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Diuretics in Chronic Kidney Disease

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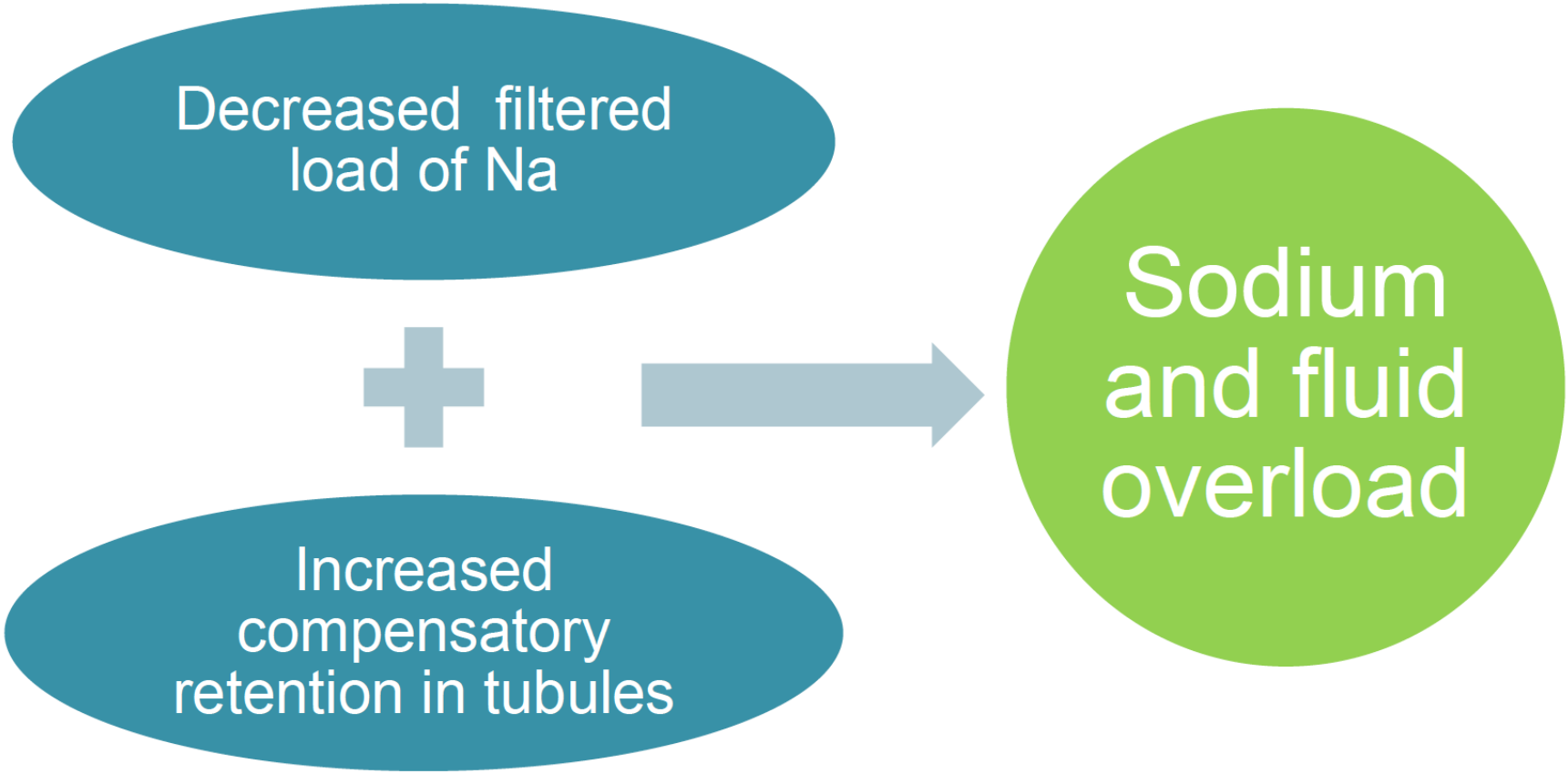
Azar 27th, 2020

Mechanism of Na retention in CKD

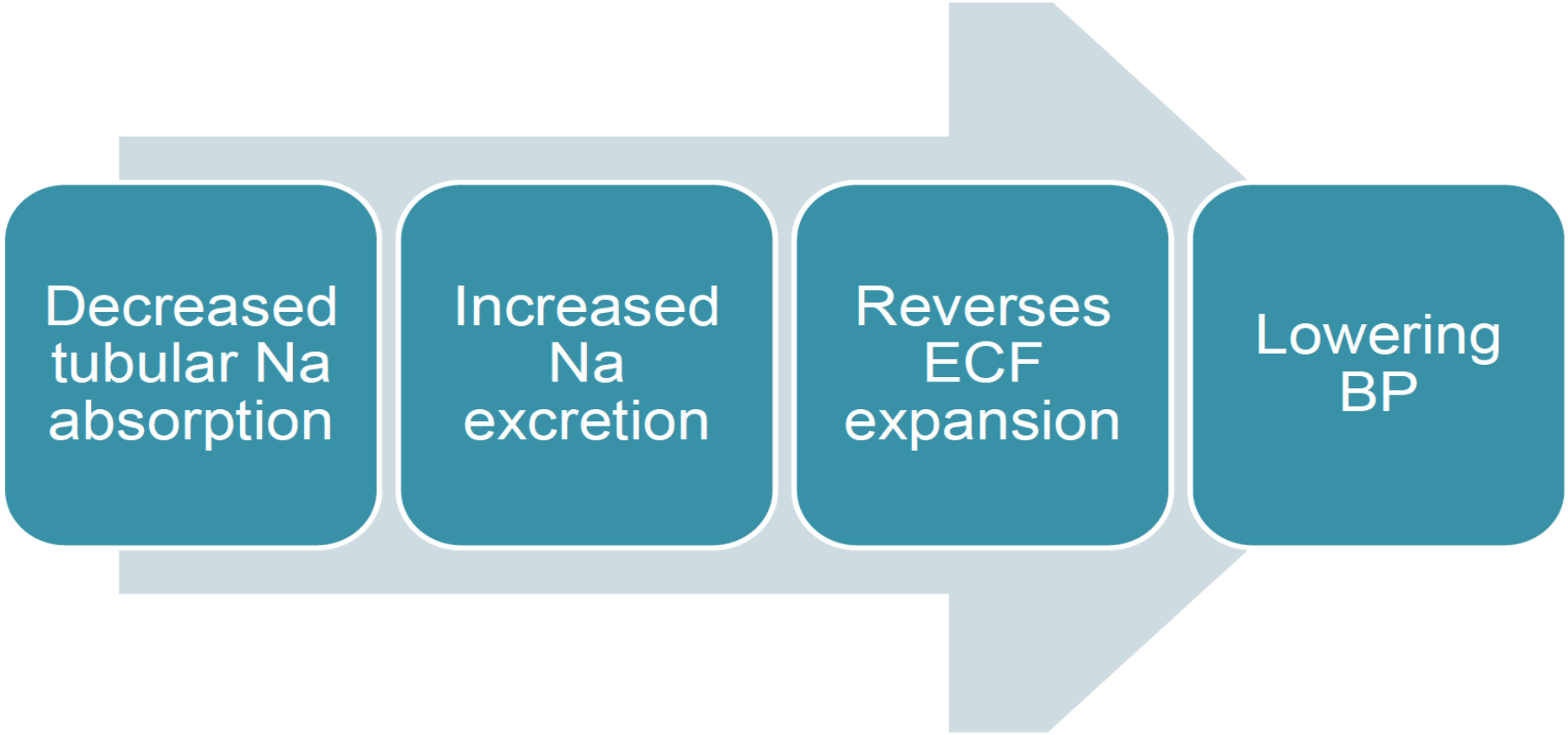


- Patients with CKD have a 10 to 30% increase in extracellular and blood volume, even in the absence of overt edema

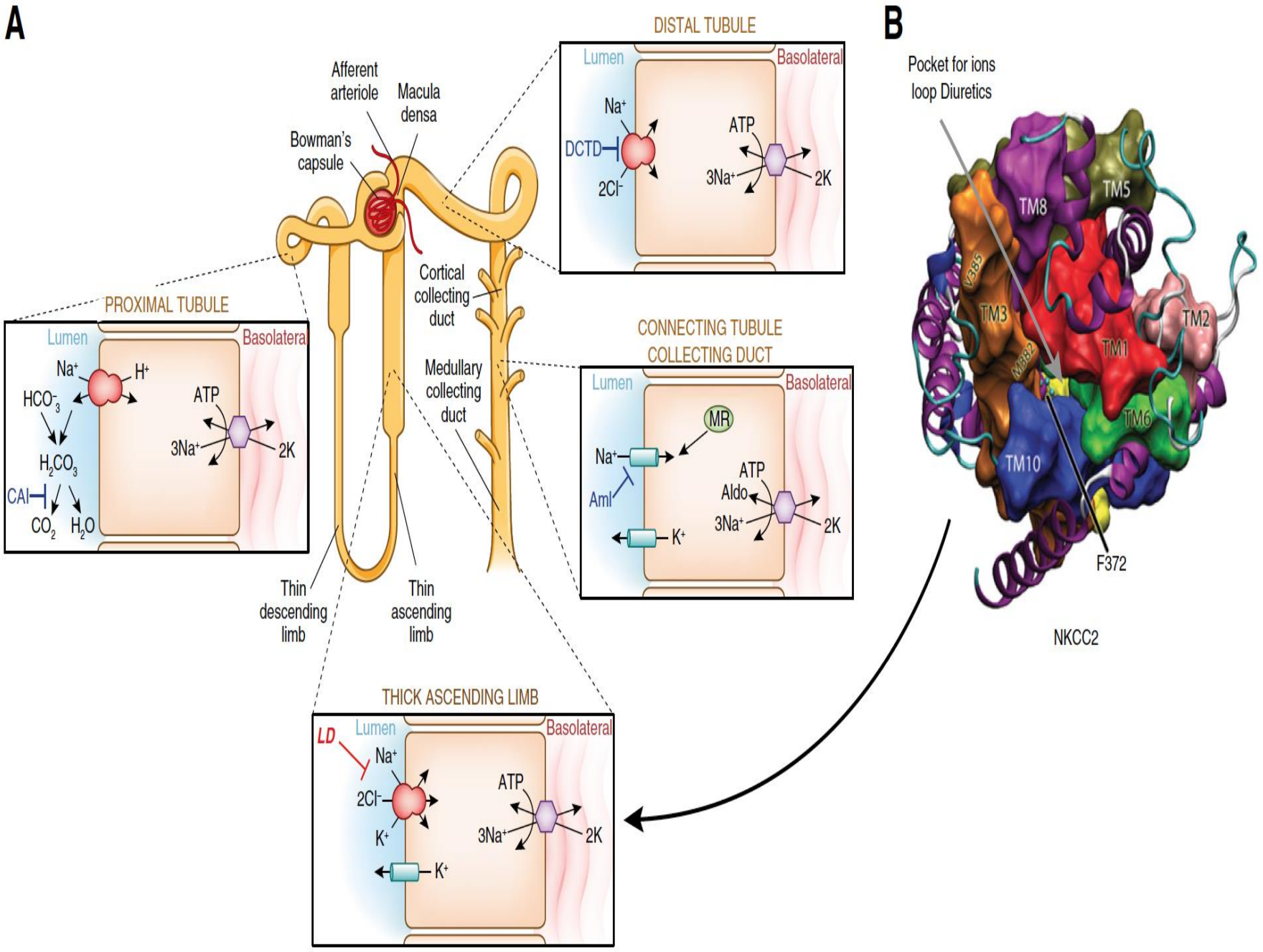
Am J Med 72: 536–550, 1982

Diuretics as Antihypertensives in CKD

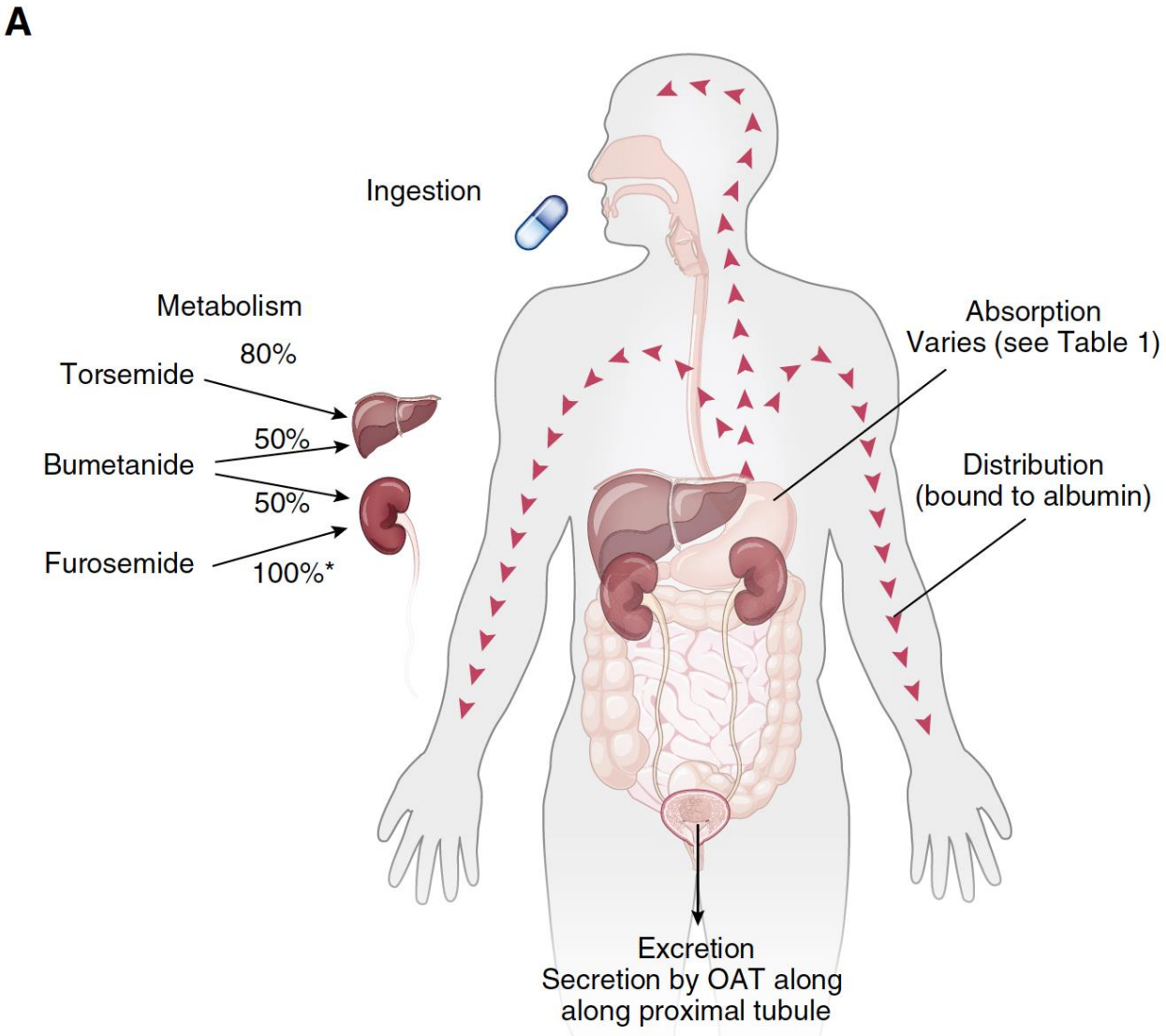
Facilitates responses to other Antihypertensives

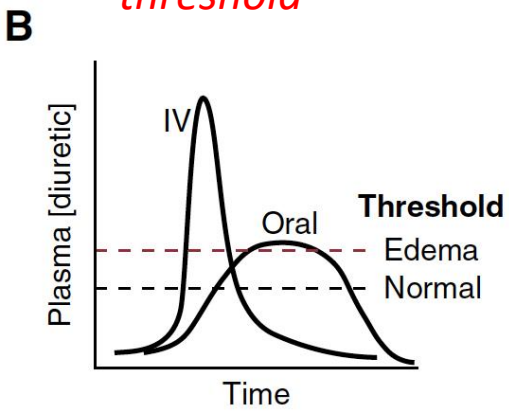


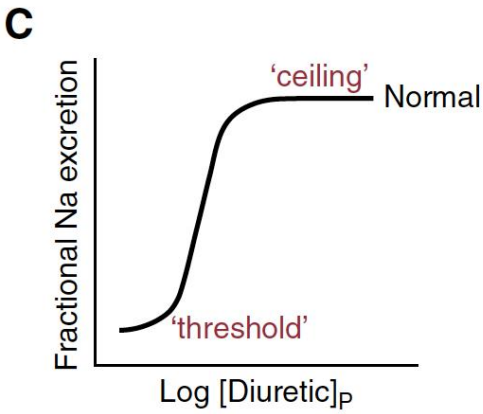
Salt Restriction


A
Afferent arteriole
Macula densa
Bowman's capsule
Cortical collecting duct
Medullary collecting duct
Thin descending limb
Thin ascending limb
DISTAL TUBULE
Lumen
Basolateral
Na+
DCTD
2Cl-
ATP
3Na+
2K
PROXIMAL TUBULE
Lumen
Basolateral
Na+
H+
HCO-3
H2CO3
CAI
CO2
H2O
ATP
3Na+
2K
CONNECTING TUBULE
COLLECTING DUCT
Lumen
Basolateral
MR
Na+
Aml
K+
ATP
Aldo
3Na+
2K
THICK ASCENDING LIMB
LD
Lumen
Basolateral
Na+
2Cl-
K+
K+
ATP
3Na+
2K
B
Pocket for ions
loop Diuretics
TM8
TM5
V385
TM3
TM2
M382
TM1
TM6
TM10
F372
NKCC2

Primary determinant of natriuresis is the time above the threshold





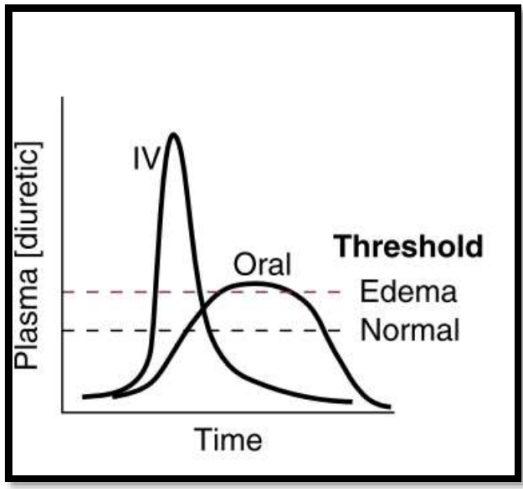


Severe hypoalbuminemia might impair diuretic effectiveness

Table 147. Classes of Diuretic Agents Used in CKD

	Thiazide	Loop	Potassium-Sparing
Pharmacodynamic Effects	Increases excretion of sodium, potassium and magnesium. Decreases excretion of calcium	Increases excretion of sodium, potassium, hydrogen ion, calcium and magnesium	Increases excretion of sodium. Decreases excretion of potassium, hydrogen ion, calcium and magnesium
Site of action	Distal tubule	Thick ascending limb	Collecting tubule
Delivery to site of action	Organic anion transporter – proximal tubule	Organic anion transporter – proximal tubule	Organic cation transporter – proximal tubule
Transporters affected	Apical Na^+-Cl^- cotransport system	Na^+-K^+-$2Cl^-$ cotransporter	Epithelial sodium channels (triamterene, amiloride) or mineralocorticoid receptors (aldosterone antagonists)
Percent of filtrate reabsorbed at site of action	6%-11%	20%-30%	Less than 5%
Bioavailability	40%-90%	50%-100%	30%-90%
Route of elimination	Liver/kidney	Liver/kidney	Liver/kidney
Elimination half-life	2.5-60 hours	1-5 hours	2-26 hours
Dose schedule	Usually once daily	Usually twice daily	Once or twice daily

Key Concepts



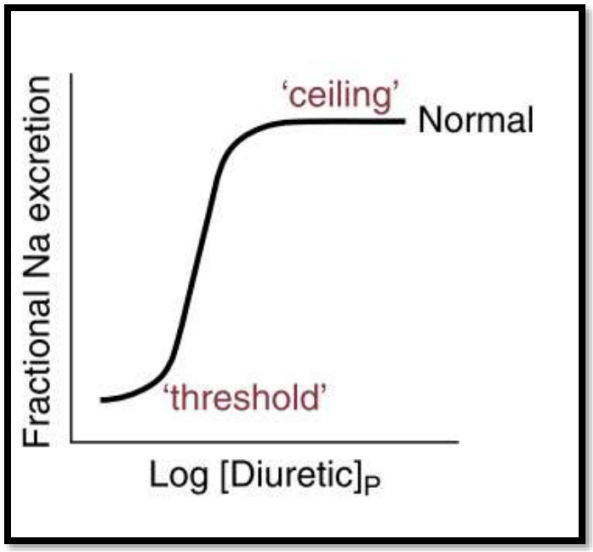
- **Threshold:** No effect below a given plasma concentration
  - Most common errors in diuretic usage
- " Doubling the dose"
- **Ceiling:** Failing to elicit more natriuresis beyond this plasma conc
- **ECF volume expansion & edema**: Altered pharmacokinetics
  - GI Absorption can be slowed in states of heart failure exacerbations[1]
  - IV drug may attain higher peak levels and may be more effective even when oral dose gives no response
- Correct approach:?
- **Volume of distribution**:
  - Loop diuretics: organic anions - bound to albumin (95%)- Low volume of distribution
  - Severe hypoalbuminemia: Impair diuretic effectiveness by reduced delivery
  - Coadministration of albumin with furosemide in hypoalbuminemic patients[2]

1. Vasko MR, Cartwright DB, Knochel JP, Nixon JV, Brater DC: Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med102: 314–318, 1985
2. Kitsios GD, Mascari P, Ettunsi R, Gray AW: Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: A meta-analysis. J Crit Care 29: 253–259, 2014

Key Concepts

- **Absorption-limited kinetics[1]:**
  - Oral administration : Bioavailability of furosemide is 50%
  - Longer duration of action : Gastrointestinal absorption may be slower than its elimination t1/2
  - Dose to be doubled when switched : **IV→ Oral**

- **Dose Response Curve:**
  - *Natriuretic response* plotted versus the *log of the plasma diuretic conc*
  - Loop diuretics – " **Steep Curve**"
  - *Understanding has clinical relevance in optimal use*



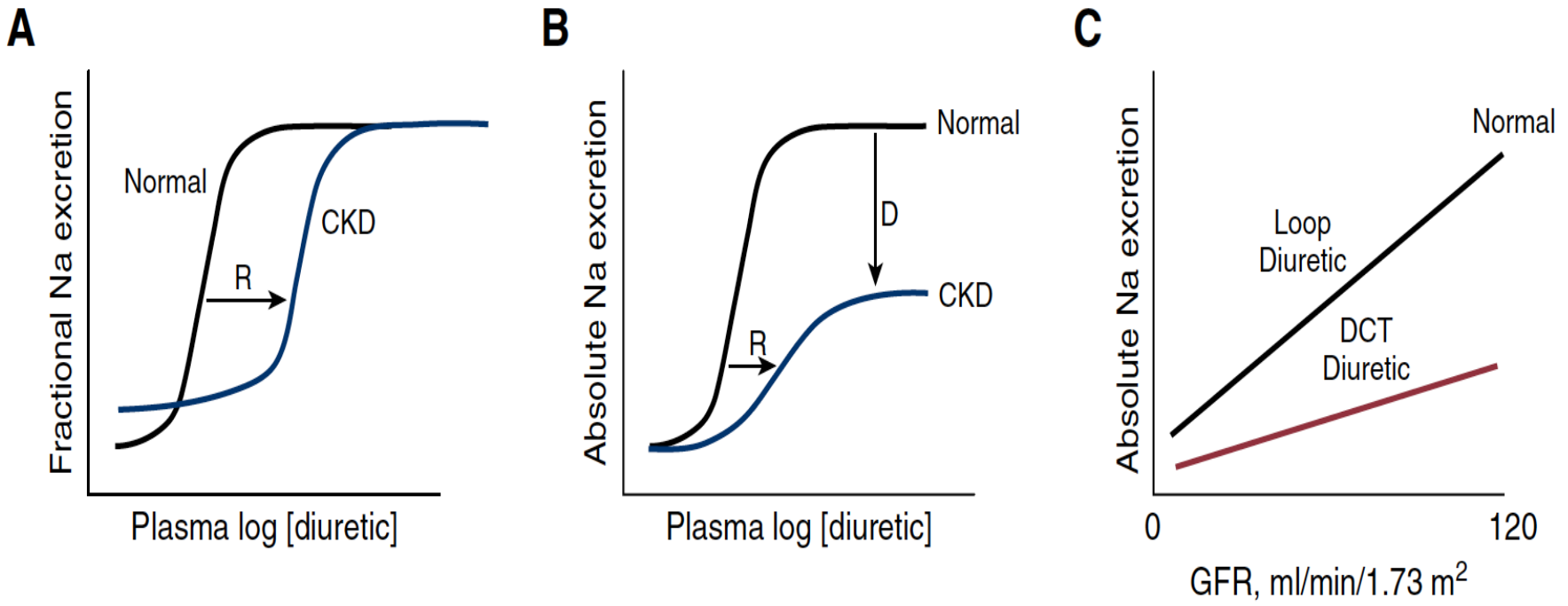
1. Hammarlund MM, Paalzow LK, Odlind B: Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis. Eur J Clin Pharmacol 26: 197–207, 1984

CEILING DOSES OF COMMON LOOP DIURETICS

Table 51.3 Ceiling Doses (in mL) of Loop Diuretics

Condition	Furosemide		Bumetanide, IV or PO	Torsemide, IV or PO
	IV	PO		
Chronic renal insufficiency:				
Moderate (GFR 20-50 mL•min^{-1})	80-160	160	6	50
Severe (GFR < 20 mL•min^{-1})	200	240	10	100
Nephrotic syndrome with normal GFR	120	240	3	50
Cirrhosis with normal GFR	40-80	80-160	1	20
Heart failure with normal GFR	40-80	80-160	1	20

GFR, Glomerular filtration rate; IV, intravenous; PO, oral.



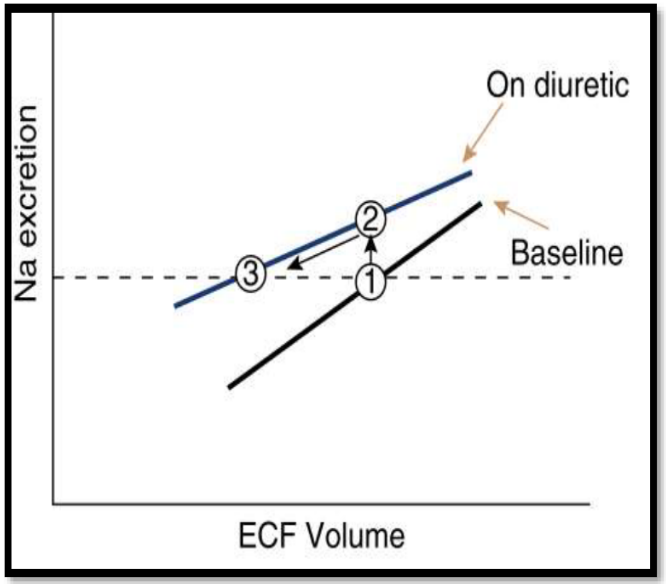
Pharmacokinetics and pharmacodynamics of diuretic action.

(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.

- **Post diuretic NaCl retention:** Urinary NaCl excretion declines below the baseline when the diuretic effect wears off [1]
  - *Recommendation to use loop diuretics twice daily*
  - *Physiologic basis of use of continued infusion Vs high dose bolus administration*[2]
- **Braking phenomenon:** *Natriuresis wanes as ECF declines*
  - *At steady state, the individual returns to NaCl balance, during which urinary NaCl excretion is equal to dietary NaCl intake once again*
    - After a diuretic is started, urinary sodium excretion rises by shifting to a new curve (from point 1 to point 2)
    - Braking phenomenon: urinary sodium excretion declines back to the baseline level, but at a new and reduced ECF volume
    - Action: Hypertrophy of cells downstream from where loop diuretics exert their action, particularly in the DCT



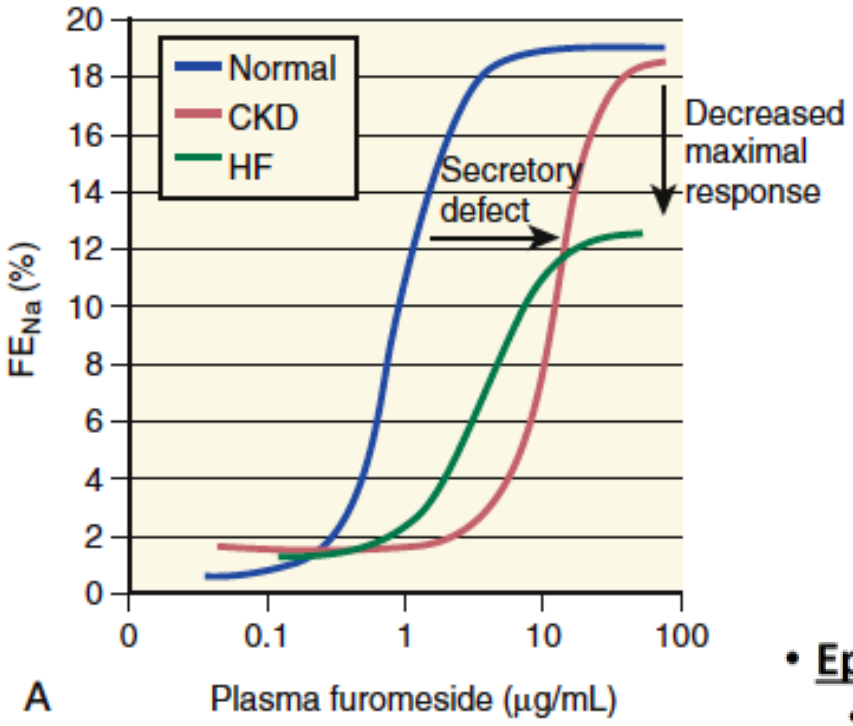
1. Ellison DH, FelkerGM:Diuretic treatment inheart failure. Nengl J Med377: 1964–1975, 2017
2. Salvador DR, Rey NR, Ramos GC, Punzalan FE: Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev (3): CD003178, 2005

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	Not changed	
Spironolactone	>90	1.5[c]	[d]		

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).

Furosemide absorption varies from day to day in an individual, and between individuals (inconsistent bioavailability). Absorption is also affected by food consumption, unlike that of bumetanide or torsemide The more consistent bioavailability of torsemide, compared with furosemide, and its relatively longer t1/2, have suggested that it may be a superior loop diuretic.

Chronic Kidney Disease



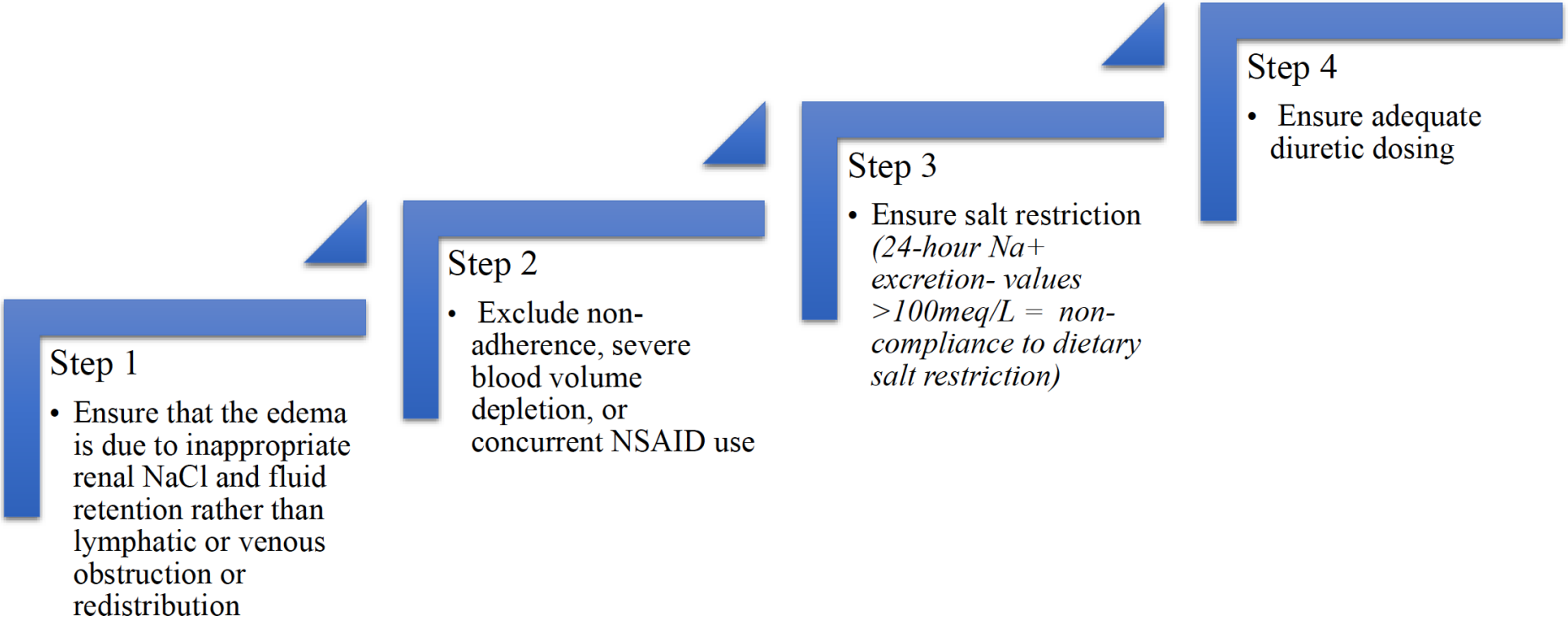
Thus, CKD causes diuretic resistance both by shifting the diuretic dose-response curve to the right (which can be overcome by higher doses) and by reducing maximal natriuresis (which cannot).
This phenomenon likely explains the reduced effectiveness of distal convoluted tubule diuretics in CKD.

- **Epidemiologic studies:** Diuretic use with CKD
  - Diuretic use in presence of residual renal function was associated with lower interdialytic weight gain, less hyperkalemia, and lower cardiac-specific mortality[1]

Table 2. Some identified mechanisms and their possible solutions for limited response to loop diuretics in patients with renal insufficiency

Limitation of Response	Potential Mechanism	Potential Solution
Decreased renal diuretic delivery	Decreased renal blood flow	Optimize BP and body fluids to restore renal blood flow
Decreased basal fractional NaCl reabsorption	Limits effects of less-active diuretics	Select a loop, not a thiazide, as initial diuretic
Decreased proximal tubule diuretic secretion	Competition with urate and organic anions for basolateral uptake by OAT	Correct uremic milieu and hyperuricemia
	Acidosis impairs secretion	Correct acidosis
	Competition with drugs for tubular secretion by OAT	Avoid codosing with probencid, NSAIAs, β-lactam and sulphonamide antibiotics, valproic acid, methorexate, cimetidine, and antiviral agents
Maintained metabolic but decreased renal clearance (furosemide only)	Hepatic metabolism of bumetanide and torsemide preserved	Consider bumetanide or torsemide to prevent accumulation and ototoxicity at high plasma levels
Enhanced NaCl reabsorption in downstream segments	Enhanced distal tubule fluid and NaCl delivery	Use thiazide or metolazine with loop diuretic in resistant patients
	Enhanced TSC expression	

APPROACH TO DIURETIC RESISTANCE



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Adding a thiazide or thiazide-like drug will help to restore diuretic efficacy. Most commonly, especially in patients with CKD, metolazone is chosen as the second agent.
At least three factors may contribute to these beneficial effects.

- First, by blocking transport along the distal tubule, a site exhibiting transport activation, the potency of these normally weak diuretics will be increased.
- Second, when oral metolazone or chlorthalidone is used in this situation, its longer t1/2 (approximately 14 and 50 hours) means that post diuretic NaCl retention may be attenuated.
- Third, these drugs may mitigate distal nephron remodeling and activation of the thiazide sensitive NCC.

KDOQI GUIDELINES

KDOQI GUIDELINE 12: USE OF DIURETICS IN CKD

- ***12.1*** **Most patients with CKD should be treated with a diuretic (A).**

- ***12.1.a*** **Thiazide diuretics given once daily are recommended in patients with GFR ≥30 mL/min/1.73 m^2 (CKD Stages 1-3) (A);**

- ***12.1.b*** **Loop diuretics given once or twice daily are recommended in patients with GFR <30 mL/min/1.73 m^2 (CKD Stages 4-5) (A);**

KDOQI GUIDELINE 12: USE OF DIURETICS IN CKD

- ***12.1.c*** **Loop diuretics given once or twice daily, in combination with thiazide diuretics, can be used for patients with ECF volume expansion and edema (A).**

- ***12.1.d*** **Potassium-sparing diuretics should be used with caution:**
  - ***12.1.d.i*** **In patients with GFR <30 mL/min/1.73 m^2 (CKD Stages 4-5) (A);**
  - ***12.1.d.ii*** **In patients receiving concomitant therapy with ACE inhibitors or ARBs (A);**
  - ***12.1.d.iii*** **In patients with additional risk factors for hyperkalemia (A).**

KDOQI GUIDELINE 12: USE OF DIURETICS IN CKD

- ***12.2*** **Patients treated with diuretics should be monitored for:**
  - ***12.2.a*** **Volume depletion, manifest by hypotension or decreased GFR (A);**
  - ***12.2.b*** **Hypokalemia and other electrolyte abnormalities (A).**
  - ***12.2.c*** **The interval for monitoring depends on baseline values for blood pressure, GFR and serum potassium concentration**
- ***12.3*** **Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence (B).**

Table 160. Use of Diuretics in CKD

1	Indications	• To reach target blood pressure and reduce CVD risk: – CKD Stages 1-3. Thiazide, loop, or potassium-sparing (use with caution with ACE inhibitor or ARB) diuretic. – CKD Stages 4-5. Loop diuretic.
2	Usual Starting Dose (mg/d)	• Thiazide diuretics: HCTZ (12.5-25 mg); chlorthalidone (12.5-25 mg). • Loop diuretics: furosemide (20-40 mg in CKD Stages 1-3; 40-80 mg in CKD Stages 4-5). • Potassium-sparing diuretics: triamterene (50-100 mg); amiloride (5-10 mg); spironolactone (25-50 mg in CKD Stages 1-2, 25 mg in CKD Stage 3); eplerenone (50-100 mg in CKD Stages 1-2, 50 mg in CKD Stage 3):
3	Side-Effects	• Hypotension, decreased GFR, hypokalemia, metabolic alkalosis, hypomagnesemia and hyperuricemia.
4	Manifestations of ECF Volume Depletion	• Light-headedness, tachycardia, decline in weight, postural changes in blood pressure, decreased skin turgor, decreased GFR, electrolyte abnormalities.
5	Causes of ECF Volume Depletion in CKD	• Urinary losses of sodium chloride: excessive diuresis, salt-wasting nephropathies. • Gastrointestinal losses of sodium chloride: vomiting; diarrhea; gastric, biliary, pancreatic or jejunal drainage. • "Third space" losses of sodium chloride: ileus, peritonitis, pancreatitis, pleural or ascitic fluid drainage, open wounds. • Cutaneous losses of sodium chloride: marked sweating, burns, erythroderma.
6	Causes of Hypokalemia in CKD	• Urinary losses of potassium chloride: specific types of CKD (renal tubular acidosis), drug induced potassium wasting (diuretics, kidney damage due to aminoglycosides, amphotericin B and cis-platinum), diabetic ketoacidosis, chloride-sensitive metabolic alkalosis (ECF volume depletion); persistent hypomagnesemia. • Gastrointestinal losses of potassium chloride: Gastric losses (vomiting, gastric drainage), colonic losses (diarrhea, laxative abuse, villous adenoma. • Inadequate intake of potassium: Anorexia, liquid diets.
7	Frequency of Monitoring for Side Effects (Blood Pressure, GFR, Serum Potassium)	• If SBP <120 mm Hg, GFR <60 mL/min/1.73 m^2, change in GFR ≥15%, and serum potassium ≤4.5 mEq/L for thiazide or loop diuretics, or serum potassium >4.0 mEq/L for potassium-sparing diuretics. – ≤4 weeks after initiation of an increase in dose, or – 1-6 months after blood pressure is at goal and dose is stable.
8	Conditions in which Diuretics Should Not Be Used or Used with Caution	• ECF volume depletion • Pregnancy • History of gout • History of immediate allergic reactions or Stevens-Johnson syndrome or toxic epidermal necrolysis • Serum potassium ≤4.0 mEq/L despite treatment, for thiazide and loop diuretics • Serum potassium >4.5 mEq/L for potassium-sparing diuretics • GFR decline >30% within 4 months without explanation

Diuretic drug dosing in CKD

Table 149. Dose Range and Selected Pharmacokinetics for Specific Diuretic Agents in CKD

Drug	Oral Bioavailability (%)	Elimination half-life in Normal Individuals (hrs)	Elimination half-life in CKD (hrs)	Usual Dose Range, (mg/day) (doses/day)
Thiazide diuretic				
Chlorthalidone	65	40-60	NA	12.5-50 (1)
Hydrochlorothiazide (HCTZ)	65-75	2.5	Increased	12.5-50 (1)
Indapamide	93	15-25	NA	1.25-5.0 (1)
Metolazone (Mykrox)	>80		NA	0.5-1.0 (1)
Metalozone (Zaroxylyn)	40-60 but reduced in disease states	8-14	Increased	2.5-20 (1)
Loop diuretics				
Bumetanide	80-100	1.0	1.6	0.5-4.0 (2-3)
Furosemide	10-100	1.5-2.0	2.8	40-240 (2-3)
Torsemide	80-100	3-4	4.5	5-100 (1-2)
Potassium-sparing				
Triamterene	30-70 but formulation dependent	2-5	Prolonged	25-100 (1-2)
Amiloride	30-90	17-26	100	5-10 (1-2)
Spironolactone	Absolute bioavailability not known - ≈ 75 % absorption	1.5	No change	25-100 (1-2)
Eplerenone	Unknown	4-6 hours	No change	50-100 (1-2)

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)

KDOQI GUIDELINE 12: USE OF DIURETICS IN CKD

Table 145. Recommended Intervals for Monitoring Blood Pressure, GFR, and Serum Potassium for Side Effects of Diuretics in CKD

Baseline Value	Baseline SBP (mm Hg)	≥120*	<120
	Baseline GFR (mL/min/1.73 m^2)	≥60	<60
	Early GFR Decline (%)	<15	≥15
	Baseline Serum Potassium (mEq/L) for Thiazide and Loop Diuretics	>4.5	≤4.5
	Baseline Serum Potassium (mEq/L) for Potassium-Sparing Diuretics	≤4.0	>4.0
Interval	After Initiation or Increase in Dose	4-12 weeks	≤4 weeks
	After Blood Pressure is at Goal and Dose is Stable	6-12 months	1-6 months

*See Guideline 7, Table 90, for recommended intervals to reach blood pressure goal.

PLOS ONE

RESEARCH ARTICLE

Chronic Kidney Disease, Fluid Overload and Diuretics: A Complicated Triangle

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To determine the extent of renal deterioration with diuretic therapy.

Methods:

A total 312 non-dialysis dependent CKD (NDD-CKD) patients were prospectively followed up for one year. Fluid overload was assessed via bioimpedance spectroscopy. Estimated GFR (eGFR) was calculated from serum creatinine values by using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation.

Table 3. Comparison of outcomes between diuretic users and non-users.

Outcomes	Total cohort N = 312	Diuretic users N = 144	Non-users N = 168	p-value
S-cr measurements	4 (3–7)	5 (3–7)	5 (3–7)	
eGFR	23.7±7.1	22.3 ± 7.4	25.1 ± 6.8	<0.001
ΔeGFR (ml/min/1.73m^2)	-2.5±1.4	-3.5 ± 1.6	-1.6 ± 0.77	0.02
RRT	36 (11.5%)	30 (20.8%)	6 (3.5%)	<0.001
Death	2 (0.6%)	2 (1.4%)	0	

p-value calculated by student t-test for continuous variables and chi-square test for categorical variables between diuretic users and non-users

S-cr: serum creatinine, ΔeGFR: change in estimated glomerular filtration rate. RRT: renal replacement therapy

Results

Overall 144 patients were using diuretics among which 98 (72.6%) were hypervolemic, 35 (30.9%) euvolemic and 11 (17.2%) were hypovolemic. The mean decline in estimated GFR of entire cohort was -2.5 ± 1.4 ml/min/1.73m2 at the end of follow up. The use of diuretics was significantly associated with decline in eGFR. A total of 36 (11.5%) patients initiated renal replacement therapy (RRT) and need of RRT was more profound among diuretic users.

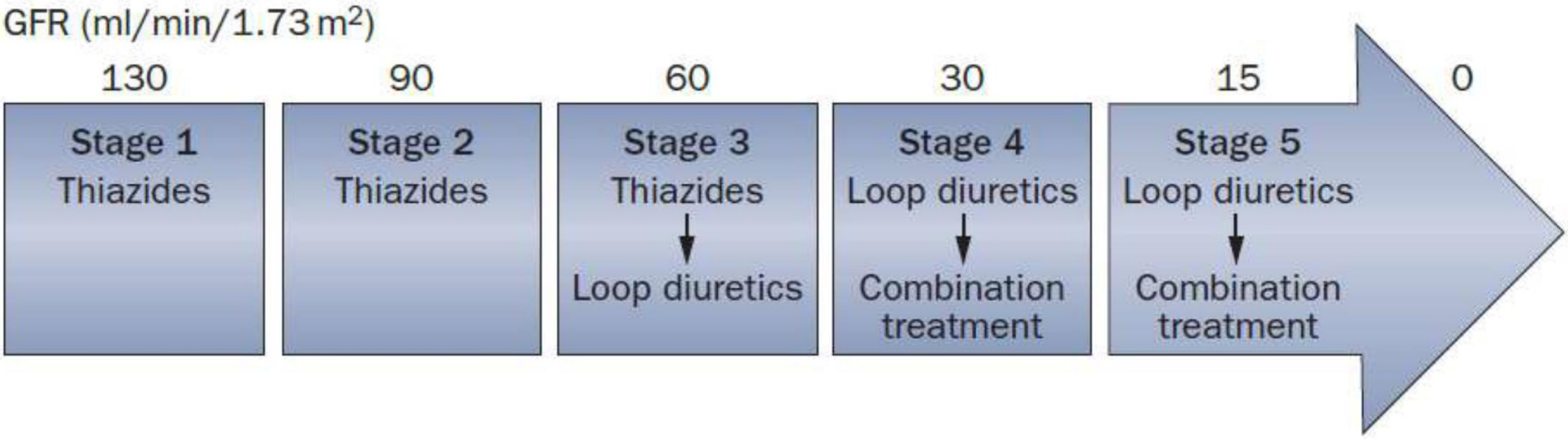
Conclusions:

The use of diuretics was associated with adverse renal outcomes indicated by decline in eGFR and increasing risk of RRT initiation in our cohort of NDD-CKD patients. Therefore, it is cautiously suggested to carefully prescribe diuretics by keeping in view benefit versus harm for each patient.

Table 2. Selected Indications and Considerations in the Choice of Antihypertensive Agents for Patients With CKD

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
Diuretics					
Thiazide (eg, hydrochlorothiazide, chlorthalidone, metolazone)	Fluid overload; may improve proteinuria if used in combination with RAS inhibitors	Kidney stone prevention (hypercalciuria); Gordon syndrome; NDI	Hyperuricemia; hypercalcemia; hyponatremia; hypokalemia; hyperglycemia (with long-term use)	Gout; hypercalcemia	May be less effective when eGFR is <30 although some studies have shown these agents remain effective even with low eGFR
Loop (eg, furosemide, bumetanide, torsemide)	Fluid overload	Heart failure; hypercalcemia	Hearing loss; hypokalemia; hypocalcemia; hyponatremia	Gout; sulfonamide-related hypersensitivity	Bumetanide and torsemide have better intestinal absorption than furosemide
Potassium-sparing (triamterene, amiloride)	Fluid overload; hypokalemia	Refractory hypomagnesemia; lithium toxicity/NDI	Hyperkalemia; metabolic acidosis	Pregnancy	

Choice of diuretic - CKD

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