XI Reunion, Insuficiencia Cardiaca, A Coruna

Diuretic use in HF. When? How? What?

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September 27, 2024

HFA Heart Failure Association
universiteit hasselt
Ziekenhuis Oost-Limburg

Declaration of interest

- Speaker fees to independent Hospital / University Fund

- Will (try to) explain what you should do in case of diuretic resistance and/or WRF….
  which is mostly reflecting ‘normal’ physiological response to HF

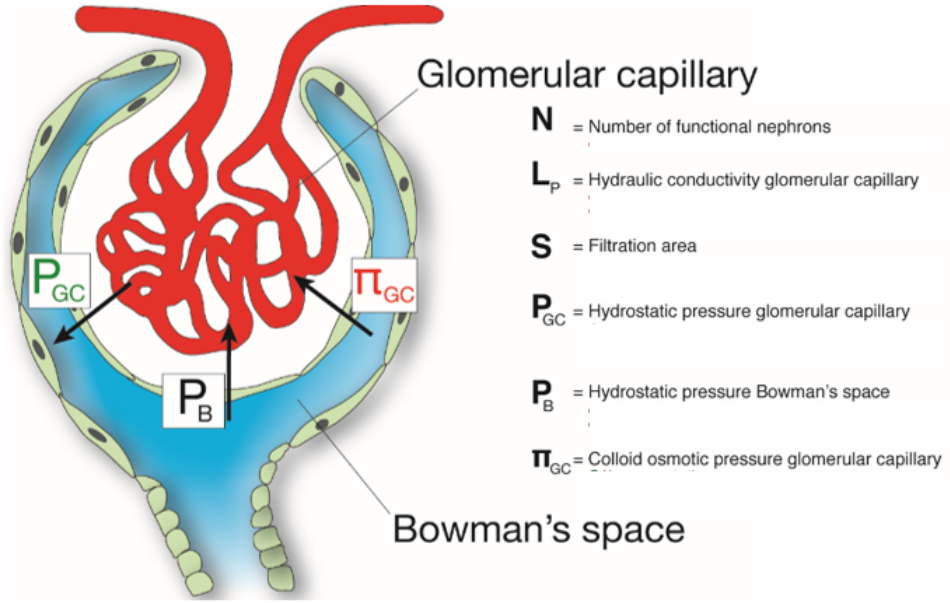
Conclusions

1. Renal function ≠ GFR
2. CKD is very prevalent and related to adverse outcomes
3. Certain agents delay the progression of CKD
4. Diuretic resistance / WRF is a normal physiological response
5. Do NOT stop decongestion / GDMT if WRF occurs

RENAL FUNCTION

Glomerular filtration rate (GFR)

$$GFR = N \times L_P \times S \times (P_{GC} - P_B - \pi_{GC})$$



N = Number of functional nephrons

L_P = Hydraulic conductivity glomerular capillary

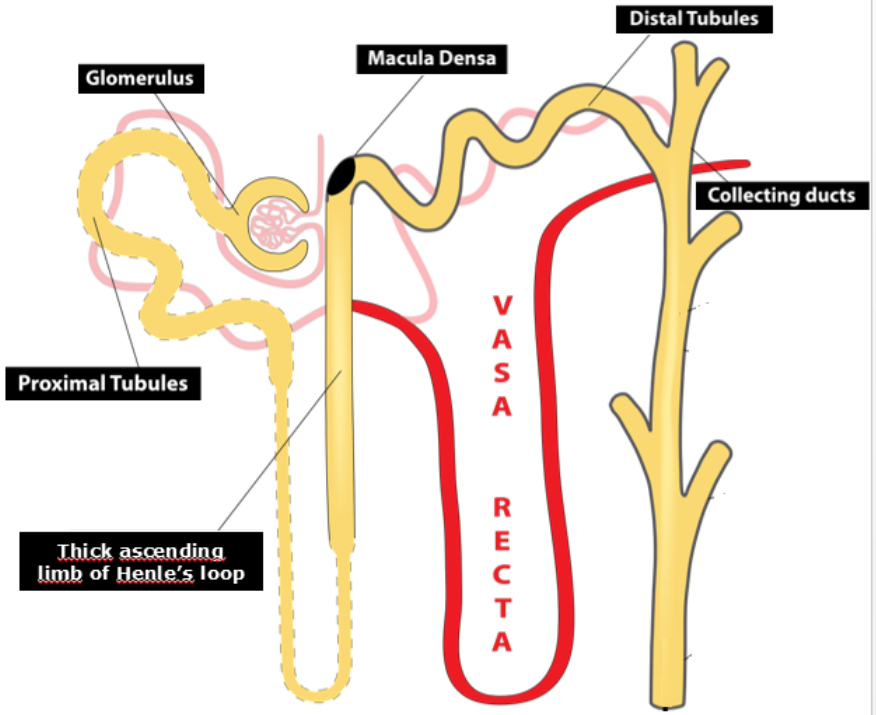
S = Filtration area

P_{GC} = Hydrostatic pressure glomerular capillary

P_B = Hydrostatic pressure Bowman's space

π_{GC} = Colloid osmotic pressure glomerular capillary

Tubular function

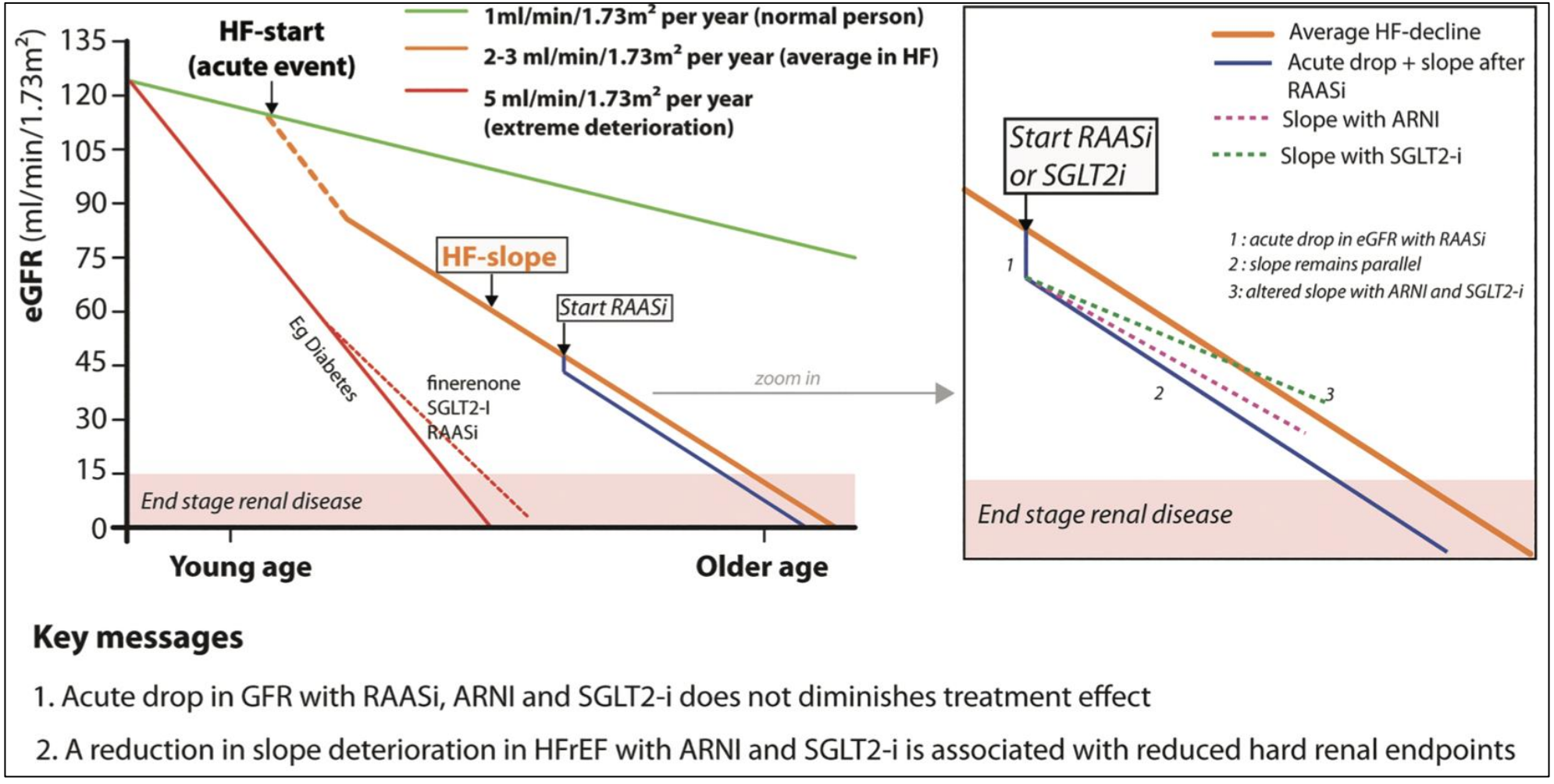


CLEARANCE

HOMEOSTASIS

Verbrugge F. Eur J Heart Fail. 2014;16:133-42
Mullens W, Eur J Heart Fail 2020; 22:584-603
Benzing T et al, N Engl J Med 2021;384:1437-46

CKD (eGFR < 60) affects > 50 % of HF patients + stronger predictor than LVEF



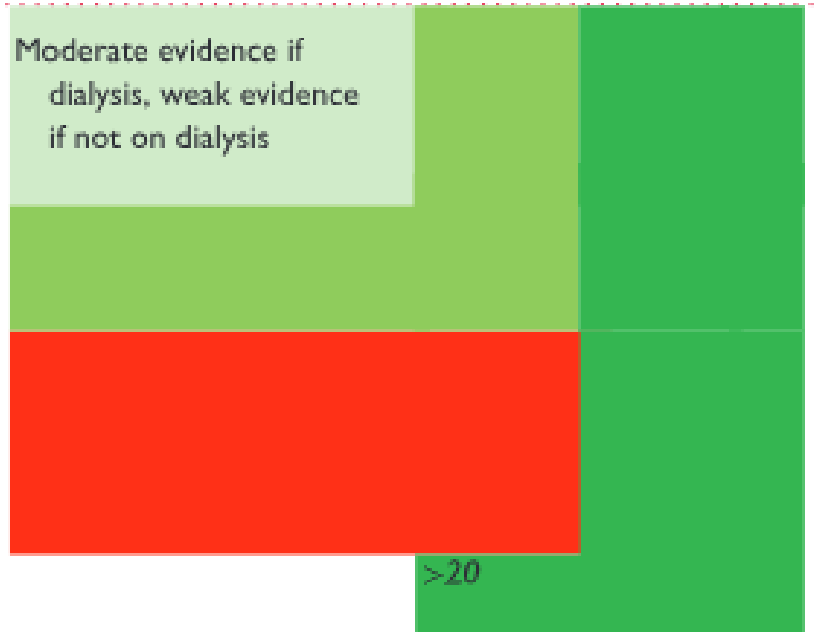
Key messages

1. Acute drop in GFR with RAASi, ARNI and SGLT2-i does not diminishes treatment effect
2. A reduction in slope deterioration in HFrEF with ARNI and SGLT2-i is associated with reduced hard renal endpoints

Mullens W, Eur J Heart Fail 2020; 22:584-603
Mullens W, Eur J Heart Fail 2022; 24:603-619.

GDMT in relation to CKD

Drug	Evidence across GFR strata according to baseline eGFR enrolment criteria	Acute drop GFR	Impact on GFR slope in HF trial	CKD treatment interaction	Treatment effect with CKD
ACE-I/ARB	Moderate evidence if dialysis, weak evidence if not on dialysis	Yes	No (beneficial effect of around 1–2 ml/min/1.73 m^2 per year in CKD trials)	No	Relative benefit: ~ Absolute benefit: ↑
Beta-blockers		No	No	Yes (potentially but some conflicting results)	Relative benefit: ~ Absolute benefit: ↑
MRA		Yes	No	No	Relative benefit: ~ Absolute benefit: ↑
ARNI		Yes	Yes (around 0.5 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
SGLT2-i	>20	Yes	Yes (around 1–2 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑



GLP1 (Semaglutide) in FLOW RCT (CKD + DM), 24% RR in progression CKD / CV death

Mullens W, Martens P. Eur J Heart Fail 2022;24:603-619.

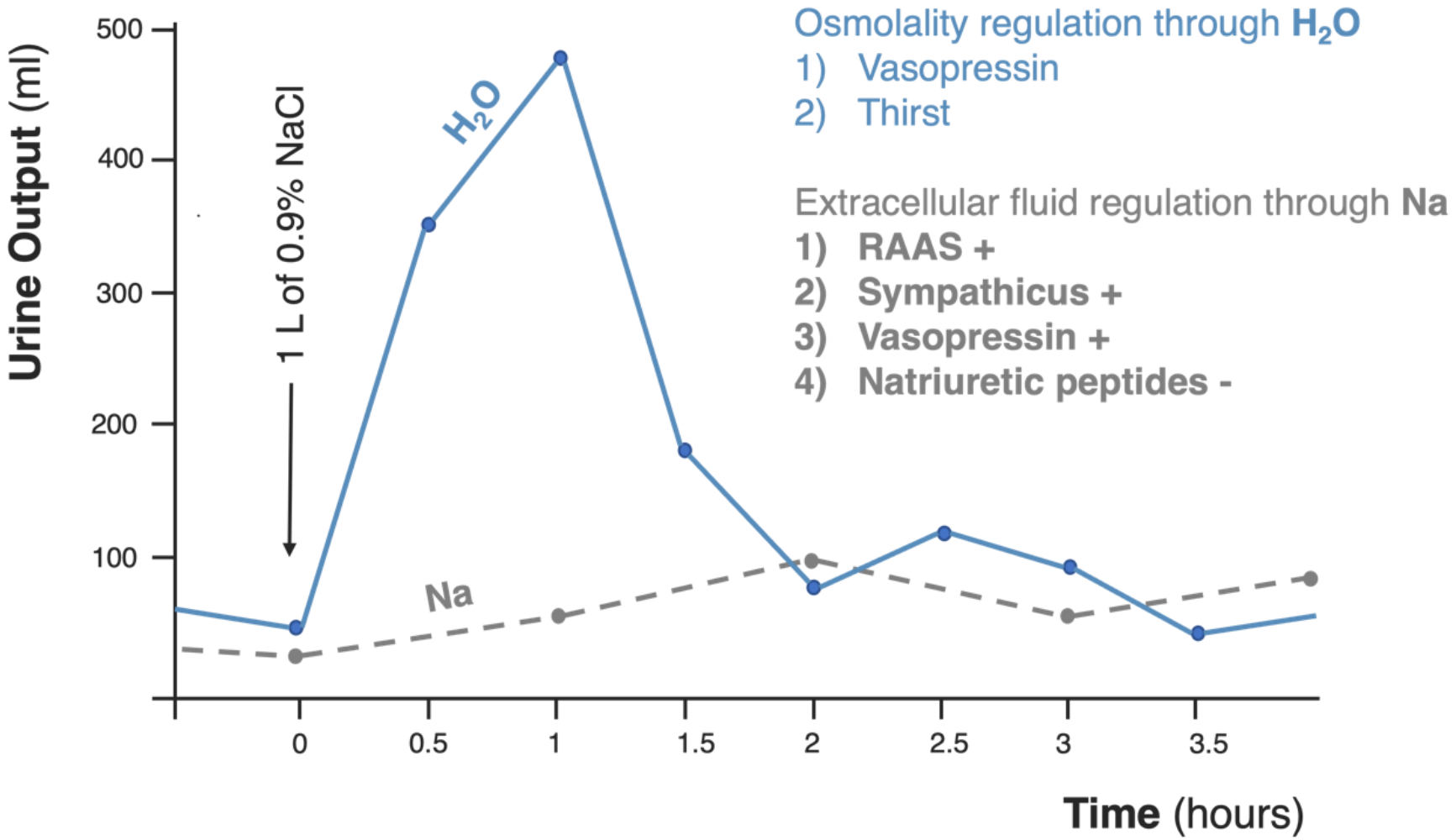
Underappreciated risk for hospitalization / death associated with residual congestion in HF

Recommendations	Class[a]	Level[b]
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.[427,472]	I	C

McDonagh T et al. Eur Heart J 2021

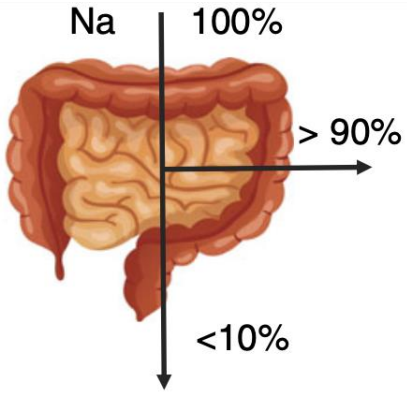
What will make you pee faster ?

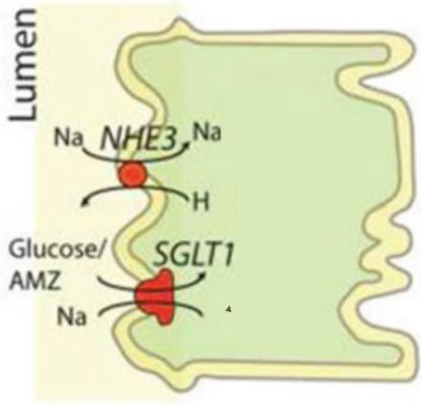
‘more difficult to loose sodium than water’



Mullens W, Damman K, Dhondt S et al. Eur J Heart Fail 2024.

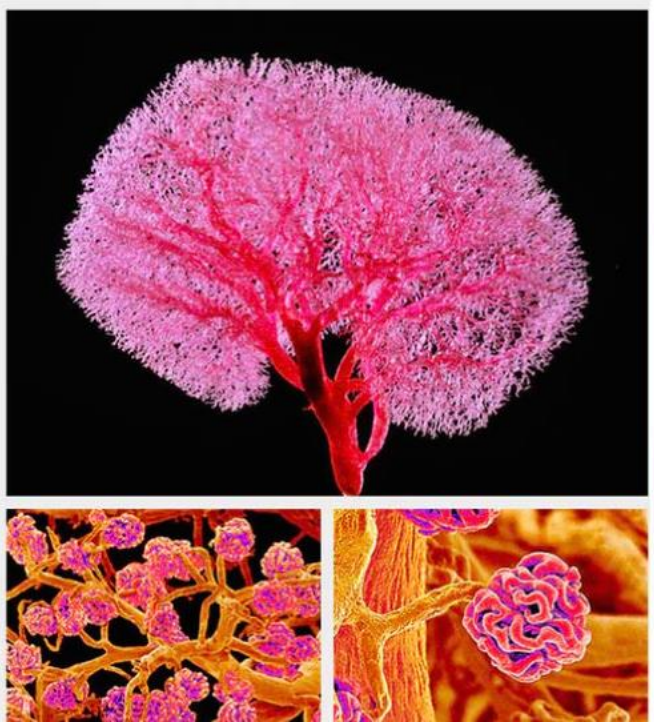
GI absorption of sodium is 100% in everybody (even without HF)

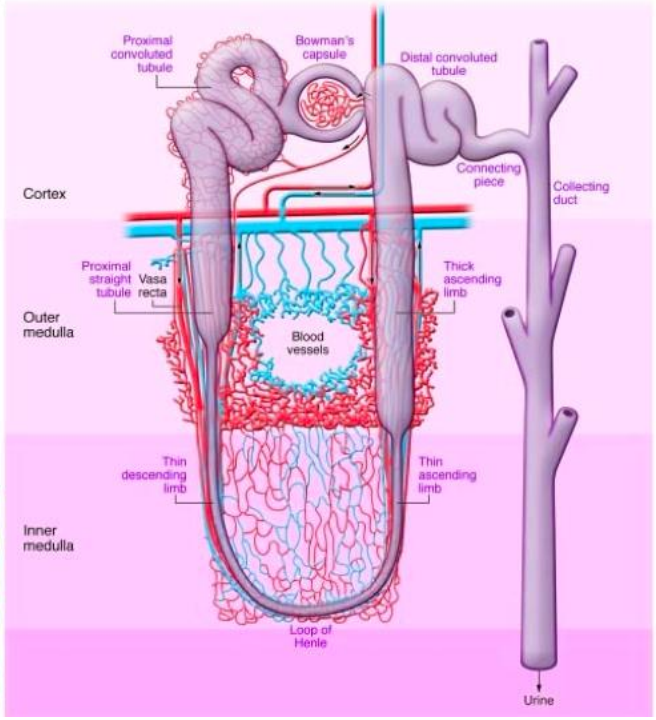


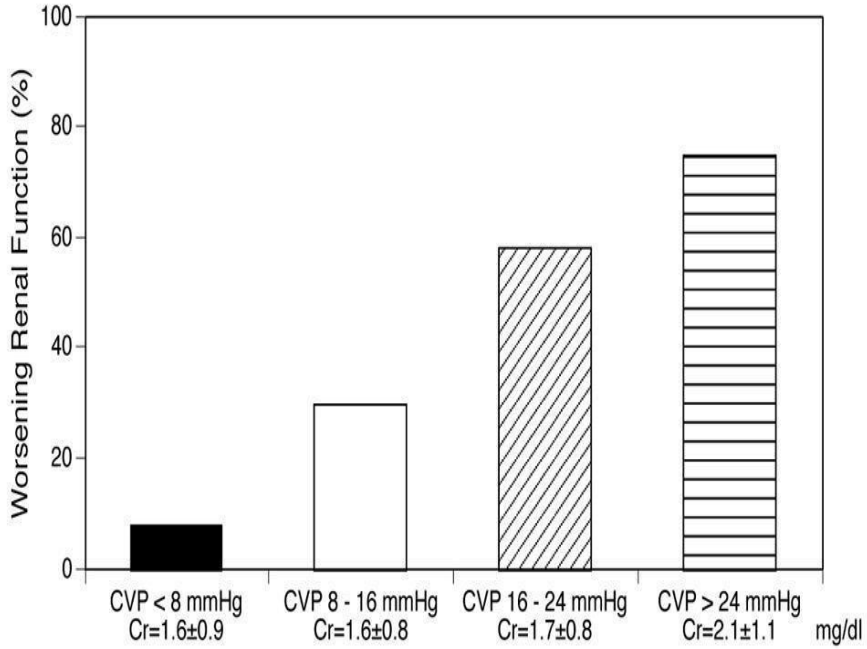


Mullens W, Damman K, Dhondt S et al. Eur J Heart Fail 2024.

Kidney: a remarkable vascular organ susceptible to congestion





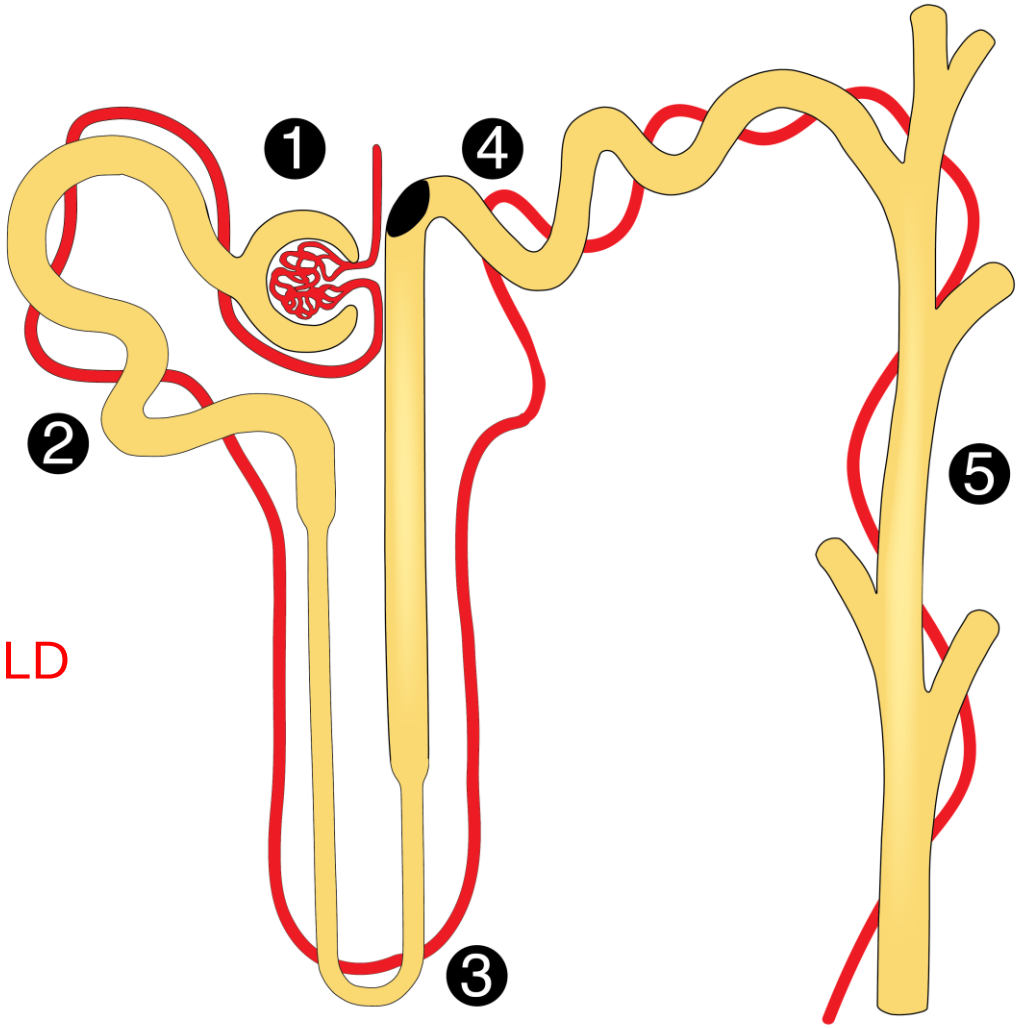


Renal Plasma flow = 600 ml /min
Renal blood flow = 1000 ml/min

Bonventre LI. J Clin Invest 2011
Mullens W et al. J Am Coll Card 2009;53:589-96.

Renal sodium reabsorption occurs mostly in proximal tubules (and is increased in HF)

1. Glomerulus
2. Proximal tubules (60-70%) ⇑ in HF with congestion
3. Loop of Henle (25%)
4. Macula densa
5. Distal / collecting tubules (5%) ⇑ in chronic high-dose LD

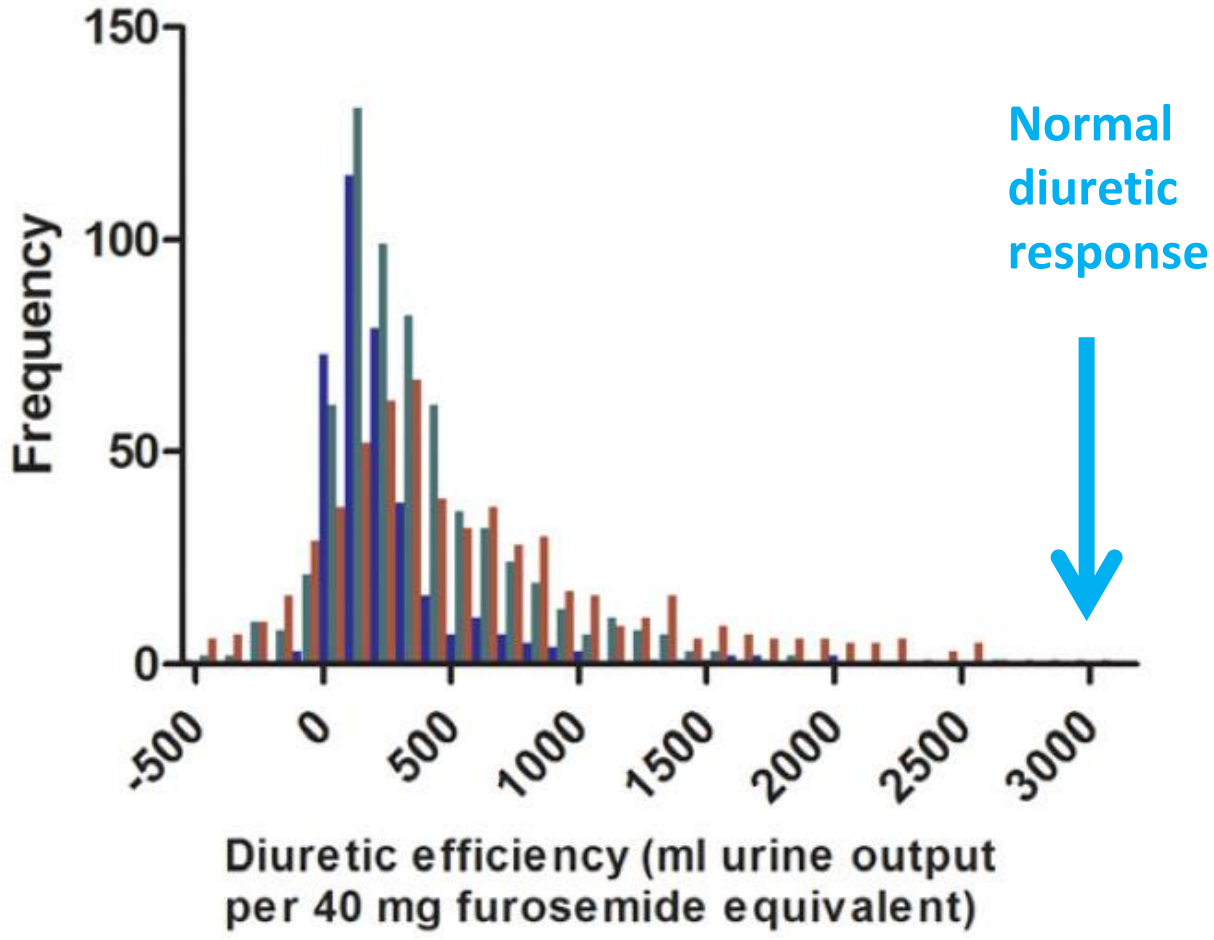


Mullens W et al. Eur Heart J, 2017;38:1872-1882

Diuretics		
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.[145]	I	C
Combination of a loop diuretic with thiazide-type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses.[145]	IIa	B

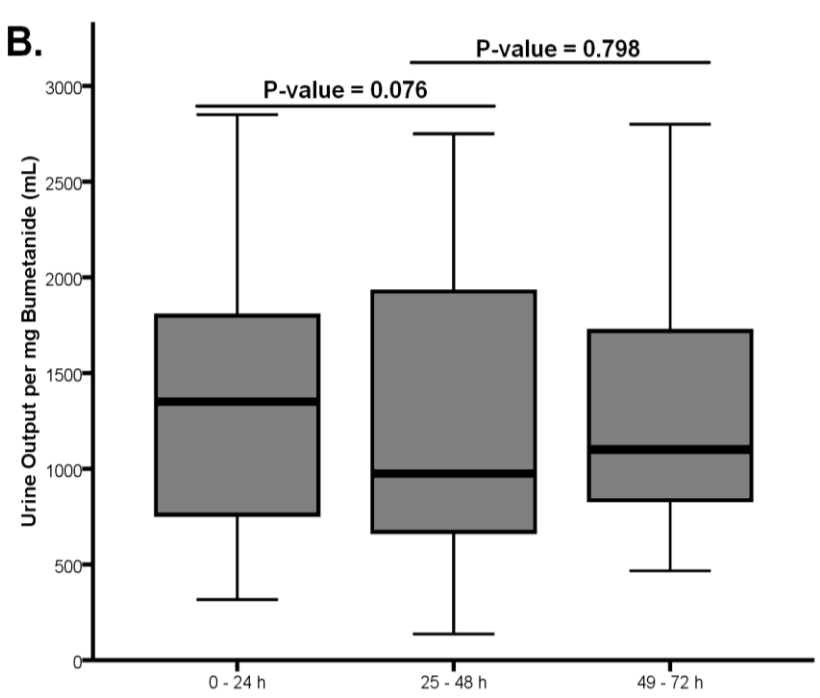
McDonagh T et al. Eur Heart J 2021

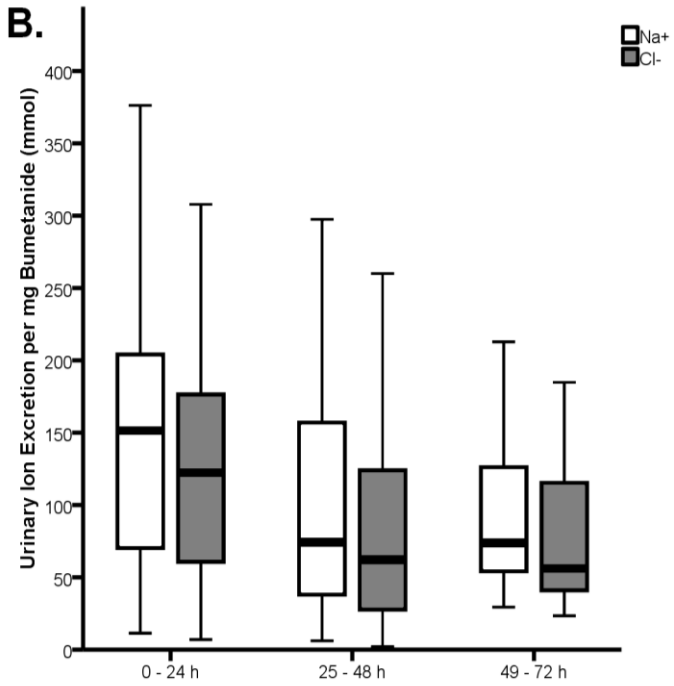
’Diuretic resistance’ is omnipresent in HF patients



Testani J et al. Circ Heart Fail 2014.

Urinary Composition during Decongestion





Progressive decrease in Urinary Na and Cl but NOT in urine output

(even after correction for diuretic dose)

Verbrugge F, Mullens W, et al. Circ Heart Fail 2014.

ESC European Society of Cardiology

European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1369

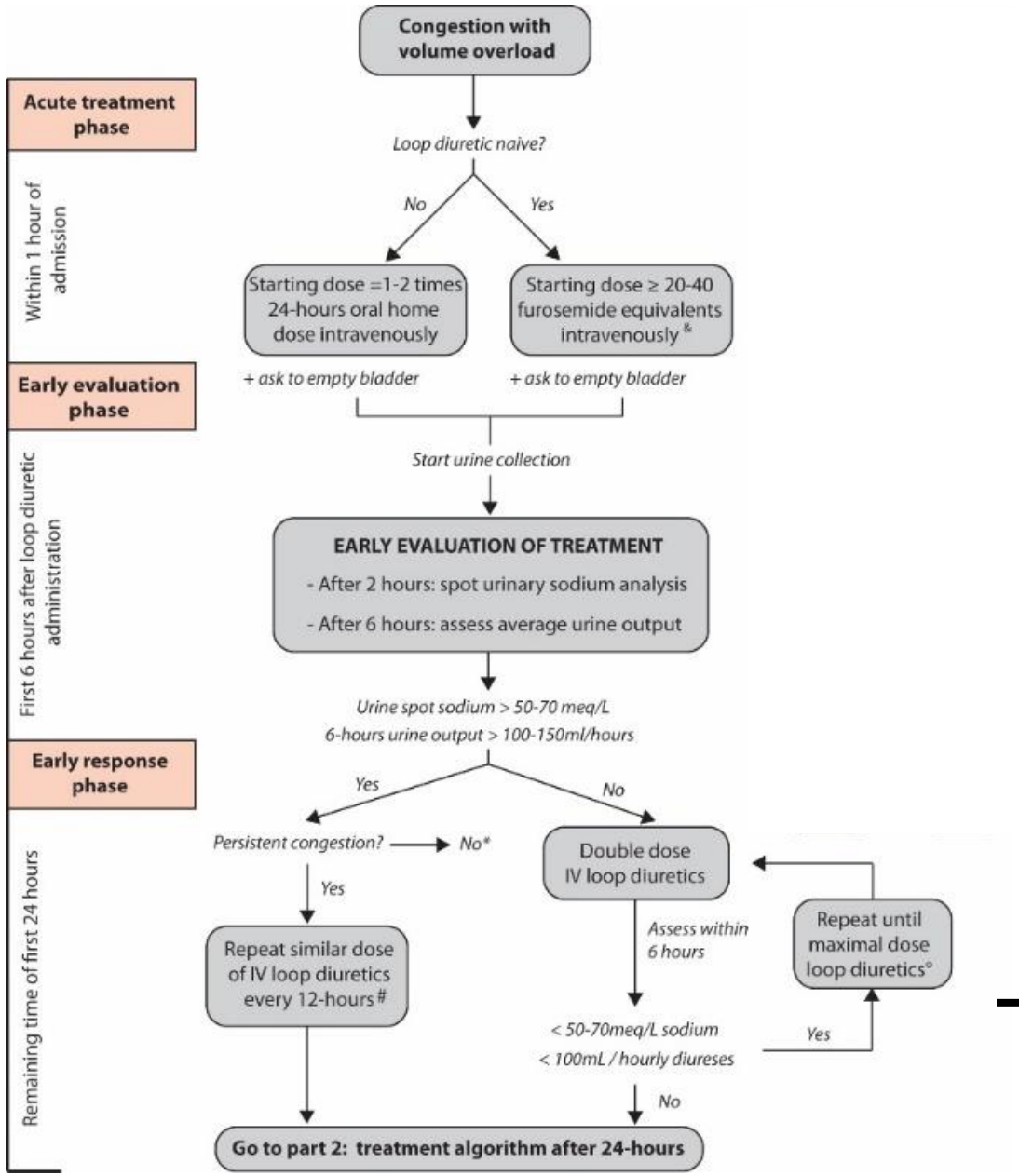
POSITION PAPER

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]

Citations: > 600
Downloads: > 500.000

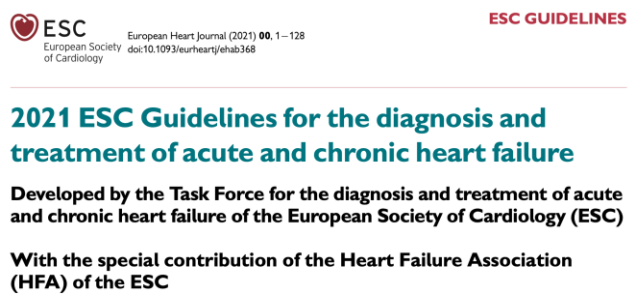
Mullens W, Eur J Heart Fail 2019; 21:137-155.



Five most important rules

1) Door to diuretic time
2) Early evaluation (within HOURS) of the diuretic effect
3) Appropriate dosing according to natriuresis/diuresis
4) Only stop when the patient is ‘dry’
5) Continue guideline-directed medical therapy

Incorporated



(590 citations)

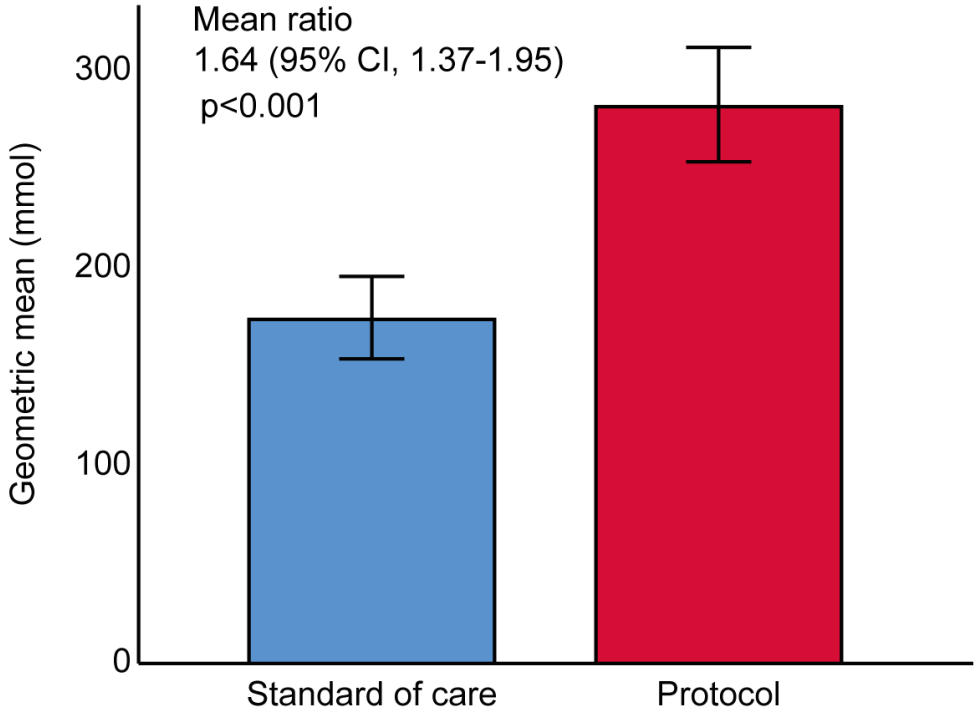
Mullens W, Eur J Heart Fail 2019; 21:137-155.

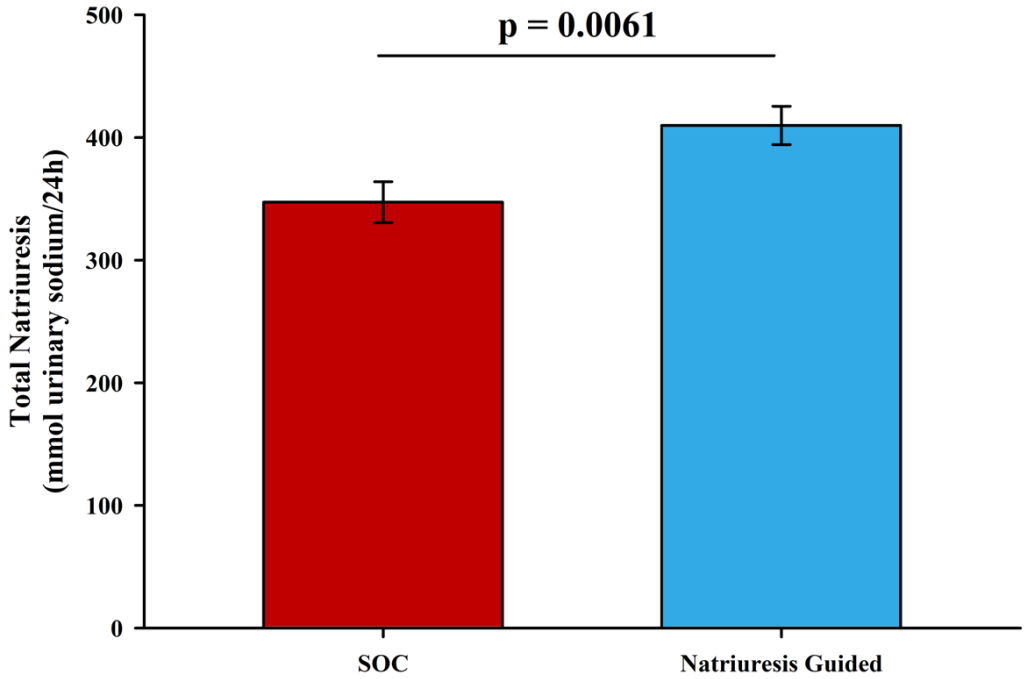
Desalination RCTs

ENACT-HF Study

PUSH-AHF trial

Primary endpoint: natriuresis after 24 hours

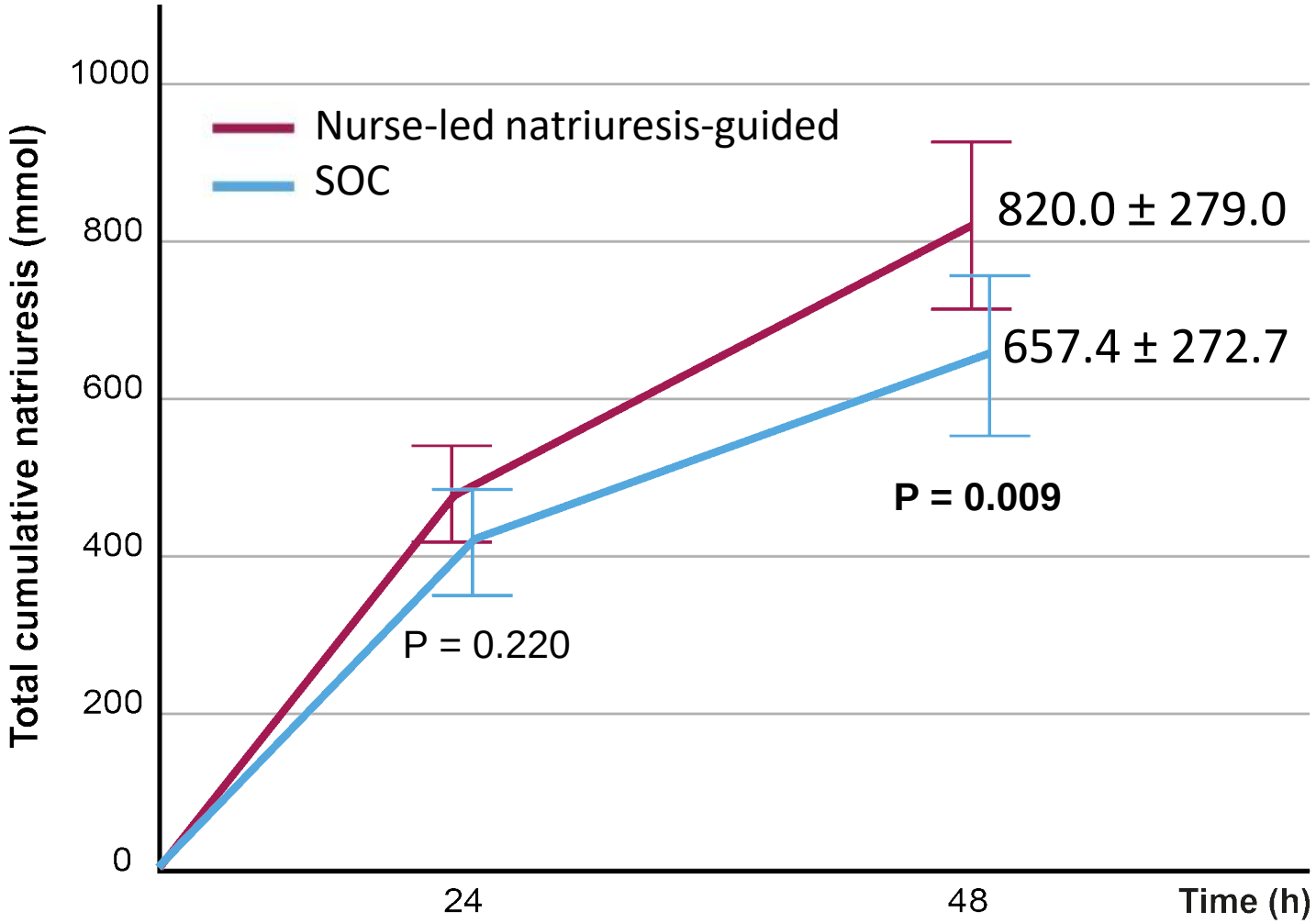




Ongoing:
DECONGEST (NCT05411991)
ESCALATE (NCT04481919)

Dauw J, Mullens W et al. Circ Heart Fail, in press 2024
Ter Maaten J et al. Nat Med 2023;29:2625-2632

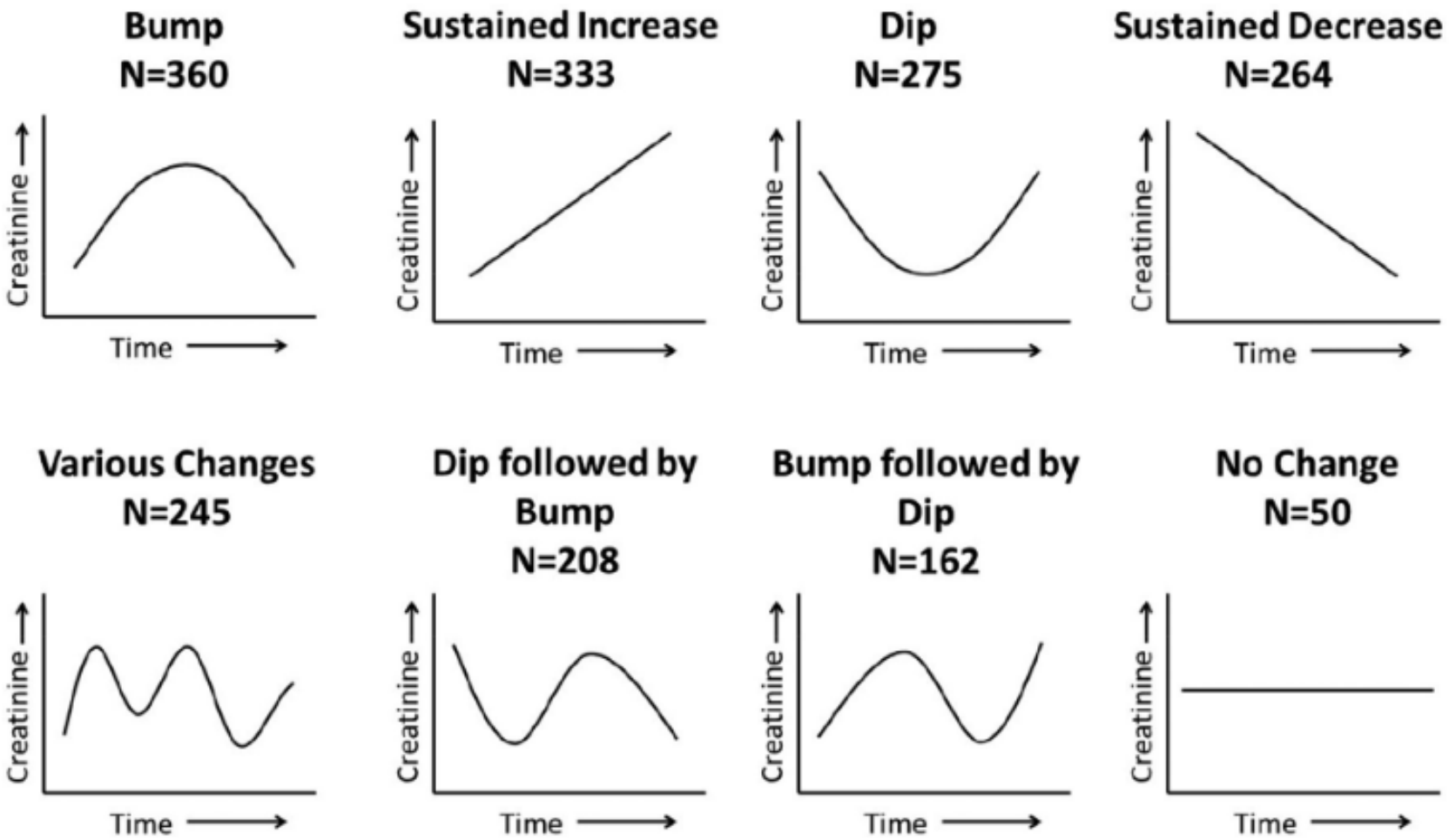
Nurse-Led Diuretic Titration via POC Urinary Sodium Sensor in ADHF
EASY-HF trial



P = 0.027
Absolute difference
163 (19 to 306)

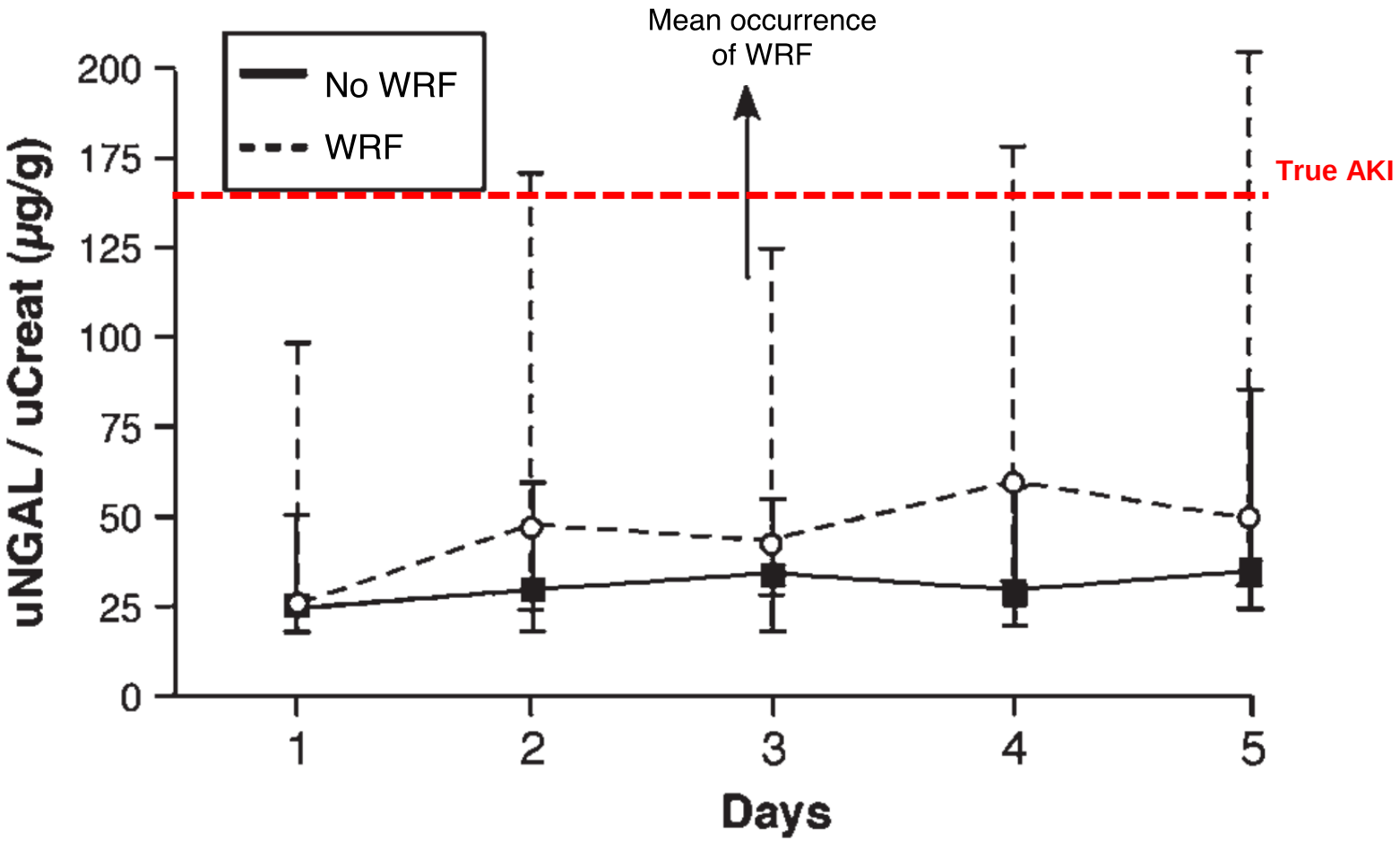
Meekers E, Mullens W. Eur J Heart Fail. 2024 In press.

Worsening renal function during Acute HF



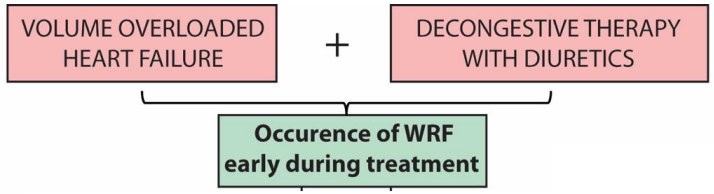
Beldhuis E, Damman K et al. J Card Fail 2019;25:866-874.

WRF during AHF does NOT lead to permanent renal damage



Dupont M. Eur J Heart Fail 2012;14:597-604.

Worsening renal function during Acute HF



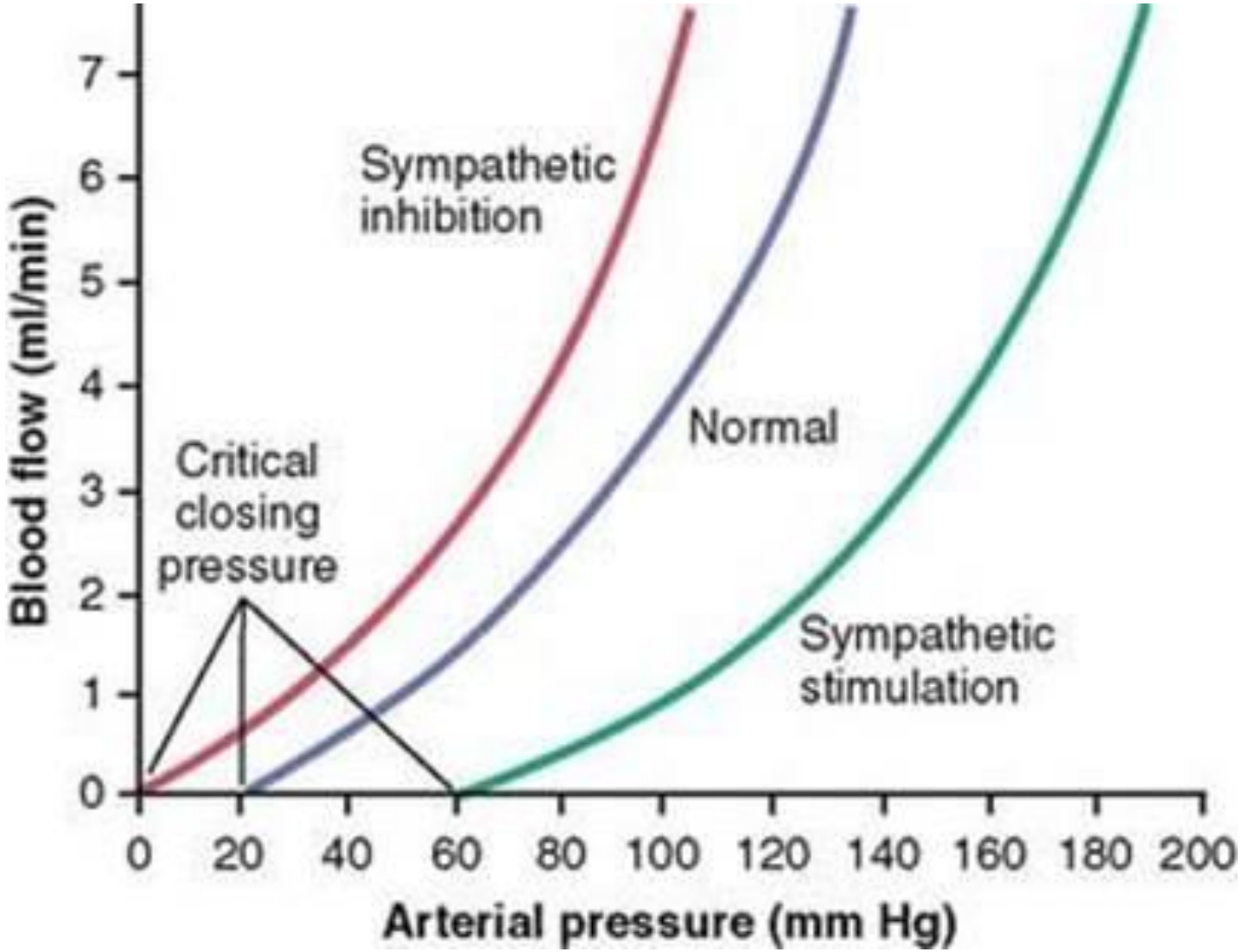
CAUTION IN CASE OF

- *Serum creatinine increases more than 100%*
- *Serum creatinine absolute increase above 3.5 mg/dl*

99% 1%

Mullens W, Eur J Heart Fail 2020; 22:584-603.

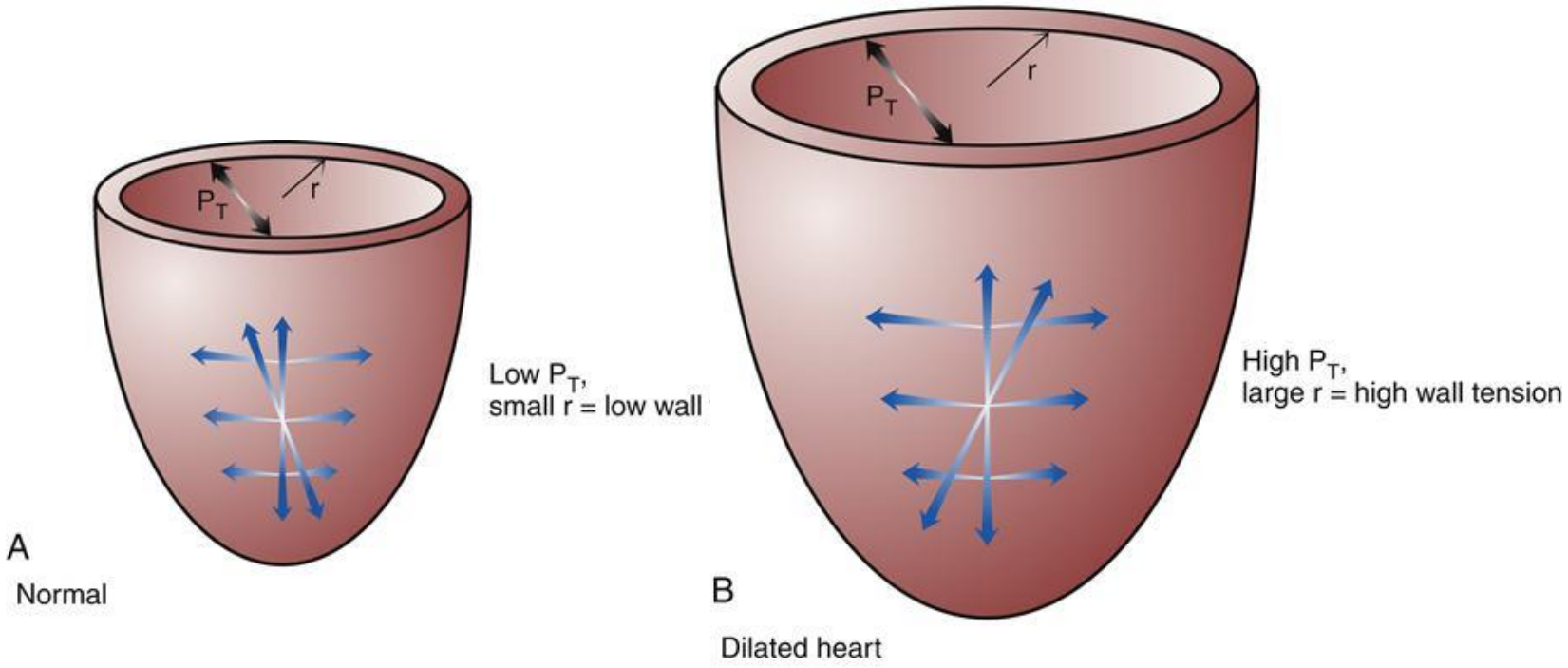
Pathophysiology: blood pressure ≠ flow



Guyton and Hall Textbook of Medical Physiology, Chapter 14

LV afterload ≠ SVR

Vasodilators only work in failing HFrEF



Law of Laplace

Wall tension = (pressure x radius) / (2x wall thickness)

Pathophysiology: failing HFrEF
Nitroprusside for Advanced Decompensated HFrEF

Start **Nitroprusside** protocol through a continuous infusion at a dose of 10-400 mcg/min (without bolus)

Titrate to MAP 60-70 mmHg

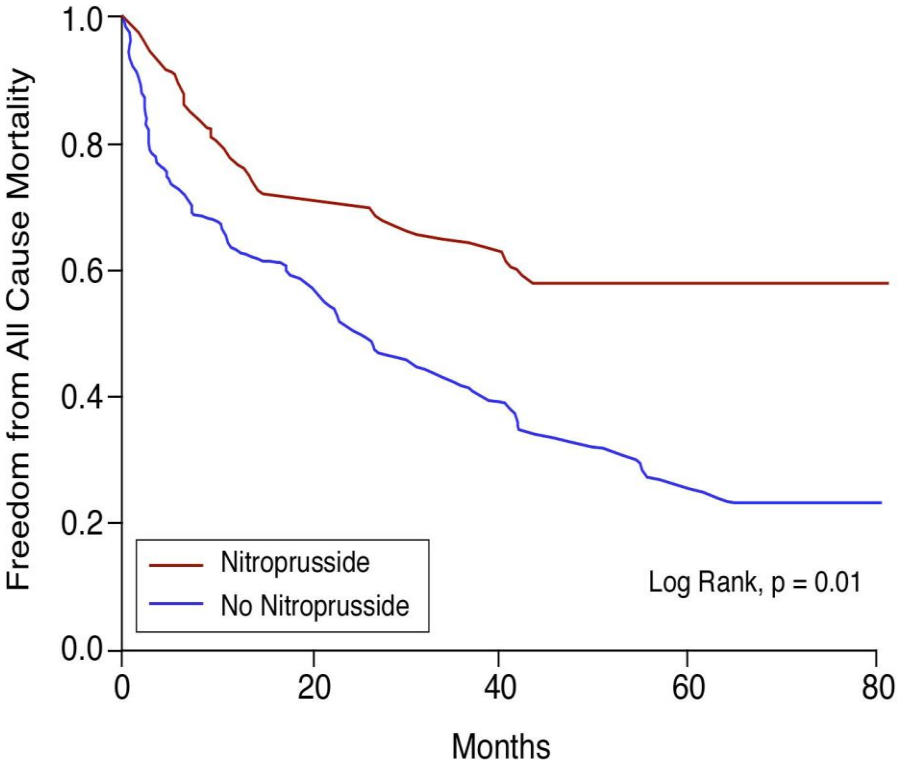
Well trained nursing staff – dose adjusted / 15 minutes

BP measured non-invasively

Optimal hemodynamic response

- decrease in PCWP to ≤ 18 mmHg,
- decrease in right atrial pressure to ≤ 8 mmHg
- improvement in cardiac index to ≥2.2 l/min/m2

Continue ACE-I, BB and spironolactone as tolerated



Mullens W et al. J Am Coll Card 2008;52:200-7.

High dose spiro for advanced decompensated heart failure
ATHENA trial

	Usual Care	Spironolactone	P
Log NTproBNP			
Baseline	8.23 (7.58, 8.94)	8.43 (7.90, 9.17)	
96 h (or discharge)	7.64 (6.93, 8.45)	7.89 (7.19, 8.68)	
Change	-0.49 (-0.98, -0.14)	-0.55 (-0.92, -0.18)	0.57
N-terminal pro B-type natriuretic peptide, pg/ml			
Baseline	3753 (1968, 7633)	4601 (2697, 9596)	
96 h (or discharge)	2080 (1025, 4675)	2672 (1326, 5896)	
Change	-1072 (-3182, -231)	-1796 (-3883, -571)	0.76

Butler J et al. JAMA Cardiol. 2017;2:950-958

CLOROTIC

Endpoint	Placebo ($n = 116$)	Hydrochlorothiazide ($n = 114$)	*P*-value
Coprimary endpoints			
Change in weight at 72 h (kg)	−1.5 (−3.2 to 0.0)	−2.3 (−3.9 to −1.2)	0.002
Adjusted estimated difference (notionally 95% confidence interval)	−1.14 [−1.84 to −0.42]		
AUC for dyspnoea at 72 h (VAS)	720 (240–1455)	960 (360–1620)	0.497

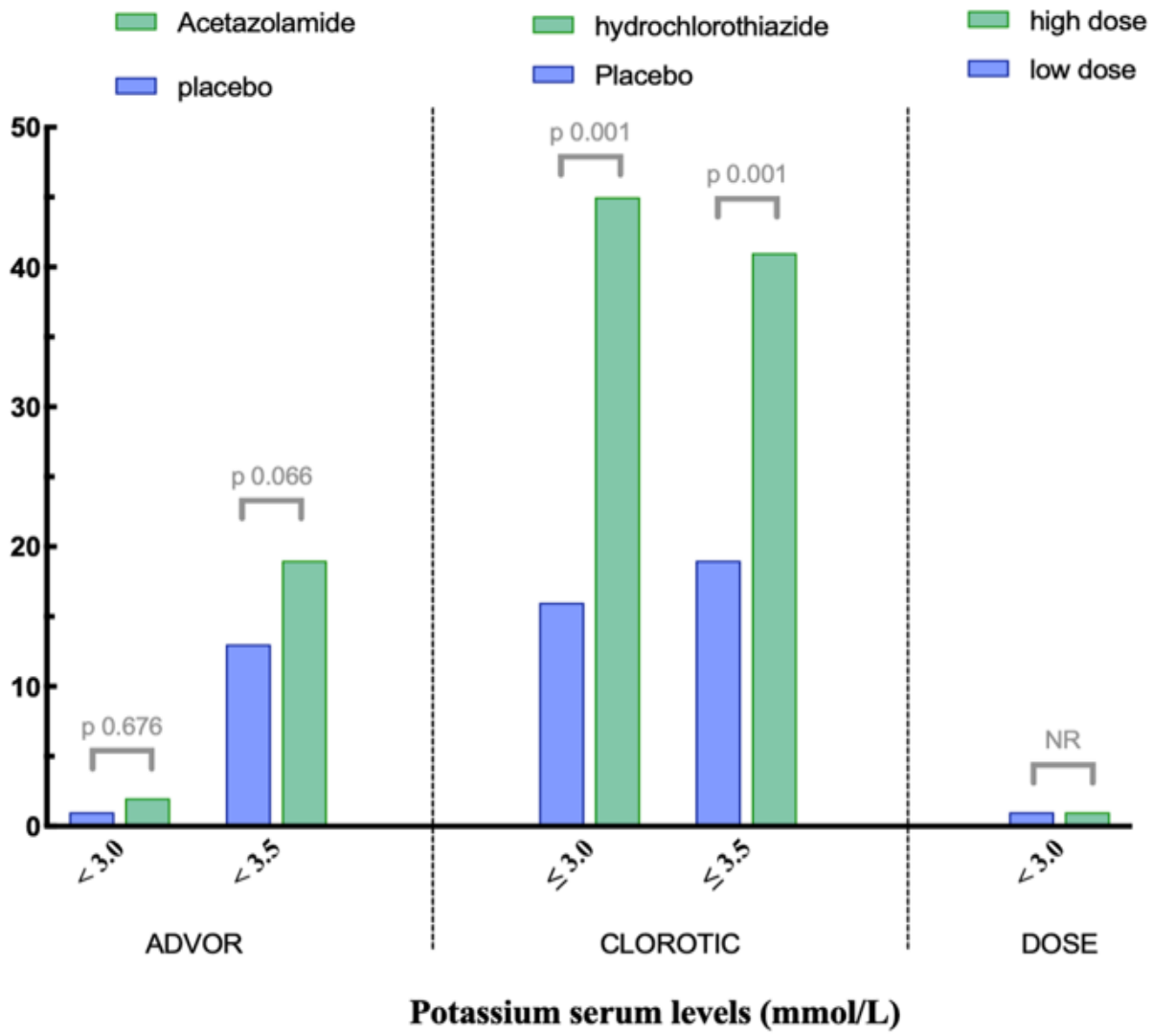
Trullas JC et al. Eur Heart J 2023;44:411-421

Subanalysis CLOROTIC trial: less effect if eGFR was lower !

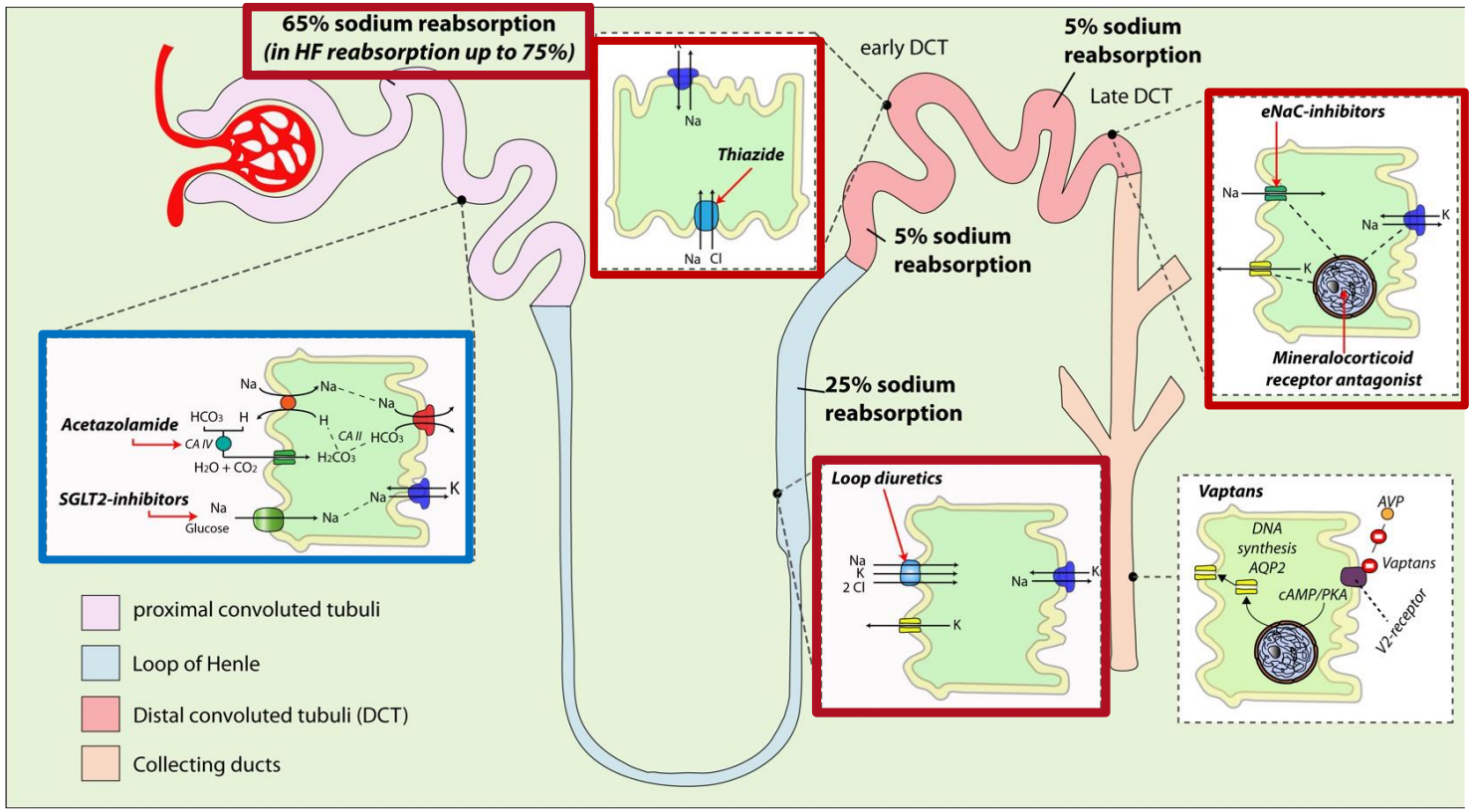
	Results for placebo	Results for HCTZ	Difference	P for interaction
Primary endpoint. Change in weight (kg) at 72 hours				
Overall	-1.6 [-2.1 to 1.1]	-2.4 [-2.7 to -1.8]	-0.8 [-1.4 to -0.2]	**0.001**
< 45 ml/min/1.73m^2	-1.8 [-2.3 to -0.9]	-1.9 [-2.4 to -1.7]	-0.1 [-1.3 to 0.4]	0.246
45 to 59 ml/min/1.73m^2	-1.2 [-2.1 to -0.7]	-2.5 [-3.3 to -0.9]	-1.3 [-2.3 to 0.2]	
≥ 60 ml/min/1.73m^2	-1.6 [-2.9 to -1.2]	-3.7 [-4.8 to -2.7]	-2.1 [-3.0 to -0.5]	

Trullas JC et al. Eur J Heart Fail 2023;25:1784-1793

Hypokalemia loop diuretics +/- acetazolamide vs thiazides



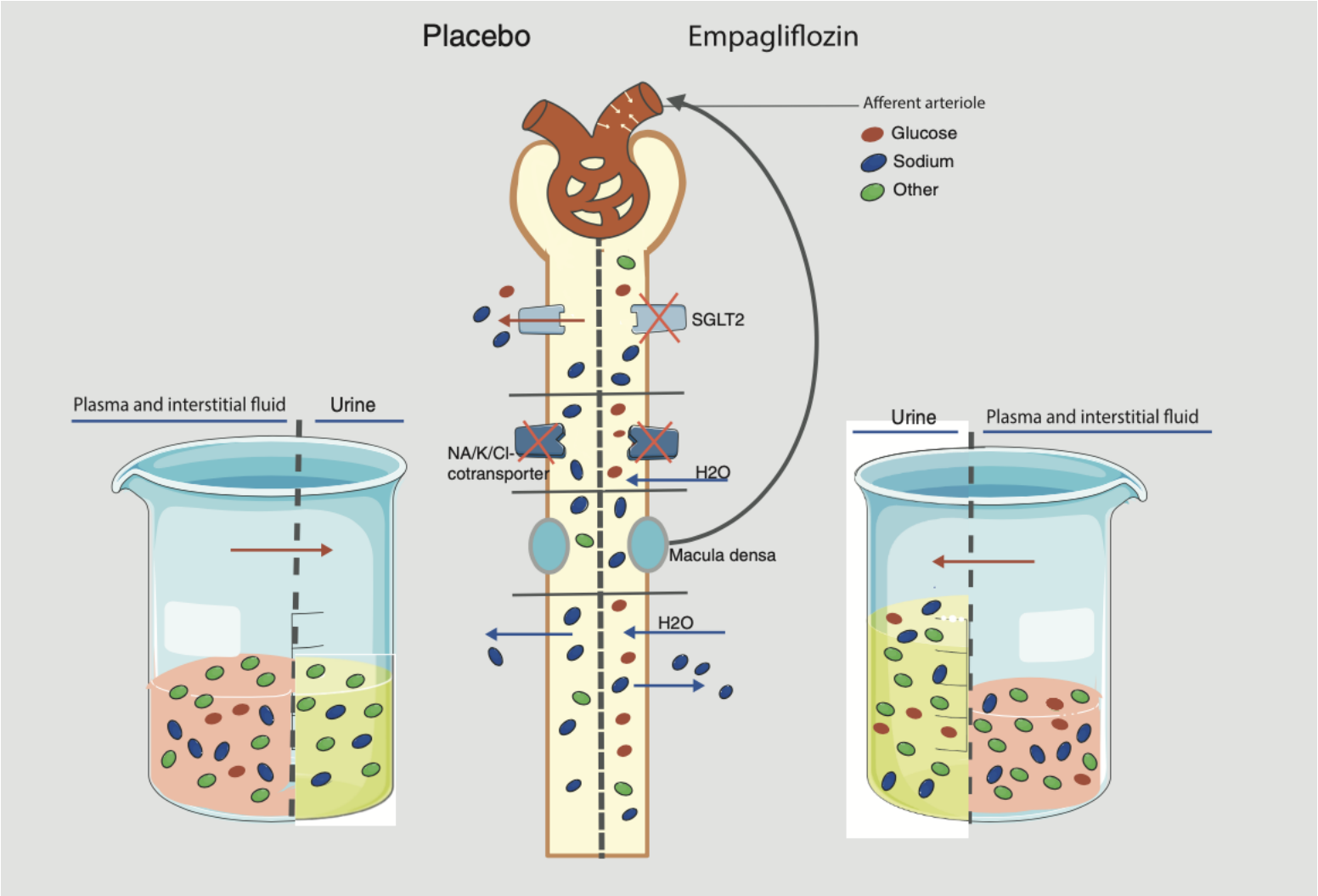
D'Hondt S, Mullens W et al. Eur J Heart Fail 2023; 25:1310-1319



HF induces a state of increased proximal renal sodium reabsorption, but loop diuretics, thiazides, MRA work distal at loop of Henle

Mullens W et al. J Am Coll Card 2009;53:589-96.
Mullens W et al. Eur J Heart Fail 2019; 21:137-155

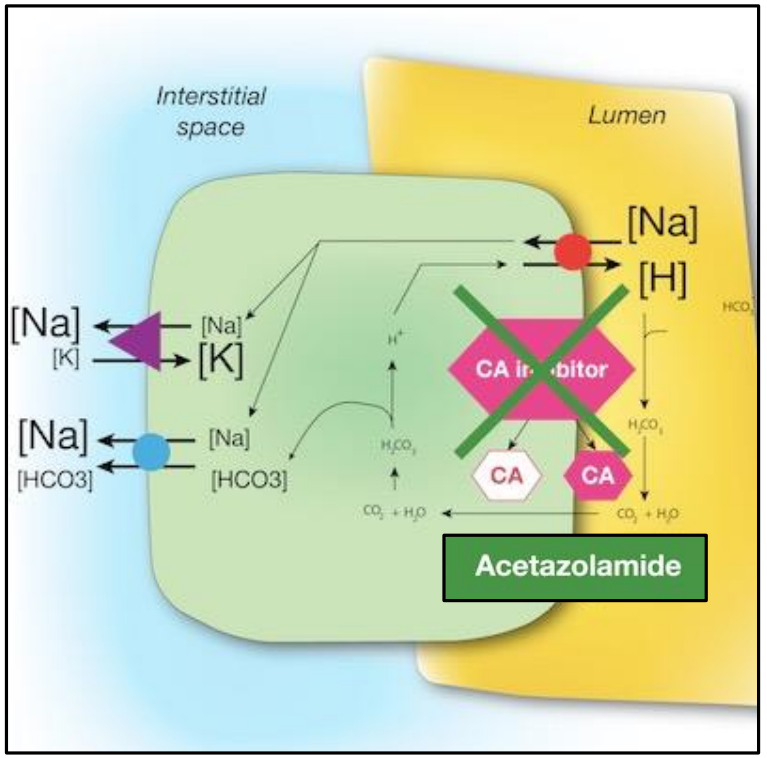
Renal Preservation: SGLT2i (EMPA-RESPONSE-AHF)

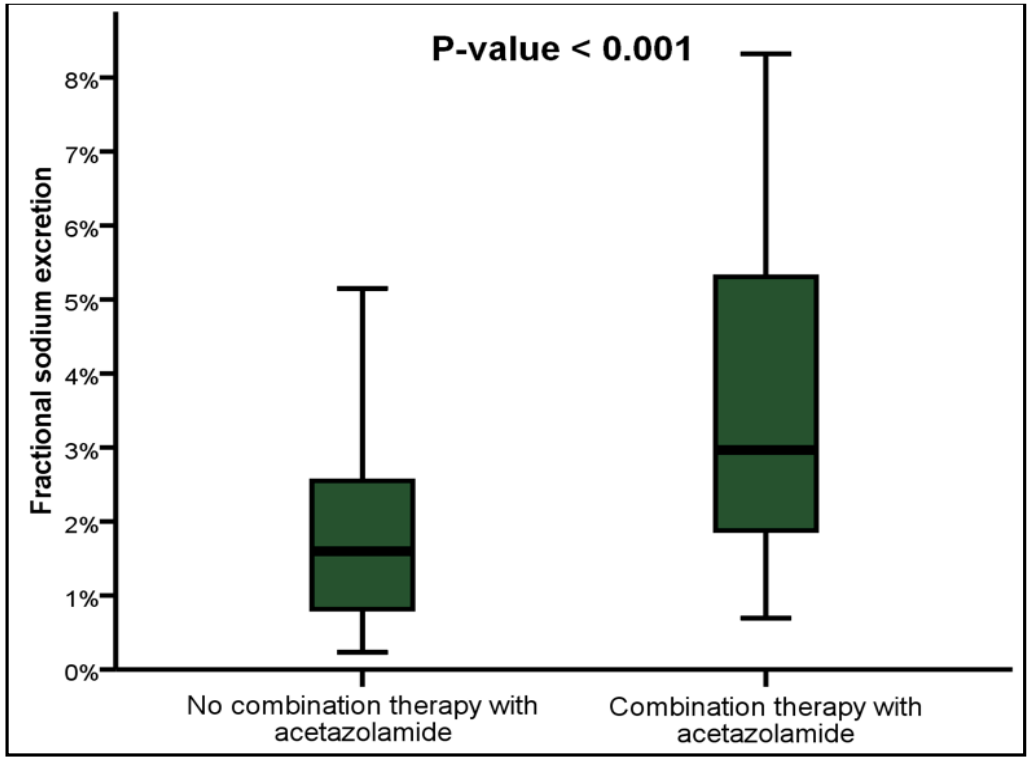


↑ FeGluc but = FeNa

Boorsma E et al. Eur J Heart Fail, 2021;23:68-78

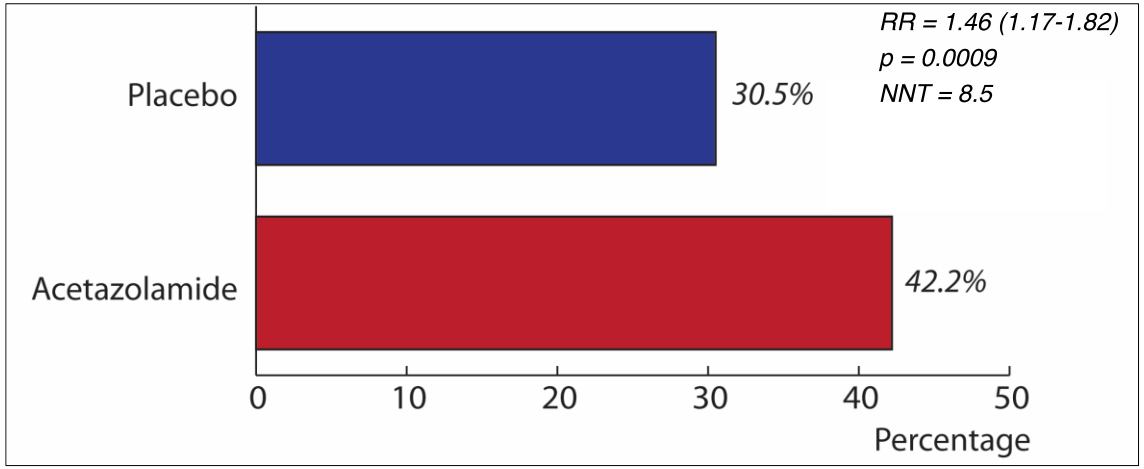
Acetazolamide might improve loop diuretic efficiency



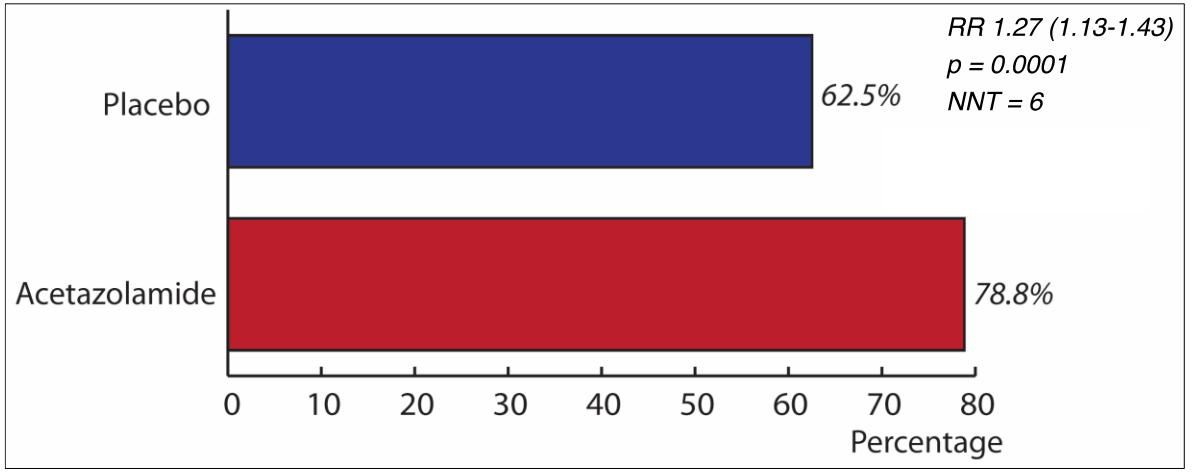


Mullens W et al. Eur Heart J 2017
Verbrugge F et al. Acta Cardiol 2015 + Eur J Heart Fail 2019

Results: successful decongestion



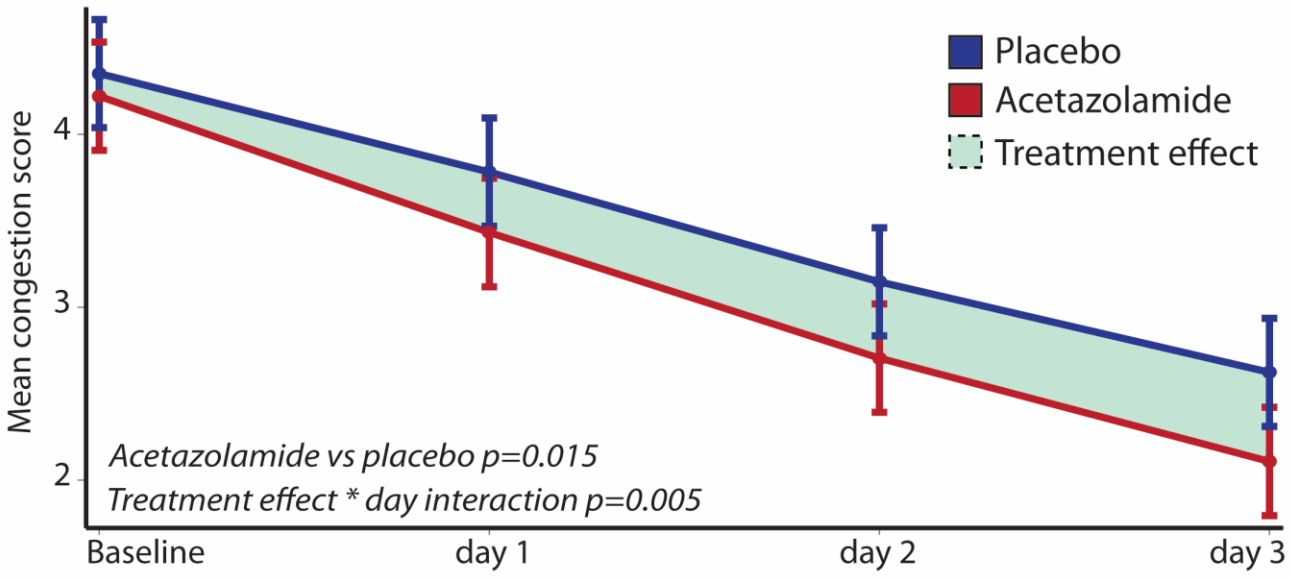
After 3 days (prim endpoint)



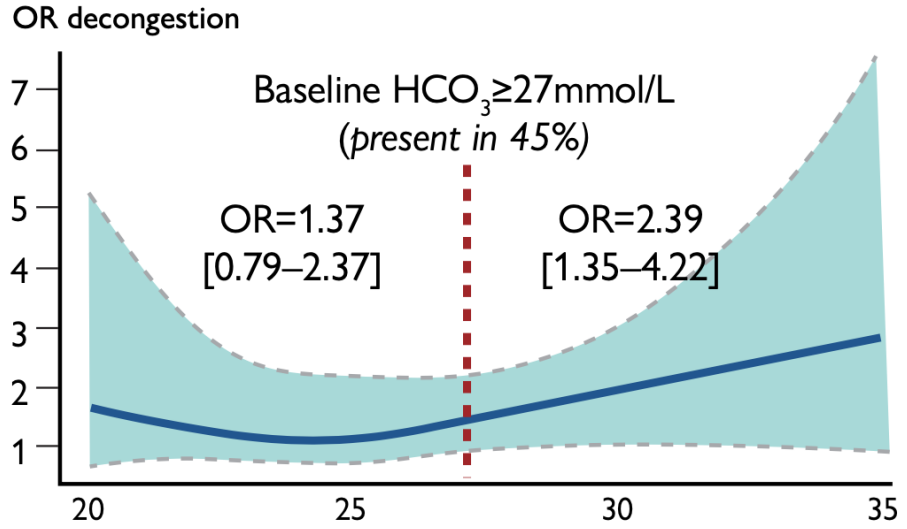
Discharge

Mullens W et al. N Engl J Med 2022;387:1185-1195

Acetazolamide prevents loop diuretic resistance



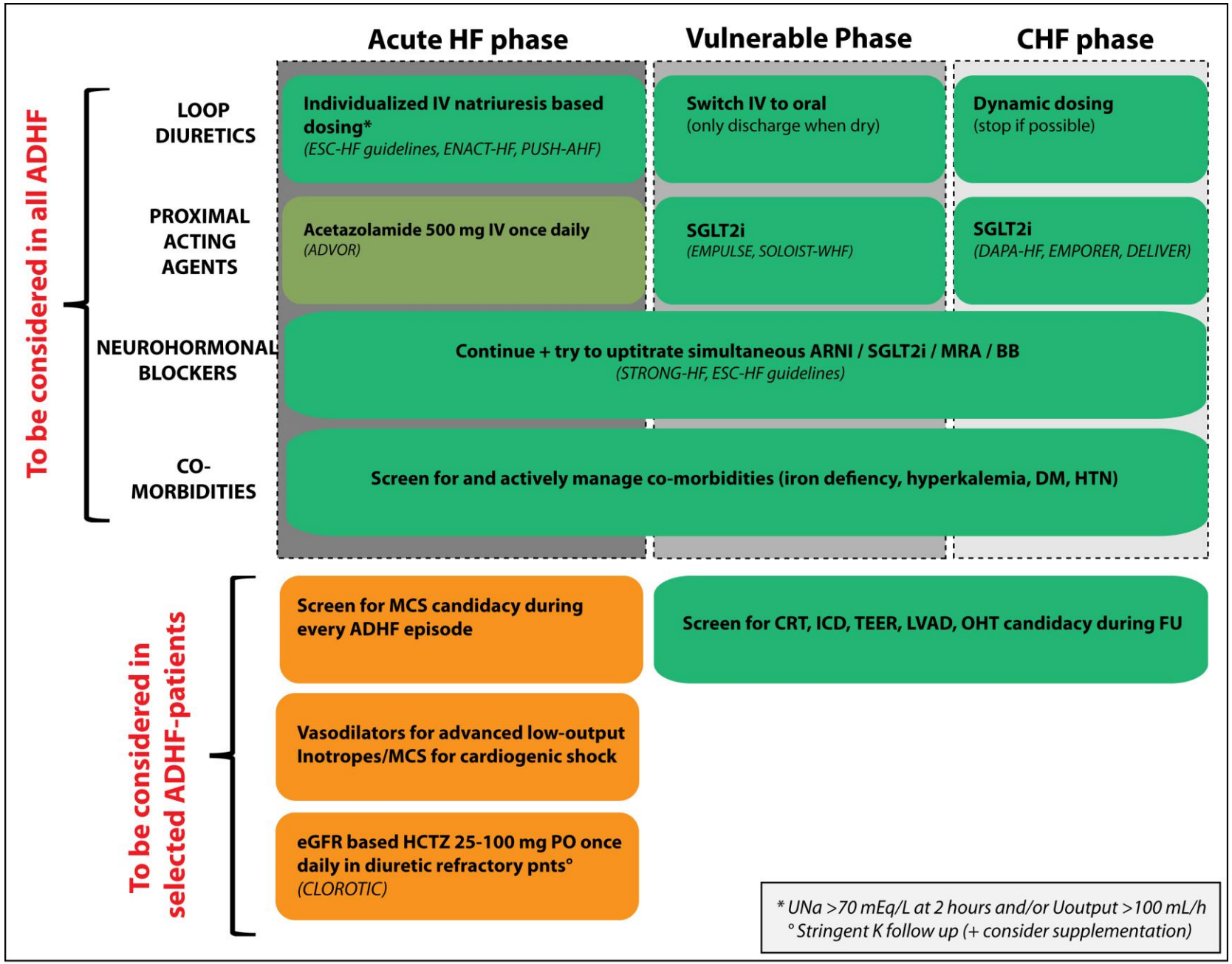
Higher decongestive response, diuresis, natriuresis and shorter LOS if baseline HCO_3 ≥27mmol/L



Mullens W et al. N Engl J Med 2022;387:1185-1195
Martens P, Mullens W et al Eur Heart J 2023; 44:1995-2005.

Misinterpretation of WRF leads to

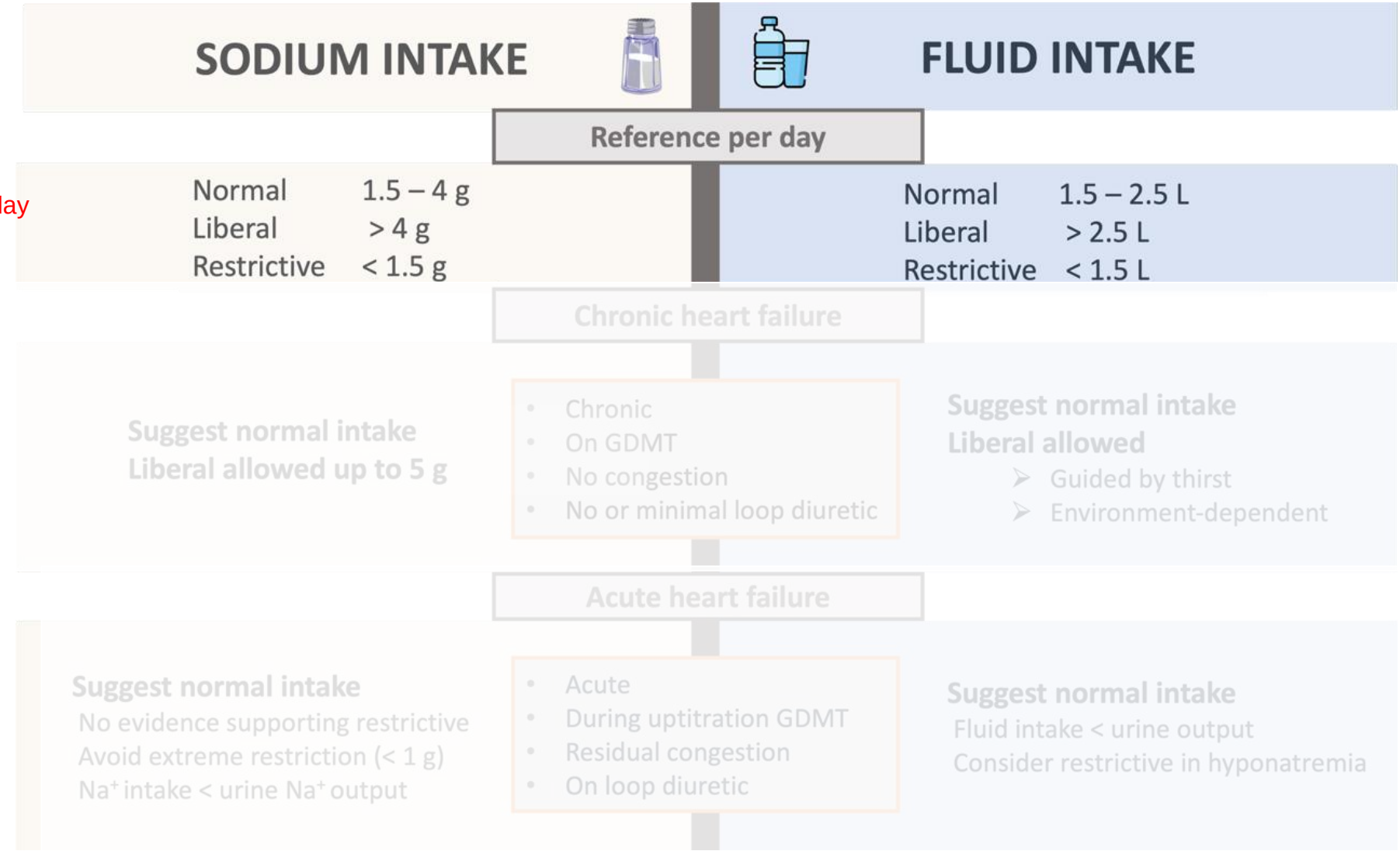
- Ineffective decongestion in AHF
- Insufficient dosing of GDMT in CHF



Adapted from Mullens W et al. Eur Heart J 2023;44:2159-2169

Water and sodium recommendations ?

HFA: avoid > 5 g NaCl / day (**2 g Na**)



Mullens W, Damman K, Dhondt S et al. Eur J Heart Fail 2024.