Diuretics: Loop diuretics. Thiazides and/or acetozalomide?

Rusudan Agladze, MD, PhD, FESC, FHFA

Baku 30 May-1 June 2025

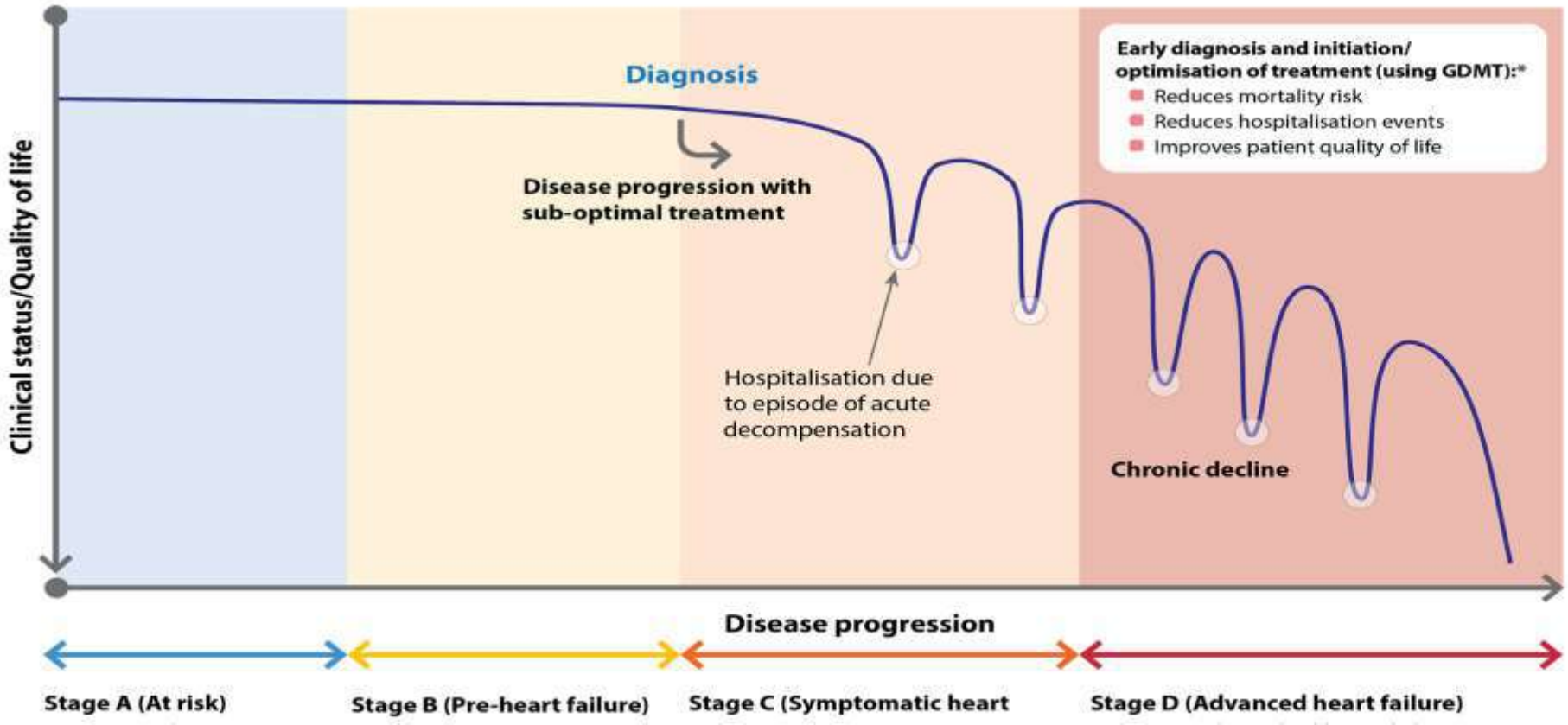
Master Course in Heart Failure

HFA
Heart Failure
Association

Declaration of interest

Speaker fees from Servier, Astra Zeneka, Novartis

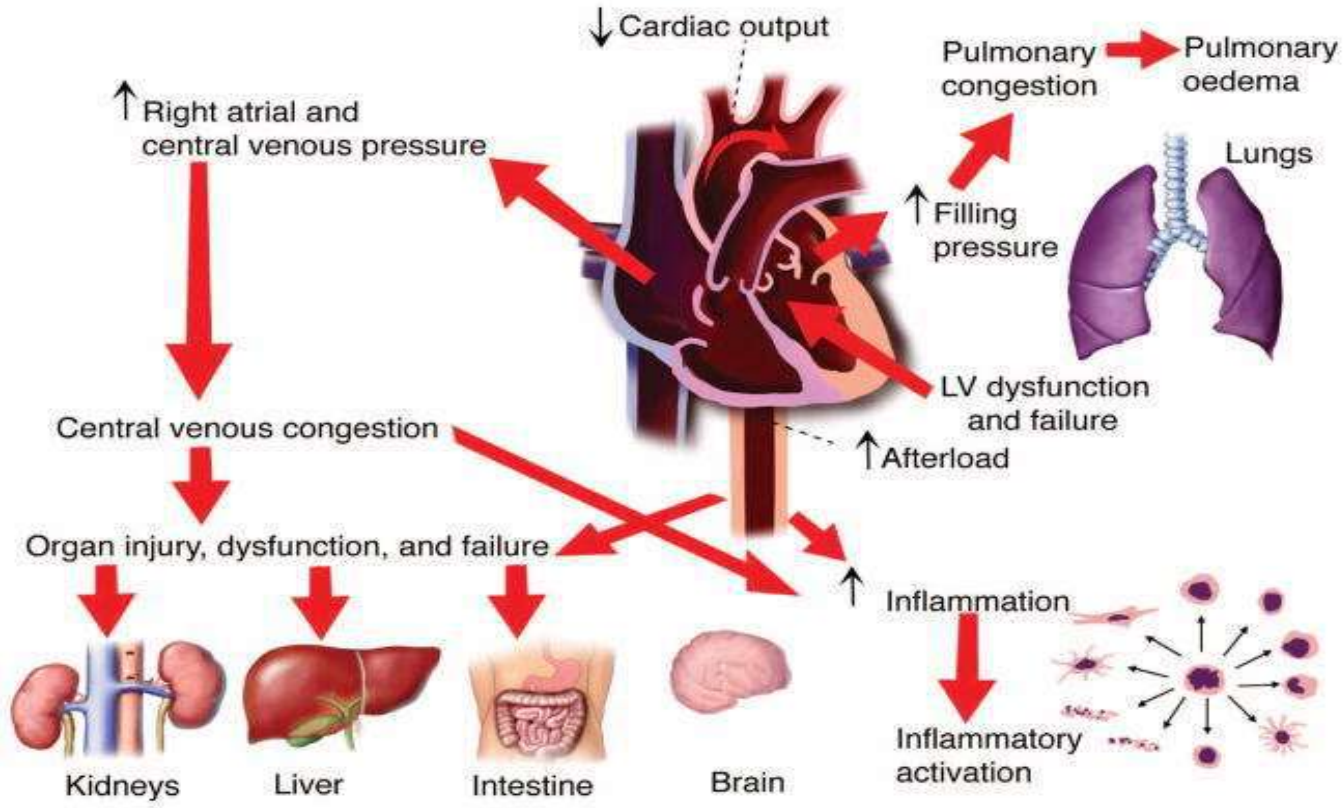
Concept of heart failure



HFA Heart Failure Association

Steinberg *et al* 2017

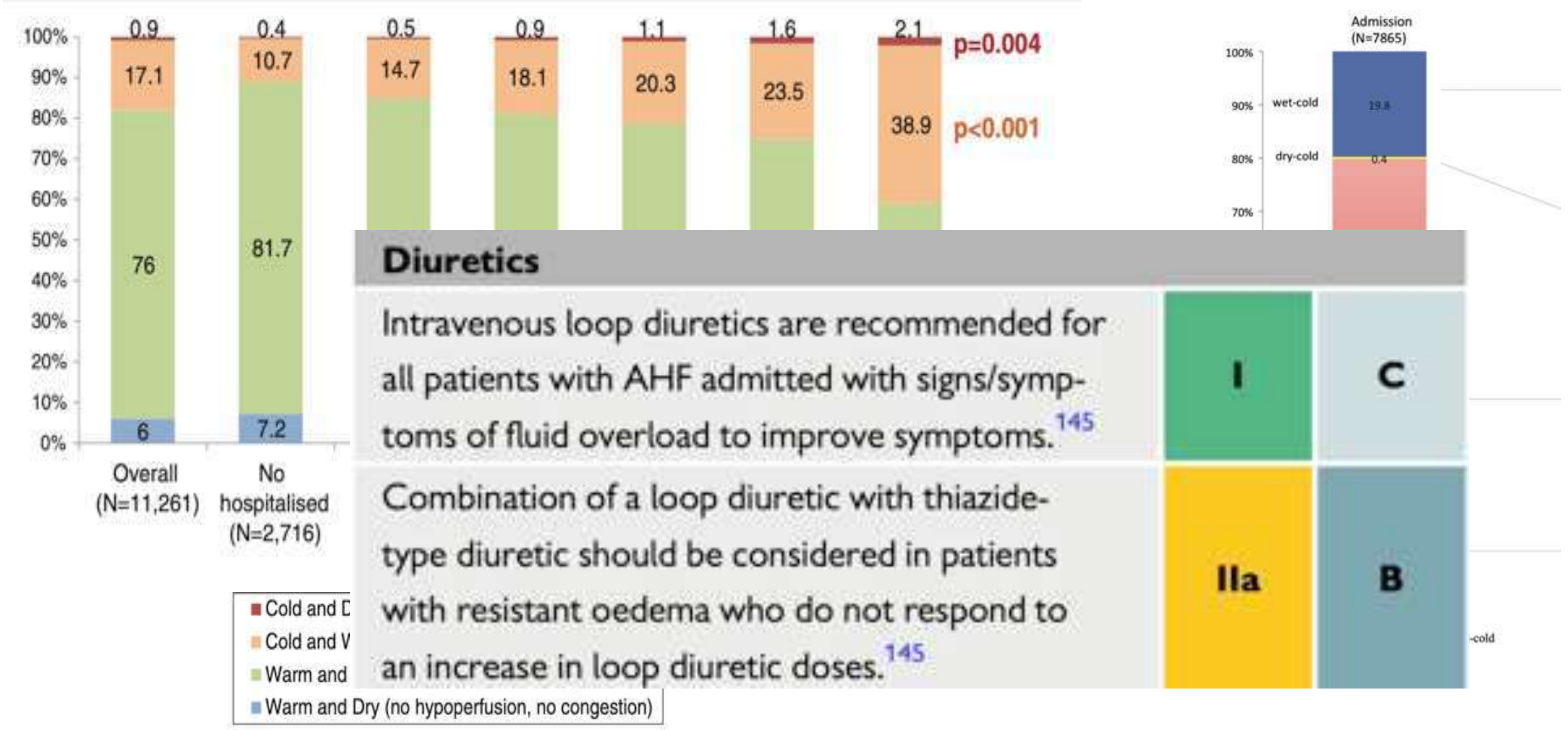
90% of all HF hospitalizations are due to volume overload



HFA Heart Failure Association

Harjola VP et al. EJHF 2017,19:821-836

Congestion as key finding in AHF



Javaloyes P. et al. Euro J Heart Fail(2019) 21, 1353–1365

Chioncel O et al , Euro J Heart Fail (2019) 21, 1338–1352

Guideline recommendations - 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

HFrEF

Other pharmacological treatments indicated in selected patients with NYHA class II–IV heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
Loop diuretics		
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.[137]	I	C

HFmrEF

Pharmacological treatments to be considered in patients with (NYHA class II–IV) heart failure with mildly reduced ejection fraction

Recommendations	Class[a]	Level[b]
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137]	I	C

HFpEF

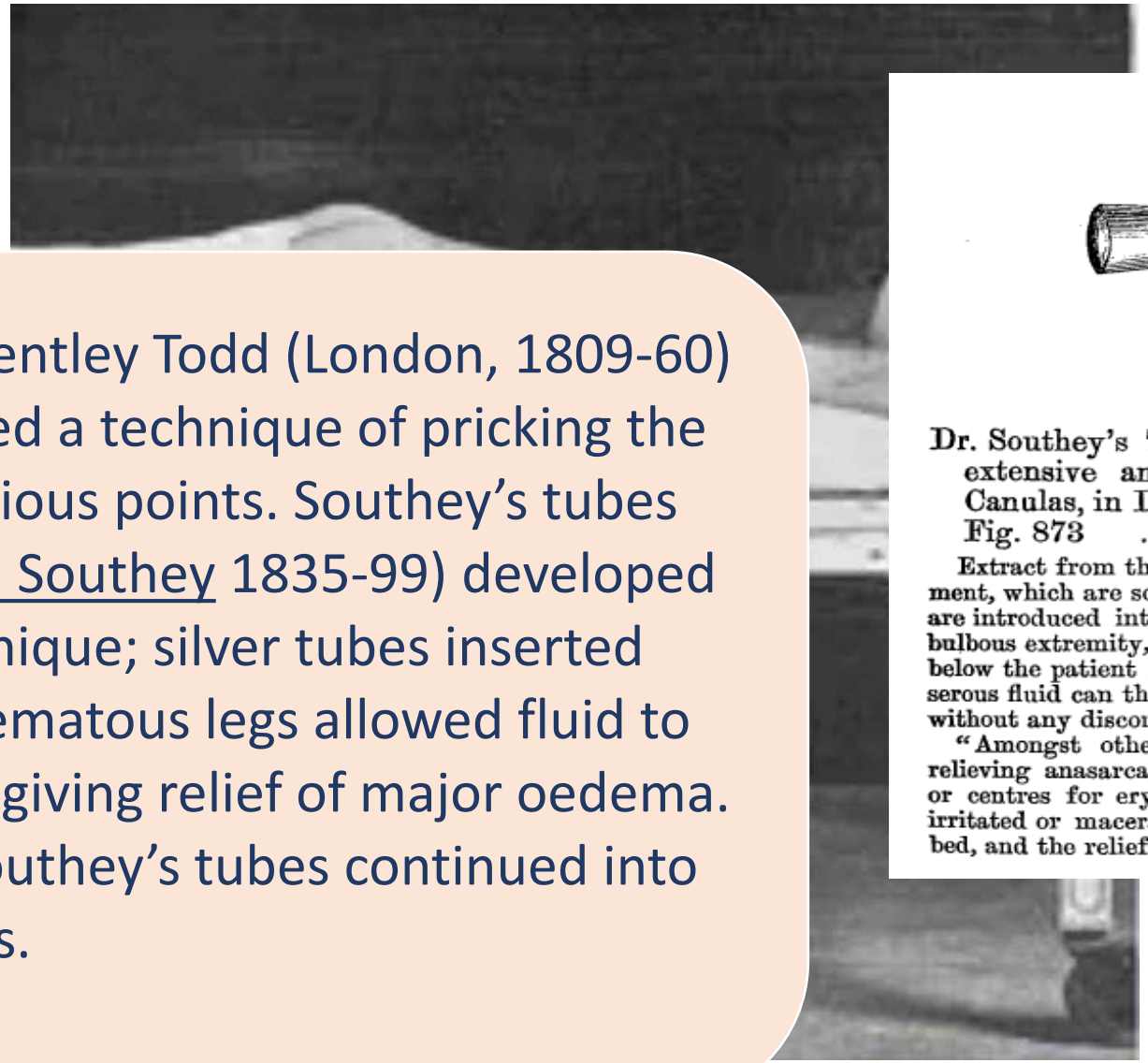
Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

HFA Heart Failure Association

McDonagh TA, Metra M et al. EHJ 2021;42(36):3599-3726

Some historical facts …



Robert Bentley Todd (London, 1809-60) mentioned a technique of pricking the leg at various points. Southey's tubes (Reginald Southey 1835-99) developed this technique; silver tubes inserted into oedematous legs allowed fluid to leak out, giving relief of major oedema. Use of Southey's tubes continued into the 1960s.

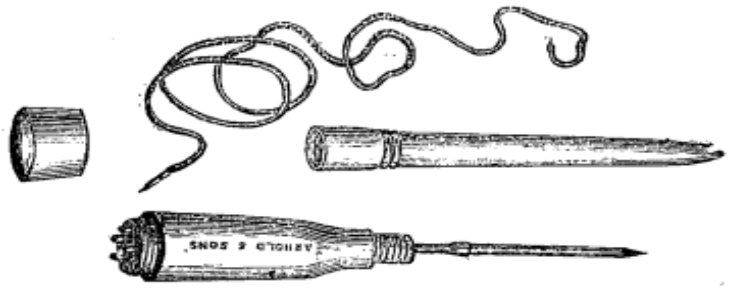


Fig. 873.

Dr. Southey's Trocar and Canulas, for the treatment of extensive and unyielding Anasarca, with four silver Canulas, in Ivory case, and Drainage Tubing, complete, Fig. 873 . . . . . 0 10 6

Extract from the *Lancet*, May 5th, 1877, p. 649:—"The canulas of this instrument, which are scarcely larger than the ordinary subcutaneous injecting needles, are introduced into dropsical limbs by a fine trocar. They terminate in a little bulbous extremity, over which a capillary drainage tube is drawn, and conducted below the patient into a pan, bottle, or other vessel. A very large quantity of serous fluid can thus be withdrawn from a single prick for many successive hours, without any discomfort to the patient.

"Amongst other recommendations of this simple and cleanly method for relieving anasarca, the following are most important:—1. No troublesome sores or centres for erysipelas are formed. 2. The skin about the puncture is not irritated or macerated by the serum. 3. The patient is kept dry and clean in bed, and the relief obtained is speedy and thorough."

Some historical facts …

1775 William Withering discovered **Digitalis**

Henry Schroeder showed in 1942 relief of oedema by limiting salt intake to less than 1g/day in patients with heart failure

Acetazolamide, introduced in 1950 by Roblin

The introduction of **Chlorothiazide** in 1957 revolutionized diuretic therapy due to its efficacy and safety profile,

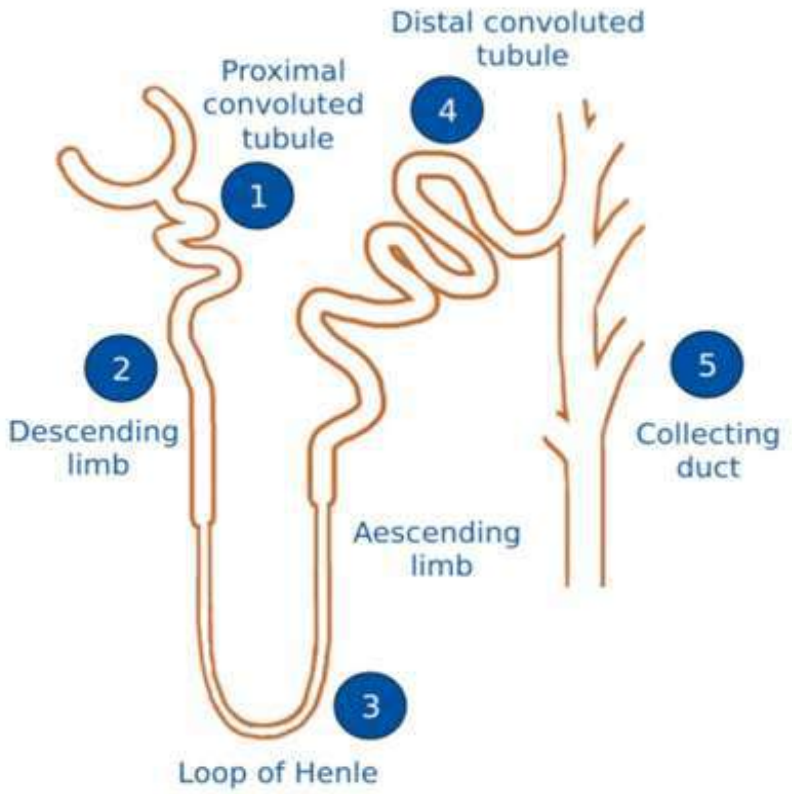
Furosemide, synthesized in 1959 and released in 1962, emerged as a highly effective prototype among loop diuretics.

Torsemide was first approved in 1993

Jyotirmoy Pa et al. JAPI 2024

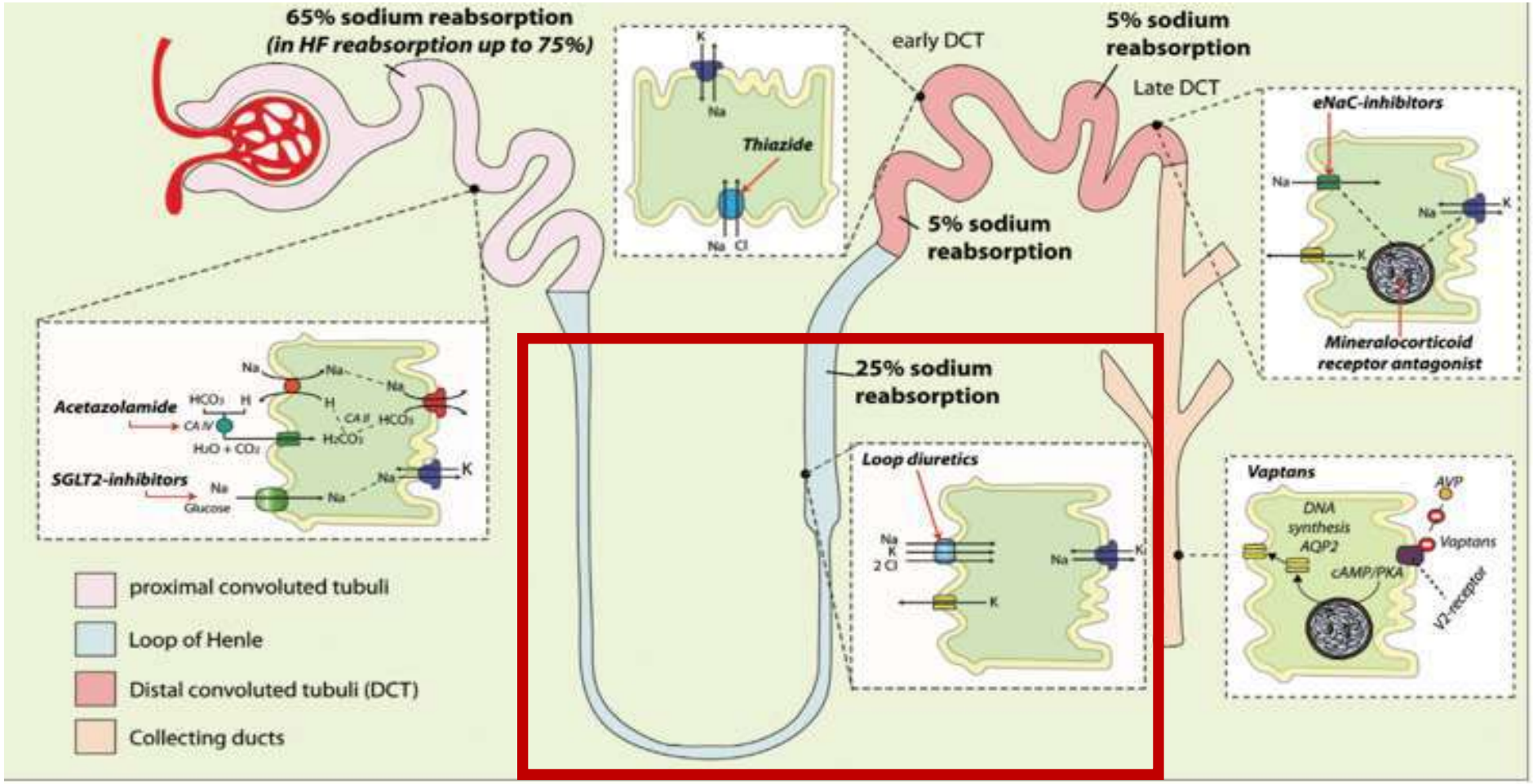
Diuretics the key stone to treat the volume overload

1. **Carbonic anhydrase inhibitors** (e.g., acetazolamide) and **SGLT-2 inhibitors** (e.g., empagliflozin)
2. **Osmotic diuretics** (e.g., mannitol)
3. **Loop diuretics** (e.g., furosemide, torasemide)
4. **Thiazides-type diuretics** (e.g., HCT, chlorthalidone)
5. **Potassium-sparing diuretics** (e.g., spironolactone, triamterene) and **Vasopressin-2-receptor antagonists** (e.g., tolvaptan)



HFA
Heart Failure Association

Site and mode of action of different diuretics – loop diuretics



HFA Heart Failure Association

*Mullens W, et al. Eur J Heart Fail (2019) **21**, 137–155*

DOSE-AHF Trial

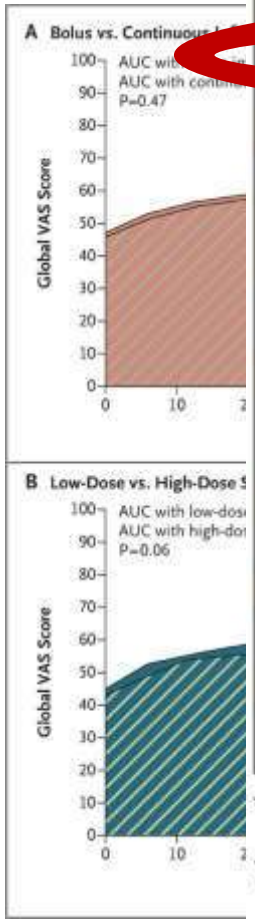
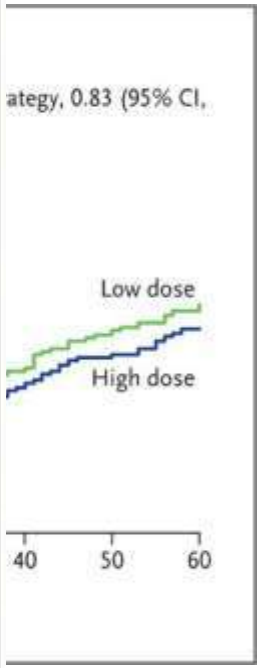


Table 2. Secondary End Points for Each Treatment Comparison.*

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for [illegible]						0.04
Freedom from congestion at 72 hr — [illegible]	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	[illegible]	[illegible]	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

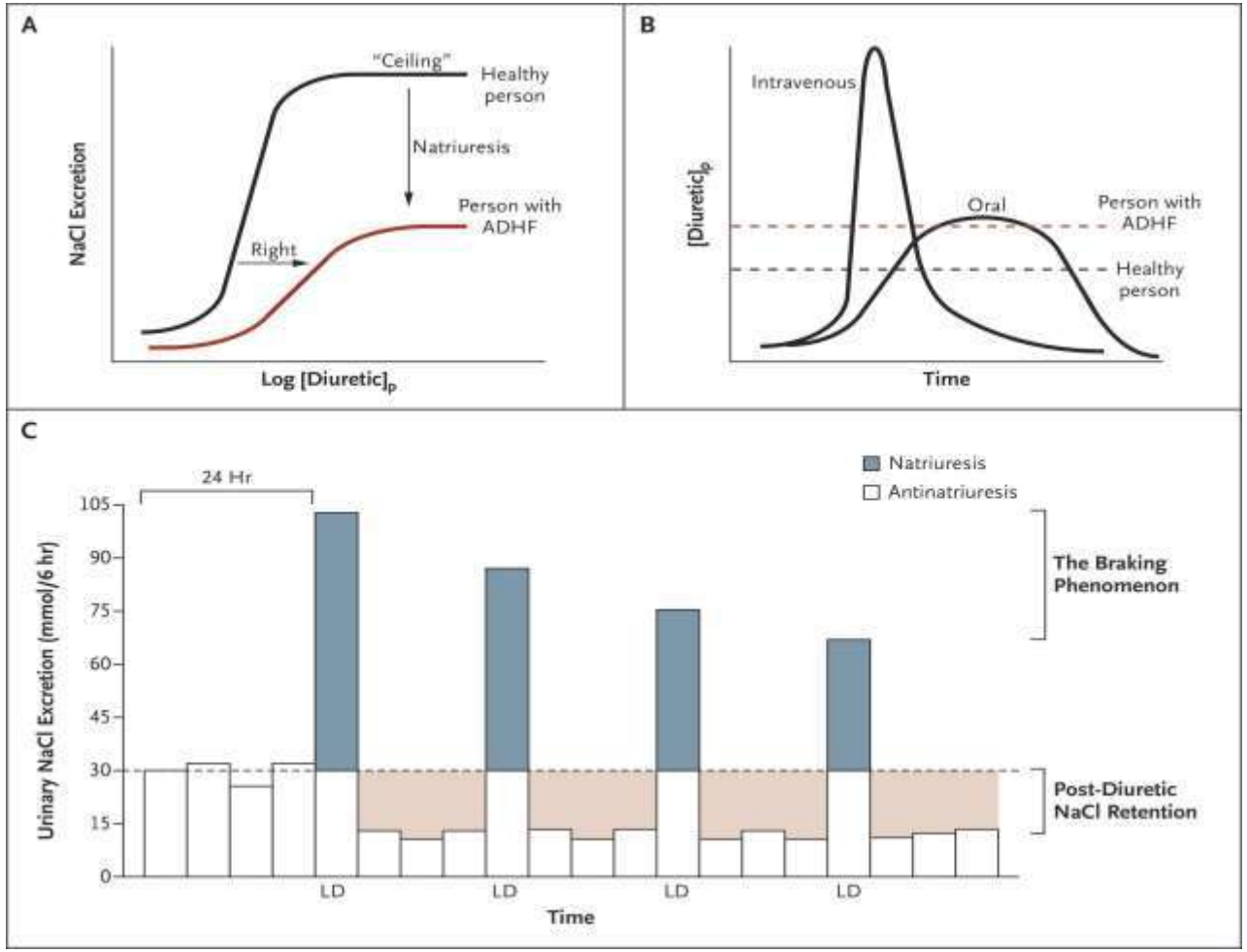
* Plus–minus values are means ±SD. To convert pounds to kilograms, divide by 2.2. AUC denotes area under the curve, and NT-proBNP N-terminal pro-brain natriuretic peptide.

† Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: increase in serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter), worsening or persistent heart failure, clinical evidence of excessive diuresis requiring intervention (e.g., administration of intravenous fluids), or death.



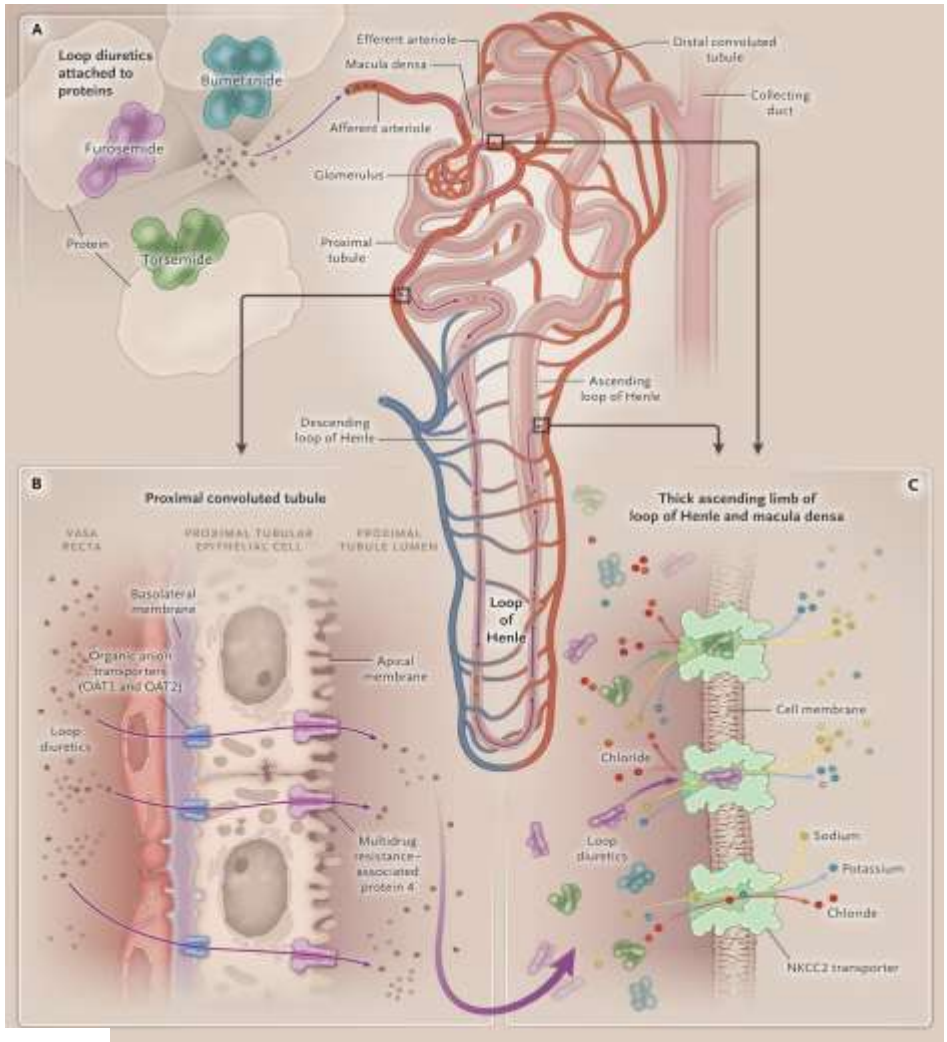
Felker GM et al. N Engl J Med 2011;364:797-805

Pharmacokinetic and Pharmacodynamic Properties of Loop Diuretics



Ellison DH, Felker GM. N Engl J *Med* 2017;377:1964-1975

Nephron Remodelling as a Mechanism of Diuretic Resistance

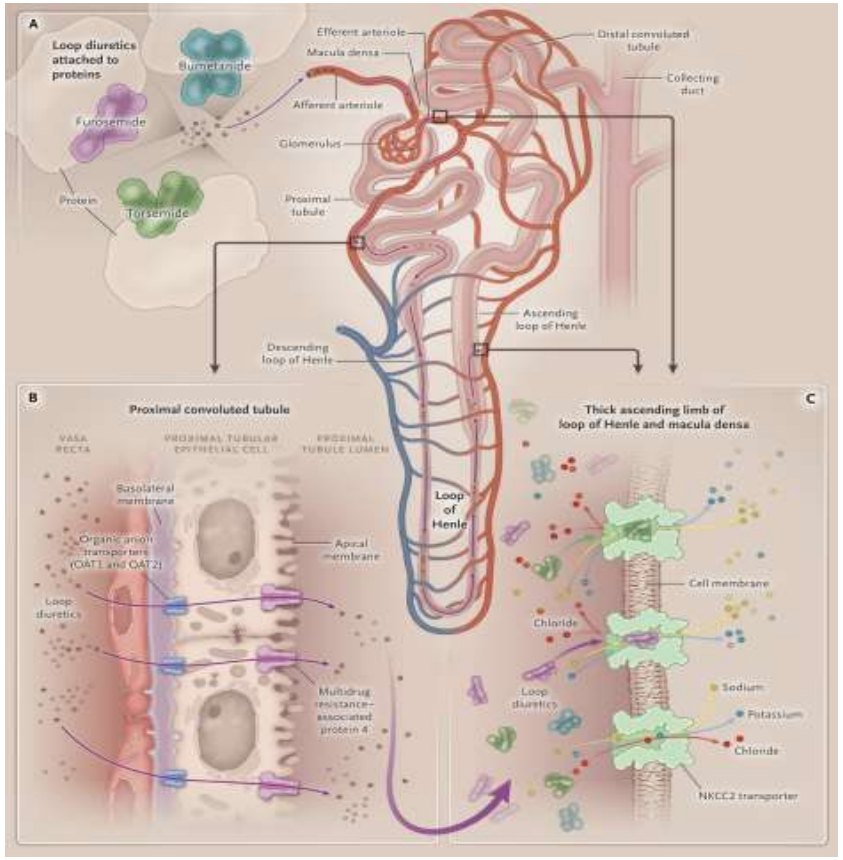


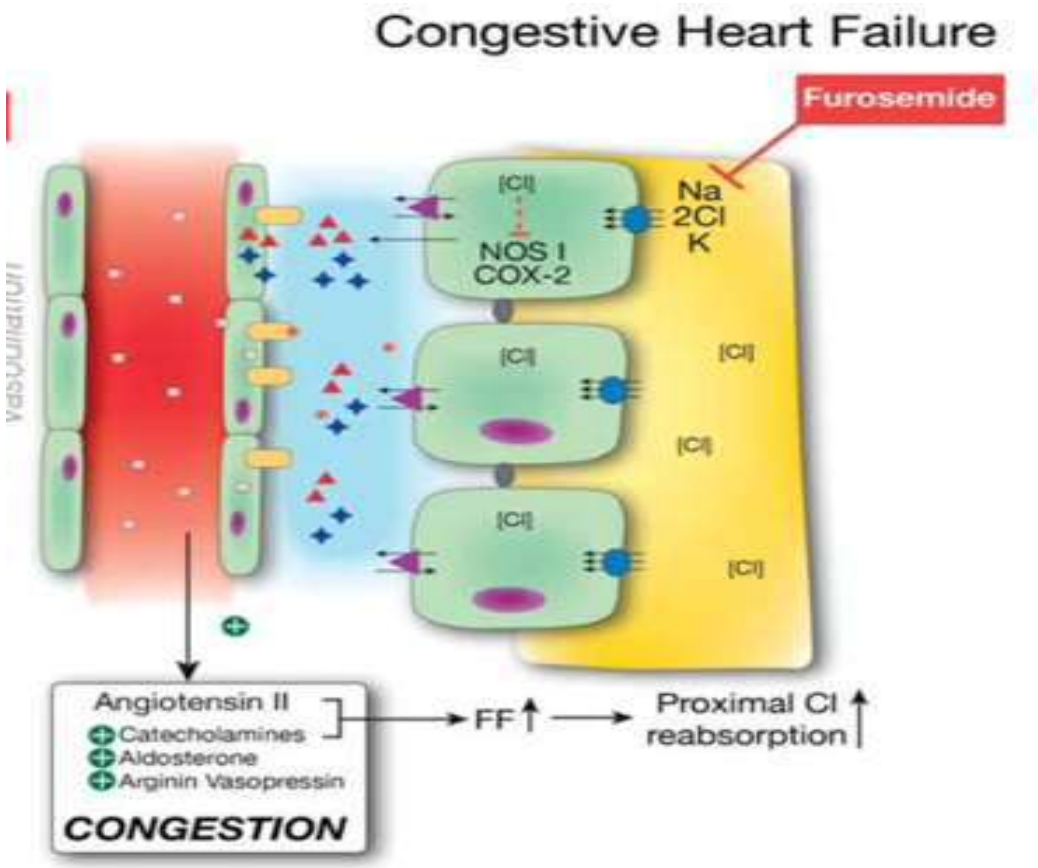
Inadequate dose of diuretic
Nonadherence
Not taking drug
High sodium intake
Pharmacokinetic factors
Slow absorption of diuretic because of gut edema
Impaired secretion of diuretic into the tubule lumen
Chronic kidney disease
Aging
Drugs
Nonsteroidal antiinflammatory drugs*
Probenecid
Hypoproteinemia
Hypotension
Nephrotic syndrome
Antinatriuretic drugs
Nonsteroidal antiinflammatory drugs*
Antihypertensive agents
Low renal blood flow
Nephron remodeling
Neurohormonal activation

HFA Heart Failure Association

Ellison DH, Felker GM. N Engl J *Med* 2017;377:1964-1975

Mechanisms of Loop Diuretic Action and Resistance





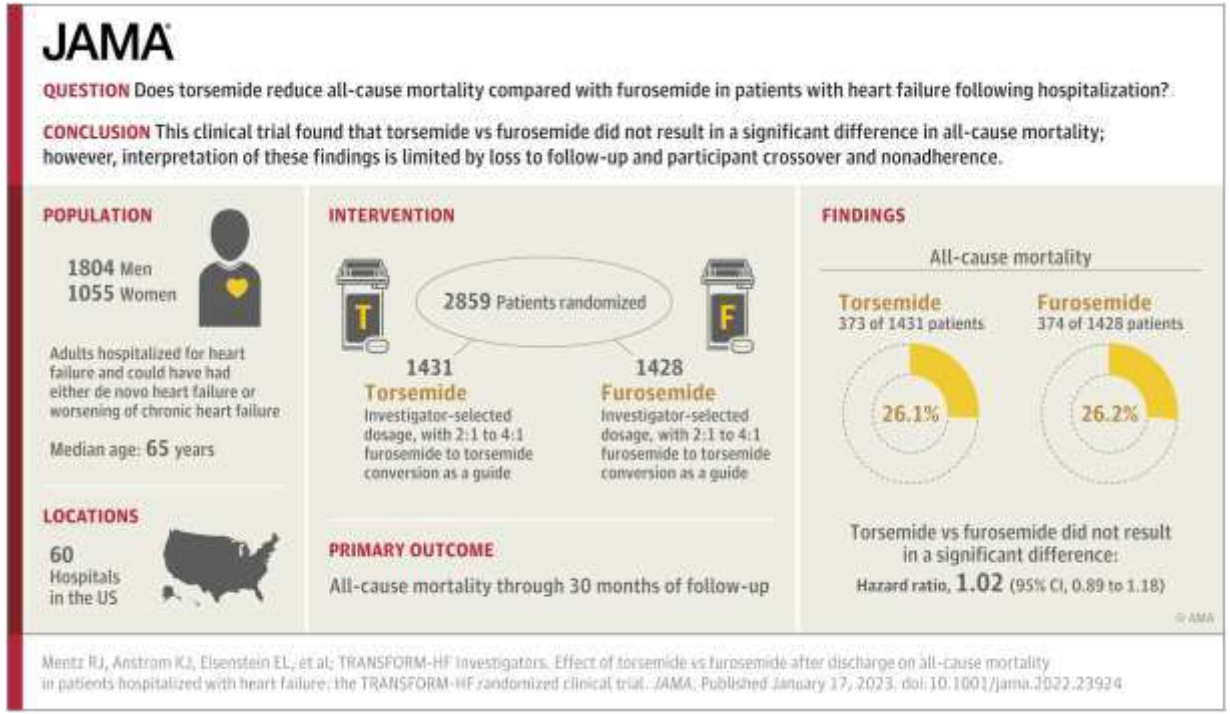
Ellison DH, Felker GM. N Engl J *Med* 2017;377:1964-1975

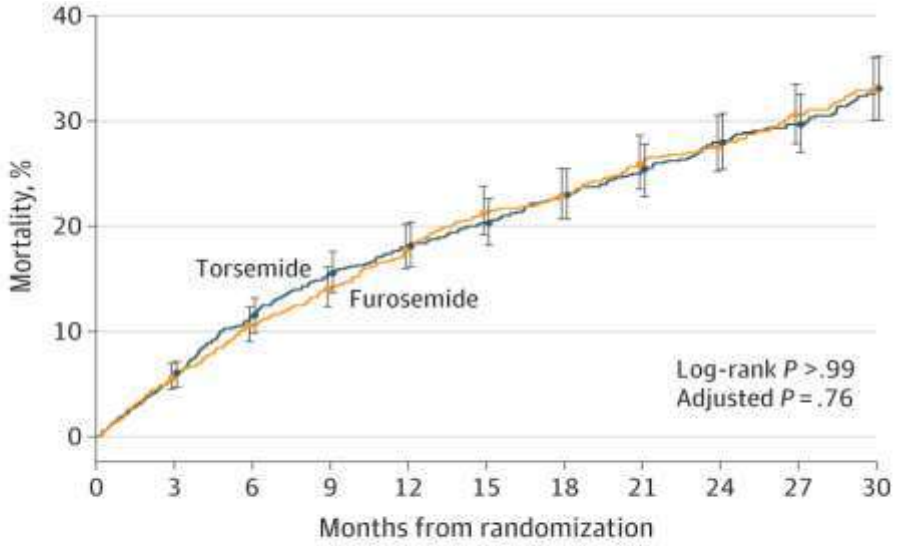
Verbrugge HF et al. Eur J Heart Fail (2014) 16, 133–142

Which loop diuretic to use?

The TRANSFORM-HF Randomized Clinical Trial

Among patients discharged after hospitalization for HF, torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months.



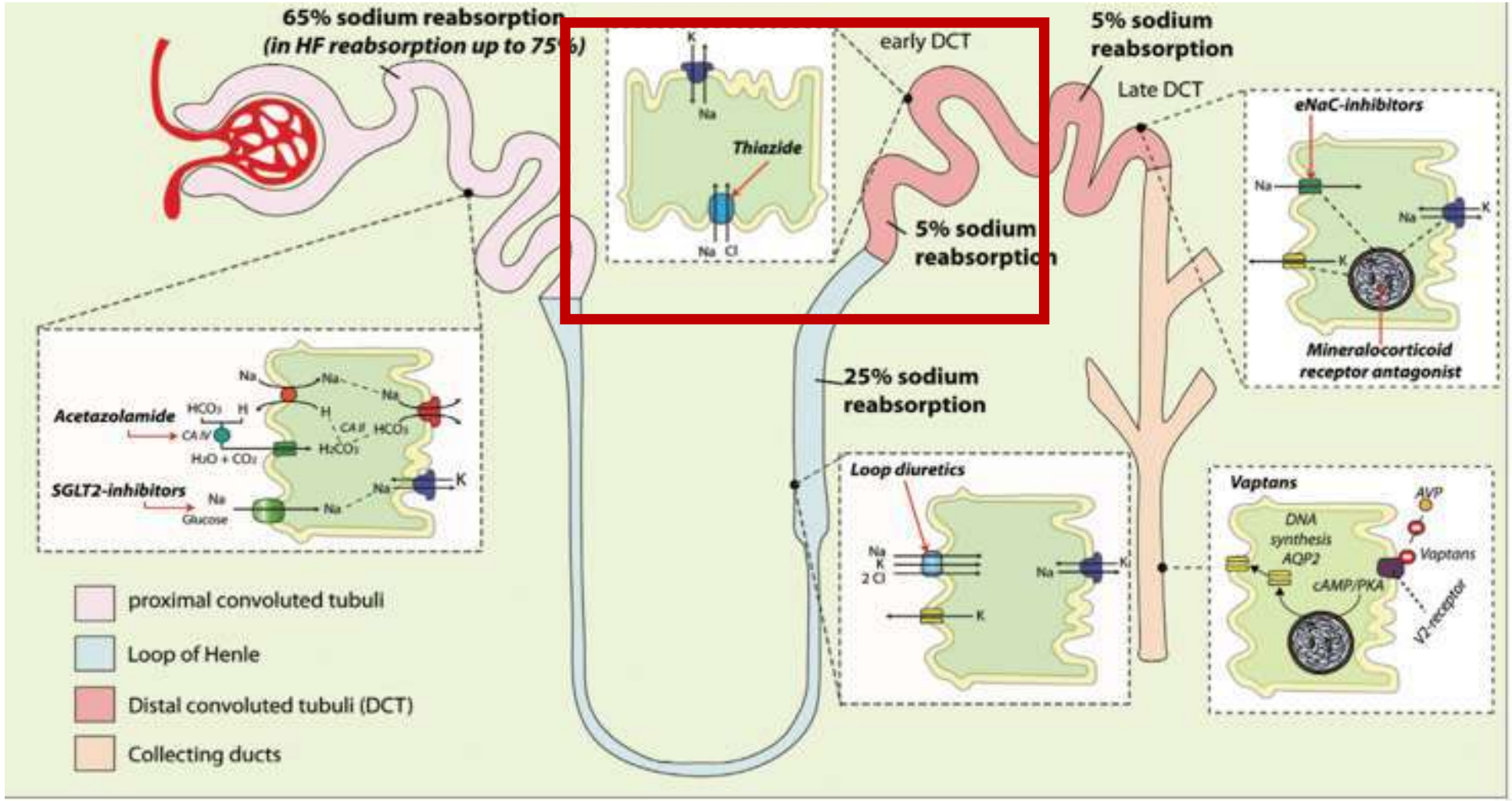


No. at risk											
Torsemide	1431	1301	1135	1027	904	787	689	661	543	434	317
Furosemide	1428	1295	1151	1036	897	782	707	658	542	428	317

Mentz R et.al.JAMA. 2023;329(3):214-223

HFA Heart Failure Association

Site and mode of action of different diuretics -thiazides



*Mullens W, et al. Eur J Heart Fail (2019) **21**, 137–155*

CLOROTIC trial

Key Question

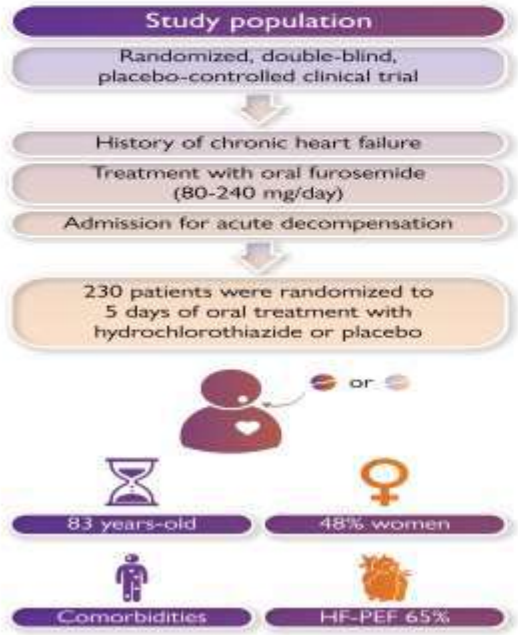
Does the addition of hydrochlorothiazide to standard intravenous loop-diuretic therapy improve the diuretic response in patients with acute heart failure (AHF)?

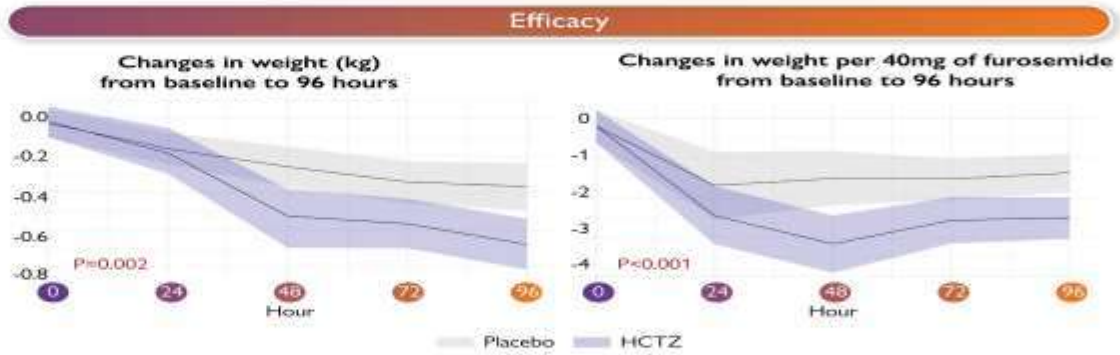
Key Finding

In patients with AHF, the combination of oral hydrochlorothiazide with intravenous loop diuretics improved the diuretic response but was associated with worsening renal function.

Take Home Message

The addition of hydrochlorothiazide to intravenous loop diuretics improves the diuretic response in patients with decompensated heart failure at the cost of worsening renal function.



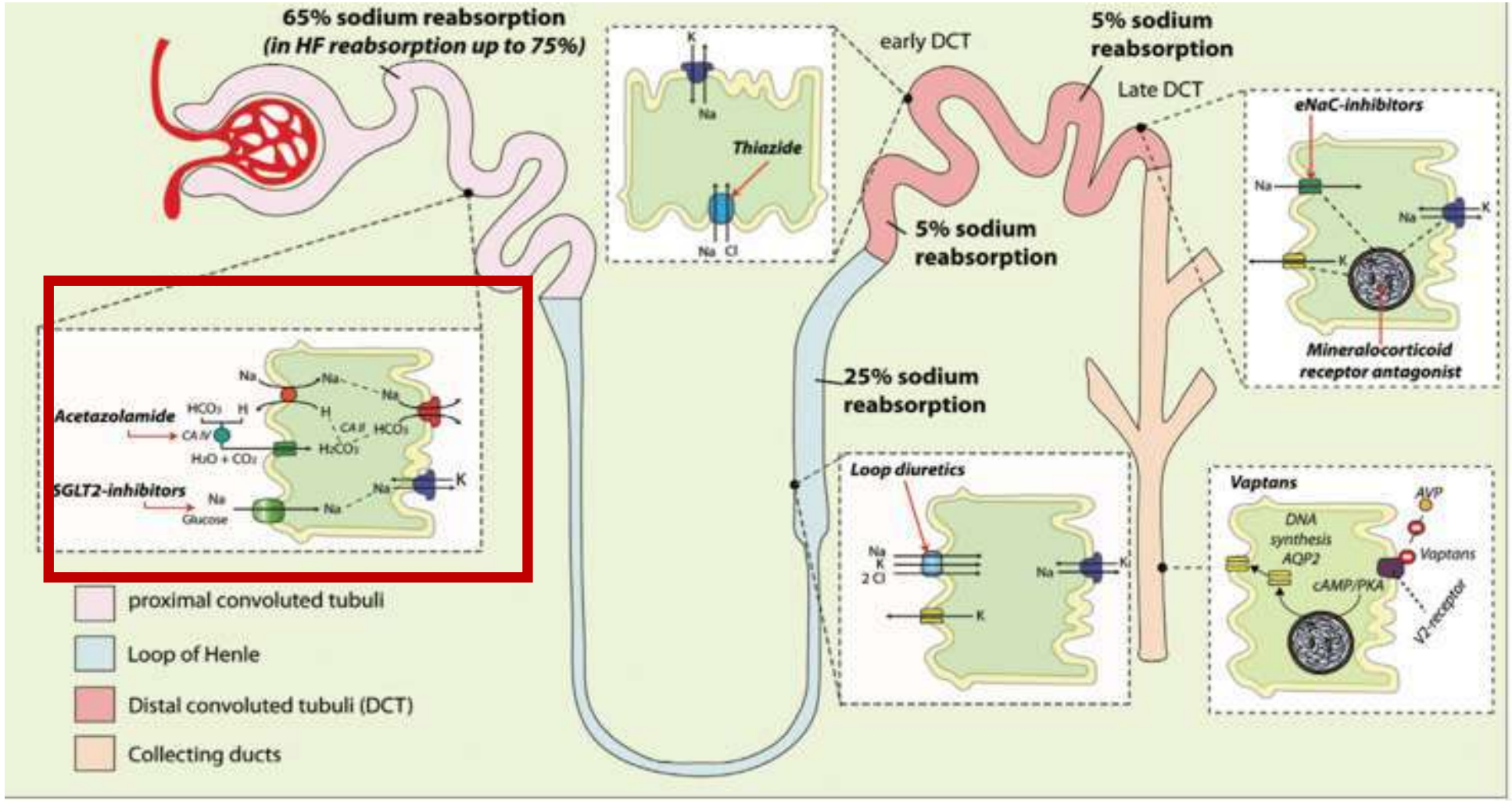


Safety	Placebo	HCTZ	p-value
All-cause mortality at 90 days	19 (16.4%)	23 (20.2%)	0.566
All-cause rehospitalizations at 90 days	40 (34.5%)	43 (37.7%)	0.709
Impaired renal function (serum creatinine and eGFR)	20 (17.2%)	53 (46.5%)	<0.001
Hyponatraemia (Na+ ≤ 130 mmol/L) - (Na+ ≤ 125 mmol/L)	6 (5.2%)–2 (1.7%)	10 (8.8%)–3 (2.6%)	0.416–0.682
Hypokalaemia (K+ ≤ 3.0 mmol/L) - (K+ ≤ 2.5 mmol/L)	18 (16.1%)–0 (0.0%)	43 (40.6%)–2 (1.8%)	<0.001–0.245
Serious adverse events	27 (23.3%)	26 (22.8%)	0.93

HFA Heart Failure Association

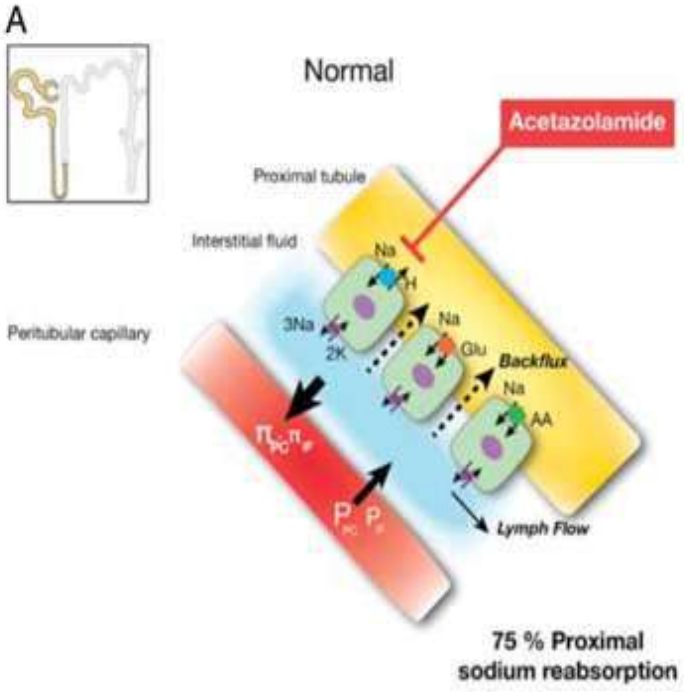
Trullas et al. Eur Heart J, Volume 44, 411–421,

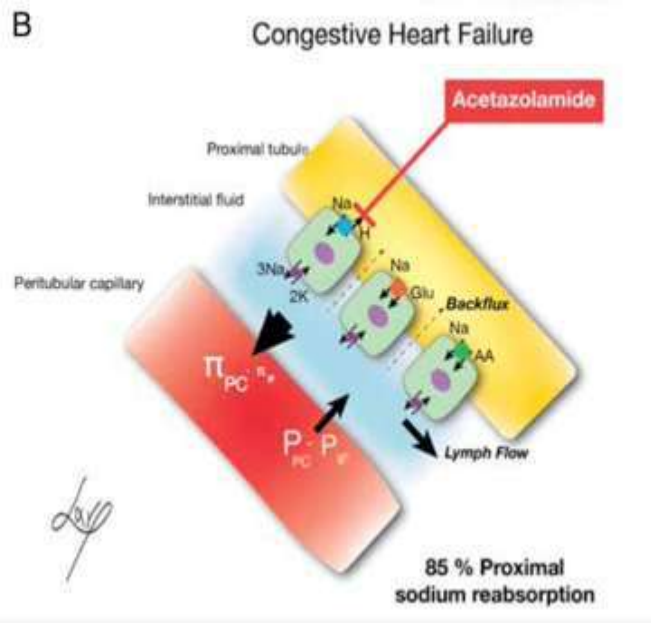
Site and mode of action of different diuretics - **Acetazolamide**



*Mullens W, et al. Eur J Heart Fail (2019) **21**, 137–155*

Site and mode of action of different diuretics - **Acetazolamide**





1. Effect on loop diuretics

2. Decrease neurohumoral activation

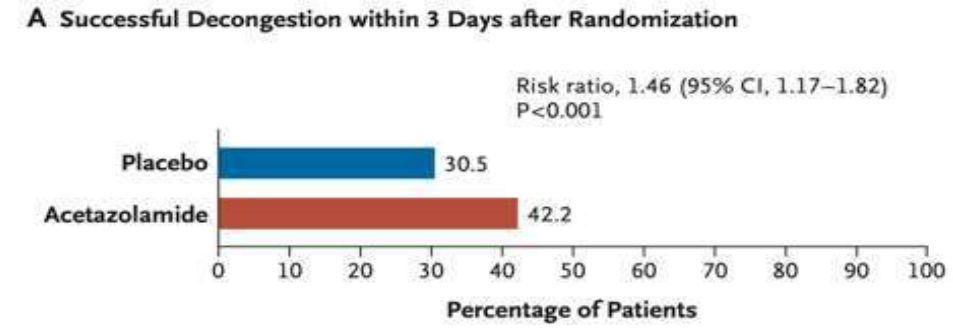
3. Increase K and Mg loss

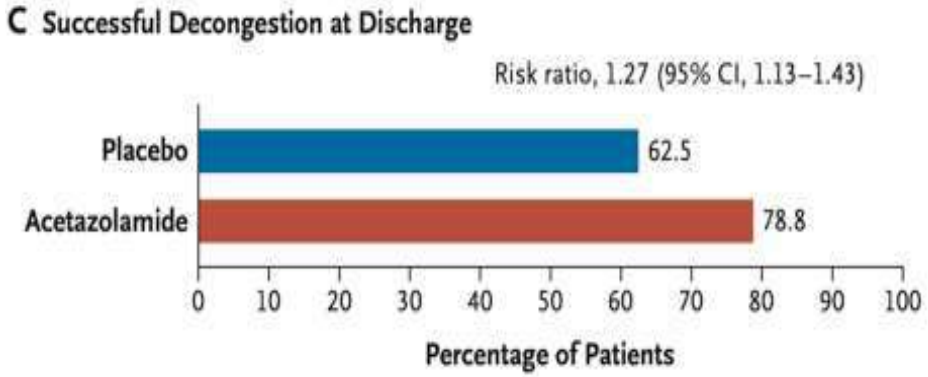
HFA Heart Failure Association

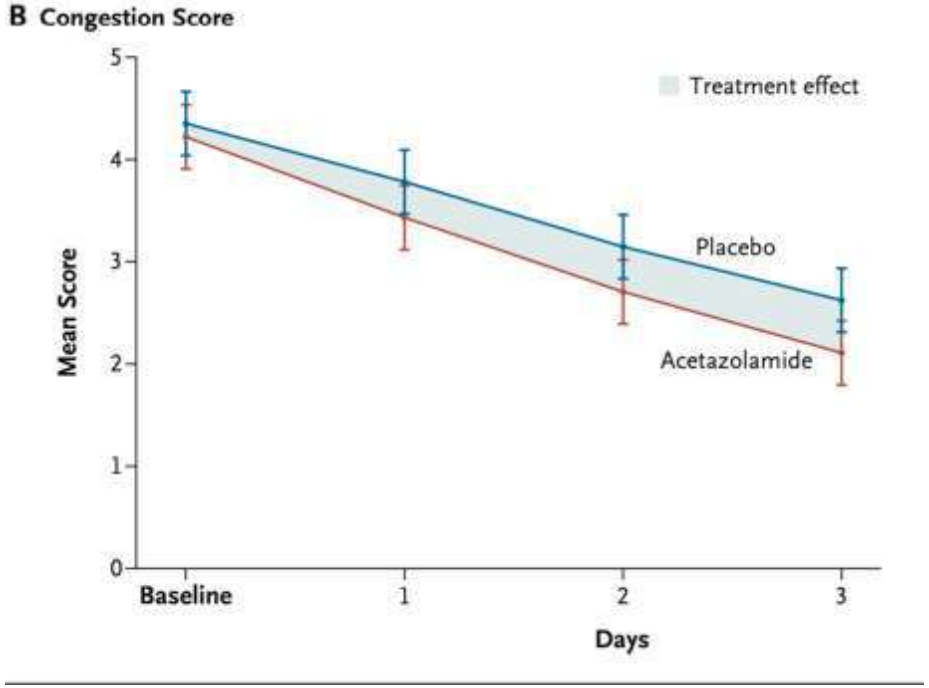
Verbrugge HF et al. Eur J Heart Fail (2014) 16, 133–142

ADVOR trial

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

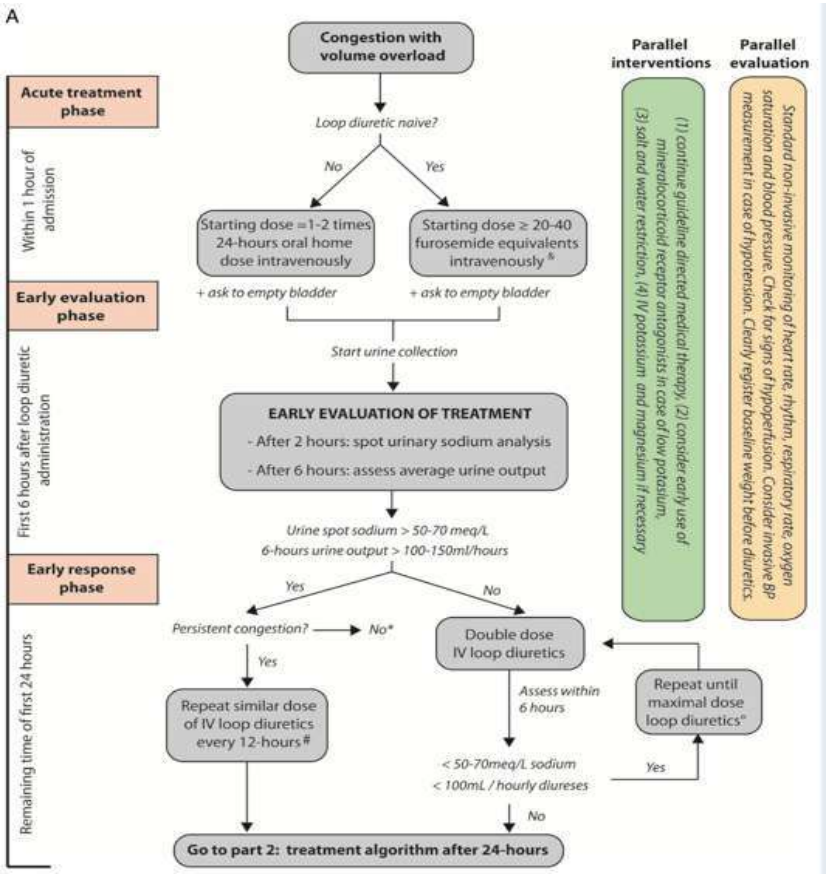


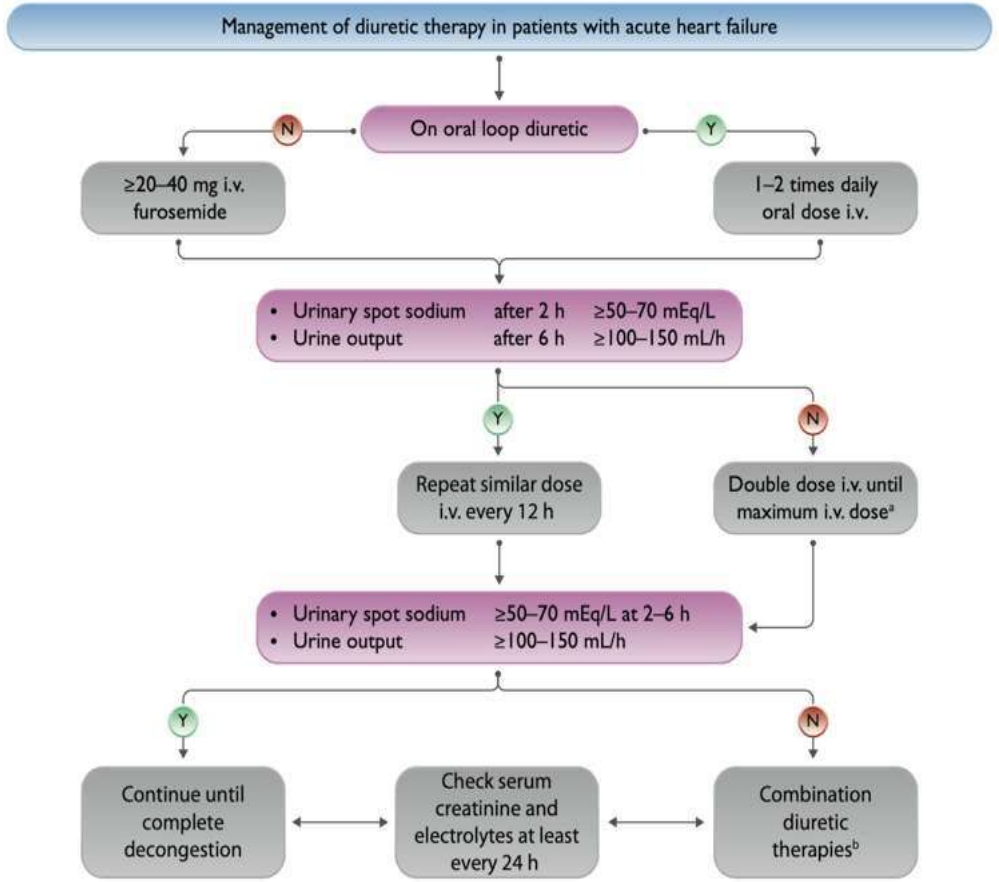




Mullens W et al. N Engl J Med2022;387:1185-1195

Treatment algorhythm

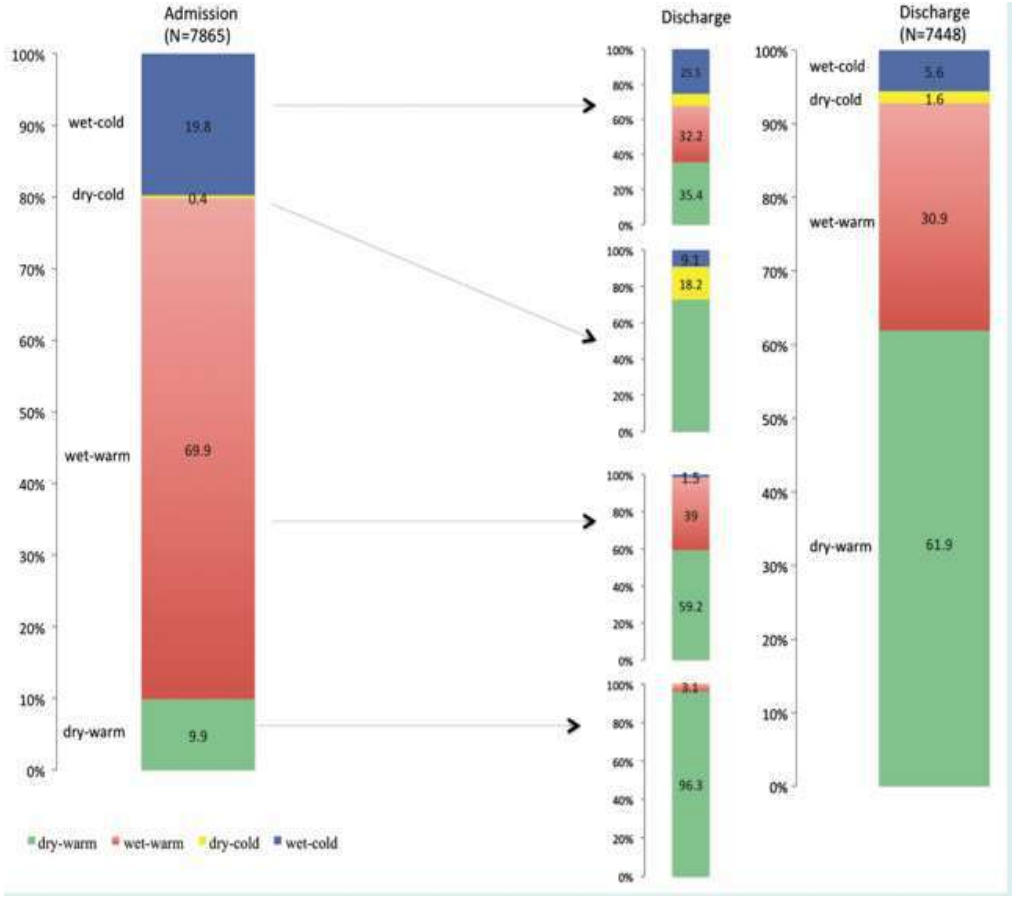


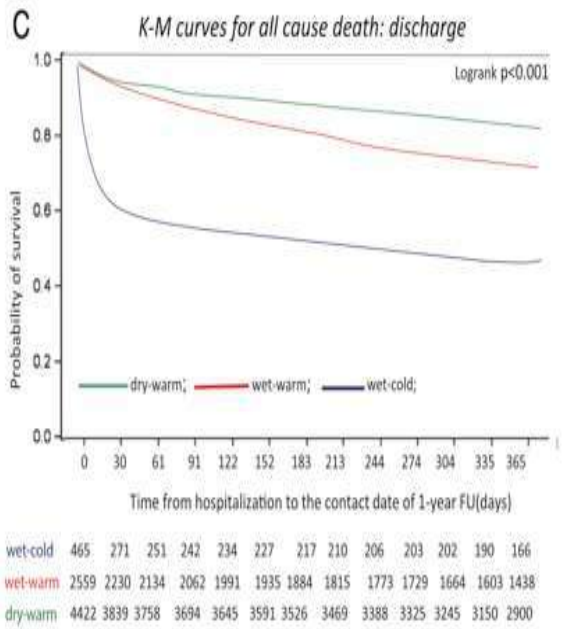


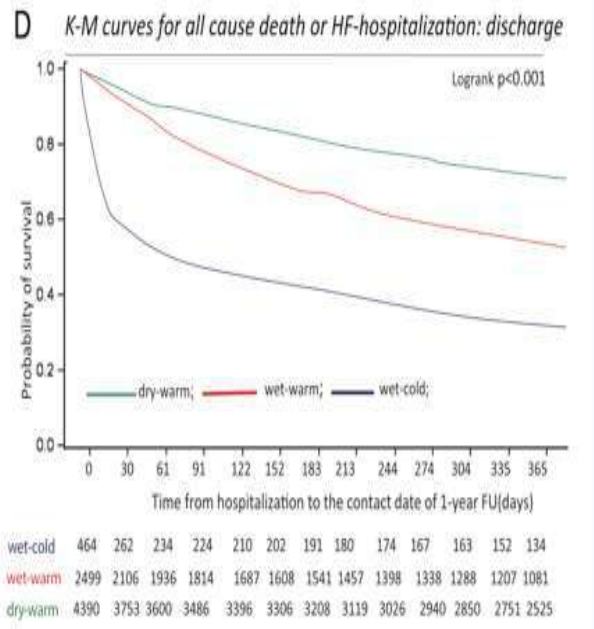
*Mullens W, et al. Eur J Heart Fail (2019) **21**, 137–155*

McDonagh TA, Metra M et al. EHJ 2021;42(36):3599-3726

Residual congestion at discharge impacts results negatively







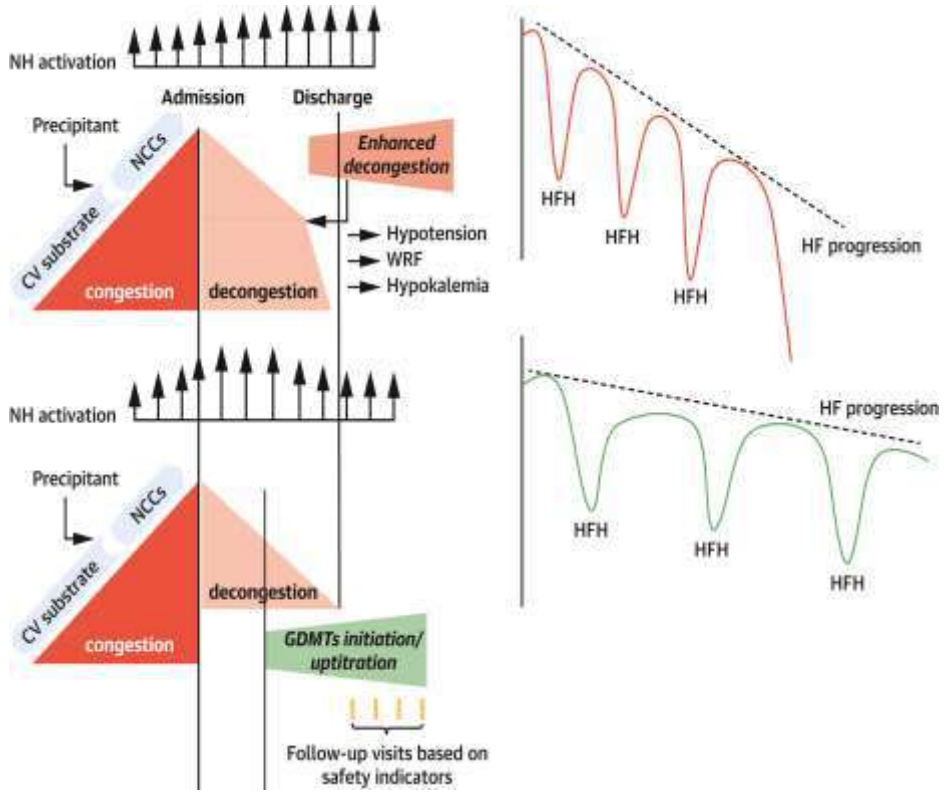
HFA Heart Failure Association

Chioncel O et al , Euro J Heart Fail (2019) 21, 1338–1352

Integrative euvolaemia/congestion evaluation at discharge

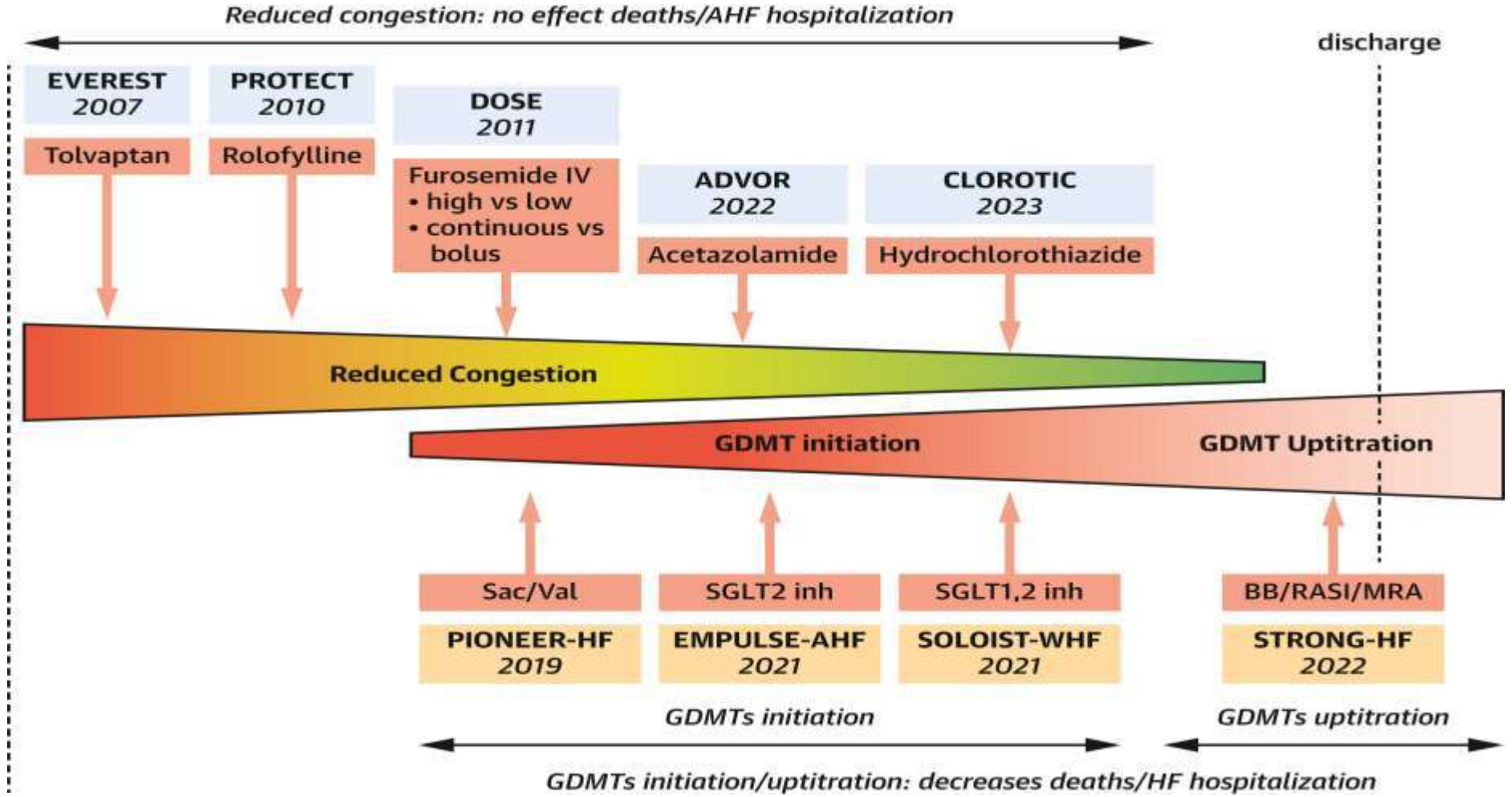
	Variable	EUVOLEMIA → CONGESTED				
Clinical congestion	Orthopnea	None		Mild	Moderate	Severe/worst
	JVP (cm)	<8 and no HJR	<8	8-10 or HJR+	11-15	>16
	Hepatomegaly		Absent	Liver edge	Moderate pulsatile enlargement	Massive enlargement and tender
	Edema		None	+1	+2	+3/+4
	6MWT	>400m	300-400m	200-300m	100-200m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



Cotter G et al. JACC 2024

Randomized Clinical Trials of Decongestion and GDMT Uptitration

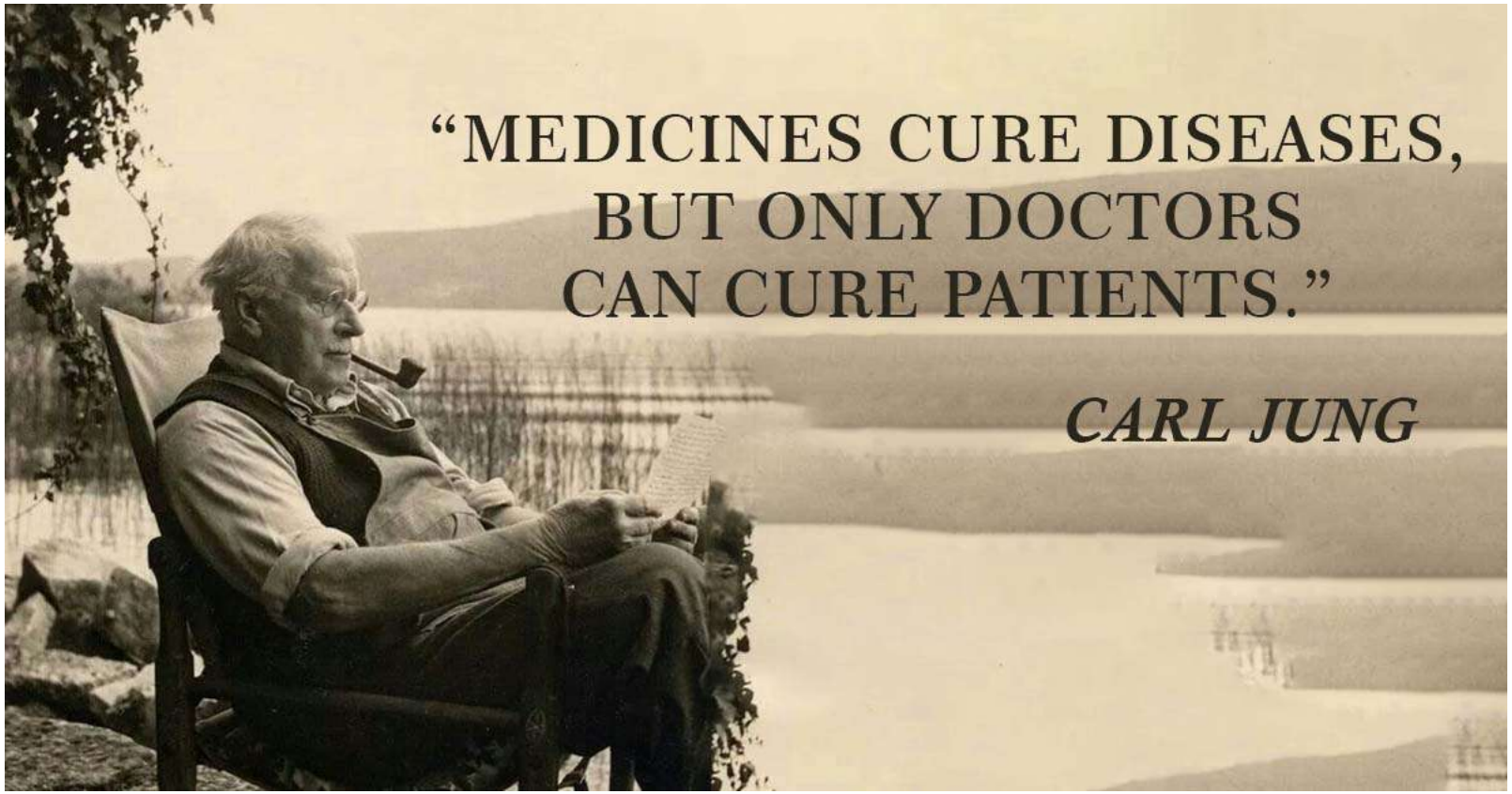


HFA Heart Failure Association

Cotter G et al. JACC 2024

Conclusion

- Congestion is the cause of symptoms and poor outcome in patients with heart failure and residual congestion is associated with increased mortality and HF hospitalizations.
- Diuretics are cornstone of decongestive therapies.
- Combination of different diuretics , early evaluation of diuretic response and natriuresis (diuresis) guided approach could be the most beneficial
- Despite the fact that there is no randomised clinical trial showing that use of diuretics improve prognosis, optimisation of diuretic therapy could allow to start GMT earlier and have more benefits for patients


"MEDICINES CURE DISEASES,
BUT ONLY DOCTORS
CAN CURE PATIENTS."
CARL JUNG

Thank you