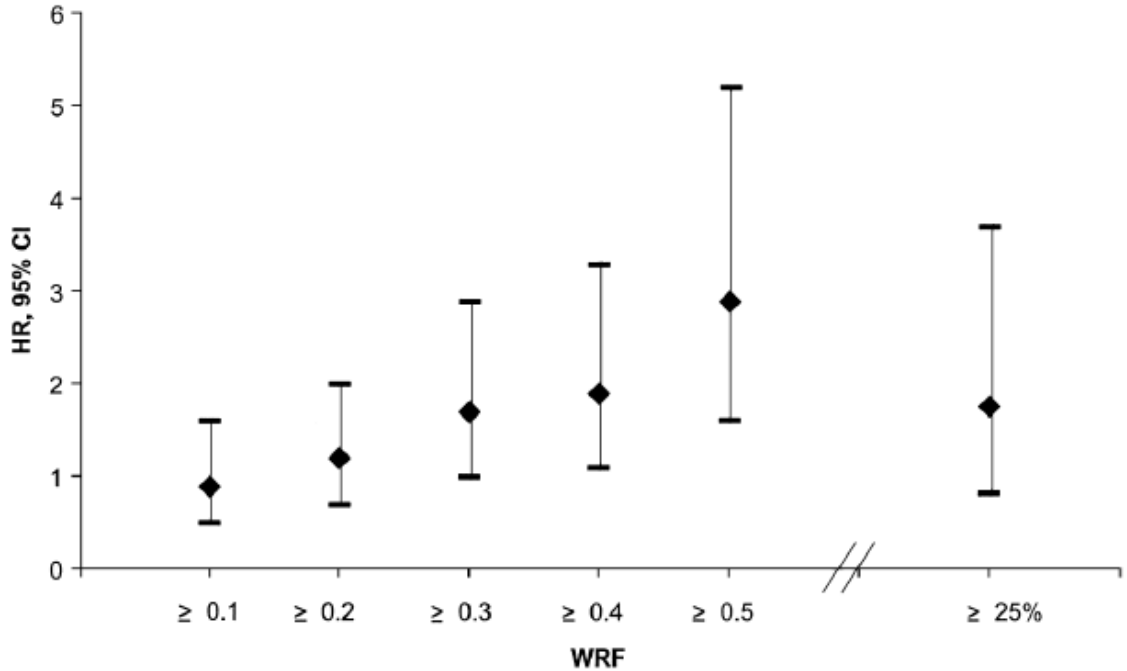


Fig. 3. Adjusted hazard ratio (HR) for mortality.

[Smith GL. J Card Fail 2003; 9: 13]

The ESCAPE Trial

433 patients

Table 2 Relationship Between Renal Parameters and 6-Month Outcomes

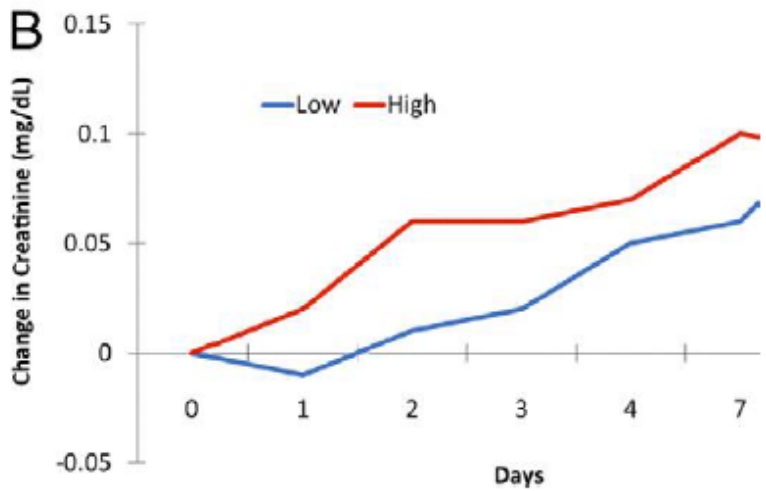
	Time to Death			Time to Death or Rehospitalization		
	HR*	95% CI	p Value	HR*	95% CI	p Value
Baseline SCr	1.20	1.11–1.29	<0.0001	1.14	1.08–1.21	<0.0001
Baseline eGFR	1.25	1.13–1.38	<0.0001	1.10	1.05–1.15	<0.0001
Discharge SCr	1.30	1.20–1.41	<0.0001	1.14	1.08–1.21	<0.0001
Discharge eGFR	1.28	1.14–1.43	<0.0001	1.09	1.03–1.15	0.002
≥0.3 mg/dl ↑ SCr†	1.31	0.81–2.10	0.27	1.26	0.96–1.64	0.09
≥25% ↓ eGFR‡	1.49	0.91–2.44	0.12	1.06	0.79–1.43	0.69

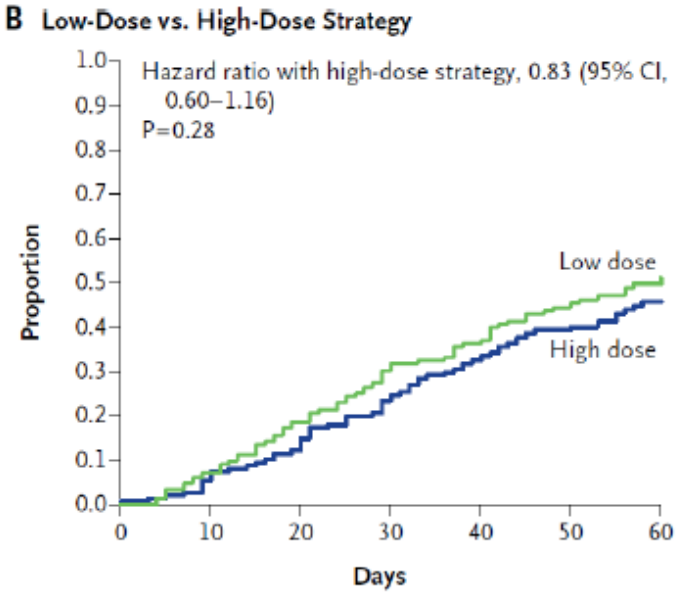
*Hazard ratio (HR) calculated per 0.3-mg/dl increments in serum creatinine (SCr) and per 10-ml/min decrements in estimated glomerular filtration rate (eGFR). Worsening renal function, defined as: 1) †an increase in SCr ≥0.3 mg/dl; and 2) ‡a decrease in eGFR ≥25% from baseline to discharge, is treated as a dichotomous variable.
CI = confidence interval.

Baseline RF (and also discharge RF) can impact outcomes, but not WRF

[Nohria A. J Am Coll Cardiol 2008; 51: 1268]

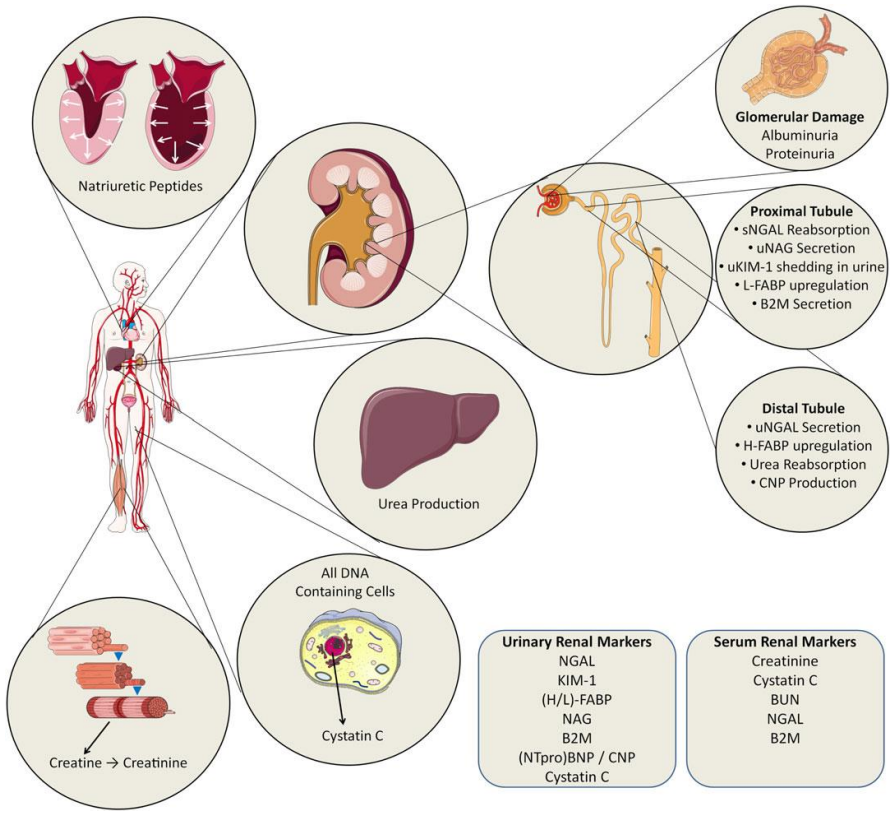
The Dose Trial

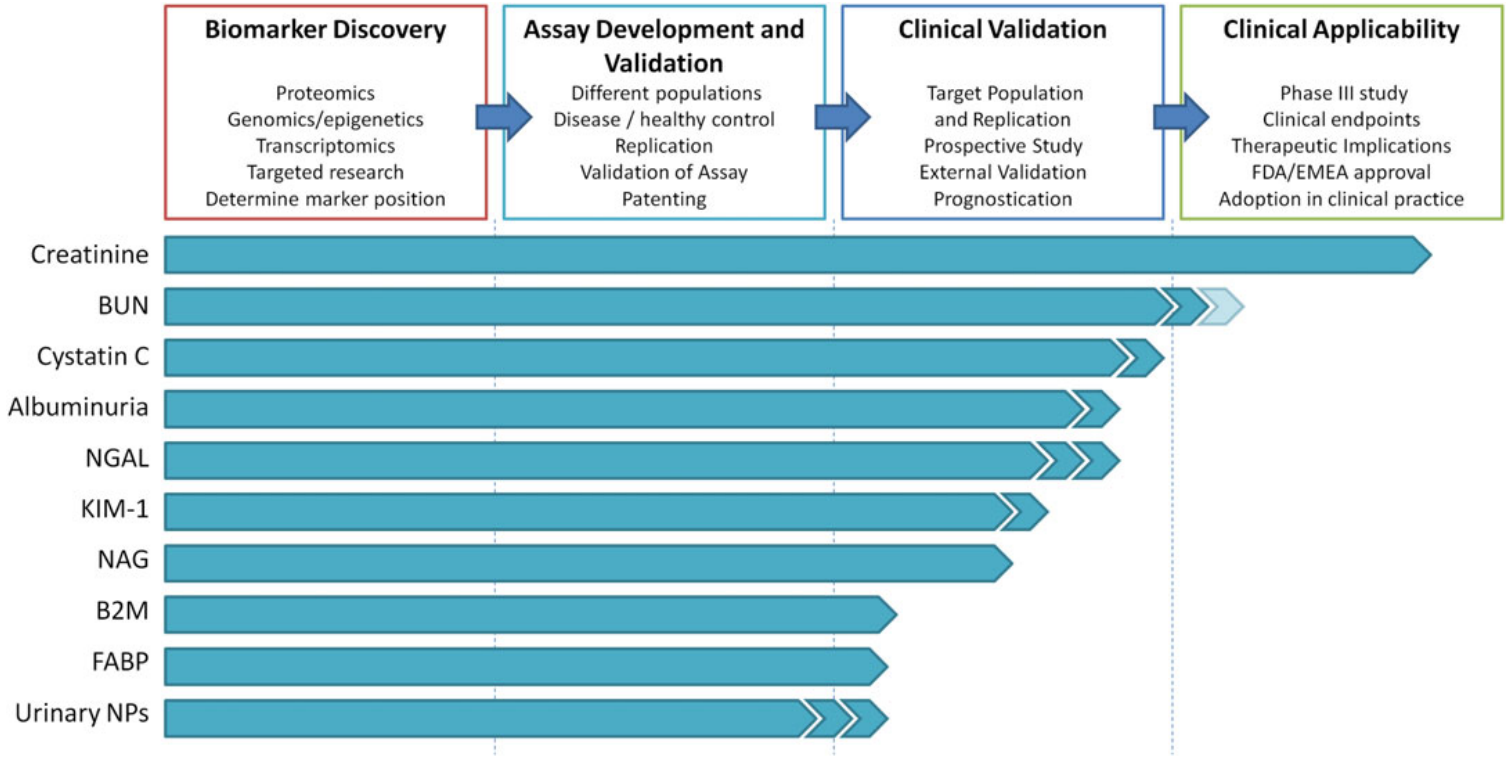




HD group: more WRF, but no impact on outcomes (death, re-hospit, ED visit)

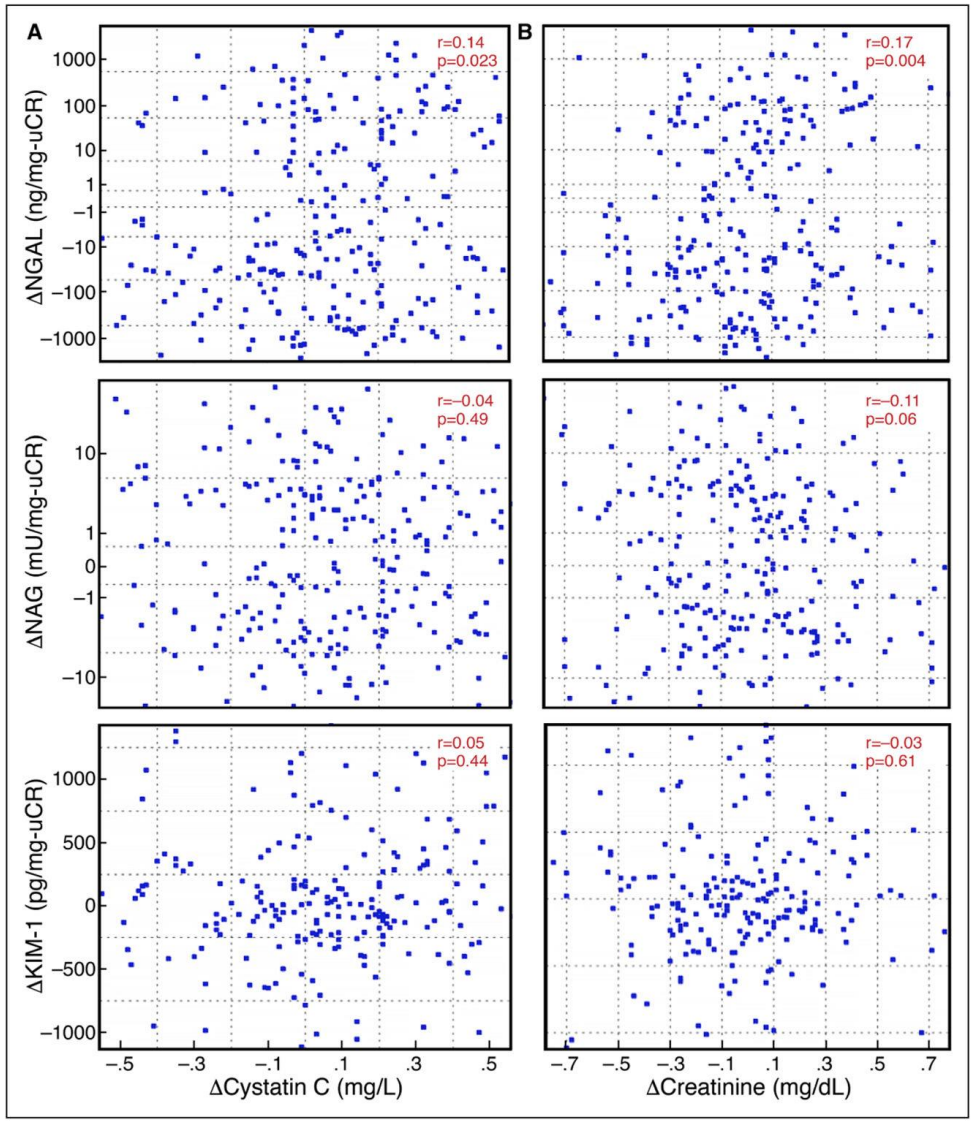
Biomarkers of renal injury and function in heart failure





van Veldhuisen, Dirk J., et al. *European Heart Journal* 37.33 (2016): 2577-2585.

Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury

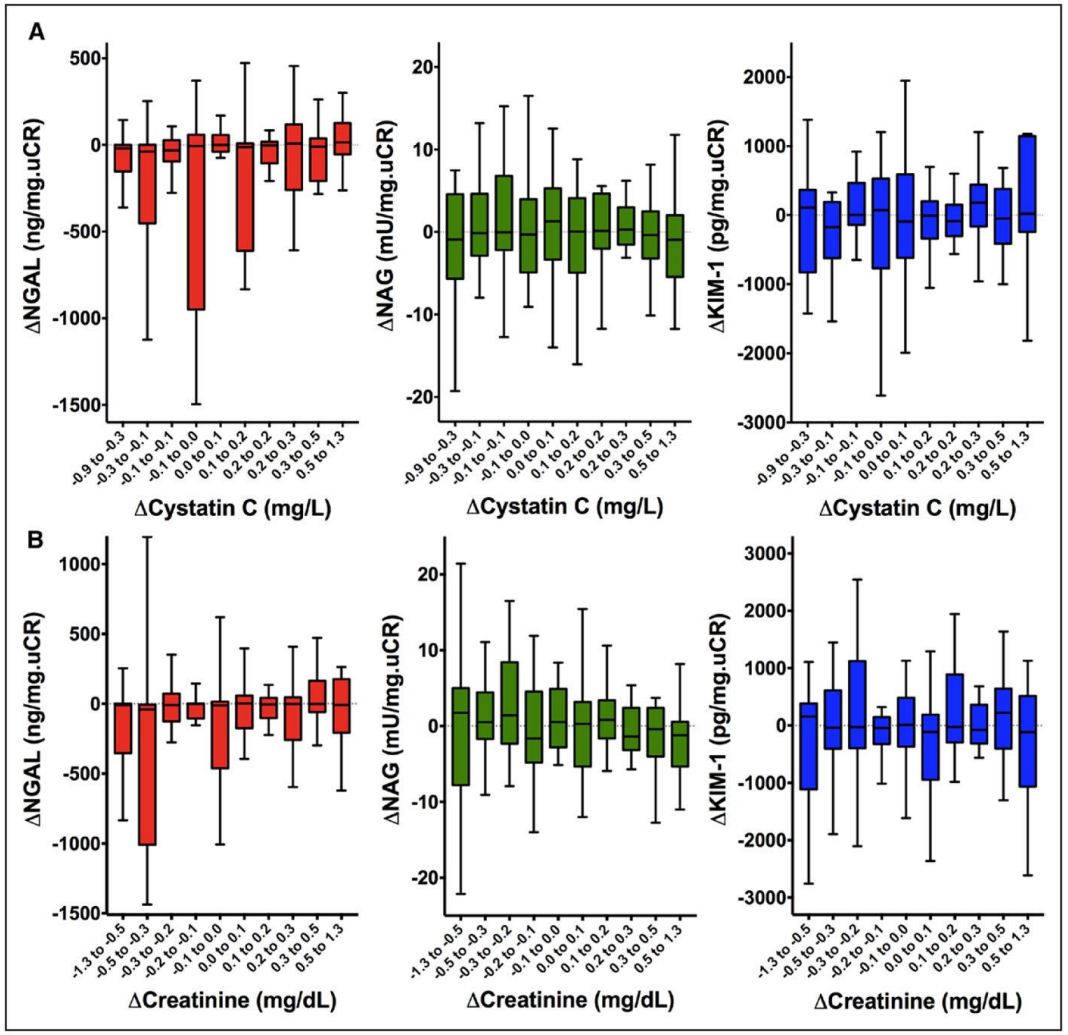


283 patient in ROSE trial

NAG and KIM-1 were not correlated with changes in Scr or cystatin C

Ahmad et al. Circulation. 2018 May 08; 137(19): 2016–2028

Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury

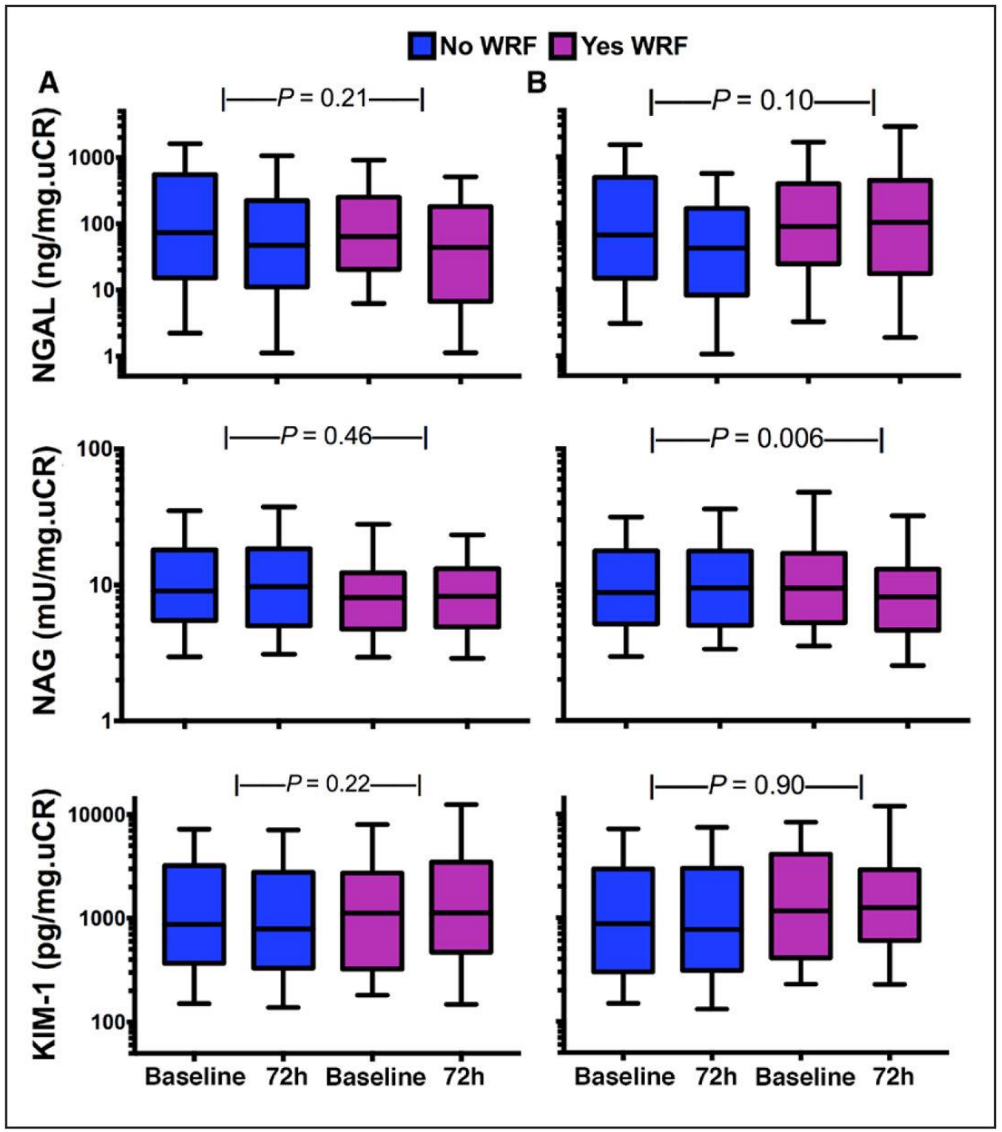


283 patient in ROSE trial

No clear threshold or non- linear relationship between Cystatin C and Scr with biomarkers of tubular injury

Ahmad et al. Circulation. 2018 May 08; 137(19): 2016–2028

Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury

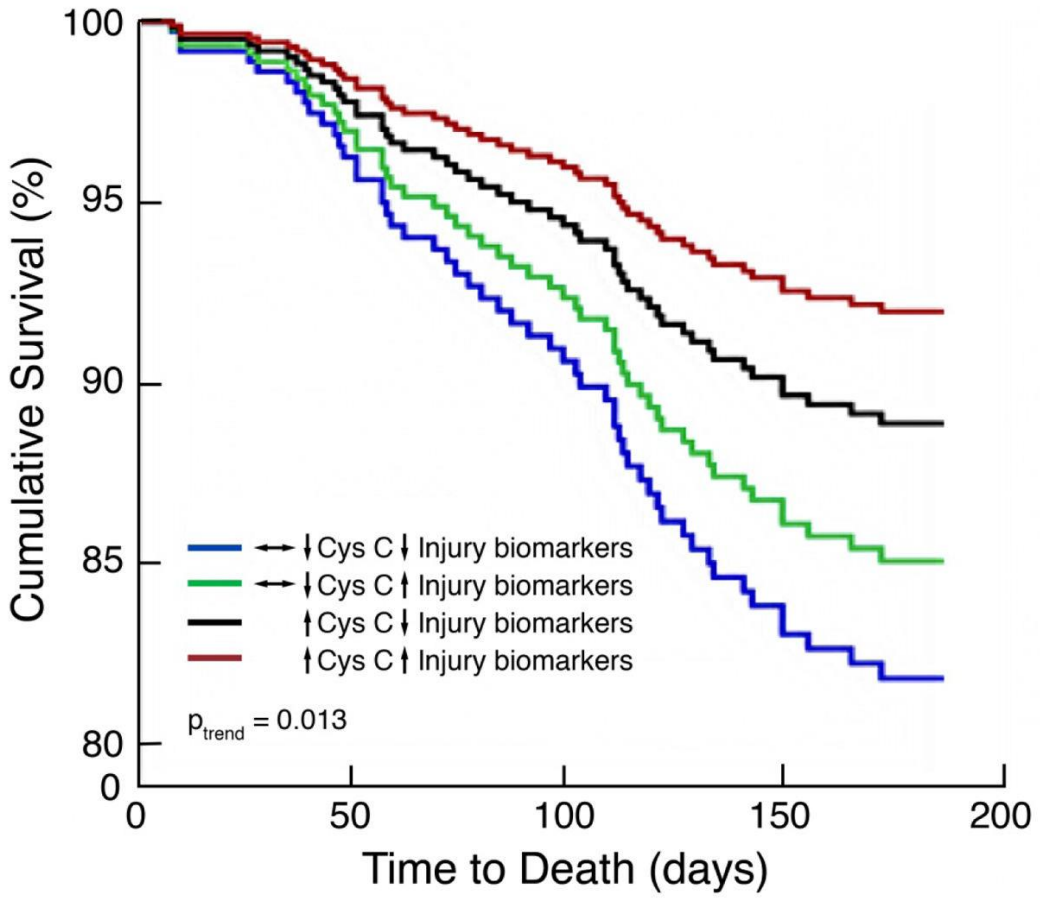


283 patient in ROSE trial

The change in tubular injury biomarker levels did not differ between patients with and without WRF

Ahmad et al. Circulation. 2018 May 08; 137(19): 2016–2028

Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury

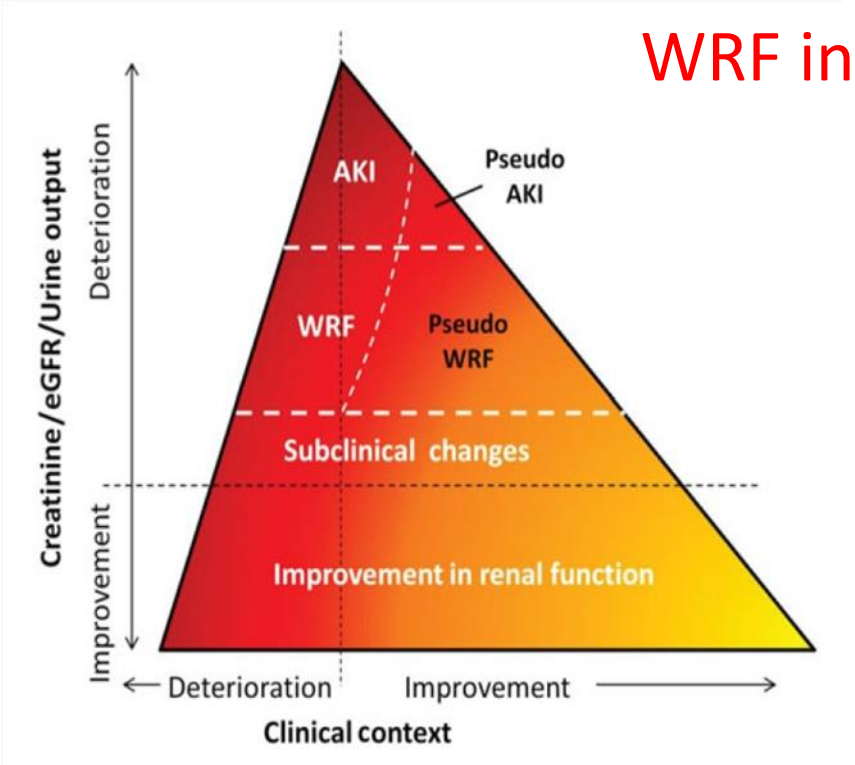


Impact on survival

Patients with a decline in kidney function and increase in tubular injury markers had the best outcomes and patients with no change or improvement in kidney function/tubular injury biomarkers had the worst outcomes

Ahmad et al. Circulation. 2018 May 08; 137(19): 2016–2028

WRF in acute HF



Causes:

- Not entirely known
  - **Persistently increased CVP / Worsening Heart Failure**
  - Intravascular depletion
  - Change Intraglomerular hemodynamics
  - Direct effect (loop) diuretics

Not associated with worse outcome if Diuretic Response is favourable!

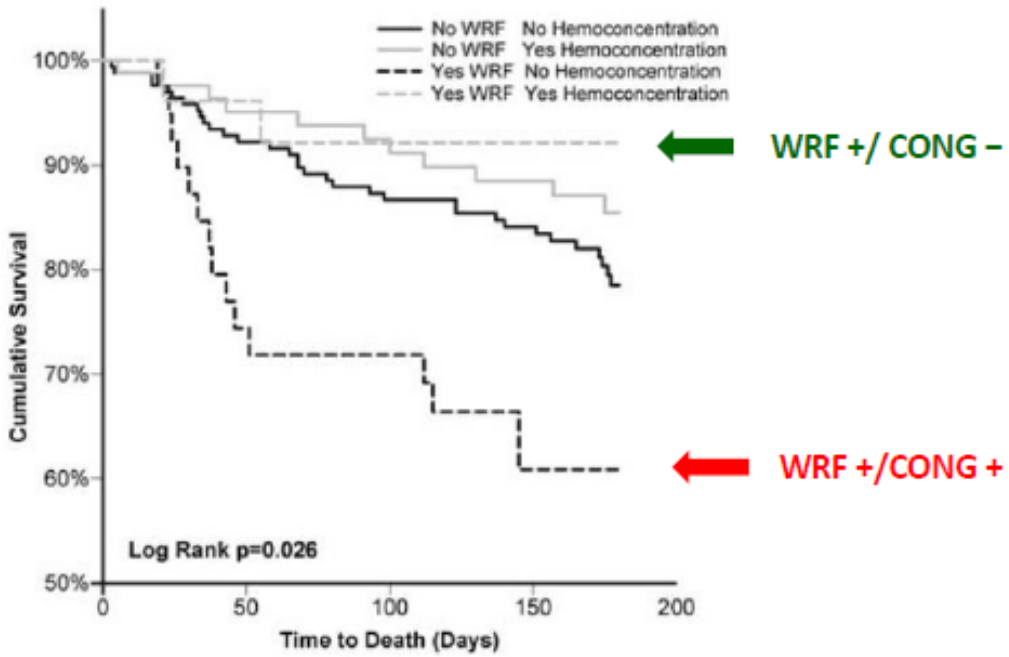
Damman et al. Eur Heart J 2014

Maybe there is “something else” more important than Rise in Serum Creatinine that is driving the outcomes in AHF.

A Confounding Factor?

Congestion Modulates the Impact of ↑Scr in ADHF

386 patients



WRF +/ CONG –

WRF +/CONG +

In ADHF , WRF is associated with adverse outcome only when congestion persists.

- 386 patients with ADHF (from the ESCAPE trial)
- Hemoconcentration (HC) defined as a change in hematocrit in the top tertile (low number of events if defined as ≥ 2 out of 3 (protein, albumin, and Hct)
- WRF: ≥ 20% reduction in eGFR
- Primary objective: to determine whether WRF was associated with in-hospital BP reduction
- In patients who experienced HC, WRF was not associated with mortality (p= 0.429)
- WRF increased mortality if no HC (p=0.019)

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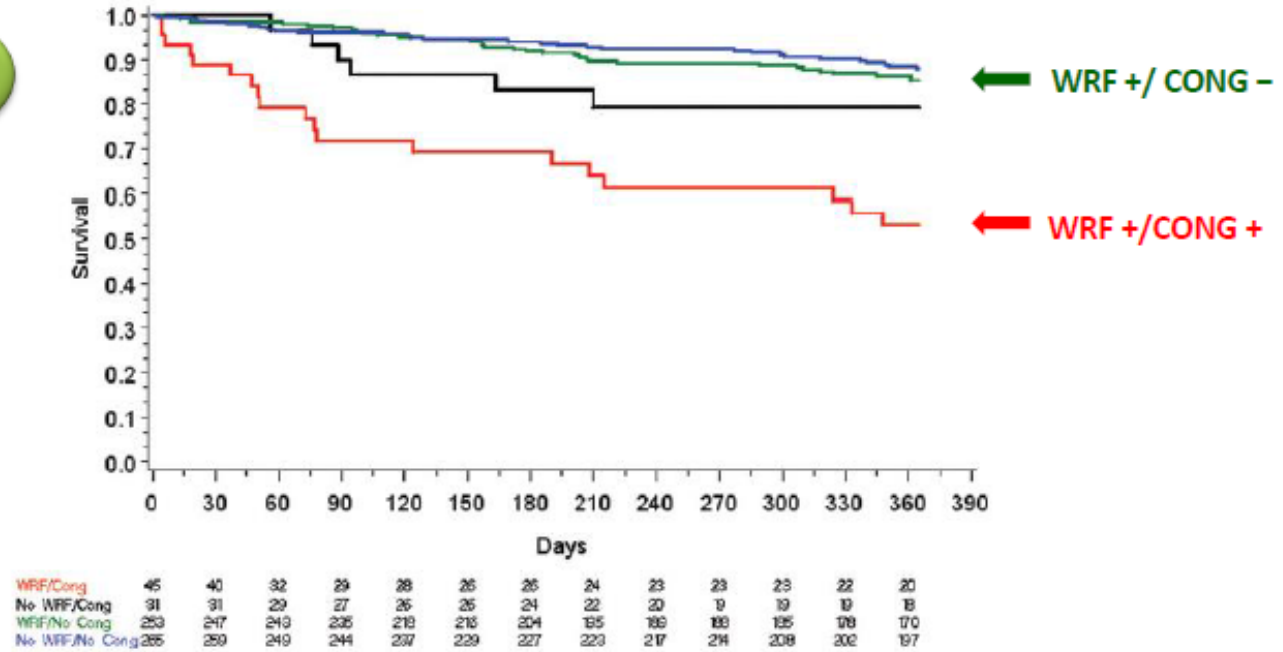
[Testani JM. Eur J Heart Fail 2011; 13: 877]

Congestion Modulates the Impact of ↑Scr in ADHF

599 patients



Endpoints: 1 year death or urgent transplantation

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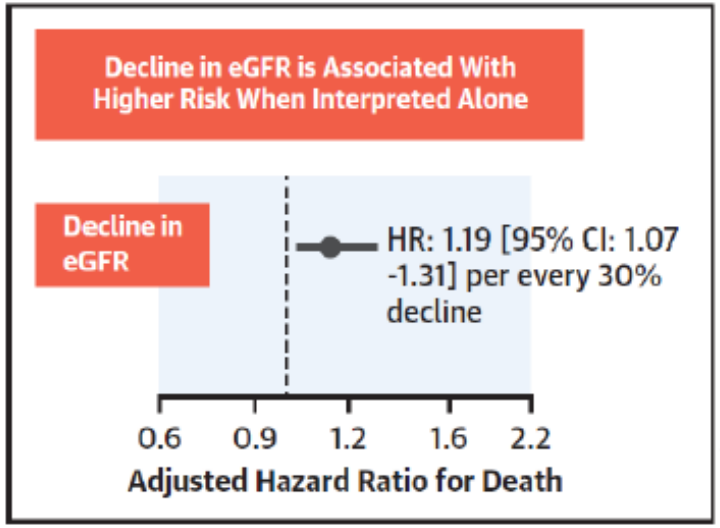
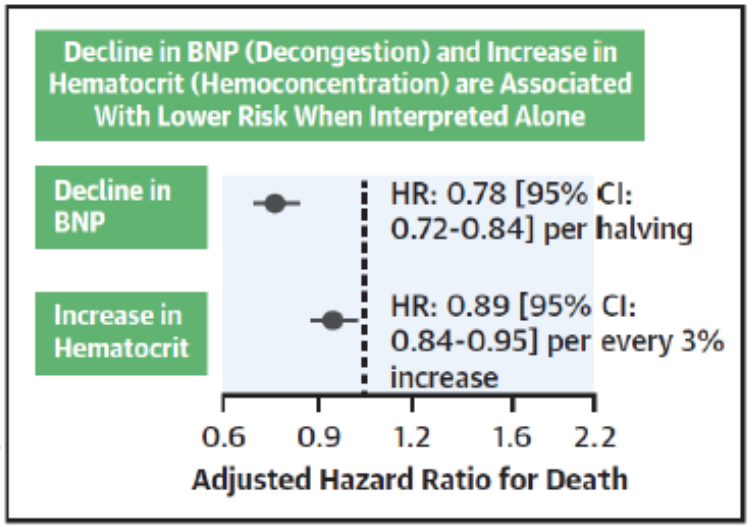
[Metra M. Circ Heart Fail 2012; 5: 54]

Congestion Modulates the Impact of ↑Scr in ADHF

3715 patients

EVEREST ad hoc





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[MaCallum W et al. JACC Heart Fail 2020;8:537]

Congestion Modulates the Impact of ↑Scr in ADHF

3715 patients

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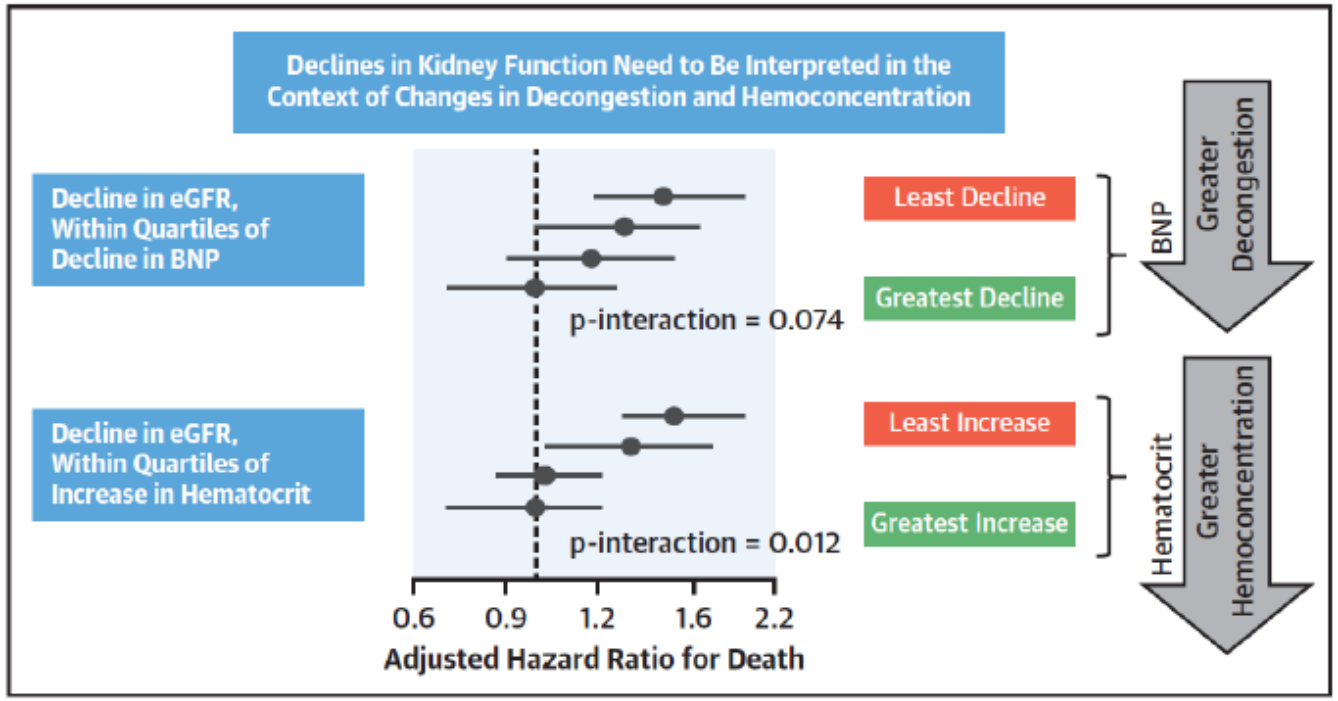

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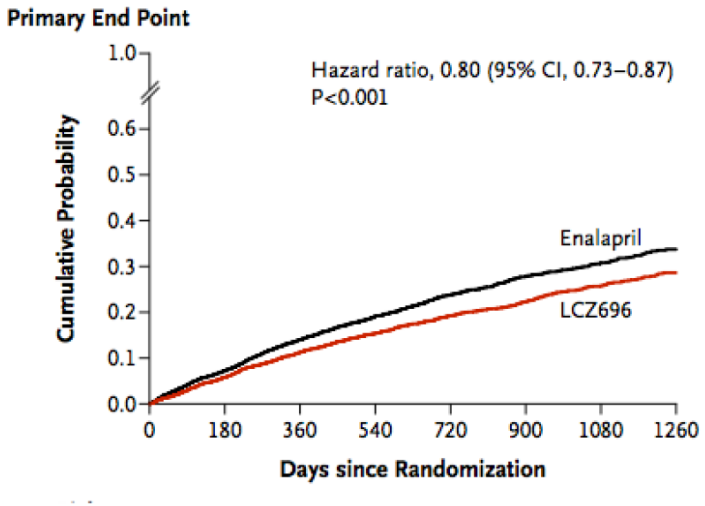
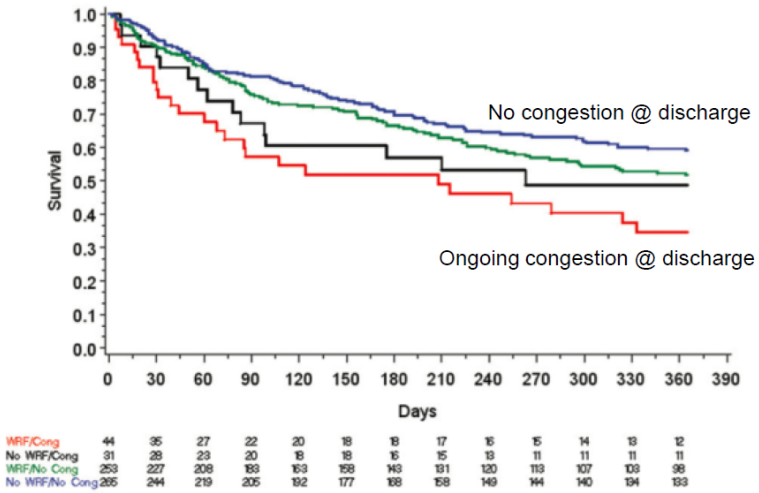
[MaCallum W et al. JACC Heart Fail 2020;8:537]

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

Ambulatory: 20% risk at 2 years

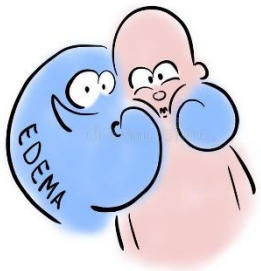
Recently Hospitalized: 60% risk at 1 year

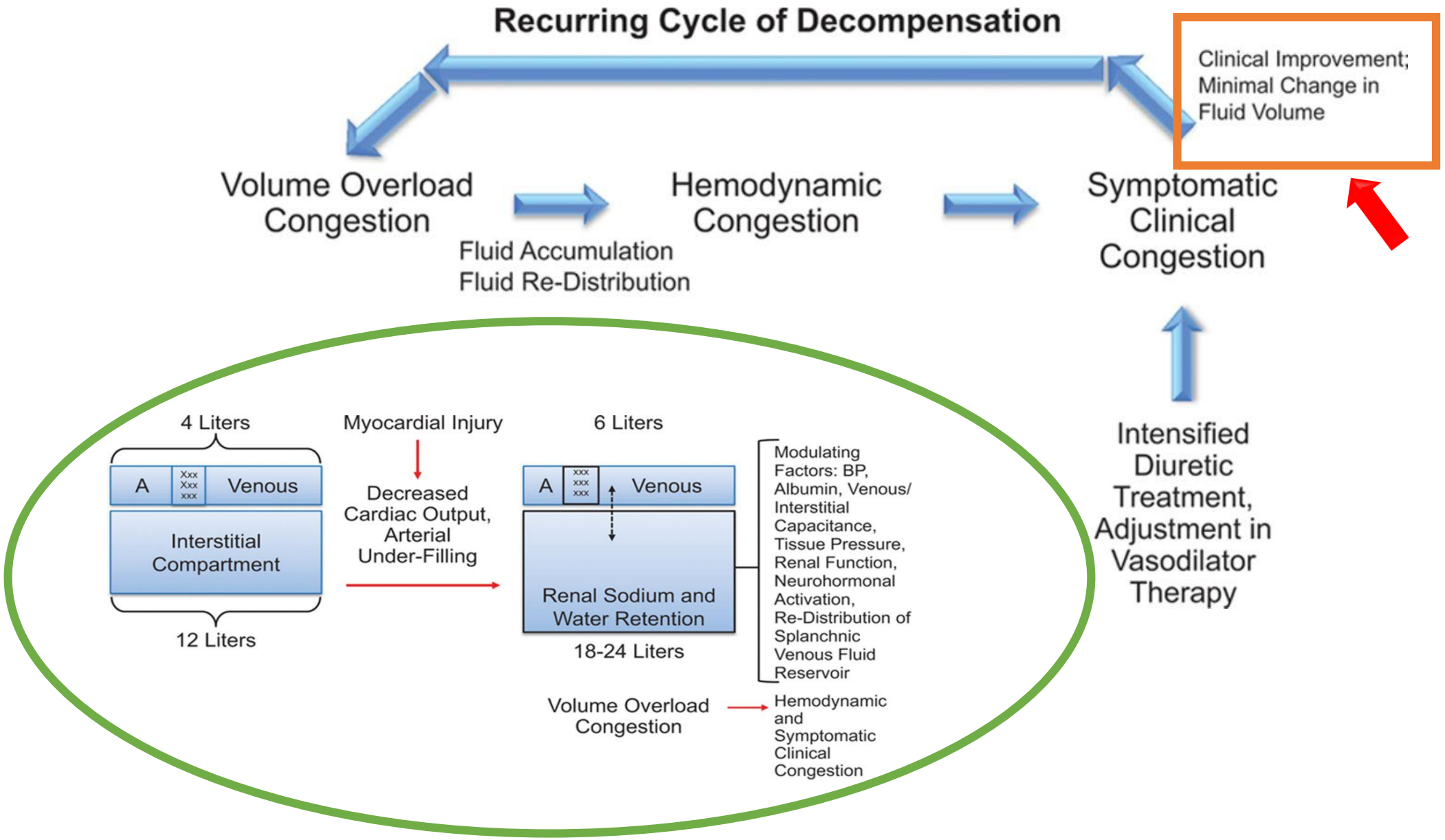




McMurray, Packer et al NEJM 2014
Metra M et al. Circ Heart Fail. 2012;5:54-62

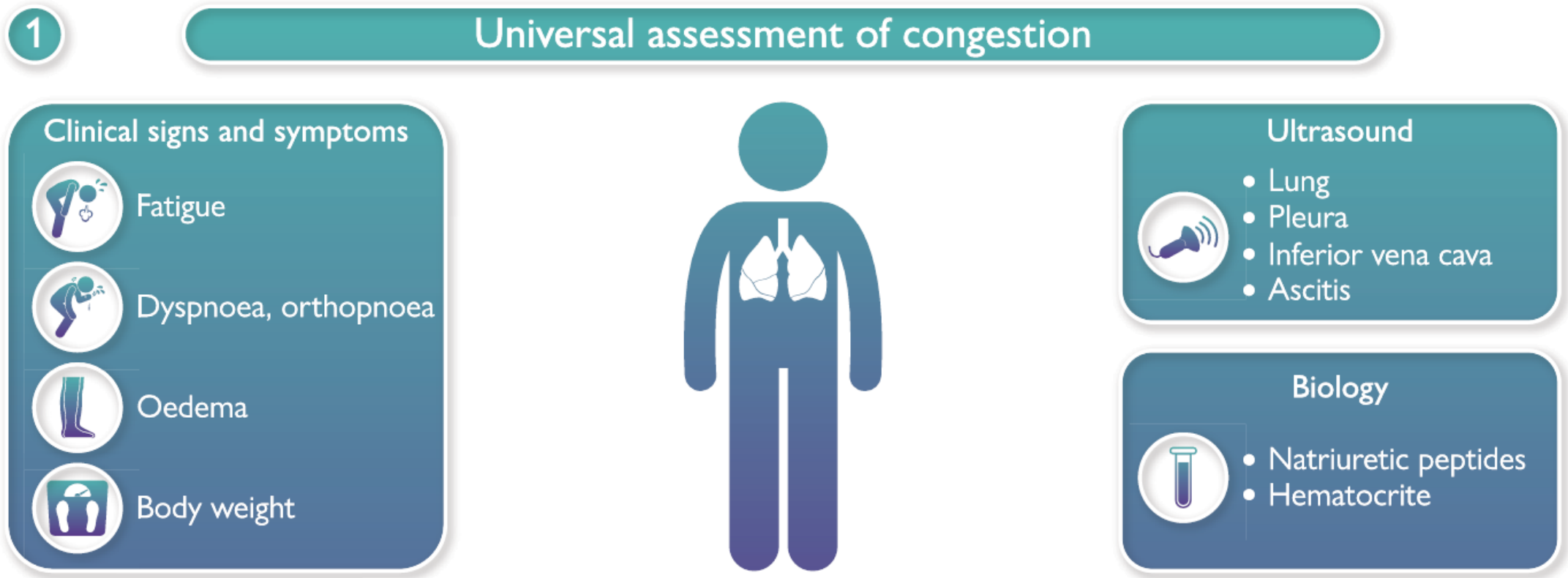
31% of acute heart failure patients leave hospital with residual congestion, having a higher risk of 1-year mortality compared with those discharged with no congestion



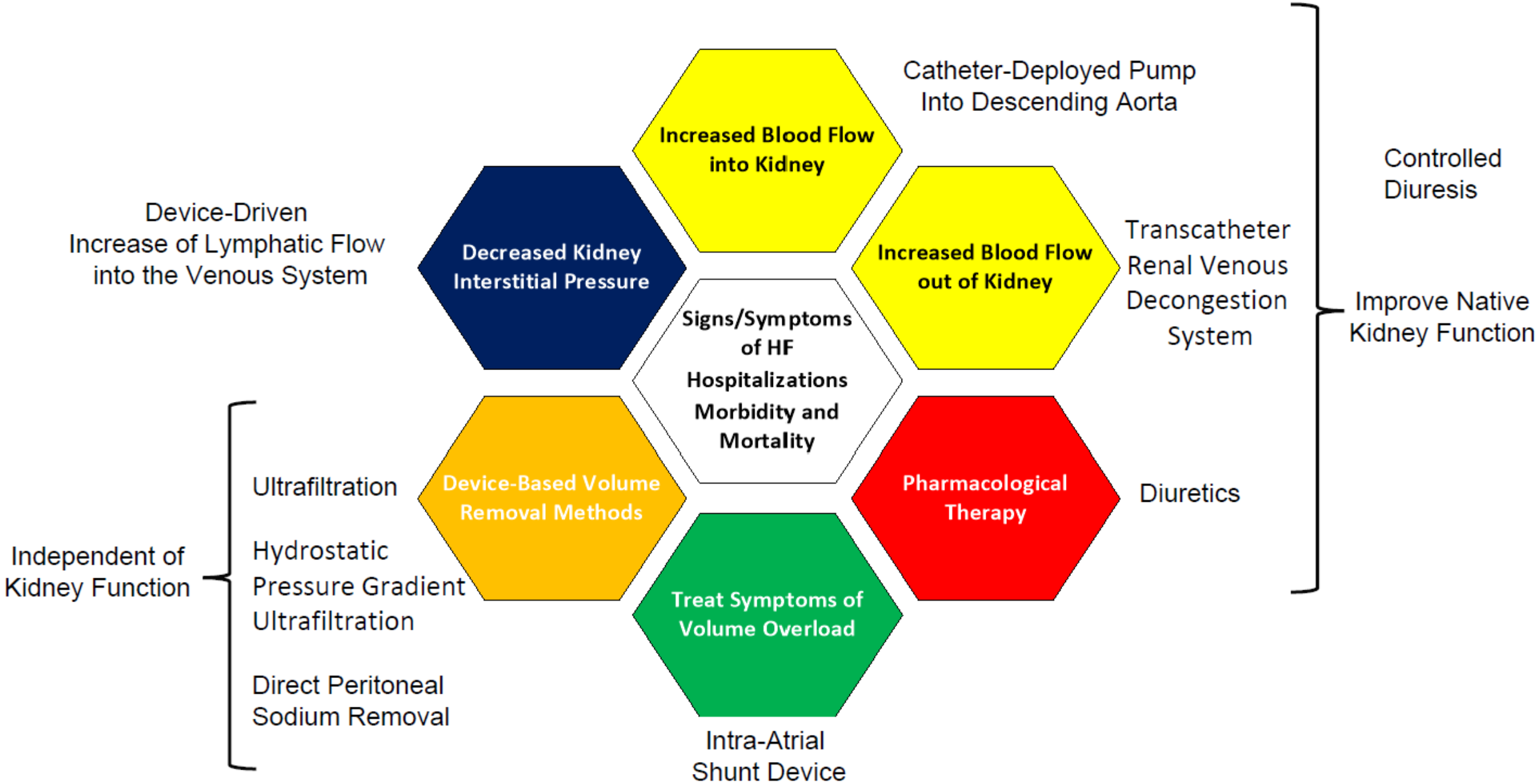


Wayne L. Miller. Circulation: Heart Failure. Fluid Volume Overload and Congestion in Heart Failure DOI: (10.1161/CIRCHEARTFAILURE.115.002922)

Graphical Abstract



Novel Decongestive Therapies



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]

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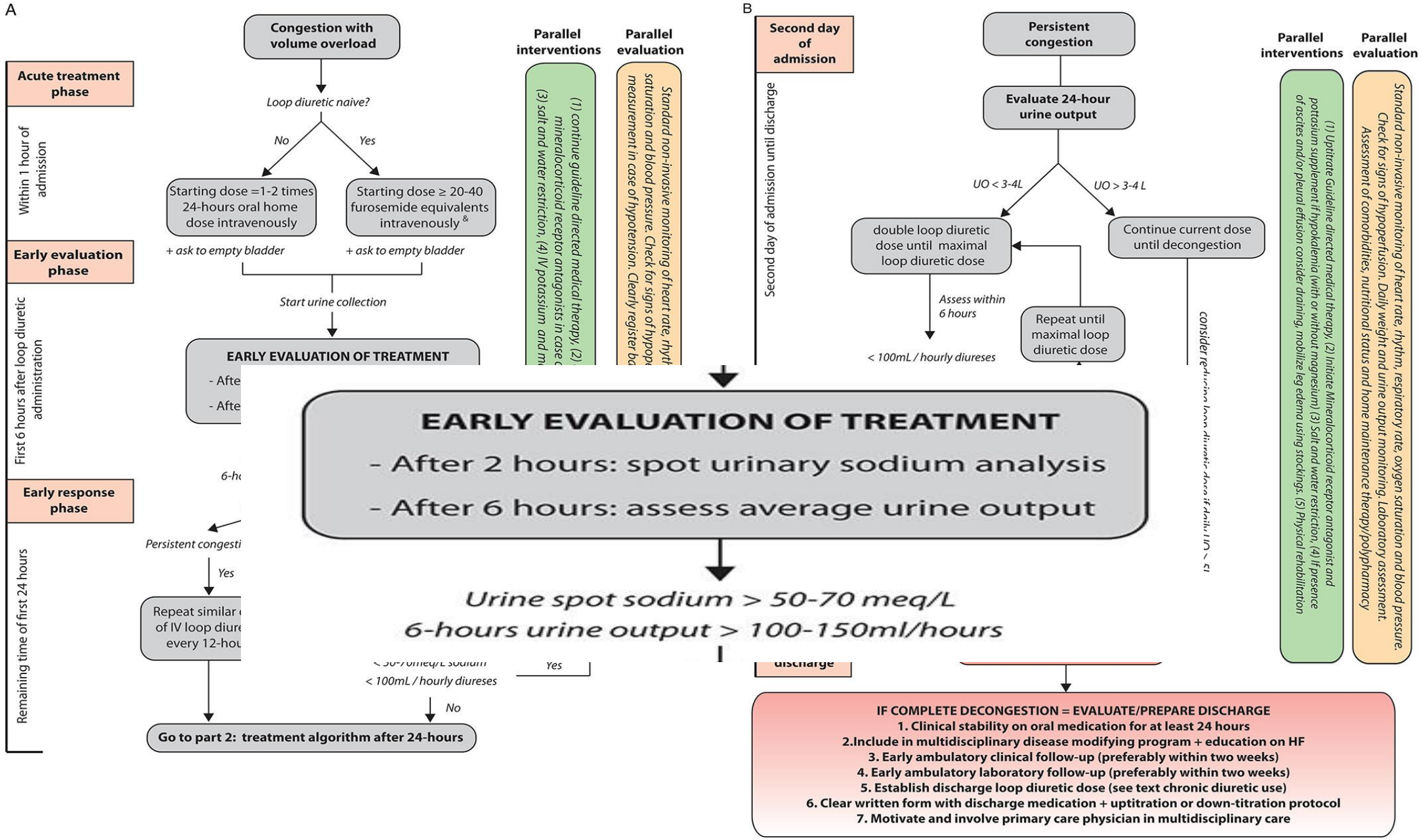
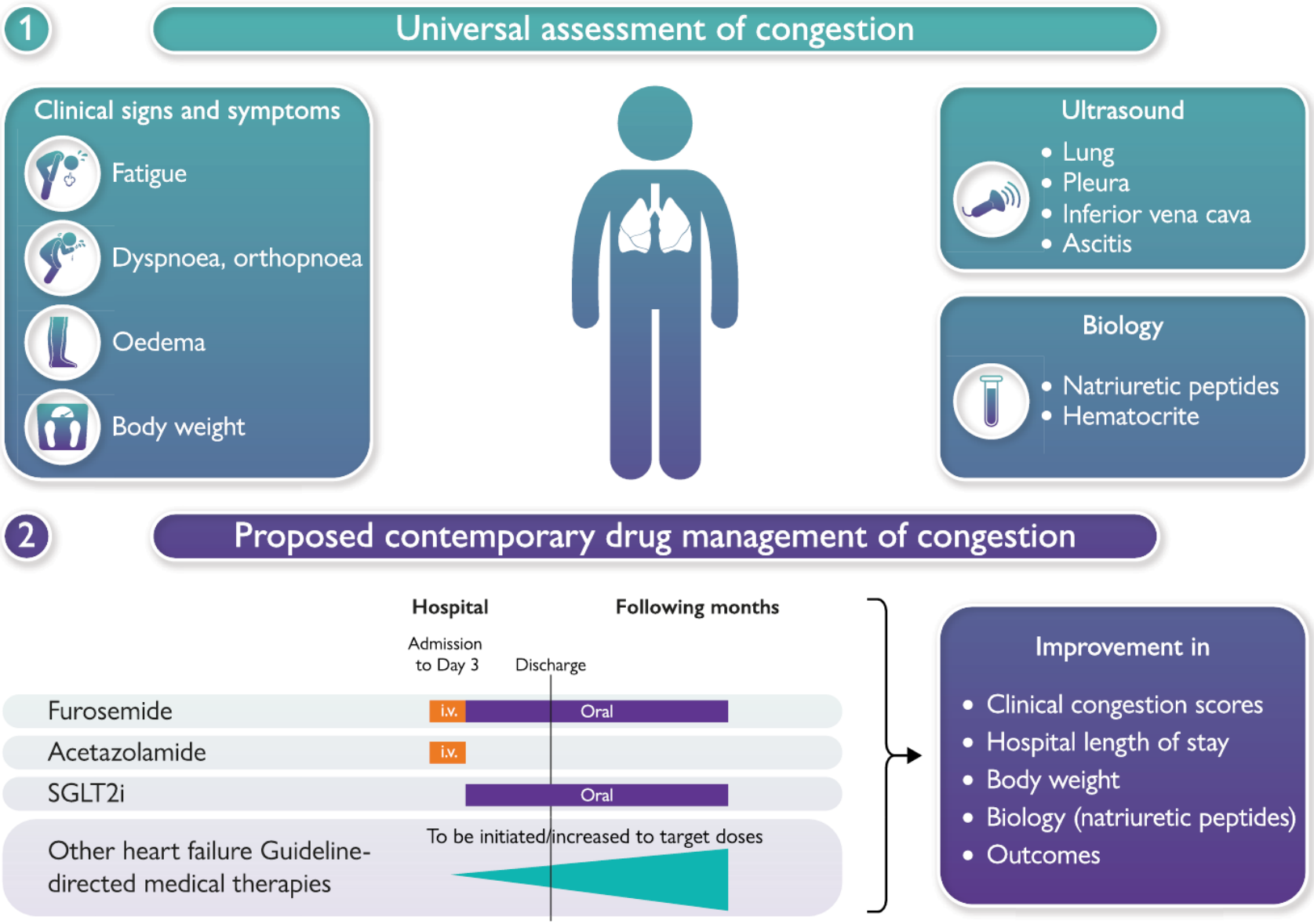

A
Acute treatment phase
Within 1 hour of admission
Early evaluation phase
First 6 hours after loop diuretic administration
Early response phase
Remaining time of first 24 hours
Congestion with volume overload
Loop diuretic naive?
No
Yes
Starting dose =1-2 times 24-hours oral home dose intravenously
Starting dose ≥ 20-40 furosemide equivalents intravenously &
+ ask to empty bladder
+ ask to empty bladder
Start urine collection
EARLY EVALUATION OF TREATMENT
Persistent congesti
Yes
Repeat similar
of IV loop diure
every 12-hou
< 100mL / hourly diureses
No
Go to part 2: treatment algorithm after 24-hours
Parallel interventions
(1) continue guideline directed medical therapy, (2)
mineralocorticoid receptor antagonists in case
(3) salt and water restriction, (4) IV potassium and m
Parallel evaluation
Standard non-invasive monitoring of heart rate, rhyth
saturation and blood pressure. Check for signs of hypop
measurement in case of hypotension. Clearly register ba
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
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
Repeat until maximal loop diuretic dose
< 100mL / hourly diureses
consider reducing loop diuretic dose if daily UO < 3L
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

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)

Graphical Abstract



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

Heart Failure 2023

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

Dr Ross Campbell
BHF Cardiovascular Research Centre, University of

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 cardiomyopathi

Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics

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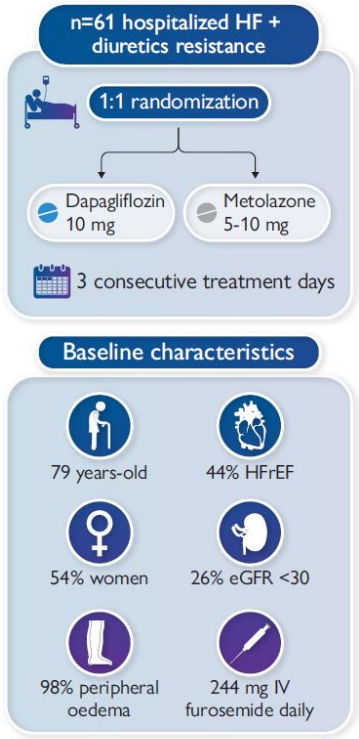
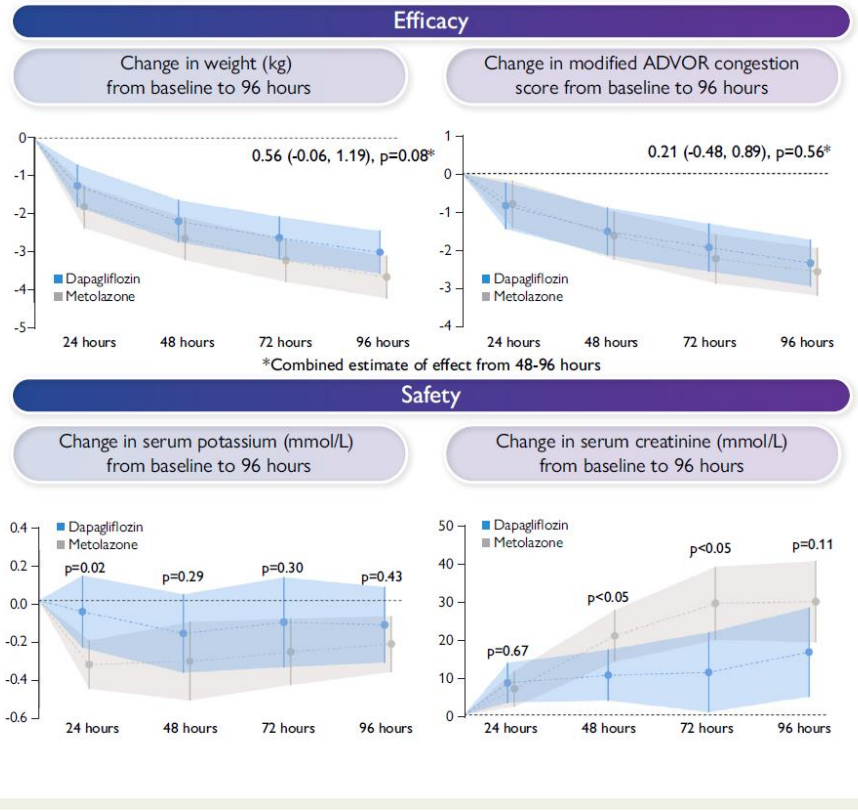
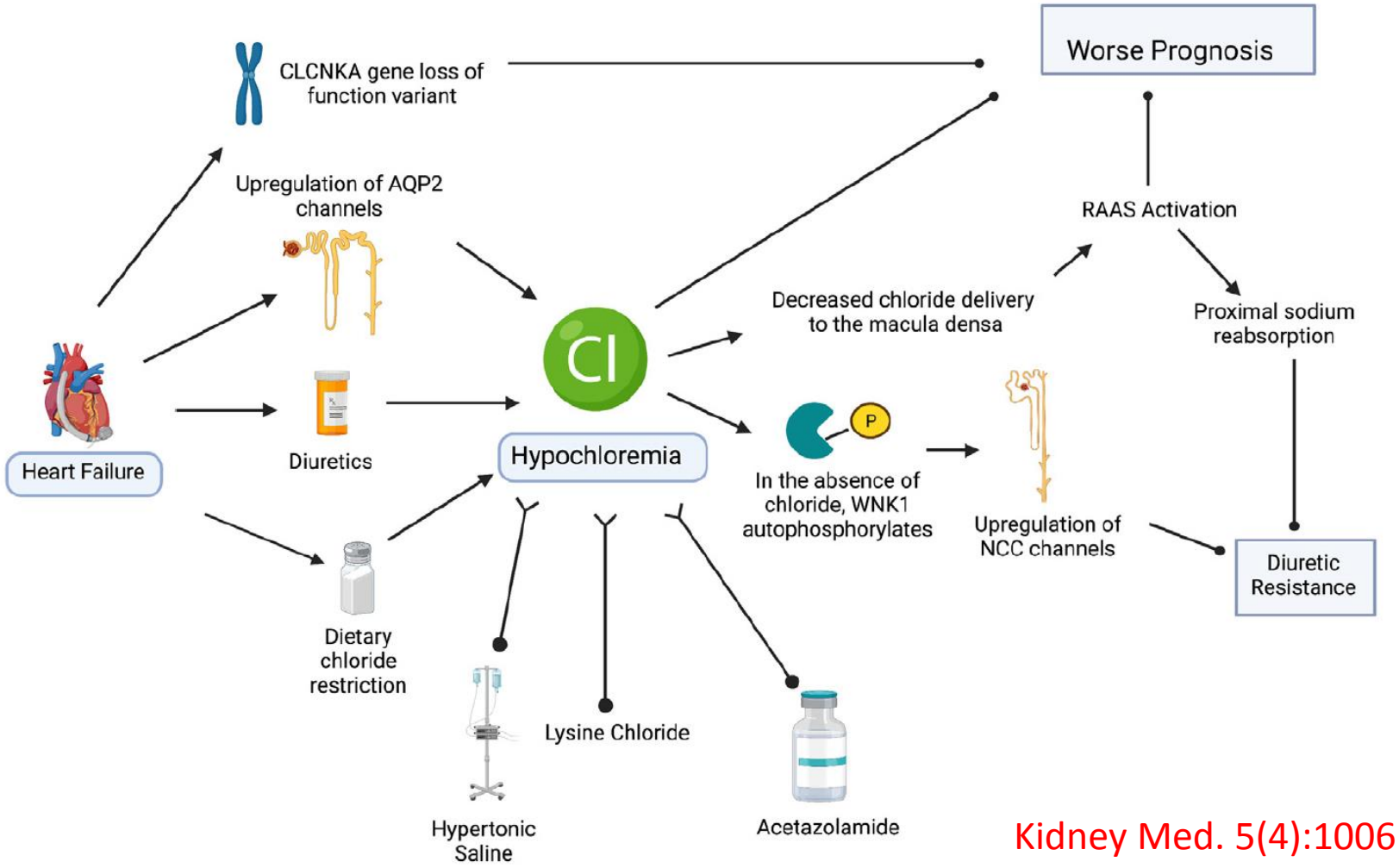




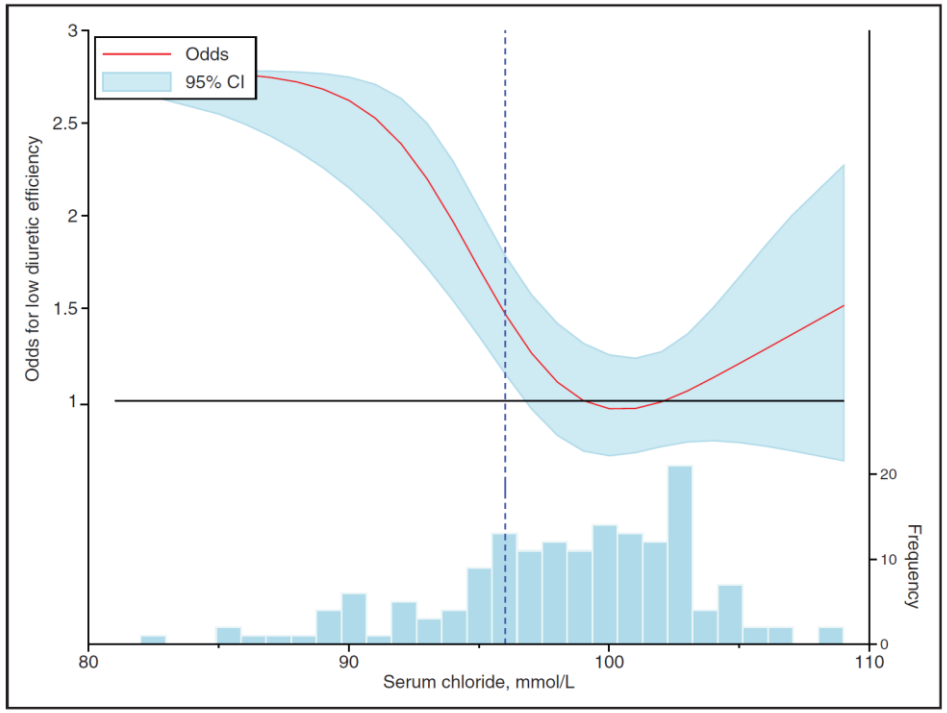
Take home message

- 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.



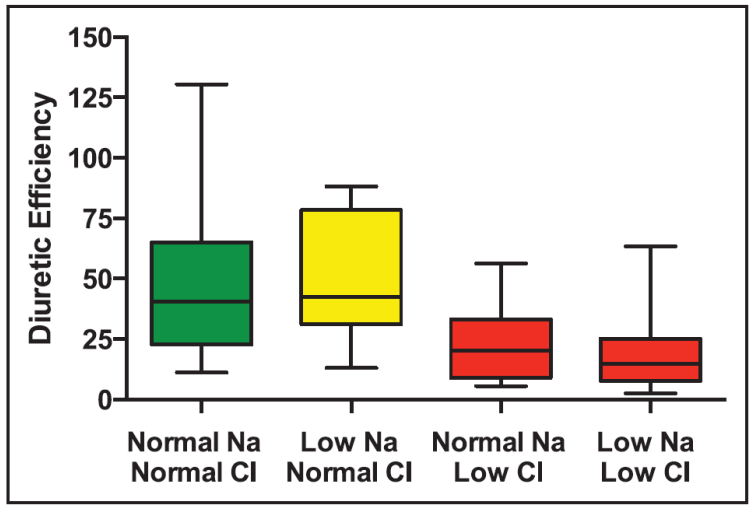
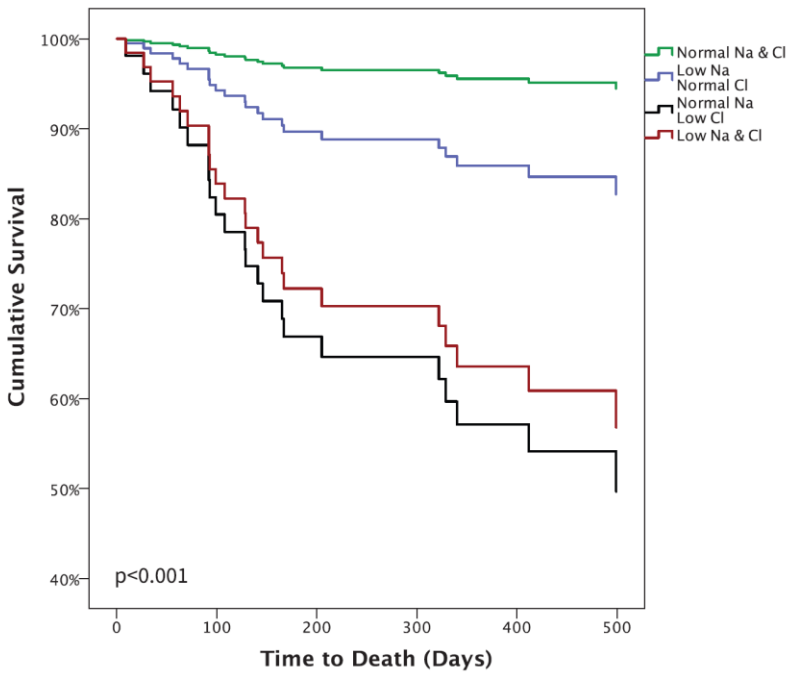
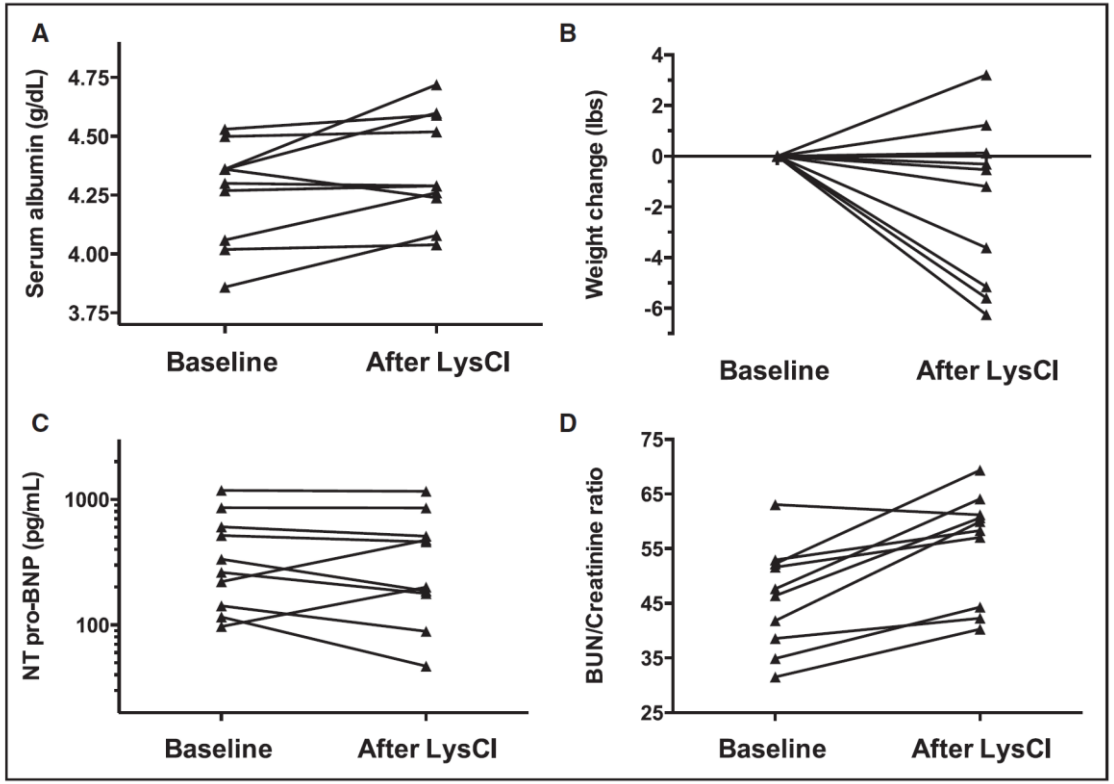
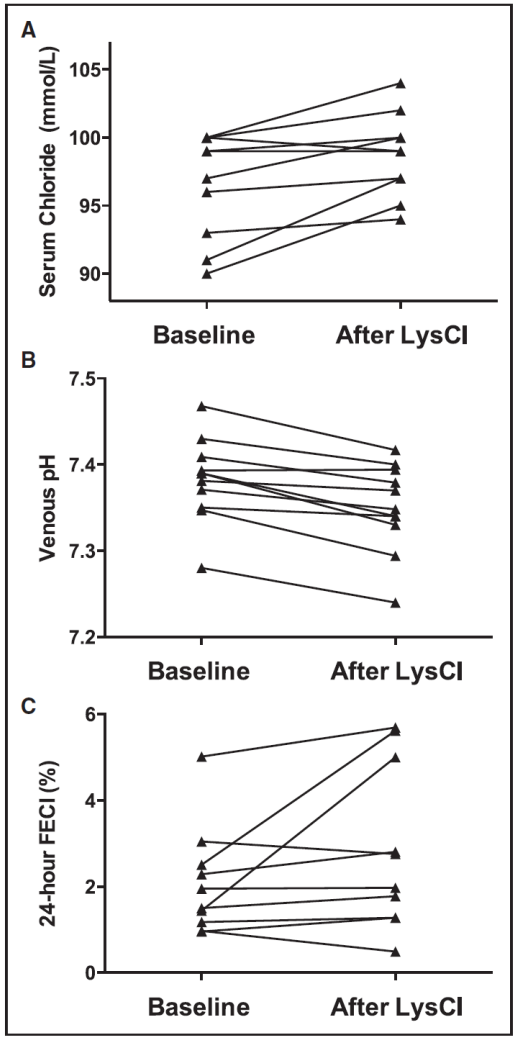


Figure 2. Diuretic efficiency in groups defined by presence or absence of hyponatremia and hypochloremia. Diuretic efficiency is expressed in mmol of sodium excreted per doubling of loop diuretic dose. Whiskers extend from 10th to 90th percentile.



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





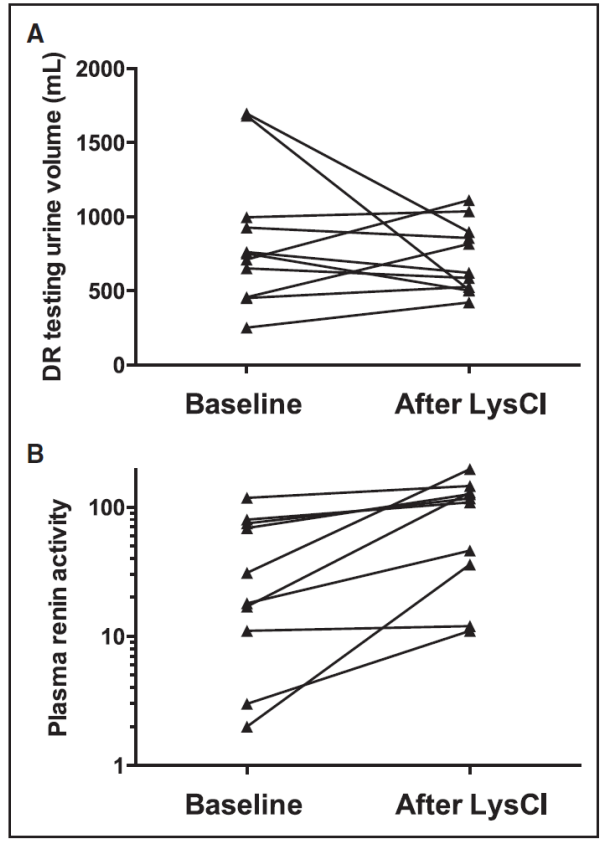


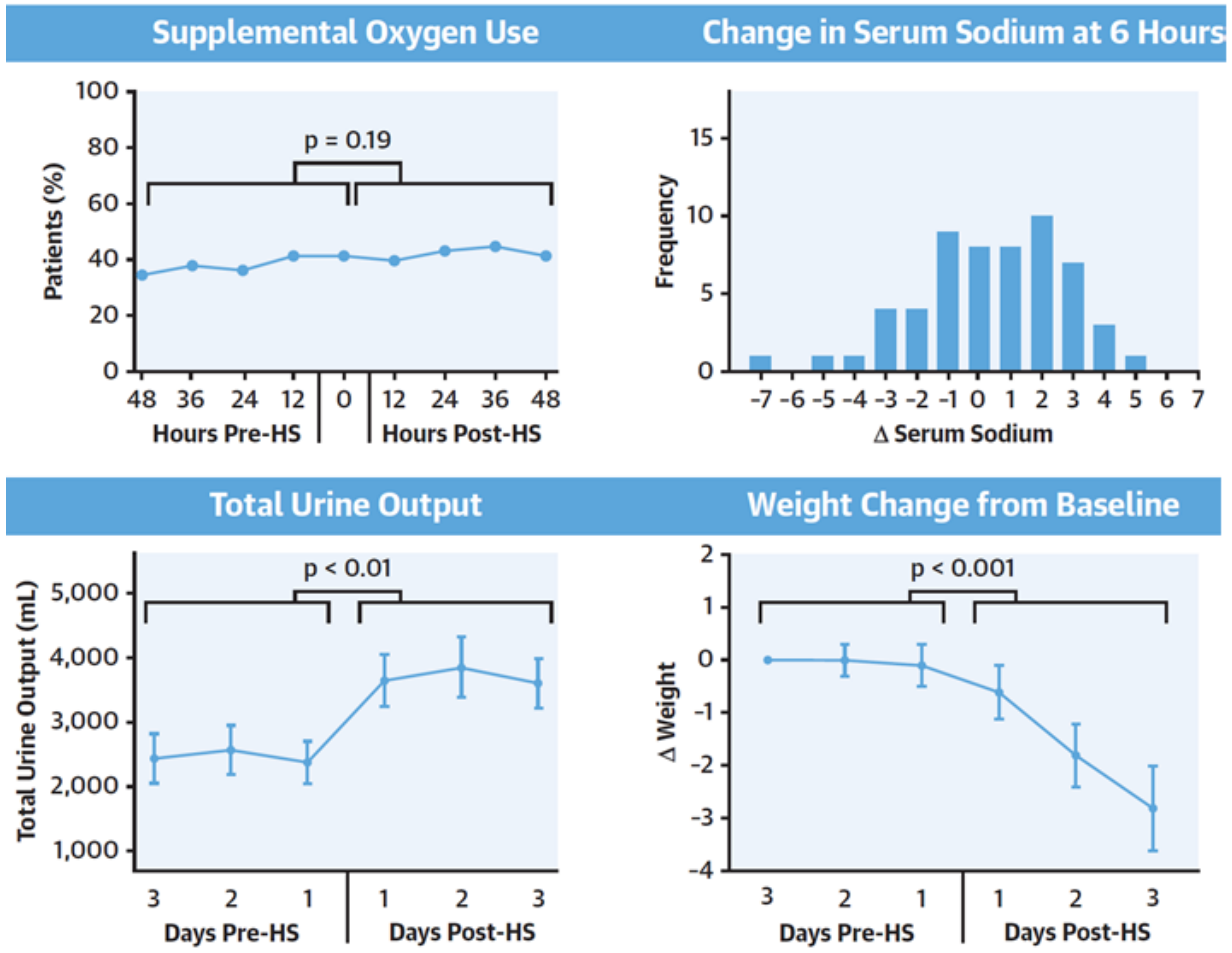
Figure 5. Diuretic induced urine volume and plasma renin activity

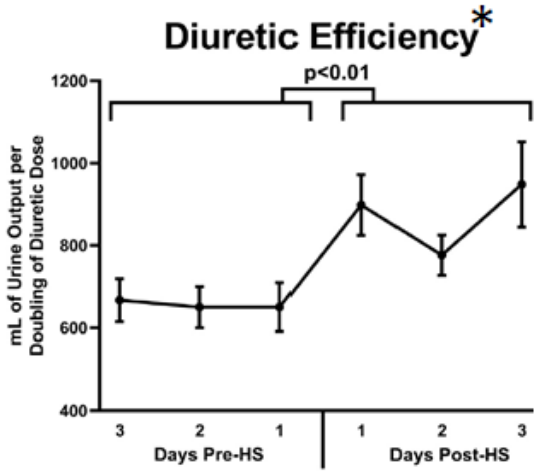
Circ Heart Fail. 2016;9:e003180. DOI: 10.1161/CIRCHEARTFAILURE.116.003180

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

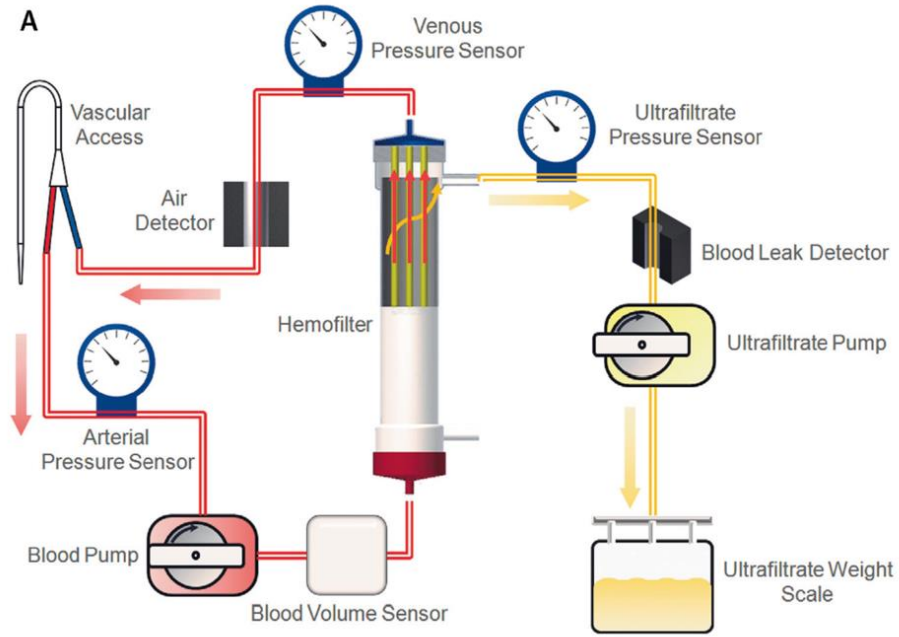
Griffin, M. et al. J Am Coll Cardiol HF. 2020;8(3):199–208.

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

Persistent congestion

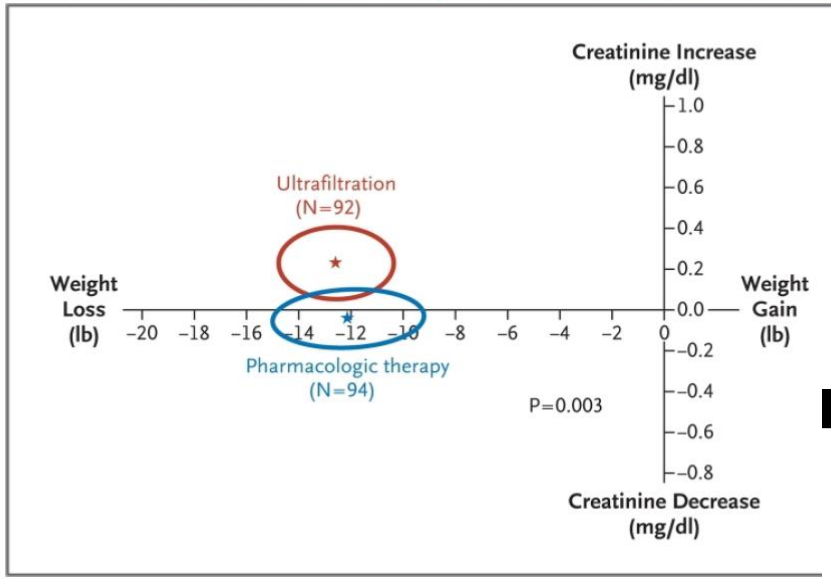
UF- bail out

Peripheral Isolated Veno-Venous Ultrafiltration



CARRESS

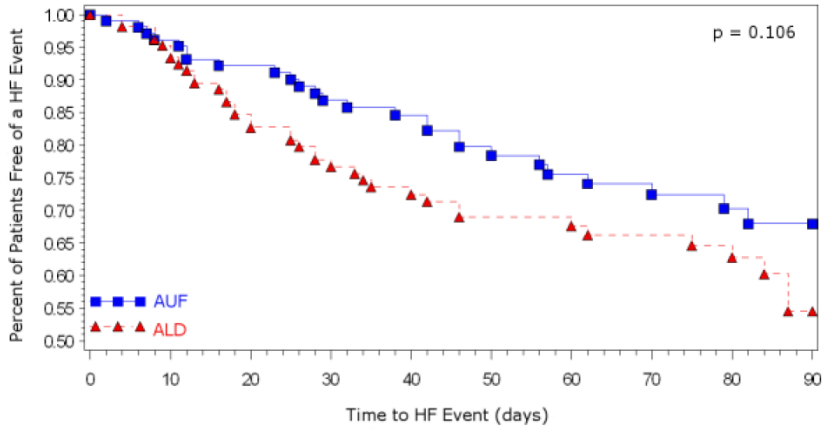
Changes in Serum Creatinine and Weight at 96 Hours (Bivariate Response)



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

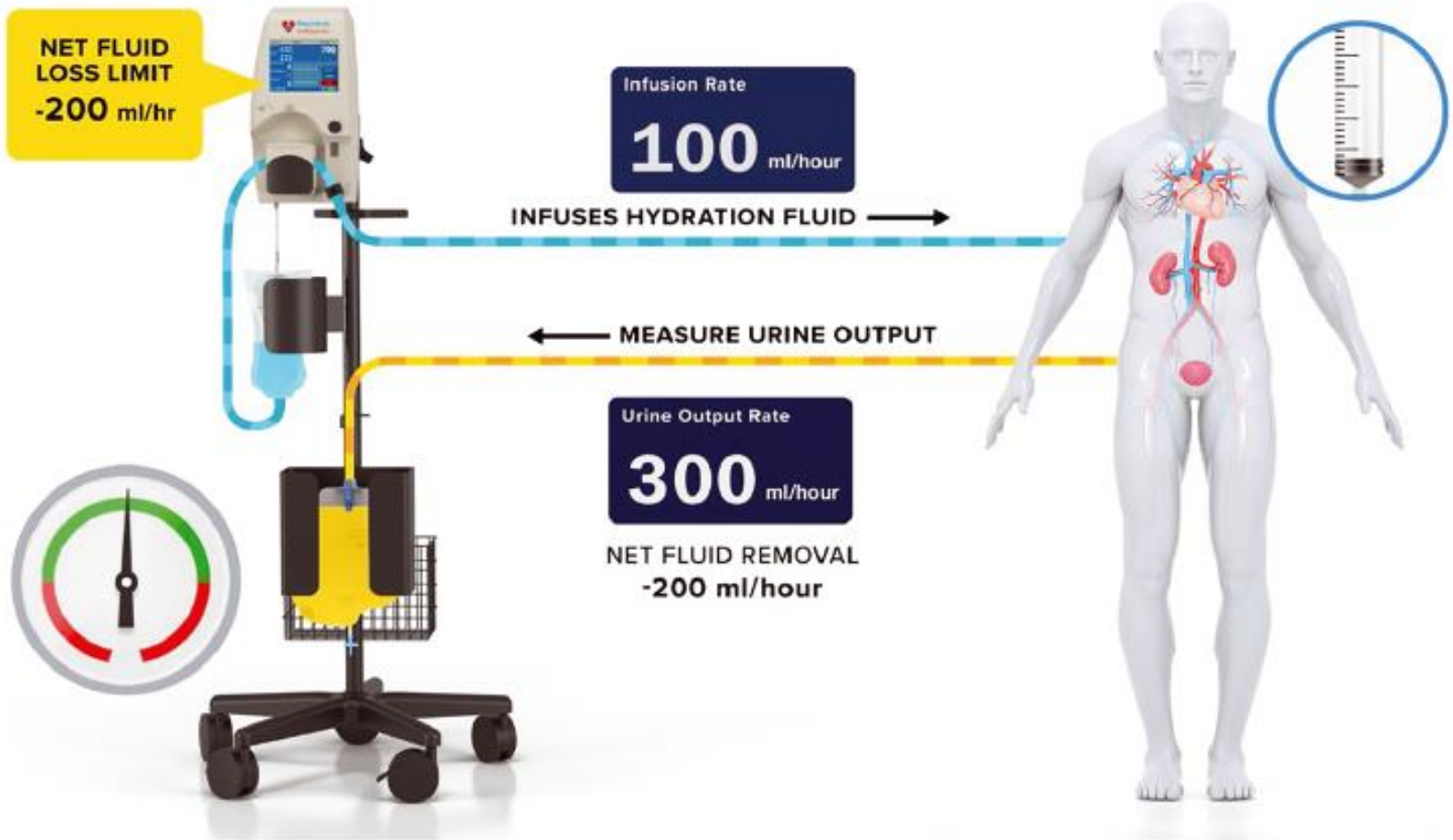
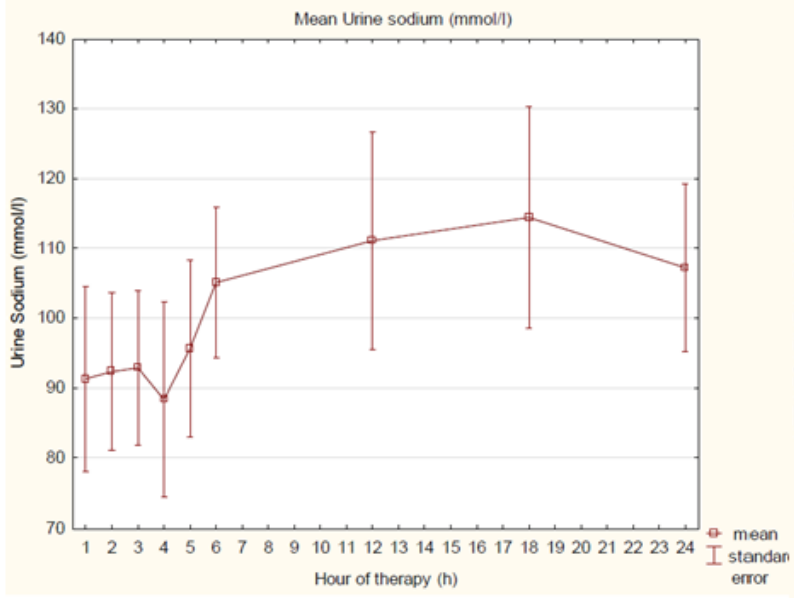
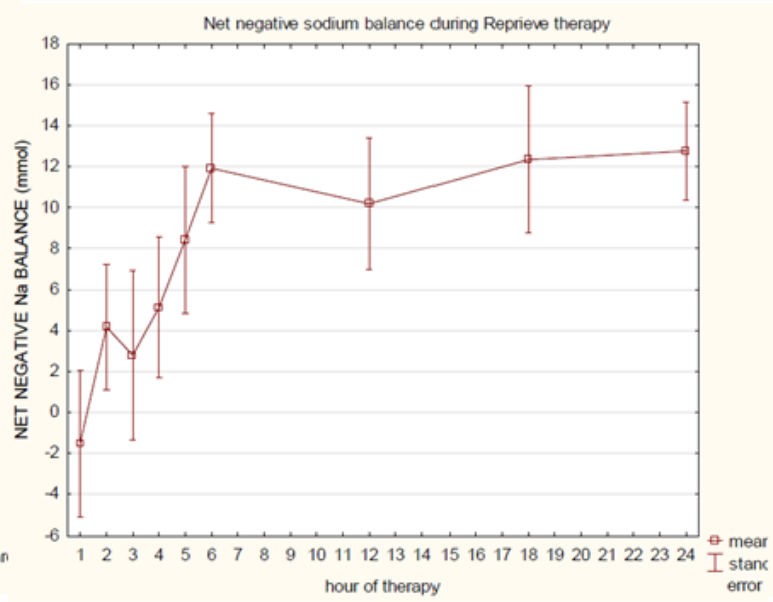


Figure 1 Scheme of the Reprieve-based therapy.

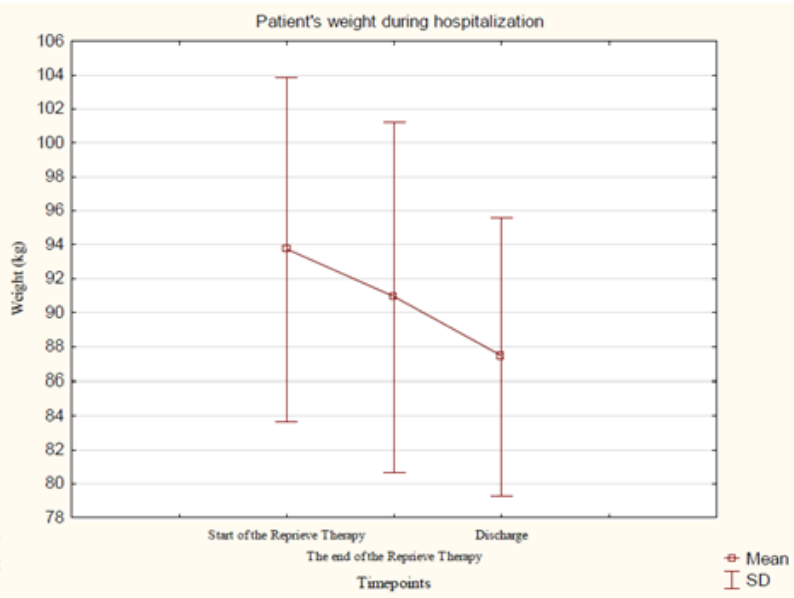
Urinary Sodium



Net Negative Sodium Balance



Weight



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

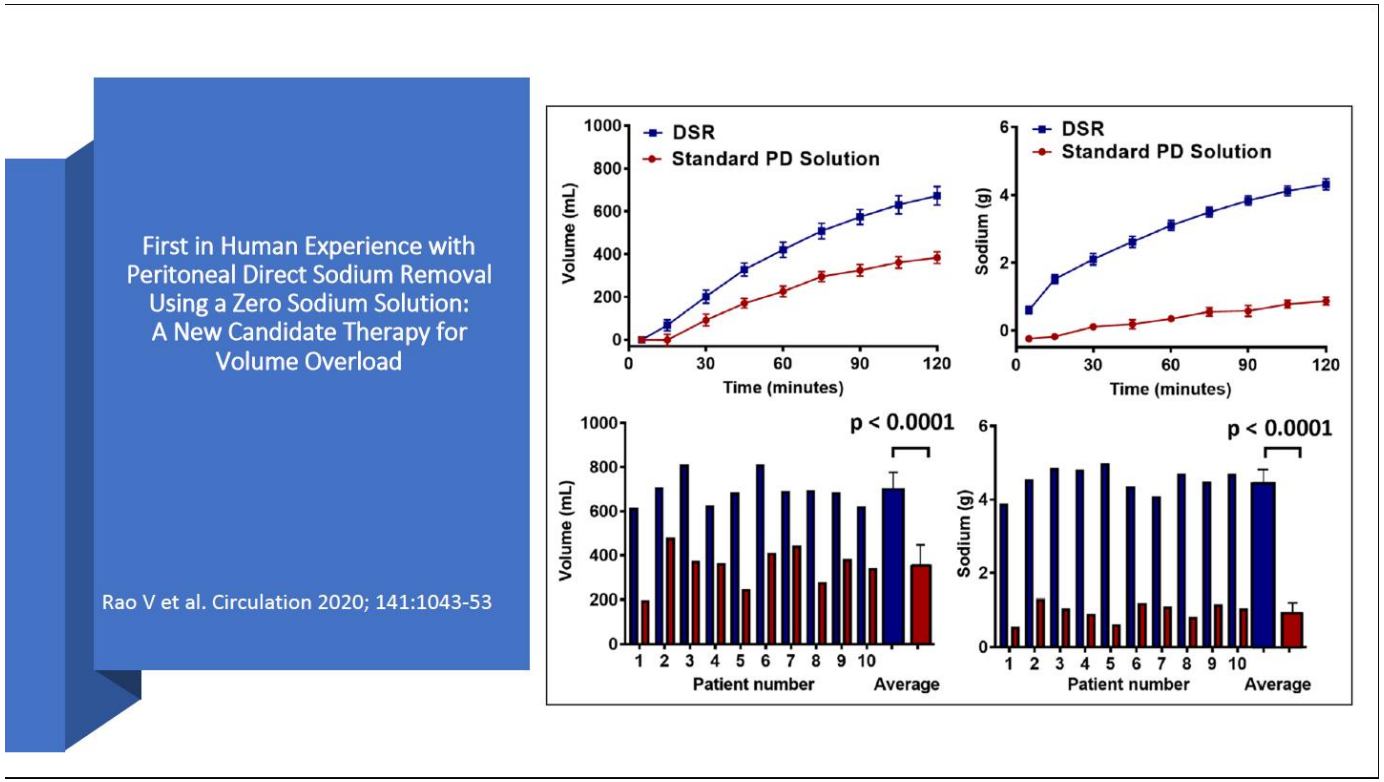
Biegus J et al. Eur J Heart Fail doi: 10.1002/ejhf.1533

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



Journal of
Clinical Medicine

MDPI

Review

The Role of Congestion Biomarkers in Heart Failure with Reduced Ejection Fraction

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Abstract: In heart failure with reduced ejection fraction, edema and congestion are related to reduced cardiac function. Edema and congestion are further aggravated by chronic kidney failure and pulmonary abnormalities. Furthermore, together with edema/congestion, sodium/water retention is an important sign of the progression of heart failure. Edema/congestion often anticipates clinical symptoms, such as dyspnea and hospitalization; it is associated with a reduced quality of life and a major risk of mortality. It is very important for clinicians to predict the signs of congestion with biomarkers and, mainly, to understand the pathophysiological findings that underlie edema. Not all congestions are secondary to heart failure, as in nephrotic syndrome. This review summarizes the principal evidence on the possible roles of the old and new congestion biomarkers in HFrEF patients (diagnostic, prognostic, and therapeutic roles). Furthermore, we provide a description of conditions other than congestion with increased congestion biomarkers, in order to aid in reaching a differential diagnosis. To conclude, the review focuses on how congestion biomarkers may be affected by new HF drugs (gliflozins, vericiguat, etc.) approved for HFrEF.

Citation: Correale, M.; Fioretti, F.; Tricarico, L.; Croella, F.; Brunetti,

Conditions with increased HF biomarkers

BNP/NT-PROBNP
- Age
- Heart muscle diseases
- Valvulopathies
- AF/ Atrial flutter
- Cardiotoxic drugs
- Renal failure
- Anemia
- Critical illness
- Stroke
- Right heart disease

Cardiac troponin
- Acute myocardial infarction
- Tachyarrhythmias
- Hypertensive emergencies
- Critical illness/ Stroke
- Myocarditis/ Takotsubo síndrome
- Valvulopathies / Aortic dissection
- Pulmonary embolism
- Renal dysfunction
- Cardiac contusion
- Drug toxicity
- Endurance efforts/ Rhabdomyolysis

CA-125
- Ovarian cancer
- Other neoplasms
- Endometriosis
- Tuberculosis
- Urinary infections
- Peritonitis
- Pericarditis
- Cirrhosis
- Pregnacy
- Menstruation

Galectin-3
- AF
- Chronic coronary disease
- Acute myocardial infarction
- Chronic kidney disease
- Cirrhosis
- Malignant neoplasms

NGAL
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Multiple sclerosis
- Acute kidney injury
- Obesity
- Acute myocardial infarction

sST2
- Asthma
- Rheumatoid arthritis
- Inflammatory bowel disease
- STEMI
- Acute aortic síndromes
- Arterial hyperthension
- AF
- Acute allograft rejection of heart transplant
- Sepsis

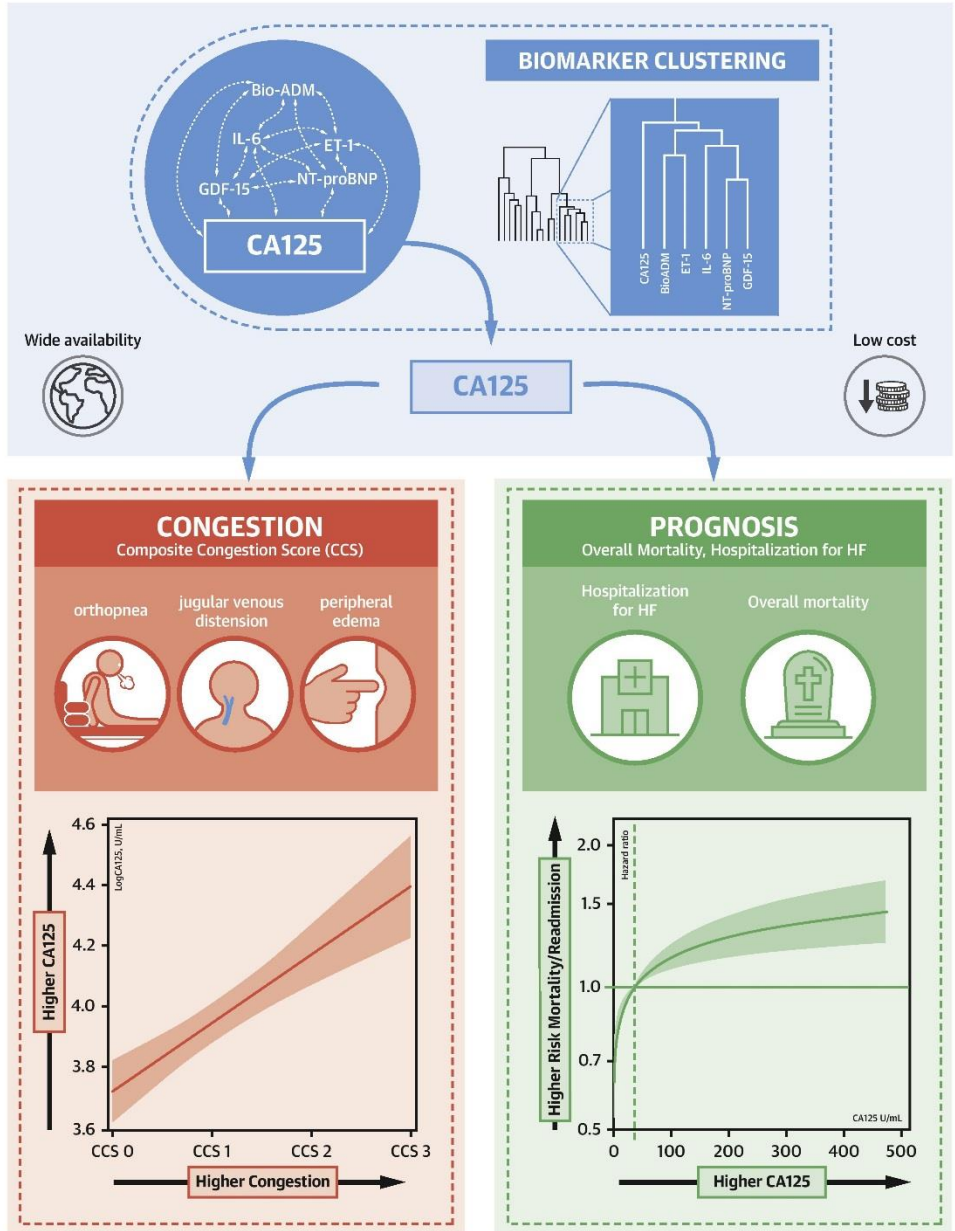
P3P
- Viral and alcoholic hepatitis
- Lung fibrosis
- Myocardial infarction
- AF

GDF-15
- Acute pulmonary embolism
- Idiopatic pulmonary arterial hypertension
- Chronic kidney disease
- Some metastatic carcinoma
- Atherosclerosis
- AF
- Obesity

Copeptin
- Acute coronary sndromes
- Pneumoniae
- Chronic obstructive pulmonary disease
- Diabetes
- Stroke
- Sepsis

MR-proADM
- Arterial hyperthension
- Pneumoniae
- ARDS
- Cirrhosis
- Cancer
- Sepsis

CENTRAL ILLUSTRATION: CA125 as a Biomarker in Patients With Worsening Heart Failure



Núñez, J. et al. J Am Coll Cardiol HF. 2020;8(5):386-97.

European Heart Journal (2023) 44 (Suppl 2)

CA-125 concentrations are associated with renal function decline but not congestion or prognosis in patients with chronic heart failure: results from EMPEROR-POOLED

J. Januzzi[1], R. Mohebi[1], On Behalf Of Emperor Committees And Investigators[1]

[1]Massachusetts General Hospital, Boston, United States of America
On behalf of EMPEROR Committees and Investigators

Funding Acknowledgements: Type of funding sources: Private company. Main funding source(s): Boehringer Ingelheim and Eli Lilly

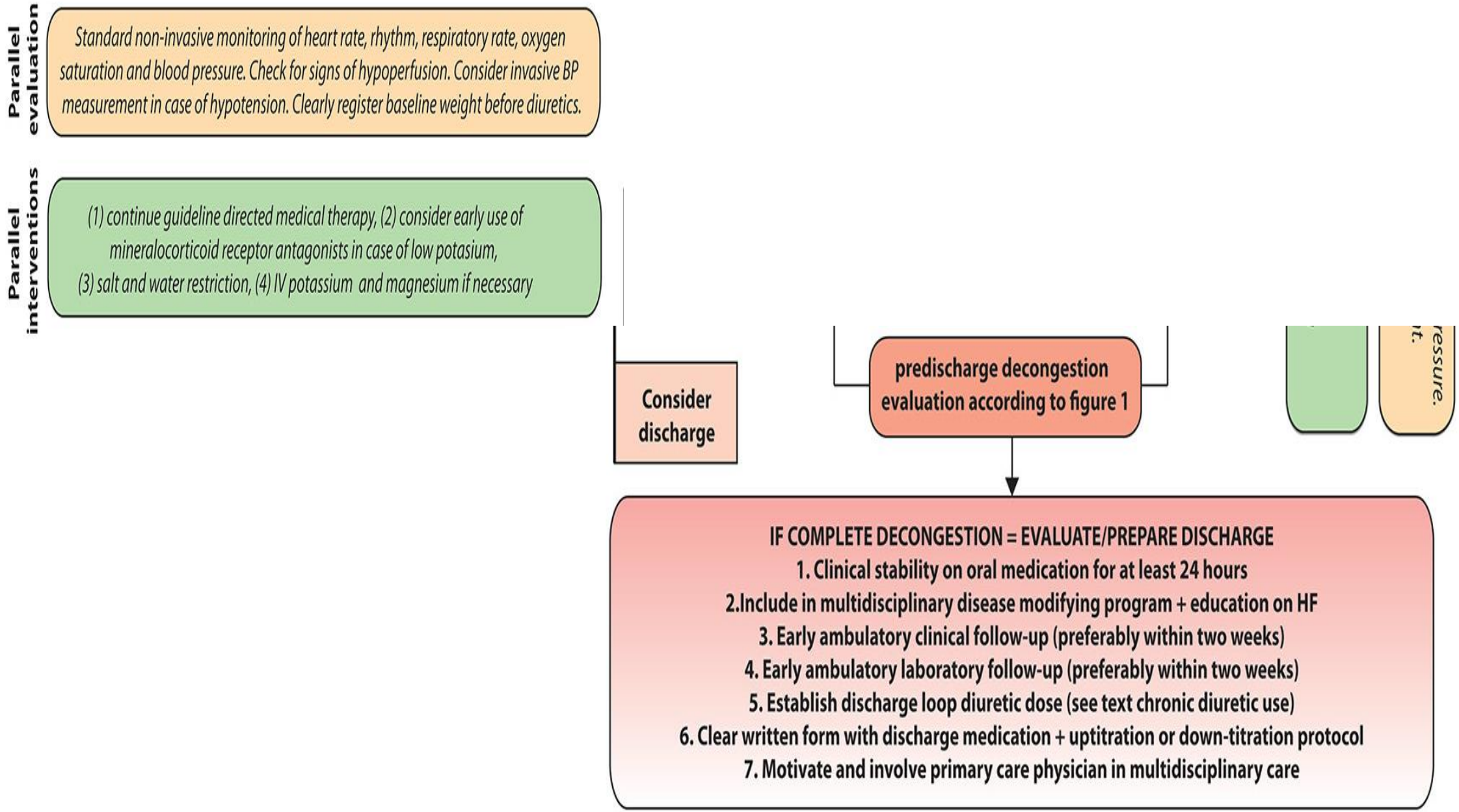
Background: Carbohydrate antigen 125 (CA-125, also described as cancer antigen 125), has emerged as a candidate biomarker of congestion in heart failure (HF). Effects of sodium/glucose cotransporter-2 inhibitor therapy on CA-125 and its role as a prognostic measure in HF remains uncertain.

Purpose: In study participants from the EMPEROR-Preserved and EMPEROR-Reduced trials, across a wide spectrum of ejection fraction (EF) and renal function, we sought to investigate associations between CA-125 and congestion, the effect of empagliflozin on CA-125 concentrations, and the ability of the biomarker to predict cardio-renal outcomes.

Methods: 1111 patients with HF and available biomarker data were included into this analysis. Serum CA-125 was measured at baseline, 12 and 52 weeks using an Electroluminescence assay. The measurements were performed within a biomarker research agreement of Boehringer Ingelheim, the sponsor of these trials and Roche Diagnostics International Ltd. Congestion signs or symptoms were evaluated across CA-125 tertiles. A mixed model for repeated measurements was used to compare the treatment effects on CA-125. Multivariable analyses adjusted for the prespecified EMPEROR baseline variables plus N-terminal pro-B type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) were used to examine the association of CA-125 with HF hospitalization or cardiovascular (CV) death and estimated glomerular filtration rate (eGFR) slope.

Results: Across CA-125 tertiles at baseline, no significant association was present with HF symptom severity, jugular vein distention, pulmonary rales, S3 gallop or peripheral oedema (all p-values >0.10). Treatment with empagliflozin was associated with 7% greater reduction of CA-125 level versus placebo to week 12 (adjusted geometric mean ratio: 0.93; 95% confidence interval [CI], 0.87-0.99, p = 0.03) but not to week 52 (adjusted geometric mean ratio: 0.97, 95% CI 0.90-1.06; p = 0.50). No significant association was found for tertiles of CA-125 at baseline with the risk of CV death/HF hospitalization; with a hazard ratio (HR) for higher vs lower CA-125 tertiles of 1.34 (95% CI 0.91–1.96). In the same model NT-proBNP and hs-cTnT were strongly prognostic (both p-values <0.0001). Compared to lower tertiles, study participants in the third CA-125 tertile had higher rate of kidney function decline with a more negative eGFR slope (p for trend = 0.03).

Conclusion: In chronic HF, across a wide range of EF and of renal function, CA-125 levels were not strongly associated with clinical signs or symptoms of congestion. Empagliflozin lowered CA-125 levels more than placebo at week 12 but not at week 52. Among individuals with HF, CA-125 concentrations did not provide additional prognostic information for CV death/HF hospitalization beyond conventional cardiac biomarkers but may predict subsequent kidney function decline.

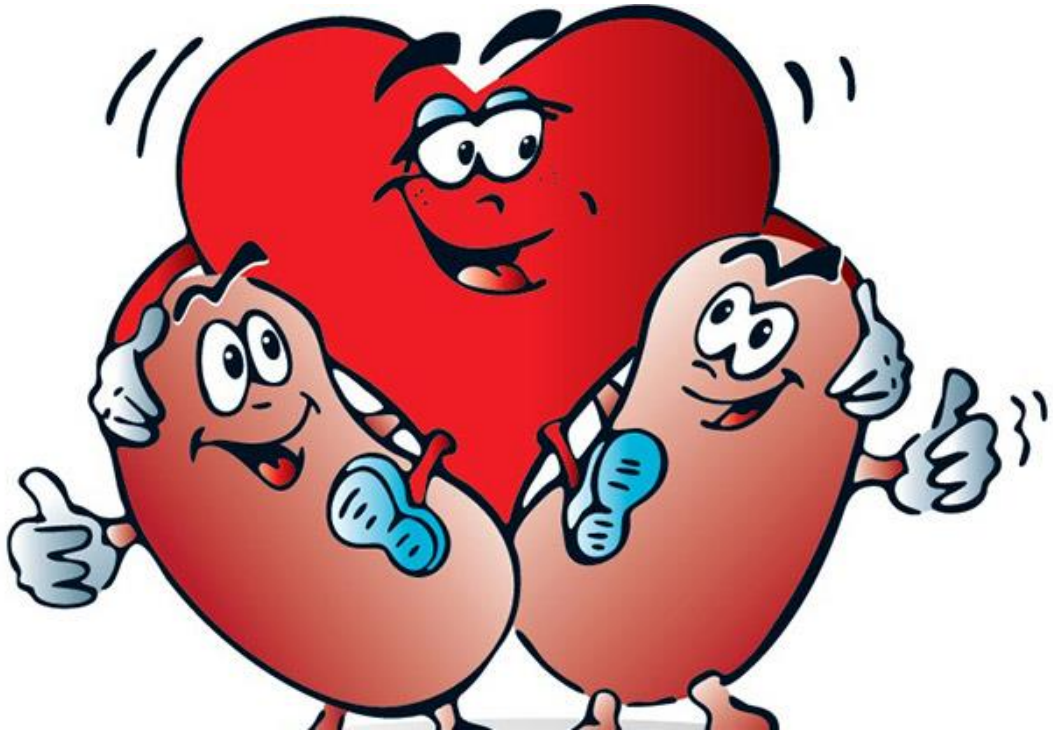

Parallel evaluation
Standard non-invasive monitoring of heart rate, rhythm, respiratory rate, oxygen saturation and blood pressure. Check for signs of hypoperfusion. Consider invasive BP measurement in case of hypotension. Clearly register baseline weight before diuretics.
Parallel interventions
(1) 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
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

Conclusions

- Renal Impairment frequently complicates acute heart failure
- Worsening Renal Function acceptable if Diuretic Response is favourable
- Both Congestion and low cardiac output predispose to (worsening) renal failure
- Dose Diuretics adequately in patients with low eGFR
- Evaluate Diuretic response!
- If Diuretic Resistant with monotherapy, consider sequential nephron blockade

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