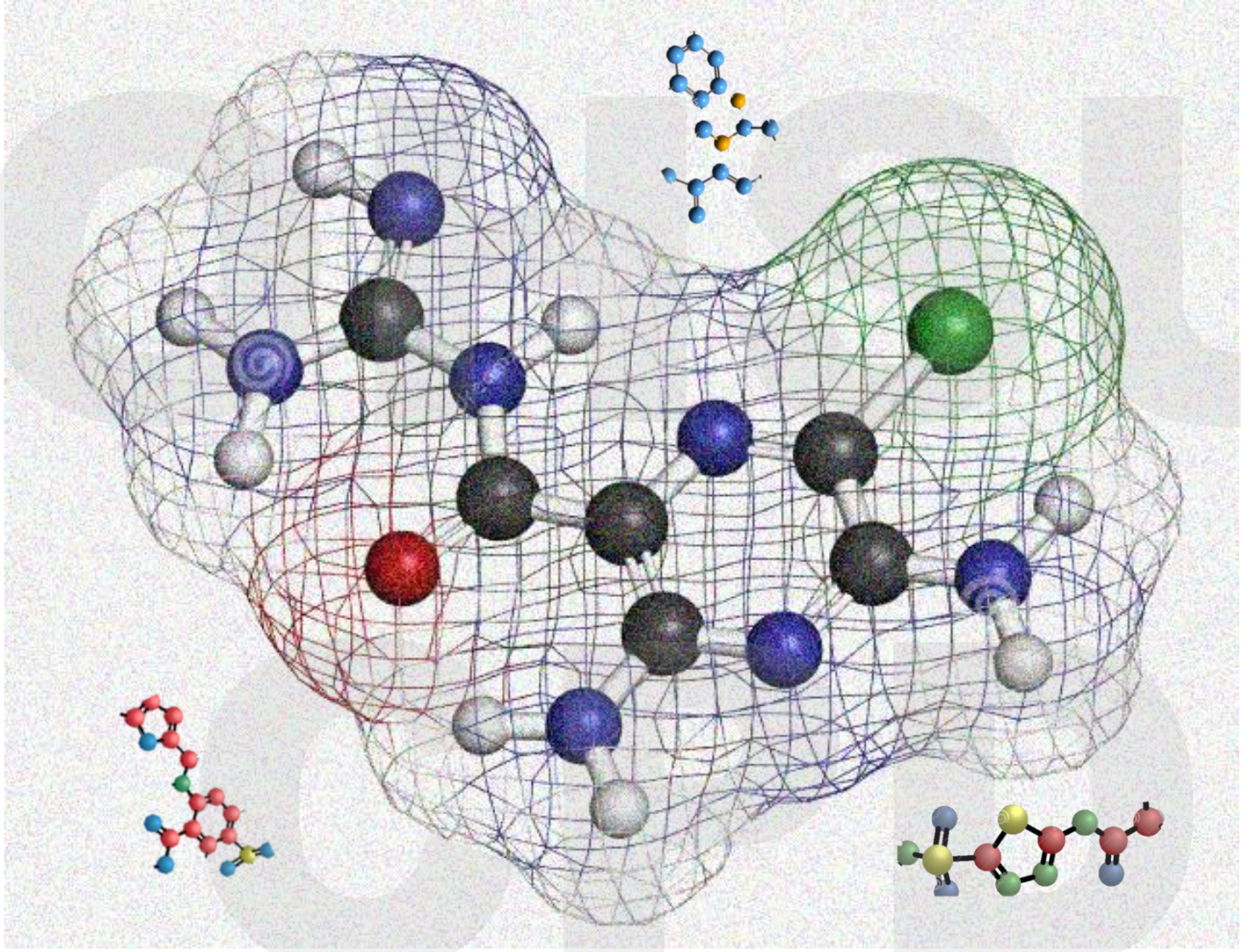
Mastering the Art of Diuretics: Tackling Congestion in Heart Failure



Carrie Puckett, DO
Heart Failure Cardiologist
Portland VA Medical Center

Harleen Singh, PharmD
Clinical Professor
UTEP School of Pharmacy

Session Objectives

- Understand the implications of congestion in HF
- Review the basic pharmacokinetic and pharmacodynamic differences between diuretics
- Evaluate the clinical trials in diuretics and decongestion
- Recognize diuretic resistance and strategies to optimize diuretic therapy
- Present clinical scenarios to illustrate dosing strategies to initiate and adjust diuretic therapy

Conflict of Interest Disclosure

We have no actual or potential conflicts of interest in relation to this program or presentation to disclose.

1974

- Diuretics
- Vasodilators
- Oxygen
- Inotropes

Ramirez and Abelmann NEJM 1974

2007

- Diuretics
- Vasodilators
- Inotropes

Fonarow GC et al. AHJ 2007

2023

- Loop diuretics
- Guideline directed medical therapy (GDMT)
- +/-vasodilators , inotropes

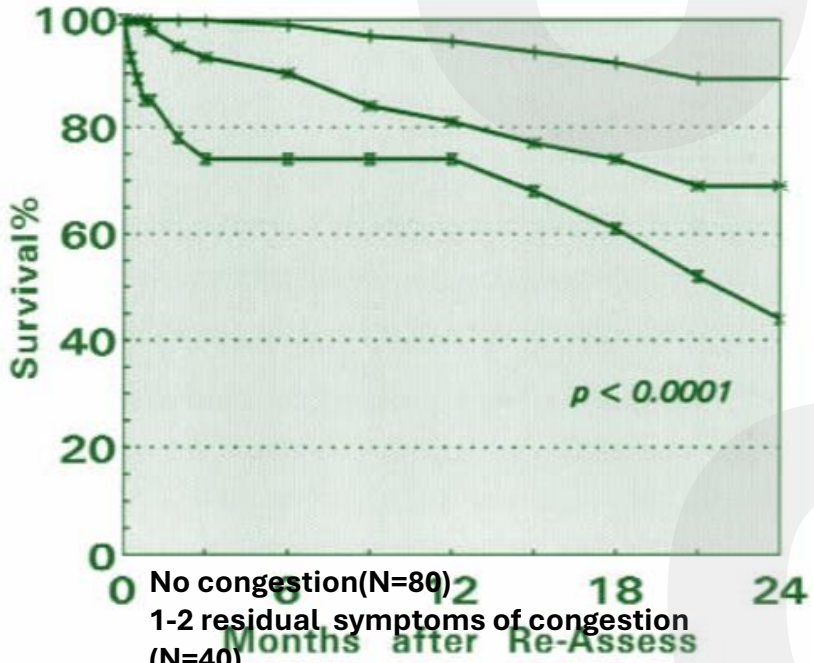
Adjunctive agents

- **Thiazides**
- **Acetazolamide**
- Tolvaptan

Heidenreich P, et al. J Card Fail 2022

Congestion Strong Predictor of Mortality

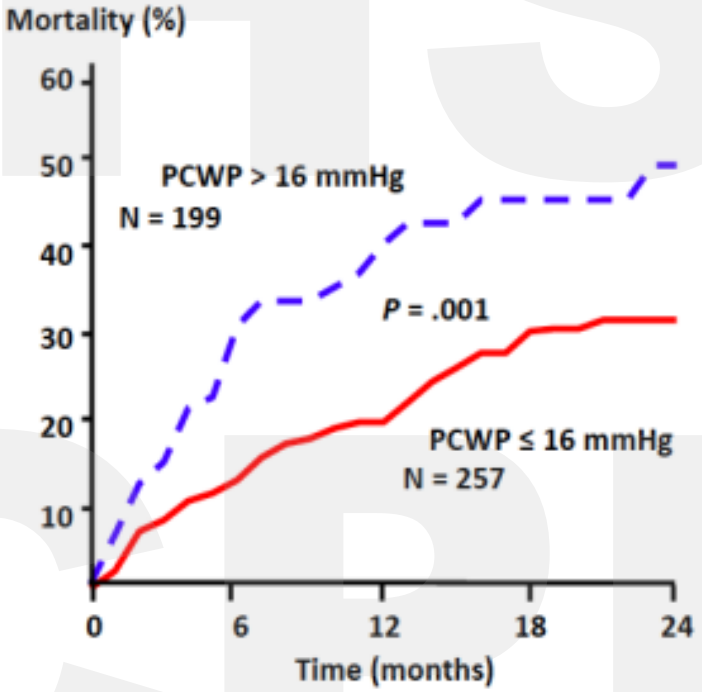
Signs & Symptoms



No congestion(N=80)
1-2 residual symptoms of congestion (N=40)
3-5 residual symptoms of congestion(N=26)

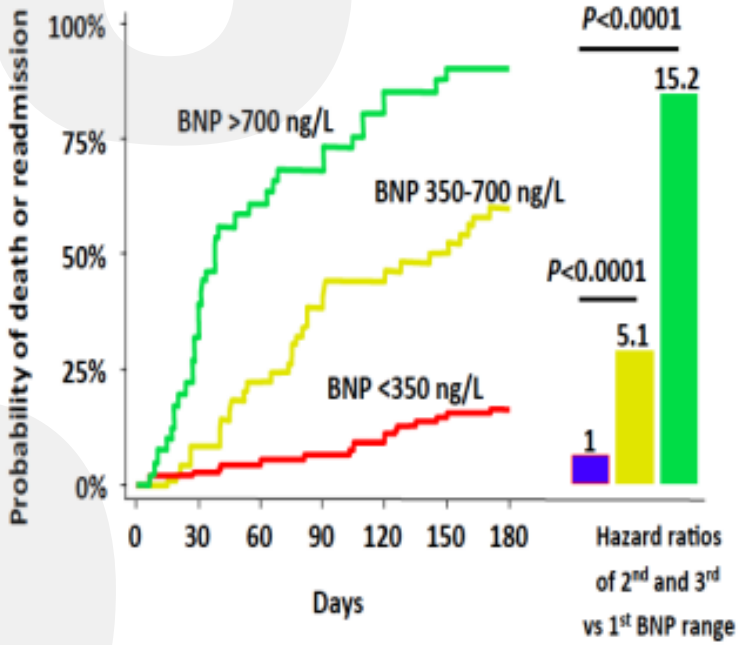
Lucas C, et al. *Am Heart J.* 2000;140:840-847.

PCWP



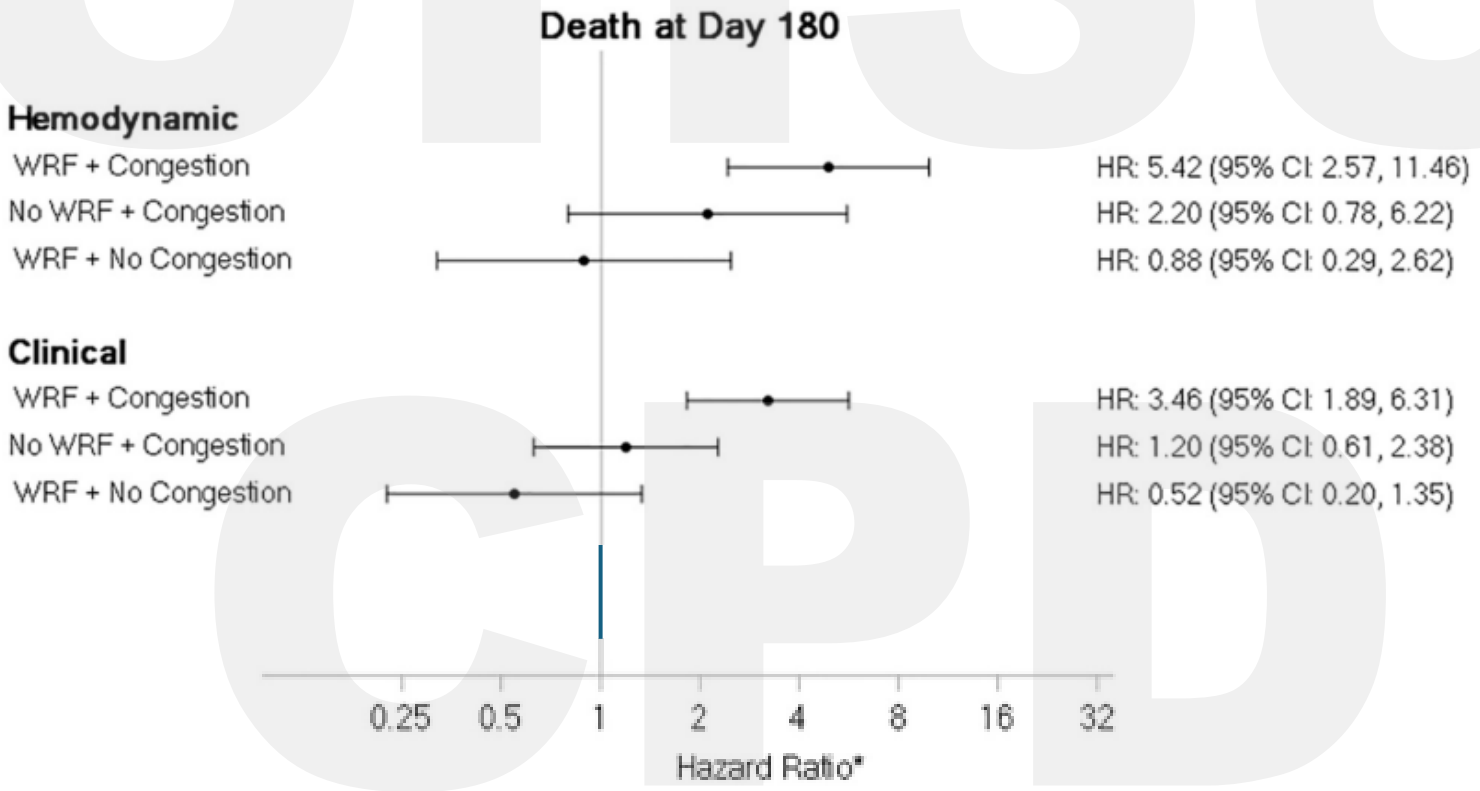
Fonarow GC, et al. *Circulation.* 1994;90(pt. 2):1-488.

BNP



Logeart D, et al. *J Am Coll Cardiol.* 2004;43:635-641

Worsening Renal failure (WRF) During Decongestion

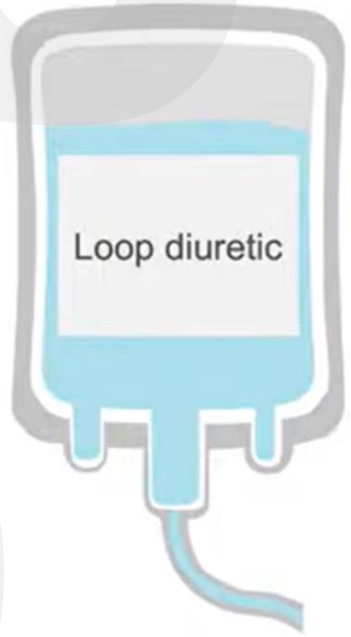


Fudim et al. Am Heart J. 2018; 204:163-173.

The Two Primary Targets in HF

GDMT Optimization

Decongestion



Cox ZL, et al. J Am Coll Cardiol. 2024;83(14):1295–1306.

Strategies to Decongest

2023 ESC Guidelines

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

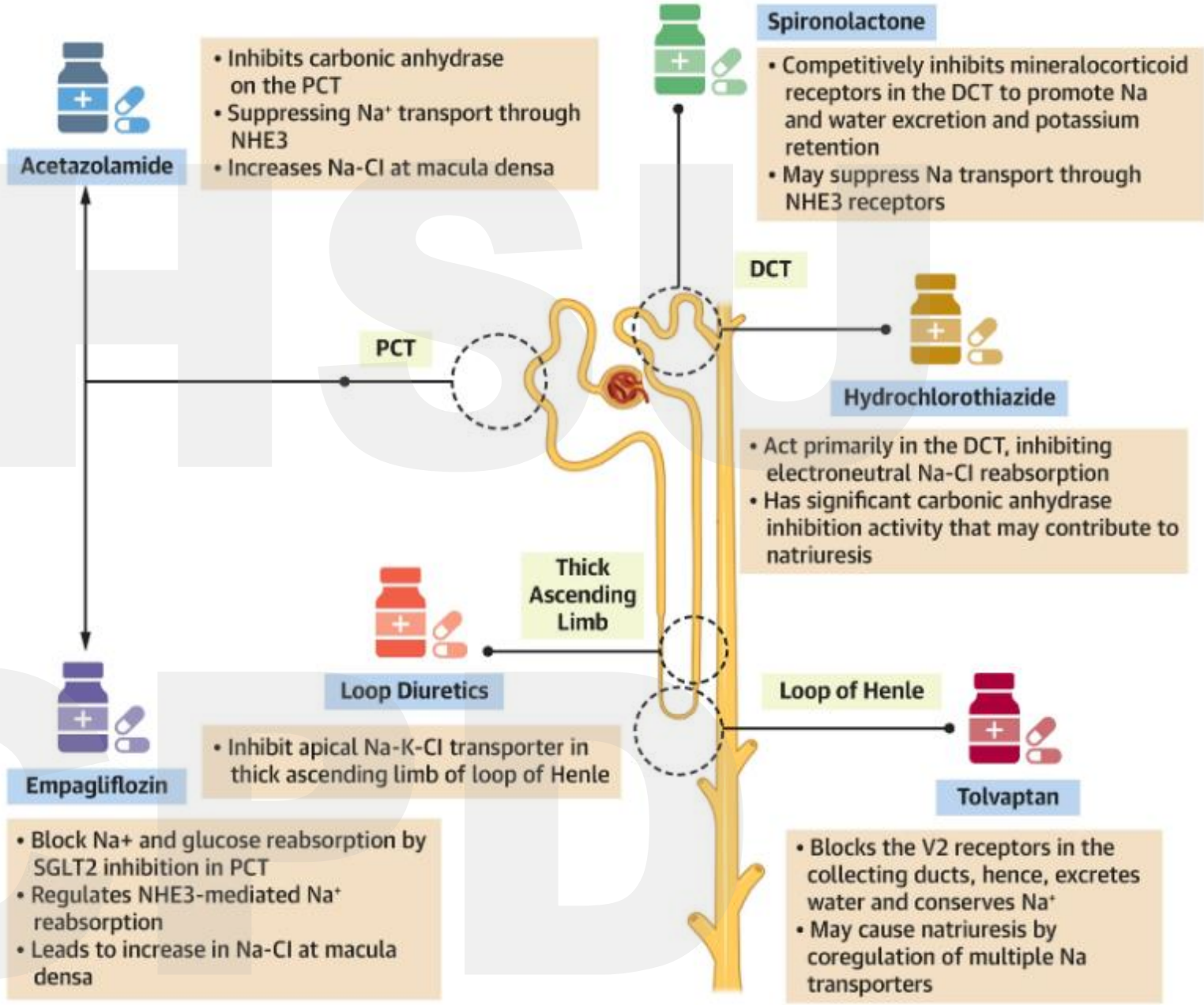
2022 AHA/ACC Guidelines

COR	LOE	Recommendations
1	B-NR	1. In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF.[1–5]
1	B-NR	2. For patients with HF and congestive symptoms, addition of a thiazide (eg, metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate- or high-dose loop diuretics to minimize electrolyte abnormalities.[6]

Eur Heart J. 2023;44(37):3627-3639. doi:10.1093/eurheartj/ehad195

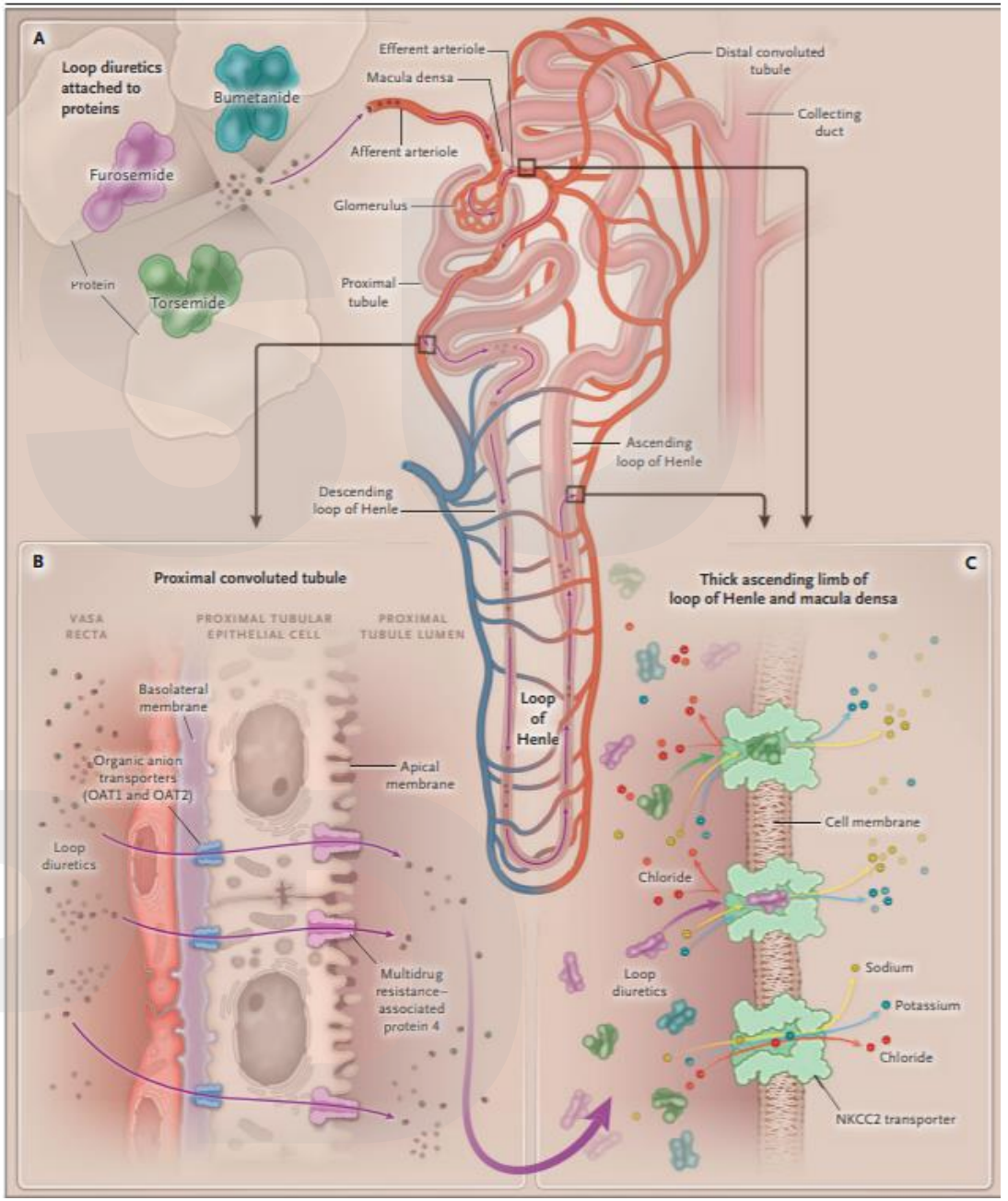
Circulation. 2022;146(24):e334-e482. doi:10.1161/CIR.0000000000001106

Diuretics MOA



Siddiqi, T, Packer, M, Ezekowitz, J. et al. Diuretic Potentiation Strategies in Acute Heart Failure. *J Am Coll Cardiol HF.* 2025 Jan, 13 (1) 14–27.

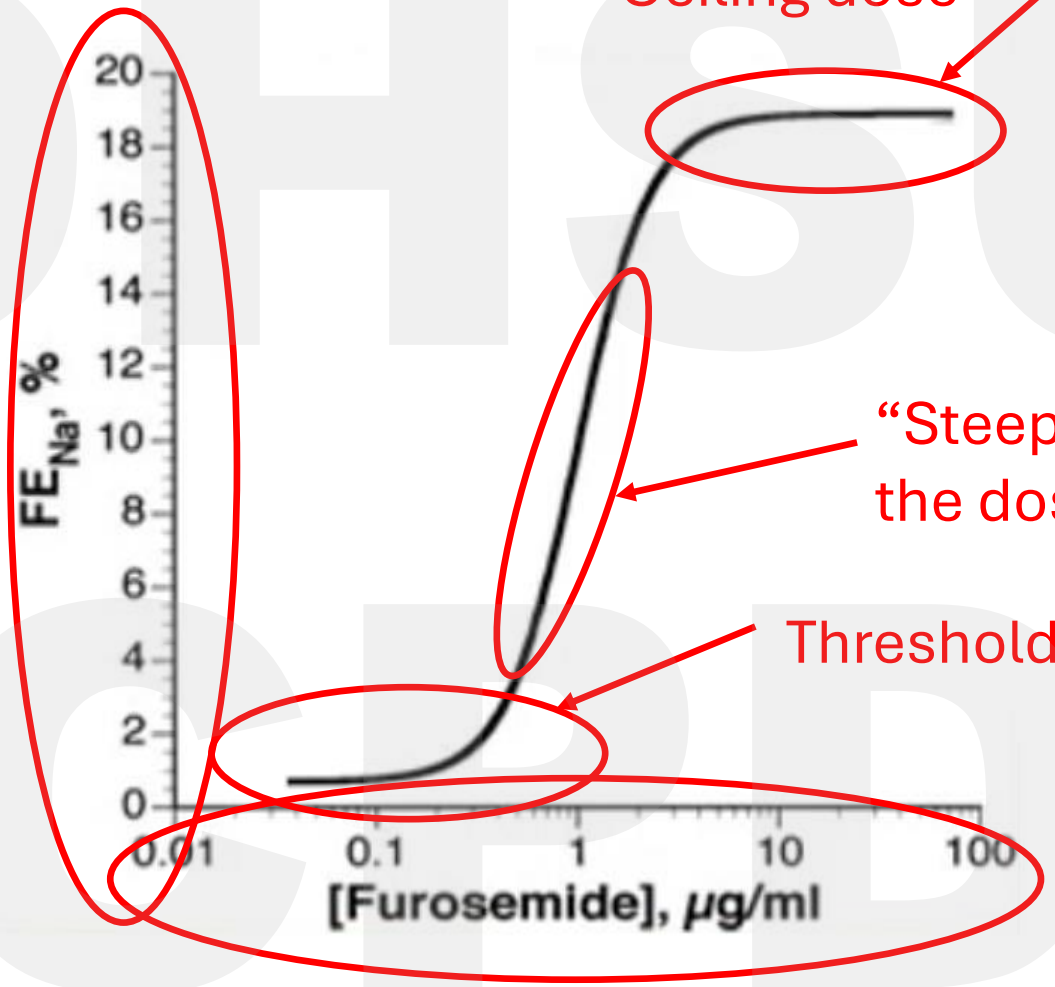
Loop Diuretics



Fekler and Ellison, NEJM 2017

Dose Response Curve for Loop Diuretics

Ceiling Dose Depends on:
- **Diuretic**
- **Disease**



Adapted from Ellison, Cardiology. 2001;96(3-4):132-43.

Pharmacokinetic Profiles: Loop Diuretics

	Bumetanide	Torsemide	Furosemide	Ethacrynic Acid
Derivative	Sulfonamide	Sulfonylurea	Sulfonamide	Phenoxyacetic acid
Potency (IV)	1	20	40	50
Oral Bioavailability (%)	~80% (80-100%)	~80% (80-100%)	~50% (10-100%)	~100%
Half-life (h)	~0.8	~3.5	~1.5	~2
Onset (min) **IV** **PO**	 2-3 30-60	 10 30-60	 5 30-60	 5 30
Duration (h)	4-6	6-16	6-8	10-12
Protein Binding	94-96%	>99%	92-99%	>90%
Metabolism	~38% Hepatic	~80% Hepatic	~35% Renal	33% Hepatic
Elimination	~62% Renal	~20% Renal	~65% Renal	67% Renal

Felker et.al JACC 2020:1178-95

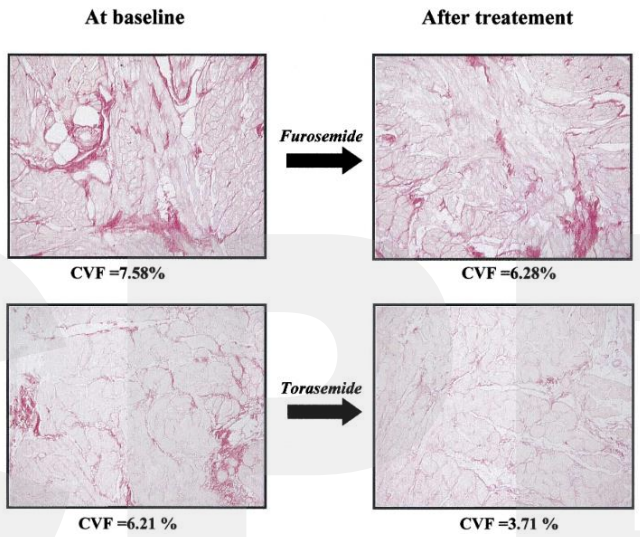
Transform-HF Background

Choosing between Furosemide and Torsemide

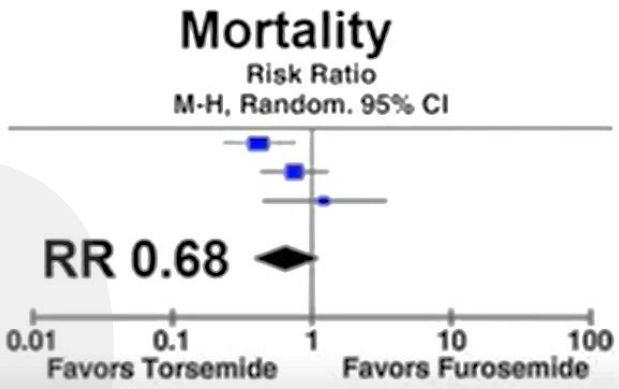
Longer half life & consistent bioavailability

	Furosemide	Torsemide
Duration	4-6 hours	6-8 hours
Half-life	1-2 hour	3-4 hours
Bioavailability	PO:50% IV:100%	PO & IV 80-90%
Oral:IV	2:1	1:1

Anti fibrotic myocardial effects



Potential outcome benefits



Lopez B et al. JACC 2007

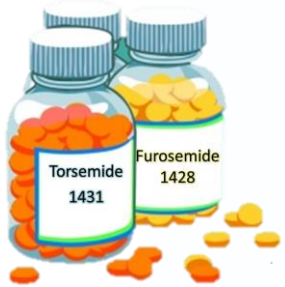
Lopez B et al. JACC 2004

Felker GM & Mentz RJ. JACC 2012

Bikdeli B, et al. JACC 2013

TRANSFORM-HF Design

2859 Total Patients



Hospitalized Patients with HF

Regardless of EF

1:1 Randomization

Torsemide | Furosemide

Open-Label
Dosing per Clinician

DCRI Call Center (30 d, 6 m, 12 m)
National Death Index

Event-Driven
721 Death Events

Primary Endpoint:

All-Cause Mortality

Secondary Endpoints:

All-cause Mortality + Hospitalization
Total Hospitalizations
Health-related Quality of Life (KCCQ)
Symptoms of Depression (PHQ-2)

60 hospitals across the United States

Greene SJ, Mentz RJ, *et al. JACC Heart Fail* 2021

ClinicalTrials.gov Identifier: NCT03296813

Baseline characteristics

Characteristic	No. (%)[a] Torsemide (n = 1431)	Furosemide (n = 1428)
Age, y		
Mean (SD)	64.0 (14.0)	65.0 (14.0)
Median (IQR)	65.0 (55.0-74.0)	65.5 (56.0-75.0)
Sex		
Female	498 (34.8)	557 (39.0)
Male	933 (65.2)	871 (61.0)
Race[b]		
American Indian or Alaska Native	9 (0.6)	3 (0.2)
Asian	37 (2.6)	26 (1.8)
Black or African American	474 (33.1)	494 (34.6)
Native Hawaiian or Pacific Islander	13 (0.9)	7 (0.5)
White	831 (58.1)	837 (58.6)
Other	44 (3.1)	35 (2.5)
Multiple	21 (1.5)	23 (1.6)
Not reported	2 (0.1)	3 (0.2)
Hispanic ethnicity, No./total (%)	75/1430 (5.2)	80/1425 (5.6)

LVEF <40% (65%)
Ischemic etiology 30%

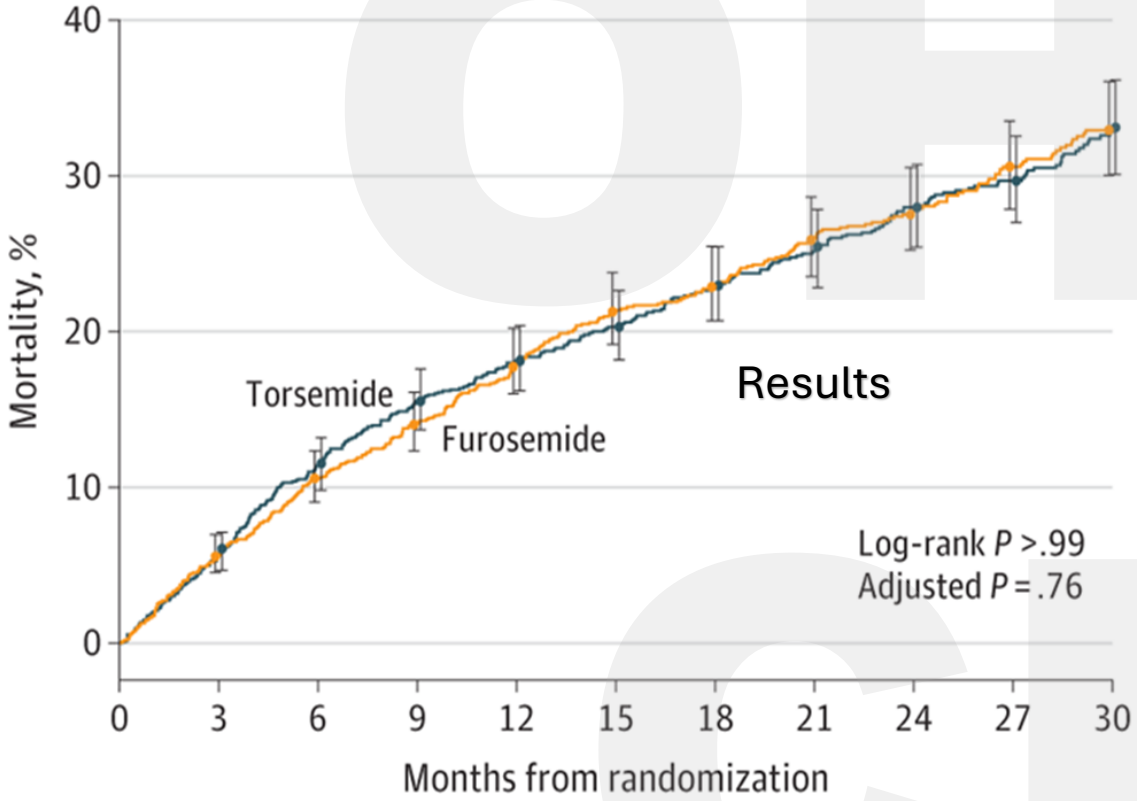
Mentez et al. JAMA. 2023;329(3):214-223

Baseline characteristics

Characteristic	Torsemide (n = 1431)	Furosemide (n = 1428)
Prior loop diuretic (before randomization)	964 (67.4)	956 (66.9)
Furosemide	754 (52.7)	778 (54.5)
Torsemide	146 (10.2)	113 (7.9)
Bumetanide	64 (4.5)	65 (4.6)
Devices and medications		
β-Blocker	1140 (79.7)	1106 (77.5)
ACE inhibitor or ARB	640 (44.7)	603 (42.2)
Mineralocorticoid receptor antagonist	524 (36.6)	498 (34.9)
Sacubitril-valsartan	264 (18.4)	272 (19.0)
SGLT2 inhibitor	89/1383 (6.4)	81/1375 (5.9)
Implantable cardioverter-defibrillator	293/1428 (20.5)	298/1426 (20.9)
Cardiac resynchronization therapy	119/1430 (8.3)	105/1427 (7.4)

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

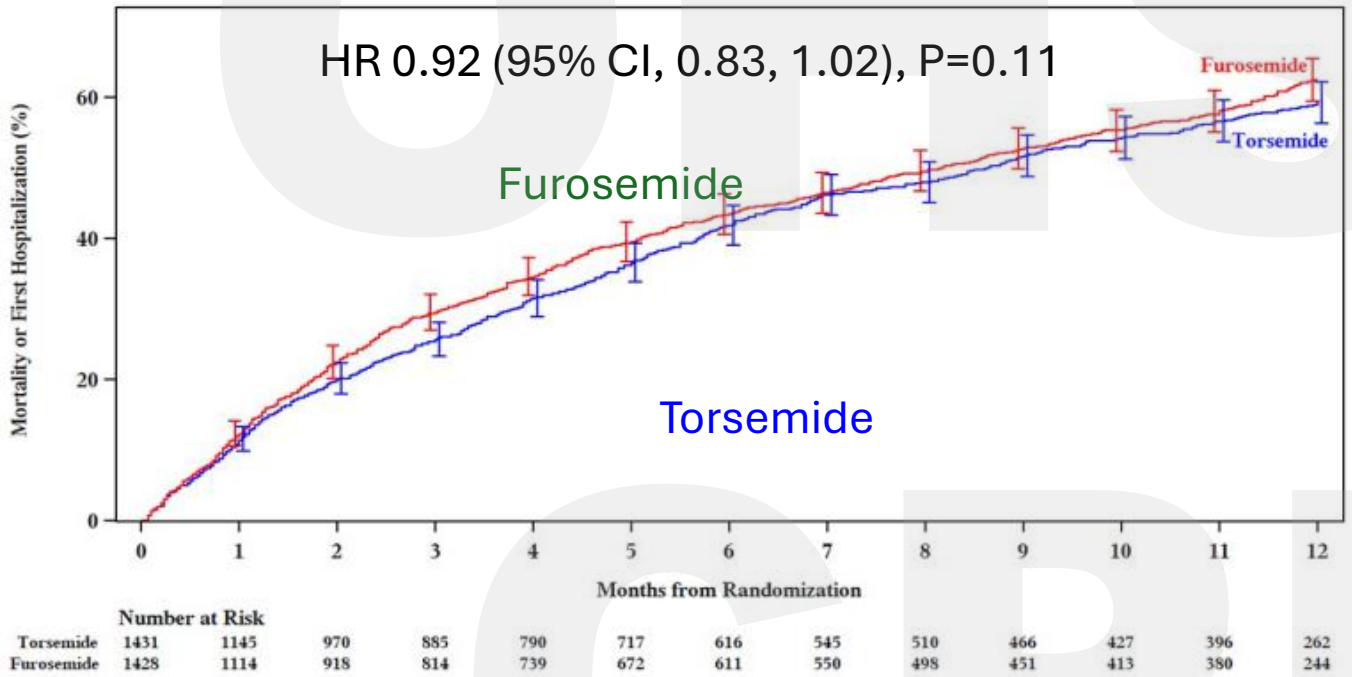
Results

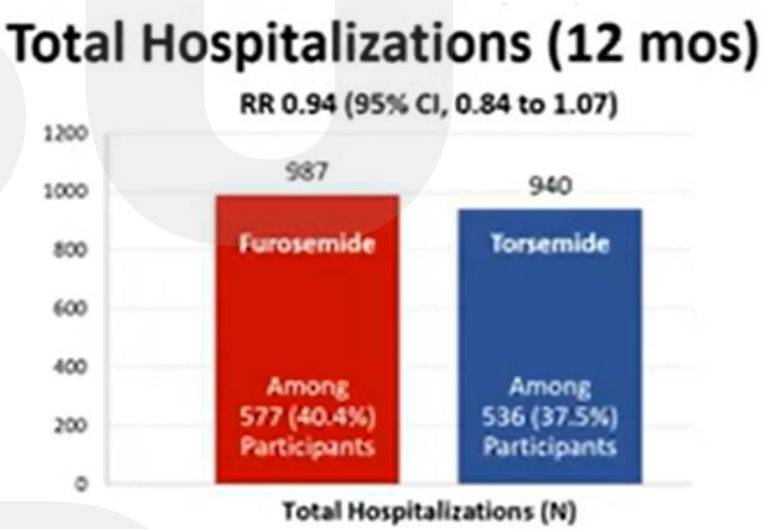


Torsemide n=1431	Furosemide n=1428	Results
373 (26.1)	374 (26.2)	P valve =**0.76**
17.0 events per 100 years	17.0 events per 100 years	Hazard ratio: 1.02(0.89 to 1.18)

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

All-cause Mortality or Hospitalizations (12months)





Similar effectiveness for both strategies for clinical outcomes of mortality and hospitalizations in ADHF.

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

Case 1

Mr. LY 52-year-old male patient who presents to the HF clinic with his wife for titration of his HF medications. He states he has been gaining weight at home and has noticed increased SOB since he was seen by his PCP 2 weeks ago. He reports an "increase in waistline and his abdomen feels full". He also states that his morning furosemide usually works well but has noticed less out put. He has gained 10 pounds since his last visit and today his weight is 314 lbs. He is not having rest symptoms. He follows a low sodium diet but notes increased thirst.

PMH and Medications

PMH: CAD, DM, Obesity, HLD, HFrEF (LVEF 25%, NYHA III)

Current Medications:
Furosemide 40 mg daily
Digoxin 0.125 mg daily
Losartan 50 mg twice daily
Metoprolol Succinate 150 mg daily
Spironolactone 25 mg daily
Aspirin 81 mg daily

Vitals

BP: 124/76 mmHg
HR: 75 bpm
SpO2: 94%

Weight:
314 lbs (Today);
304 lbs (Last visit);
Dry weight 300 lbs

Examination:
NAD, CTAB
JVP elevated 8 cm , +1 pedal edema
Abdomen slightly distended, no fluid wave

Laboratory Values:
Na+: 139 mEq/L
K+: 3.9 mEq/L
BUN: 16 mg/dL
SCr: 1.2 mg/dL (eGFR 58 mL/min/1.73m^2)
NT-proBNP: 341 pg/ml (Today); 256 pg/ml (Last visit)
Digoxin: 0.6 ng/mL

What is the Pertinent Information?

- Patient has been gaining weight at home
- Noticed his shortness of breath has gotten worse -Waist line has increased and belly is distended
- Patient has gained 10 pounds since last PCP visit
- Chem7 within normal limits, JVP elevated and
- 1+ pitting Pedal edema
- Medications to note: Furosemide and spironolactone

How should we Manage this Patient?

- Should we double the dose of furosemide?
- Should we dose furosemide twice daily?
- Should we switch to another loop diuretic?
- When do we follow up ?

Key Things to Determine if the Dose is Working

- When you take the medication, what do you notice regarding how much you urinate?
- How long does that effect last?
- Diuresis vs frequent urination?

Case 1

Mr. LY 52-year-old male patient who presents to the HF clinic with his wife for titration of his HF medications. He states he has been gaining weight at home and has noticed increased SOB since he was seen by his PCP 2 weeks ago. He reports an "increase in waistline and his abdomen feels full". He also states that his morning furosemide usually works well but has noticed less out put. He has gained 10 pounds since his last visit and today his weight is 314 lbs. He is not having rest symptoms. He follows a low sodium diet but notes increased thirst.

PMH and Medications

PMH: CAD, DM, Obesity, HLD, HFrEF (LVEF 25%, NYHA III)

Current Medications:
Furosemide 40 mg daily
Digoxin 0.125 mg daily
Losartan 50 mg twice daily
Metoprolol Succinate 150 mg daily
Spironolactone 25 mg daily
Aspirin 81 mg daily

Vitals

BP: 124/76 mmHg
HR: 75 bpm
SpO2: 94%

Weight:
314 lbs (Today);
304 lbs (Last visit);
Dry weight 300 lbs

Examination:
NAD, CTAB
JVP elevated 8 cm , +1 pedal edema
Abdomen slightly distended, no fluid wave

Laboratory Values:
Na+: 139 mEq/L
K+: 3.9 mEq/L
BUN: 16 mg/dL
SCr: 1.2 mg/dL (eGFR 58 mL/min/1.73m^2)
NT-proBNP: 341 pg/ml (Today); 256 pg/ml (Last visit)
Digoxin: 0.6 ng/mL

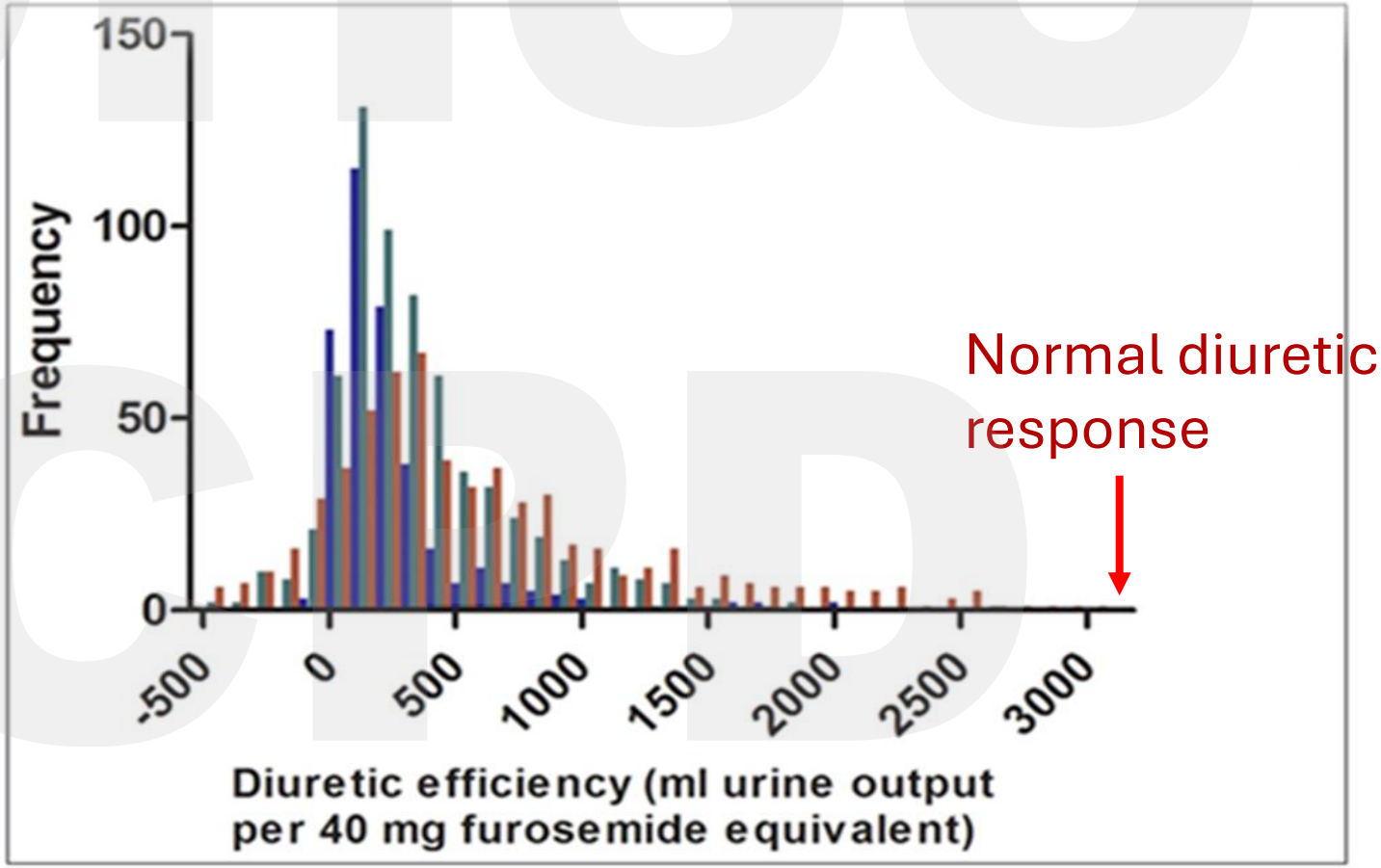
Back to the Patient

- Should we double the dose of furosemide?
- Should we dose furosemide twice daily?
- Should we switch to another loop diuretic?
- When do we follow up?

  - Loop diuretic was doubled to furosemide 80 daily and empagliflozin 12.5 daily added.
  - Repeat blood work obtained ~7 days after change with follow up on home data to guide next steps.
  - Attempting manage outpatient is reasonable based on clinical course.

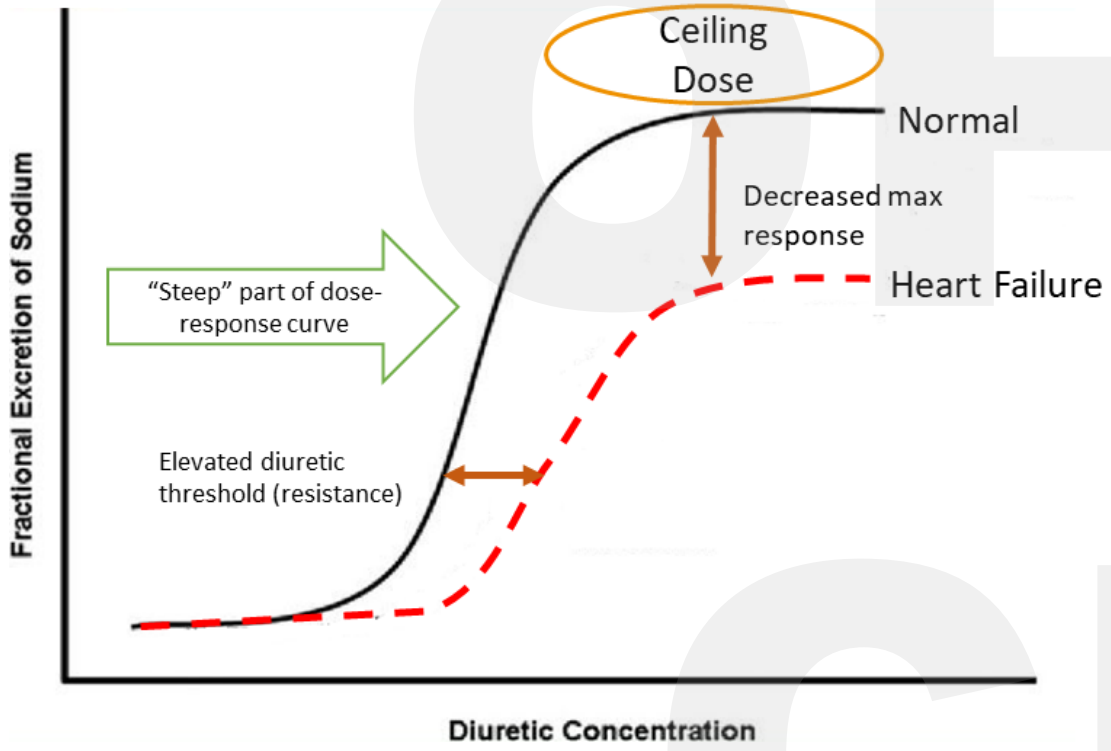
Diuretic Resistance

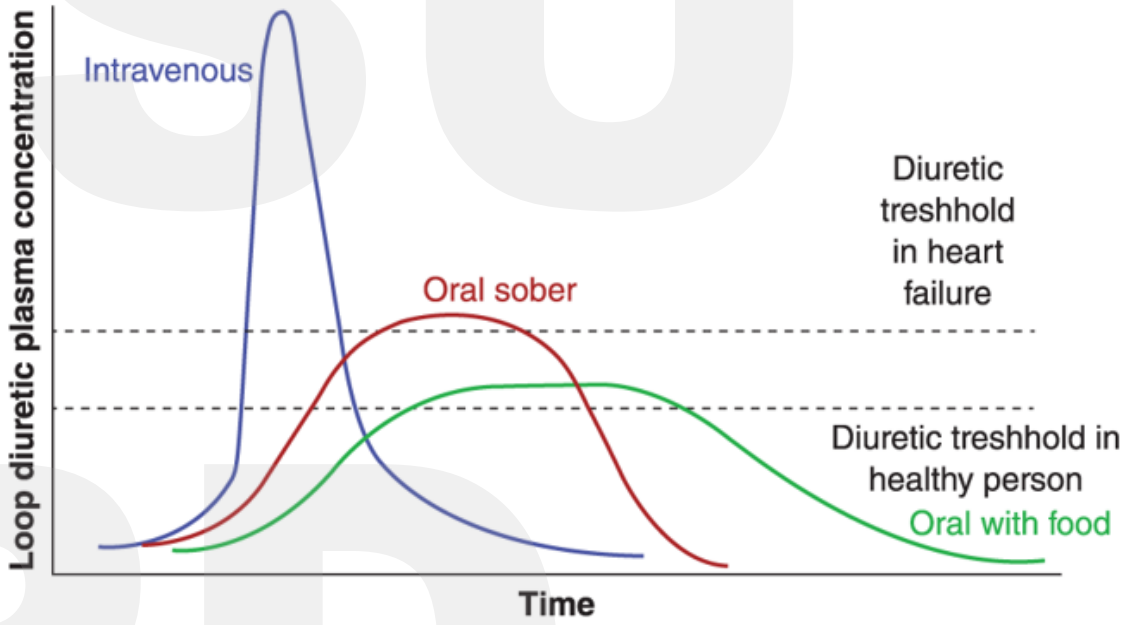
Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic.



Testani JM et al. Circ HF 2014

Dose-Response Relationship



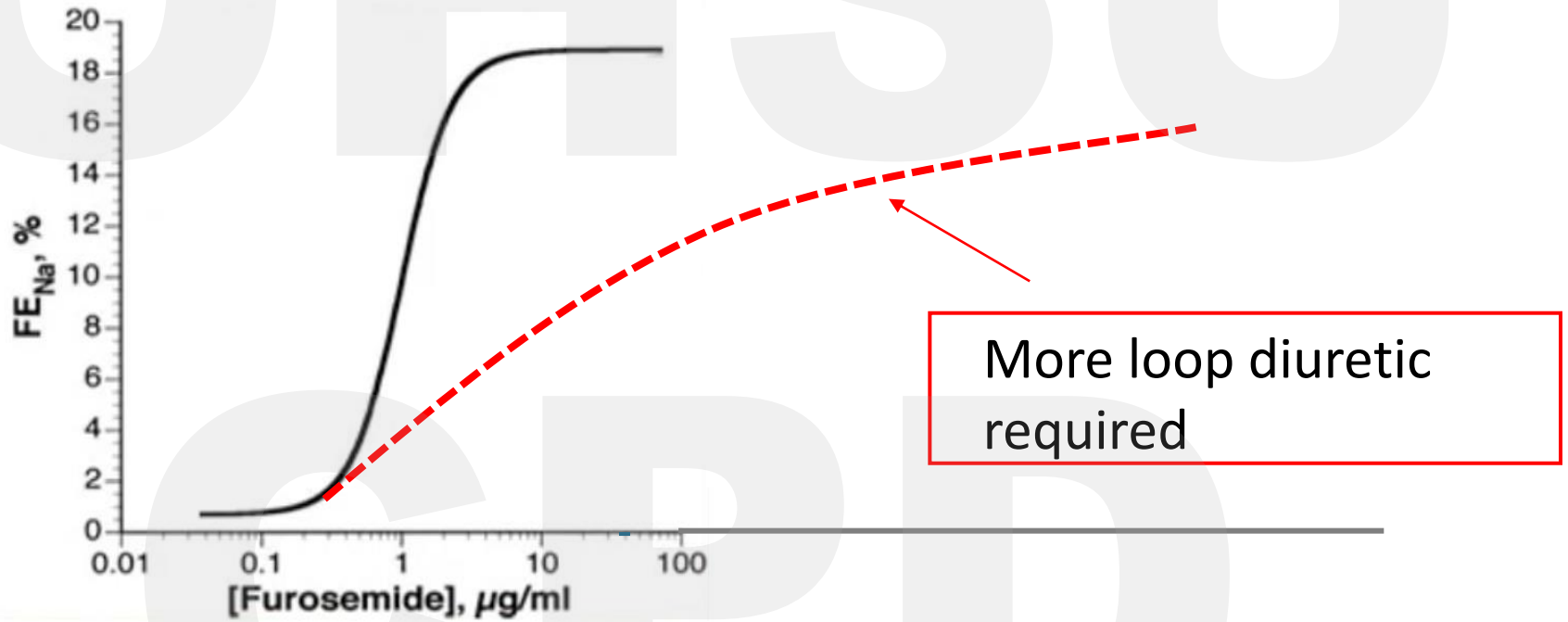


Patients with heart failure require a **higher** serum diuretic concentration to elicit the same diuretic response (diuretic resistance) and have **diminished** responses to ceiling doses of loop diuretics.

Future Cardiol. 2012;8:707-28
N Engl J Med. 20107;377(20):1964-1975

Journal of Cardiac Failure, Volume 20, Issue 8, 2014, 611–622

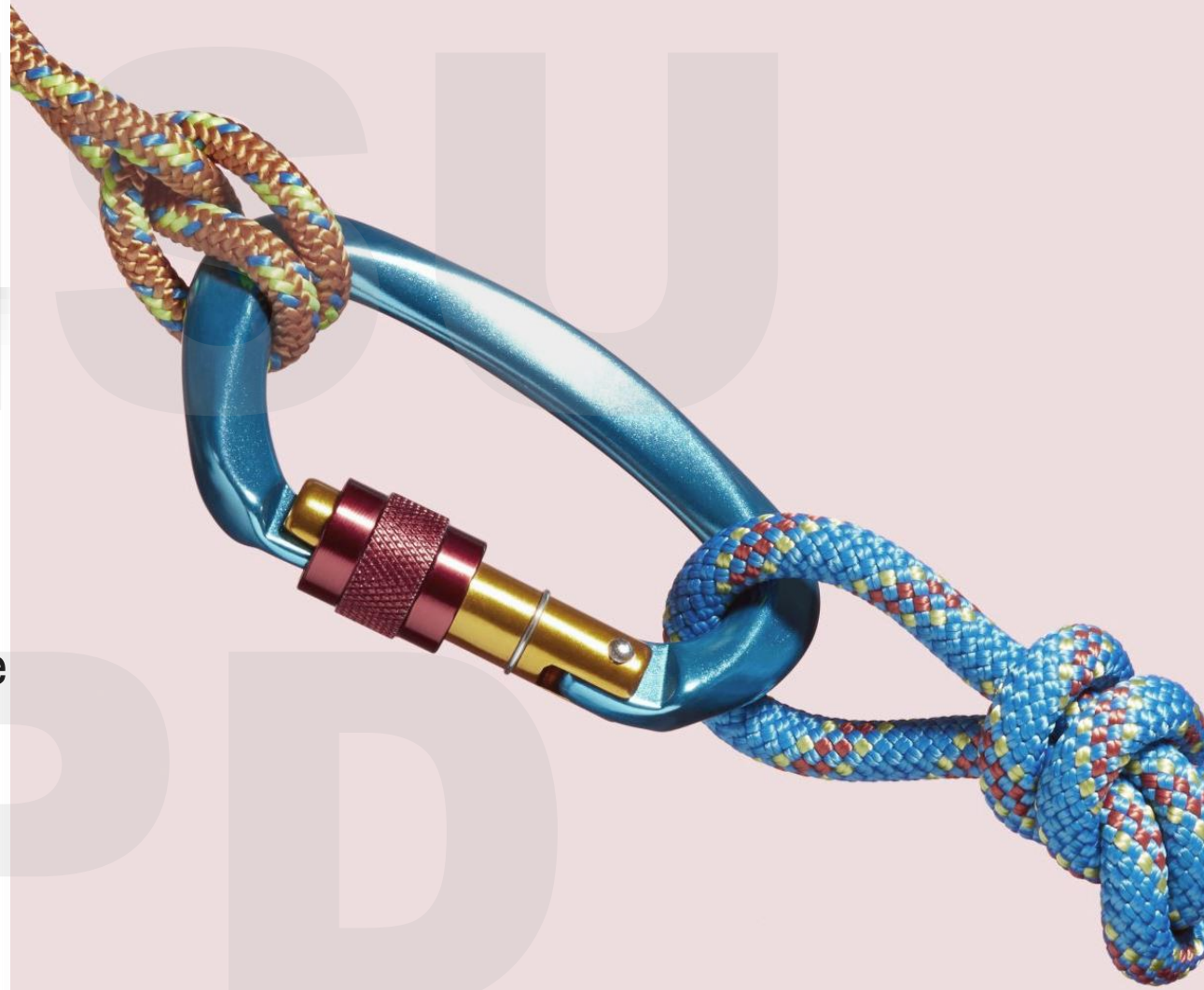
Diuretic Resistant Patient



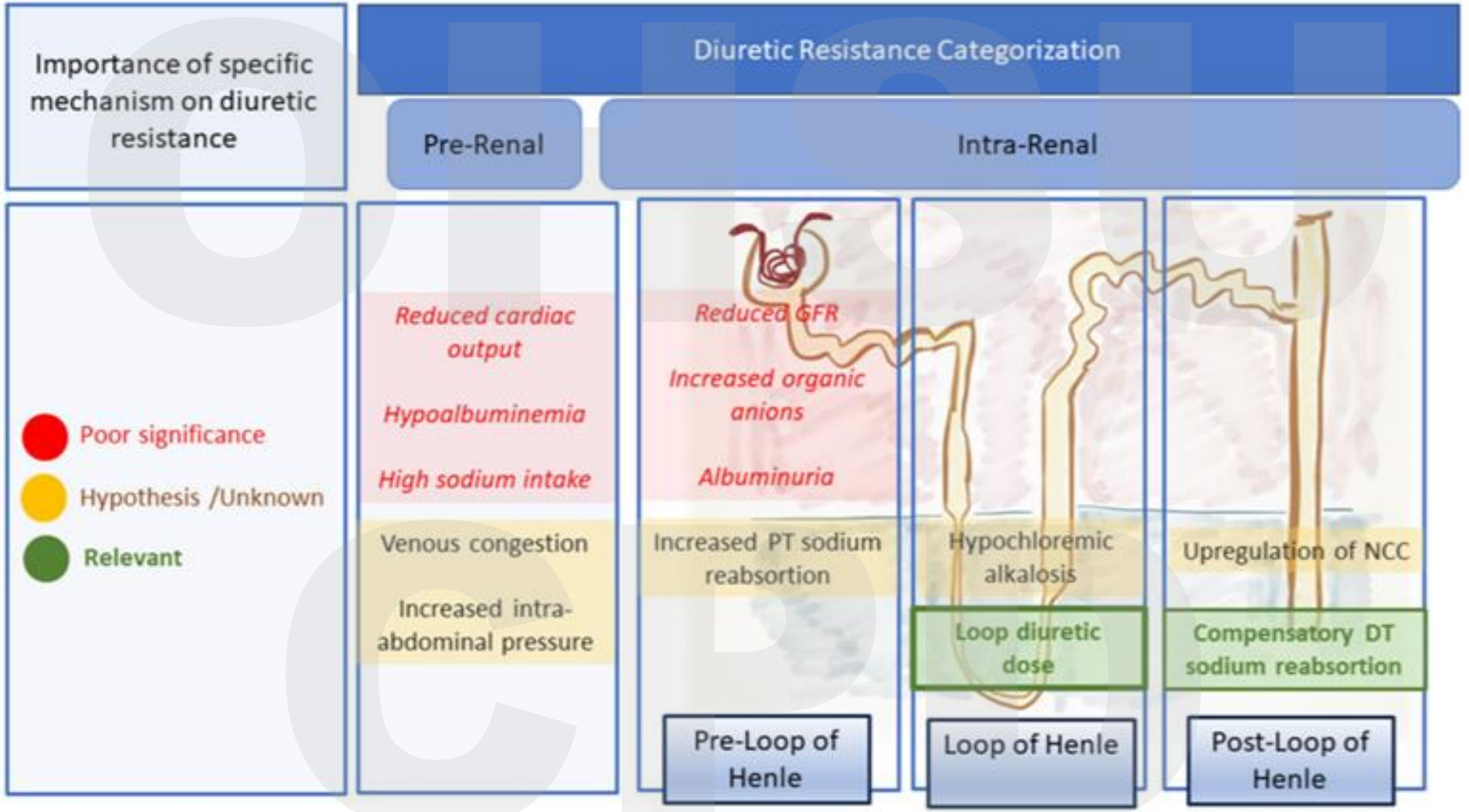
Adapted from Ellison, Cardiology. 2001;96(3-4):132-43.

What to do When we See Diuretic Resistance?

- Give more loop diuretic
- Give lots more loop diuretic
- Give lots more loop diuretic with thiazide
- Try random stuff that we don't really know if its safe or works



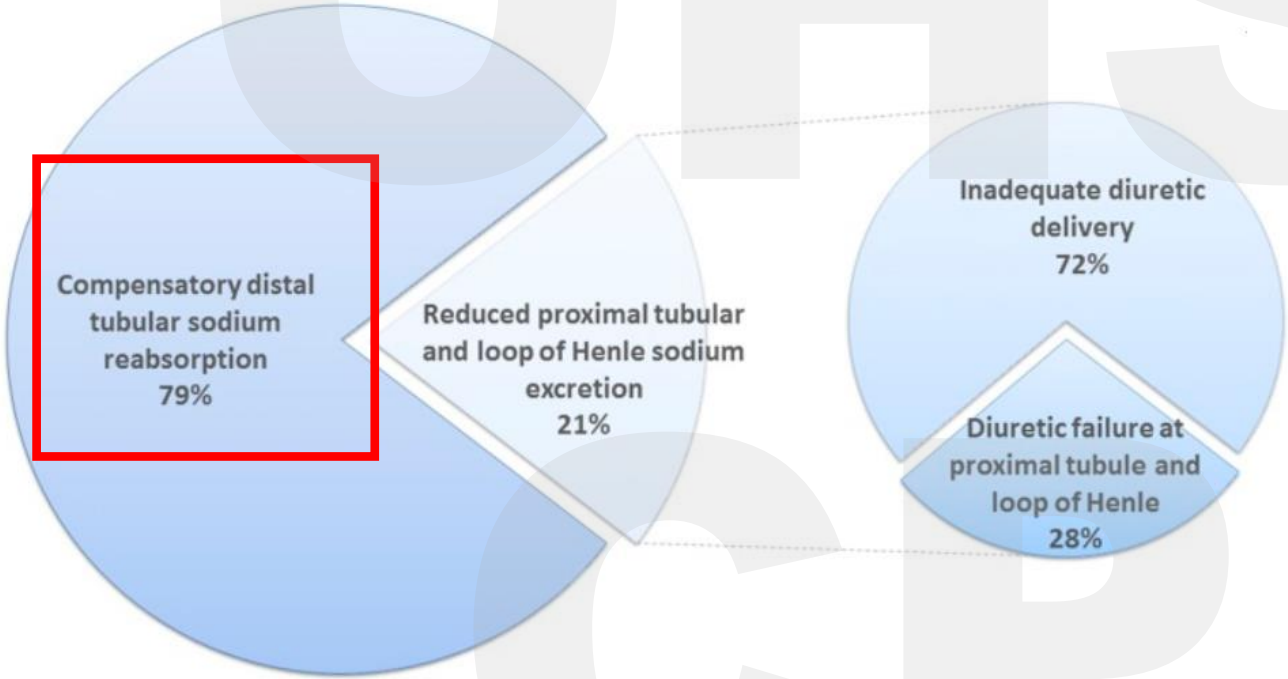
Mechanisms of Diuretic Resistance

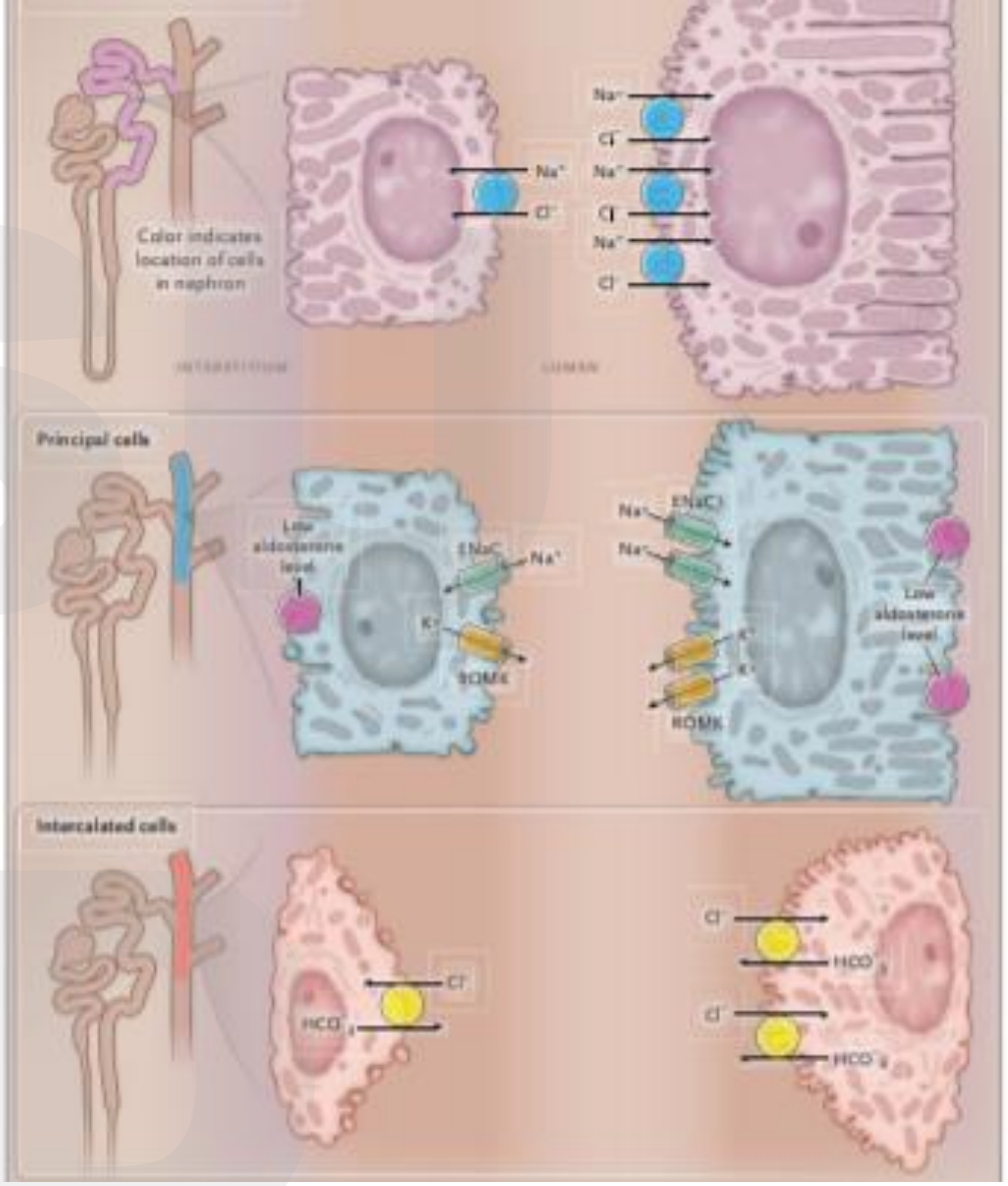


GFR: Glomerular Filtration Rate; PT: Proximal Tubule; NCC: sodium-chloride co-transporter; DT: Distal Tubule. Adapted from Felker et al. (9)

Trullàs JC et al. Current Heart Failure Reports 2024

Distal Nephron Hypertrophy





Fekler and Ellison, NEJM 2017

Testani et al. J Am Soc Nephrol 28: 3414–3424, 2017

Thiazide Diuretics for CDT

ACCF/AHA recommends the following for sequential nephron blockade:

Agent	Dose	Frequency
Metolazone	2.5 to 10 mg	Once daily
Hydrochlorothiazide	25 to 100 mg	Once or twice daily
Chlorothiazide (IV)	500 to 1000 mg	Once daily

Circulation. 2013; 128:e240-e327

Metolazone

- Metolazone is most prescribed for combination therapy in the U.S.
- Retains efficacy in advanced renal failure
- However, other thiazides at equipotent doses are likely to have the same synergistic effects

Pharmacokinetics	Metolazone	Hydrochlorothiazide
Bioavailability	65%	65-75%
Onset of action	~60 min	2 hours
Elimination half-life	6-20 hours	6-15 hours
Duration of action	>24 hours	6-12 hours

J Am Coll Cardiol. 2010;56(19):1527-34

Adjuvant Thiazides Safety

Observational data on thiazides found associations between thiazide use and:

- Deterioration in renal function
- Hyponatremia
- Severe hypokalemia
- Increased death/re-hospitalization

Evidence with thiazide diuretics

Table 2 Summary of Reviewed Studies in Heart Failure Patients

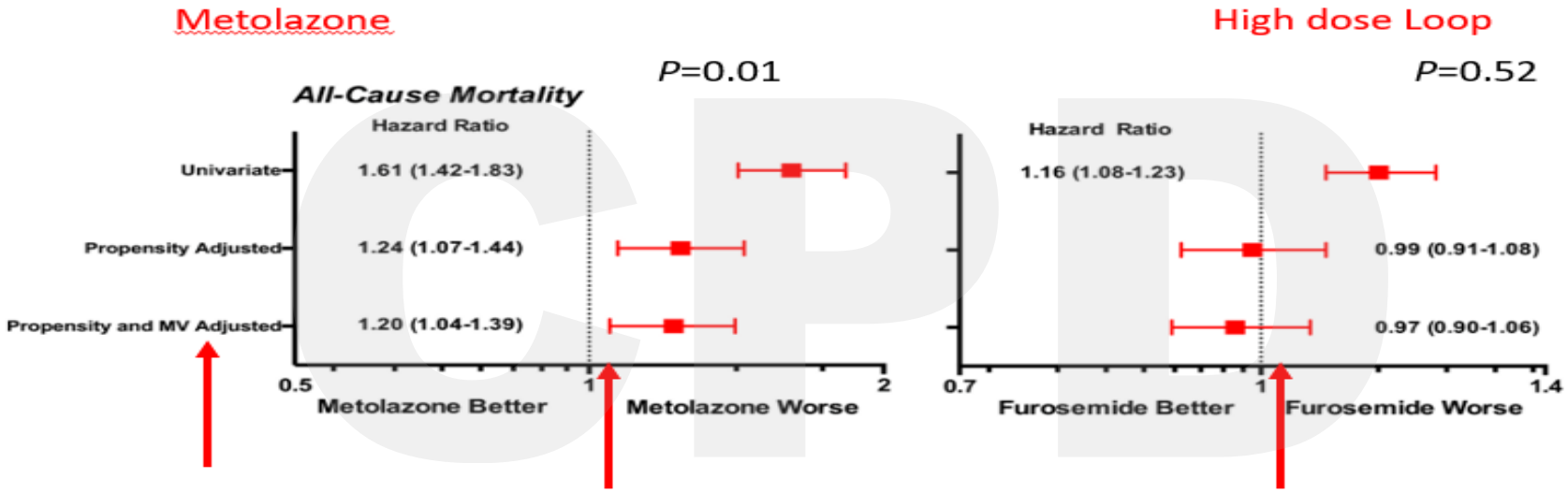
First Author (Ref. #), Year	Patients	Design	TD Dose	LD Dose	Benefits	Adverse Events
Robson et al. (18), 1964	1 CHF	Observational	HCTZ 100 mg IV	FSM 50–100 mg IV + 1–5 mg/min	None	Not reported
Dettli and Spring (17), 1966	18 mixed edematous	Observational	HCTZ 200 mg	FSM 30–240 mg/day	Improved diuresis, similar to 4× higher FSM dose	Hypochloremic alkalosis + hypokalemia
Olesen et al. (19), 1970	24 CHF	active-control	QEZ 50–100 mg/day	FSM 40–80 mg/day	Superior diuresis to doubled FSM dose in mild CHF only	Hypokalemia (−0.5 mEq/l) bigeminy
Olesen et al. (20), 1971a	12 CHF	Randomized active-control	QEZ 50 mg/day	FSM 40 mg/day	Doubled UNa, mean weight loss 0.5 kg/day	Not reported
Olesen et al. (21), 1971b	24 CHF	Randomized active-control	QEZ 50 mg/day BDFZ 5 mg/day	FSM 80 mg BID	Doubled UNa, weight loss ~0.7–0.8 kg/day	Hypokalemia (−0.3 mEq/l)
Beck and Asscher (22), 1971	1 CHF		MTZ 5 mg/day	FSM 80 mg/day	Clearance of edema	Hypokalemia
Gunstone et al. (23), 1971	13 CHF	Observational	MTZ 2.5–10 mg/day		in >2/3 overall	Azotemia in most patients, hypokalemia
Asscher (24), 1974	4 CHF	Observational	MTZ 5 mg/day			Hypokalemia
Sigurd et al. (25), 1975	18 CHF	Randomized active-control	BDFZ 5 mg/day		0.8 kg/day	Hypokalemia (−0.45 mEq/l)
Epstein et al. (26), 1977	1 CHF	Observational	MTZ ≥5 mg/day		ly reduced GFR	Hypokalemia
Ram and Reichgott (27), 1977	5 CHF + CKD	Observational	MTZ 5 mg/day			Hypokalemia (−0.3 mEq/l), creatinine ↑ 28%
Sigurd and Olesen (28), 1978	18 CHF	Randomized active-control	BDFZ 5 mg/day		hinophylline	None
Furrer et al. (29), 1980	11 ADHF		MTZ ≥2.5 mg/day			Excessive/uncontrolled diuresis
Ghose and Gupta (30), 1981	3 CHF	Observational	MTZ 2.5–5 mg/day			Not reported
Allen et al. (31), 1981	4 CHF	Observational	MTZ 5 mg/day			Hypokalemia
Bamford (32), 1981	1 CHF	Observational	MTZ 5 mg QOD			Not reported
Grosskopf et al. (33), 1986	10 ADHF	Randomized active-control	MTZ 5 mg/day	FSM 120 mg/day IV	Improved diuresis, weight loss ~2.2 kg over 3 days	Hypokalemia (−0.4 mEq/l)
Gage et al. (34), 1986	14 CHF	Observational	MTZ 2.5 mg QOD up to 15 mg/week	FSM 160 mg/day	Mean 4.4 kg weight loss + edema clearance	Hypokalemia (−0.6 mEq/l), BUN ↑ ~33%
Aravot et al. (35), 1989	12 CHF	Observational	MTZ 2.5–5 mg 2×/week	FSM 160 mg/day	Eliminated need for IV diuresis	Not reported
Friendland and Ledingham (36), 1989	1 ADHF	Observational	MTZ 5–10 mg/day	FSM 240 mg/day IV	16 kg weight loss	Not reported
Klyingi et al. (37), 1990	10 CHF	Observational	BDFZ 10 mg/day	FSM 200–400 mg/day IV	Mean weight loss 7.7 kg	Hypokalemia (<2.9 mEq/l) in 20%
Channer et al. (38), 1990	17 ADHF	Observational	MTZ 1.25–10 mg/day	FSM 250–500 mg/day PO	Responders (71%) had mean 8.3 kg weight loss + d/c home	Hypokalemia, creatinine ↑ 25%
Kröger et al. (39), 1991	10 ADHF	Observational	MTZ 2.5–5 mg/day	FSM 80–500 mg/day	Mean 8.9 kg weight loss	Hyponatremia, hypokalemia
Dormans and Gerlag (40), 1993	8 CHF	Observational	HCTZ 25–100 mg/day	FSM 500– 4000 mg/day	Doubled UNa, mean 1.3 kg/day weight loss	Creatinine ↑ 50%, ClCr ↓ 33%, hypokalemia
Channer et al. (41), 1994	40 ADHF	Randomized active-control	MTZ 10 mg/day BDFZ 10 mg/day	FSM 80 mg IV BID	5–5.6 kg mean weight loss, hospital d/c in 90%	Hypokalemia (<3.5 mEq/l) in 65%
Mouallem et al. (42), 1995	32 ADHF		CTZ 500 mg/day	FSM 160–320 mg/day	Mean 4.8 kg weight loss, clearance of edema	Hypokalemia (−0.4 mEq/l)
Dormans and Gerlag (43), 1996	20 ADHF	Observational	HCTZ 25–100 mg/day	FSM 250–4000 mg/day	Doubled UNa, mean weight loss 6.7 kg, d/c home in 70%	Hypokalemia (−0.8 mEq/l), persistent dehydration
Vanky et al. (44), 1997	20 post-CABG	Observational	HCTZ 50 mg/day + amiloride 5 mg/day	FSM 80 mg/day	Mean 2.3 kg weight loss after one dose	None
Rosenberg et al. (45), 2005	21 CHF	Observational	MTZ 2.5–5 mg/day	FSM mean 260 mg/day	Mean 2 kg weight loss + 10/8 mm Hg	BUN ↑ 58%, hypokalemia (−0.8 mEq/l),

Severe hypokalemia
Commonly noted

Entzer et al. JACC Vol. 56, No. 19, 2010

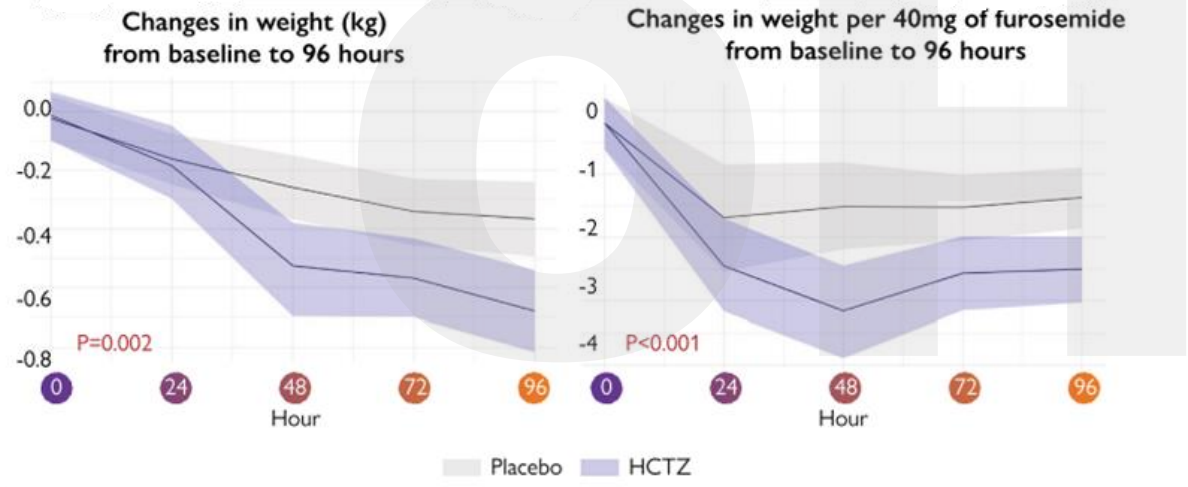
Adjuvant Metolazone or High-Dose Loop Diuretics

- 13,898 admissions across 3 hospitals in the Yale health system with common EMR
- propensity-adjusted multivariate analysis of all-cause mortality.

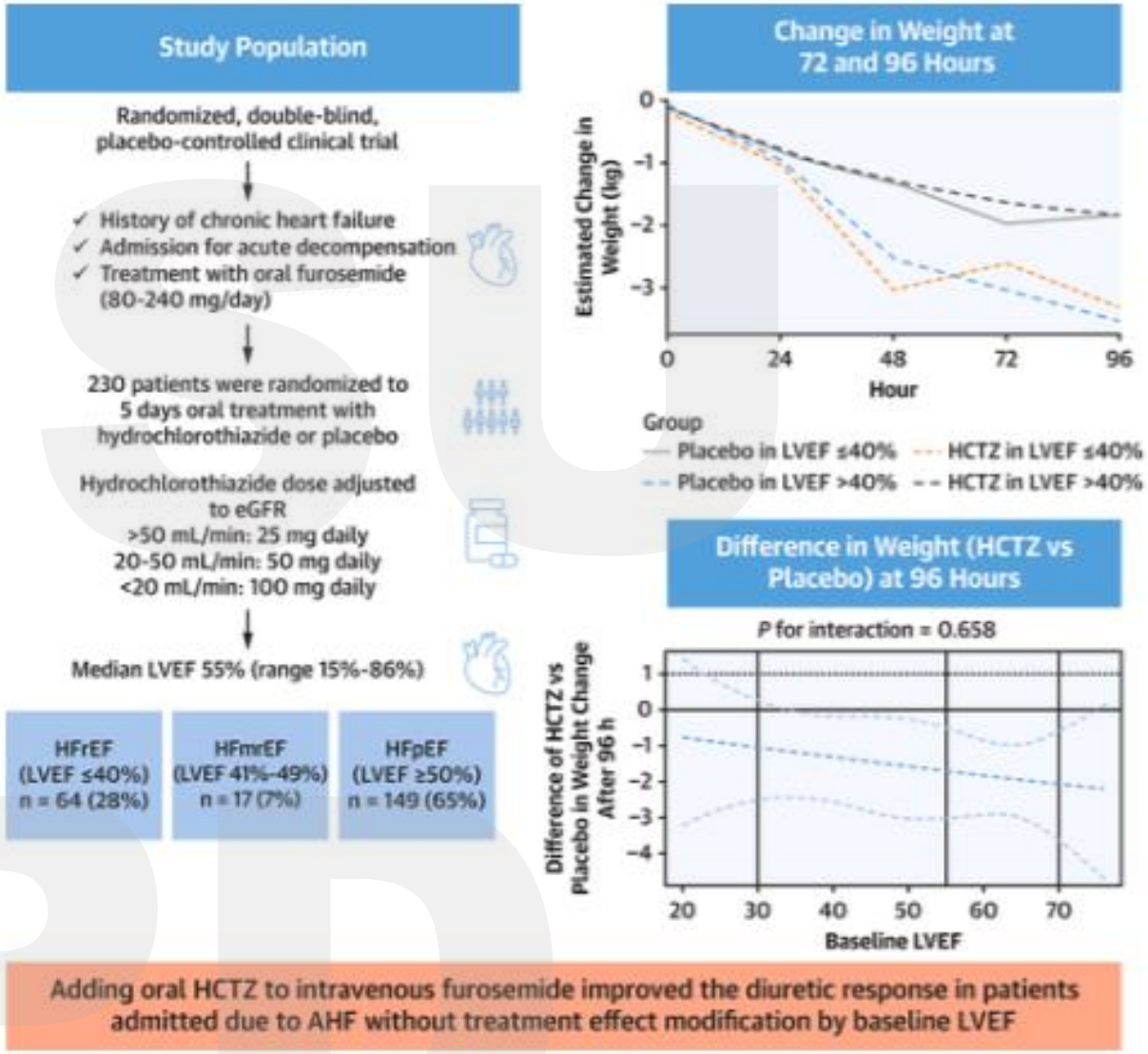


Brisco-Bacik, JAHA 2018

CLOROTIC TRIAL



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



More weight loss
No difference in Dyspnea
Inc WRF

Trullàs JC et al. EHJ (2023) 44, 411–421
Sánchez-Marteles et al. JACC HF 2024

Thiazide Bottom line

- Thiazide diuretics as adjuvants work great
- It doesn’t matter which one you use
  - But most of us still use Metolazone
- Max out the loop diuretic first
  - Probably safer

Other Combination Therapies

Acetazolamide

-Rationale: 55-70% Na reabsorbed in Proximal convoluted tubule

Aldosterone antagonist

- Rationale: blocking excess sodium reabsorption in collecting duct due to secondary hyperaldosteronism

-Higher doses have natriuretic effects compared to lower doses

-Can be considered in combination with loop plus thiazides

SGLT2 inhibitors

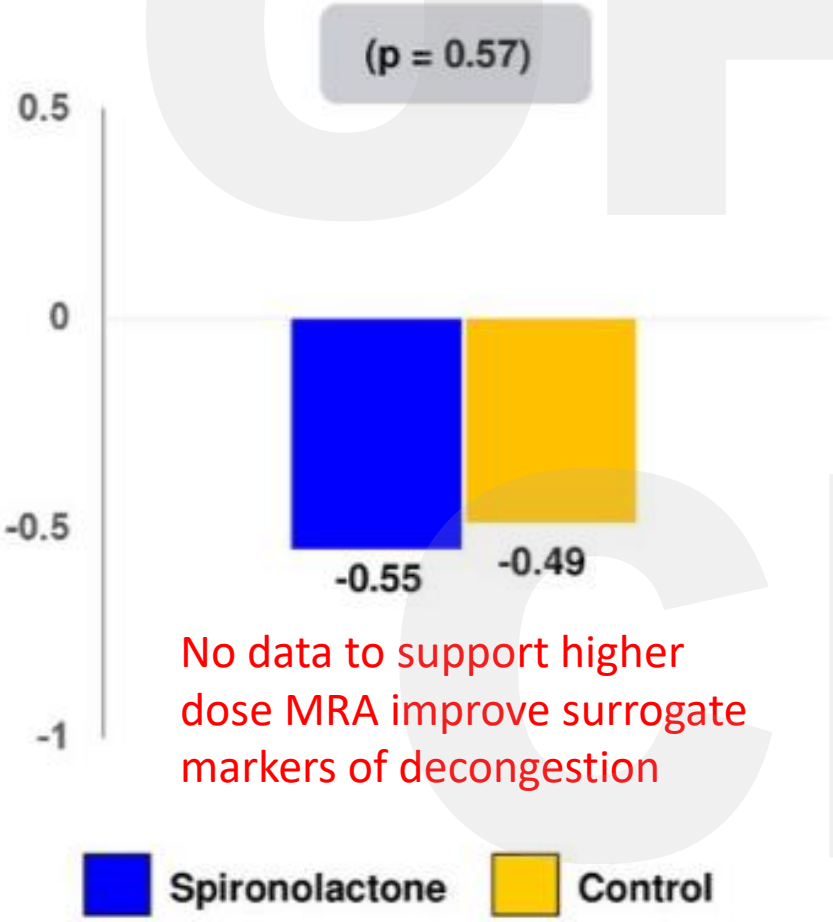
-Inhibiting the absorption of sodium and glucose from the proximal tubule

-Transiently enhance urinary sodium excretion and urinary volume

ATHENA-HF Trial

Trial design: Patients with acute heart failure were randomized to spironolactone 100 mg daily (n = 182) vs. placebo/low-dose spironolactone (n = 178).

N= 360
HFrEF or
HFpEF



No data to support higher dose MRA improve surrogate markers of decongestion

Results

- Primary outcome, log change in NT-proBNP at 96 hours: -0.55 in the spironolactone group vs. -0.49 in the placebo group (p = 0.57)
- Net urine output: 6.1 L in the spironolactone group vs. 5.6 L in the placebo group (p = 0.57)

Conclusions

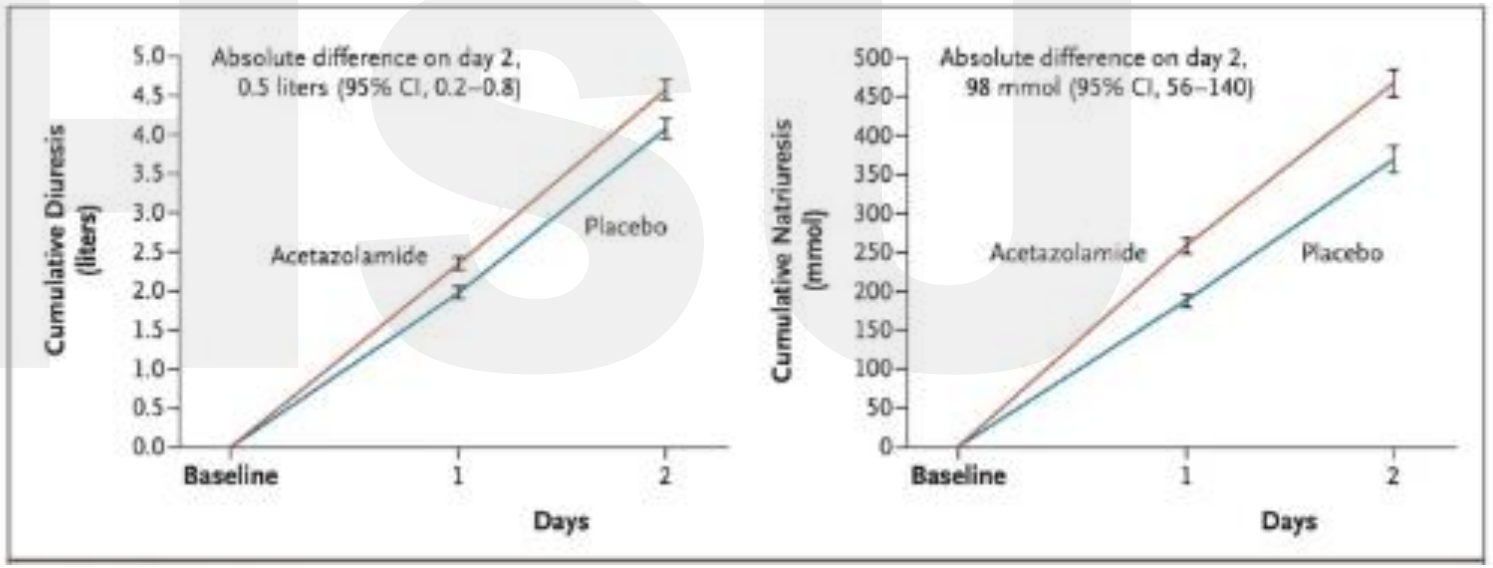
- Among patients admitted with acute heart failure, high-dose spironolactone was not effective at reducing NT-proBNP levels
- Secondary outcomes, including urine output, were also similar between treatment groups

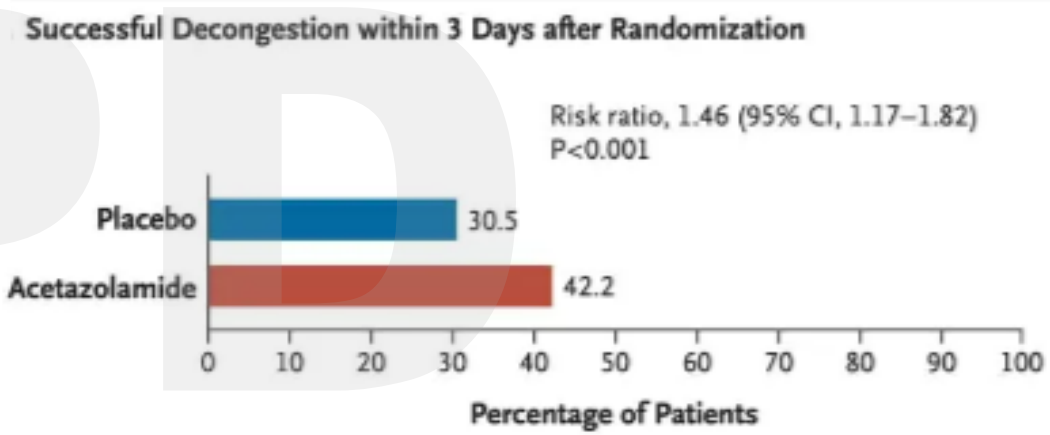
Butler J, et al. JAMA Cardiol 2017

Acetazolamide plus furosemide for decongestion of Heart Failure (ADVOR trial)

500 mg IV acetazolamide daily versus placebo x 3 days (both in combination with furosemide)

N-519
HFrEF vs HFpEF
Exclusion: SGLT2i , eGFR<20ml/min

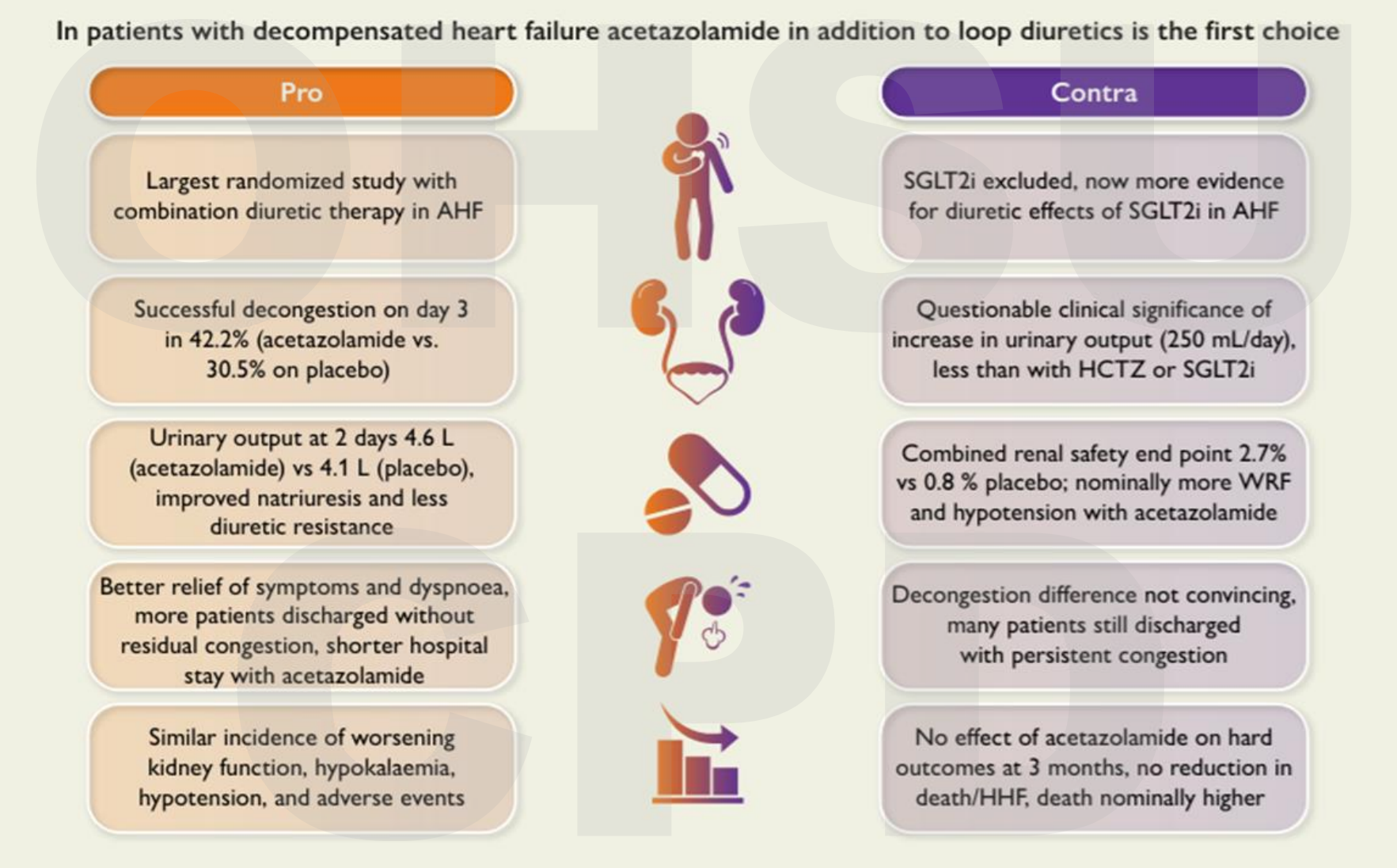




↑46% decongestion
0.5L more diuresis
98 mmol more natriuresis

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

Pro – Con addition of acetazolamide to loop diuretics

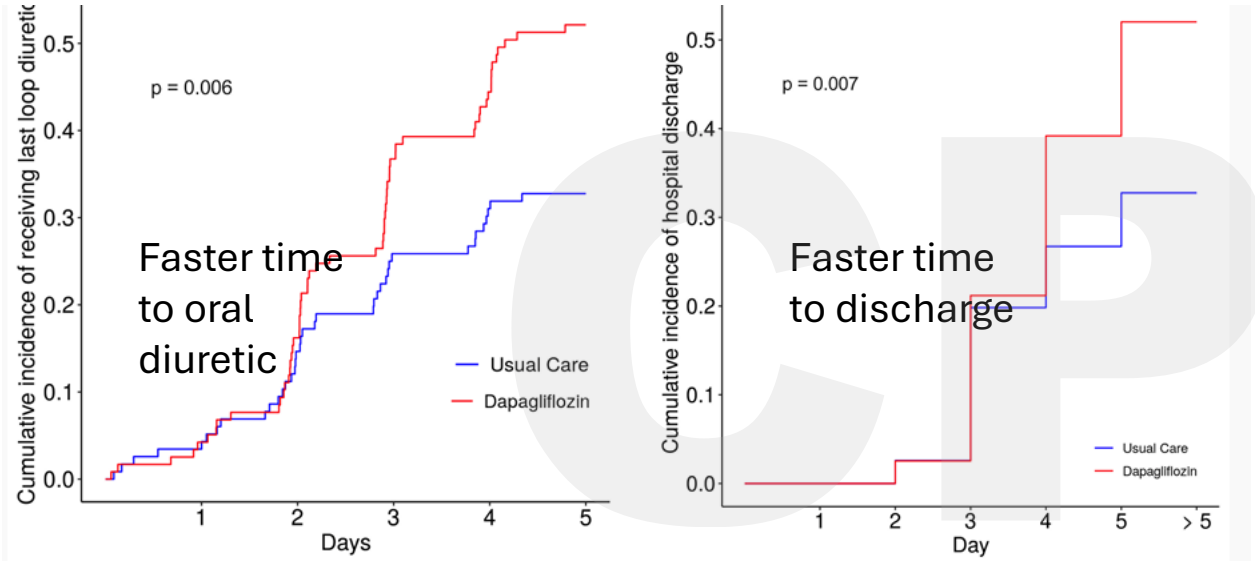


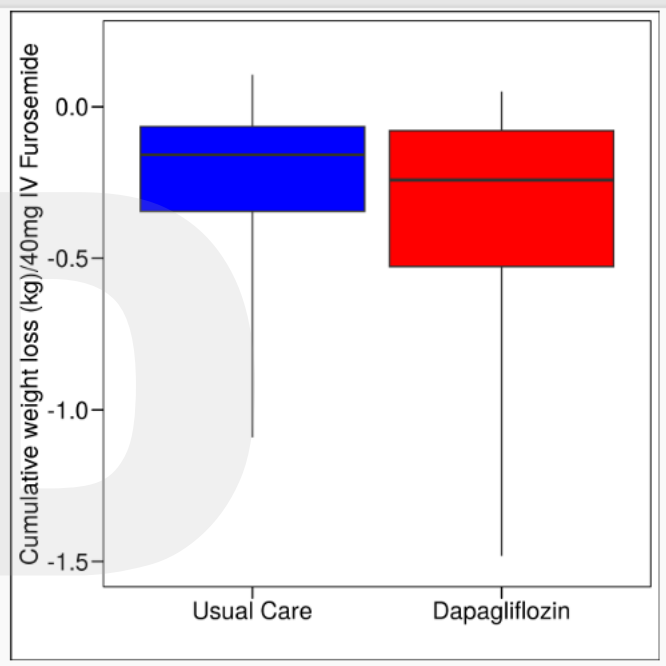
Mullens W et al EHJ 2023

DICTATE AHF

SGLT2i use in acute HF and outcomes

- Dapagliflozin had strong signal to improve diuretic efficiency.
  - Increased natriuresis and diuresis per 40 mg of IV furosemide
  - Decreased total dose and duration of loop diuretics required during stay
  - Decrease time to hospital discharge.
- Safe! Early use was safe across all diabetic and cardiorenal outcomes.





Adjusted odds ratio 0.65 (95% CI 0.41-1.01); p=-0.06

Cox ZL, J Am Coll Cardiol 2024;83:1295-1306.

DAPA –RESIST Trial

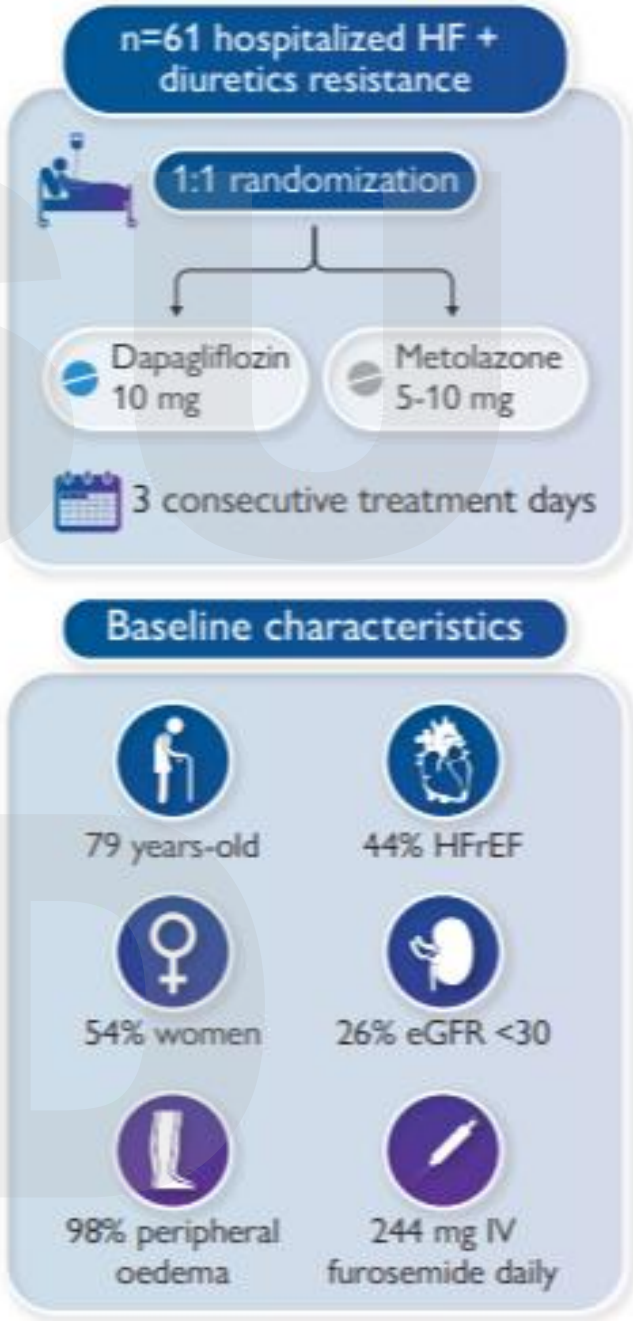
Inclusion criteria:

- HF admission
- Diuretic resistance as defined as:
  - Weight loss <1kg

  or
  - <1 litre -ve fluid balance preceding 24 hours
- Loop diuretic (equivalent of ≥160mg IV furosemide in 24 hours)

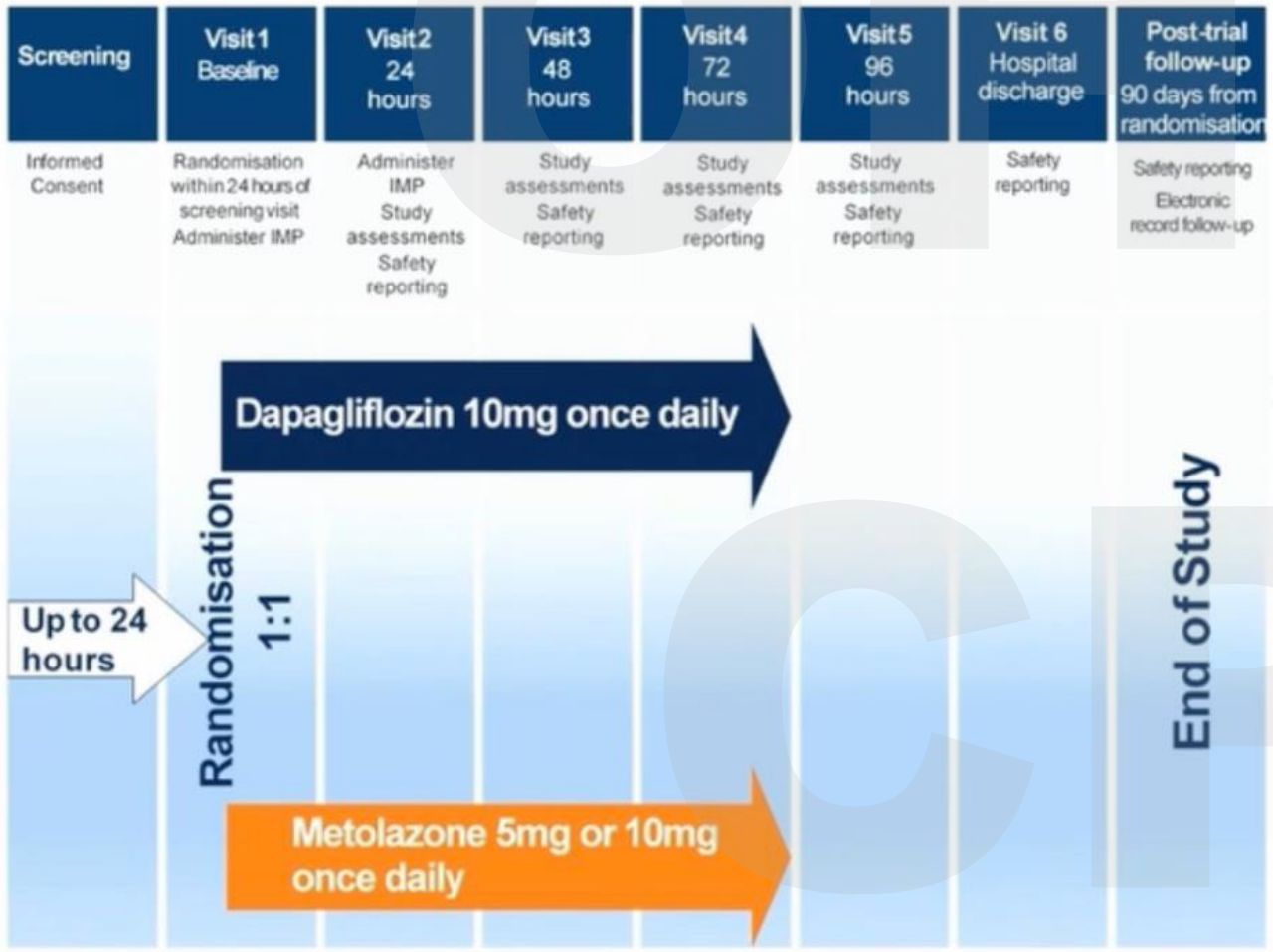
Exclusion criteria:

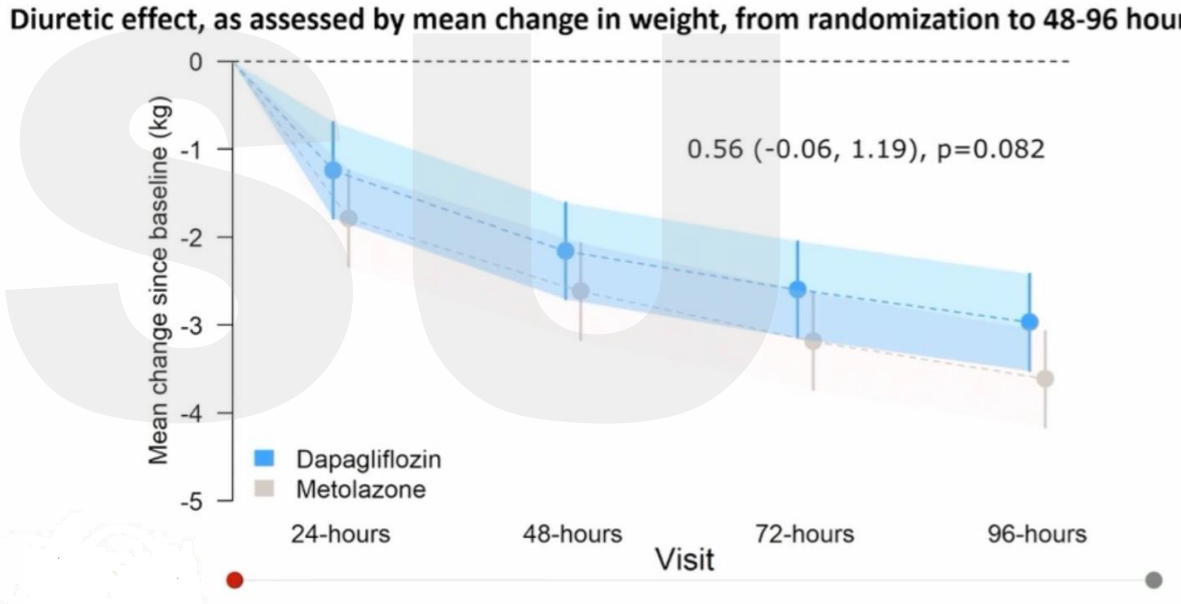
- eGFR <20 ml/min/1.73 m^2
- SGLT2i, thiazide or thiazide-like diuretic use previous 48 hrs
- Stenotic valve disease requiring intervention
- Active genital tract infection



Yeoh SE et al. **EHJ** 2023;44:2966-77.

DAPA –RESIST Trial



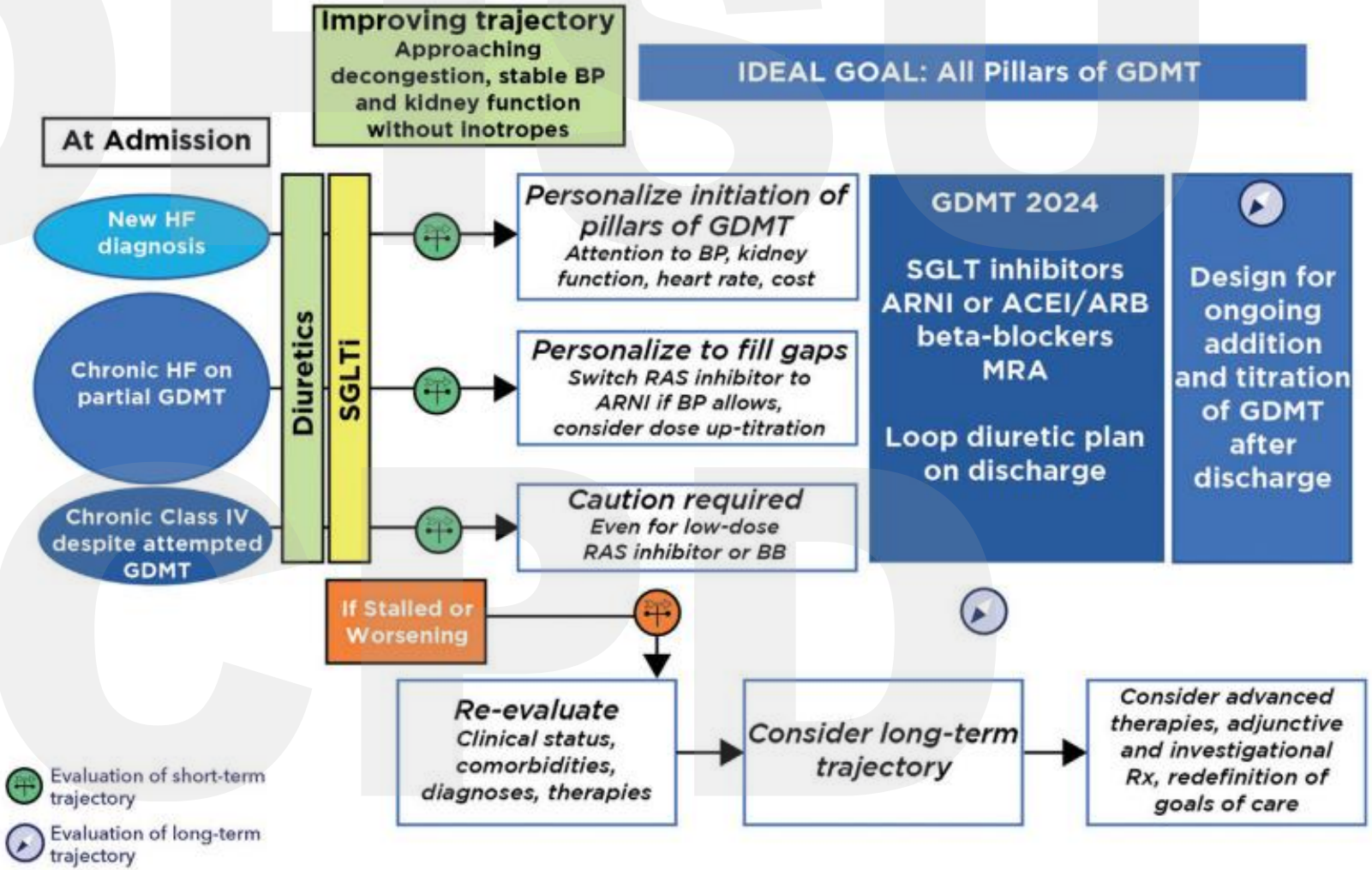


No significant difference between metolazone and SGT2i. Fewer biochemical upset

Yeoh SE et al. EHJ 2023;44:2966-77.

	Decongestion	Guideline Directed Medical Therapy Optimization
Loop diuretic alone	☑	⊘
Loop + thiazide	☑	⊘
Loop + Acetazolamide	☑	⊘
Loop + SGLT2i	Increased diuretic efficiency and shorter length of stay	☑
Loop + MRA	⊘	☑

Optimization of GDMT



https://doi.org/10.1016/j.jacc.2024.06.002

Fight Resistance with Right Strategies

- Loop diuretic resistance is nearly ubiquitous in patients with heart failure
- Don’t be shy when dosing loop diuretics
- Resistance is mostly driven by distal hypertrophy
- Patients that don’t respond to high dose loop + thiazide are fortunately rare but very sick
- Optimize GDMT

Questions?