Is there a role for sequential dual nephron blockade?

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Clinical and technical evaluation of congestion

	Variable	EUVOLEMIA → CONGESTED				
Clinical congestion	Orthopnea	None		Mild	Moderate	Severe/worst
	JVP (cm)	<8 and no HJR	<8	8-10 or HJR+	11-15	>16
	Hepatomegaly		Absent	Liver edge	Moderate pulsatile enlargement	Massive enlargement and tender
	Edema		None	+1	+2	+3/+4
	6MWT	>400m	300-400m	200-300m	100-200m	<100m

	Variable	EUVOLEMIA → CONGESTED				
Technical evaluation	NP (one of both): -BNP -NT-proBNP		<100 <400°	100-299 400-1500	300-500 1500-3000	>500 >3000
	Chest X-ray	clear	clear	cardiomegaly	- pulmonary venous congestion* - small pleural effusions*	- Interstitial or alveolar edema
	Vena Cava imaging [45]	**none of two:** - Max diameter >2.2 cm - collapsibility <50%		**One of two:** - Max diameter >2.2 cm - collapsibility <50%		**Both:** - Max diameter >2.2 cm - collapsibility <50%
	Lung Ultrasound [44]	<15 B-lines when scanning 28-sites		15-30 B-lines when scanning 28-sites		>30 B-lines when scanning 28-sites

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

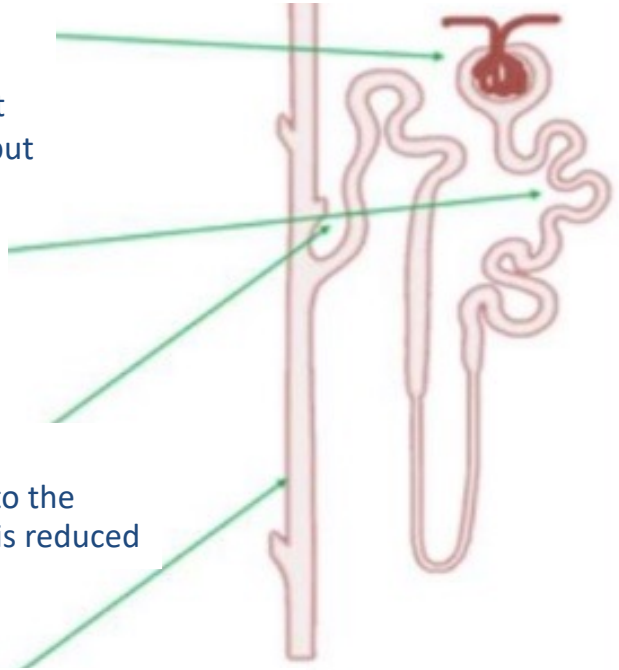
Pathophysiology of congestion in HF

- Reduced cardiac output
- Increased neurohormonal activation – SNS & RAAS - AVP
- Increased venous hydrostatic pressure
- Hypoalbuminemia

Glomerulus
Sympathetic overdrive with vasoconstriction and efferent congestion reduces throughput and glomerular filtration

Proximal Tubule
Ang II levels increases Na reabsorption with lack of natriuretic effect

Distal Tubule
Delivery of Na to the distal nephron is reduced



Collecting Duct
Aldosterone increases Na reabsorption

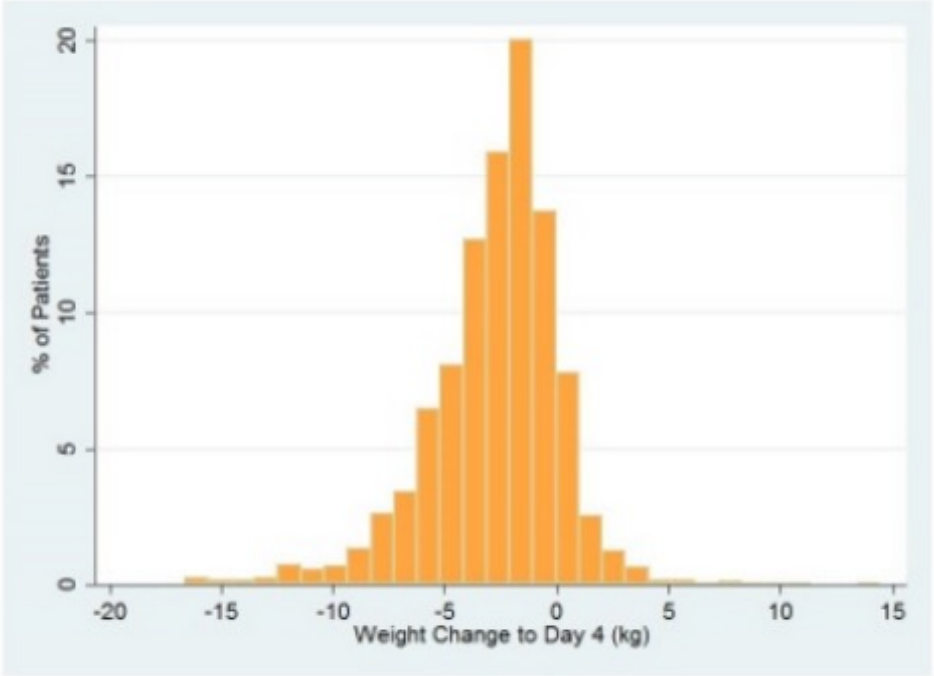
Diuretics for symptoms and signs of congestion

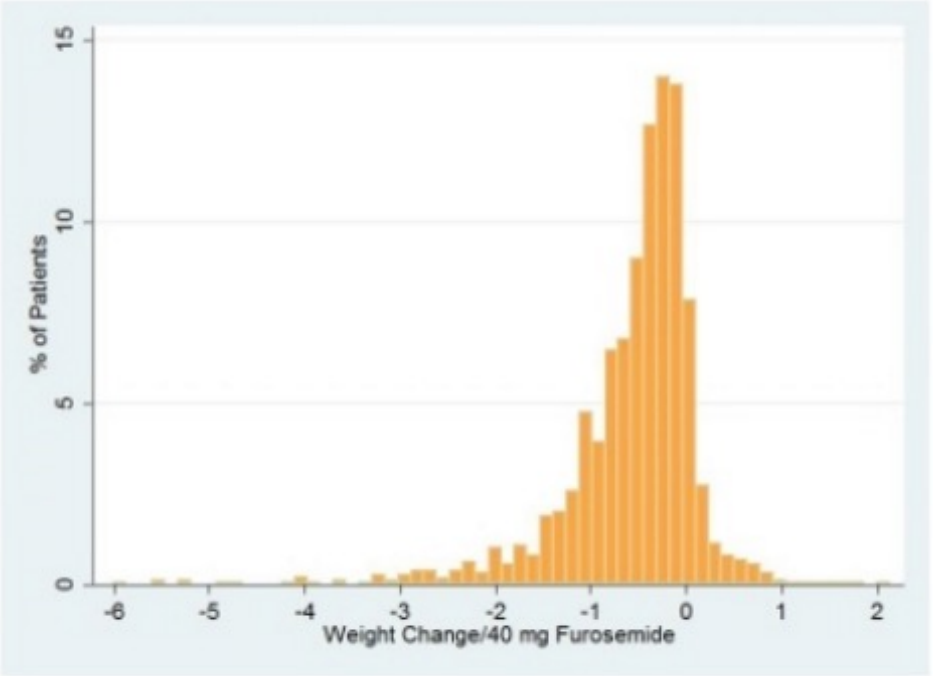
Recommendations	Class	Level
Diuretics		
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion	I	B
Diuretics should be considered to reduce the risk of hospitalization in patients with signs and/or symptoms of congestion	IIa	B

Ponikovsky P, et al. Eur J Heart Fail 2019;21:137-155.

Diuretic response in HF

Weight change in the PROTECT trial

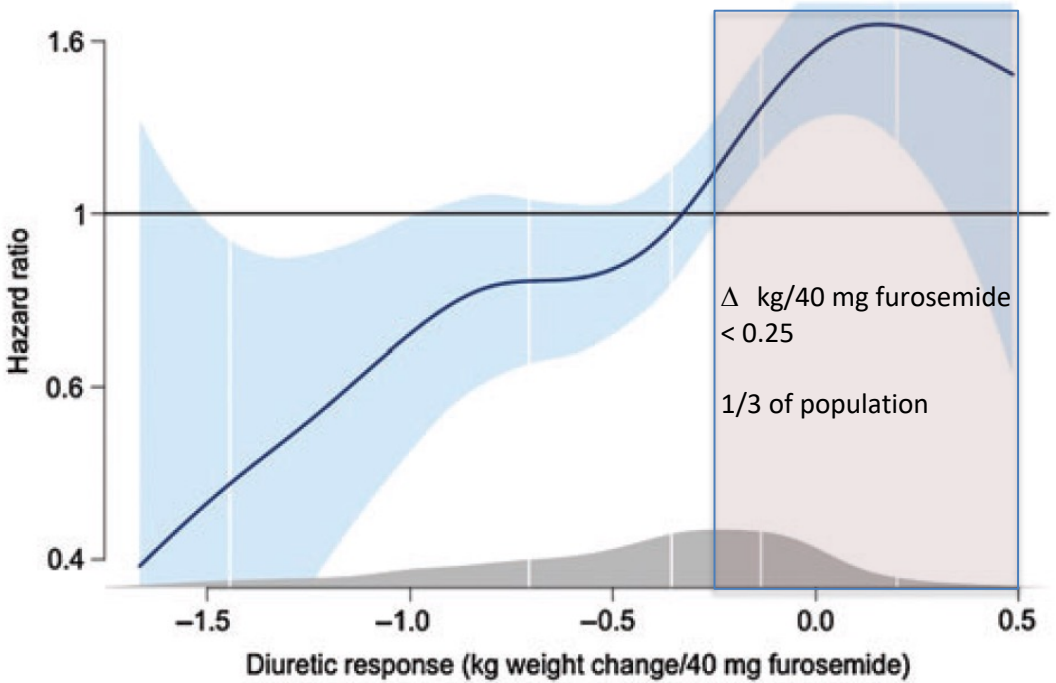




Valente M, et al. Eur Heart J 2014;35:1284-93.

Diuretic response in HF

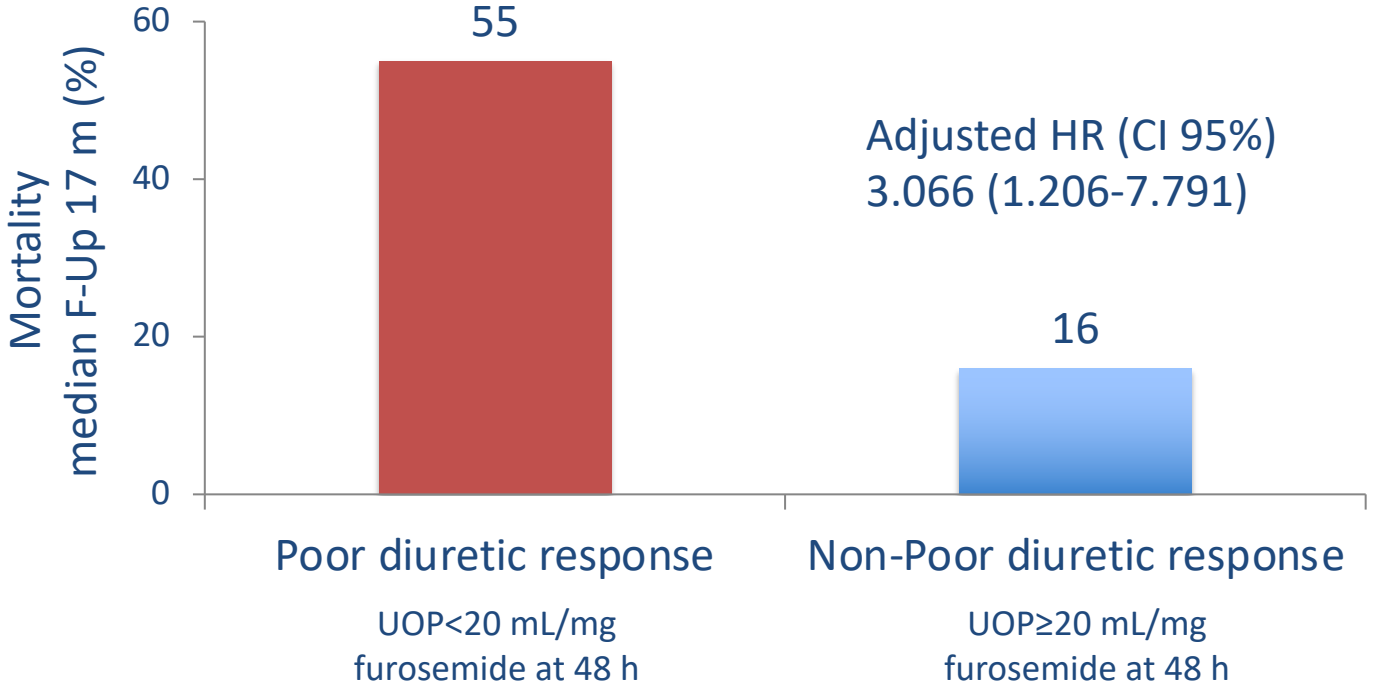
Impact on adjusted 180-day mortality in the PROTECT trial



Valente M, et al. Eur Heart J 2014;35:1284-93.

Diuretic response in HF

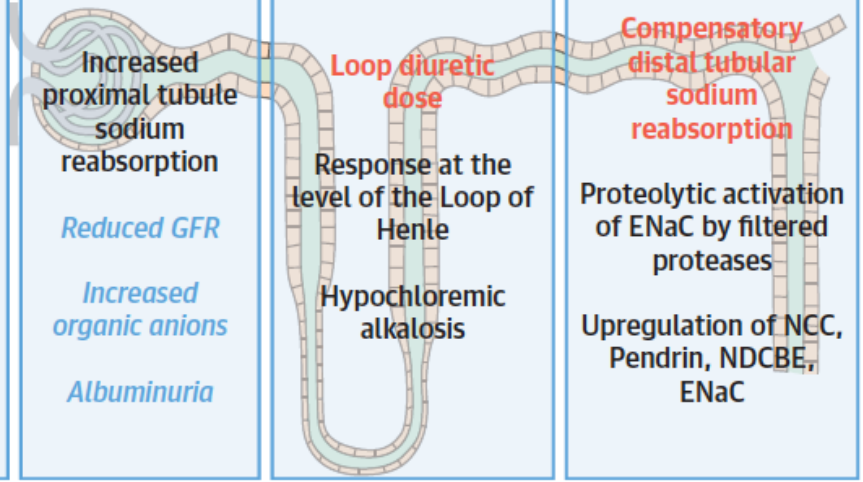
- 98 patients admitted for AHF, between Oct/2012 and Mar/2013



Freitas P, et al. Eur J Heart Fail 2014;35:1284-93

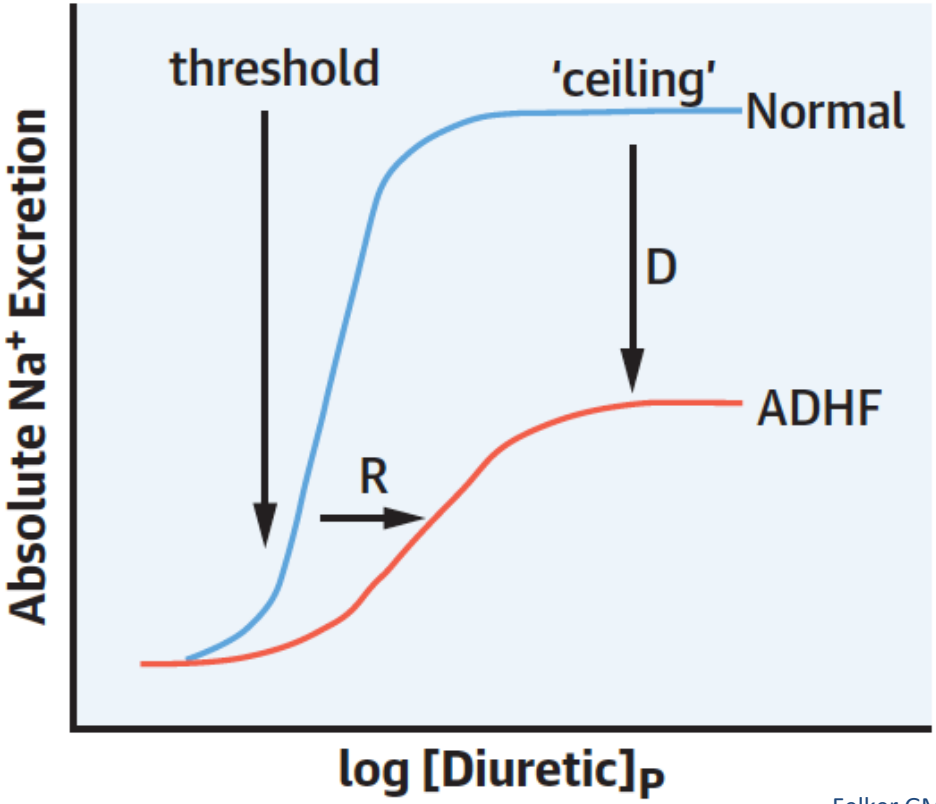
Renal mechanisms of diuretic response

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



Felker GM, et al. J Am Coll Cardiol 2020;75:1178-95.

Pharmacodynamics of loop diuretics



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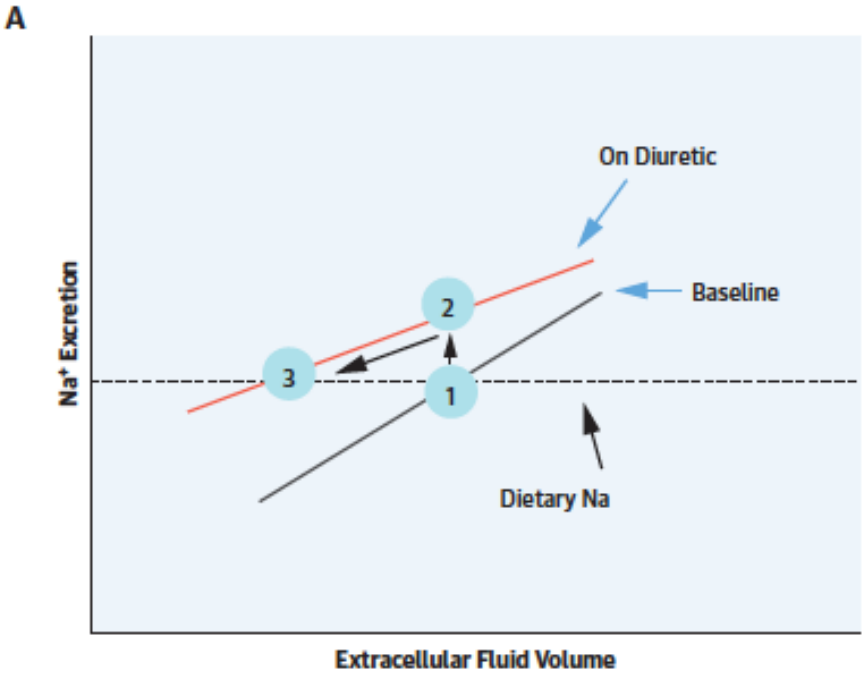
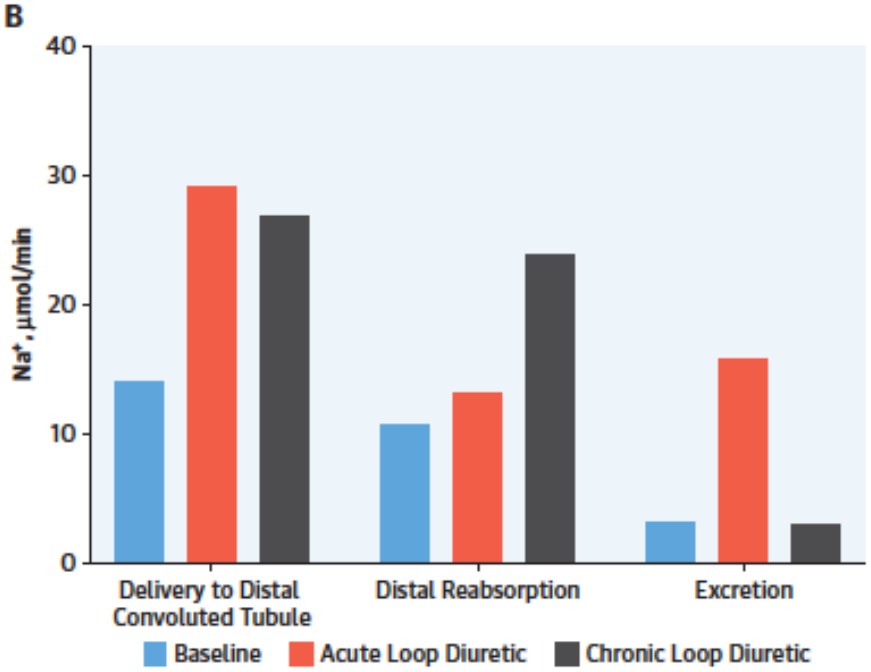
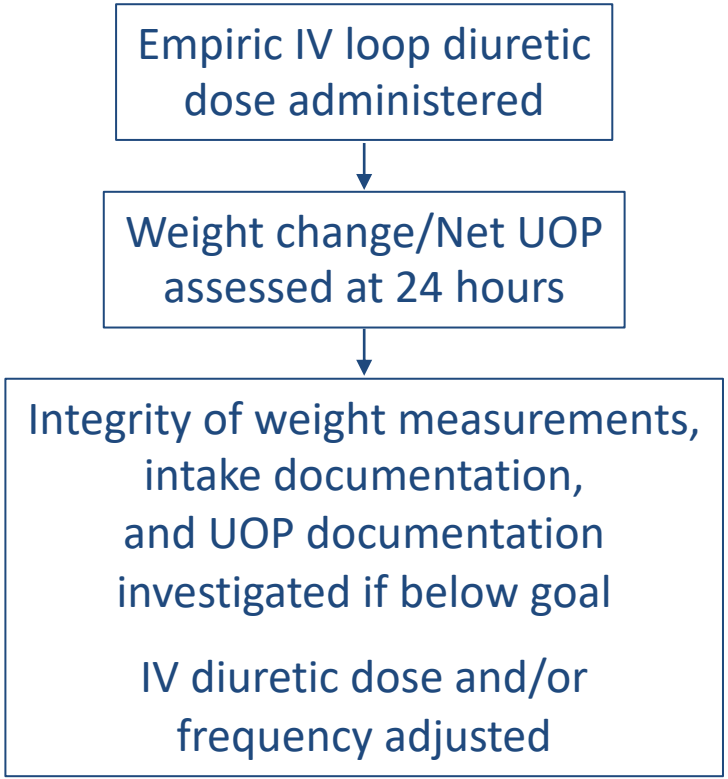
Fundamentals of loop diuretic adaption





Felker GM, et al. J Am Coll Cardiol 2020;75:1178-95.

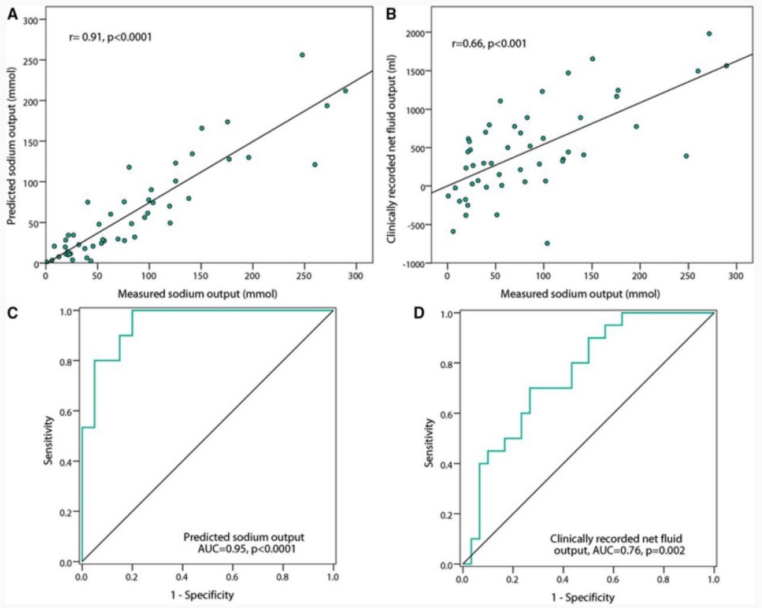
Diuretic use – Traditional strategy



Testani JM, et al. Circ Heart Fail 2016;9:e002370.

Assessment of diuretic response

1. Spot urine sodium at 1-2 hours
2. Urine output after 6 hours
3. Calculate* or measure 6-hour total sodium excretion



* eGFR x (BSA/1.73) x (Cr_{serum}/Cr_{urine}) x 60 min x 2.5 h x (Na_{urine}/1000 mL)

Testani JM, et al. Circ Heart Fail 2016;9:e002370. Mullens W, et al. Eur J Heart Fail 2019;21:137-155. Felker GM, et al. J Am Coll Cardiol 2020;75:1178-95.

Diuretic use – Sodium/UOP guided strategy

1. Empiric IV loop diuretic administered as 1 to 2.5x the home dose (20-40 mg of furosemide equivalent in loop diuretic naive)
2. Double loop diuretic dose (< 300-500 mg furosemide equivalent) if [UNa] < 50-70 mmol/L in 1-2 h spot urine or 6-h UOP < 150 mL/h
3. Repeat similar dose of IV loop diuretics every 12-h
4. Assess diuretic response after each IV loop diuretic dose

Testani JM, et al. Circ Heart Fail 2016;9:e002370. Mullens W, et al. Eur J Heart Fail 2019;21:137-155. Felker GM, et al. J Am Coll Cardiol 2020;75:1178-95.

Strategies for persistent congestion and diuretic resistance

- A quantitative definition of diuretic resistance remains elusive. Qualitatively, can be described as an inadequate rate/quantity of natriuresis despite an adequate diuretic regimen
- Ensure the patient remains hypervolemic; confirm the adequacy of loop diuretic dose, and assess the rate of net negative urine and sodium balance
- Failure to meet Na/UOP goals? → Dual sequential nephron blockade
    1. Add thiazide
    2. Add acetazolamide, amiloride, or diuretic doses of MRA
    3. Add SGLT2 inhibitor

Testani JM, et al. Circ Heart Fail 2016;9:e002370. Mullens W, et al. Eur J Heart Fail 2019;21:137-155. Felker GM, et al. J Am Coll Cardiol 2020;75:1178-95.

Dual nephron blockade with LD + thiazides

- No randomized controlled trial published in HF testing thiazides
- A stepwise diuretic titration algorithm combining loop diuretic uptitration with thiazide therapy compared favorably to ultrafiltration in a randomized trial with 188 AHF patients (CARRESS-HF)[1]
- Observational study with 13,898 AHF patients, metolazone added in 1048 patients showed increased risk of hypokalemia (OR 2.8), hyponatremia (OR 2.1), worsening renal function (OR 3.0) and death (OR 1.2) in a protensity adjusted analysis[2]
- Currently, there is a study ongoing comparing Metolazone Versus Chlorothiazide for AHF With Diuretic Resistance (NCT03574857)

1. Grodin JL, et al. Eur J Heart Fail 2018;20:1148-56. 2. Brisco-Bacik MA, et al. J Am Heart Assoc 2018;7:e009149.

Dual nephron blockade with LD + MRA

- Therapy with 100 mg of spironolactone per day was not superior to 25 mg in reducing NT-proBNP or increase UOP after 96 h (ATHENA-HF)[1]
- Spironolactone is a pro-drug with onset of action 48–72 h after oral intake, which could account for the observed nil-effect
- High-dose MRA was safe, as it did not result in hyperkalemia or worsening of renal function
- MRA therapy might be useful in offsetting the hypokalemic effect of potassium-wasting diuretics and there is a marked under-utilization of MRAs as a disease-modifying drug class in HFrEF

1. Butler J, et al. JAMA Cardiol 2017;2:950-8. Mullens W, et al. Eur J Heart Fail 2019;21:137-155.

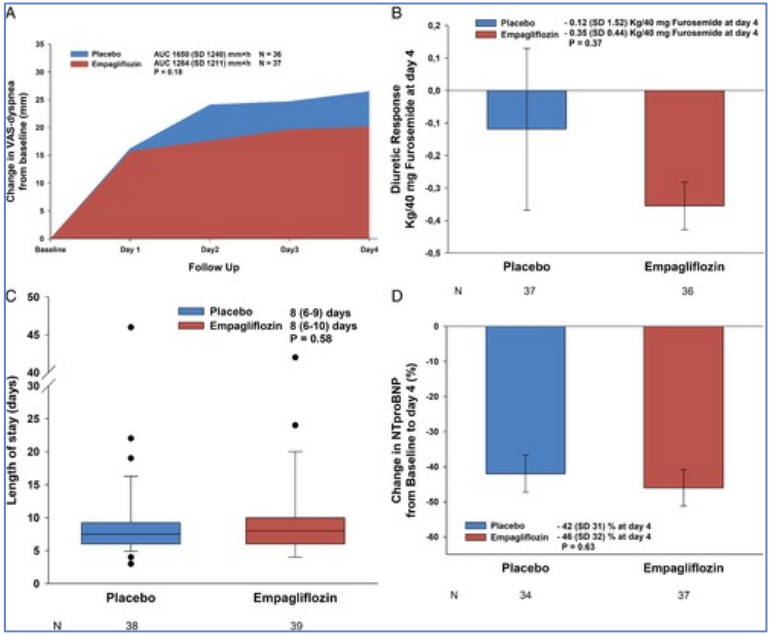
LD + proximal tubule Na reabsorption

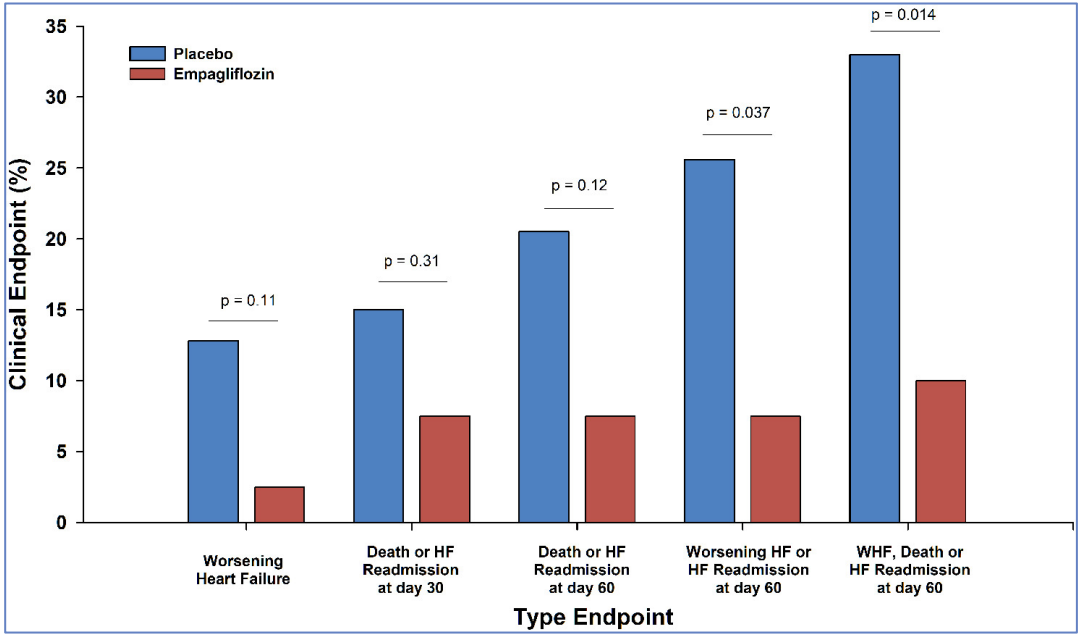
- Acetazolamide is currently being investigated in the ADVOR trial (NCT03505788)
- SGLT2 inhibitors have several ongoing clinical trials to establish the acute natriuretic effects

1. Butler J, et al. JAMA Cardiol 2017;2:950-8. Mullens W, et al. Eur J Heart Fail 2019;21:137-155.

EMPA-RESPONSE-AHF – Empagliflozin in AHF

- Pilot study: N=80 with or without DM, randomized to empagliflozin 10 mg/day or placebo

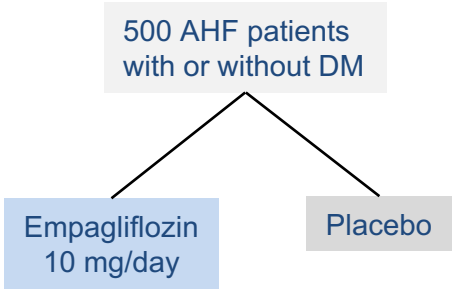




Damman K, et al. *Eur J Heart Fail* 2020;22:713-22.

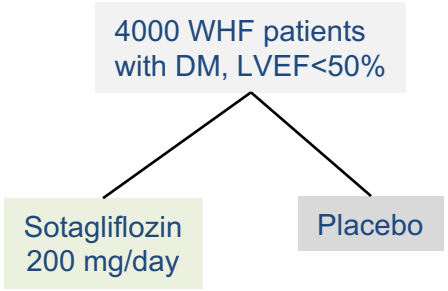
Ongoing trials of SGLT2 inhibitors in AHF

- EMPULSE[1]



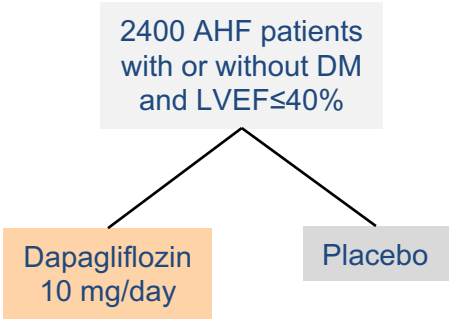
Composite of all-cause death, nr HF events time to 1st HF event and change in KCCQ-CSS at 90 days

- SOLOIST-WHF[2]



Time to first occurrence of CV death or hospitalization for HF (32 months)

- DAPA-ACT HF TIMI 68[3]



Time to first occurrence of CV death or worsening heart failure

1. NCT04157751; 2. NCT03521934; 3. NCT04363697

Take-home messages

- LD is the cornerstone of treatment for congestion but there is sparse robust clinical evidence to guide use
- LD have steep dose-response curves, with a threshold level and a ceiling level
- Diuretic resistance is a complex clinical problem with poor prognosis and ill defined treatment options
- Dual sequential nephron blockade with addition of a complementary diuretic to LD is attractive but the evidence is scarce