The Fluid Fix: Advanced Approaches to Diuretic Resistance in Heart Failure

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Disclosures

The following faculty speakers and/or planning committee members have disclosed the following:

Faculty Name	Name of Ineligible Companies	Nature of Relationship
Stormi Gale PharmD, BCPS, BCCP, FHFSA	American Regent	Panel speaker

The other planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose. All the relevant financial relationships listed for Stormi Gale have been mitigated.

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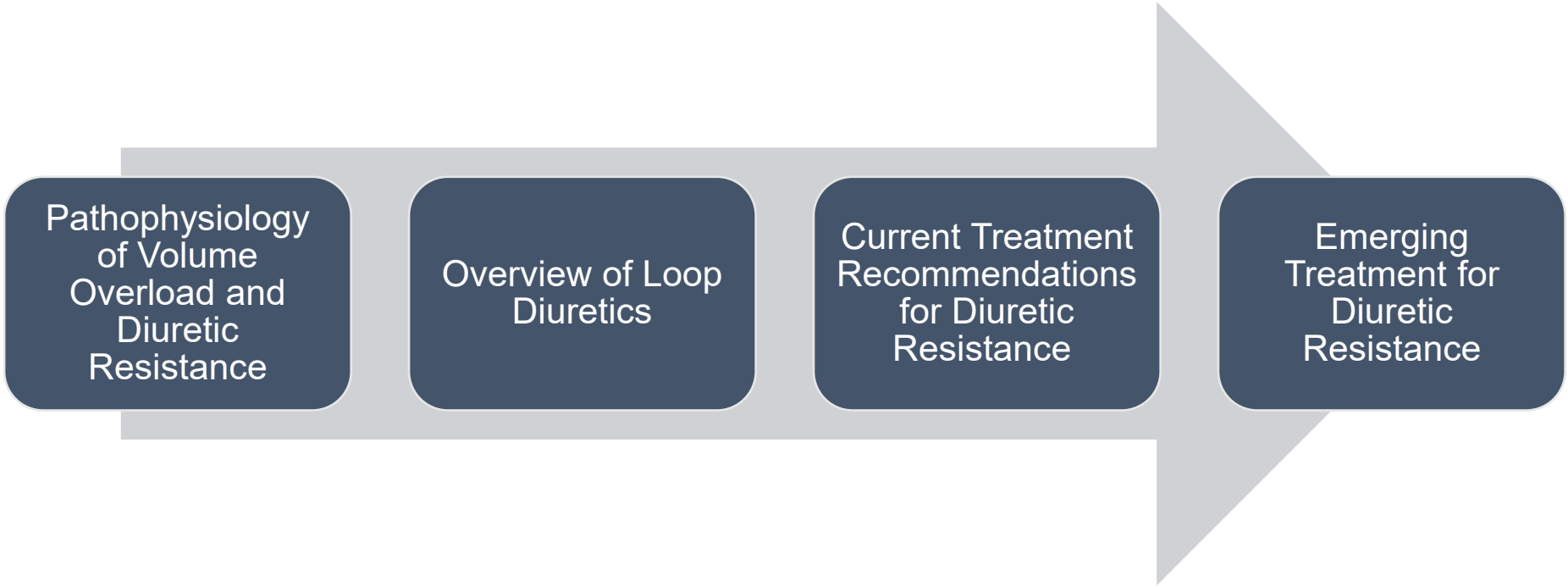
Learning Objectives

At the end of this session, learners should be able to:

- Identify mechanisms of diuretic resistance and clinical presentation of volume overload in heart failure patients
- Recall the mechanism of action, dosing, and adverse effects of loop diuretics
- Compare current strategies and emerging therapies for managing diuretic resistance in patients with decompensated heart failure

Outline



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Abbreviation Key

- **ADHF:** acute decompensated heart failure
- **BUN:** blood urea nitrogen
- **CV:** cardiovascular
- **DCT:** distal convoluted tubule
- **eGFR:** estimated glomerular filtration rate
- **HF:** heart failure
- **LD:** loop diuretic
- **LOS:** length of stay
- **IV:** intravenous
- **MOA:** mechanism of action
- **MRA:** mineralocorticoid receptor antagonist
- **NKCC-2:** sodium, potassium, and chloride cotransporter 2

Abbreviation Key

- **PCT:** proximal convoluted tubule
- **PO:** by mouth
- **RAAS:** renin-angiotensin-aldosterone system
- **SGLT-2:** sodium glucose cotransporter 2
- **SNS:** sympathetic nervous system
- **UF:** ultrafiltration
- **UOP:** urine output
- **WRF:** worsening renal function

Volume Overload and Diuretic Resistance

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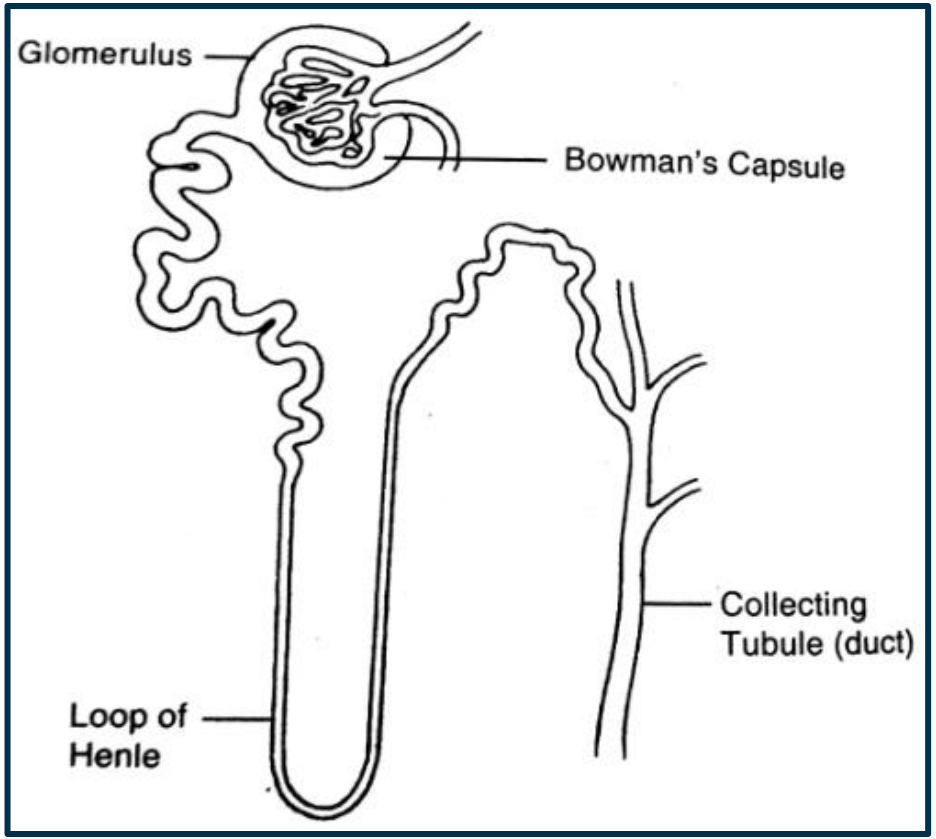
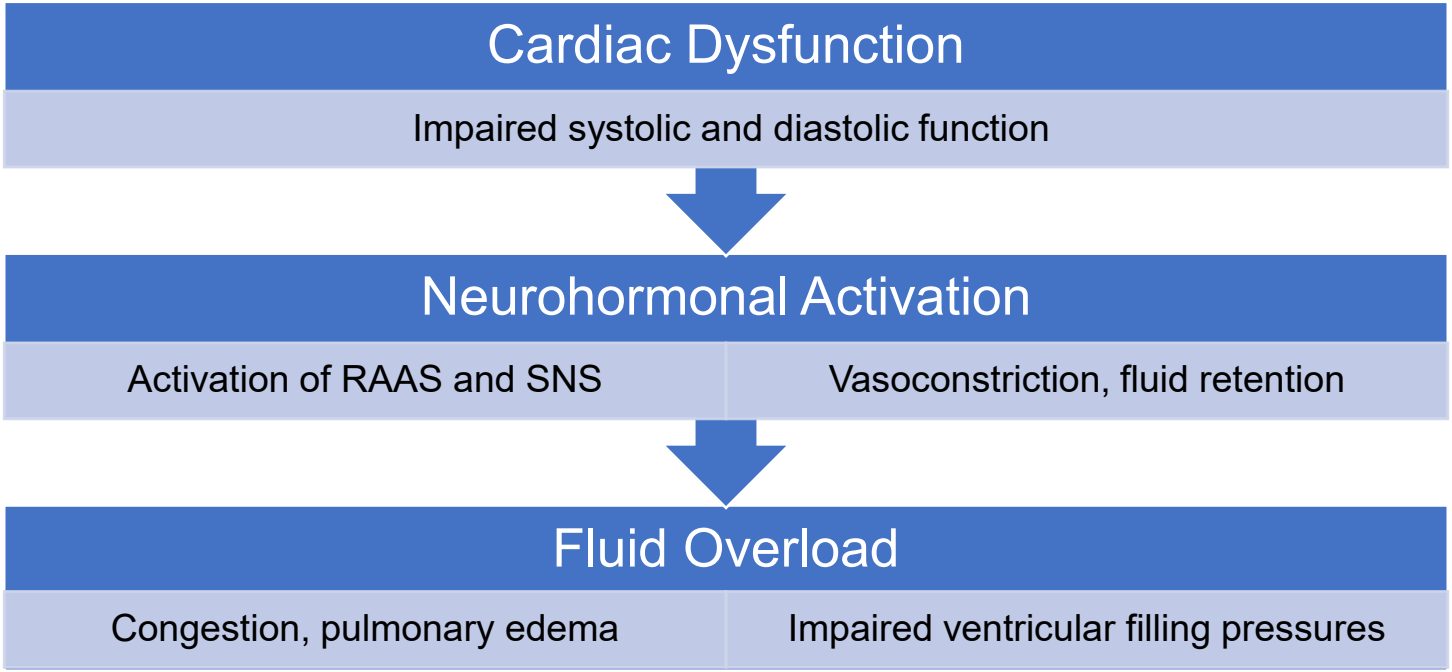
The Nephron

- Filtration
- Reabsorption
- Secretion
- Excretion



Gopalan C. Filtration, Reabsorption, and Secretion.In: Essentials of Physiology for Nurse Anesthetists I (Gopalan). Med LibreTexts. 2025.

Pathophysiology of Congestion



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Njoroge JN, et al. Circ Res. 2021;128(10):1468-1486.

Clinical Presentation

Shortness of breath	Bilateral pitting edema
Dyspnea on exertion	Weight gain
Orthopnea	Jugular venous pressure
Pulmonary rales	Hepatojugular reflex
Third heart sounds	Lethargy

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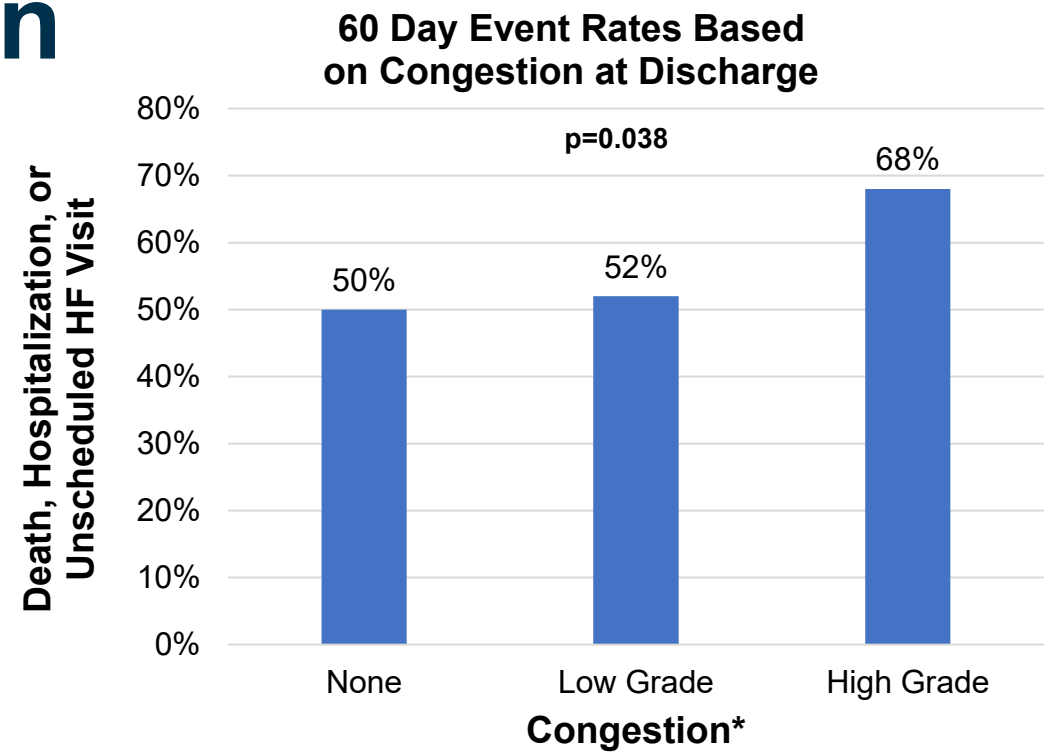
King M, et al. Am Fam Physician. 2012;85(12):1161-1168

The Importance of Successful Decongestion

IV loop diuretics are used in ~90% of HF admissions

~50% of patients are discharged with residual congestion

*Based on discharge orthodema score



Felker GM, et al. N Engl J Med. 2011;364(9):797-805.
Shochat MK, et al. J Card Fail. 2019;25(8).

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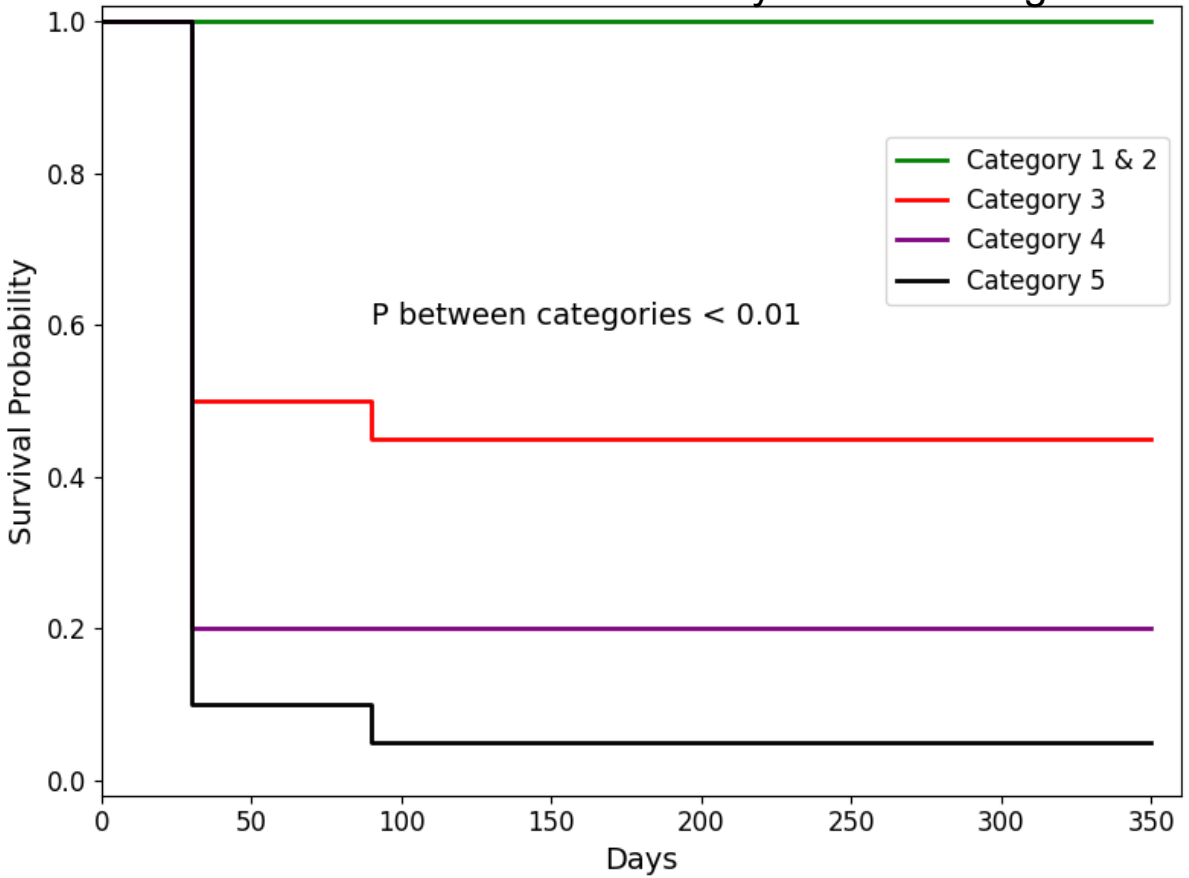
Heart Failure Survival Predicted by Level of Congestion*



Persistent congestion at discharge is associated with worse post-discharge outcomes, including increased mortality

*Measured by lung impedance (higher category = greater congestion)

Shochat MK, et al. J Card Fail. 2019;25(8).

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Diuretic Resistance

No universally accepted definition

Affects ~20-50% of patients with HF

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Felker GM, et al. Am Coll Cardiol. 2020;75(10):1178-95

Mechanism of Diuretic Resistance

Pre-Renal	Intra-Renal		
	Pre-Loop of Henle	Loop of Henle	Post-Loop of Henle
Venous congestion Increased intra-abdominal pressure **Reduced cardiac output** **Hypoalbuminemia** **High sodium intake**	Increased proximal tubule sodium reabsorption Reduced GFR Increased organic anions Albuminuria	**Inadequate loop diuretic dose** Response at level of Loop of Henle Hypochloremic alkalosis	**Compensatory distal tubular sodium reabsorption** Proteolytic activation and upregulation of select sodium channels

Mechanistic Importance:

Significant | Unknown (likely significant) | **Not significant**

Felker GM, et al. Am Coll Cardiol. 2020;75(10):1178-95

Assessment Question #1

Which of the following is a significant contributor to diuretic resistance?

a. Decreased cardiac output
b. Inadequate loop diuretic doses
c. Hypoalbuminemia
d. High sodium intake

Loop Diuretics in Volume Overload

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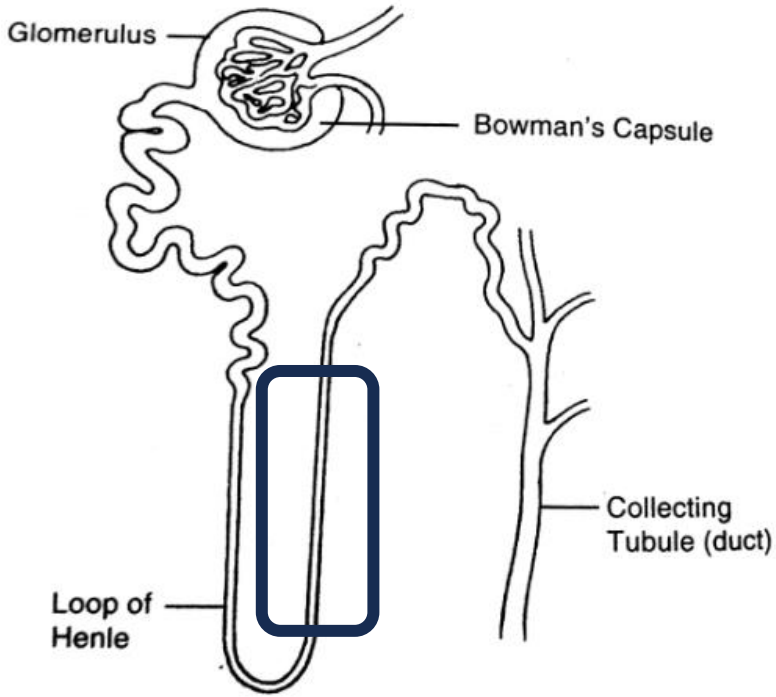
Mechanism of Action

- Inhibit NKCC-2 cotransporter across the cell membrane along the ascending Loop of Henle
  - Results in reduced reabsorption of sodium and chloride



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Ferrari F, et al. Clin Pharmacokinet. 2025;64(7):987-997.

Adverse Effects and Monitoring

- Electrolyte imbalances
- Dehydration
- Hypotension
- Gout
- Ototoxicity
- Nephrotoxicity

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Sica DA. *J Clin Hypertens (Greenwich)*. 2004;6(9):532-540.

Worsening Renal Function

- 20-30% decrease in GFR has been observed in ADHF
- Often transient and **not** associated with worse outcomes long-term

ESCAPE Trial	
Incidence of WRF	36%
Key Findings	
Transient creatinine rise during successful decongestion is usually NOT harmful	
Persistent congestion at discharge lead to worse outcomes	

Wu L, et al. J Clin Med. 2024;13(15):4470.

Comparison of Loop Diuretics

Characteristic	Furosemide	Bumetanide
Bioavailability	10 to 100%	80 to 100%
Half-life	1.5 to 2 hours	1 hour
Elimination	Urine	Urine
PO to IV	2:1	1:1

Torsemide* 20 mg PO = Furosemide 40 mg PO = Furosemide 20 mg IV = Bumetanide 1 mg PO/IV

*not used for ADHF

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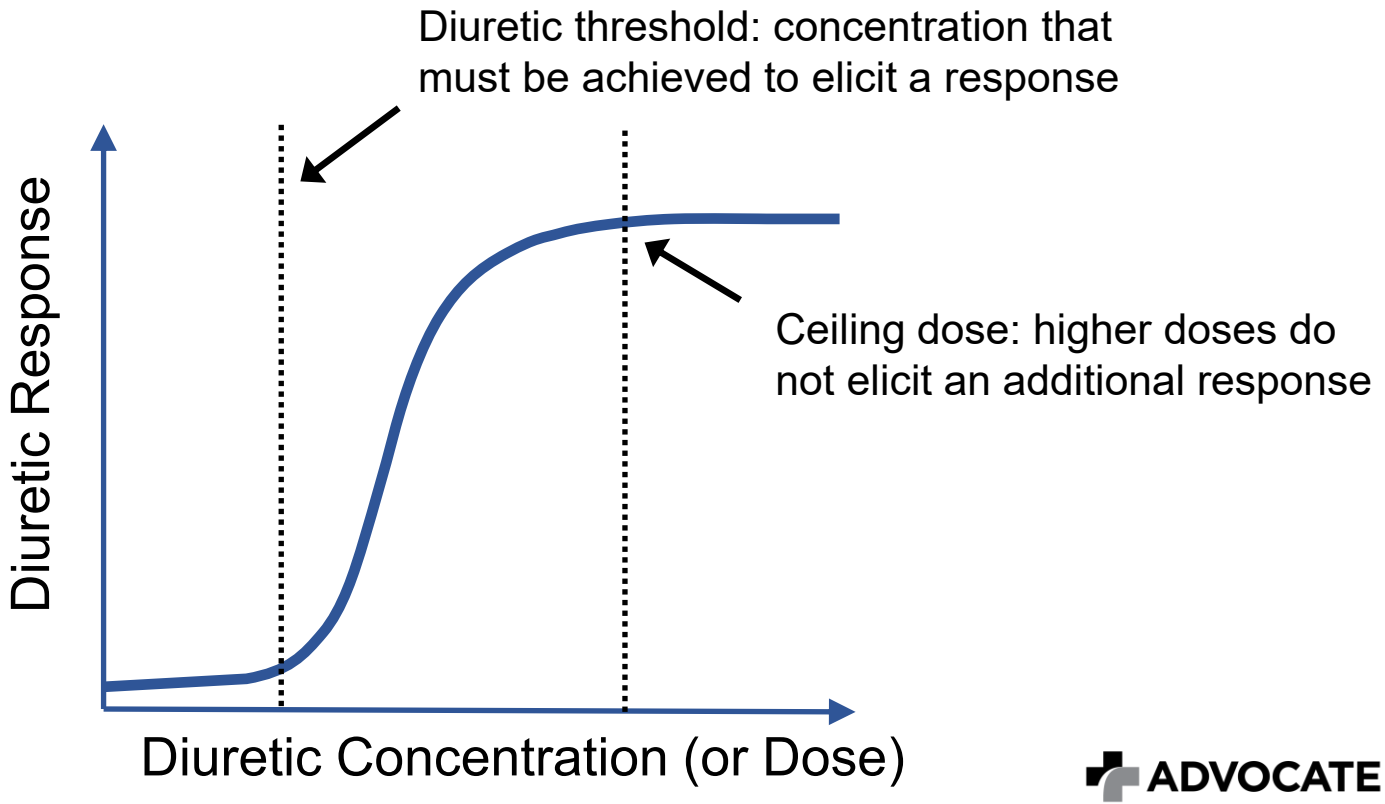
Jentzer JC, at al. J Am Coll Cardiol. 2010;56(19):1427-34.

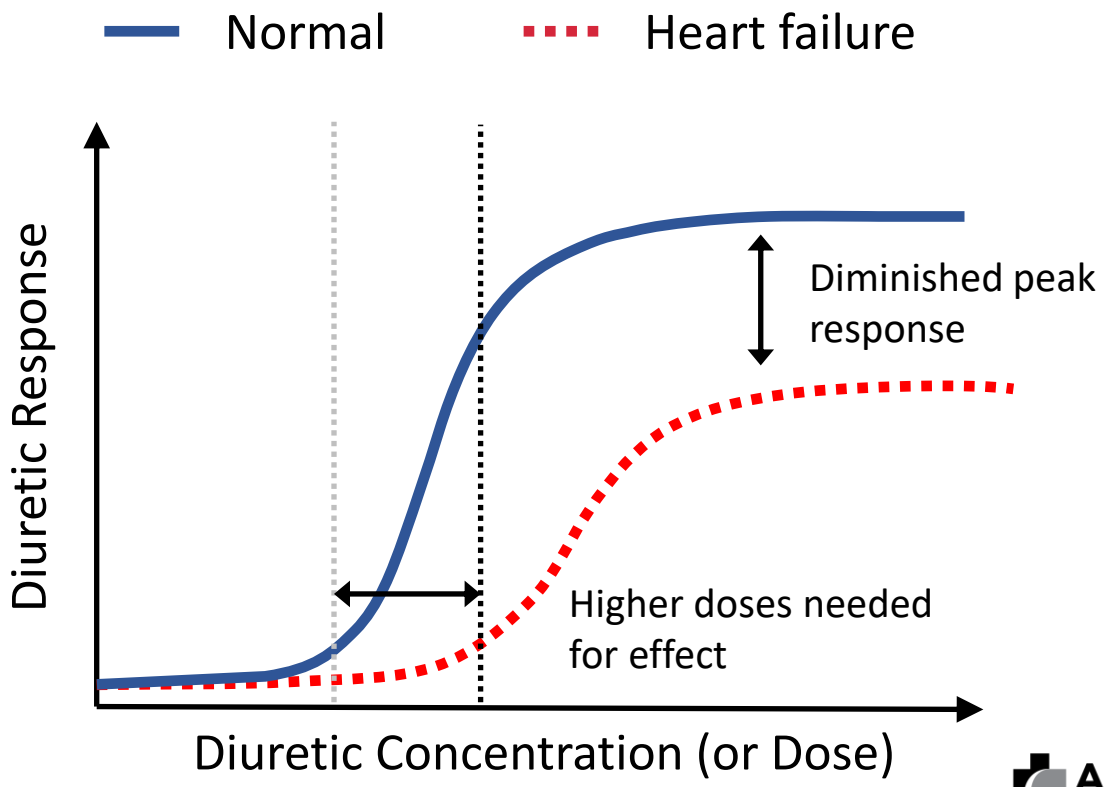
Sigmoid Dose-Response Curve



ADVOCATE HEALTH

Adapted from: *Cardiology*. 2001;96(3–4):132–43.

Diuretic Response in HF



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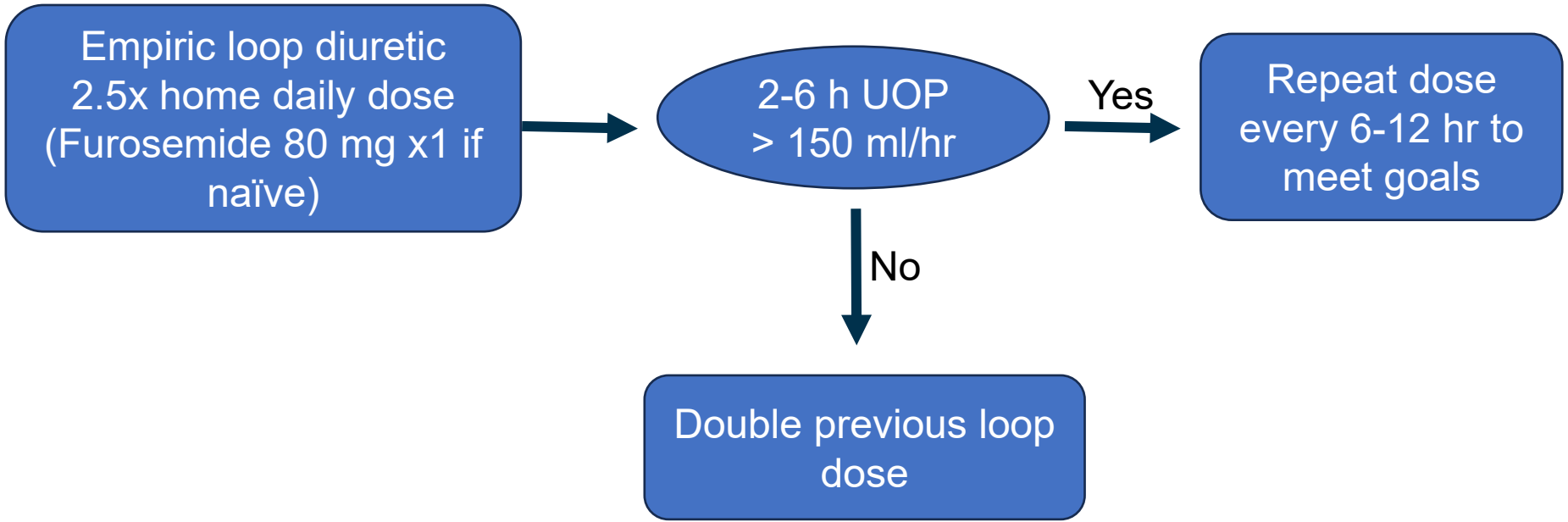
Adapted from: *Cardiology*. 2001;96(3–4):132–43.

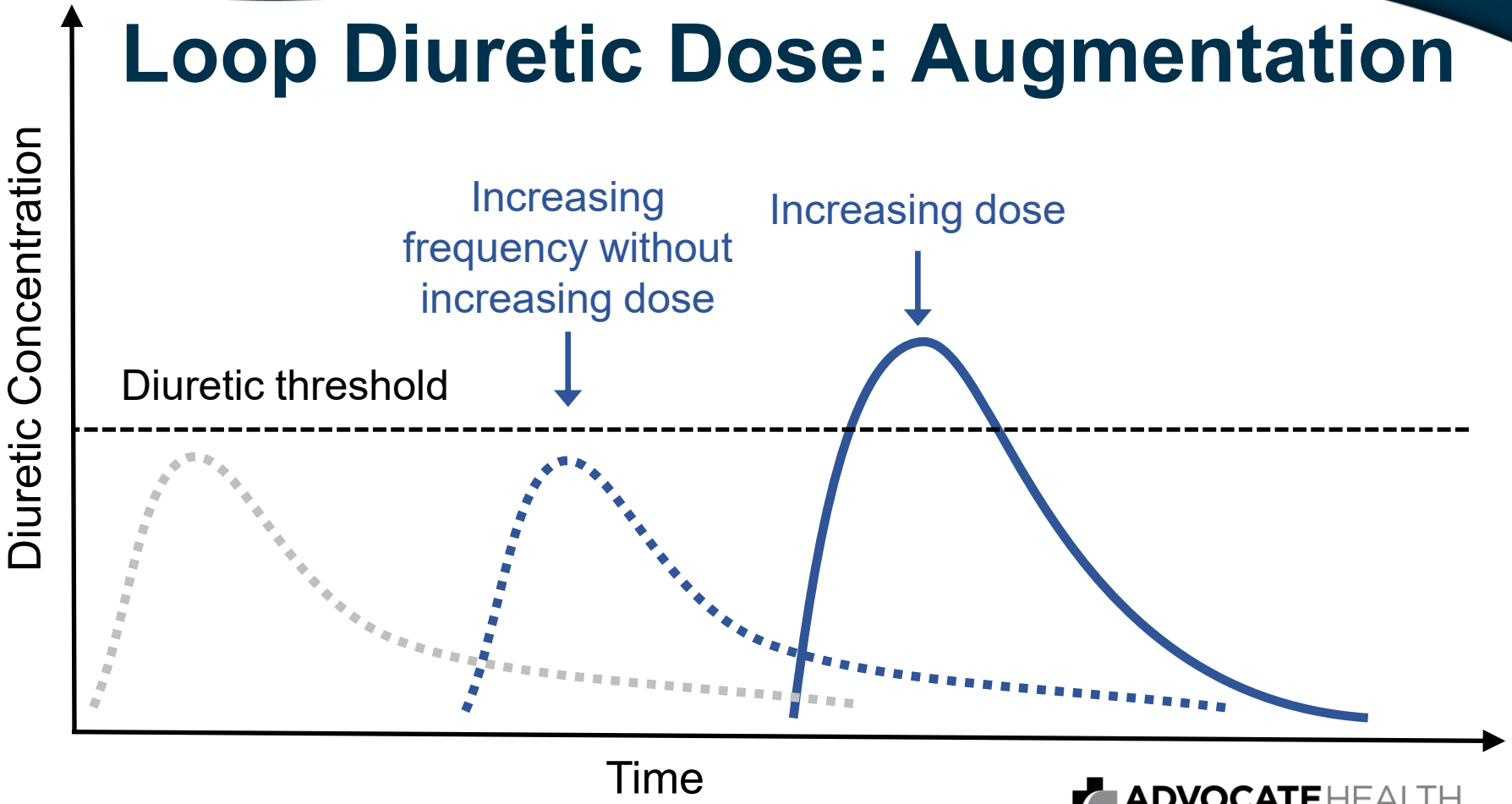
Diuretic Augmentation Process



ADVOCATE HEALTH

Felker GM, et al. Am Coll Cardiol. 2020;75(10):1178-95

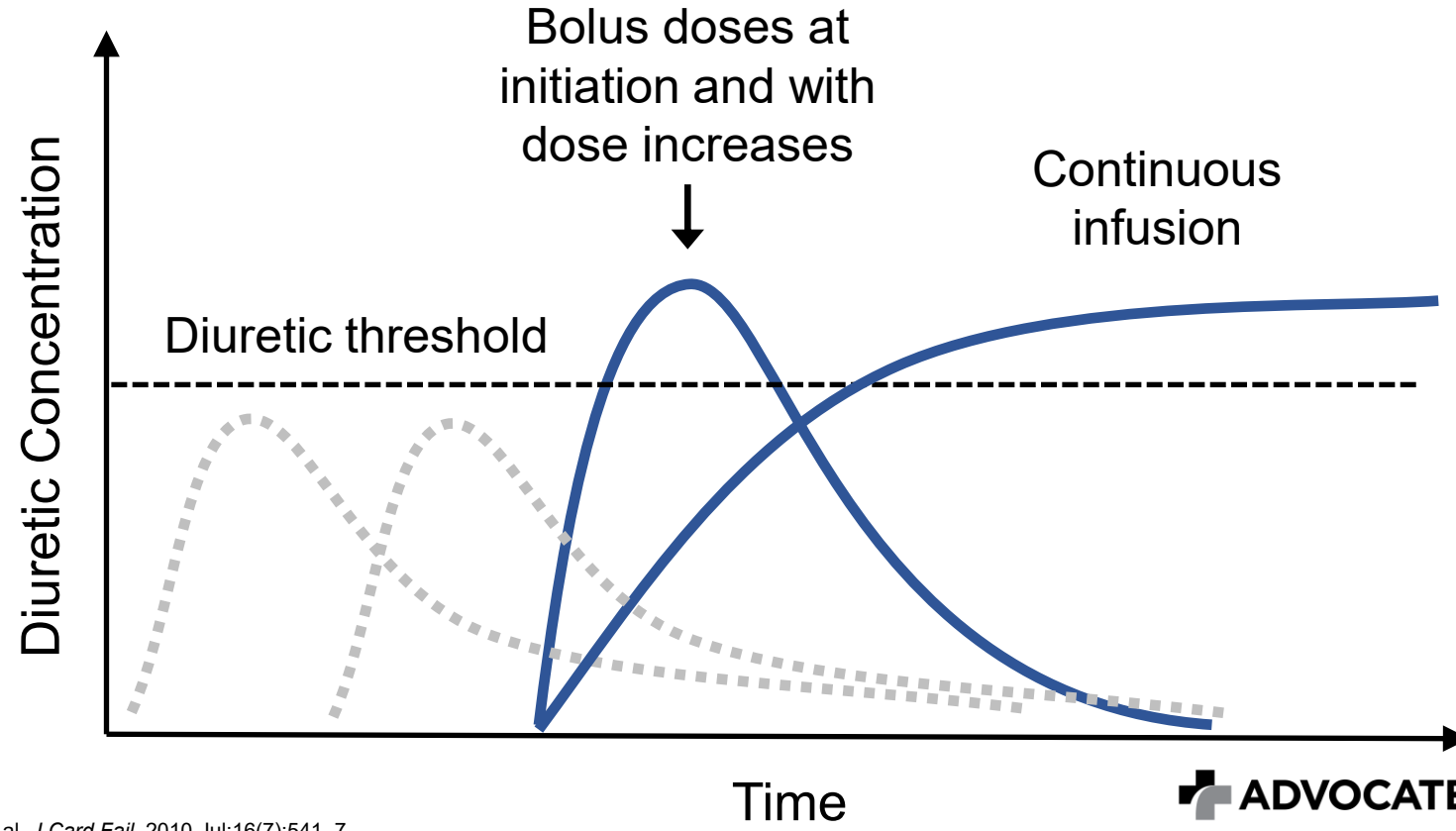
Loop Diuretic Dose: Augmentation



ADVOCATE HEALTH

Ellison DH et al. *Cardiology*. 2001;96(3-4):132-43.

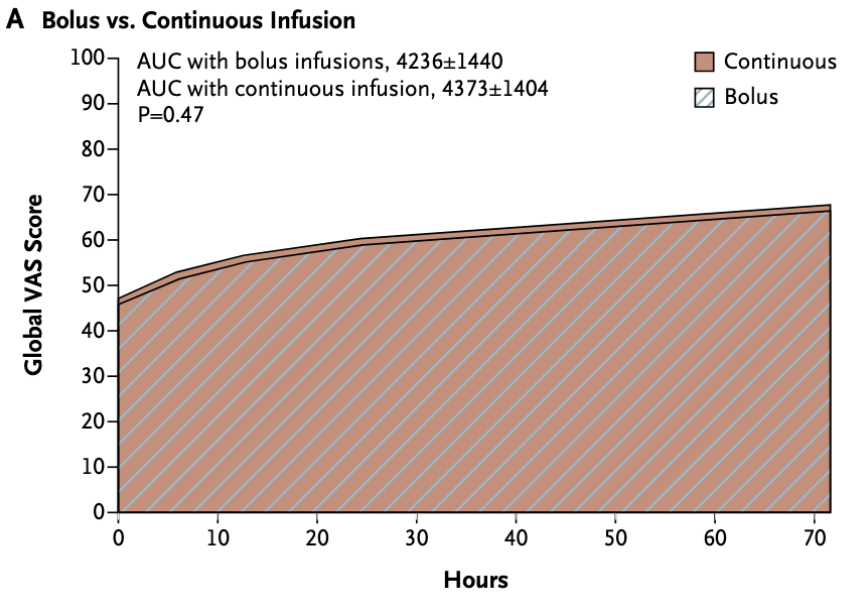
Continuous Infusions

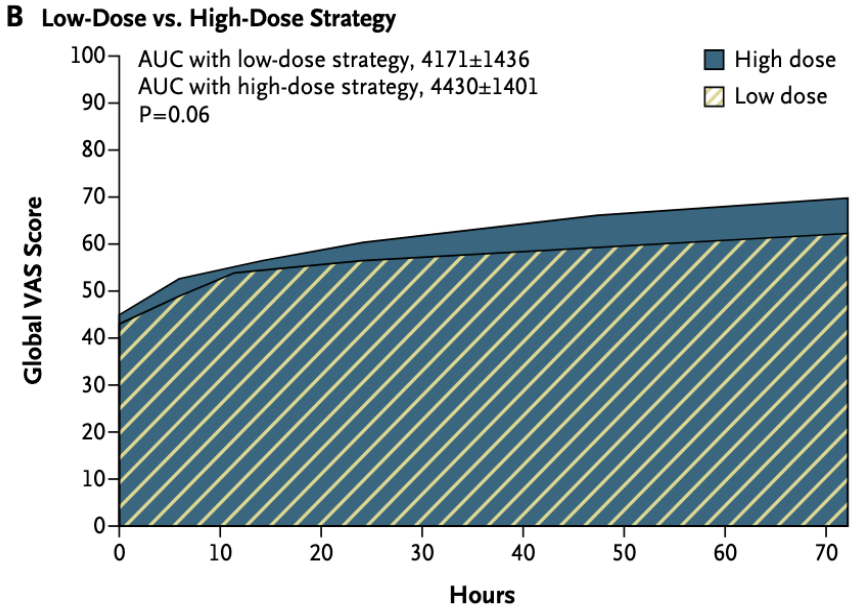


ADVOCATE HEALTH

Aronson, D, et al. *J Card Fail*. 2010 Jul;16(7):541–7.

DOSE Trial





Key Takeaway

No differences between bolus and continuous infusion.
Higher doses provided greater diuresis effects compared to low-dose

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Felker GM, et al. N Engl J Med. 2011;364(9):797-805.

Assessment Question #2

JD is hospitalized with acute decompensated heart failure. His home furosemide dose is 40 mg PO daily. Which is the most appropriate option for this patient to be started on in the ED?

a. Furosemide 80 mg PO
b. Bumetanide 8 mg IV
c. Torsemide 100 mg PO
d. Furosemide 80 mg IV

Current Treatment Recommendations for Diuretic Resistance

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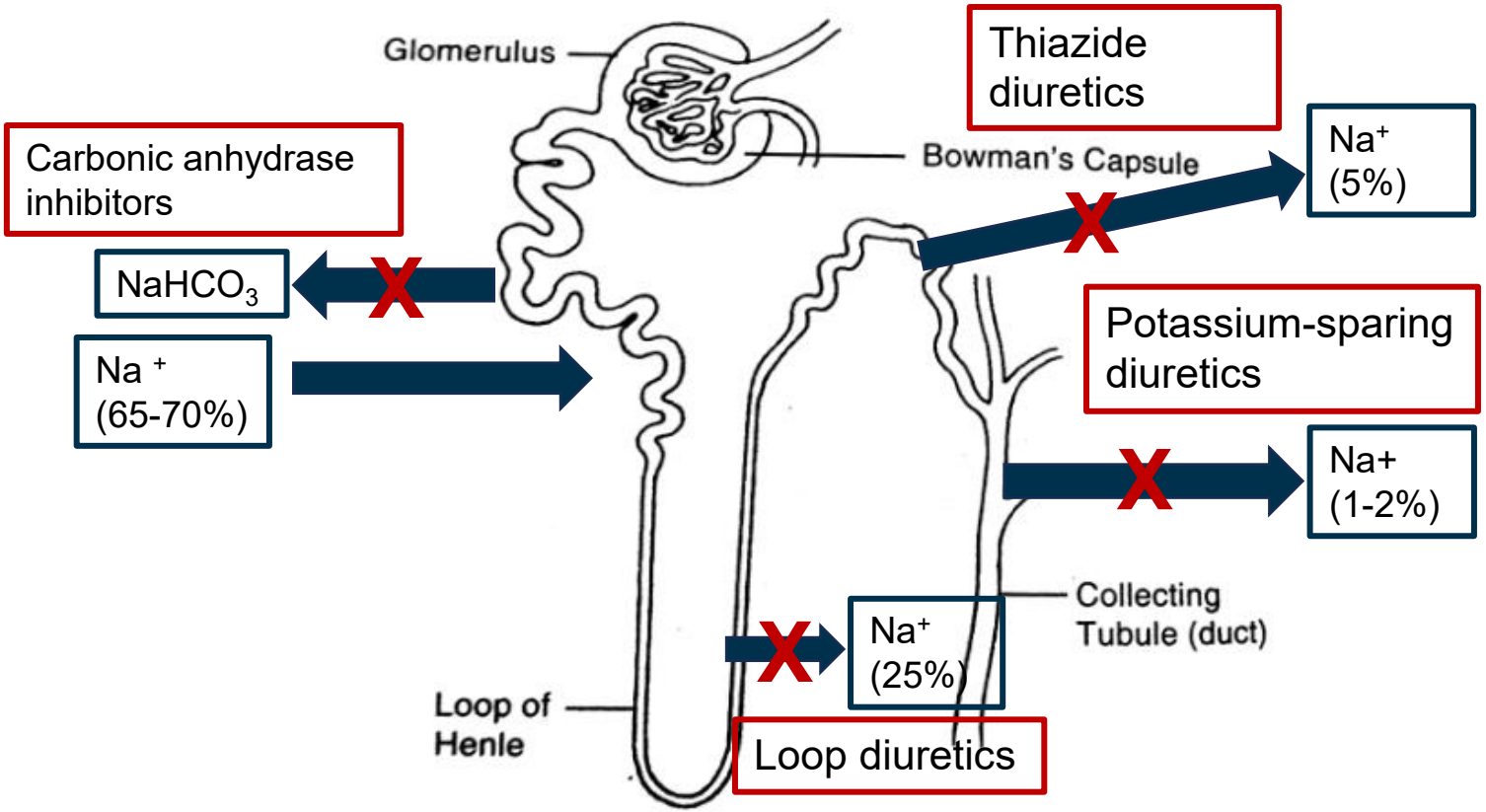
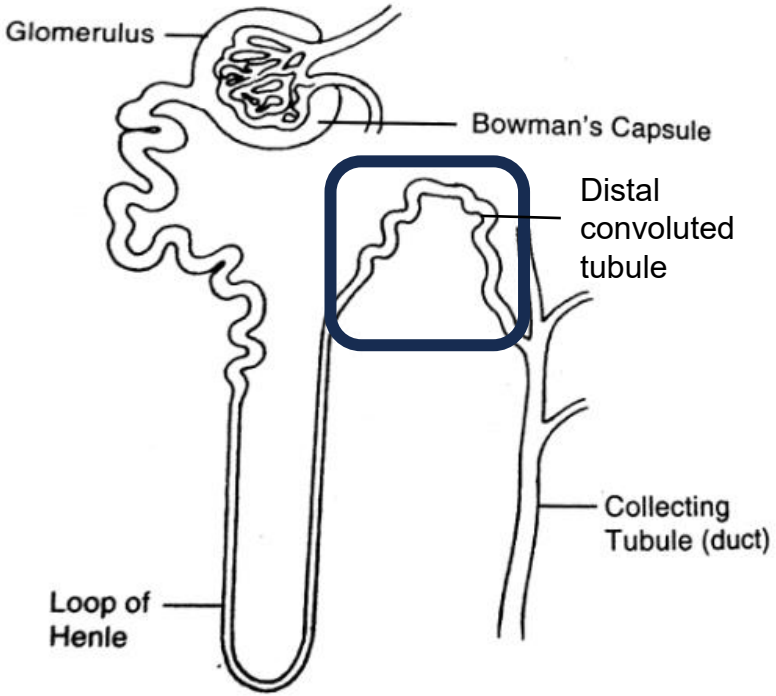
Combination Diuretic Therapy



ADVOCATE HEALTH

Bell R, et al. *BJA Educ*. 2022;22(6):216-223. doi:10.1016/j.bjae.2022.02.003

Thiazides



Monitoring:

- Volume status
- Electrolytes
- BUN
- Serum creatinine

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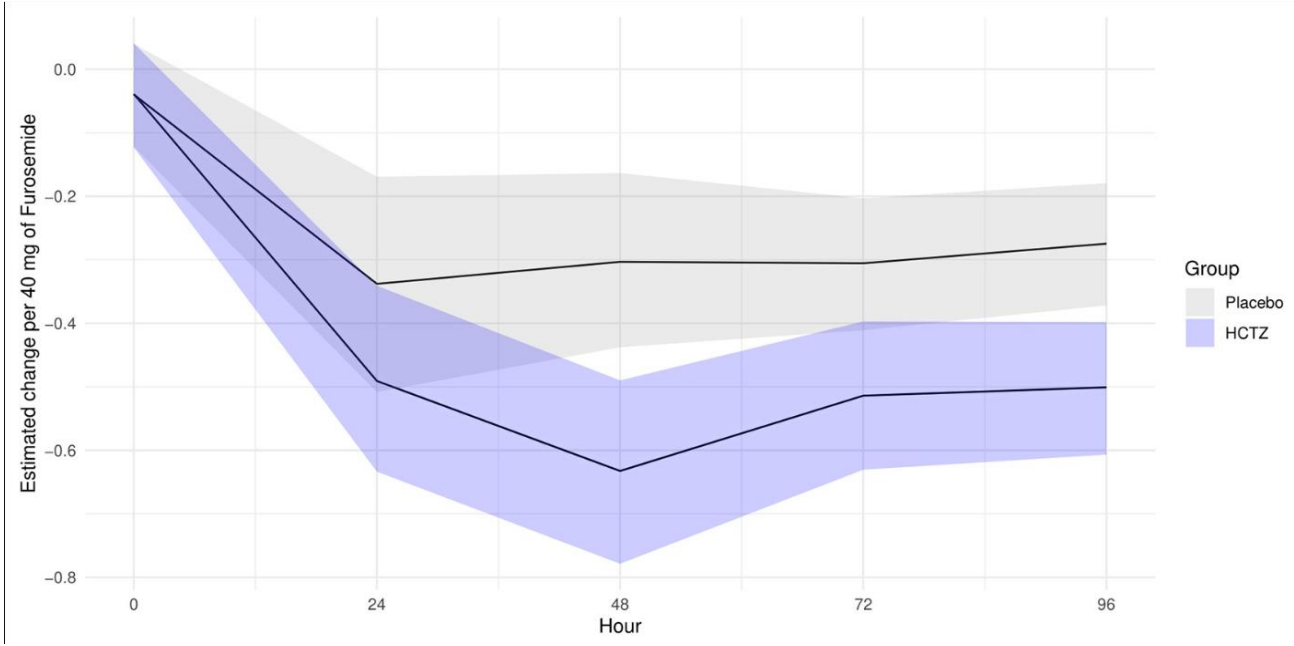
Ferrari F, et al. *Clin Pharmacokinet*. 2025;64(7):987-997.

CLOROTIC Trial



Key Takeaway

Adding thiazide diuretic onto loop diuretic therapy can improve diuretic response in ADHF

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Trullàs JC, et al. *European Heart Journal*. 2022;44(5):411-421.

Comparing Thiazides

Agent	Oral Bioavailability	Dose (max/day)	Time to onset (peak)	Duration
Chlorothiazide (IV)	N/A	500-1000 mg (1000 mg)	2 h (3-6 h)	6-12 h
Hydrochlorothiazide (PO)	65-75%	25-50 mg (200 mg)	2 h (3-6 h)	6-12 h
Metolazone (PO)	40-65%	5-10 mg (20 mg)	2-3 h (6-8 h)	12-24 h

ADVOCATE HEALTH

Jentzer JC, at al. J Am Coll Cardiol. 2010;56(19):1427-34.

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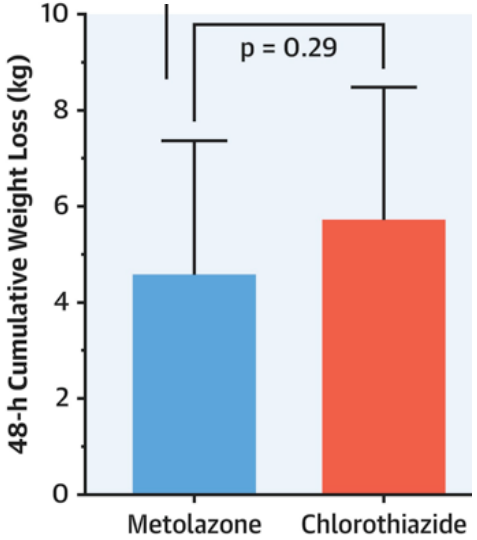
Jentzer JC, at al. J Am Coll Cardiol. 2010;56(19):1427-34.

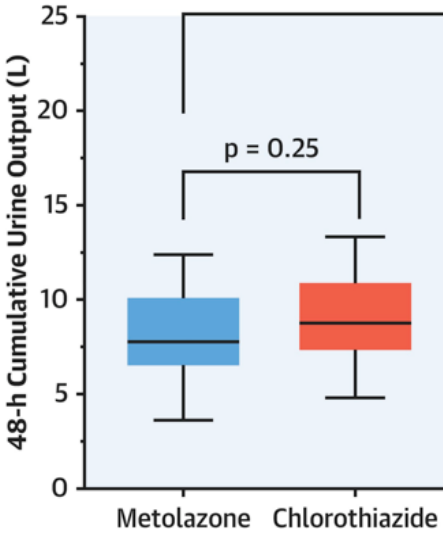
3T Trial

CENTRAL ILLUSTRATION: 48-Hour Diuretic Efficacy

A



B



Key Takeaway

Metolazone is more cost-effective than chlorothiazide and has not been shown to be less effective

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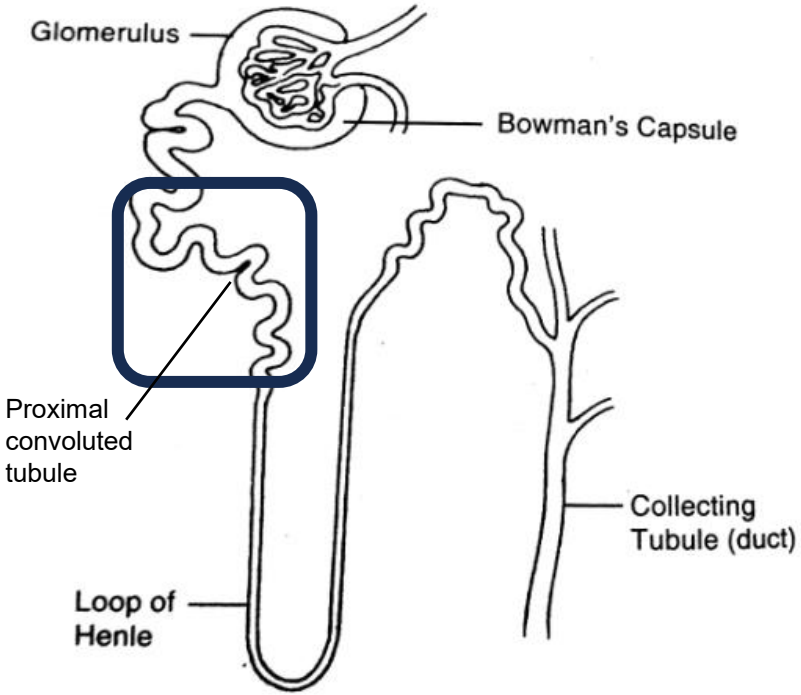
Cox, ZL, et al. J Am Coll Cardiol HF. 2020;8(3):157-68.

Acetazolamide

Carbonic anhydrase inhibitor



Dosing: 250 to 500 mg once daily or every other day

Monitoring:

- Electrolytes
- Volume status
- Serum creatinine
- Creatinine clearance

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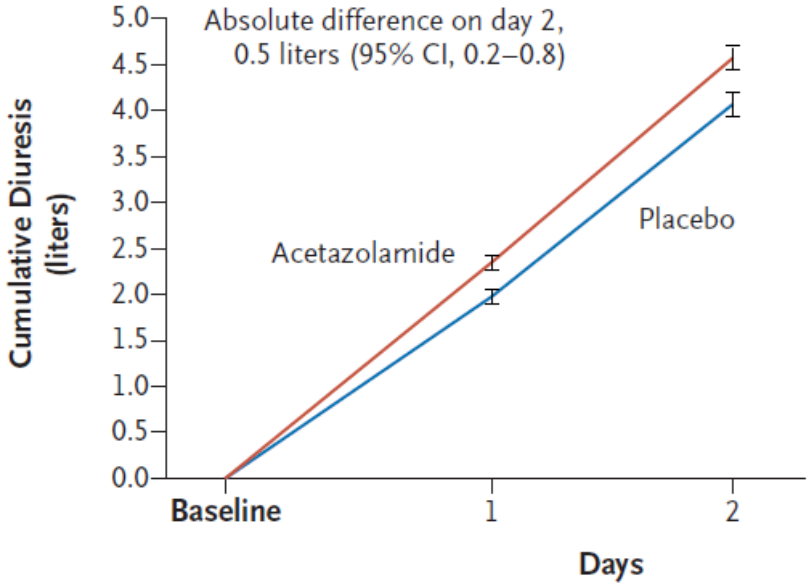
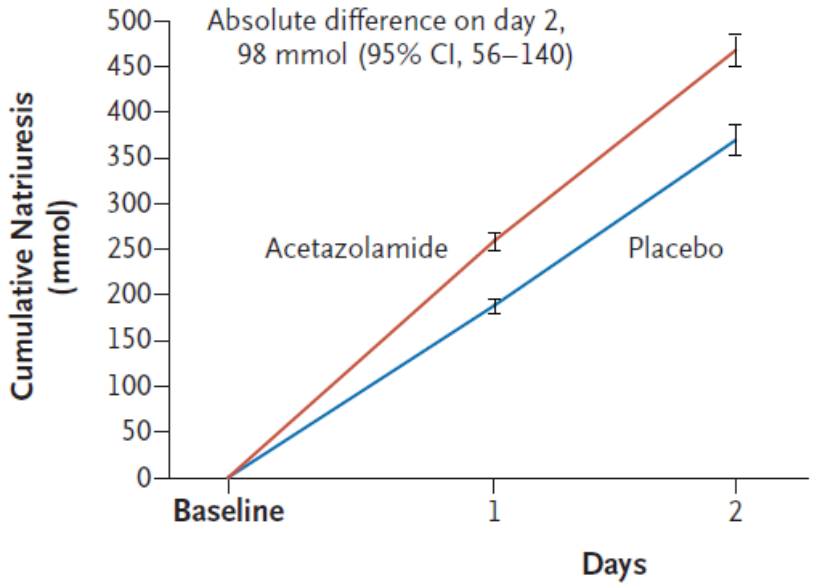
Ferrari F, et al. *Clin Pharmacokinet*. 2025;64(7):987-997.

ADVOR Trial





Key Takeaway

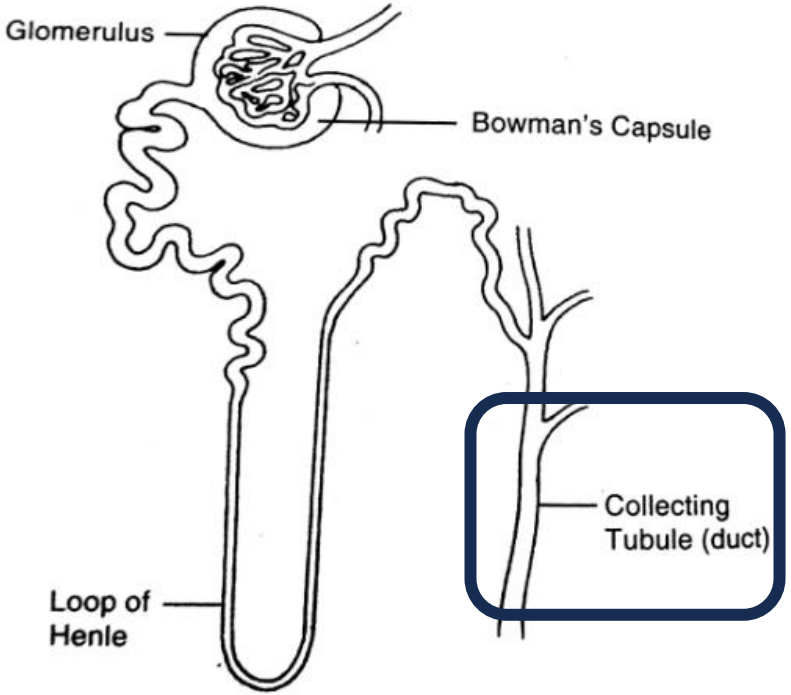
IV acetazolamide added to loop diuretic therapy significantly improved early decongestion rates

ADVOCATE HEALTH

Mullens W, et al. *N. Engl. J. Med.* 2022;387(13):1185-1195.

Tolvaptan

Arginine Vasopressin Antagonist



Dosing: 15 mg PO daily (max 60 mg/day)

Monitoring:

- Serum sodium
- Volume status
- Liver function tests

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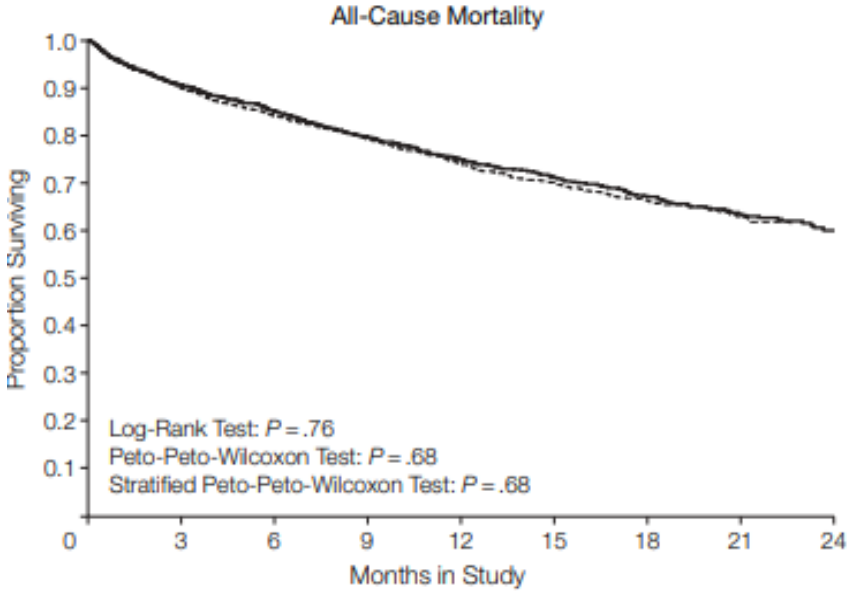
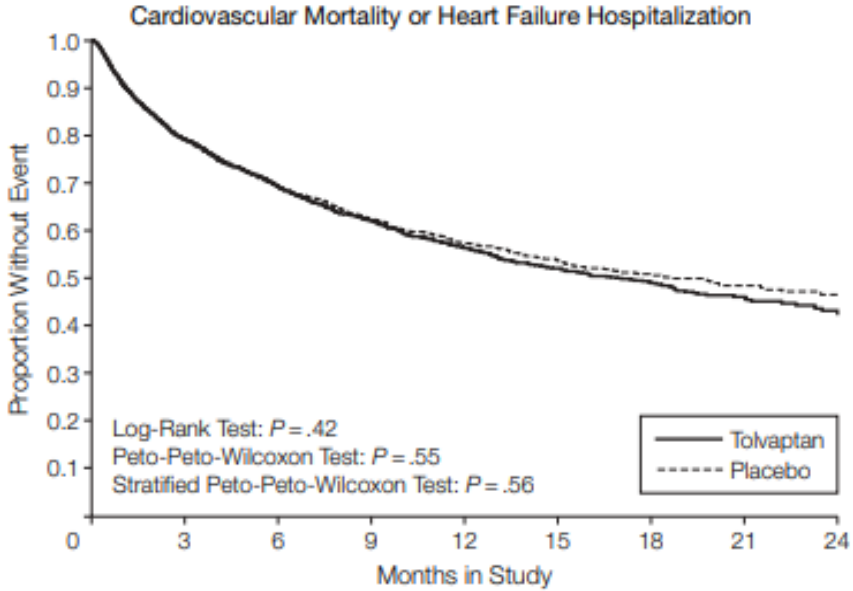
Ferrari F, et al. *Clin Pharmacokinet*. 2025;64(7):987-997.

EVEREST Trial





Key Takeaway

Tolvaptan did not improve long-term outcomes, such as all-cause mortality or CV death/HF hospitalization

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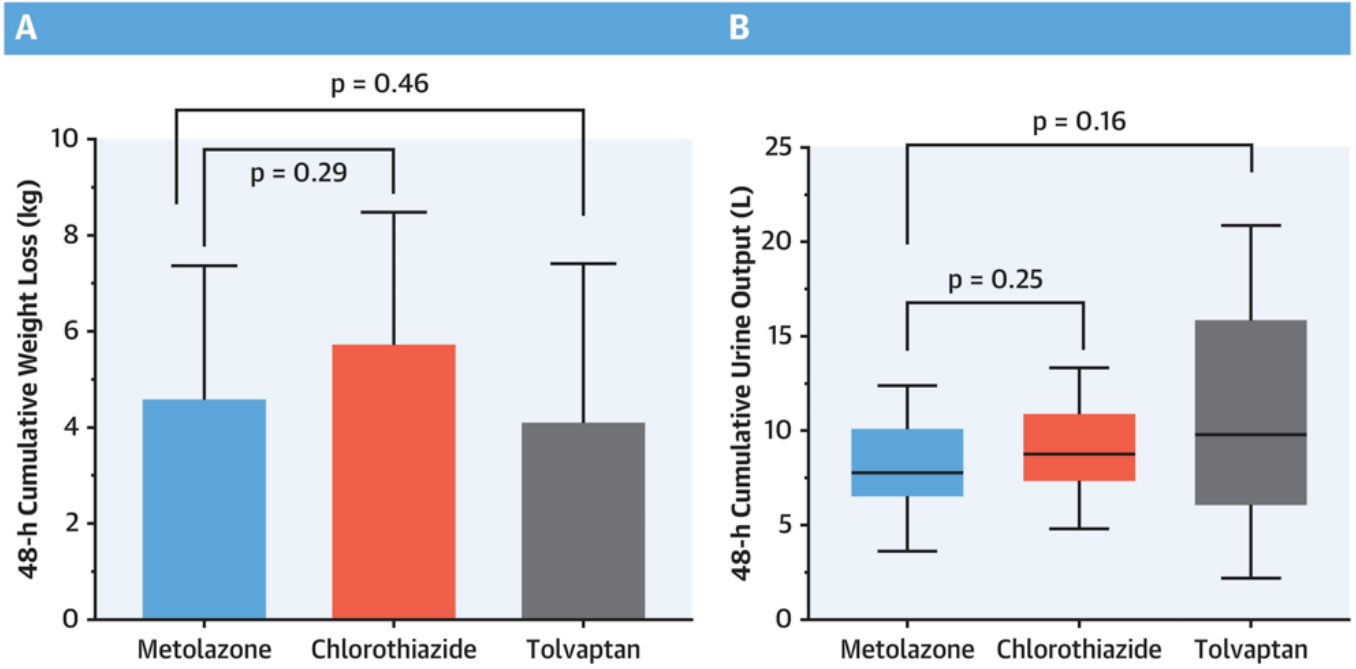
Konstam MA. *JAMA*. 2007;297(12):1319.

3T Trial

CENTRAL ILLUSTRATION: 48-Hour Diuretic Efficacy



Key Takeaway

Diuretic agents show similar efficacy; tolvaptan adds cost without improving outcomes

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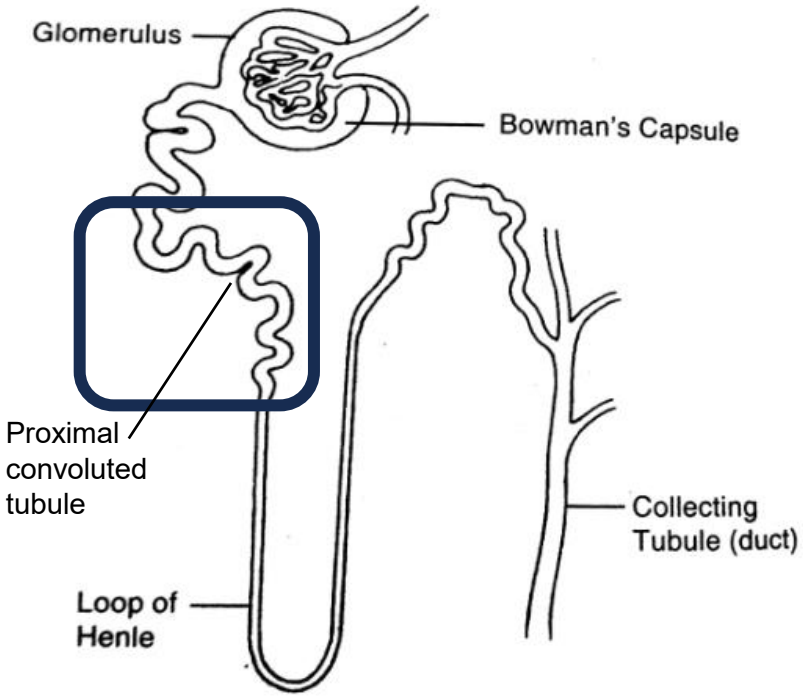
Cox, ZL, et al. J Am Coll Cardiol HF. 2020;8(3):157-68.

SGLT-2 Inhibitors



Empagliflozin and Dapagliflozin Dosing:
10 mg PO daily

Monitoring:

- Serum creatinine
- eGFR
- Genital mycotic infections
- Volume status

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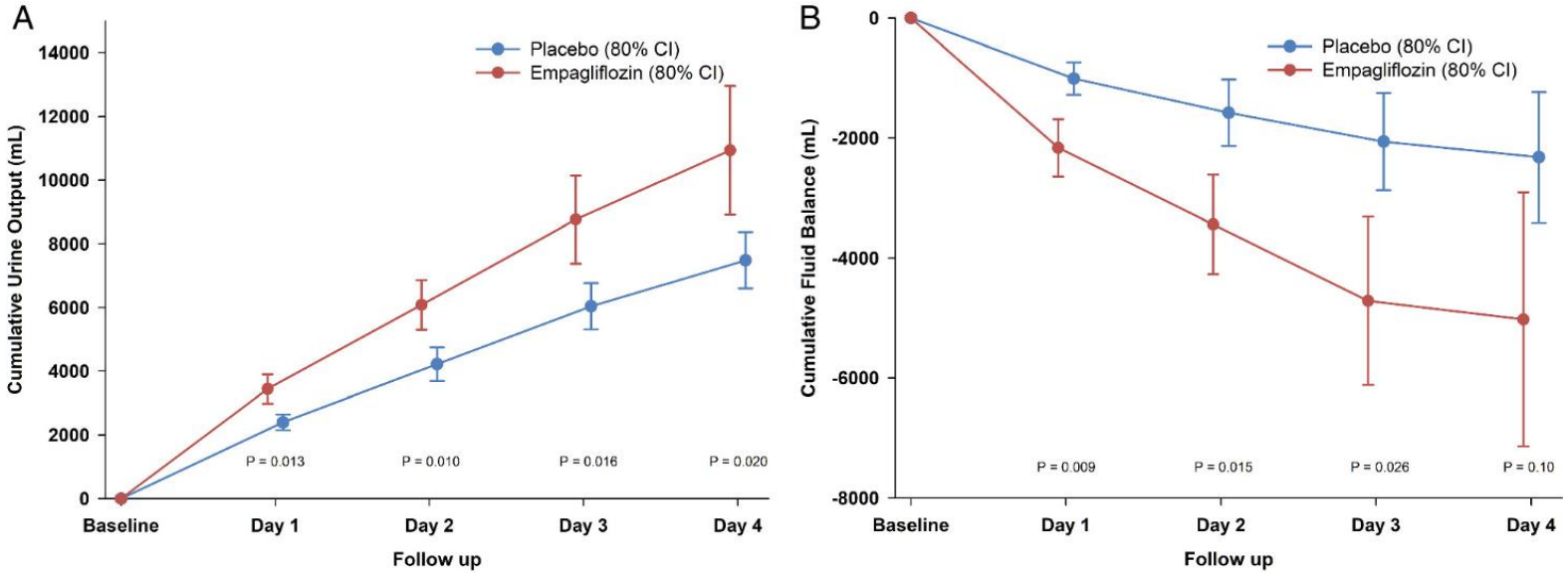
Ferrari F, et al. *Clin Pharmacokinet*. 2025;64(7):987-997.

EMPA-RESPONSE-AHF Trial



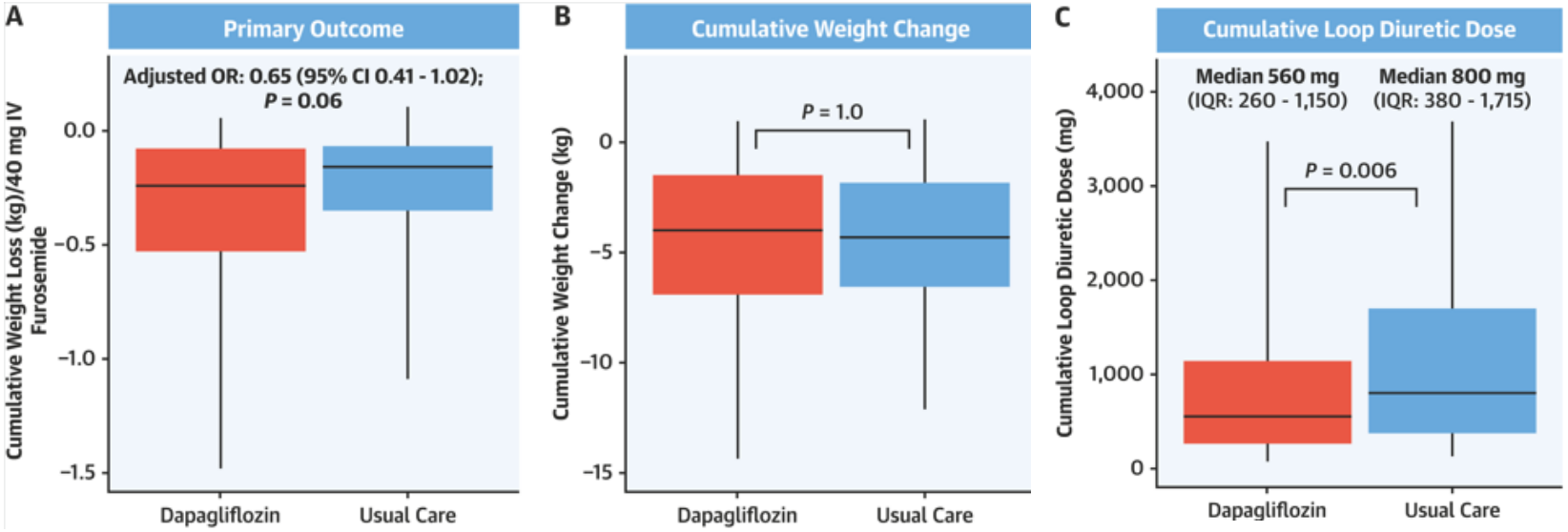
Key Takeaway

SGLT-2 inhibitors increased diuresis when added onto loop diuretic therapy, with trend toward improve clinical outcomes

ADVOCATE HEALTH

Damman K, et al. *European Journal of Heart Failure*. 2020;22(4):713-722.

DICTATE-AHF



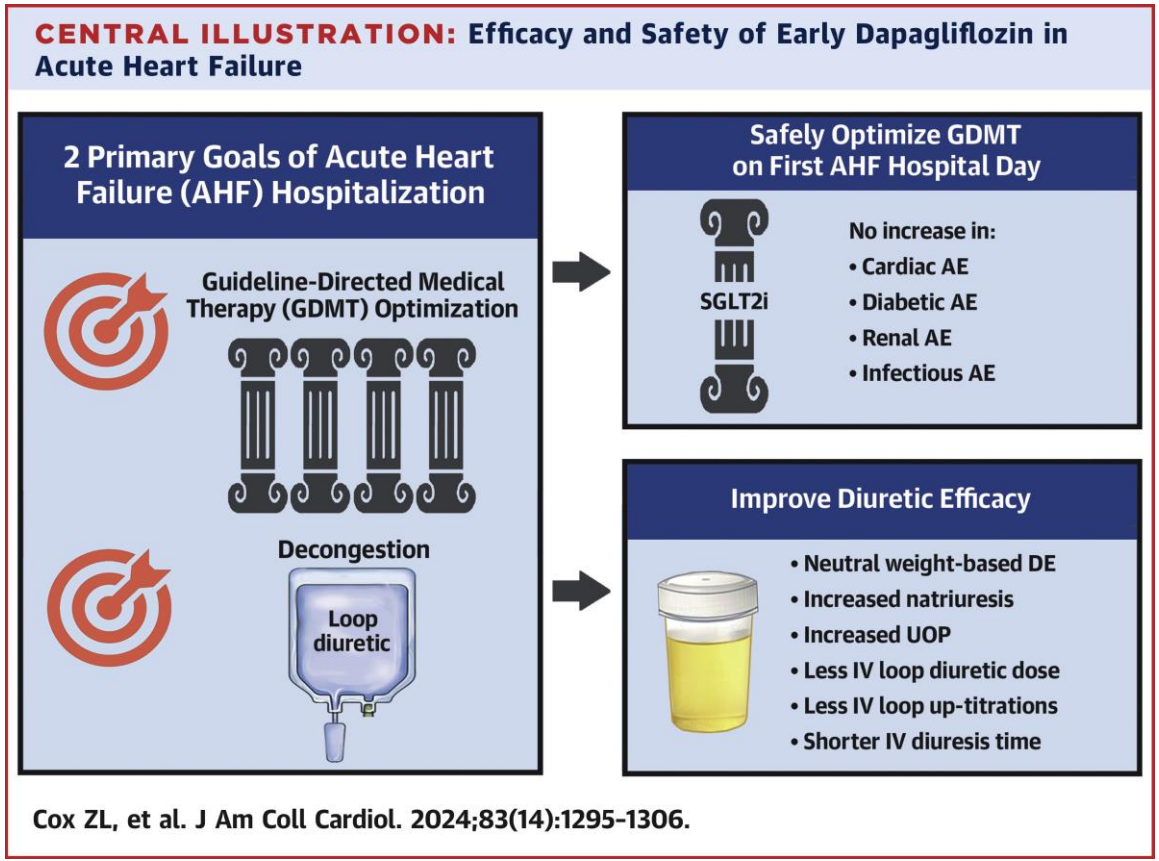
Key Takeaway

Dapagliflozin is a safe option that may optimize diuretic effectiveness and facilitate early GDMT implementation.

ADVOCATE HEALTH

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

DICTATE-AHF: Key Takeaways



Patients discharged on SGLT2i

SGLT2i	Usual Care
64%	46%

P=0.006

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Assessment Question #3

Which of the following statements best reflects the current understanding of SGLT-2 inhibitors in the management of ADHF?

a. SGLT2 inhibitors are contraindicated in ADHF
b. SGLT2 inhibitors do not improve diuretic efficiency in ADHF
c. SGLT2 inhibitors are well tolerated when started early in ADHF
d. SGLT2 inhibitors worsen renal function in ADHF

Reconsidered Strategies

due to lack of benefit and/or increased risk

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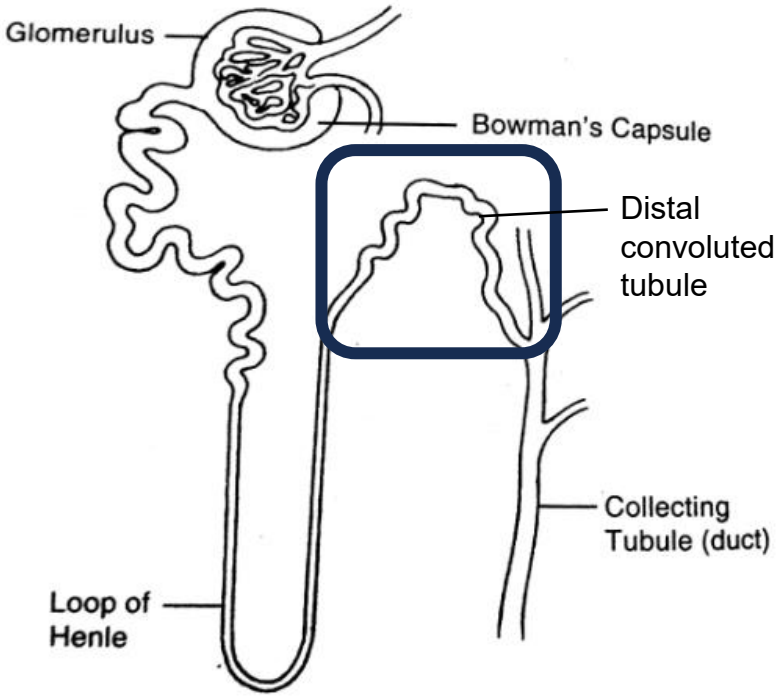
MRAs



Spironolactone Dosing:
12.5 mg PO daily
(max 50 mg/day)

Monitoring:

- Blood pressure
- Serum electrolytes
- Kidney function
- Volume status

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Ferrari F, et al. *Clin Pharmacokinet*. 2025;64(7):987-997.

ATHENA-HF Trial

High-dose spironolactone (100 mg)

VS.

Placebo or 25 mg spironolactone

Primary Outcomes:
No significant difference in log NT-proBNP reduction between the 2 groups (P=0.57)

Key Takeaway
MRAs do not improve diuresis but may aid in diuretic efforts limited by hypokalemia.

ADVOCATE HEALTH

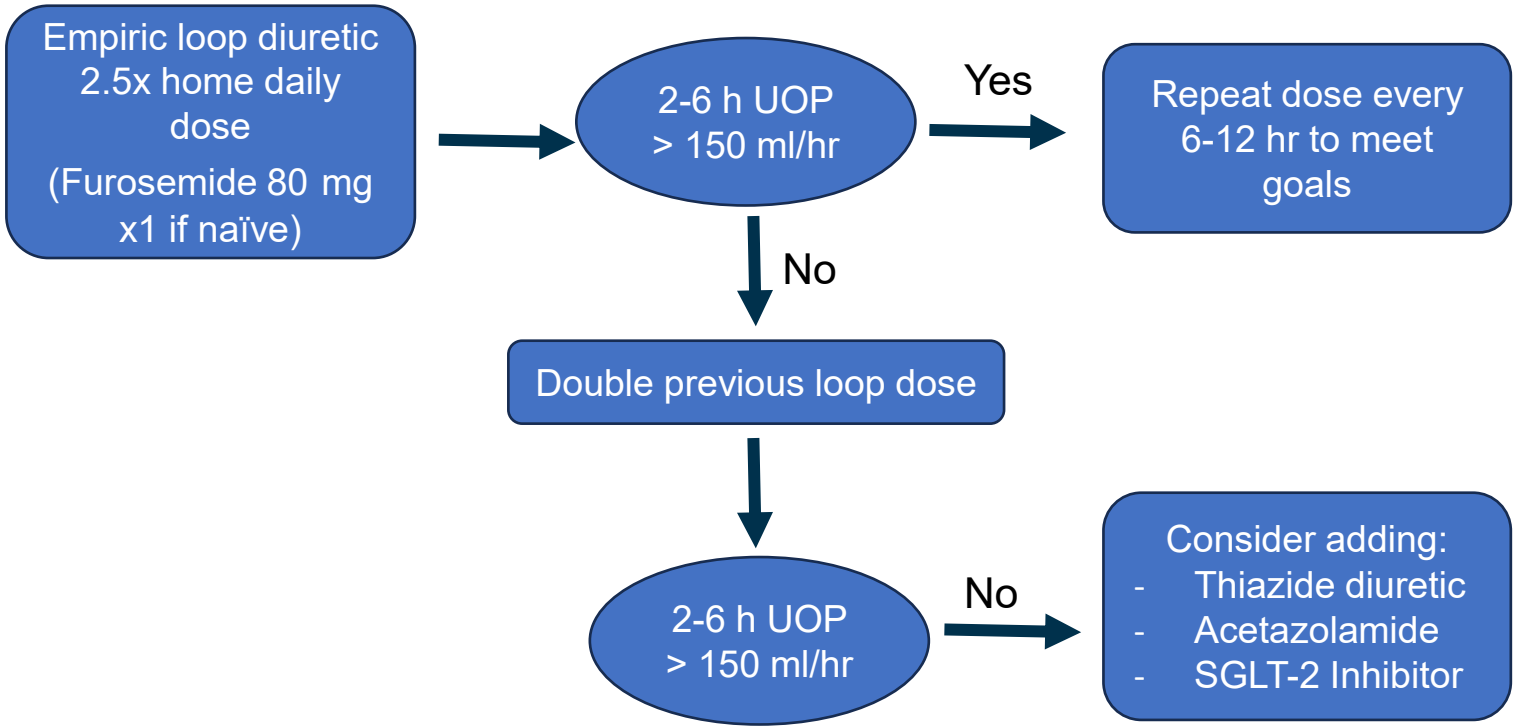
Butler J, et al. *JAMA Cardiology*. 2017;2(9):950. doi:10.1001/jamacardio.2017.2198

Miscellaneous Strategies

Albumin	Low-Dose Dopamine	Ultrafiltration
Meta-analysis: Limited benefit when combined with loop diuretics	DAD-II & ROSE-AHF: No effect on renal or clinical outcomes when added to diuretic therapy	CARRESS-HF: No benefit compared to escalating diuretics ↑ adverse events with UF

Kitsios JD, et al. J Crit Care, 2014;29(2):253-9.
Grodin JL, et al. J Card Fail. 2016;22(11):884-890.
Chen HH, et al. JAMA. 2013;310(23):2533–2543.
Butler J, et al. JAMA Cardiol. 2017;2(9):950.
Bart BA, et al. *NEJM*. 2012;367(24):2296-2304.

Diuretic Augmentation Process



ADVOCATE HEALTH

Felker GM, et al. Am Coll Cardiol. 2020;75(10):1178-95

Summary of Combination Diuretic Strategies

Medications	Location of MOA	Evidence	Diuretic Utility	Considerations
Thiazides	DCT	CLOROTIC, 3T	✅	Improves diuresis; metolazone as effective as CTZ (3T)
Acetazolamide	PCT	ADVOR	✅	Best if HCO_3 ↑
SGLT-2 Inhibitors	PCT	EMPA-RESPONSE-AHF, DICTATE AHF	✅ *	Safe; GDMT; *modest diuretic effect
Spironolactone	DCT	ATHENA	⚠️	Mitigate hypokalemia; GDMT
Tolvaptan	Collecting duct	EVEREST, 3T	❌	Expensive; no added benefit vs thiazides; may be considered in symptomatic hyponatremia

*High utility given overall HF benefits in addition to diuretic benefit
CTZ: chlorothiazide; HCO_3: bicarbonate GDMT: guideline directed medication therapy;

ADVOCATE HEALTH

Emerging Strategies for Diuretic Resistance

ADVOCATEHEALTH

	Hypertonic Saline	Chloride Supplementation	Urine Sodium Monitoring
Rationale	↑ intravascular volume, ↑ renal sodium delivery, ↓ neurohormonal activation	Hypochloremia linked to ↑ neurohormonal activation and ↓ natriuresis	Early marker of diuretic response
Evidence of Benefit*	↑ diuretic efficiency without ↑ adverse events	↑ diuretic efficiency	↑ natriuresis, ↓ LOS

*Evidence primarily derived from small studies, retrospective analyses, or observational data; randomized controlled trial evidence is limited or lacking.

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Key Takeaways

- Diuretic resistance is multifactorial, primarily driven by intra-renal mechanisms
- Loop diuretics remain the foundation of therapy, but are often underdosed or used sub-optimally
- Adjunctive therapies (thiazides, acetazolamide, SGLT2i) can enhance diuresis
- Emerging strategies (chloride supplementation, urine sodium monitoring) are under evaluation

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Questions?

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