Diuretics in HTN

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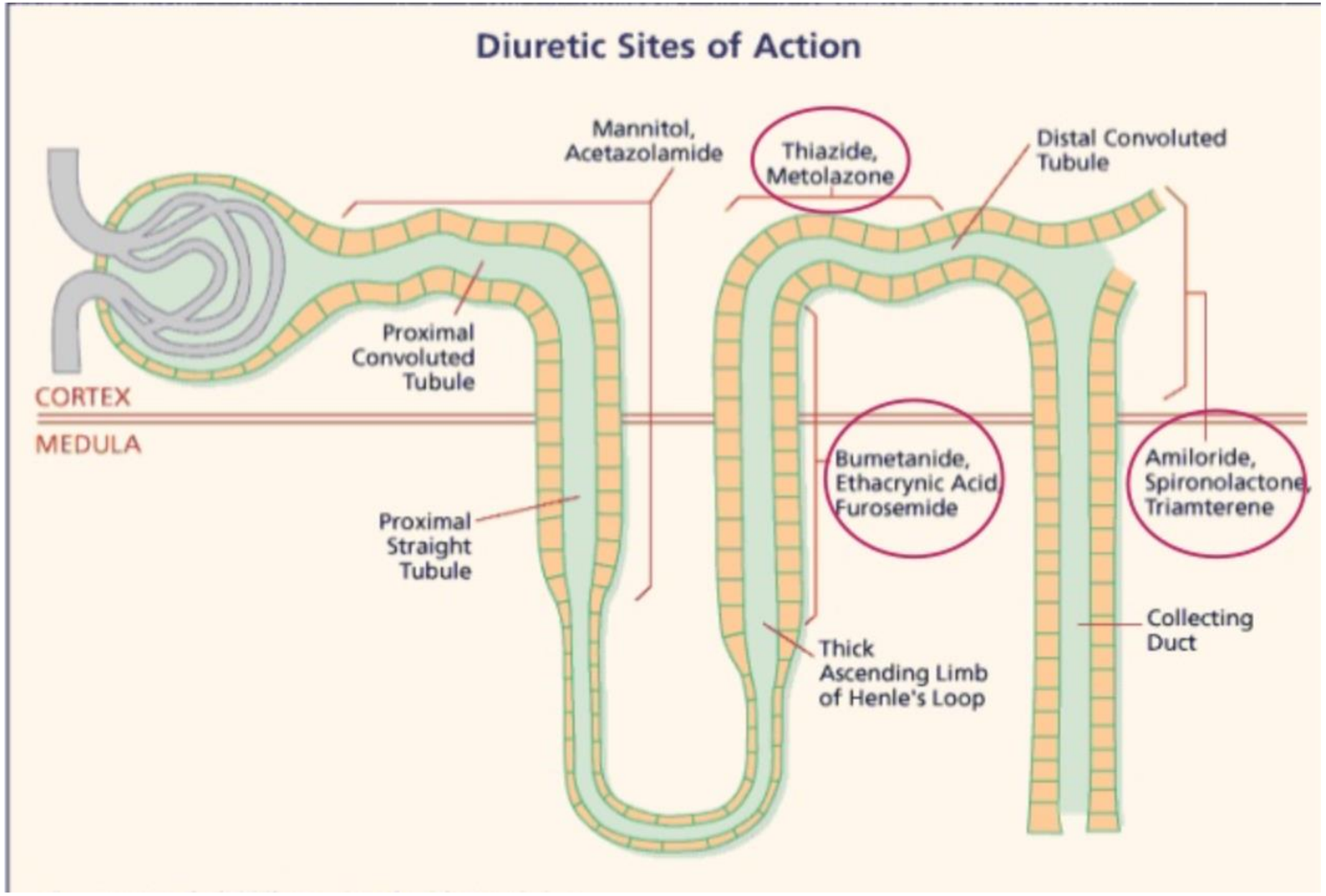
Diuretics are a popular, heterogenous class of antihypertensives with several decades of clinical application.

In hypertension, diuretics are recommended as first-line therapy, especially because a network metaanalysis found low-dose diuretics the most effective first-line treatment for prevention of cardiovascular complications.



Psaty BM, et al, JAMA 2003

First line antihypertensive drugs

	ACE-I	AT-1	DIURETIC	CA-ANTAGONISTS	B-BLOCKERS
JNC 8	+	+	+	+	-
JNC 7	+	+	+	+	+
NSH	+	+	+	+	-
AHA	+	+	+	+	-
ESH/ESC	+	+	+	+	+
WHO	+	+	+	+	-

- However…concomitant administration of NSAID.
- Excess salt ingestion blocks the antihypertensive effect of diuretics.
- selection of the appropriate medication….
- In the setting of low renin HTN, diuretics elevate renin in a dose-dependent manner and…
- Diuretics are critical in the management of resistant HTN...
- The number of salt-sensitive patients (i.e., the obese and elderly) is increasing...
- diuretics will become even more prominent in the management of hypertension.

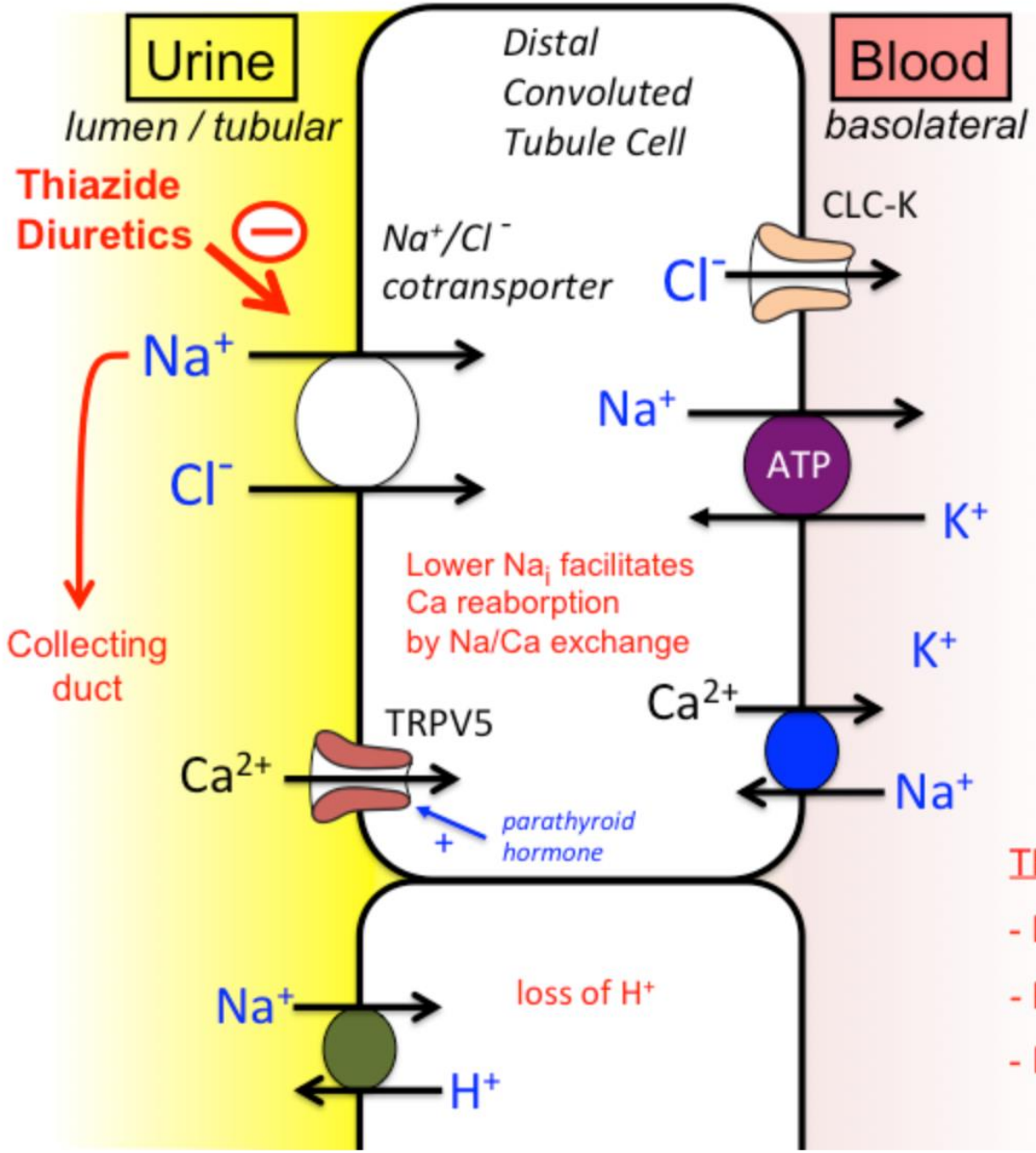
Pharmacology of diuretics used to treat hypertension

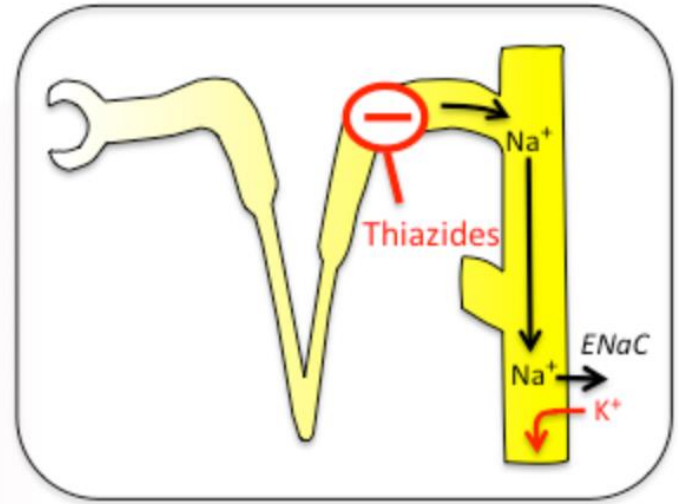
Pharmacology of diuretics used to treat hypertension

	Bioavailability (%)	Half-life (hours)	Duration of action (hours)
Thiazide diuretics*			
Bendroflumethiazide	90	3-4	6-12
Chlorothiazide	9-56 (dose dependent)	Biphasic: Initially 1-2, then ~12	6-12
Hydrochlorothiazide	65-75	Biphasic: Initially ~5, then 6-15	6-12
Thiazide-like diuretics			
Chlorthalidone	65	40-60¶	24-72
Indapamide	90	Biphasic: Initially ~14, then 25	16-36
Metolazone	65	6-20	18-25
Loop diuretics			
Bumetanide	80-90	1-1.5	4-6
Furosemide	47-64 (oral absorption is reportedly more variable in organ dysfunction and with gut-wall edema)	0.5-2	6-8
Torsemide	80	3.5	6-8
Ethacrynic acid	~100	2-4	12
Potassium-sparing diuretics			
Amiloride	15-25 (variable)	Biphasic: Initially 6-9, then ~20	24
Triamterene	50	2-4	7-9
Aldosterone antagonists, potassium sparing			
Eplerenone	69	4-6	Insufficient data
Spironolactone	65	1.5 (15)Δ	48-72

Data shown are for oral administration in patients with normal renal and cardiac function.

* Maximal antihypertensive effect is seen with low doses after several weeks of use.
¶ Prolonged serum half-life of chlorthalidone does not fully predict the duration of clinical effect.
Δ The half-life of one active metabolite, canrenone, is 15 hours.





Enhanced Na^+ delivery results in K^+ loss in the collecting duct

10% of filtered Na
is normally reabsorbed
in the distal convoluted tubule

Thiazide diuretics:

- Loss of Na & Water
- Hypokalemic metabolic alkalosis
- Increased Ca^{2+} reabsorption

- **ANTIHYPERTENSIVE MECHANISM** of thiazides:
- incompletely understood.
- initial volume loss ….CO
- Longer-acting diuretics vs short-acting.
- hypovolemia-induced activation of the RAS ..

- Long-term maintenance of the decrease in BP : partial reversal of the initial hemodynamic changes: the plasma volume and CO partially rise toward the baseline level, while the systemic vascular resistance falls .

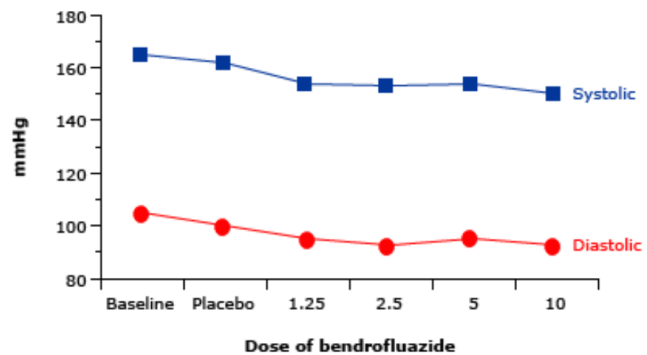
- **Mechanism of vasodilation** :
- The factors responsible for the secondary vasodilation remain unclear.
- One hypothesis …..inhibits the cellular Na-K-ATPase pump .
- leading sequentially to a rise in Na-K-ATPase activity, a fall in cell sodium concentration
- The ensuing decline in the cell calcium concentration..

- Another possibility is a direct effect upon potassium channels.

Diuretics	Dose	Duration of action
Hydrochlorothiazide	12.5-25mg(for BP) 25-100mg (for CHF)	16-24hr
Chlorothiazide	250-1000mg	6-12hr
Trichlormethiazide	1-4mg	24hr
Benzthiazide	50-200mg	12-18h
Chlorthalidone	12.5-15mg(for BP)	40-60hr
Metolazone	2.5-5mg(for BP) 5-20mf(for CHF)	24 h
xiapamide	5mg(for BP)	6-12hr
Indapamide	1.25-2.5mg 1.25mg(prefered for BP) 2.5-5mg (for CHF)	24h

Antihypertensive dose response to thiazide therapy

Antihypertensive dose response to thiazide therapy



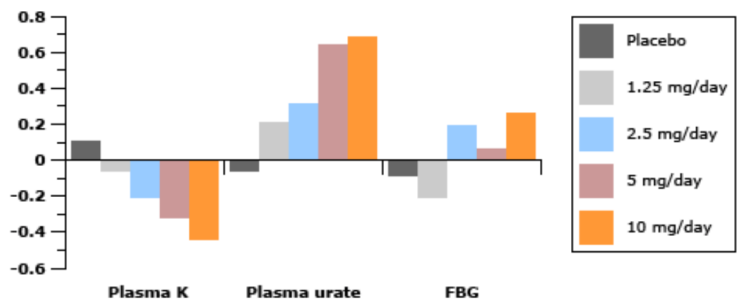
Antihypertensive response to bendrofluazide in relation to daily dose (in mg; multiply by 10 to get approximate equivalent doses of hydrochlorothiazide). The initial dose of 1.25 mg/day lowers the blood pressure in comparison with placebo; however, higher doses produced little further antihypertensive response. Each treatment group contained approximately 52 patients.

Data from: Carlsen JE, Kober L, Torp-Pedersen C, Johannsen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. BMJ 1990; 300:975.

Graphic 61248 Version 4.0

Dose dependence of thiazide-induced side effects

Dose dependence of thiazide-induced side effects



Metabolic complications induced by bendrofluazide in relation to daily dose (multiply by 10 to get equivalent doses of hydrochlorothiazide). Increasing the dose led to progressive hypokalemia and hyperuricemia and a greater likelihood of a mild elevation in the FBG, all without a further reduction in the systemic blood pressure. Each treatment group contained approximately 52 patients.

FBG: fasting blood glucose.

Data from: Carlsen JE, Kober L, Torp-Pedersen C, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. BMJ 1990; 300:975.

Graphic 69912 Version 5.0

Chlortalidone vs hydrochlorothiazide

- Both HCTZ and CTD have demonstrated risk reduction in clinical trials.

- However, the largest trials including HDFP,MRFIT,SHEP,ALLHAT primarily used CTD as initial therapy and more consistently showed reduction in cardiovascular events than studies primarily used HCTZ.

Trials favoring CTD

- **ALLHAT:**

→ ~ 35000 patients

→ Amlodipine or Lisinopril vs Chlorthalidone (2.5-10mg) (10-40mg) (12.5-25mg)

- Conclusion:
- Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.

Thus, when a diuretic is used either as initial therapy or in combination with other antihypertensive therapies, we and others suggest indapamide (1.5 to 2.5 mg/day) or chlorthalidone (12.5 to a maximum of 25 mg/day) .

which produced the best outcomes in ALLHAT, rather than hydrochlorothiazide at the same doses.

Clinicians should be aware that chlorthalidone is associated with somewhat greater risks of hypokalemia, glucose intolerance, and new onset diabetes mellitus than hydrochlorothiazide [53].

- *JAMA. 2002;288(23):2981-2997*

Trial favoring CTD

- Multiple Risk Factor Intervention Trial (MRFIT)

- 8012 patients

- HCTZ vs CTD
- (50-100mg) (up to 50mg)

- Conclusion
- Through 48 and 84 months of follow up BP and LVH decrease more by CTD than HCTZ.

- *HYPERTENSION 2011:58;1001-1007*

Trial favoring CTD

➡ Systolic Hypertension in Elderly Programme (**SHEP** Trial)

Conclusion-

- In persons aged 60 years and over with ISH, low-dose chlorthalidone (12.5mg)reduced the incidence of total stroke by 36% & major cardiovascular events were also reduced.

- *JAMA. 1991 Jun 26;265*

Trial favoring CTD

In a Meta analysis of 108 trials of HCTZ and 29 trials of CTD ,CTD was somewhat better in lowering SBP at the cost of more hypokalemia.

- Ernst ME et al,Am J Hypertension 2010,April 23(4)

Lower dose vs high dose diuretics

➡ Lower doses of HCTZ and CTD gave approximately as much as BP reduction as did the higher.

➡ Low dose should be used to avoid metabolic problems especially in elderly.

- *Carter BL et al,Hypertension 2004 Jan;43(1):4-9.*

• INDAPAMIDE:

- *Vasodilation property*
- *More lipid & Glucose neutral than other thiazides.*
- *Max T/P Ratio of 100%*
- *Reduce BP variability.(X-CELLENT study) ⋆*

- *Curr Med Res Opin 2005;21:37-46 Drugs Safety 2001;24:1155-65.*

- The Hypertension in the Very Elderly Trial – latest data

HYVET:

The Trial:

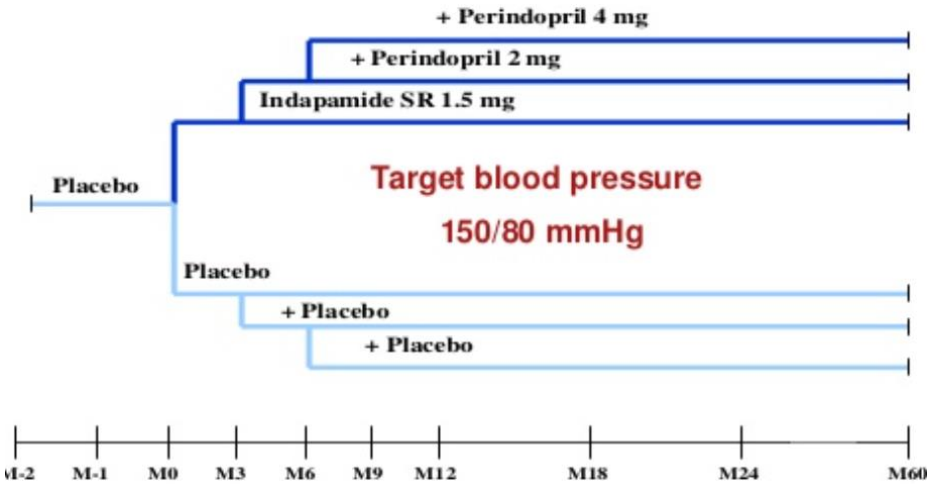
International, multi-centre, randomised double-blind placebo controlled

Inclusion Criteria:

Aged 80 or more,
Systolic BP 160 -199mmHg
diastolic BP <110 mmHg,
Informed consent

Exclusion Criteria:

Standing SBP < 140mmHg
Stroke in last 6 months +
Dementia
Need daily nursing care



Primary Endpoint: All strokes (fatal and non-fatal)
Target blood pressure 150/80 mmHg
Total Patients- 3845

- Reduction of 21% for total mortality (p=0.019)
- 39% for stroke mortality (p=0.046)
- 30% for stroke (p=0.055)
- 64% for heart failure (p<0.001)
- 34% for all cardiovascular events, a composite of cardiovascular causes of stroke, myocardial infarction or heart failure, (p<0.001)

- Conclusion-
- *Antihypertensive treatment with indapamide (sustained release), with or without perindopril,in persons 80 years of age or older is beneficial.*

- HYVET-COG substudy- blood pressure lowering may reduce or delay dementia

•INDAP VS HCT

- Head-to-head comparisons of HCTZ with indapamide and chlorthalidone: antihypertensive and metabolic effects.

- 14 RCT with 883 patients

- Conclusion-
- Like CTD, INDAP is more potent than HCTZ at commonly prescribed doses without evidence for greater adverse metabolic effects.

- *Roush GC,Hypertension 2015 May;65(5)*

Trial favoring indapamide : **PROGRESS**

- Total patients-7121
- ACEI vs Placebo --- NS difference in Stroke
- ACEI + D(Indapamide)--- 43% reduction in Stroke

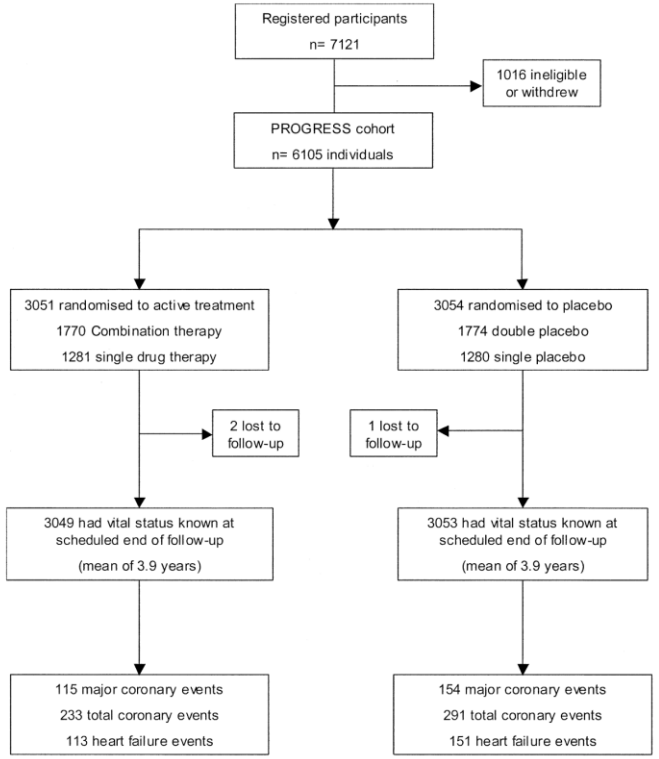


Fig. 1 Trial profile.

blood pressure lowering with a regimen involving perindopril for all patients, and indapamide for just over half, reduced the risks of coronary events and heart failure, as well as the risk of stroke.

- This regimen resulted in the avoidance of one stroke, coronary event or case of heart failure among every 17 (95% CI: 12–27) patients treated for 5 years.19

- Treatment with both agents simultaneously over the same period resulted in the avoidance of one such event in every 10 (95% CI: 8–15) patients.

- Conclusion- Perindopril + Indapamide is effective in BP reduction with secondary prevention of stroke.

Conclusions

LIVE is the first large, long-term study with a rando-
mized, centralized, blind, end-study reading of echocar
diograms to compare the efficacy of two anti-
hypertensive drugs in the reduction of LVMI.
LIVE found that :

indapamide SR 1.5 mg was significantly
more effective than enalapril 20 mg at LVMI reduction
while blood pressure was equally reduced.

Indapamide SR 1.5 mg progressively reduced wall thicknesses
throughout the 1-year treatment period.

In contrast, the effect of enalapril 20 mg observed at 6 months was not
maintained at 12 months.
Indapamide SR 1.5 mg can therefore be proposed as an:
effective treatment in hypertensive patients with LVH.

Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study

Philippe Gosse[a], Desmond J. Sheridan[b], Faiez Zannad[c], Olivier Dubourg[d], Pascal Guéret[e], Yuri Karpov[f], Peter W. de Leeuw[g], Jose-Luis Palma-Gamiz[h], Achille Pessina[i], Wolfgang Motz[j], Jean-Paul Degaute[k] and Claude Chastang[l], on behalf of the LIVE investigators

Objective To compare the efficacy of indapamide sustained release (SR) 1.5 mg and enalapril 20 mg at reducing left ventricular mass index (LVMI) in hypertensive patients with left ventricular hypertrophy (LVH).

Design The LIVE study (left ventricular hypertrophy regression, indapamide versus enalapril) was a 1 year, prospective, randomized, double-blind study. For the first time, a committee validated LVH before inclusion, provided on-going quality control during the study, and performed an end-study reading of all echocardiograms blinded to sequence.

Setting European hospitals, general practitioners and cardiologists.

Patients Hypertensive patients aged ⩾ 20 years with LVH (LVMI in men > 120 g/m²; LVMI in women > 100 g/m²). Data were obtained from 411 of 505 randomized patients.

Interventions Indapamide SR 1.5 mg, or enalapril 20 mg, daily for 48 weeks.

Main outcome measures LVMI variation in the per-protocol population.

Results Indapamide SR 1.5 mg significantly reduced LVMI (−8.4 ± 30.5 g/m² from baseline; $P < 0.001$), but enalapril 20 mg did not (−1.9 ± 28.3 g/m²). Indapamide SR 1.5 mg reduced LVMI significantly more than enalapril 20 mg: −6.5 g/m², $P = 0.013$ (−4.3 g/m² when adjusted for baseline values; $P = 0.049$). Both drugs equally and significantly reduced blood pressures ($P < 0.001$), without correlation with LVMI changes. Indapamide SR progressively reduced wall thicknesses throughout the 1-year treatment period. In contrast, the effect of enalapril observed at 6 months was not maintained at 12 months.

Conclusions Indapamide SR 1.5 mg was significantly more effective than enalapril 20 mg at reducing LVMI in hypertensive patients with LVH. *J Hypertens* 18:1465–1475 © 2000 Lippincott Williams & Wilkins.

Journal of Hypertension 2000, 18:1465–1475

Keywords: hypertension, left ventricular hypertrophy, left ventricular mass, echocardiography, diuretic, angiotensin converting enzyme inhibitor, indapamide SR 1.5 mg; enalapril 20 mg

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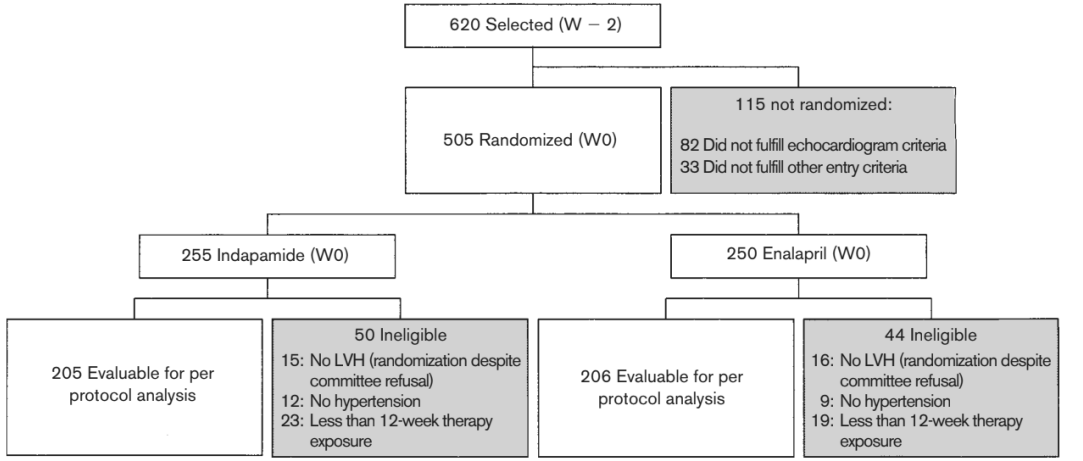

Patient disposition. Evaluable, patients treated with monotherapy for at least 12 weeks. LVH, left ventricular hypertrophy; W, week.

Loop diuretics —

Sulphonamides (except Ethacrynic acid) ⟹

- maximum dose, ….excretion of up to 20 to 25 percent of filtered sodium .
- medullary and cortical aspects of the TALH including the macula densa.
- Na-K-2Cl carrier isoform 2 (NKCC2, encoded by *SLC12A1*) .
- compete for the chloride site on this carrier..

Loop diuretics

Drug	Dose	Pharmacokinetics				
		Onset of action	Peak Diuresis	Duration of Action	Excretion	Absorption
Furosemide	10-20mg PO 2X for BP 20-80mg 2-3X for CHF	10-20min 5min(IV)	1.5hr	4-5hr 2hr(IV)	Renal	10-100%
Bumetanide	0.5-2mg PO 1-2X for BP 5mg PO or IV for Oliguria Not Licensed for BP	~20min	75-90min	4-5hr	Renal	80-100%
Torsemide	5-10mgPO or IV	10min	1hr(IV) 1-2hr(PO)	6-8hr(PO)	Hepatic	80-100%

1mg Bumetanide = 40mg Furosemide
10mg Torsemide = 40mg Furosemide

- Inhibition of a different isoform of this cotransporter (NKCC1, encoded by *SLC12A2*) in the inner ear is thought to be responsible for the ototoxicity that is rarely seen with high dose intravenous loop diuretic therapy.

- Loop diuretics also have important effects on renal calcium handling.
- The reabsorption of calcium in the loop of Henle is primarily passive, being driven by the electrochemical gradient created by NaCl transport and occurring through the paracellular pathway.

- As a result, inhibiting the reabsorption of NaCl leads to a parallel reduction in that of calcium, thereby increasing calcium excretion.

- A potential concern is that the calciuric response can lead to kidney stones and/or nephrocalcinosis. These complications have been primarily reported in premature infants in whom a loop diuretic can induce more than a 10-fold rise in calcium excretion .

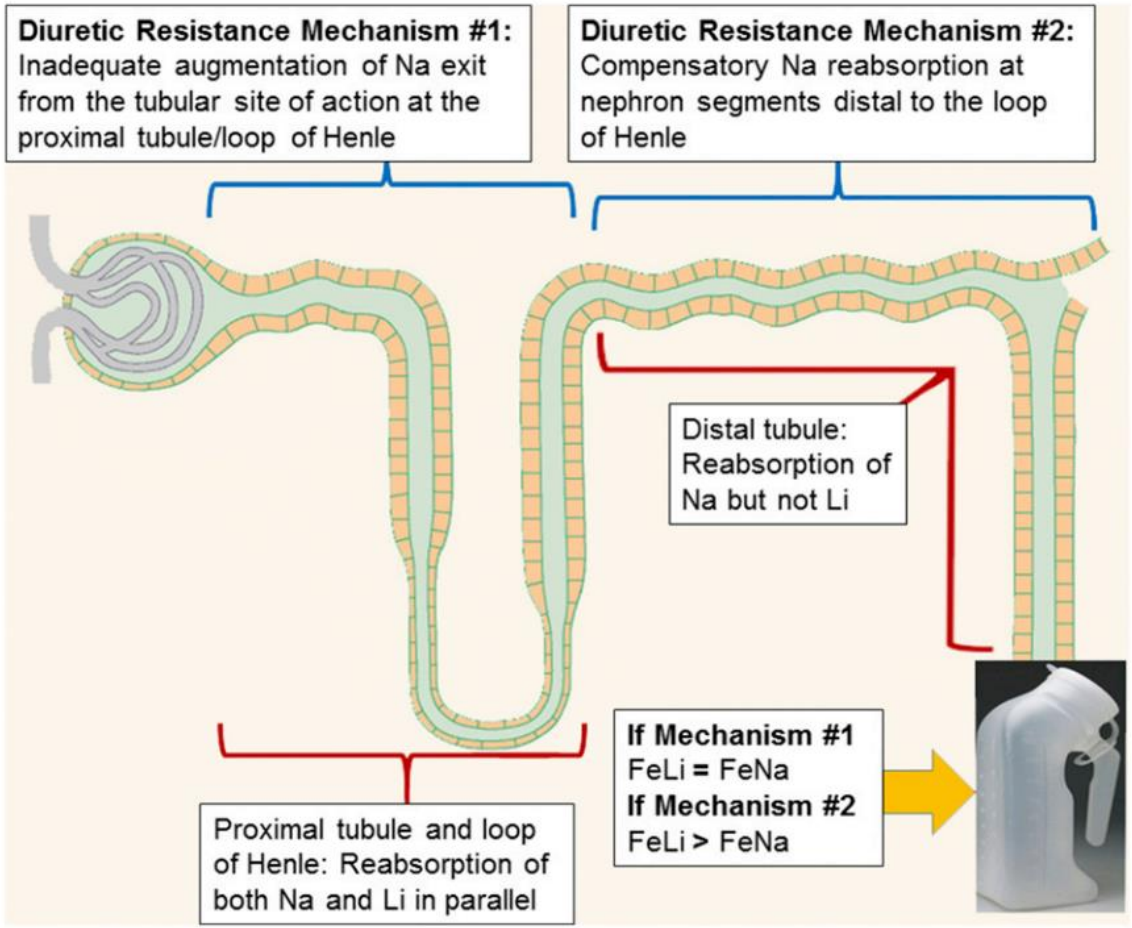

Figure 1. Schematic of the renal tubular mechanisms for DR and how the FELi can be used to probe these mechanisms. The mechanism underlying a poor loop diuretic response can be grouped into proximal tubular (Mechanism #1) or distal tubular (Mechanism #2). Lithium reabsorption occurs in parallel with sodium in the proximal tubule and loop of Henle, but is relatively uncoupled to sodium reabsorption in the distal tubule. Thus by measuring loop diuretic induced changes in lithium excretion, we can query the response of the proximal tubule and loop of Henle to the loop diuretic, regardless if the sodium is ultimately reabsorbed in the distal tubule. Li, lithium; Na, sodium.

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Compensatory Distal Reabsorption Drives Diuretic Resistance in Human Heart Failure

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ABSTRACT

Understanding the tubular location of diuretic resistance (DR) in heart failure (HF) is critical to developing targeted treatment strategies. Rodents chronically administered loop diuretics develop DR due to compensatory distal tubular sodium reabsorption, but whether this translates to human DR is unknown. We studied consecutive patients with HF (n=128) receiving treatment with loop diuretics at the Yale Transitional Care Center. We measured the fractional excretion of lithium (FELi), the gold standard for *in vivo* assessment of proximal tubular and loop of Henle sodium handling, to assess sodium exit after loop diuretic administration and FENa to assess the net sodium excreted into the urine. The mean±SD pre-diuretic FELi was 16.2%±9.5%, similar to that in a control cohort without HF not receiving diuretics (n=52; 16.6%±9.2%; P=0.82). Administration of a median of 160 (interquartile range, 40–270) mg intravenous furosemide equivalents increased FELi by 12.6%±10.8% (P<0.001) but increased FENa by only 4.8%±3.3%. Thus, only 34% (interquartile range, 15.6%–75.7%) of the estimated diuretic-induced sodium release did not undergo distal reabsorption. After controlling for urine diuretic levels, the increase in FELi explained only 6.4% of the increase in FENa (P=0.002). These data suggest that administration of high-dose loop diuretics to patients with HF yields meaningful increases in sodium exit from the proximal tubule/loop of Henle. However, little of this sodium seems to reach the urine, consistent with findings from animal models that indicate that distal tubular compensatory sodium reabsorption is a primary driver of DR.

J Am Soc Nephrol 28: 3414–3424, 2017. doi: https://doi.org/10.1681/ASN.2016111178

Inadequate dose of diuretic
Nonadherence
Not taking drug
High sodium intake
Pharmacokinetic factors
Slow absorption of diuretic because of gut edema
Impaired secretion of diuretic into the tubule lumen
Chronic kidney disease
Aging
Drugs
Nonsteroidal antiinflammatory drugs*
Probenecid
Hypoproteinemia
Hypotension
Nephrotic syndrome
Antinatriuretic drugs
Nonsteroidal antiinflammatory drugs*
Antihypertensive agents
Low renal blood flow
Nephron remodeling
Neurohormonal activation

* These drugs inhibit the efficacy of loop diuretics through several mechanisms.

- **ANTIHYPERTENSIVE DIFFERENCES BETWEEN THIAZIDE AND LOOP DIURETICS**
- **Patients without CKD:**

- When used in patients with primary hypertension and relatively normal kidney function, the thiazide diuretics, particularly chlorthalidone and indapamide, are more effective antihypertensive drugs than the loop diuretics .

- The difference in efficacy is probably related to duration of action of these diuretics .

- Commonly used loop diuretics, such as furosemide and bumetanide, have a short duration of action (less than six hours);
-
- the antihypertensive efficacy of these medications may be limited since the initial fluid loss can be counteracted by activation of the RAAS , leading to sodium retention during the period when the diuretic effect has worn off .

- Longer-acting loop diuretics are available; torsemide, for example, has a duration of action up to 12 hours.
- In a blinded, randomized trial, furosemide, given twice daily, and torsemide, given once daily, produced similar systolic pressure reductions in patients with chronic kidney disease (CKD) [8].

- **Patients with CKD:**

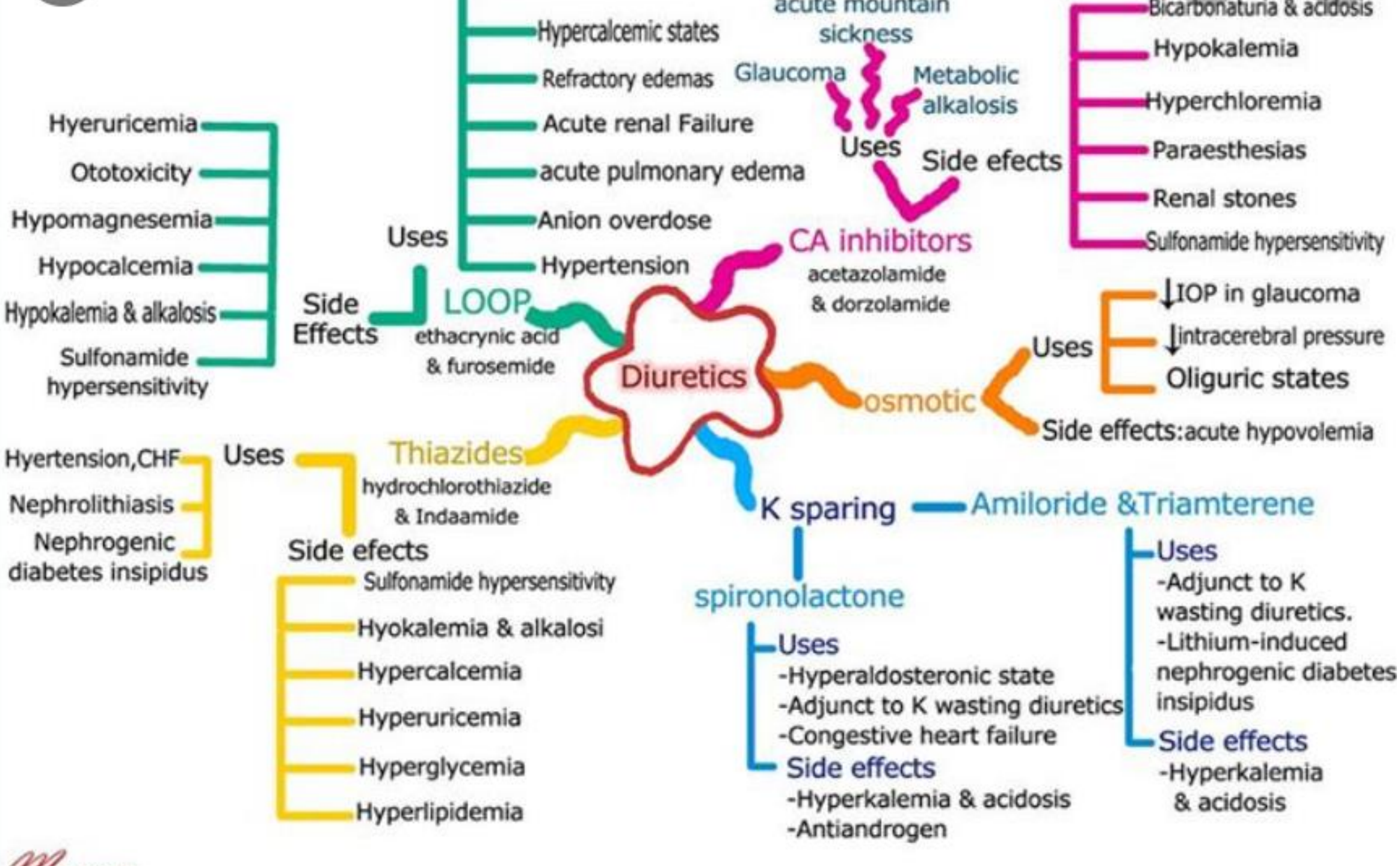
- It is a commonly held belief that the above observations do not necessarily apply to patients with renal insufficiency and that thiazide diuretics are less effective in such patients.
- However, several studies indicate that thiazide diuretics are effective in such patients.
- All diuretics are less effective in patients with impaired kidney function. Both thiazide and loop diuretics must reach the lumen of the renal tubule to act, a process mediated by OAT in the PT.

- As GFR decreases, organic acid levels increase, and these acids compete with diuretics for transport into the tubular lumen.
- Thiazides are less effective in competing with accumulating organic acids than loop diuretics in this setting .

Thiazide diuretics are therefore considered by many to be less effective in patients with a GFR less than 30 mL/min .

Because fluid retention is thought to play a major role in the elevation in blood pressure in CKD, such patients are often prescribed loop diuretics as antihypertensive agents, rather than thiazide diuretics.

- However, several interventional studies suggest that thiazides are effective even among patients with advanced CKD …. CTD & metolazone


Diuretics
CA inhibitors
acetazolamide
& dorzolamide
Uses
Glaucoma
acute mountain sickness
Metabolic alkalosis
Side efects
Bicarbonaturia & acidosis
Hypokalemia
Hyperchloremia
Paraesthesias
Renal stones
Sulfonamide hypersensitivity
LOOP
ethacrynic acid
& furosemide
Uses
Hypercalcemic states
Refractory edemas
Acute renal Failure
acute pulmonary edema
Anion overdose
Hypertension
Side Effects
Hyeuricemia
Ototoxicity
Hypomagnesemia
Hypocalcemia
Hypokalemia & alkalosis
Sulfonamide hypersensitivity
osmotic
Uses
↓IOP in glaucoma
↓intracerebral pressure
Oliguric states
Side effects:acute hypovolemia
Thiazides
hydrochlorothiazide
& Indaamide
Uses
Hyertension,CHF
Nephrolithiasis
Nephrogenic diabetes insipidus
Side efects
Sulfonamide hypersensitivity
Hyokalemia & alkalosi
Hypercalcemia
Hyperuricemia
Hyperglycemia
Hyperlipidemia
K sparing
Amiloride &Triamterene
spironolactone
Uses
-Hyperaldosteronic state
-Adjunct to K wasting diuretics
-Congestive heart failure
Side effects
-Hyperkalemia & acidosis
-Antiandrogen
Uses
-Adjunct to K wasting diuretics.
-Lithium-induced nephrogenic diabetes insipidus
Side effects
-Hyperkalemia & acidosis

- **MAJOR SIDE EFFECTS of loop diuretic :**
- those related to the diuresis and natriuresis, hypersensitivity reactions, and ototoxicity.
- **1-Diuresis related** :
- Hypokalemia ●Metabolic alkalosis ●Hypovolemia, hypotension, and azotemia●Hyperuricemia .●Hyponatremia (primarily due to hypovolemia-induced release of antidiuretic hormone)

- **2-Hypersensitivity reactions** — Furosemide, bumetanide, and torsemide, which are sulfonamides, can cause hypersensitivity reactions, usually manifested as a rash or rarely acute interstitial nephritis, similar to those produced by other sulfonamide drugs.
- **Alternative loop diuretic therapy with ethacrynic acid** — Ethacrynic acid, a non-sulfonamide loop diuretic, can be used in patients who develop a hypersensitivity reaction to furosemide, bumetanide, torsemide, or a sulfonamide-based thiazide diuretic.

- Ethacrynic acid is rarely used in the absence of this indication because it may be more ototoxic than the sulfonamide diuretics when given in high doses; in addition, it is relatively insoluble and therefore cumbersome to administer intravenously.

- **Lack of allergic cross-reactivity with sulfonamide antimicrobials :**There is minimal evidence of allergic cross-reactivity between sulfonamide antimicrobials and non-antimicrobials. Thus, patients with a history of allergy to sulfonamide antimicrobial drugs would be expected to tolerate nonantimicrobial sulfonamides such as loop diuretics. Allergic reactions that do occur appear to be related to a predisposition to allergic reactions rather than sulfonamide cross-reactivity .

- **3-Ototoxicity** — Loop diuretic-induced ototoxicity can lead to transient (usually lasting 30 minutes to 24 hours) or permanent deafness. Ototoxicity primarily occurs with high-dose intravenous therapy (eg, furosemide doses above 240 mg/hour) or at lower doses in patients with kidney function impairment or concurrent use of other ototoxins such as aminoglycosides.
- Ethacrynic acid, which is rarely used, may be more ototoxic in high doses than furosemide, torsemide, and bumetanide.

- **Mechanism** :Transport in the loop of Henle that is mediated by a Na-K-2Cl cotransporter is inhibited by loop diuretics. A secretory isoform of this cotransporter is present in the inner ear and plays an important role in the composition of endolymph.

- What is underappreciated is the time course with which these complications occur, which has been best studied with loop and thiazide diuretics.

- Assuming that the diuretic dose and dietary solute (eg, sodium and potassium) and water intake are relatively constant and that the patient is hemodynamically stable, most of the above problems develop during the first two to three weeks of therapy if they are going to occur .

- The reason for this time limitation is that the initial solute and water losses lead to compensatory changes that limit further losses.

- Thus, after the initial period of solute and water loss, a new steady state is attained in which solute and water intake and excretion are roughly equal, as they were before diuretic therapy was initiated. This phenomenon has been called **diuretic braking**.

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- Hyperuricemia is a relatively common finding in people treated with a loop or thiazide diuretic and may, over a period of time, contribute to new-onset gout or, more promptly, recurrence of established gout .

- Diuretics reduce urate excretion by both directly and indirectly increasing urate reabsorption and decreasing urate secretion ; the effect is dose dependent .

- Treatment of asymptomatic hyperuricemia is not recommended in most countries.

- If diuretic-induced gout occurs, it is usually treated with a urate-lowering drug such as allopurinol.
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The concurrent administration of an ACE inh or an ARB can minimize the diuretic-induced rise in serum urate concentration:

1-proximal sodium and urate reabsorption of angiotensin II.

2- Direct uricosuric effect of EXP3174

Little risk of uric acid nephropathy with losartan because of a concurrent elevation in urine pH due to reduced bicarbonate reabsorption.

Other dose-dependent side effects :

HCT enhances DNA damage induced by UV radiation ……increase the risk of skin cancer ……SCC of the lip and also with nonmelanoma skin cancers .

No association was observed with other diuretics. The risk with HCT was dose dependent and was evident only with large cumulative doses. …fewer than five years, would not have detected this relationship.

Thiazide-like diuretics are used much less frequently than HCT : fewer data are therefore available…

Non-dose-dependent side effects :

- sexual function .
- Sleep disturbances.
- AIN
- Pancratitis

Loop versus thiazide diuretics in hyponatremia:

Their tubular site of action :

First step in the generation of the hyperosmotic gradient

ADH

Loop diuretic interferes with this process….

Thus, although the loop diuretic can increase ADH levels by inducing volume depletion, responsiveness to ADH is reduced ….

- The thiazides….. diluting ability …..impaired water excretion.
- Also Thiazides increase water permeability and water reabsorption in the IMCD, …independent of ADH .

Many patients with thiazide-induced hyponatremia appear to have an underlying tendency to increased water intake (polydipsia).

- **Impaired water excretion** :

- Approximately 50 percent of patients who develop thiazide-induced hyponatremia carry a SNP in the gene encoding the PG transporter, expressed in the renal collecting duct…higher levels of luminal PG E2, which activate the luminal PG E2 receptor 4, thereby activating water reabsorption in the CD, despite suppression of ADH.

- In the aggregate, there are two different forms of diuretic-induced hyponatremia:

- one in which volume depletion stimulates the release of ADH and another in which the patient may be slightly volume expanded.

- In most patients, the combination of sodium plus potassium loss and water retention accounts for essentially all of the fall in the plasma sodium concentration .

- **INCIDENCE AND PATIENTS AT RISK:** —
- Most ….thiazides …. first three months of treatment.
- more common :
- (above 60 years of age).
- older age, …low body weight.
- Alcoholics, ..beer drinkers, ..psychogenic polydipsia.
- genetic factors …gene encoding the ROMK potassium channel

hyponatremia often ..**first one to two weeks of therapy** if diuretic dose and dietary intake …constant.

- However, in many patients with diuretic-induced hyponatremia, the disorder first appears after many months of uncomplicated thiazide therapy .In these patients, perturbation of the steady state, such as an acute gastrointestinal or respiratory illness; an increase in diuretic dose; or the development of heart failure, may explain the hyponatremia.
- The hyponatremia …. corrects ….days to two weeks after the cessation of therapy .

- **TREATMENT** : …discontinuing …..isotonic saline or…. hypertonic saline .

- **Prevention:** no proven way …
- prudent to avoid thiazide diuretics in high risk …to measure the plasma sodium concentration within a few days after therapy …

- Patients should be told to temporarily stop the diuretic during intercurrent illnesses that result in decreased dietary intake or increased gastrointestinal fluid losses.

- A thiazide diuretic should generally **not** be used in patients who have had a previous episode of hyponatremia.

Potassium–sparing diuretics :

relatively weak natriuretic activity, …only 1 to 2 percent of filtered sodium .

combination…to diminish the degree of potassium loss.

- All 4, act in the principal cells. Sodium entry …aldosterone-sensitive sodium channels . The reabsorption of cationic sodium without an anion creates a lumen-negative electrical gradient … hyperk and met acidosis.
- Amiloride and triamterene are cations that directly block ENAC but do not affect the MR. Another cation, the antibiotic trimethoprim, ..similar effects.

primary aldosteronism or CHF and cirrhosis.

lower incidence of endocrine side effects …

- Amiloride ..polyuria and polydipsia .. lithium-induced nDI. The resistance to ADH …lithium accumulation in the CD by movement through the ENAC in the luminal membrane. Blocking these channels with amiloride..

- Amiloride is better tolerated than triamterene. It ..once a day and …few side effects other than hyperkalemia. Triamterene,.. is a potential nephrotoxin , ..crystalluria and cast formation (in up to one-half of patients) , and rarely to triamterene stones or to ARF due either to intratubular crystal deposition ... faintly radiopaque; …pH-independent.

higher plasma aldosterone levels in patients with resistant HTN .However, can also lower the BP in patients with resistant HTN who have normal plasma and urine aldosterone levels .

The effect of spironolactone in patients with resistant HTN has been evaluated in **several** randomized trials, each of which found that it was more effective than placebo or other anti HTN drugs.

- **ASCOT**, 1411 patients whose BP was not controlled on three antihypertensive drugs (mean BP 157/85 mmHg) . The mean baseline K= 4.2 mEq/L, and the mean serum cr= 1.1 mg/dL . The addition of spironolactone (median dose 25 mg/daily) as a fourth drug was associated with a mean 22/10 mmHg reduction in BP at one-year follow-up. The mean rise in serum K was 0.4 mEq/L, with hyperkalemia occurring in 4 percent.

- The best data come from the **PATHWAY-2 trial**, a RCT crossover study comparing spironolactone (25 to 50 mg/day) with placebo, doxazosin, or bisoprolol in 285 patients with resistant HTN despite therapy with an ACE inh or ARB, a CCB and a diuretic. Spironolactone significantly reduced mean home SBP at 12 weeks by 10 mmHg compared with placebo, by 5 mmHg compared with doxazosin, and by 6 mmHg compared with bisoprolol..

Thank you