Clinical Aspects of Diuretic use in Hypertensive Patients and Cardiao-Nephrologic Disorders

Diuretics Use , an Overview

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Treatment of Diuretic Resistance

AJKD

2016

Ewout J. Hoorn, MD, PhD,[1] and David H. Ellison, MD

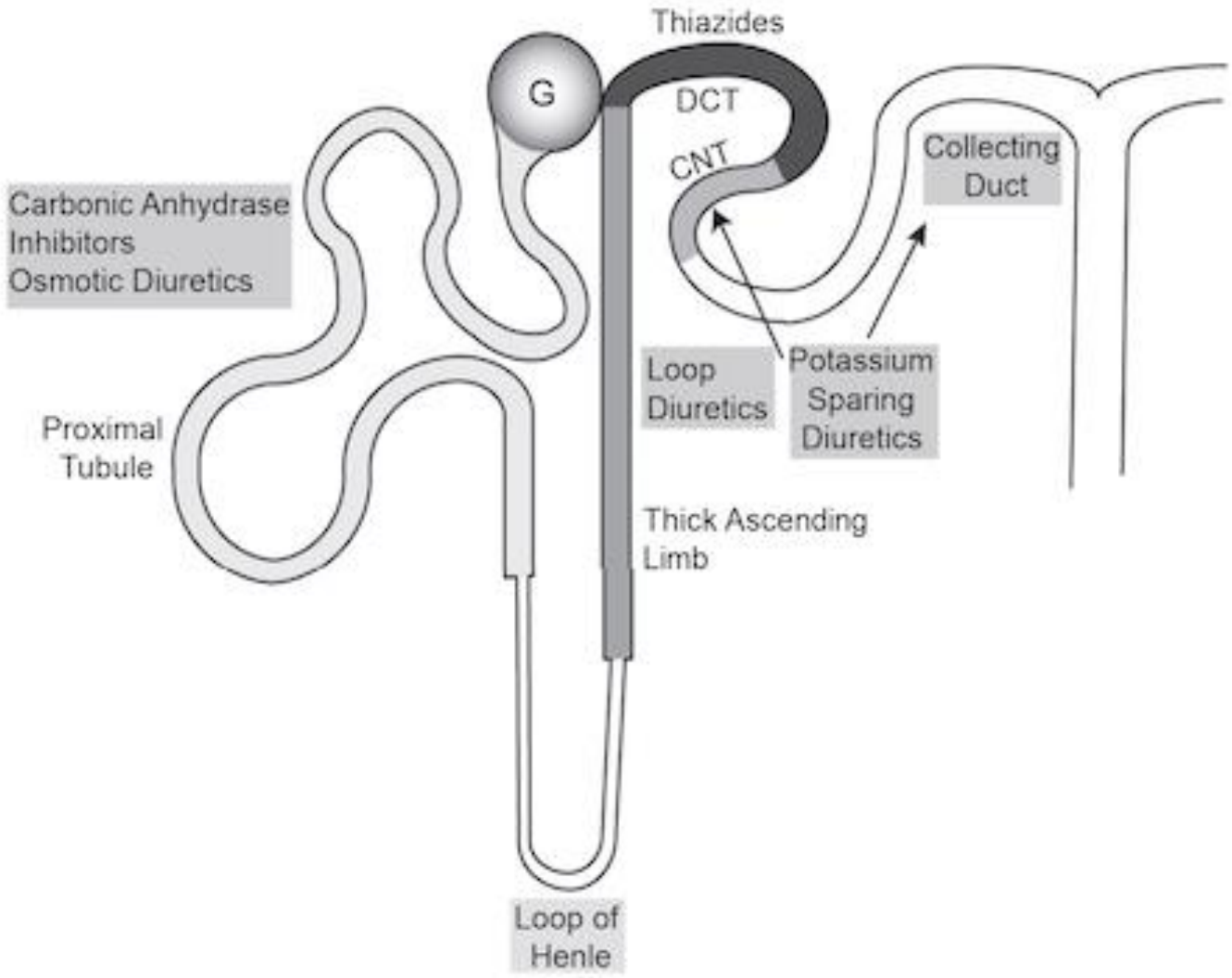

Figure 2. Schematic of a nephron shows sites of action of diuretics along the various segments. Abbreviations: CNT, connecting tubule; DCT, distal convoluted tubule; G, glomerulus.

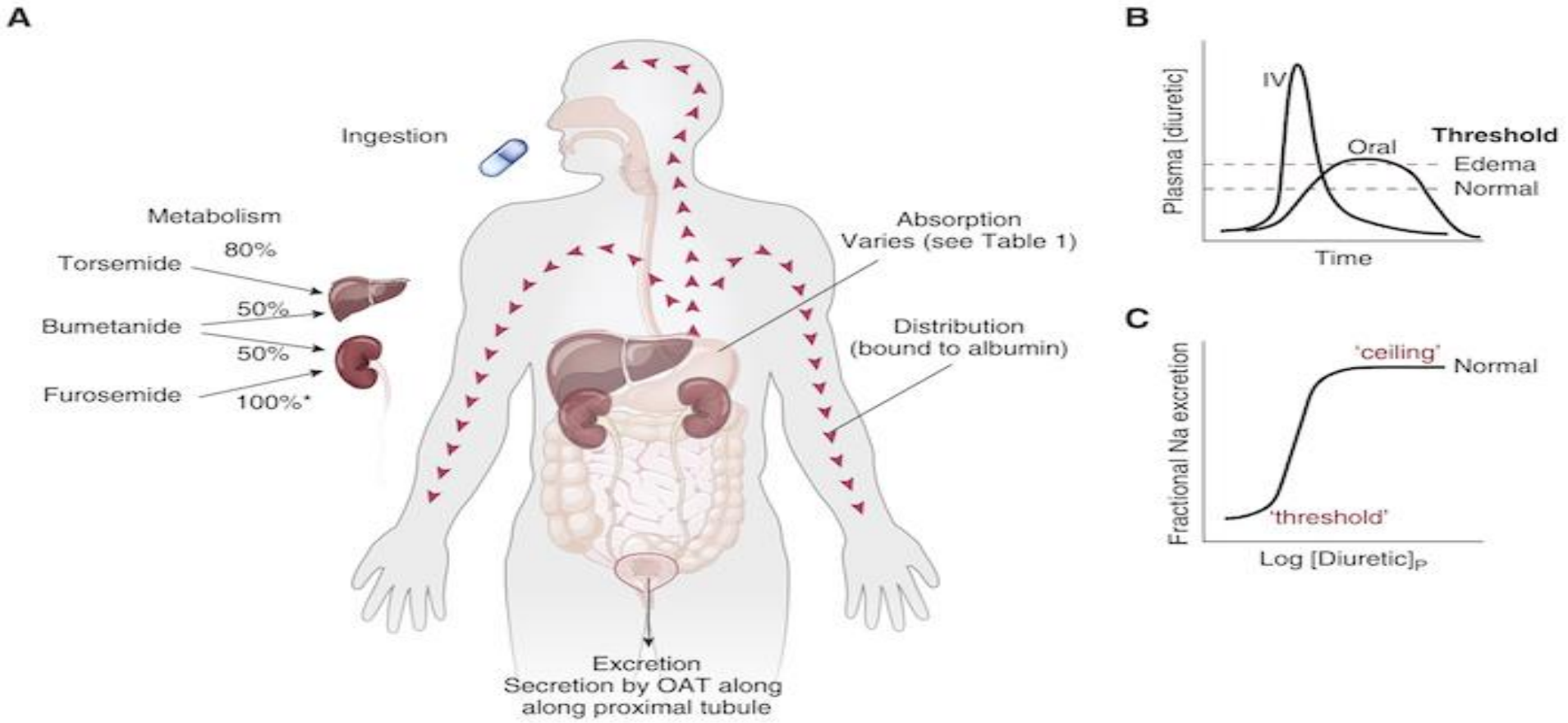

Figure 2. | **(A) Features of absorption, distribution, metabolism, and excretion (so-called ADME) of drugs.** (B) Comparing the plasma diuretic concentration as a function of time after oral or intravenous diuretic administration. The dashed lines show natriuretic thresholds in normal individuals and in those with edema. Note that the primary determinant of natriuresis is the time above the threshold, indicating why route of administration has different effects in stable patients and in those with severe edema. In a normal individual, an oral dose may be effective, whereas it may not be in edema despite retained bioavailability. (C) Classic dose-response curve, plotted versus the logarithm of the plasma concentration. Note the threshold for natriuresis and the maximal level, often called the ceiling. IV, intravenous.

Clinical Pharmacology in Diuretic Use
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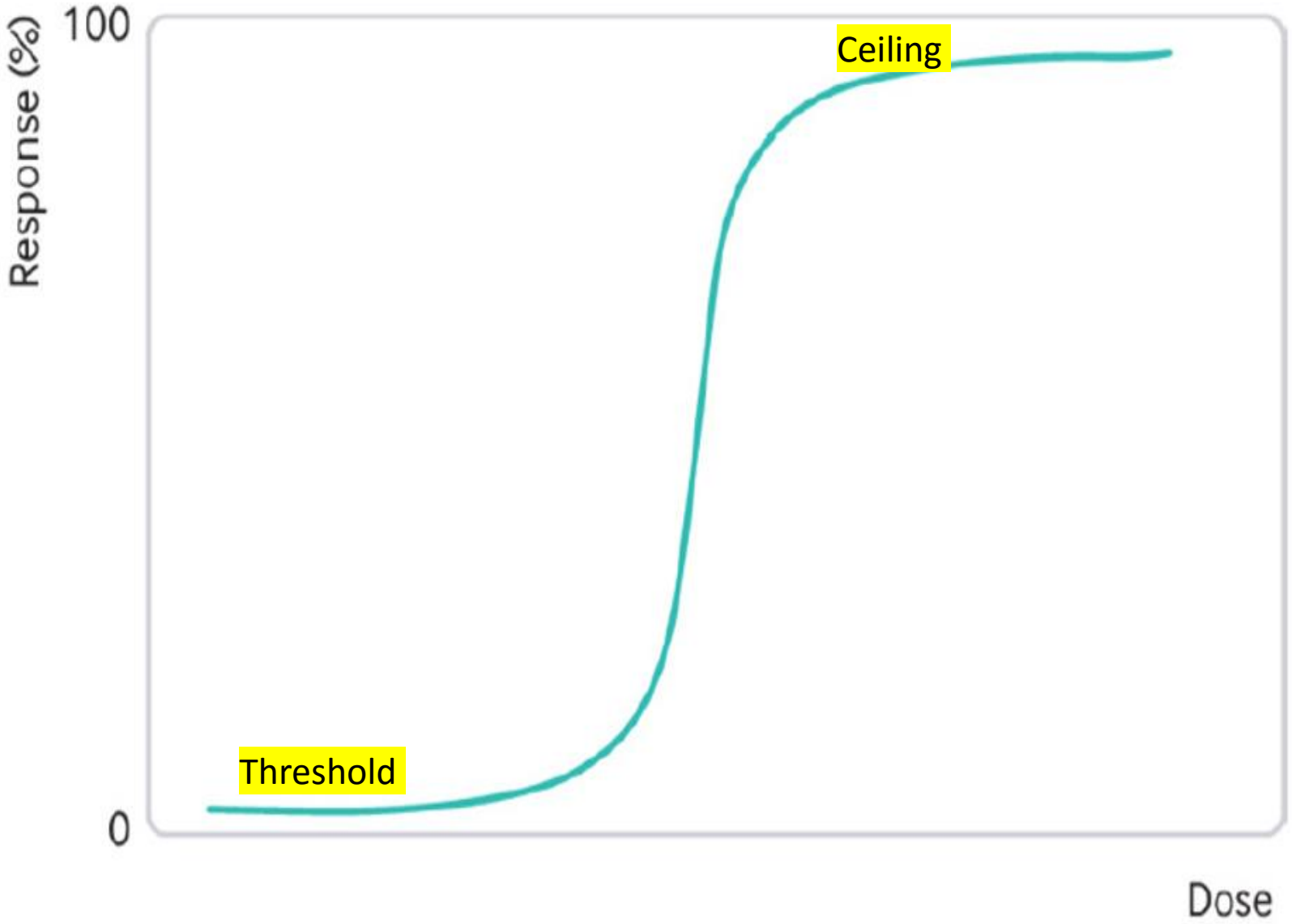

Fig 2 Dose-response curve (logarithmic) for loop diuretics. For a given individual, any dose above the therapeutic threshold will result in maximal diuresis. Adapted from Brater 1998[1] and Brater 2011[2]

How to prescribe loop diuretics in oedema
Steven D Anisman invasive cardiologist 1, Stephen B Erickson clinical nephrologist 2, Nancy E Morden primary care physician
BMJ 2019;364:l359 doi: 10.1136/bmj.l359 (Published 21 February 2019)

Table 1: Summary of Diuretic Drugs used in Heart Failure

Drug	Site of Action	Duration of Action	Common Starting Dosage	Maximum Dosage	Common Side Effects
Loop diuretics	Inhibition of Na-K-Cl co-transporter in the thick ascending loop of Henle				Hypokalaemia, hypomagnesaemia, hyperuricaemia, hypocalcaemia, hyponatraemia, otoxicity
Furosemide		7 h	20 to 40 mg once or twice	600 mg	
Bumetanide		4 to 6 h	0.5 to 1.0 mg once or twice	10 mg	
Torasemide		12 to 16 h	10 to 20 mg once	200 mg	
Ethacrynic acid		6 h	25–50 mg once or twice	200 mg	
Thiazide-like diuretics	Inhibition of Na-Cl transporter at distal nephron				Hypokalaemia, hypomagnesaemia, hypercalcaemia, hyponatraemia, hyperuricaemia
Chlorothiazide		6 to 12 h	250 to 500 mg	Once or twice	1,000 mg
Chlorthalidone		24 to 72 h	12.5 to 25 mg once	100 mg	
Indapamide		36 h	2.5 mg once	20 mg	
Potassium-sparing diuretics	Inhibition of mineral corticoid receptor or its effectors at distal nephron				Hyperkalaemia
Amiloride		24 h	5 mg once	20 mg	
Triamterene		7 to 9 h	50 to 75 mg twice	200 mg	
Spironolactone		1 to 3 h	12.5 to 25.0 mg once	50 mg	Gynaecomastia

Table 2. Pharmacokinetics of commonly used diuretics

Diuretic	Oral Bioavailability, %	Elimination $t_{1/2}$, h			
		Normal	CKD	Cirrhotic Ascites	Heart Failure
Furosemide	50 (10–100)	1.5–2	2.8	2.5	2.7
Bumetanide	80–100	1	1.6	2.3	1.3
Torsemide	68–100	3–4	4–5	8	6
Hydrochlorothiazide	55–77	6–15	Prolonged		
Chlorthalidone	61–72	40–60	Prolonged		
Metolazone	70–90[a]	14–20	Prolonged		
Amiloride	~50[b]	6–26	100[d]	Not changed	
Spironolactone	>90	1.5[c]			

Data are presented as single reported values or range of reported values. Values for furosemide are given as the mean (range). When precise values were not provided, descriptive terms are provided.
[a]Absorption may be decreased in heart failure.
[b]Decreased by food.
[c]Active metabolites of spironolactone have $t_{1/2}$ of >15 hours.
[d]Active metabolites accumulate in CKD. Adapted from Karin (82).

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Clinical Use of Diuretics in Heart Failure, Cirrhosis, and Nephrotic Syndrome
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International Journal of Nephrology
Volume 2015, Article ID 975934, 9 pages
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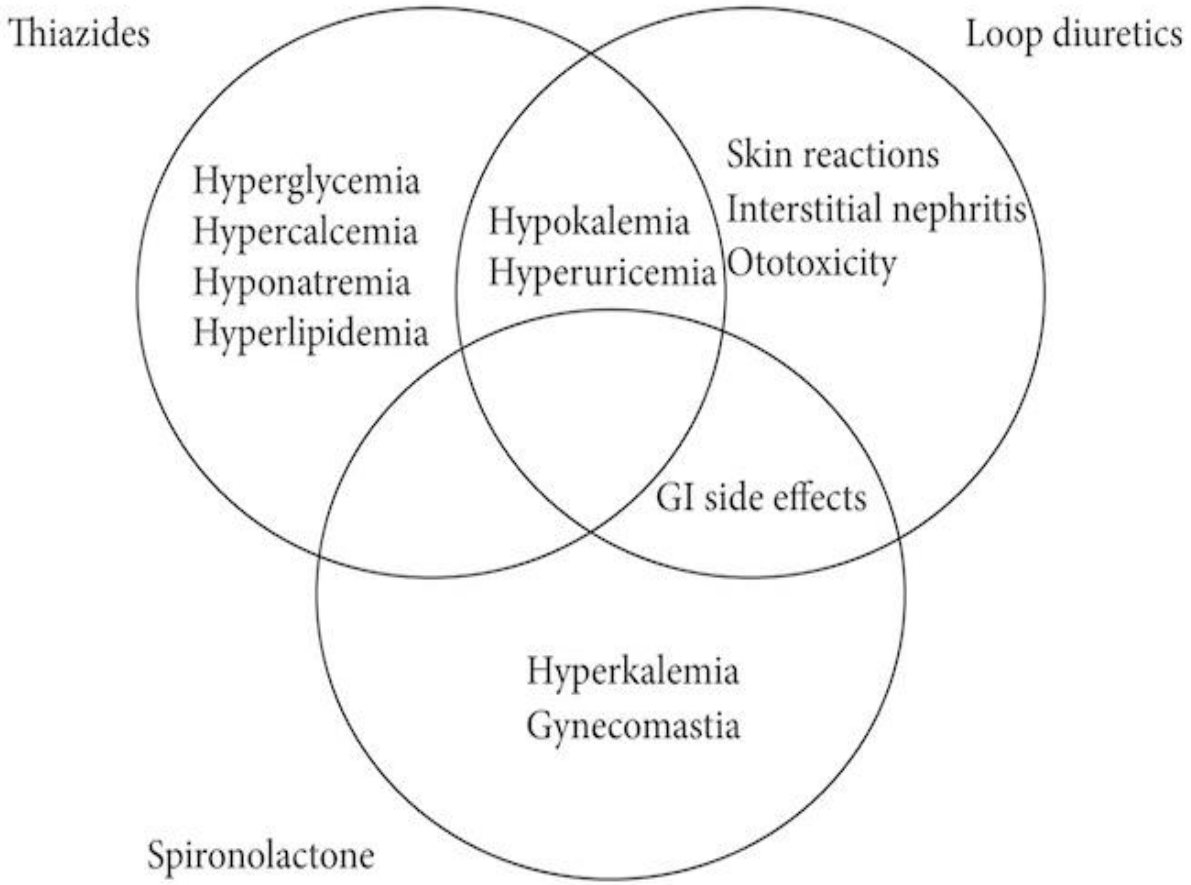

FIGURE 2: Adverse effects of major diuretics [11, 12, 34–38].

CJASN 14: 1248–1257, August, 2019

Table 1. Common side effects of diuretics

Loop diuretics
Hypersensitivity reactions
Extracellular fluid volume depletion
Hypokalemic alkalosis
Hypomagnesemia
Ototoxicity
Distal convoluted tubule diuretics
Hypersensitivity reactions
Hyponatremia
Hypokalemic alkalosis
hyperglycemia/diabetes
Hyperuricemia/gout
Hypomagnesemia
Hypokalemia and prerenal azotemia, when combined with loop diuretics
Potassium-sparing diuretics
Hypersensitivity
Hyperkalemia
Metabolic acidosis
Azotemia
Gynecomastia, vaginal bleeding (spironolactone)

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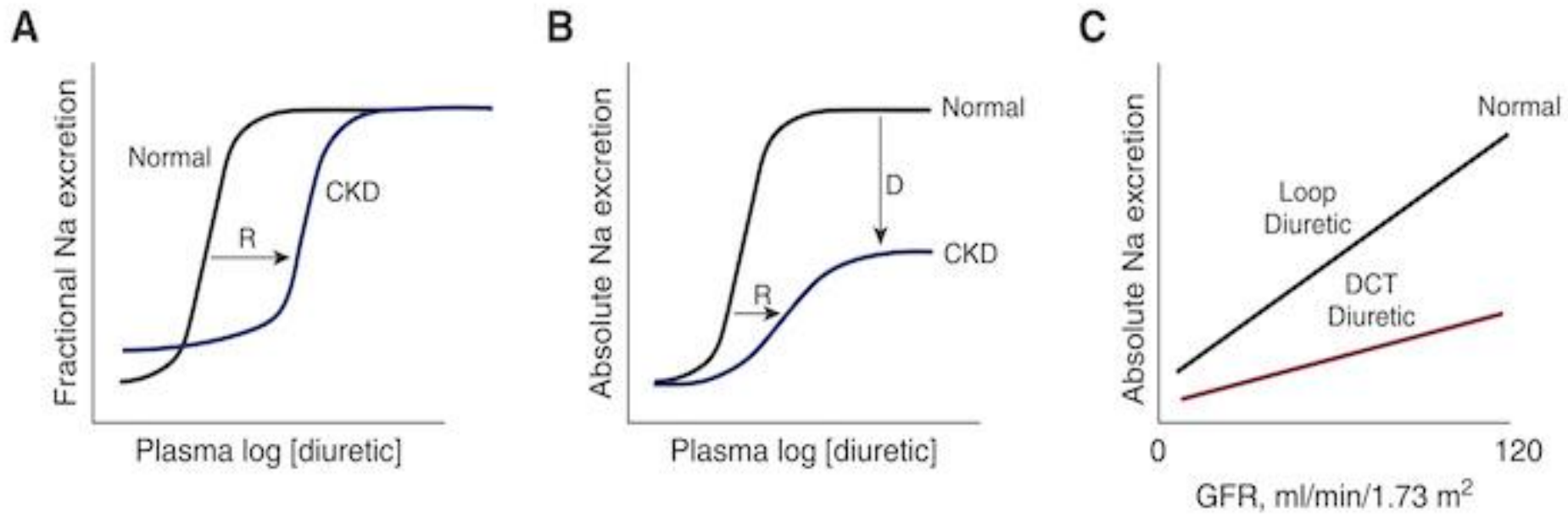

Figure 3. | **Pharmacokinetics and pharmacodynamics of diuretic action.** (A) Effects of CKD on diuretic actions. Note that in CKD, baseline fractional sodium excretion is high, to maintain absolute rates of sodium excretion equal to intake. There is a shift in the dose-response curve to the right (R), primarily owing to impaired diuretic secretion, but no change in the ceiling effect. (B) The same relationship plotted versus absolute rates of sodium excretion. The same rightward shift is evident, but the ceiling is lower, owing to the GFR reduction (as indicated by D). (C) Comparing effects of loop diuretics and distal convoluted tubule (DCT) diuretics on absolute sodium excretion, given a retained effect on fractional excretion.

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Some Facts about Furesemide:

Drug action ***lasts 6 hours***.

Phenomenon"***postdiuretic NaCl retention***" This accounts for the usual recommendation to use loop diuretics twice daily.

On the basis of oral bioavailability, when a patient is switched from intravenous to oral loop diuretic, the dose of bumetanide or torsemide should be maintained, whereas the ***dose of furosemide should be doubled.***

Adjust the dose according to the response.

Bioavailability: Furosemide ***absorption varies from day to day in an individual***, and between individuals. Absorption is also affected by ***food consumption***, unlike that of bumetanide or torsemide.

Gastrointestinal absorption can be slowed, especially during exacerbations of edematous disorders such as heart failure, although again, this may be true primarily of furosemide.

Loop diuretics are organic anions that circulate ***tightly bound to albumin*** (95%).
Thus, their volumes of distribution are low, except during extreme hypoalbuminemia.
This has suggested that severe hypoalbuminemia might impair diuretic effectiveness, owing to impaired delivery to the kidney, and that albumin administration might enhance natriuresis.

Deafness and tinnitus from loop diuretics appear to result primarily from high serum concentrations, which inhibit an Na-K-2Cl isoform (NKCC1, encoded by SLC12A2)., this led to secretion of potassium-rich endolymph.

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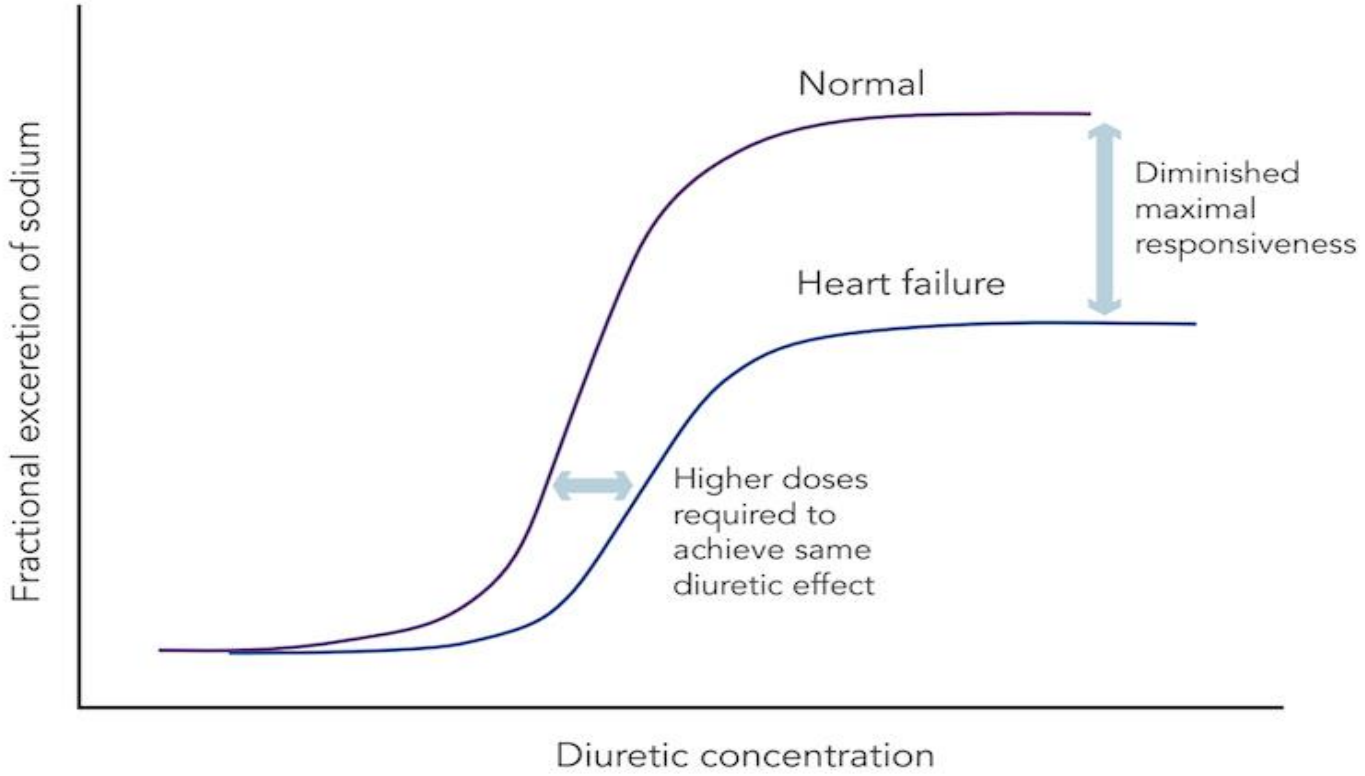
Cardiomyopathy and Heart Failure

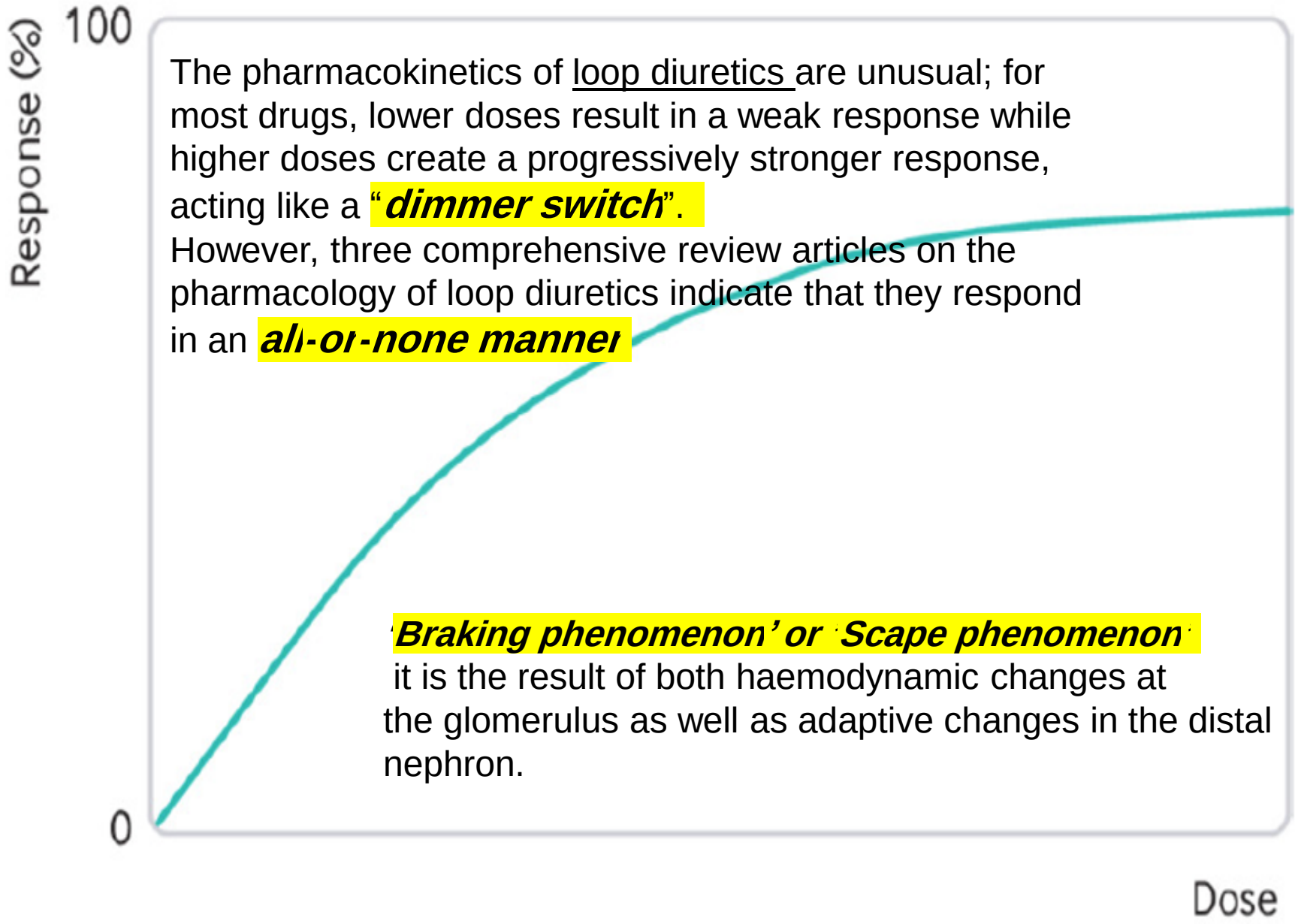
Figure 1: Schematic of a Dose-response Curve of Loop Diuretics in Heart Failure Patients Compared with Controls



In heart failure patients, higher doses are required to achieve a given diuretic effect and the maximal effect is blunted. Adapted, with permission, from Ellison[21] and reprinted, with permission, from Felker Reproduced with permission from Felker.[22]

Diuretic Therapy in Heart Failure – Current Approaches
Gavino Casu and Pierluigi Merella

EUROP EAN CARDIOLOGY R E V I EW



The pharmacokinetics of loop diuretics are unusual; for most drugs, lower doses result in a weak response while higher doses create a progressively stronger response, acting like a "***dimmer switch***".
However, three comprehensive review articles on the pharmacology of loop diuretics indicate that they respond in an ***all-or-none manner***

'***Braking phenomenon' or 'Scape phenomenon***'
it is the result of both haemodynamic changes at the glomerulus as well as adaptive changes in the distal nephron.

Fig 1 Common (linear) dose-response curve seen in many drugs (but not loop diuretics). Adapted from Merck Manual[4]

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Box 3: Equivalent doses of loop diuretics

80 mg PO furosemide ≈ 40 mg IV furosemide ≈ 40 mg PO or IV torsemide ≈ 1 mg PO or IV bumetanide ≈ 100 mg PO or IV ethacrynic acid diuretics

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Box 4: Common myths about loop diuretics

Myth Avoid oral diuretics in oedematous patients, because absorption is compromised

Fact Absorption may be slower with oedema, but the overall dose absorbed and the diuretic effect is essentially the same with or without intestinal oedema[2]

Myth Do not use loop diuretics in patients with a sulfa allergy

Fact All loop diuretics except ethacrynic acid contain a sulfa moiety. However, many patients with allergies to sulfonamide antibiotics are *not* allergic to loops.[33] Thus antibiotic sulfa allergy should *not* be considered an absolute contraindication to loop diuretics

Myth Intravenous drip is more effective than bolus dosing for severe oedema

Fact The largest trial comparing bolus dosing with continuous infusion in heart failure showed no difference in any measured outcome.[34] A meta-analysis of 10 trials drew the same conclusion.[35] One review suggested infusion may be beneficial despite lack of evidence[36]

Myth Stop diuresis if creatinine is rising

Fact Some increase in blood urea nitrogen/urea and creatinine may be unavoidable, or even an indication of effective diuresis. An observational substudy of the ESCAPE trial found aggressive diuresis causing haemoconcentration positively correlated with a statistically significant 180 day mortality benefit[37]

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Determine if the dose is working

If there is ***no short term increase in urine output***, or if patients report ***polyuria unrelated to dosing*** ("I pee all day and all night"), the dose is likely to be ***subtherapeutic*** and should be increased until the diuretic threshold is reached.

Diuresis caused by a ***loop diuretic*** (frequent urination for 4-6 hours) is ***distinct from*** the frequent urination caused by ***hypervolaemia***, where excess fluid chronically fills the intravascular space and causes continuous polyuria, often worse at night when lying down.

Nocturia typically indicates ineffective daytime diuresis, not excessive diuretic response.

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Good choice when patients need “gentle” diuresis for relatively mild hypervolemia or oedema.

For example, thiazides may cause only 25% of the urine output expected from a loop diuretic.

Potassium sparing diuretics on their own are only 3% as effective as loop diuretics

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Cirrhotic ascites

Here, relative ***gastrointestinal absorption*** tends to be preserved.

Coupled with the tendency for relative ***underfilling*** in this setting, it is typically recommended to:
avoid intravenous diuretics, if possible.

In this situation, a combination of :
Furosemide with spironolactone,
in a ratio of 40 mg furosemide to 100 mg spironolactone, is recommended in most patients.

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What patients need to know about as-needed dosing

Ask the patient to weigh him/herself daily, and to take an effective loop diuretic dose if the weight is higher than the target. If the weight is at or below target, no loop diuretic is taken. For example, "Take 20 mg of torsemide if your weight is 93 kg (205 lb) or above; if it is 92 kg (203 lb) or less, take no torsemide." Base target weights on patient wellbeing—if the patient reports no notable swelling, nor difficulty breathing in any position, and there is no weakness or dizziness to suggest dehydration, that is a clinically reasonable "dry weight" and should be used as an aid for deciding when to take these medications.

If daily weights are not possible, consider using an alternative trigger for use of an appropriate dose. Examples might include visible swelling (typically in the legs and/or feet), shortness of breath, or difficulty breathing while lying down. Doses other than the prescribed dose should not be taken (ie, do not take less or more than the prescribed dose; there is only one best dose).

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Box 2. Key Teaching Points

- Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic
- The causes of diuretic resistance include poor adherence to drug therapy or diet, pharmacokinetic issues, and compensatory sodium reabsorption
- Impaired tubular secretion of diuretics is a common cause of diuretic resistance
- A key strategy to overcome diuretic resistance frequently relies on combining 2 types of diuretic (diuretic synergism)
- In patients with proteinuria, activation of ENaC by plasmin may contribute to salt retention, suggesting efficacy of an ENaC blocker

Abbreviation: ENaC, epithelial sodium channel.

Diuretic Resistance in Cardio-Nephrology: Role of Pharmacokinetics, Hypochloremia, and Kidney Remodeling
Cristina Masella a Davide Viggiano b, c Ida Molfino, et al
Kidney Blood Press Res 2019;44:915–927

AJKD

Box 1. Common Causes of Diuretic Resistance

- Incorrect diagnosis (eg, venous or lymphatic edema)
- Nonadherence to recommended sodium and/or fluid restriction
- Drug not reaching the kidney
  - ◇ Nonadherence
  - ◇ Dose too low or too infrequent
  - ◇ Poor absorption
- Reduced diuretic secretion
  - ◇ Tubular uptake of diuretic impaired by uremic toxins
  - ◇ Decreased kidney blood flow
  - ◇ Decreased functional kidney mass
- Insufficient kidney response to drug
  - ◇ Low glomerular filtration rate
  - ◇ Decreased effective intravascular volume despite elevated total extracellular fluid volume
  - ◇ Activation of the renin-angiotensin system
  - ◇ Nephron adaptation
  - ◇ Use of nonsteroidal anti-inflammatory drugs

Based on Hoorn et al.[2]

Diuretic Resistance
Ewout J. Hoorn, MD, PhD,1 and David H. Ellison, MD
Am J Kidney Dis. 2016

Post-diuretic sodium retention is enhanced when the drug-free intervals are longer than:
four half-lives of the LD.

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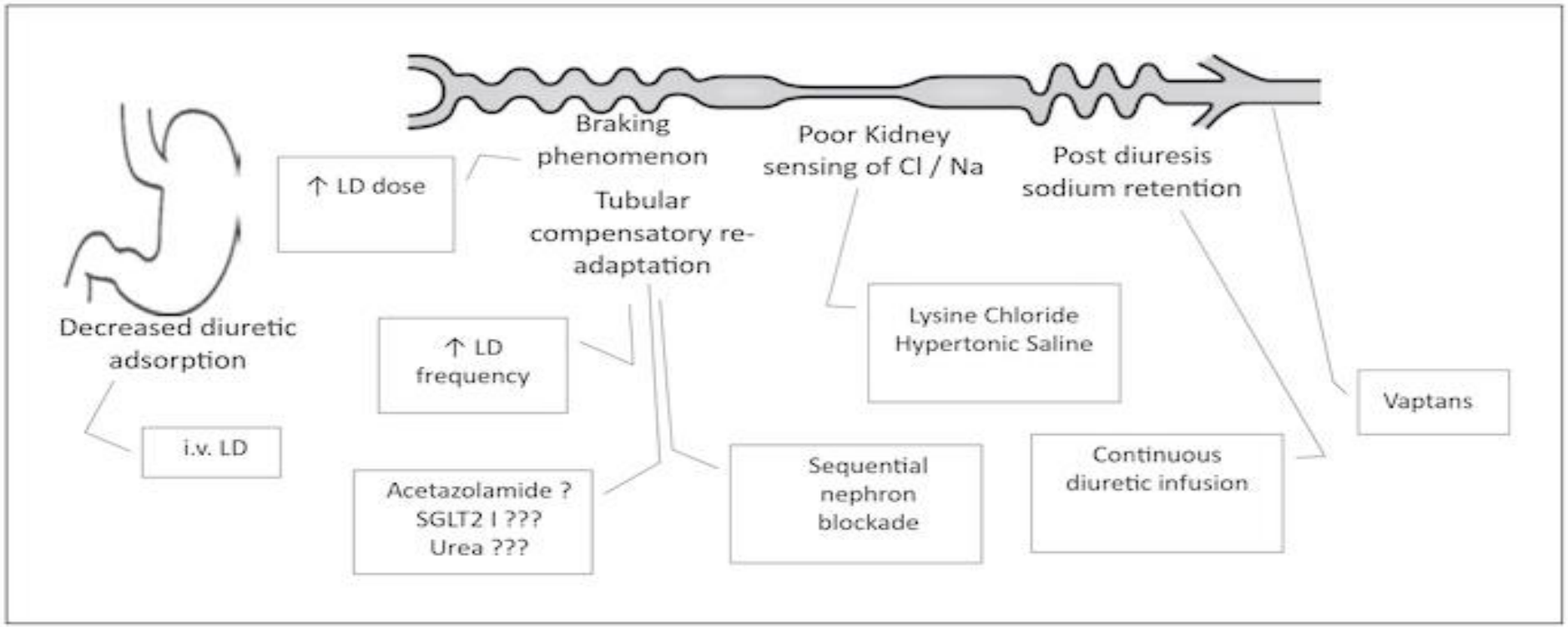

Fig. 3. Pathways involved in diuretic resistance and the therapeutic options (gray boxes) aimed at overcoming these mechanisms. LD, loop diuretics.

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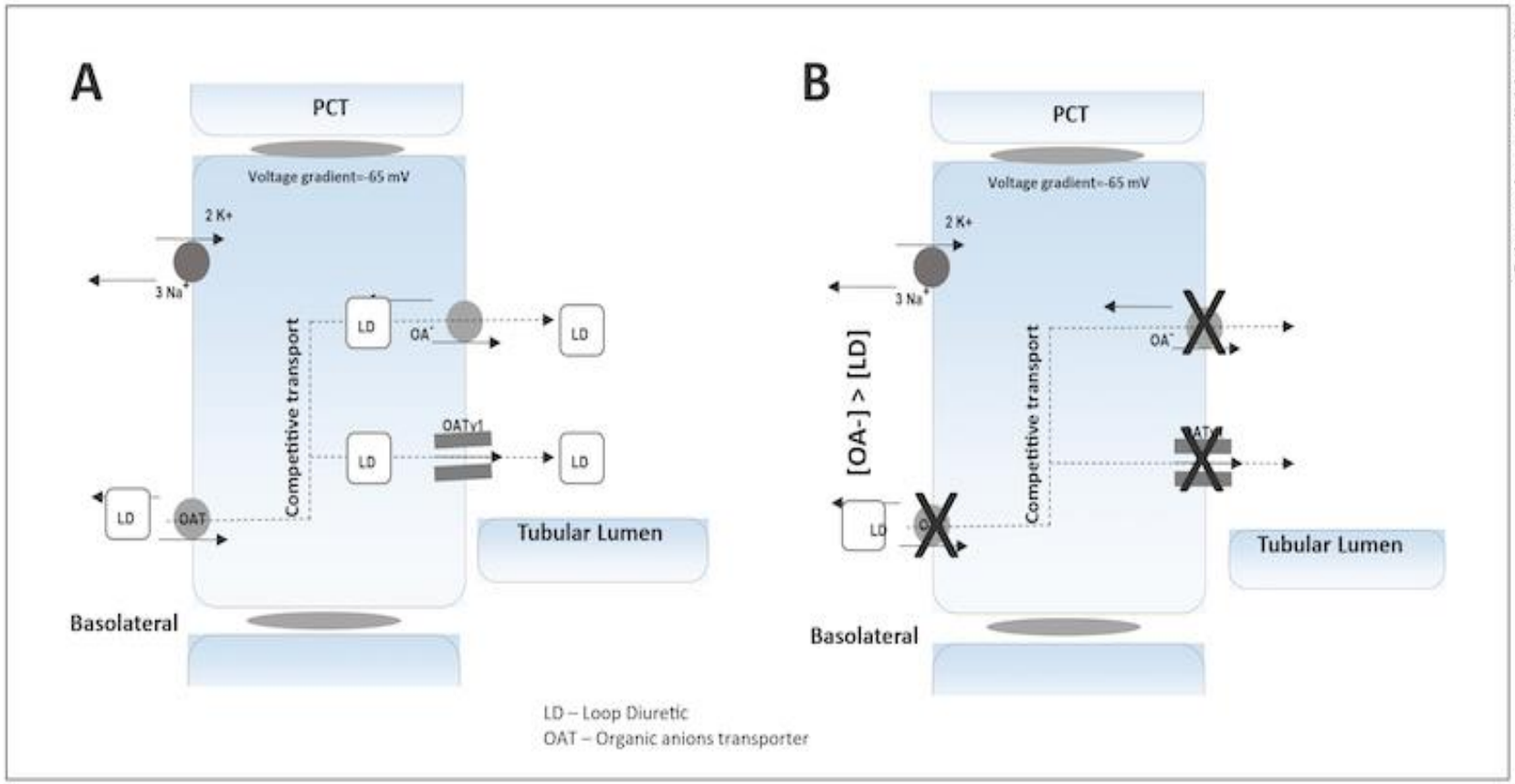

Fig. 2. A LD secretion by proximal tubular cells is mediated by a competitive transport on OATs. **B** In CKD, the accumulation of organic anions in the blood overcomes LD transport ability by epithelial proximal tubular cells.

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The epidemiological evidence of hypochloremia as a poor prognostic factor raises the question whether this is mediated by LD resistance or simply indicates the intensity of diuretic treatment.

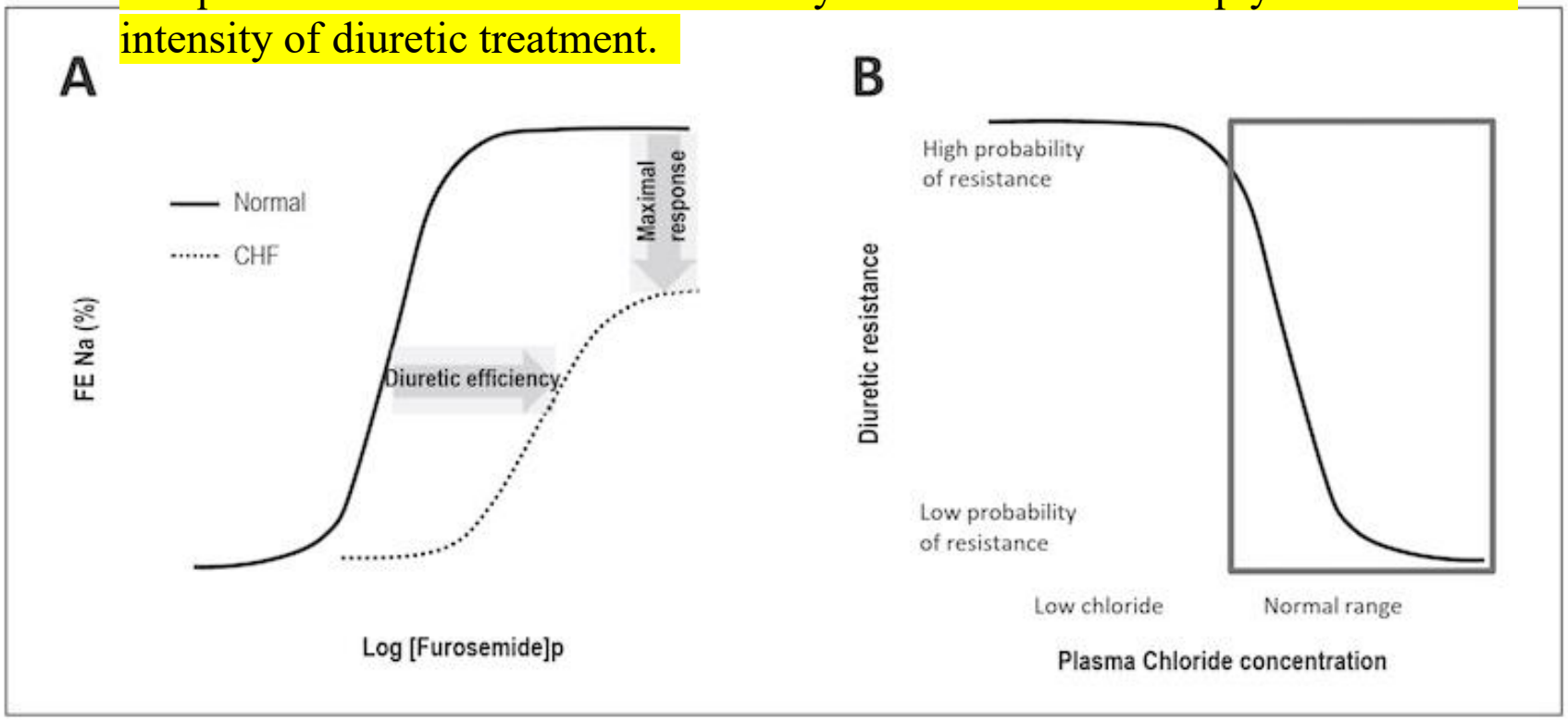

Fig. 1. A Changes of urinary sodium excretion fraction in response to furosemide administration. A shift of the dose-response curve is evident in CHF patients. **B** Relationship between serum chloride and the probability of developing diuretic resistance (redrawn from Hanberg et al. [22]).

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Acetazolamide inhibits **pendrin.**

Because pendrin is increasingly recognized as an important sodium reabsorption route and there are no specific inhibitors for pendrin, acetazolamide may be considered as a second diuretic in edematous disorders.

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It was postulated that tubular urokinase type plasminogen activator converts filtered plasminogen to plasmin.

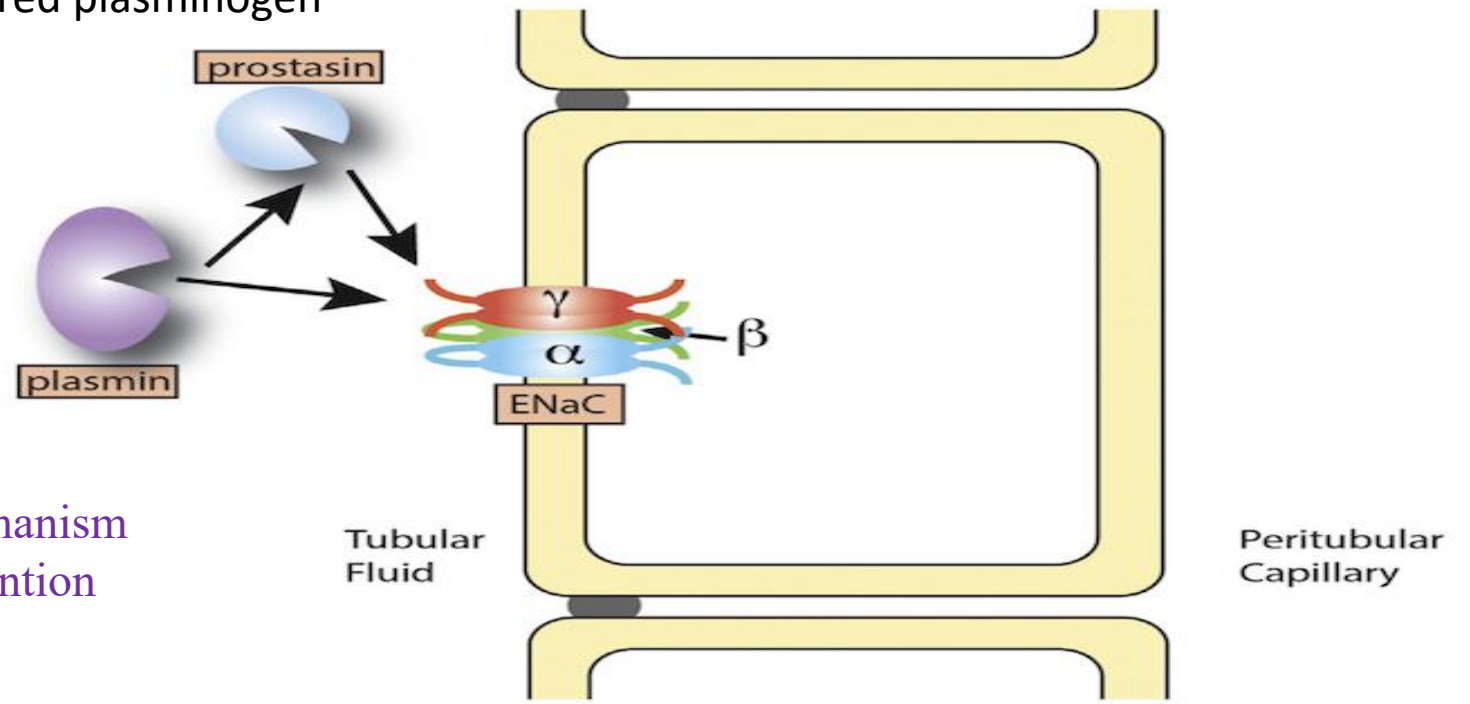

Figure 3. Schematic of proposed mechanism by which luminal plasmin in nephrotic patients activates the epithelial sodium channel (ENaC) in the collecting duct. eNaC comprises 3 subunits, α, β, and γ, each with extracellular loops, as shown. Plasmin, derived from filtered plasminogen in nephrotic patients, cleaves eNaC extracellular loops (γ subunit shown here). Plasmin may also activate prostasin, which can also cleave ENaC. Notches in plasmin and prostasin indicate active enzymatic activity. When cleaved, ENaC is activated, increasing sodium reabsorption. Epithelial cells are shown schematically, separating tubular fluid (lumen) from peritubular capillary.

Studies have indicated that this mechanism could also play a role in sodium retention associated with preeclampsia, resistant hypertension, heart failure, and diabetic nephropathy.

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CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Diuretic Use and Risk of Vertebral Fracture in Women

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CLINICAL SIGNIFICANCE

- Thiazide diuretic use is independently associated with an increased risk of vertebral fracture in women.
- Loop diuretic use is independently associated with an increased risk of vertebral fracture in women.
- Among women with hypertension who are at high risk for vertebral fracture, diuretics should be used cautiously. Further research is warranted on diuretics and vertebral fracture risk, especially because thiazides are so commonly prescribed for the treatment of hypertension.

The higher risk of vertebral fracture with thiazide use might be mediated by Hyponatremia.

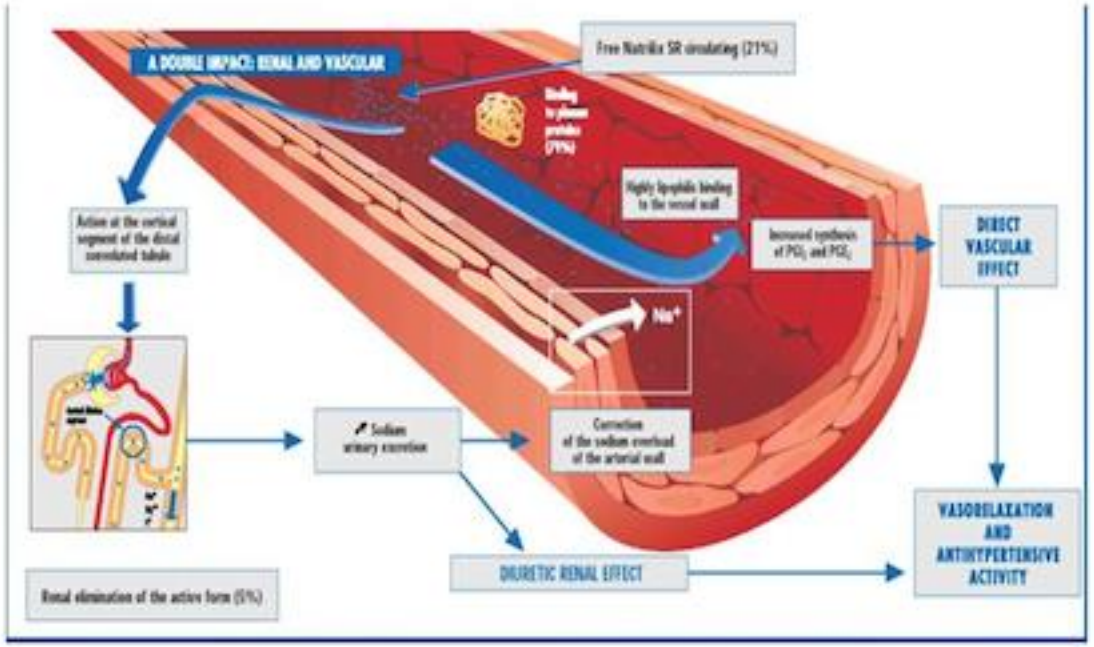
Skeletal bone is a rich reservoir of sodium and may play a key role in maintaining sodium homeostasis, but possibly at the expense of the bone's structural integrity.

The spine is particularly susceptible to microdamage. The potential harmful effect of hyponatremia on the spine's ability to repair local microdamage may explain the increased vertebral fracture risk seen with thiazide use.

Thiazide-like diuretic of choice in the latest guidelines

	POSITIVE POINTS TO LEVERAGE
ESC ESH 2018	• Explicit mention of Indapamide, a thiazide-like diuretic, among diuretics indicated as the basis of antihypertensive treatment strategies (class I, level A) • Rationale for better efficacy and higher level of CV evidence: *"Chlorthalidone and indapamide have been used in a number of, RCTs showing CV benefits and these agents are more potent per mg than HCTZ in lowering BP, with a longer duration of action compared with HCTZ and no evidence of a greater incidence of side effects. Lower dose thiazide like diuretics (typical of modern antihypertensive treatment regimens) also have more evidence from RCTs demonstrating reductions in CV events and mortality, when compared with lower dose thiazide diuretics."*
ACC-AHA 2017	• No clear recommendation for TZD like DIU except chlorthalidone • **Resistant form of hypertension**: "Treatment of resistant HT includes maximization of diuretic therapy (*chlorthalidone or indapamide instead of HCTZ)*
ADA 2019	• Preference for thiazide-like diuretics in diabetes: *Thiazide-like diuretic; long-acting agents shown to reduce CV events, such as chlorthalidone and indapamide, are preferred."*
HT CANADA 2018	• Initial treatment "*Although both thiazide and thiazide-like diuretics remain initial treatment options, preference is now given to the longer-acting, thiazide-like diuretics (e.g.,chlorthalidone and indapamide)."* • Isolated systolic hypertension: *Initial therapy should be single-agent therapy with a thiazide/ thiazide-like diuretic* (Grade A), a long-acting dihydropyridine CCB (Grade A), or an ARB (Grade B).
NICE 2019	• « Thiazide-like Diuretics like *Chlortalidone (*12.5-25 mg once daily) or *Indapamide (2.5 or 1.5 SR*

Thiazide-like diuretic, with a dual mechanism of action



Indapamide appears to reduce oxidative stress, whereas chlorthalidone and HCTZ do not.[1,2]
As the endothelium mediates direct vasodilation at least in part by responding to nitric oxide, beneficial cardiovascular effects of indapamide may also be related to improvements in endothelial function, which, improves vasomotor tone, arterial stiffness and remodeling, inflammation, and target organ damage.[3]

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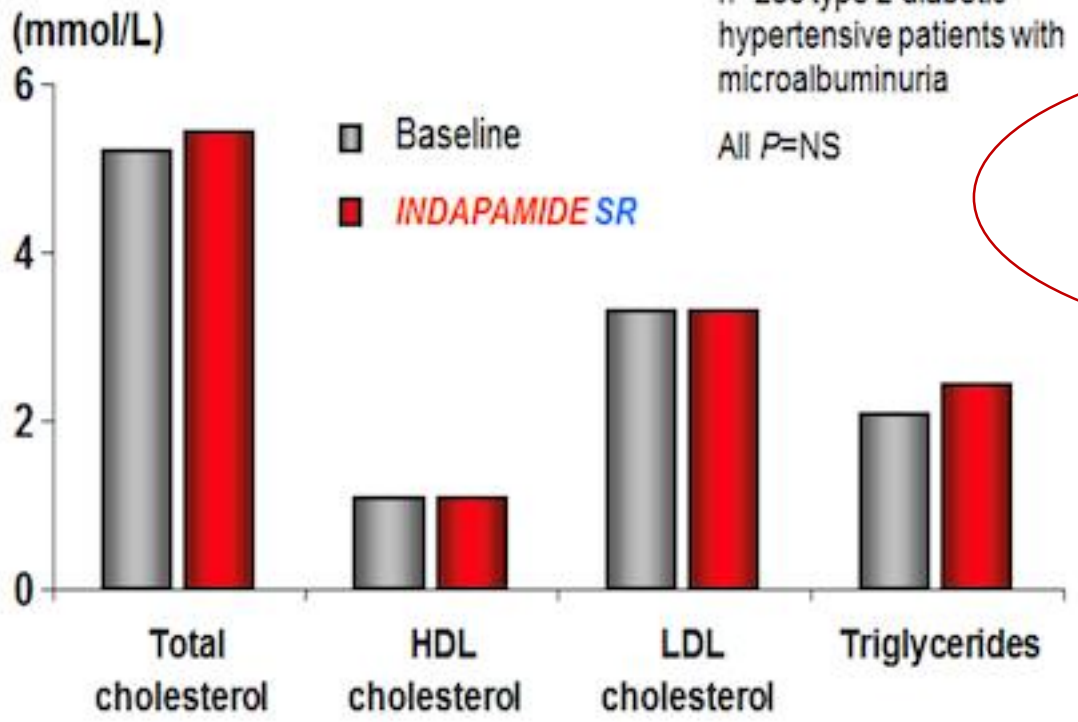
1. Zhou M et al. *J Hypertens.* 2008;26:494–500. 2. Ma F et al. *Mol Pharmacol.* 2013;84:286–295. 3. Thuillez C et al. *J Hum Hypertens.* 2005;19 (Suppl 1):S21–S25.

NESTOR Natrilix SR vs Enalapril Study in Type 2 Diabetic Hypertensives with MicrOalbuminuRia

Long-term lipid neutrality



n=283 type 2 diabetic hypertensive patients with microalbuminuria

All *P*=NS

After a 1-year treatment with Natrilix SR, diabetic hypertensive patients maintained a stable lipid profile.

Natrilix SR avoided the occurrence of lipid increases, and thus did not add a risk factor to this fragile population.

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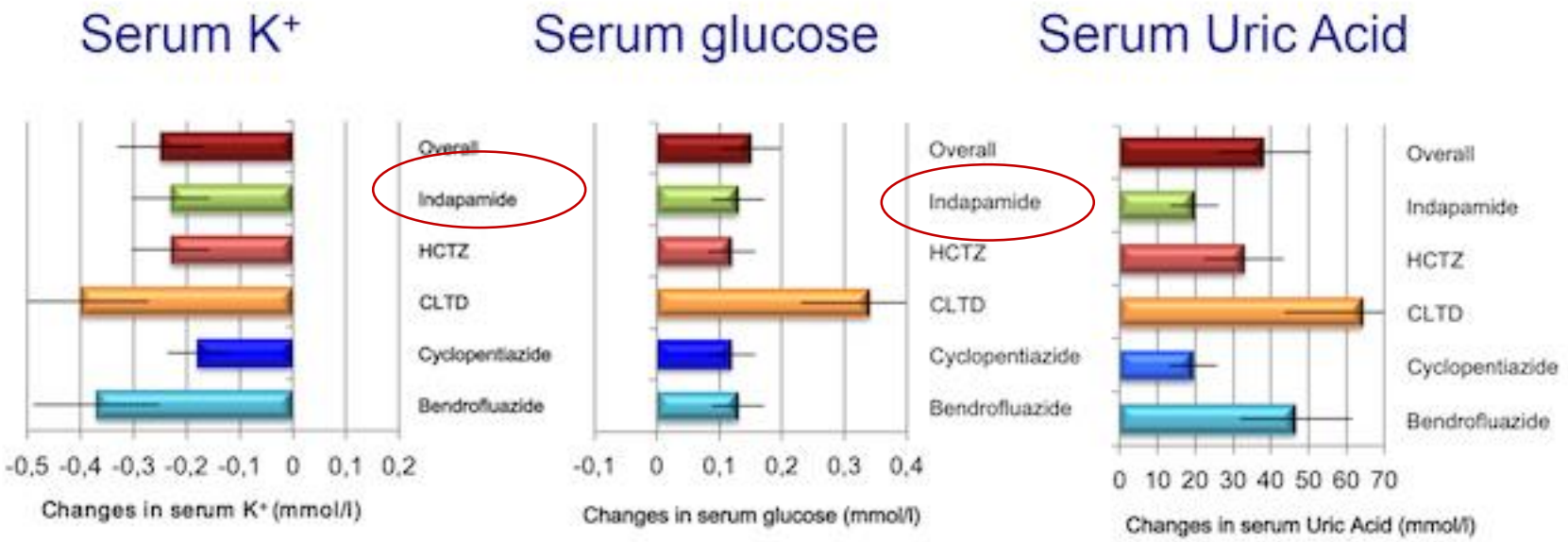
Marre M et al. *J Hypertens.* 2004;22:1613-1622

Effects of diuretics on metabolic profile. Cochrane / RCT



Musini VM et al, Cochrane Coll Library, 2014

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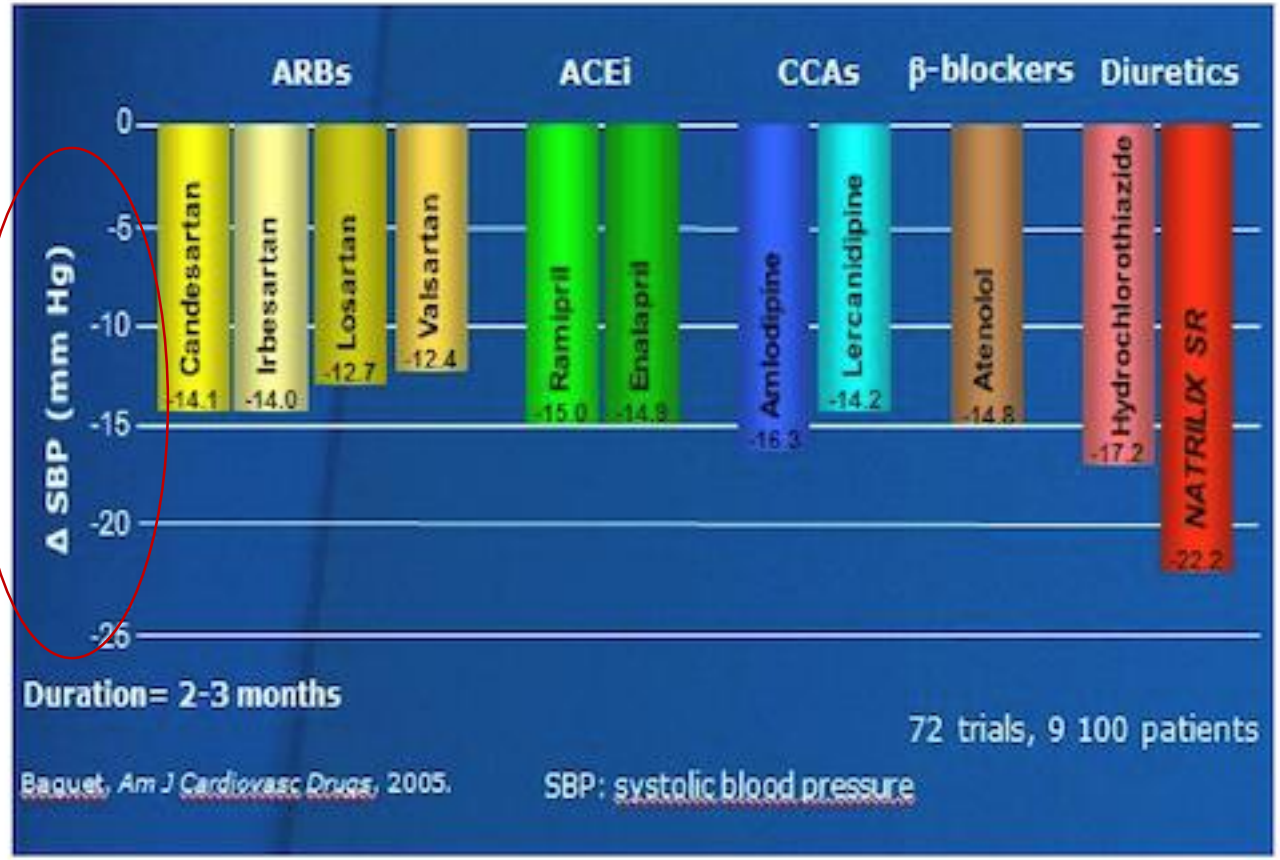
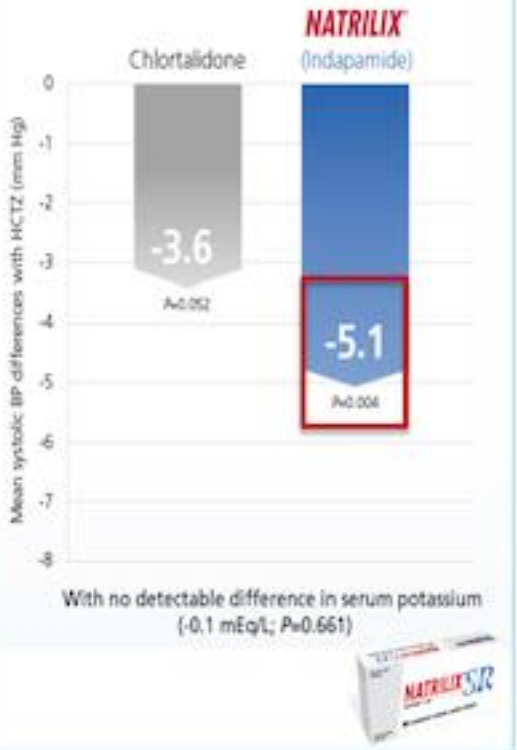
Indapamide SR 1.5 mg has a good efficacy

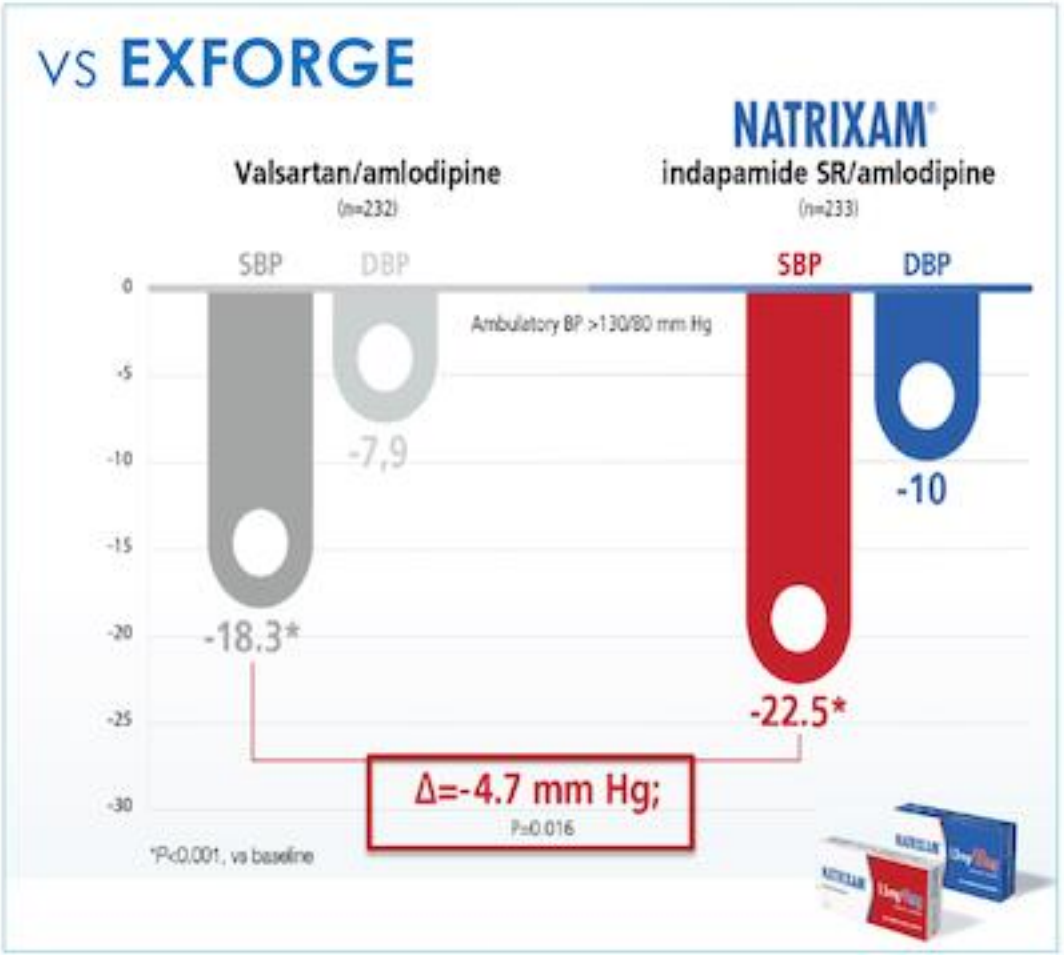


Indapamide: based provides superior SYSTOLIC BP reduction[1,2]

vs HCTZ



vs EXFORGE



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RESEARCH ARTICLE

Empagliflozin in Heart Failure

Diuretic and Cardiorenal Effects

Matthew Griffin, Veena S. Rao, Juan Ivey-Miranda, James Fleming, Devin Mahoney, Christopher Maulion, Nisha Suda, Krishmita Siwakoti, Tariq Ahmad, Daniel Jacoby, Ralph Riello, ... See all authors

Originally published 15 May 2020 | https://doi.org/10.1161/CIRCULATIONAHA.120.045691 | Circulation. 2020;142:1028–1039

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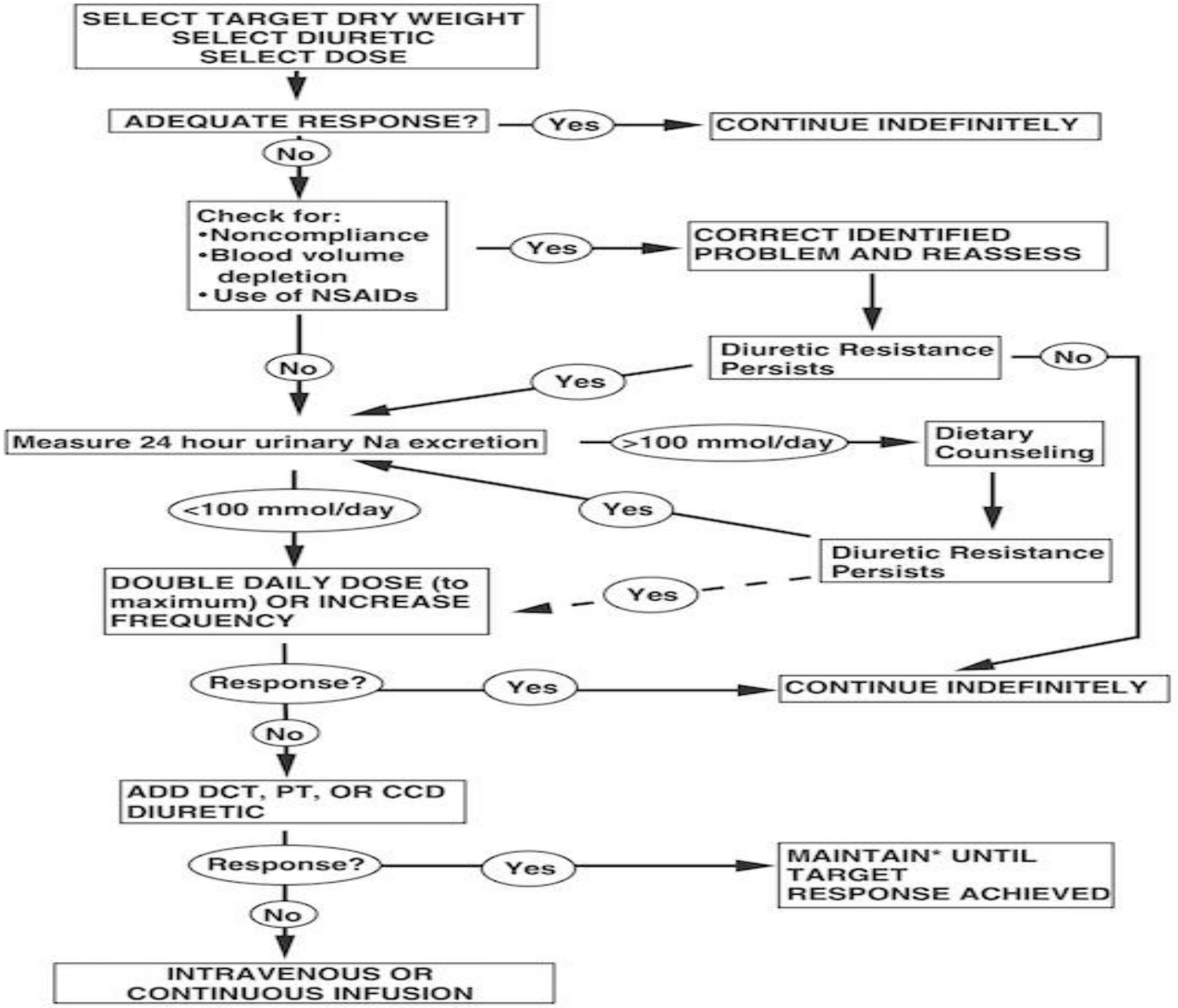

Figure 4. Stepwise approach to assess and manage diuretic resistance. *Consider reducing the dose or frequency of distal convoluted tubule (DCT) diuretic when control of edema has been achieved. Abbreviations: CCD, cortical collecting duct; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, proximal tubule. Adapted from Brady and Wilcox[37] with permission of Elsevier.


C Dasht, Totkabon, Guilan