Il corretto uso dei diuretici nello scompenso cardiaco

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Presentation outline

- **Pharmacokinetic and pharmacodynamic mechanisms of diuretic resistance in heart failure**
- **Sequential nephron blockade: two-drug combination or a multilevel approach?**

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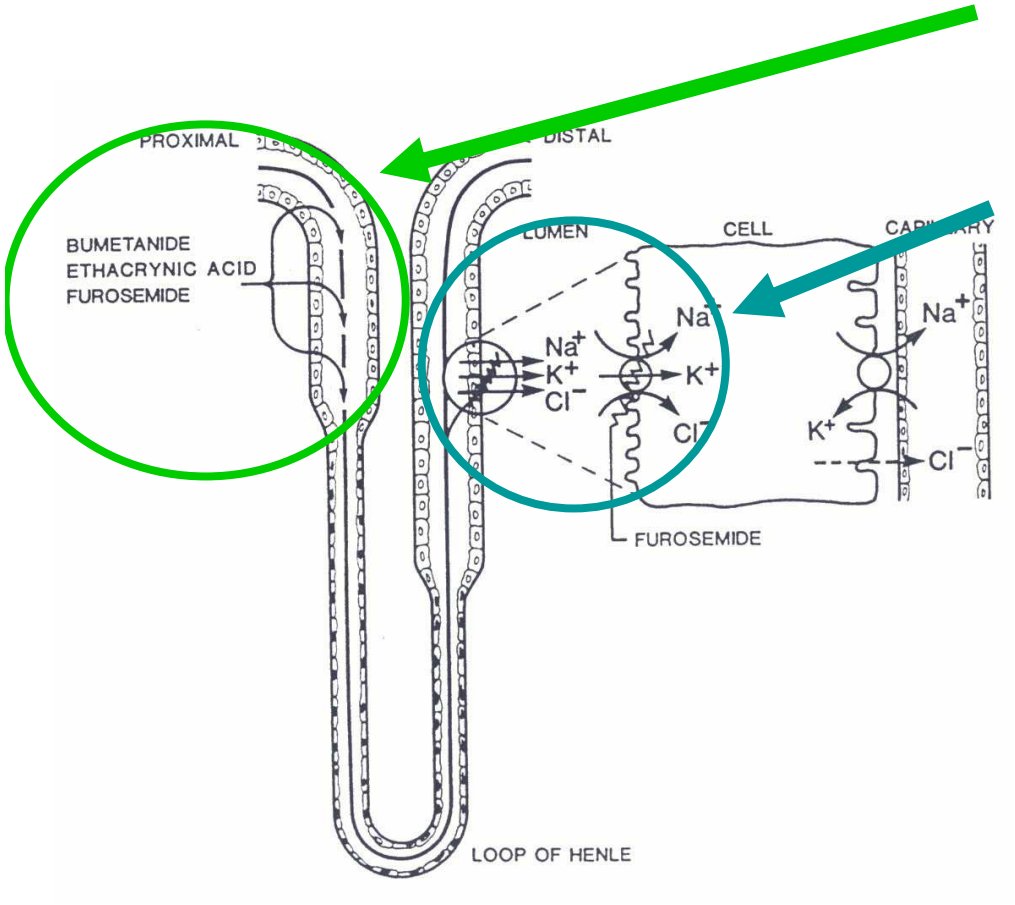
- **Sequential nephron blockade: two-drug combination or a multilevel approach?**

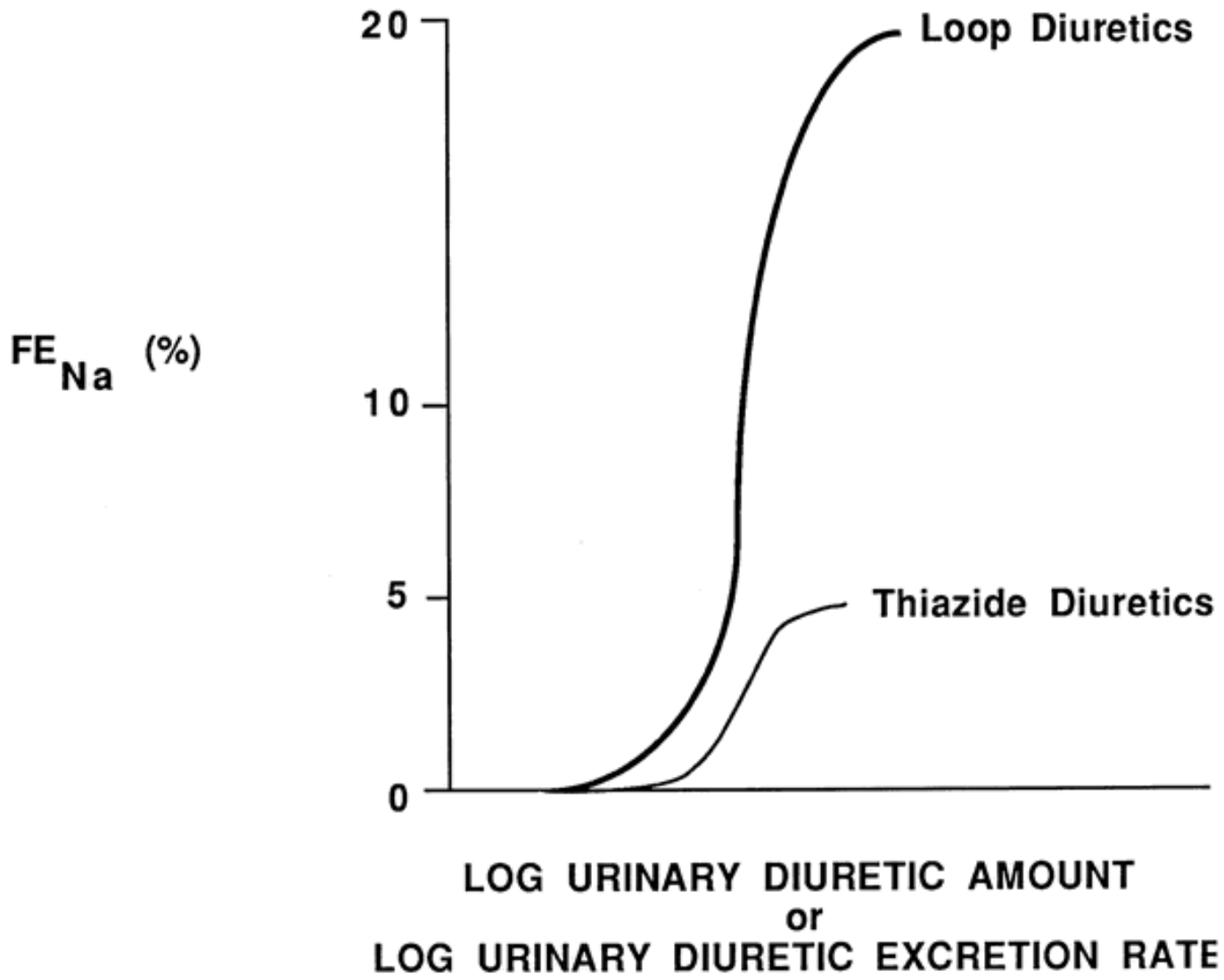
Characteristics of loop diuretics



J Am Soc Nephrol 13: 798–805, 2002

- LD inhibit Na, K e Cl reabsorption in the THAL
- They are secreted into the PT (S_2 segment) lumen through organic acid transporters
- They are effective only if present on the luminal side
- Dose-dependent efficacy. A response threshold dose exists
- The natriuretic effect tends to plateau at a urinary diuretic excretion rate achieving complete saturation of the Na-K-2Cl co-transporter

Characteristic dose-response curve of diuretics



Ellison DH, Cardiology 2001; 96: 132-43

Conditions to be satisfied for an optimal response to LD

- Achieving ***threshold dose*** and maintaining ***plateau effect*** (i.e., *eliminating pharmacokinetic sources of resistance*)

- ***Maintaining drug effect beyond site of molecular interaction site*** (i.e., *eliminating pharmacodynamic sources of resistance*)

Pharmacokinetic mechanisms of diuretic resistance

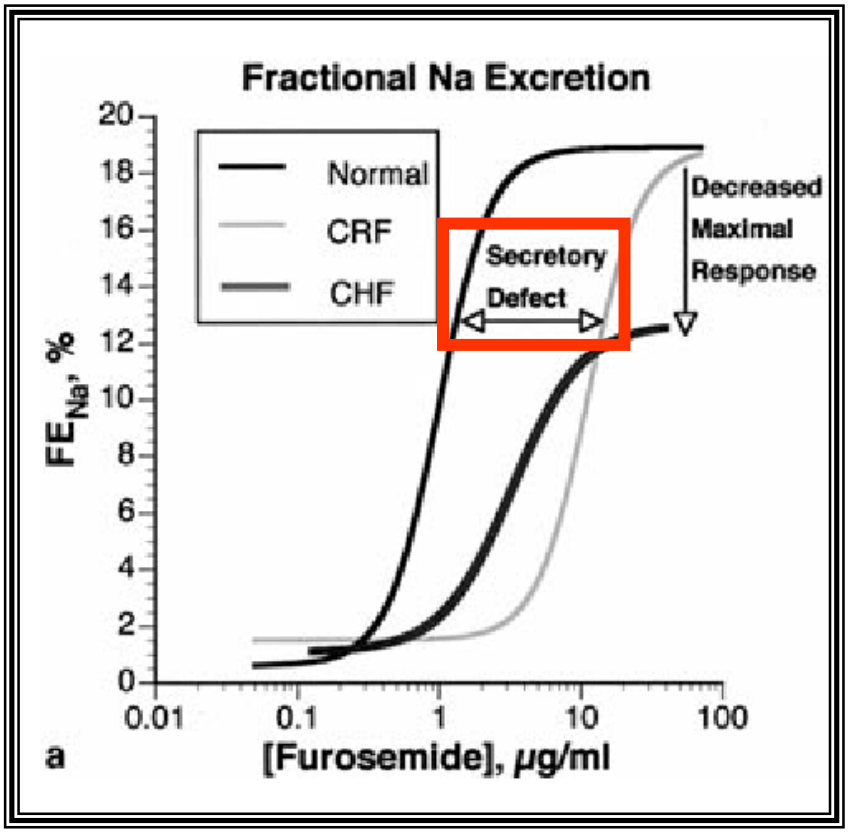
(lower drug availability at site of action)

Rightward shift of the dose-response curve (increased threshold for diuretic effect)

→ diuretic concentration in the tubular fluid is reduced

Causes

-Slower intestinal absorption
-Decreased renal perfusion
-Increased distribution volume
-Altered tubular secretion



Actions

- **Increase dose**
- **Oral → IV**
- **Boluses (at least x 2/day)**
- ***Continuous IV infusion***.

Optimization of diuretic treatment in severe heart failure: Practical aspects (1)

- ***Dose***:
  - is there really a maximum dose beyond which we should deem a patient “diuretic resistant”?

Effective IV doses of loop diuretics in CHF and CRF

	Renal Insufficiency		
	Moderate	Severe	Heart Failure*
Mechanism of diminished response to diuretic	Impaired delivery to site of action		Diminished nephron response
Therapeutic strategy	Sufficient dose to attain effective excretion rates of diuretic at site of action		Increased frequency of effective dose
Ceiling dose, mg (iv)			
Furosemide	80–160	160–200	40–80
Bumetanide	4–8	8–10	1–2
Torsemide	20–50	50–100	10–20

*Preserved renal function (e.g., creatinine clearance >75 ml/min)

	Creatinine Clearance, ml/min			
	All levels	<25	25–75	>75
	Intravenous loading dose, mg	Infusion rate, mg/h		
Furosemide	40	20, then 40	10, then 20	10
Bumetanide	1	1, then 2	0.5, then 1	0.5
Torsemide	20	10, then 20	5, then 10	5

Shankar SS & Brater DC , Am J Physiol 2003;284:F11-F21

Optimization of diuretic treatment in severe heart failure: Practical aspects (2)

- ***Mode of iv administration of loop diuretics***:
  - ➢boluses or continuous infusion?

Diuretic Efficacy of High Dose Furosemide in Severe Heart Failure: Bolus Injection Versus Continuous Infusion

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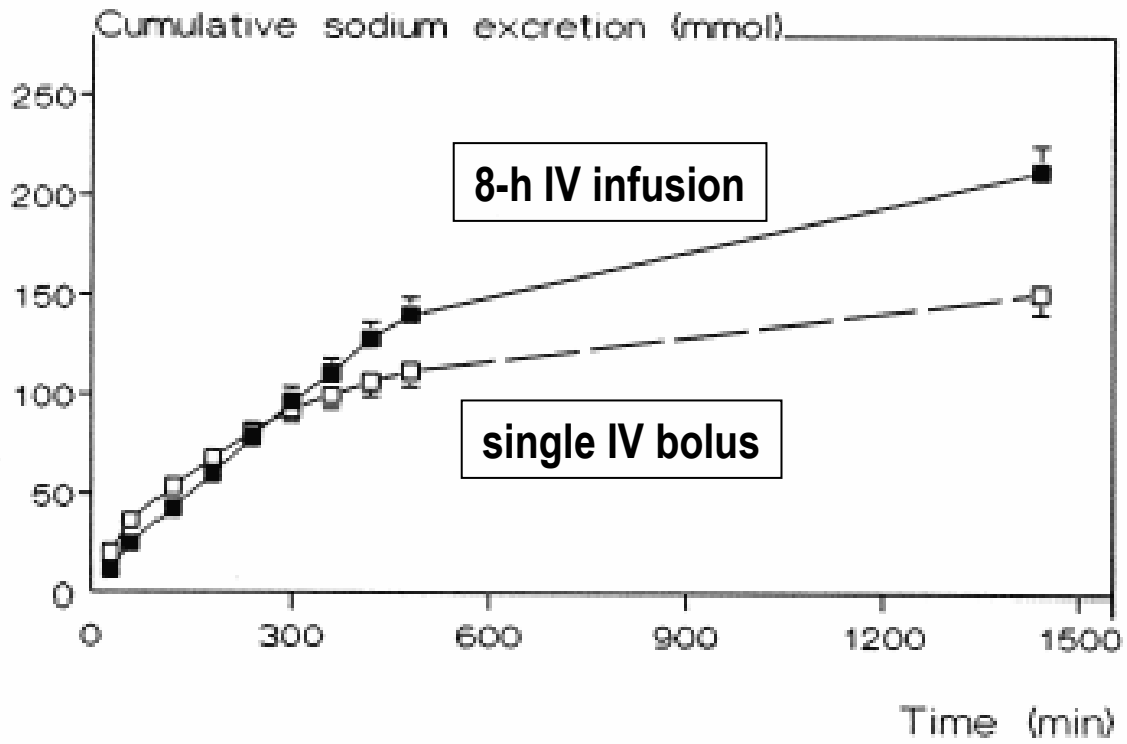

(J Am Coll Cardiol 1996;28:376–82)

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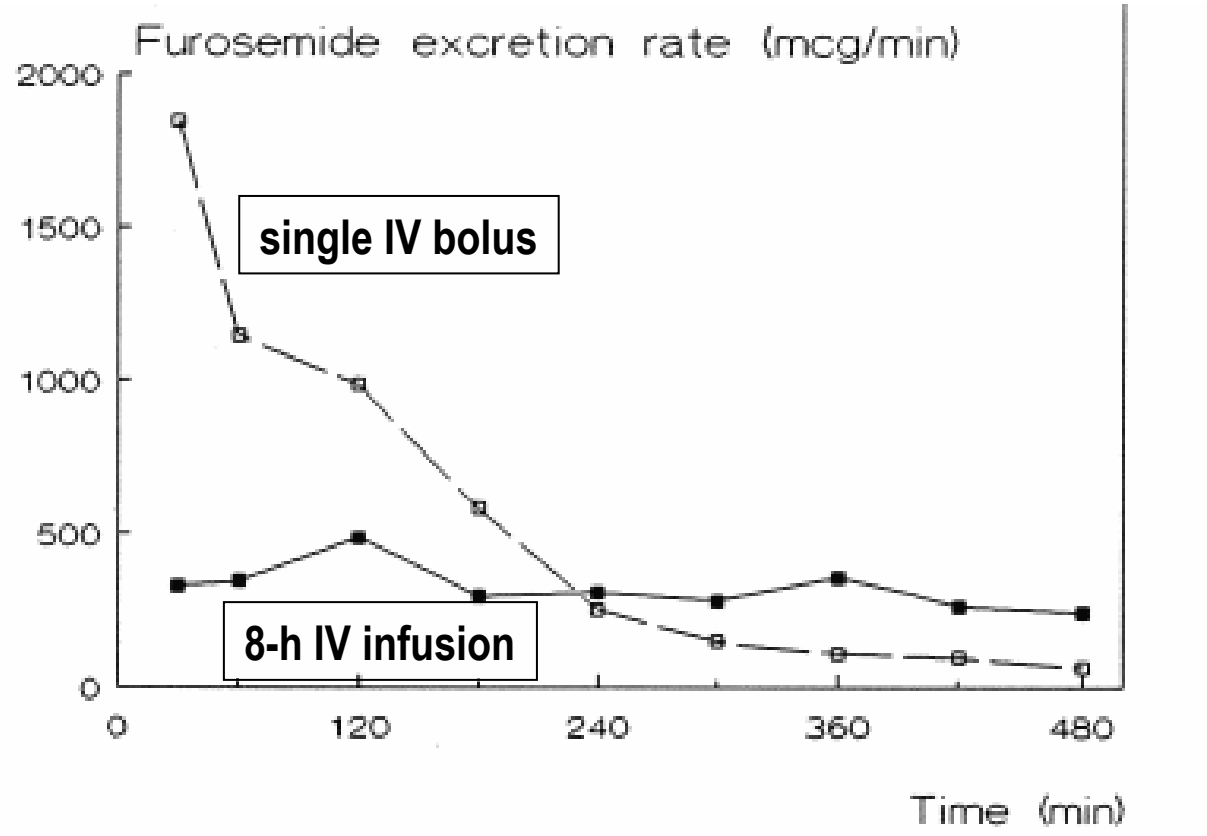

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IV administration of loop diuretics: low or high doses? Bolus or continuous infusion?

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Diuretic Strategies in Patients with Acute Decompensated Heart Failure

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METHODS

In a prospective, double-blind, randomized trial, we assigned 308 patients with acute decompensated heart failure to receive furosemide administered intravenously by means of either a bolus every 12 hours or continuous infusion and at either a low dose (equivalent to the patient's previous oral dose) or a high dose (2.5 times the previous oral dose). The protocol allowed specified dose adjustments after 48 hours. The

N Engl J Med 2011;364:797-805.

Intermittent boluses (every 12 h) or continuous infusion?

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 dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	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

N Engl J Med 2011;364:797-805.

Total diuretic received during randomization period

DOSE allowed for adjustment of randomized study treatment at 48 hours, as well as allowing the need for additional diuretics as "rescue therapy". Total diuretic dosage (median IV furosemide equivalents) received during the 72 hours between randomization and the assessment of the primary end points is shown below for each treatment comparison.

Median Loop Diuretic Received over 72 hours (in IV furosemide equivalents)							
	Q12	Cont.	P value		Low-dose	High-dose	P value
Study drug (mg) Median (25^{th}, 75^{th})	518 (292, 832)	406 (240, 628)	0.008		285 (200, 480)	688 (429, 1067)	< 0.0001
Open label loop diuretic (mg) Median (25^{th}, 75^{th})	80 (60,200)	95 (40, 160)	0.74		120 (60, 210)	80 (40, 160)	0.08
Total loop diuretic (mg) Median (25^{th}, 75^{th})	592 (370, 884)	480 (300, 773)	0.06		358 (238, 560)	773 (518, 1100)	< 0.0001

At least 25% of the patients in the continuous infusion arm received daily doses of loop diuretic likely insufficient to reach the pharmacokinetic threshold

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The median total dose of LD received by the patients in the bolus arm was marginally higher compared to that in the continuous infusion arm

N Engl J Med 2011;364:797-805.

Thiazide diuretic use

Thiazide diuretics were allowed in DOSE even given chronically. The need for the addition of a new thiazide diuretic during the 72 period of study drug treatment was considered as a treatment failure, which is summarized below.

	Q12	Cont.	P value		Low-dose	High-dose	P value
Thiazide added during the 72 hour treatment period (%, n)	16% (25)	7% (11)	0.02		15% (23)	8% (13)	0.06

A greater number of patients in the bolus arm needed the addition of a new thiazide diuretic

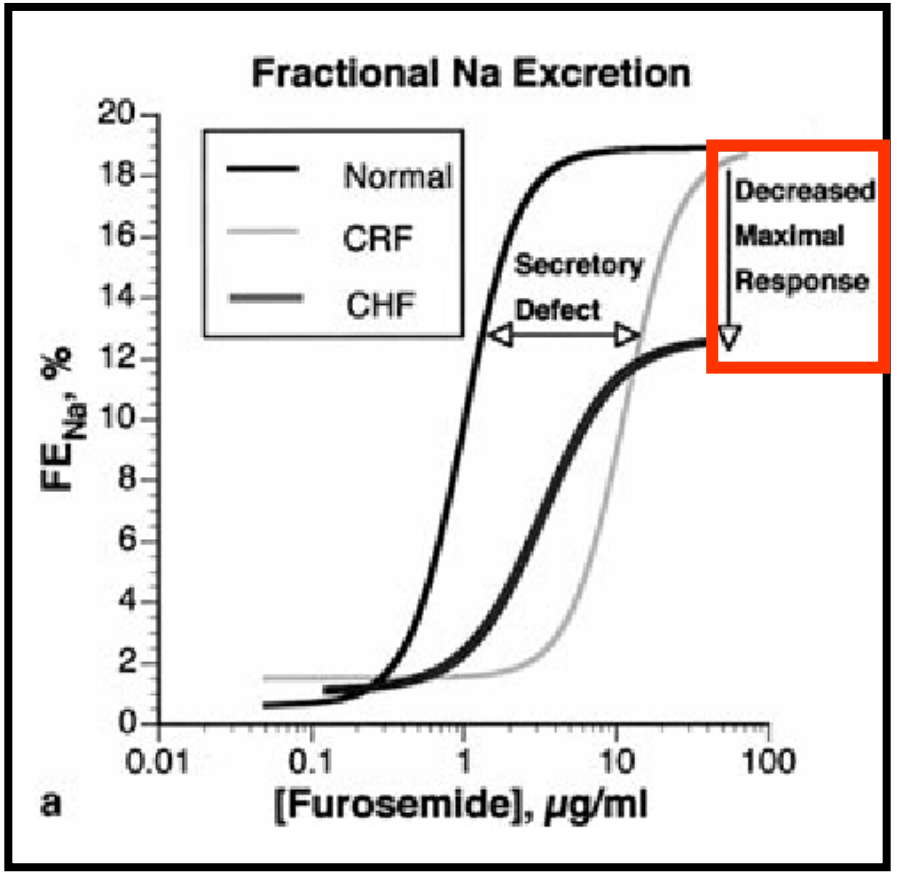
N Engl J Med 2011;364:797-805.

Pharmacodynamic mechanisms of diuretic resistance
(Impaired tubular response)

Decreased maximum effect ("plateau") despite appropriate diuretic concentration in the tubular fluid

Causes

- **Post-diuretic rebound (increased Na^+ reabsorption in the PT)**
- **Late braking (hypertrophy of DT cells)**
- **Renal failure**

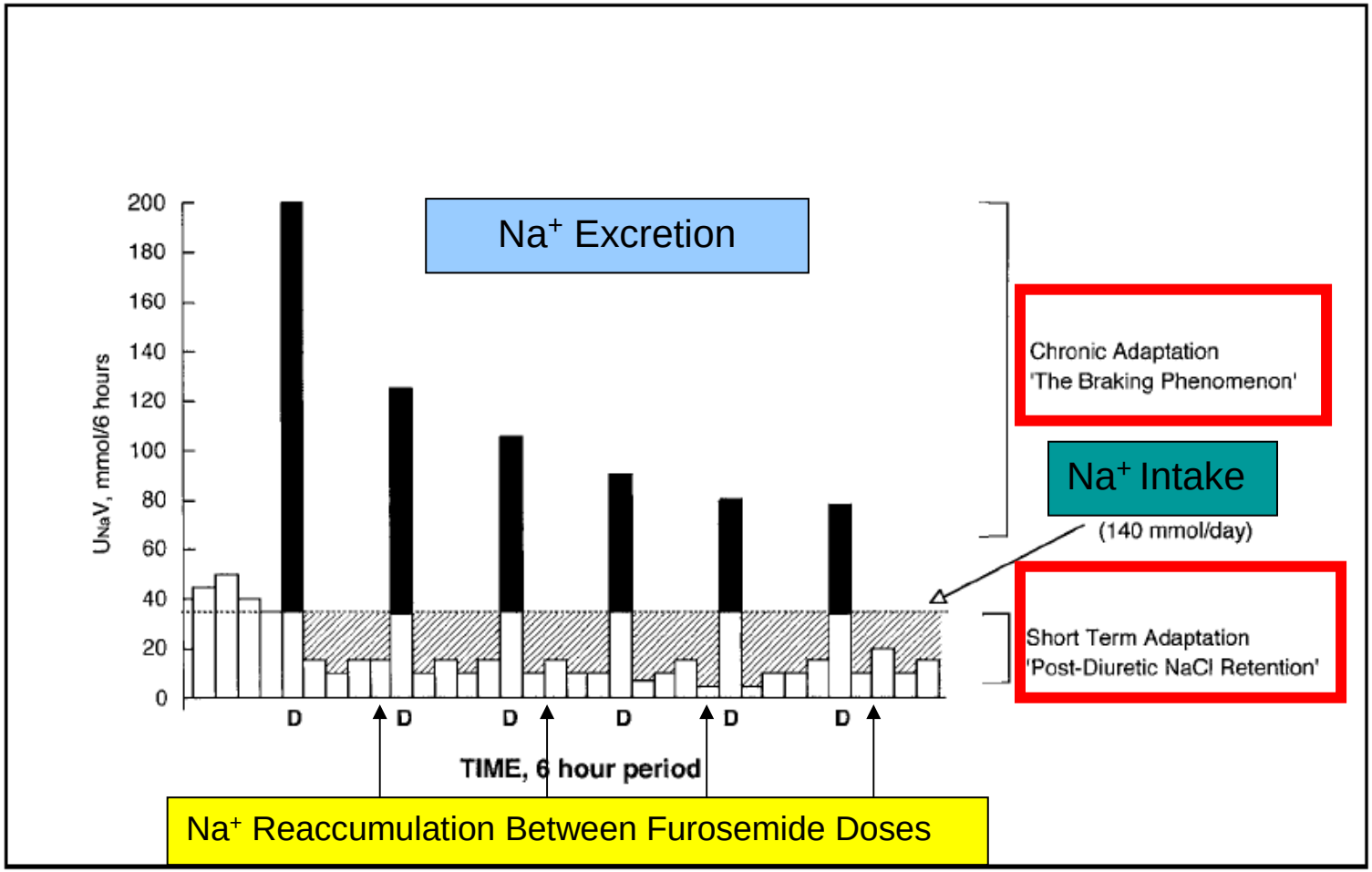


Actions

- repeated doses over 24 hours
- ***sequential nephron blockade***

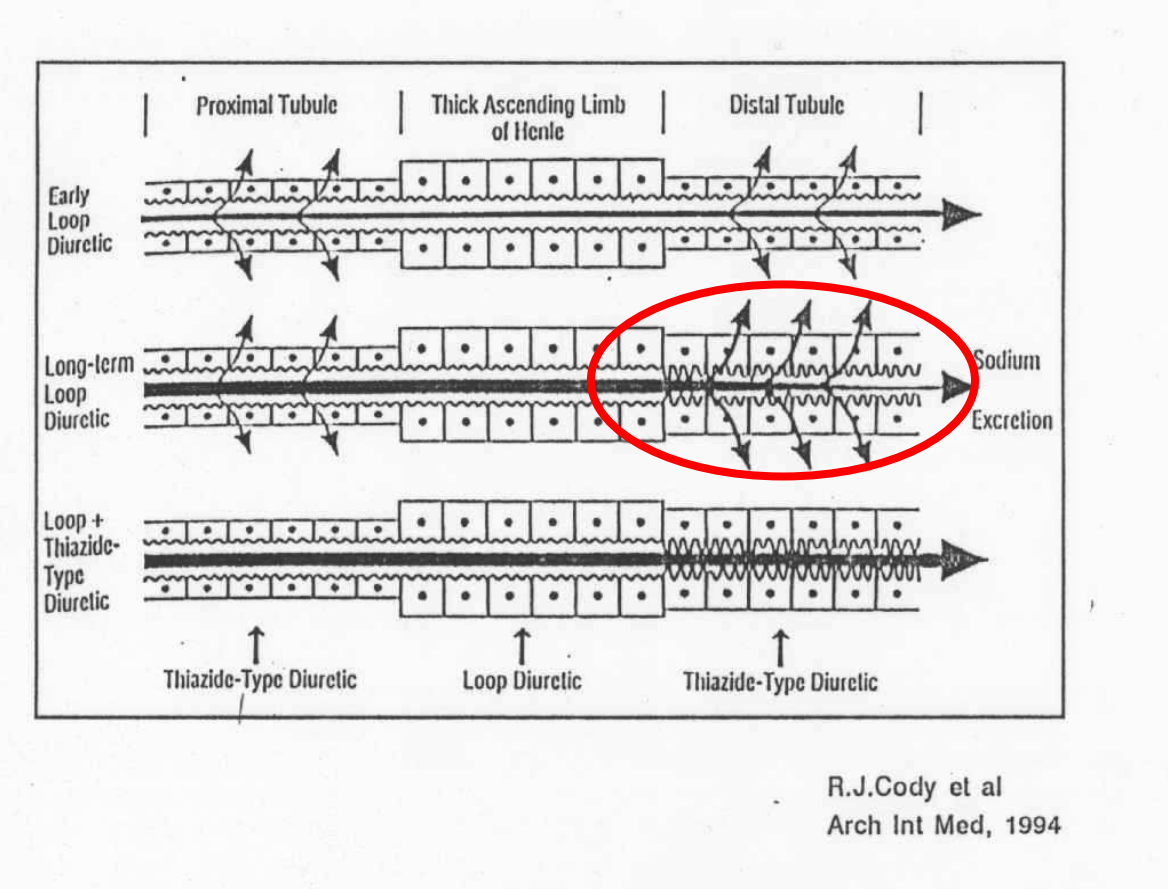
Resistance to loop diuretics in heart failure
Pharmacodynamic mechanisms

1. **Post-diuretic rebound (early braking)**
2. **Late braking phenomenon**



Wilcox et al, Kidney Int 1987;31:135-42

The late braking phenomenon: increased NaCl reabsorption capacity in the distal nephron following exposure to a chronic sodium load



Mechanisms

- **Hypertrophy of DT cells**
- **Increased activity of the basolateral Na^+/K^+-ATPase**
- **Increased number of thiazide-sensitive NaCl transporters**

Presentation outline

- Pharmacokinetic and pharmacodynamic mechanisms of diuretic resistance in heart failure

✓**Sequential nephron blockade: two-drug combination or a multilevel approach?**

Optimization of diuretic treatment in severe heart failure: Practical aspects (3)

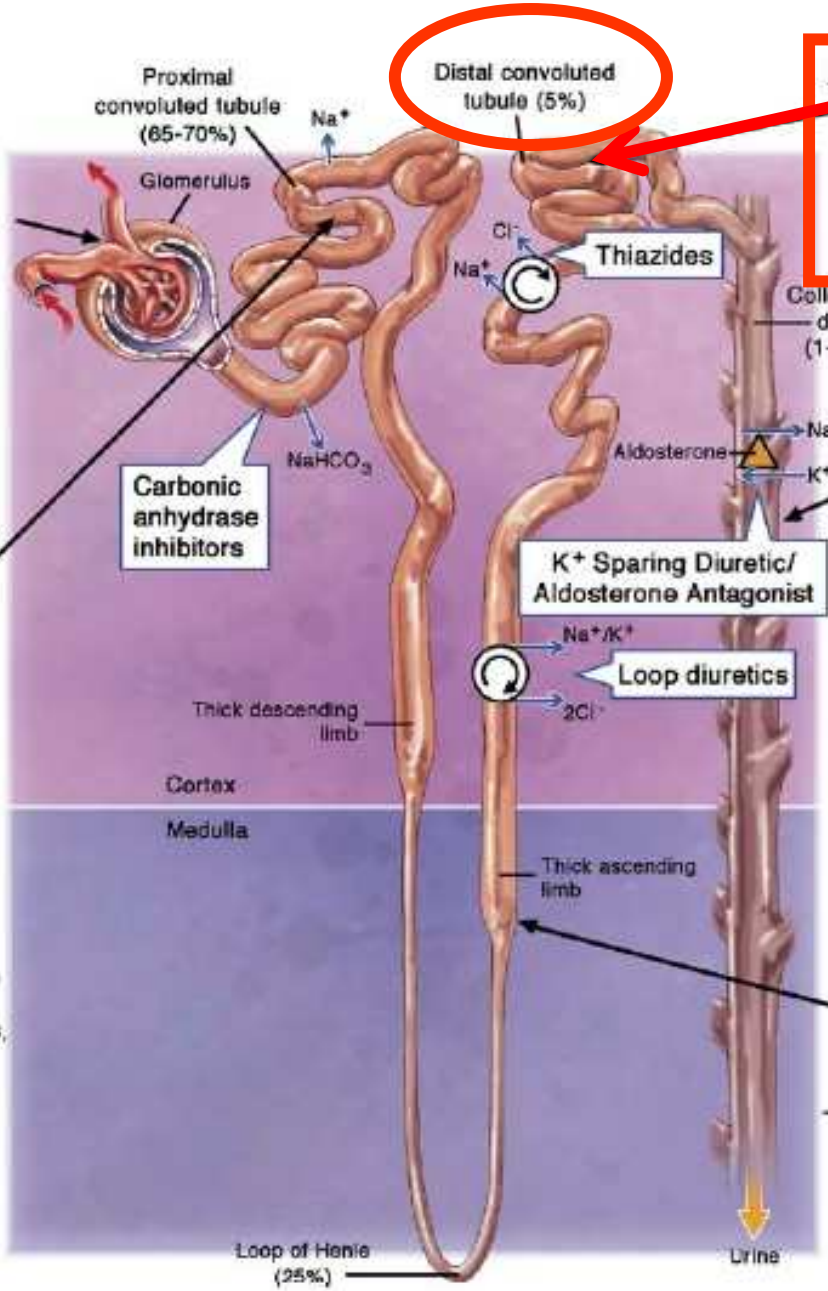
- ***Sequential nephron blockade***:
  - ➢ an important opportunity frequently overlooked
    - **Why?** (Rationale)
    - **How?** (Which types of diuretics should be combined?)
  - ➢ *Open question:*
    - **When?** (On top of maximum doses of LD, or start with multidrug low-dose combination?)

Reduced GFR:

Barriers	Potential solution
Abnormal glomerular hemodynamics	Discontinue NSAIDs, consider holding ACEI/ARB
Low cardiac output	Hemodynamic support
Chronic kidney disease or functional renal hypoperfusion	Increase LD dose

Proximal Tubule Hyperfunction:

Barriers	Potential solution
Neuro-hormonal activation	ACEI/ARB
Sodium-avid states	Increased LD doses, proximal tubule diuretics (i.e. acetazolamide)
Post-diuretic effect	Multiple daily doses, continuous LD infusion
Excessive daily sodium intake	Sodium restriction



Distal Tubule Hypertrophy:

Barriers	Potential solution
Rebound sodium retention	Sequential nephron blockade (Combination diuretic therapy)

Distal Nephron Hyperfunction:

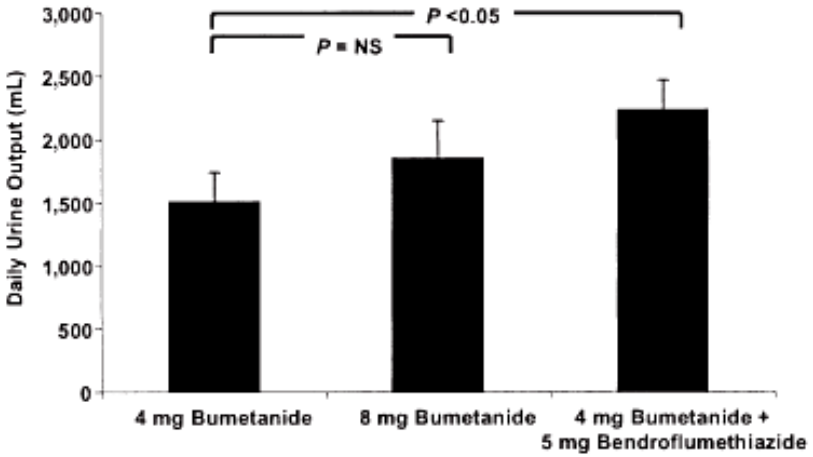
Barriers	Potential solution
Excessive aldosterone-mediated sodium retention	Aldosterone antagonist, K+ - sparing diuretic (ENaC blocker)
Excessive vasopressin-mediated water retention	Vasopressin antagonist, free water restriction

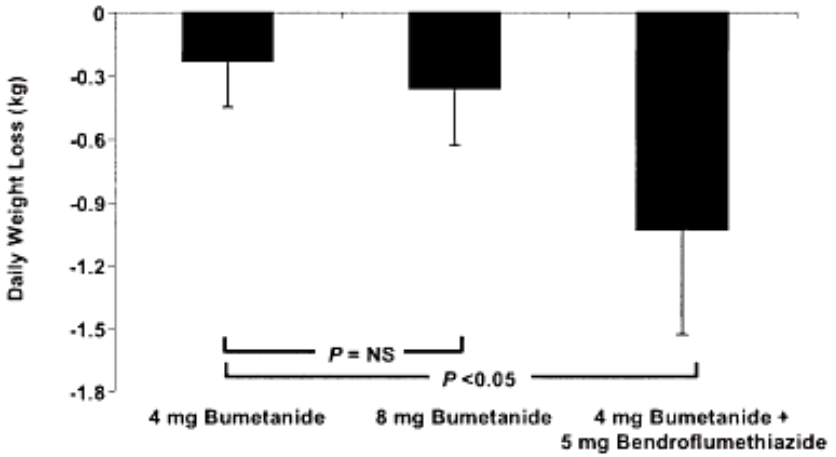
Loop of Henle Hyperfunction:

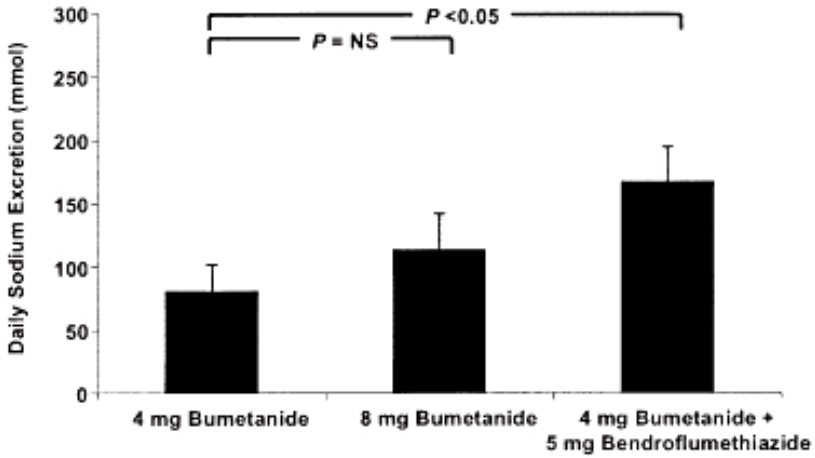
Barriers	Potential solution
Braking effect	Higher LD doses

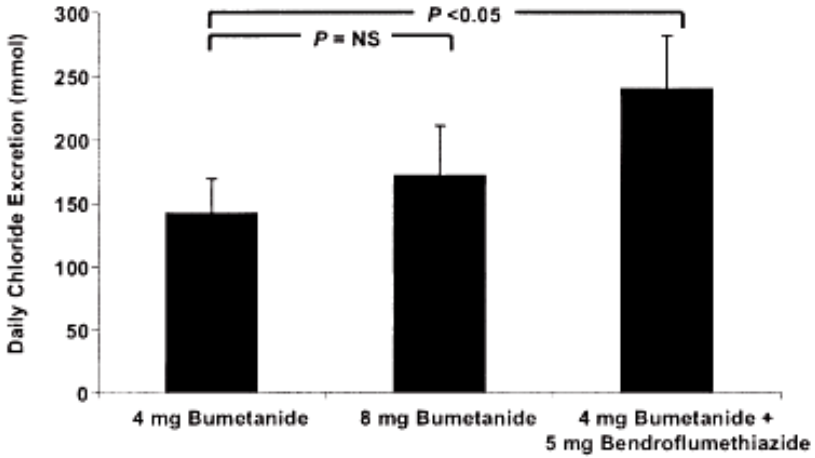
J Am Coll Cardiol 2010;56:1527–34)

Effects of the combination of a loop diuretic and a thiazide on urine output, weight loss and NaCl excretion in pts with HF









Sigurd B et al , Am Heart J 1975;89:163-70

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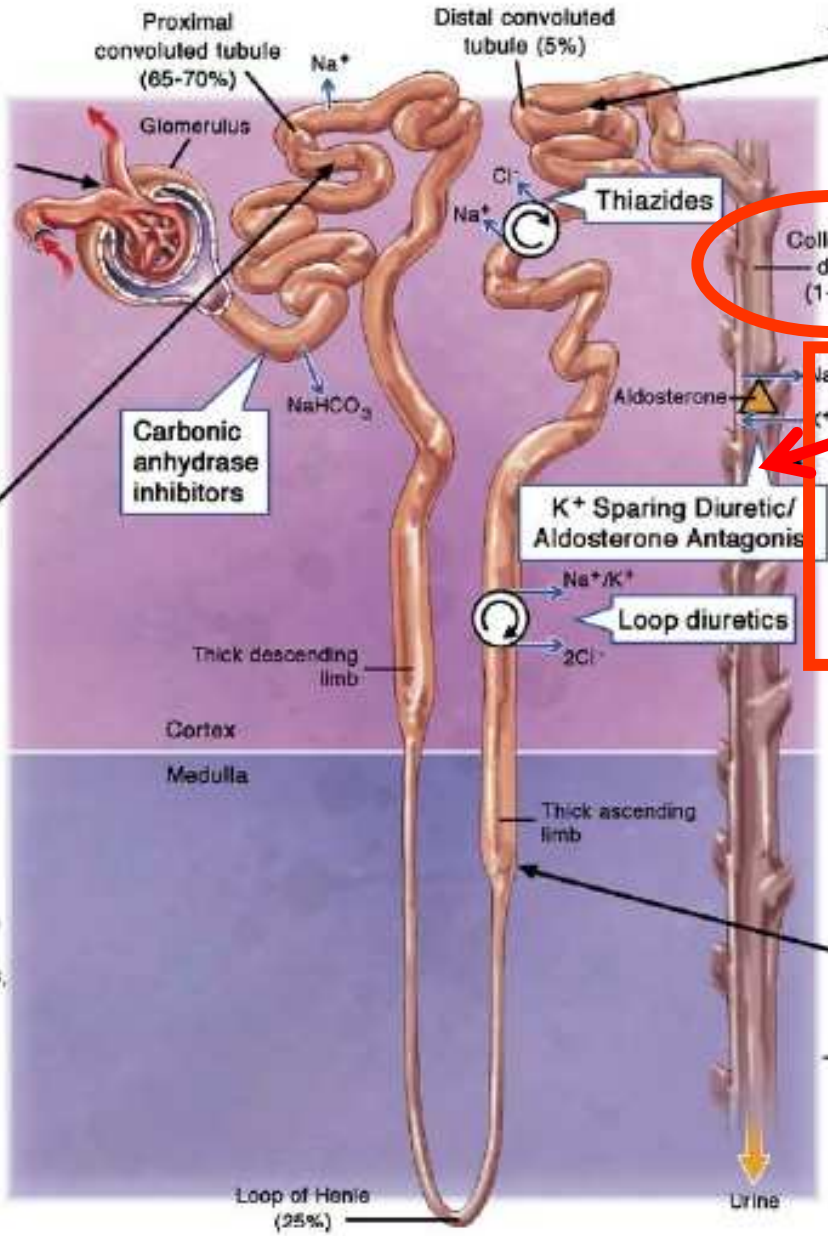

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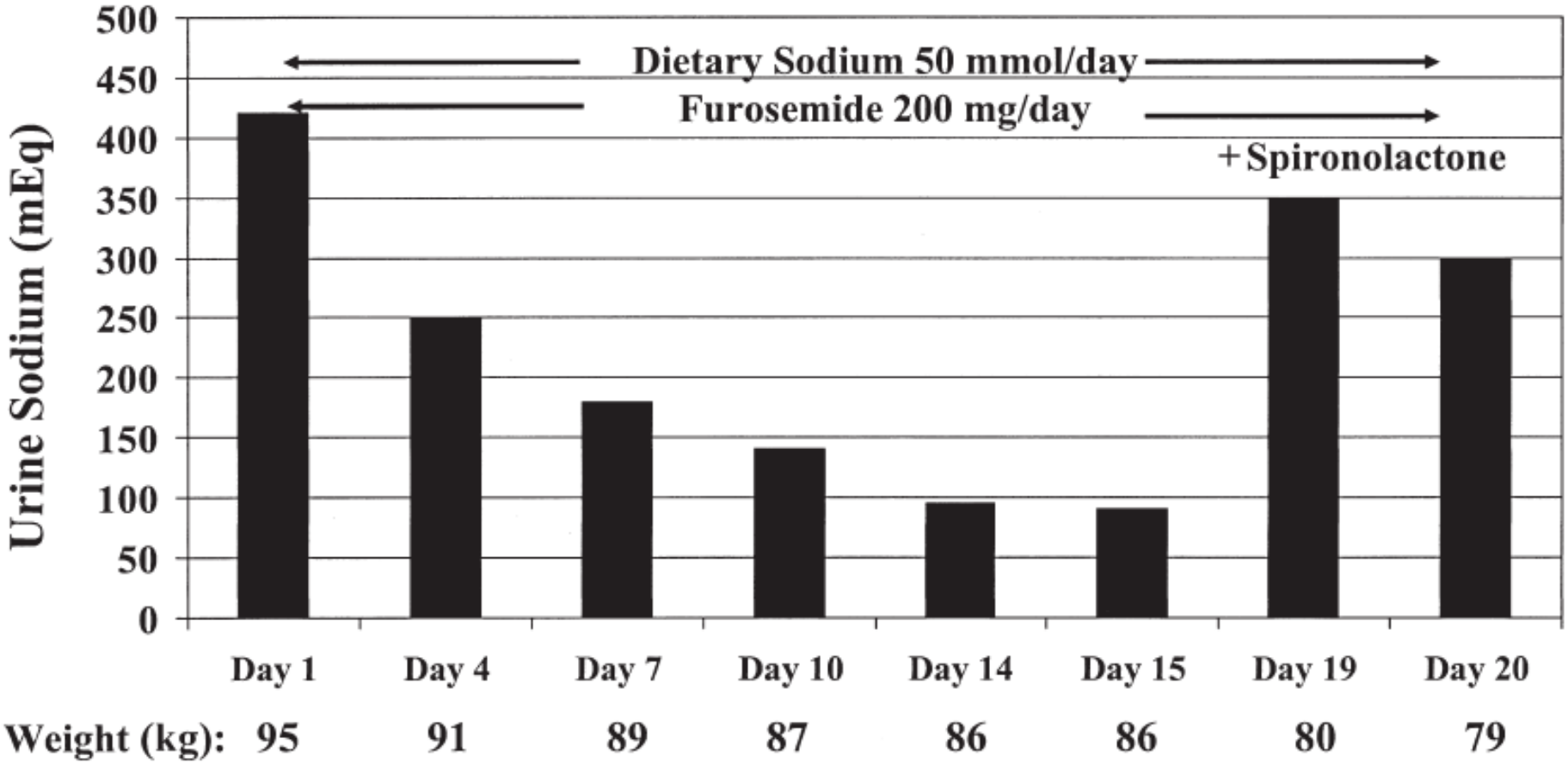
J Am Coll Cardiol 2010;56:1527–34)

Effects of the combination of a loop diuretic and spironolactone on Na^+ excretion and weight loss in HF pts unresponsive to ordinary therapy



Van Vliet AA et al , Am J Cardiol 1993;71:21A-27A

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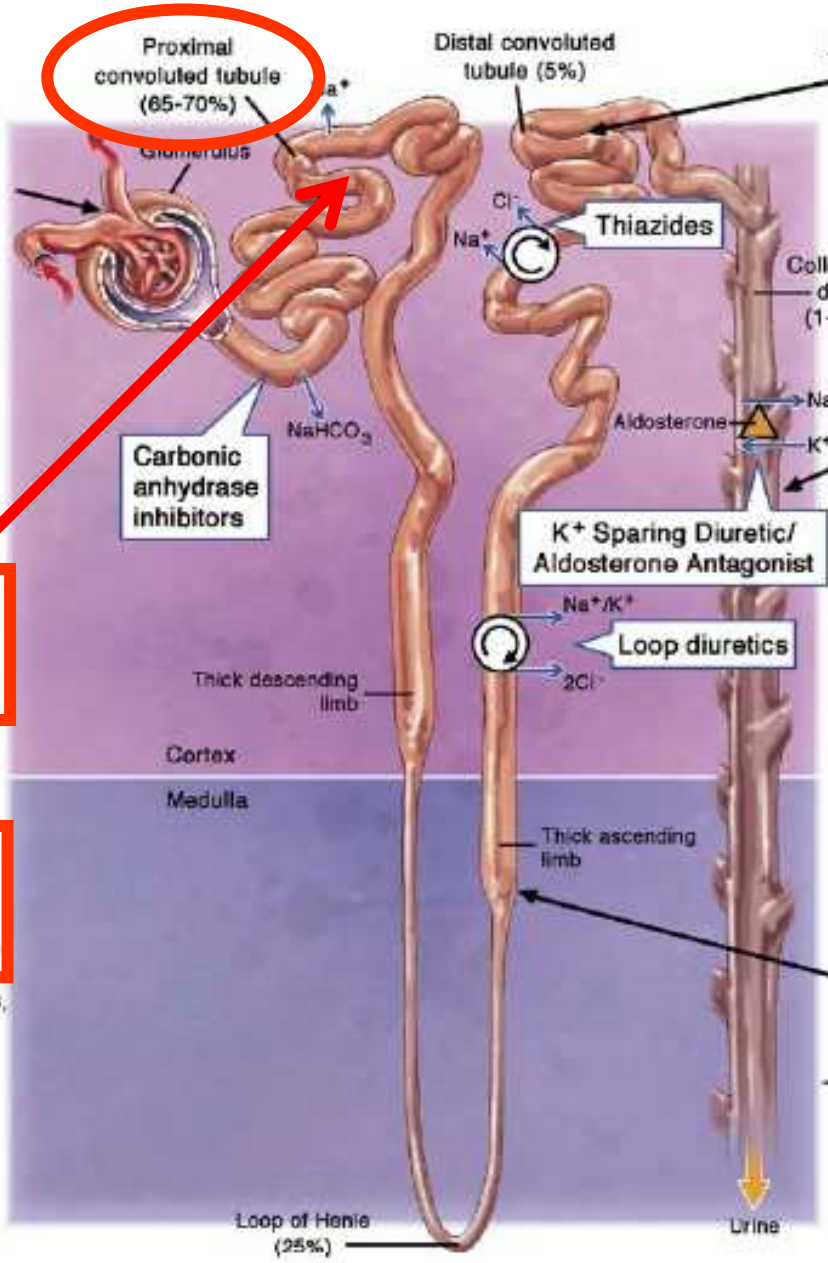

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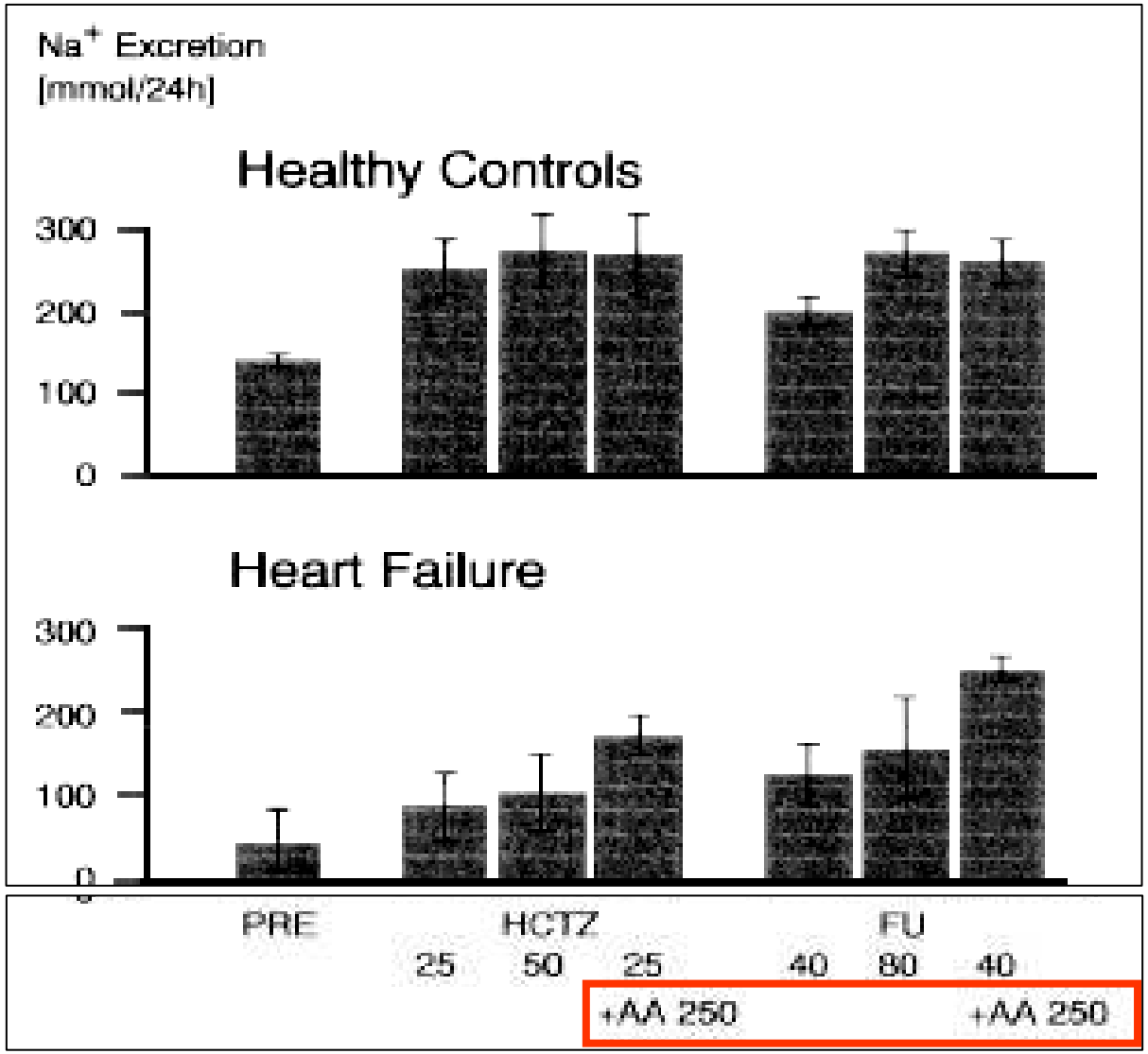
Inhibition of proximal Na^+ reabsorption with acetazolamide breaks resistance to loop diuretics and thiazides in heart failure



Knauf H & Mutschler E, J Cardiovasc Pharmacol 1997; 29:367-72

Sequential nephron blockade in advanced HF: adequate doses of thiazides, acetazolamide and K-sparing agents

To a ceiling dose of a loop diuretic (table 1) add:

DCT diuretics

metolazone 2.5–10 mg per os daily[1]

hydrochlorothiazide (or equivalent) 25–100 mg per os daily

chlorothiazide 500–1,000 mg intravenously

Proximal tubule diuretics

acetazolamide 250–375 mg daily or up to 500 mg intravenously

Collecting duct diuretics

spironolactone 100–200 mg daily

amiloride 5–10 mg daily

[1] Metolazone is generally best given for a limited period of time (3–5 days) or should be reduced in frequency to 3 times per week once ECF volume has declined to the target level. Only in patients who remain volume expanded should full doses be continued indefinitely, based on the target weight.

Take home messages

- Diuretic treatment is still a therapeutic mainstay in advanced HF. ***A major cause of diuretic resistance is in fact the incorrect use of diuretics***, due to inadequate consideration of both pharmacokinetic and pharmacodynamic principles.

- Sequential nephron blockade with at least a loop diuretic and a thiazide, plus an antialdosteronic agent except in pts with severe renal dysfunction, is mandatory to achieve negative fluid and sodium balance.

- Acetazolamide may be useful to circumvent excess proximal Na^+ reabsorption, especially with concomitant metabolic alkalosis.