

### 4 – Diuretics

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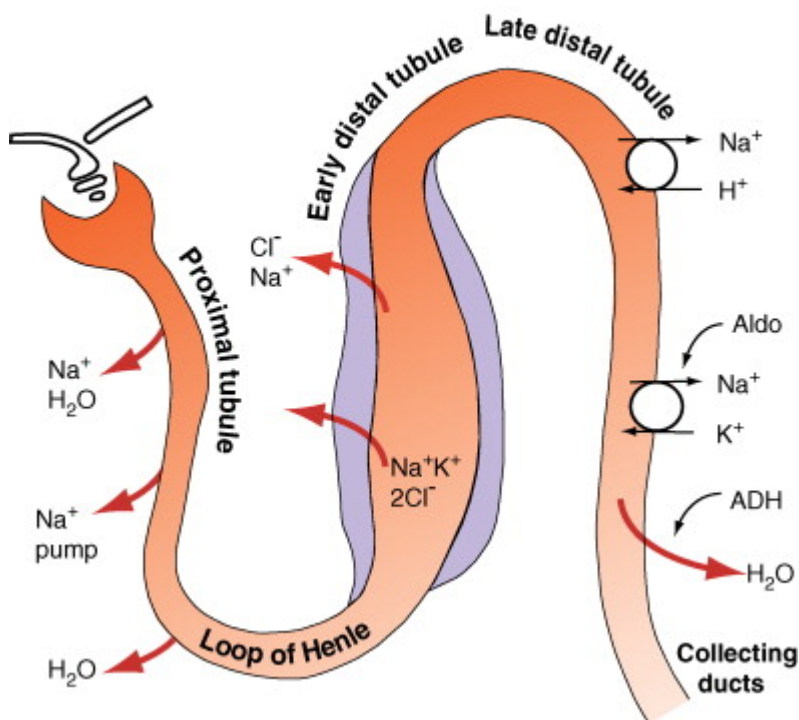
*“Little benefit is to be derived from using large doses of oral diuretics to reduce blood pressure.”*

*Cranston et al., 1963<sup>[1]</sup>*

Diuretics alter physiologic renal mechanisms to increase the flow of urine with greater excretion of sodium (natriuresis, Fig. 4-1). Diuretics have traditionally been used in the treatment of symptomatic heart failure with fluid retention, added to standard therapy such as angiotensin-converting enzyme (ACE) inhibition. 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.<sup>[2]</sup> However, increased awareness of diuretic-associated diabetes<sup>[3]</sup> has dampened but not extinguished enthusiasm for first-line diuretics.<sup>[4]</sup> New diabetes is an even greater risk of diuretic-β-blocker combinations for hypertension (see Chapter 7, p. 257). Thus current emphasis is toward diuretic combinations with ACE inhibitors or angiotensin receptor blockers (ARBs) to allow lower diuretic doses, to reduce the blood pressure (BP) quicker, and to offset adverse renin-angiotensin activation.

#### NEPHRON FUNCTION

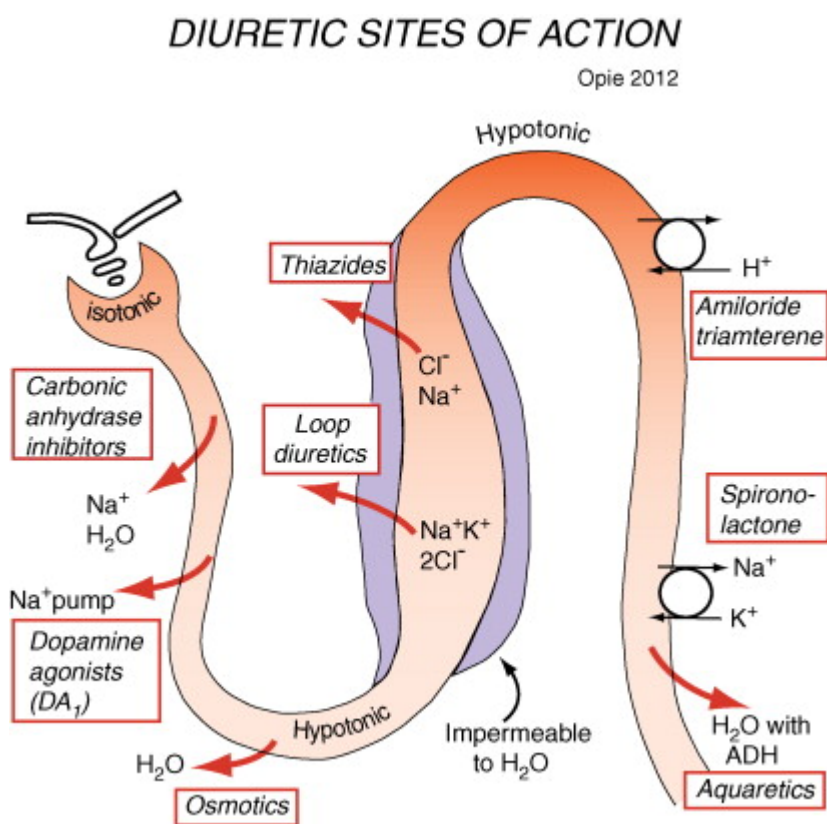
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**Figure 4-1** Nephron anatomy and function. *ADH*, Antidiuretic hormone; *aldo*, aldosterone.  
(Figure © L.H. Opie, 2012.)

## Differing effects of diuretics in congestive heart failure and hypertension

In heart failure with fluid retention, diuretics are given to control pulmonary and peripheral symptoms and signs of congestion. In noncongested heart failure, diuretic-induced renin activation may outweigh advantages.<sup>[5]</sup> Diuretics should rarely be used as monotherapy, but rather should be combined with ACE inhibitors and generally a  $\beta$ -blocker.<sup>[6]</sup> Often the loop diuretics (Fig. 4-2) are used preferentially, for three reasons: (1) the superior fluid clearance for the same degree of natriuresis; (2) loop diuretics work despite renal impairment that often accompanies severe heart failure; and (3) increasing doses increase diuretic responses, so that they are "high ceiling" diuretics. Yet in mild fluid retention thiazides may initially be preferred, especially when there is a background of hypertension. In general, diuretic doses for congestive heart failure (CHF) are higher than in hypertension.



**Figure 4-2** The multiple sites of action of diuretic agents from which follows the principle of sequential nephron block. A common maximal combination, using this principle, is a loop diuretic plus a thiazide plus a  $K^+$ -sparing agent. For aquaretics, see Figure 4-4. *ADH*, Antidiuretic hormone.  
(Figure © L.H. Opie, 2012.)

In hypertension, to exert an effect, the diuretic must provide enough natriuresis to achieve some persistent volume depletion. Diuretics may also work as vasodilators<sup>[7]</sup> and in other ways. Therefore, once-daily furosemide is usually inadequate because the initial sodium loss is quickly reconstituted throughout the remainder of the day. Thus a longer-acting thiazide-type diuretic is usually chosen for hypertension.<sup>[8],[9]</sup>

The three major groups of diuretics are the loop diuretics, the thiazides, and the potassium-sparing agents. Aquaretics constitute a recent fourth. Each type of diuretic acts at a different site of the nephron (see Fig. 4-2), leading to the concept of sequential nephron blockade. All but the potassium spacers must be

transported to the **luminal** side; this process is **blocked** by the buildup of **organic acids** in renal **insufficiency** so that **progressively larger** doses are needed. Especially **thiazides lose** their potency as renal **function falls**.

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## Loop diuretics

### Furosemide

Furosemide (*Lasix, Dryptal, Frusetic, Frusid*), one of the standard loop diuretics for severe CHF, is a **sulfonamide** derivative. Furosemide is initial therapy in acute pulmonary edema and in the pulmonary congestion of left-sided failure of acute myocardial infarction (AMI). Relief of dyspnea even **before** diuresis results from **venodilation** and preload reduction.<sup>[10]</sup>

#### Pharmacologic effects and pharmacokinetics.

Loop diuretics including furosemide inhibit the **Na<sup>+</sup>/K<sup>+</sup>/2Cl<sup>-</sup>** cotransporter concerned with the transport of chloride across the lining cells of the **ascending** limb of the **loop of Henle** (see Fig. 4-2). This site of action is reached **intraluminally**, after the drug has been **excreted** by the **proximal tubule**. The effect of the cotransport inhibition is that chloride, sodium, potassium, and hydrogen ions all remain intraluminally and are lost in the urine with the possible side effects of hyponatremia, hypochloremia, hypokalemia, and alkalosis. However, in comparison with thiazides, there is a **relatively greater** urine **volume** and relatively **less** loss of **sodium**. **Venodilation** reduces the preload in acute left ventricular (LV) failure within **5-15 min**; the mechanism is not well understood. Conversely, there may follow a reactive vasoconstriction.

#### Dose.

**Intravenous furosemide** is usually started as a slow **40-mg** injection (no more than **4 mg/min** to reduce **ototoxicity**; give **80 mg** over **20 min** intravenously **1 hour later** if needed). When **renal function** is **impaired**, as in older adult patients, **higher doses** are **required**, with **much higher** doses for **renal failure** and **severe CHF**. **Oral furosemide** has a wide dose range (20 to 240 mg/day or even more; 20, 40, and 80 mg tablets in the United States; in Europe, also scored 500 mg tablets) because of absorption varying from 10% to 100%, averaging 50%.<sup>[11]</sup> In contrast, absorption of bumetanide and torsemide is nearly complete. Furosemide's short duration of action (4 to **5** hours) means that **frequent** doses are needed when sustained diuresis is required. Twice-daily doses should be given in the early morning and midafternoon to obviate nocturia and to protect against volume depletion. For **hypertension**, furosemide 20 mg twice daily may be the approximate equivalent of hydrochlorothiazide (HCTZ) 25 mg. Furosemide causes a greater earlier (0 to 6 hours) absolute loss of sodium than does HCTZ but, because of its short duration of action, the total 24-hour sodium loss may be insufficient to maintain the slight volume contraction needed for sustained antihypertensive action,<sup>[12]</sup> thus requiring furosemide twice daily. In **oliguria** (not induced by volume depletion), as the glomerular filtration rate (**GFR**) **drops** to less than 20 mL/min, **from 240 mg up to 2000 mg** of furosemide may be **required** because of **decreasing luminal excretion**. Similar arguments lead to increasing doses of furosemide in **severe refractory heart failure**.

#### Indications.

Furosemide is frequently the diuretic of choice for **severe heart failure** and acute pulmonary edema for reasons already discussed. After initial intravenous use, oral furosemide is usually continued as standard diuretic therapy, sometimes to be replaced by thiazides as the heart failure ameliorates. In **AMI** with clinical failure, intravenous furosemide has rapid beneficial hemodynamic effects and is often combined with ACE inhibition.<sup>[13]</sup> In **hypertension**, twice-daily low-dose furosemide can be effective even as monotherapy or combined with other agents and is increasingly needed as renal function deteriorates.<sup>[14]</sup> In **hypertensive crisis**, intravenous furosemide is used if fluid overload is present. In a placebo-controlled study, **high-dose furosemide** given for **acute renal failure** **increased** the urine **output** but **failed** to alter the number of **dialysis sessions** or the time on dialysis.<sup>[15]</sup>

#### Contraindications.

In heart failure without fluid retention, furosemide can increase aldosterone levels with deterioration of LV function.<sup>[16]</sup> Anuria, although listed as a contraindication to the use of furosemide, is sometimes treated (as is oliguria) by furosemide in the hope for diuresis; first exclude dehydration and a history of hypersensitivity to furosemide or sulfonamides.

*Hypokalemia with furosemide.*

Clearly, much depends on the doses chosen and the degree of diuresis achieved. *Furosemide should not be used intravenously when electrolytes cannot be monitored.* The risk of hypokalemia is greatest with high-dose furosemide, especially when given intravenously, and at the start of myocardial infarction when hypokalemia with risk of arrhythmias is common even in the absence of diuretic therapy. Carefully regulated intravenous potassium supplements may be required in these circumstances. In heart failure, digitalis toxicity may be precipitated by overdiuresis and hypokalemia.

*Other side effects.*

The chief side effects, in addition to hypokalemia, are hypovolemia and hyperuricemia. Hypovolemia, with risk of prerenal azotemia, can be lessened by a low starting initial dose (20 to 40 mg, monitoring blood urea). A few patients on high-dose furosemide have developed severe hyperosmolar nonketotic hyperglycemic states. Atherogenic blood lipid changes, similar to those found with thiazides, may also be found with loop diuretics. Occasionally diabetes may be precipitated. Minimizing hypokalemia should lessen the risk of glucose intolerance. Furosemide (like other sulfonamides) may precipitate photosensitive skin eruptions or may cause blood dyscrasias. Reversible dose-related ototoxicity (electrolyte disturbances of the endolymphatic system) can be avoided by infusing furosemide at rates not greater than 4 mg/min and keeping the oral dose less than 1000 mg daily. Urinary retention may be noted from vigorous diuresis in older adults. In pregnancy, furosemide is classified as Category C. In nursing mothers, furosemide is excreted in the milk.

*Loss of diuretic potency.*

Braking is the phenomenon whereby after the first dose, there is a decrease in the diuretic response caused by renin-angiotensin activation and prevented by restoring the diuretic-induced loss of blood volume.<sup>[11]</sup> Long-term tolerance refers to increased reabsorption of sodium associated with hypertrophy of the distal nephron segments (see “Diuretic Resistance” later in this chapter). The mechanism may be increased growth of the nephron cells induced by increased aldosterone.<sup>[12]</sup>

*Drug interactions with furosemide.*

Co-therapy with certain aminoglycosides can precipitate ototoxicity. Probenecid may interfere with the effects of thiazides or loop diuretics by blocking their secretion into the urine of the proximal tubule. Indomethacin and other nonsteroidal antiinflammatory drugs (NSAIDs) lessen the renal response to loop diuretics, presumably by interfering with formation of vasodilatory prostaglandins.<sup>[17]</sup> High doses of furosemide may competitively inhibit the excretion of salicylates to predispose to salicylate poisoning with tinnitus. Steroid or adrenocorticotrophic hormone therapy may predispose to hypokalemia. Furosemide, unlike thiazides, does not decrease renal excretion of lithium, so that lithium toxicity is not a risk. Loop diuretics do not alter blood digoxin levels, nor do they interact with warfarin.

**Bumetanide**

The site of action of bumetanide (Bumex, Burinex) and its effects (and side effects) are very similar to that of furosemide (Table 4-1). As with furosemide, higher doses can cause considerable electrolyte disturbances, including hypokalemia. As in the case of furosemide, a combined diuretic effect is obtained by addition of a thiazide diuretic. In contrast to furosemide, oral absorption is predictable at 80% or more.<sup>[11]</sup>

**Table 4-1 -- Loop Diuretics: Doses and Kinetics**

Drug	Dose	Pharmacokinetics
Furosemide (Lasix)	10-40 mg oral, 2× for BP 20-80 mg 2-3× for CHF	Diuresis within 10-20 min Peak diuresis at 1.5 h

Drug	Dose	Pharmacokinetics
	Up to 250-2000 mg oral or IV	Total duration of action 4-5 h Renal excretion Variable absorption 10%-100%
Bumetanide (Bumex in the US, Burinex in the UK)	0.5-2 mg oral 1-2× daily for CHF 5 mg oral or IV for oliguria (not licensed for BP)	Peak diuresis 75-90 min Total duration of action 4-5 h Renal excretion Absorption 80%-100%
Torsemide (Demadex in the US)	5-10 mg oral 1× daily for BP 10-20 mg oral 1× daily or IV for CHF (up to 200 mg daily)	Diuresis within 10 min of IV dose; peak at 60 min Oral peak effect 1-2 h Oral duration of diuresis 6-8 h Absorption 80%-100%

*BP*, Blood pressure control; *CHF*, congestive heart failure; *IV*, intravenous.

### Dosage and clinical uses.

In *CHF*, the usual oral dose is 0.5 to 2 mg, with 1 mg bumetanide being approximately equal to 40 mg furosemide. In acute pulmonary edema, a single intravenous dose of 1 to 3 mg over 1 to 2 minutes can be effective; repeat if needed at 2- to 3-hour intervals to a maximum of 10 mg daily. In *renal edema*, the effects of bumetanide are similar to those of furosemide. In the United States, bumetanide is not approved for hypertension.

### Side effects and cautions.

Side effects associated with bumetanide are similar to those of furosemide; ototoxicity may be less and renal toxicity more. The combination with other potentially nephrotoxic drugs, such as aminoglycosides, must be avoided. In patients with renal failure, high doses have caused myalgia, so that the dose should not exceed 4 mg/day when the GFR is less than 5 mL/min. Patients allergic to sulfonamides may also be hypersensitive to bumetanide. In pregnancy, the risk is similar to furosemide (Category C).

### Conclusion.

Most clinicians will continue to use the agent they know best (i.e., furosemide). Because furosemide is widely available in generic form, its cost is likely to be less than that of torsemide or bumetanide.

### Torsemide

Torsemide (*Demadex*) is a loop diuretic with a longer duration of action than furosemide (see Table 4-1). A subdiuretic daily dose of 2.5 mg may be antihypertensive and free of changes in plasma potassium or glucose, yet in the United States the only doses registered for antihypertensive efficacy are 5 to 10 mg daily. It remains uncertain whether torsemide or other loop diuretics cause less metabolic disturbances than do thiazides in equipotent doses.

In *heart failure*, an intravenous dose of torsemide 10 to 20 mg initiates a diuresis within 10 minutes that peaks within the first hour. Similar oral doses (note high availability) give an onset of diuresis within 1 hour and a peak effect within 1 to 2 hours, and a total duration of action of 6 to 8 hours. Torsemide 20 mg gives approximately the same degree of natriuresis as does furosemide 80 mg but absorption is much higher and constant.<sup>[12]</sup> In *hypertension*, an oral dose of 5-10 mg once daily may take 4-6 weeks for maximal effect. There are no long-term outcome studies available for either of these indications.

In *renal failure*, as in the case of other loop diuretics, the renal excretion of the drug falls as does the renal function. Yet the plasma half-life of torsemide is unaltered, probably because hepatic clearance increases. In *edema of hepatic cirrhosis*, the dose is 5 to 10 mg daily, titrated to maximum 200 mg daily, given with aldosterone antagonist. In *pregnancy*, torsemide may be relatively safe (Category B versus Category C for

furosemide).

*Metabolic and other side effects, cautions, and contraindications are similar to those of furosemide.*

### ***Class side effects of loop diuretics***

#### ***Sulfonamide sensitivity.***

**Ethacrynic acid** (*Edecrin*) is the only **non**-sulfonamide diuretic and is used only in patients allergic to other diuretics. It closely resembles furosemide in dose (25 and 50 mg tablet), duration of diuresis, and side effects (except for more ototoxicity). If ethacrynic acid is not available for a sulfonamide-sensitive patient, a gradual challenge with furosemide or, even better, torsemide may overcome sensitivity.<sup>[18]</sup>

#### ***Hypokalemia.***

Hypokalemia may cause vague symptoms such as fatigue and listlessness, besides electrocardiographic and rhythm abnormalities. In the doses used for mild hypertension (furosemide 20 mg twice daily, torsemide 5 to 10 mg), hypokalemia is limited and possibly less than with HCTZ 25 to 50 mg daily. In heart failure, hypokalemia is more likely; similar cautions apply.

#### ***Hyperglycemia.***

Diuretic-induced **glucose intolerance** is likely **related** to **hypokalemia**, or to total body potassium depletion.<sup>[19]</sup> An interesting proposal is that the **transient postprandial fall** of **potassium impairs** the effect of **insulin** at that time and hence leads to **intermittent hyperglycemia**.<sup>[20]</sup> Although there are no large prospective studies on the effects of loop diuretics on insulin insensitivity or glucose tolerance in hypertensive patients, it is clearly prudent to avoid hypokalemia and to monitor both serum potassium and blood glucose values.

#### ***Gout.***

Use of loop diuretics more than **doubles** the risk of **gout**, with a hazard ratio (HR) of 2.31. (See "Urate Excretion and Gout" later in this chapter.)

#### ***Metabolic changes with loop diuretics: Recommendations.***

The overall evidence suggests that loop diuretics, like the thiazides, can cause dose-related metabolic disturbances. High doses used for heart failure might therefore pose problems. It makes sense to take special precautions against the hypokalemia of high-dose loop diuretics because of the **link** between **intermittent falls** in plasma **potassium** and **hyperglycemia**. A sensible start is **addition** of an **ACE inhibitor** or ARB.

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## Thiazide diuretics

Thiazide diuretics (Table 4-2) remain the most widely recommended first-line therapy for hypertension,<sup>[8],[9]</sup> although challenged by other agents such as ACE inhibitors, ARBs, and calcium channel blockers (CCBs). Thiazides are also standard therapy for chronic CHF, when edema is modest, either alone or in combination with loop diuretics. Recently, chlorthalidone a “thiazide-like diuretic” have been distinguished from HCTZ and other standard thiazides; chlorthalidone is preferred for hypertension, the major reason being that HCTZ has no outcome studies in hypertension when used at the presently recommended doses.<sup>[21]</sup>

**Table 4-2 -- Thiazide and Thiazide-Type Diuretics: Doses and Duration of Action**

	Trade Name (UK-Europe)	Trade Name (US)	Dose	Duration of Action (H)
Hydrochlorothiazide	Esidrex HydroSaluric	HydroDiuril, Microzide	12.5-25 mg, 12.5 mg preferred (BP); 25-100 mg (CHF)	16-24
Hydroflumethiazide	Hydrenox	Saluron, Diucardin	12.5-25 mg, 12.5 mg preferred (BP); 25-200 mg (CHF)	12-24
Chlorthalidone	Hygroton	Thalitone	12.5-50 mg, 12.5 to 15 mg preferred (BP)	≈40-60
<b>Metolazone</b>	Metenix; Diulo	Zaroxolyn, Mykrox	2.5-5 mg (BP); <b>5-20 mg (CHF)</b>	<b>24</b>
Bendrofluzide (bendroflumethiazide)	Aprinox; Centyl; Urizide	Naturetin	1.25-2.5 mg, 1.25 mg preferred (BP); 10 mg (CHF)	12-18
Benzthiazide	—	Aquatag, Exna, Diurin, Fovane, Hydrex, Proaqua, Regulon	50*-200 mg	12-18
Chlorothiazide	Saluric	Diuril, Chlotride	250*-1000 mg	6-12
Trichlormethiazide	Fluitran (not in UK)	Metahydrin, Naqua, Diurese	1*-4 mg	24
Indapamide	Natrilix	Lozol	1.25-2.5 mg, 1.25 mg preferred (BP); 2.5-5 mg (CHF)	24
Xipamide	Diurexan	—	10-20 mg, 5 mg preferred (BP)	6-12

BP, Blood pressure; CHF, congestive heart failure.

Julie M Groth, MPH, Heart Institute, Cedars Sinai Medical Center, is thanked for valuable assistance.

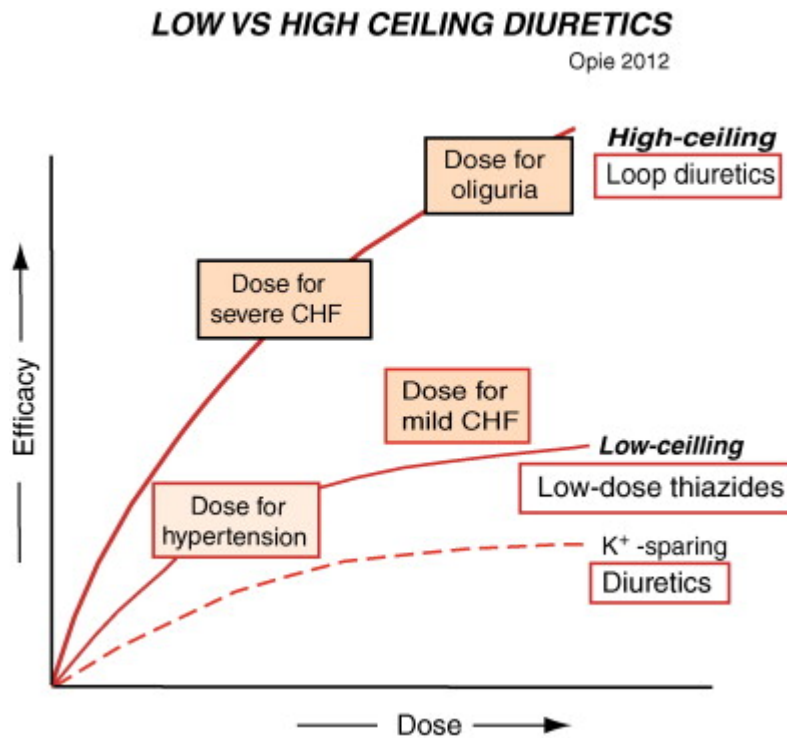
NB: The doses given here for antihypertensive therapy are generally *lower* than those recommended by the manufacturers (exception: Lozol 1.25 mg is recommended).

\* Lowest effective antihypertensive dose not known; may prefer to use other agents for BP control.

### Pharmacologic action and pharmacokinetics.



Thiazide diuretics act to inhibit the reabsorption of sodium and chloride in the more distal part of the nephron (see Fig. 4-2). This co-transporter is insensitive to the loop diuretics. More sodium reaches the distal tubules to stimulate the exchange with potassium, particularly in the presence of an activated renin-angiotensin-aldosterone system. Thiazides may also increase the active excretion of potassium in the distal renal tubule. Thiazides are rapidly absorbed from the gastrointestinal (GI) tract to produce a diuresis within 1 to 2 hours, which lasts for 16 to 24 hours in the case of the prototype thiazide, HCTZ.<sup>[22]</sup> Some major differences from the loop diuretics are (1) the longer duration of action (Table 4-2), (2) the different site of action (see Fig. 4-2), (3) the fact that thiazides are low ceiling diuretics because the maximal response is reached at a relatively low dosage (Fig. 4-3), and (4) the much decreased capacity of thiazides to work in the presence of renal failure (serum creatinine >2 mg/dL or approximately 180  $\mu\text{mol/L}$ ; GFR below 15 to 20 mL/min).<sup>[11]</sup> The fact that thiazides, loop diuretics and potassium-sparing agents all act at different tubular sites explains their additive effects (sequential nephron block).



**Figure 4-3** High- and low-ceiling diuretics, their differences, and the doses of each group used for various indications. Lowest doses are used for hypertension. *CHF*, Congestive heart failure. (Figure © L.H. Opie, 2012.)

### Thiazide doses and indications.

In hypertension, low-dose diuretics are often the initial agent of choice especially in low-renin groups such as older adults and in black patients.<sup>[23]</sup> By contrast, in younger whites (mean age 51 years) only one-third responded to escalating doses of HCTZ over 1 year.<sup>[24]</sup> The thiazide doses generally used have been too high. Lower doses with fewer biochemical alterations provide full antihypertensive as shown in several large trials. In the SHEP (Systolic Hypertension in the Elderly Program) study, chlorthalidone 12.5 mg was initially used and after 5 years 30% of the subjects were still on this lower dose.<sup>[25]</sup> Overall, documented biochemical changes were small including an 0.3 mmol/L fall in potassium, a rise in serum uric acid, and small increases in serum cholesterol and in glucose (1.7% more new diabetes than in placebo). Regarding HCTZ, exceeding 25 mg daily clearly creates metabolic problems.<sup>[26],[27]</sup> Increasing the dose from 12.5 to 25 mg may precipitate hyperglycemia<sup>[28]</sup> and only induces a borderline better reduction of BP.<sup>[29]</sup> In the case of bendrofluazide, a low dose (1.25 mg daily) causes less metabolic side effects and no effects on postabsorptive hepatic insulin production when compared with the conventional 5-mg dose.<sup>[30]</sup> Even higher doses have greater risks of undesirable side-effects (Table 4-3).

**Table 4-3 -- Side Effects of High-dose Diuretic Therapy for Hypertension**

<b>Causing Withdrawal of Therapy:</b>
Impaired glucose tolerance, diabetes mellitus
Gout
Impotence, erectile dysfunction
Nausea, dizziness, or headache
<b>Blood Biochemical Changes:</b>
Potassium: hypokalemia
Glucose: hyperglycemia
Uric acid: hyperuricemia
Urea, creatinine: prerenal fall in glomerular filtration rate
Lipid profile: rise in serum cholesterol, triglyceride, and ratio apolipoprotein B to A; fall in high-density lipoprotein cholesterol level

Dose of bendrofluzide was 10 mg daily (Peart, Lancet 1981;2:539–543), but now would be 1.25-2.5 mg. All effects are minimized by appropriately lower doses such as hydrochlorothiazide 12.5 mg daily.

The *response rate in hypertension* to thiazide monotherapy is variable and may be disappointing, depending in part on the age and race of the patient and probably also on the sodium intake. With HCTZ, the full antihypertensive effect of low dose 12.5 mg daily may take up to 6 weeks. By 24-hour ambulatory monitoring, 12.5 to 25 mg of HCTZ lowers BP less than the commonly prescribed doses of the other antihypertensive drug classes, with no difference in BP reduction between 12.5 and 25 mg doses of HCTZ.<sup>[31]</sup>

Combination therapy, for example, with an ACE inhibitor or ARB, becomes preferable rather than increasing the dose beyond 25 mg daily<sup>[22]</sup> or even beyond 12.5mg daily.<sup>[28].<sup>[29]</sup></sup> In *CHF*, higher doses are justified (50 to 100 mg HCTZ daily are probably ceiling doses), while watching the serum potassium. Considerable diuretic advantage in CHF can result from combining a loop diuretic with a thiazide.<sup>[11]</sup> Specifically, the thiazides block the nephron sites at which hypertrophy occurs during long term loop diuretic therapy (see “Diuretic Resistance” later in this chapter).

*Which thiazide?* In the United States, *HCTZ* is by far the most popular. *Bendrofluzide* is still popular in the United Kingdom, but the British *Hypertension Society* has come out *against* its prime use. The standard dose is 2.5 versus previous 5-10 mg daily with fewer serious side effects (see Table 4-3). However, a lower dose (1.25 mg once daily) reduces the BP without metabolic side effects.<sup>[30].<sup>[32]</sup></sup> Benzthiazide is available in the United States (see Table 4-2). As with the other thiazides, there are no outcome studies with these drugs.

#### *Thiazide contraindications.*

Contraindications to thiazide include hypokalemia, ventricular *arrhythmias*, and co-therapy with *proarrhythmic* drugs. In hypokalemia (including early AMI), thiazide diuretics may precipitate arrhythmias. Relative contraindications include pregnancy hypertension because of the risk of a decreased blood volume (category B or C); moreover, thiazides can cross the placental barrier with risk of neonatal jaundice. In mild renal impairment, the GFR may fall further as thiazides decrease the blood volume.

#### *Thiazides in chronic kidney disease.*

The traditional teaching has been that thiazide diuretics become *ineffective* when *GFR* falls *below 30* mL/min, whereas *loop* diuretics *remain effective* in advanced chronic kidney disease. Although widely accepted, this traditional notion has been called into *question* by a recent pilot study: in a randomized, double-blind, crossover trial of 23 patients with hypertension and Stage 4 or 5 chronic kidney disease, 3 months of treatment with either HCTZ (25 mg daily) or a long-acting preparation of furosemide (60 mg daily) were equally effective with respect to natriuresis and BP control.<sup>[33]</sup> Larger studies are needed to determine

if these provocative findings can be confirmed and extended to renal and cardiovascular outcomes.

### Thiazide side effects.

In addition to the metabolic side effects seen with previously used high doses (see Table 4-3), thiazide diuretics rarely cause sulfonamide-type immune side effects including intrahepatic jaundice, pancreatitis, blood dyscrasias, angitis, pneumonitis, interstitial nephritis, and photosensitive dermatitis. Erectile dysfunction is seen more commonly than with any other class of drugs in the TOMH study.<sup>[34]</sup>

Adherence (measured by medication refill data) is lower with thiazide diuretics than with the other major classes of antihypertensive drugs, including  $\beta$ -blockers, CCBs, ACEs, and ARBs.<sup>[35]</sup>

### Thiazide drug interactions.

Steroids may cause salt retention to antagonize the action of thiazide diuretics. Indomethacin and other NSAIDs blunt the response to thiazide diuretics.<sup>[17]</sup> Antiarrhythmics that prolong the QT-interval, such as Class IA or III agents including sotalol, may precipitate torsades de pointes in the presence of diuretic-induced hypokalemia. The nephrotoxic effects of certain antibiotics, such as the aminoglycosides, may be potentiated by diuretics. Probenecid (for the therapy of gout) and lithium (for mania) may block thiazide effects by interfering with thiazide transport into the tubule. Thiazide diuretics also interact with lithium by impairing renal clearance with risk of lithium toxicity.

### Thiazide-like agents

These differ from the standard thiazides in structure and by being evidence-based.

#### Chlorthalidone.

Chlorthalidone was chosen for the two most important trials: SHEP<sup>[25]</sup> and ALLHAT.<sup>[36]</sup> Lower doses gave approximately as much BP reduction as did the higher, suggesting that low doses should be used to avoid metabolic problems, especially in older adults.<sup>[22]</sup>

#### Chlorthalidone versus hydrochlorothiazide.

A small comparative study set the ball rolling by finding that chlorthalidone was better than HCTZ in reducing nocturnal BP, in agreement with its longer half-life.<sup>[37]</sup> The doses were chlorthalidone 12.5 mg/day (force-titrated to 25 mg/day) and HCTZ 25 mg/day (force-titrated to 50 mg/day). In a metaanalysis of 108 trials, chlorthalidone was somewhat better in lowering systolic BP, at the cost of more hyperkalemia.<sup>[38]</sup>

Retrospective analyses of the large Multiple Risk Factor Intervention Trial (MRFIT) add to the arguments for chlorthalidone.<sup>[39],[40]</sup> In this prolonged trial, lifestyle, active BP and statin therapy were given as needed with long-term follow up of men 35 to 57 years of age beginning in 1973. Chlorthalidone addition for hypertension was compared with HCTZ, both in the dose range of 50-100 mg per day, which were the standard doses used at that time. Chlorthalidone had lower systolic BP, lower total cholesterol, and lower low-density lipoprotein (LDL) cholesterol, but also lower potassium and higher uric acid (all comparisons  $P < 0.001$ ). Compared with neither diuretic, cardiovascular events were lower both in those on chlorthalidone (HR: 0.51;  $P < 0.0001$ ) and those on HCTZ (HR: 0.65;  $P < 0.0001$ ), but chlorthalidone was better than HCTZ. Furthermore, left ventricular hypertrophy (LVH) also decreased more with chlorthalidone.<sup>[40]</sup> Importantly, however, MRFIT was not randomized but was rather a retrospective cohort study. Nonetheless, in summary, the overall data favor chlorthalidone instead of HCTZ.

#### Indapamide.

Indapamide (*Lozol*, *Natrilix*) is a thiazide-like diuretic, albeit with a different indoline structure and added vasodilation.<sup>[41]</sup> Widely used in Europe, it is available but less used in the United States. Indapamide has a terminal half-life of 14 to 16 hours, and effectively lowers the BP over 24 hours. The initial dose is 1.25 mg once daily for 4 weeks, then if needed 2.5 mg daily. Indapamide appears to be more lipid-neutral than other thiazides<sup>[42]</sup> but seems equally likely to cause dose-dependent metabolic problems such as hypokalemia, hyperglycemia, or hyperuricemia. In the slow-release formula (not available in the United States), it reduced BP variability<sup>[43]</sup> and hence decreased a new risk factor for stroke.<sup>[44]</sup>

The major outcome trial is the HYVET study.<sup>[45]</sup> Patients 80 years of age or older with a sustained systolic BP of 160 mm Hg or more received indapamide (sustained release, 1.5 mg), with the ACE inhibitor perindopril (2 or 4 mg) added if necessary to achieve the target BP of 150/80 mm Hg. Benefits were a 21% reduction in death from any cause (95% confidence interval [CI], 4 to 35;  $P = 0.02$ ), with 39% reduction in stroke deaths ( $P = 0.05$ ), and a 64% reduction in heart failure (95% CI, 42 to 78;  $P < 0.001$ ). Fewer serious adverse events occurred in the active-treatment group ( $P = 0.001$ ).

Regarding side effects, with a reduced but still antihypertensive dose of only 0.625-1.25 mg of the standard preparation, combined with the ACE inhibitor perindopril 2-4 mg, the serum potassium fell by only 0.11 mmol/L over 1 year, whereas the blood glucose was unchanged from placebo.<sup>[46]</sup> This combination reduced mortality in ADVANCE, a megatrial in diabetics.<sup>[47]</sup> Regarding *regression of LVH*, indapamide was better than enalapril in the LIVE study (LVH with Indapamide Versus Enalapril).<sup>[48]</sup> In *cardiac edema*, higher doses such as 2.5 to 5 mg give a diuresis. In general, its side-effect profile resembles that of the thiazides, including the low risk of sulfonamide sensitivity reactions. In Europe, a new sustained release preparation (1.5 mg) gives equal BP reduction to 2.5 mg indapamide, yet the incidence of hypokalemia at less than 3.4 mmol/L is more than 50% lower.<sup>[49]</sup>

### Metolazone.

Metolazone (*Zaroxolyn, Diulo, Metenix*) is a **powerful diuretic** with a quinazoline structure falling within the overall thiazide family and with similar side effects. There may be an **additional site** of action beyond that of the standard thiazides. An important advantage of metolazone is **efficacy even despite reduced renal function**. The duration of action is **up to 24 hours**. The standard dose is **5 to 20 mg once daily for CHF** or renal edema and 2.5 to 5 mg for hypertension. In **combination with furosemide**, metolazone may provoke a **profound diuresis**, with the risk of excessive **volume** and **potassium depletion**. Nonetheless, metolazone may be added to furosemide with care, especially in patients with renal as well as **cardiac failure**. Metolazone 1.25 to **10 mg once daily** was given in titrated doses to 17 patients with **severe CHF**, almost all of whom were already on furosemide, captopril, and digoxin; most responded by a **brisk diuresis within 48 to 72 hours**.<sup>[50]</sup> Consequently, metolazone is often used in addition to a prior combination of a loop diuretic, a thiazide, and aldosterone inhibitor in patients with chronic heart failure and resistant peripheral edema.

### Mykrox.

Mykrox is a rapidly acting formulation of metolazone with high bioavailability, registered for use in hypertension only in a dose of 0.5 to 1 mg once daily. The maximum antihypertensive effect is reached within 2 weeks.

### Metabolic and other side effects of thiazides

Many side effects of thiazides are **similar** to those of the loop diuretics and are dose dependent (see Table 4-3).

### Hypokalemia.

Hypokalemia is probably an over-feared complication, especially when low doses of thiazides are used.<sup>[51]</sup> Nonetheless, the frequent choice of combination of thiazides with the potassium-retaining agents including the ACE inhibitors, ARBs, or aldosterone blockers is appropriate, with the alternative, but lesser, risk of *hyperkalemia*, especially in the presence of renal impairment.

### Ventricular arrhythmias.

Diuretic-induced hypokalemia can contribute to torsades de pointes and hence to sudden death, especially when there is co-therapy with agents prolonging the QT-interval. Of importance, in the SOLVD study on heart failure, the baseline use of a non-potassium-retaining diuretic was associated with an increased risk of arrhythmic death compared with a potassium-retaining diuretic.<sup>[52]</sup> In hypertension, the degree of hypokalemia evoked by low-dose thiazides seldom matters.

### Therapeutic strategies to avoid hypokalemia.

In patients with a higher risk of arrhythmias, as in ischemic heart disease, heart failure on digoxin, or hypertension with LV hypertrophy, a potassium- and magnesium-sparing diuretic should be part of the

therapy unless contraindicated by renal failure or by co-therapy with an ACE inhibitor or ARB. A potassium sparer may be better than potassium supplementation, especially because the supplements do not correct hypomagnesemia.

### Hypomagnesemia.

Conventional doses of diuretics rarely cause magnesium deficiency,<sup>[53]</sup> but hypomagnesemia, like hypokalemia, is blamed for arrhythmias of QT-prolongation during diuretic therapy. Hypomagnesemia may be prevented by adding a potassium-retaining component such as amiloride to the thiazide diuretic.

### Hyponatremia.

Thiazides and thiazide-like diuretics can cause **hyponatremia** especially in older patients (more so in women) in whom **free water excretion is impaired**. In the Systolic Hypertension in the Elderly Program (SHEP),<sup>[25]</sup> hyponatremia occurred in 4% of patients treated with chlorthalidone versus 1% in the placebo group. Occurring rapidly (within 2 weeks), mild thiazide-induced hyponatremia can cause vague symptoms of fatigue and nausea, but when severe, can cause confusion, seizures, coma, and death.

### Diabetogenic effects.

Diuretic therapy for hypertension increases the risk of new diabetes by approximately one-third, versus placebo.<sup>[3]</sup> The thiazides are more likely to provoke diabetes if combined with a  $\beta$ -blocker.<sup>[54-58]</sup> This risk presumably depends on the thiazide dose and possibly on the type of  $\beta$ -blocker, in that carvedilol or nebivolol are exceptions (see Chapter 1, sections on these agents). Patients with a familial tendency to diabetes or those with the metabolic syndrome are probably more prone to the diabetogenic side effects, so that thiazides should be avoided or only given in low doses, such as HCTZ 12.5 mg daily or chlorthalidone 6.25 to 15 mg daily. In addition, plasma potassium and glucose should be monitored. Common sense but no good trial data suggest that the lowest effective dose of HCTZ (12.5 mg) should be used with the expectation that a significant proportion of the antihypertensive effect should be maintained without impairing glucose tolerance, as in the case of low-dose bendrofluazide.<sup>[30]</sup> *There is no evidence that changing from a thiazide to a loop diuretic improves glucose tolerance.*

*How serious is new diuretic-induced diabetes?* During the 4.5 years of follow-up in the VALUE trial, new-onset diabetes posed a cardiac risk between no diabetes and prior diabetes, and in the longer follow-up, equal risks.<sup>[59]</sup>

### Urate excretion and gout.

Most diuretics decrease urate excretion with the risk of increasing blood uric acid, causing gout in those predisposed. In 5789 persons with hypertension, 37% were treated with a diuretic. Use of any diuretic (HR 1.48; CI 1.11-1.98), a thiazide diuretic (HR 1.44; CI 1.00-2.10), or a loop diuretic (HR 2.31; CI 1.36-3.91) increased the risk of gout.<sup>[60]</sup> Thus a personal or family history of gout further emphasizes that only low-dose diuretics should be used. Co-therapy with *losartan* lessens the rise in uric acid.<sup>[61]</sup> When *allopurinol* is given for gout, or when the blood urate is high with a family history of gout, the standard dose of 300 mg daily is only for a normal creatinine clearance. With a clearance of only 40 mL/min, the dose drops to 150 mg daily and, for 10 mL/min, down to 100 mg every 2 days. *Dose reduction is essential* to avoid serious reactions, which are dose-related and can be fatal. *Benemid*, a uricosuric agent may protect against hyperuricemia with less potential toxicity.<sup>[62]</sup>

### Atherogenic changes in blood lipids.

Thiazides may increase the total blood cholesterol in a dose-related fashion.<sup>[63]</sup> LDL cholesterol and triglycerides increase after 4 months with HCTZ (40-mg daily mean dose).<sup>[27]</sup> In the TOMH study, low-dose chlorthalidone (15 mg daily) increased cholesterol levels at 1 year but not at 4 years.<sup>[64]</sup> Even if total cholesterol does not change, triglycerides and the ratio of apolipoprotein B to A may rise, whereas high-density lipoprotein cholesterol may fall.<sup>[57]</sup> During prolonged thiazide therapy occasional checks on blood lipids are ideal and a lipid-lowering diet is advisable.

### Hypercalcemia.

Thiazide diuretics tend to retain calcium by increasing proximal tubular reabsorption (along with sodium).

The benefit is a decreased risk of hip fractures in older adults.<sup>[65]</sup> Conversely, especially in hyperparathyroid patients, hypercalcemia can be precipitated.

### **Erectile dysfunction.**

In the TOMH study, low-dose chlorthalidone (15 mg daily given over 4 years) was the only one of several antihypertensive agents that doubled impotence.<sup>[34]</sup> Pragmatically, sildenafil or similar drugs should help, provided the patient is not also receiving nitrates.

### **Prevention of metabolic side effects.**

Reduction in the dose of a diuretic is the basic step. In addition, restriction of dietary sodium and additional dietary potassium will reduce the frequency of hypokalemia. Combination of a thiazide with a potassium sparer lessens hypokalemia, as does the addition of an ACE inhibitor or ARB. In the treatment of hypertension, standard doses of diuretics should not be combined, if possible, with other drugs with unfavorable effects on blood lipids, such as the  $\beta$ -blockers, but rather with ACE inhibitors, ARBs, or CCBs, which are lipid-neutral (see Table 10-5).

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## Potassium-sparing agents

Potassium-retaining agents lessen the incidence of serious ventricular arrhythmias in heart failure<sup>[52]</sup> and in hypertension.<sup>[66]</sup>

### Amiloride and triamterene.

Amiloride acts on the renal epithelial sodium channel (ENaC)<sup>[67]</sup> and triamterene inhibits the sodium-proton exchanger, so that both lessen sodium reabsorption in the distal tubules and collecting tubules. Thereby potassium loss is indirectly decreased (Table 4-4). Relatively weak diuretics on their own, they are frequently used in combination with thiazides (Table 4-5).<sup>[68]</sup> Advantages are that (1) the loss of sodium is achieved without a major loss of potassium or magnesium, and (2) there is potassium retention independent of the activity of aldosterone. Side effects are few: hyperkalemia (a contraindication) and acidosis may seldom occur, mostly in renal disease. In particular, the thiazide-related risks of diabetes mellitus and gout have not been reported with these agents. Amiloride also helps to retain magnesium and is of special benefit to the relatively small percentage of black patients with low-renin, low-aldosterone hypertension and a genetic defect in the epithelial sodium channel.<sup>[69]</sup>

**Table 4-4 -- Potassium-sparing Agents (Generally also Magnesium Sparing)**

	Trade Names	Dose	Duration of Action
Amiloride	Midamor	2.5-20 mg	6-24 h
Triamterene	Dytac, Dyrenium	25-200 mg	8-12 h
Spirolactone	Aldactone	25-200 mg	3-5 days
Eplerenone	Inspira	50-100 mg	24 h

**Table 4-5 -- Some Combination K<sup>+</sup>-Retaining Diuretics**

	Trade Name	Combination (mg)	Preferred Daily Dose
Hydrochlorothiazide + triamterene	Dyazide	2550	½ (up to 4 in CHF)
Hydrochlorothiazide + amiloride	Moduretic	505	¼* (up to 2 in CHF)
Hydrochlorothiazide + triamterene	Maxzide	5075	¼*
Hydrochlorothiazide + triamterene	Maxzide-25	2537.5	½
Spirolactone + hydrochlorothiazide	Aldactazide	2525	1-4/day
Furosemide + amiloride	Frumil†	405	1-2/day

CHF, Congestive heart failure.

For hypertension, see text; low doses generally preferred and high doses are contraindicated.

\* Quarter <sup>[68]</sup> is best avoided by use of alternate combinations.

† Not in the United States.

### Spirolactone and eplerenone.

Spirolactone and eplerenone are aldosterone blockers that spare potassium by blocking the mineralocorticoid receptor that binds aldosterone as well as cortisol and deoxycorticosterone. Eplerenone is a more specific blocker of the mineralocorticoid receptor, thereby preventing the gynecomastia and sexual

**dysfunction** seen in up to **10%** of those given **spironolactone**. Eplerenone should become the **preferred** potassium sparer for primary hypertension, especially if costs of the generic preparation go down as expected. In patients with hypertensive heart disease, eplerenone was as effective as enalapril (40 mg daily) in regressing LVH and lowering BP and was equally effective in lowering BP in black and white patients with hypertension.<sup>[70]</sup> Another advantage of mineralocorticoid receptor antagonists over thiazides is that they do **not** cause **reflex sympathetic** activation.<sup>[71],[72]</sup> Aldosterone receptor blockers have an obvious place in the treatment of primary aldosteronism.

In patients with *resistant hypertension* without primary aldosteronism, aldosterone receptor blockers are becoming standard add-on therapy, and are potentially more used even in the larger population of patients with primary hypertension while monitoring serum potassium.<sup>[73]</sup> Eplerenone (100-300 mg daily) was only half as effective as spironolactone (75-225 mg daily) in lowering BP in patients with primary aldosteronism.<sup>[74]</sup> The real problem is that there are no good prospective outcome studies of resistant hypertension.<sup>[75]</sup> A metaanalysis of five small randomized crossover studies<sup>[76]</sup> found that spironolactone reduced BP by 20/7 mmHg, with *daily doses of more than 50 mg not producing further BP reductions*.

### **ACE inhibitors and ARBs.**

Because **ACE inhibitors** and ARBs ultimately exert an **antialdosterone effect**, they too act as mild potassium-retaining diuretics. **Combination** therapy with other **potassium retainers** should be **avoided** in the presence of **renal impairment**, but can successfully be undertaken with care and **monitoring** of serum **potassium**, as in the RALES study.<sup>[77]</sup>

### **Hyperkalemia: A specific risk.**

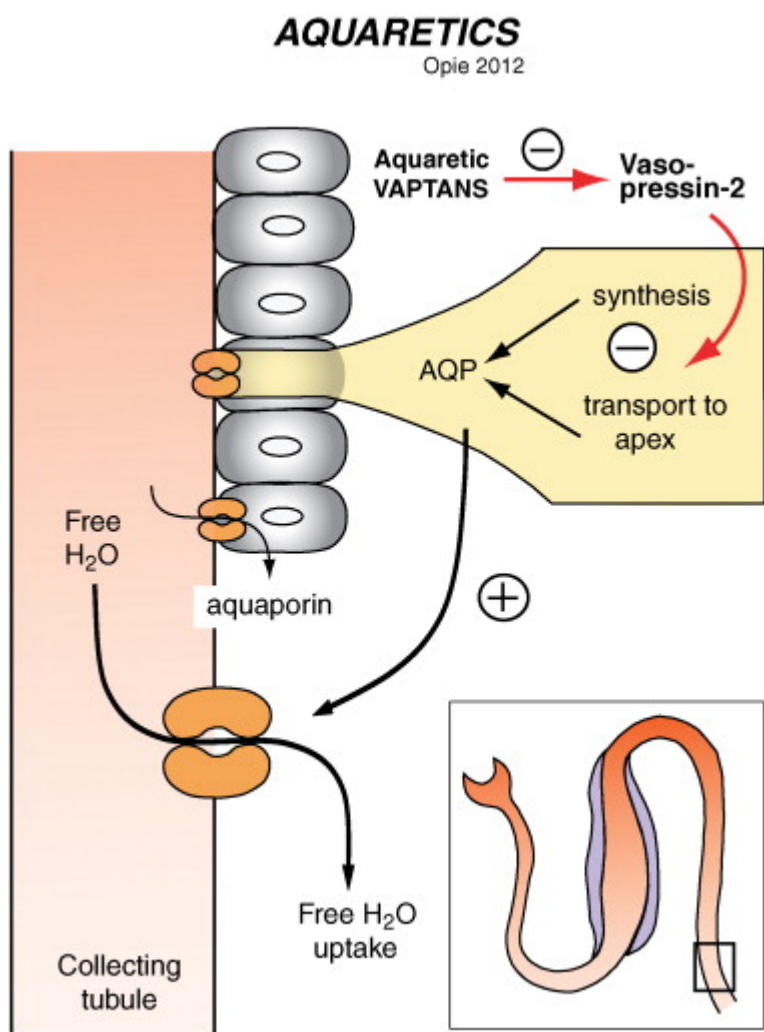
Amiloride, triamterene, spironolactone and eplerenone may all **cause hyperkalemia** (serum potassium equal to or exceeding 5.5 mEq/L), especially in the presence of preexisting renal disease, diabetes (type IV renal tubular acidosis), in older adult patients during co-therapy with ACE inhibitors or ARBs, or in patients receiving possible nephrotoxic agents. Mechanisms causing hyperkalemia include prolonged solute-driven water loss as well as diuretic-driven renin-angiotensin aldosterone activation and negative diuretic effects on nephron function.<sup>[78]</sup>

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**Aquaretics**

Chronic heart failure is often associated with increased vasopressin plasma concentrations, which may underlie the associated fluid retention and hyponatremia. Arginine vasopressin (AVP) acts via V1 and V2 receptors to regulate vascular tone (V1), and fluid retention (V2). Aquaretics are antagonists of AVP-2 receptors in the kidney to promote solute-free water clearance to correct hyponatremia. Specific examples are tolvaptan, conivaptan, satavaptan, and lixivaptan, a grouping often called the vaptans. Experimentally, they inhibit aquaporin-2, the AVP-sensitive water transport channel found in the apices of the renal collecting duct cells (Fig. 4-4).<sup>[79]</sup> In clinical trials, vaptans increase free water clearance and urine volume, while decreasing urine osmolality, thereby increasing serum sodium when administered to patients with hyponatremia. Hypotension and thirst are among the side effects.



**Figure 4-4** Mechanism of action of aquaretics ("vaptans"). These inhibit the vasopressin-2 receptors whose activity promotes the synthesis and transport of aquaporin (AQP) to the apex of the cells of the collecting duct. Aquaporin is the vasopressin-regulated water channel that mediates water transport across the apical cell membranes of the renal collecting duct. AQP, Aquaporin.  
(Figure © L.H. Opie, 2012.)

**Conivaptan** is a combined **V1/V2** receptor antagonist now approved and available in the United States for intravenous administration in treatment of euvoletic or hypovolemic hyponatremia in hospitalized patients (intravenous 20 mg loading dose over 30 min, then 20-40 mg continuously infused over 24 hours; up to 40 mg to correct hyponatremia; infuse up to 3 days thereafter, the total duration not exceeding 4 days). In 74 hyponatremic patients, oral doses (20-40 mg twice daily) increased serum sodium by 3 and 4.8 mEq/L, respectively (placebo corrected).<sup>[80]</sup>

**Tolvaptan**, an **oral V2** antagonist (30-90 mg once daily) added to standard therapy for patients hospitalized with worsening heart failure, decreased body weight, increased urine output, and increased serum sodium by approximately 4 mEq/L from approximately 138 mEq/L.<sup>[81]</sup> However, a mortality trial (EVEREST) with 30 mg daily given to selected heart failure patients for a mean of 9.9 months was negative, although early changes were loss of body weight, decreased edema, and increased serum sodium.<sup>[82]</sup>

**Lixivaptan**, also an oral V2 antagonist, increased solute-free urine flow in chronic heart failure without renin-angiotensin system stimulation at single doses of 30-400 mg.<sup>[83]</sup> Further studies are underway.

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## Combination diuretics with K<sup>+</sup> sparing

For *heart failure*, a standard combination daily therapy might be one to two tablets of **HCTZ** 50 mg, **amiloride** 5 mg (**Moduretic**); two to four tablets of HCTZ 25 mg, triamterene 50 mg (Dyazide); or one to two tablets of HCTZ 50 mg, triamterene 75 mg (Maxzide). When used for *hypertension*, special attention must be given to the thiazide dose (25 mg HCTZ in Dyazide, 50 mg in Moduretic, and both 25 mg and 50 mg in Maxzide), in which the initial aim is only 12.5 mg HCTZ. With Aldactazide (25 mg of spironolactone and 25 mg of HCTZ), the starting dose should be half a tablet. A potassium-retaining furosemide combination is available and much used in Europe (furosemide 40 mg, amiloride 5 mg [*Frumil*]). A logical combination is that of ACE inhibitor or ARB with low-dose thiazide, for example, low dose perindopril with low dose indapamide.<sup>[46]</sup> Thiazide diuretics increase renin levels and ACE inhibitors or ARBs decrease the metabolic side effects of thiazides (see Chapter 5, p. 134).

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## Minor diuretics

### *Carbonic anhydrase inhibitors.*

Carbonic anhydrase inhibitors such as acetazolamide (*Diamox*) are weak diuretics. They decrease the secretion of hydrogen ions by the proximal renal tubule, with increased loss of bicarbonate and hence of sodium. These agents, seldom used as primary diuretics, have found a place in the therapy of glaucoma because carbonic anhydrase plays a role in the secretion of aqueous humor in the ciliary processes of the eye. They also protect from altitude illness. In salicylate poisoning, the alkalinizing effect of carbonic anhydrase inhibitors increases the renal excretion of lipid-soluble weak organic acids.

### *Calcium channel blockers.*

CCBs are mild direct diuretics that may contribute to the long-term antihypertensive effect.<sup>[84]</sup>

### *Dopamine.*

Dopamine has a diuretic action apart from the improvement in cardiac function and indirect diuresis that it induces. The mechanism of the diuresis, found only in conditions of fluid retention, appears to involve dopamine agonists (DA<sub>1</sub>) receptors on the renal tubular cells where dopamine stimulation opposes the effects of antidiuretic hormone (ADH).

### *A<sub>1</sub>-adenosine receptor antagonists.*

A<sub>1</sub>-adenosine receptor antagonists are another new approach to diuresis that increase urine flow and natriuresis. They may act by afferent arteriolar dilation, thereby increasing glomerular filtration. In patients with acute heart failure, they enhance the response to loop diuretics.<sup>[85]</sup>

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## Limited role of potassium supplements

The use of potassium supplements with loop diuretics is usually unnecessary and does not appear to protect from the adverse effects of non-K-sparing diuretics. Supplements lead to extra cost and loss of compliance. Rather, addition of low-dose potassium-retaining agents is usually better (see Table 4-4) and can often be accompanied by a lower dose of the loop diuretic. Even high doses of furosemide may not automatically require potassium replacement because such doses are usually given in the presence of renal impairment or severe CHF when renal potassium handling may be abnormal. *Clearly potassium levels need periodic checking during therapy with all diuretics.* A high-potassium, low-salt diet is advised and can be simply and cheaply achieved by choosing fresh rather than processed foods and by the use of salt substitutes. If problematic hypokalemia develops, then a potassium supplement may become necessary. Persistent hypokalemia in hypertension merits investigation for primary aldosteronism.

### Potassium chloride.

Potassium chloride (KCl) in liquid form is theoretically best because (1) co-administration of chloride is required to fully correct potassium deficiency in hypokalemic hypochloremic alkalosis,<sup>[86]</sup> and (2) slow-release tablets may cause GI ulceration, which liquid KCl does not.<sup>[87]</sup> The dose is variable. At least 20 mEq daily are required to avoid potassium depletion and 60 to 100 mEq are required to treat potassium depletion. Absorption is rapid and bioavailability good. To help avoid the frequent GI irritation, liquid KCl needs dilution in water or another liquid and titration against the patient's acceptability. KCl may also be given in some effervescent preparations. To avoid esophageal ulceration, tablets should be taken upright or sitting, with a meal or beverage, and anticholinergic therapy should be avoided. *Microencapsulated KCl* (Micro-K, 8 mEq KCl or 10 mEq KCl) may reduce GI ulceration to only 1 per 100,000 patient years. Nonetheless, high doses of Micro-K cause GI ulcers, especially during anticholinergic therapy.

### Recommendations.

Diet is the simplest recommendation, with high-potassium, low-sodium intake achieved by fresh foods and salt substitutes. When K<sup>+</sup> supplements become essential, KCl is preferred. The best preparation is one that is well tolerated by the patient and that is inexpensive. No comprehensive adequately controlled studies of the relative efficacy of the various KCl preparations in clinical settings are available.

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## Special diuretic problems

### Overdiuresis

During therapy of edematous states, overvigorous diuresis is common and may reduce intravascular volume and ventricular filling so that the cardiac output drops and tissues become underperfused. The renin-angiotensin axis and the sympathetic nervous system are further activated. Overdiuresis is most frequently seen during hospital admissions when a rigid policy of regular administration of diuretics is carried out. Symptoms include fatigue and listlessness. Overdiuresis is also seen when a thiazide diuretic is combined with a loop diuretic to produce diuretic synergy via sequential nephron blockade (see Fig. 4-3). Although this diuretic combination can overcome loop diuretic resistance in acute and chronic heart failure, this practice can also cause massive diuresis leading to hypokalemia, hyponatremia, hypovolemic hypotension, and acute renal failure.<sup>[88]</sup> These authors call for “pragmatic clinical trials for this commonly used therapy.”

*Clinical situations in which overdiuresis is most likely* include (1) patients with mild chronic heart failure overtreated with potent diuretics; (2) patients requiring a high filling pressure, particularly those with a “restrictive” pathophysiologic condition as in restrictive cardiomyopathy, hypertrophic cardiomyopathy, or constrictive pericarditis; and (3) patients in early phase AMI, when excess diuresis by potent intravenous diuretics can cause a pressor response that attenuated by ACE inhibition.<sup>[13]</sup> It may be necessary to cautiously administer a fluid challenge with saline solution or a colloid preparation while checking the patient’s cardiovascular status. If the resting heart rate falls, renal function improves, and BP stabilizes, the ventricular filling pressure has been reduced too much by overdiuresis.

Patients can manage their therapy well by tailoring a flexible diuretic schedule to their own needs, using a simple bathroom scale. Knowing how to recognize pedal edema and the time course of maximal effect of their diuretic often allows a patient to adjust his or her own diuretic dose and administration schedule to fit in with daily activities. A practical approach is to stabilize the patient on a combination of drugs, and then to allow self-modification of the furosemide dose, within specified limits, and according to body weight.

### Diuretic resistance.

Diuretic resistance may occur late or early, with the latter occurring even after one dose of a diuretic and resulting from intravascular fluid contraction (Table 4-6).<sup>[11]</sup> Repetitive diuretic administration leads to a leveling off of the diuretic effect, because (in the face of a shrunken intravascular volume) the part of the tubular system not affected reacts by reabsorbing more sodium (see Fig. 4-4). Such decreased sodium diuresis is associated with hypertrophy of distal nephron cells,<sup>[11]</sup> thought to be the result of aldosterone-induced growth.<sup>[12]</sup> Of therapeutic interest, the thiazides block the nephron sites at which the hypertrophy occurs,<sup>[11]</sup> thereby providing another argument for combined thiazide-loop therapy.<sup>[89]</sup> Apparent resistance can also develop during incorrect use of diuretics (see Table 4-6), or when there is concomitant therapy with indomethacin, with other NSAIDs, or with probenecid. The thiazide diuretics will not work well if the GFR is less than 20 to 30 mL/min; metolazone is an exception (see Table 4-6). When potassium depletion is severe, all diuretics work poorly for complex reasons.

**Table 4-6 -- Some Causes of Apparent Resistance to Diuretics in Therapy of Cardiac Failure**

Incorrect Use of Diuretic Agent
Combination of two thiazides or two loop diuretics instead of one of each type
Use of thiazides when GFR is low* (exception: metolazone)
Excessive diuretic dose
Poor compliance, especially caused by multiple tablets of oral K <sup>+</sup> supplements

<b>Electrolyte Imbalance</b>
Hyponatremia, hypokalemia
Hypomagnesemia may need correction to remedy hypokalemia
<b>Poor Renal Perfusion: Diuretic-Induced Hypovolemia</b>
Cardiac output too low
Hypotension (ACE inhibitors or ARBs in high renin states)
<b>Excess Circulating Catecholamines</b>
Frequent in severe congestive heart failure
Correct by additional therapy for CHF
<b>Interfering Drugs</b>
Nonsteroidal antiinflammatory agents inhibit diuresis
Probenecid and lithium inhibit tubular excretion of thiazides and loop diuretics

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CHF, congestive heart failure; GFR, glomerular filtration rate.

\* GFR less than 15 to 20 mL/min.

To achieve diuresis, an ACE inhibitor or ARB may have to be added cautiously to thiazide or loop diuretics, or metolazone (or other thiazide) may have to be combined with loop diuretics, all following the principle of sequential nephron blockade. Sometimes spironolactone is also required. Furthermore, intravenous dopamine may, through its action on DA<sub>1</sub>-receptors, help induce diuresis acting in part by increasing renal blood flow. In outpatients, compliance and dietary salt restriction must be carefully checked and all unnecessary drugs eliminated. Sometimes fewer drugs work better than more (here the prime sinners are potassium supplements, requiring many daily tablets frequently not taken).

### Hyponatremia.

In heart failure, hyponatremia may occur in patients severely ill with CHF and in some older adult patients who consume large amounts of water despite an increased total body sodium in heart failure. Predominant water retention is caused by (1) the inappropriate release of AVP-ADH (see ADH in Fig. 4-1), and (2) increased activity of angiotensin-II.<sup>[90]</sup> Treatment is by combined furosemide and an ACE inhibitor (see Chapter 6, p. 193); restriction of water intake is also critical. Aquaretics are novel agents that help to overcome hyponatremia (see p. 107). In hypertension, hyponatremia may occur especially in older women receiving a thiazide dose of 25 mg daily or more.<sup>[91]</sup>

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## Less common uses of diuretics

Less common indications are:

1. Intravenous furosemide used in **malignant hypertension**, especially if there is associated CHF and fluid retention.
2. High-dose furosemide used for *acute or chronic* **renal failure** when it is hoped that the drug may initiate diuresis.
3. In **hypercalcemia**, high-dose loop diuretics increase urinary **excretion** of **calcium**; intravenous **furosemide plus saline** is used in the emergency treatment of severe hypercalcemia.
4. **Thiazides** used for the **nephrogenic form of diabetes insipidus**—the mechanism of action is not clear, but there is a diminution in “free water” clearance.
5. **Thiazide** diuretics **decrease** the urinary **calcium output** by promoting proximal reabsorption, so that they are used in *idiopathic hypercalciuria* to decrease the formation of renal stones. (In contrast, **loop** diuretics **increase** urinary **excretion** of calcium.)

The inhibitory effect of **thiazides** on urinary calcium loss may explain why these agents may **increase bone mineralization** and **decrease** the incidence of **hip** fractures.<sup>[92]</sup> The latter benefit is another argument for first-line low-dose diuretic therapy in older adult patients with hypertension.

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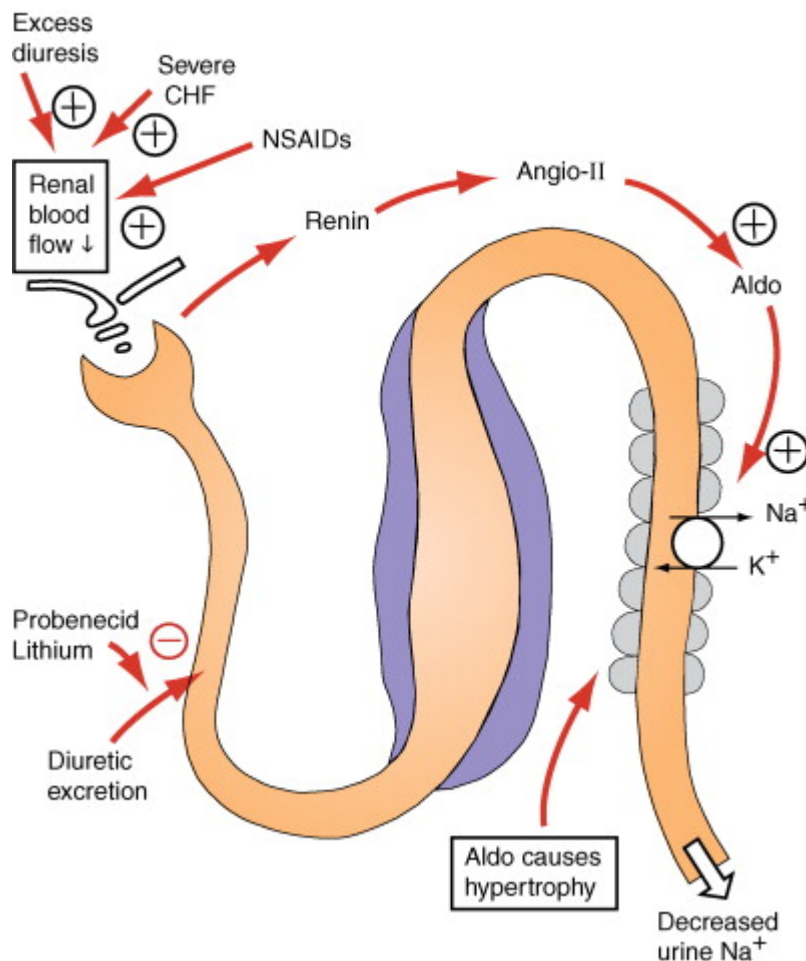


**Diuretics in step-care therapy of CHF**

In *mild to moderate heart failure with fluid retention*, diuretics are standard first-line therapy (Fig. 4-5). The choice of diuretic lies between standard thiazide, a K-retainer plus thiazide, furosemide, **spironolactone**, and **eplerenone**. The **latter** are known to **save lives** in **severe** CHF when added to otherwise standard therapy. [77].[93] Furthermore, a retrospective analysis showed that use of **non-K** retaining diuretics in the SOLVD study was associated with **increased arrhythmic death**. [52] By contrast, a K-retainer alone or in **combination** with a non-K retainer, gave **no** such **increase** in risk of arrhythmic death. ACE inhibition plus a non-K retaining diuretic also did not protect from arrhythmic death. These studies, although retrospective and observational, are bound to influence clinicians toward the **preferential** use of **spironolactone**, eplerenone or **combination** diuretics containing K-retainers (see Tables 4-4 and 4-5).

**DIURETIC RESISTANCE IN CHF**

Opie 2012



**Figure 4-5** Diuretic **resistance** has several causes including **reduced renal blood** flow and the **stimulation** of the **renin-angiotensin-aldosterone system**. Hypothetically, increased **aldosterone** (aldo) may **promote** distal tubular **hypertrophy** to **reabsorb** greater amounts of **sodium**. For early “braking,” not shown here, see text. *Angio II*, angiotensin II; *CHF*, congestive heart failure; *NSAID*, nonsteroidal antiinflammatory drug. (Figure © L.H. Opie, 2012.)

*Step-care diuretic therapy* in symptomatic heart failure (see Fig. 6-9) with fluid retention is not clearly delineated by adequate trials, but **four** potential agents are (1) **thiazide diuretics with ACE inhibitors**, (2) low-dose **furosemide with ACE inhibitors**, (3) **thiazides together with low-dose furosemide with ACE inhibitors**, and (4) **spironolactone or eplerenone added to the others**. **High-dose furosemide** is now less used, **chiefly for acute heart failure**. The current practice is to **add ACE inhibitors** or ARBs whenever the patient is given a diuretic, **unless there is a contraindication**. **ACE inhibition or ARBs should offset the deleterious renin-angiotensin activation induced by diuretics**. Regarding *sodium restriction*, modest restriction is advisable throughout, starting with no added salt, then cutting out obvious sources of salt as in processed or fast foods, and then going on to salt-free bread. Downregulation of the salt-sensitive taste buds means that after approximately 6 weeks of modest sodium restriction, a low-salt diet becomes the preferred norm.

For **severe CHF**, when congestion and edema are prominent symptoms, initial therapy is usually with furosemide, especially when renal perfusion may be impaired. In severely ill patients complete bed rest, although old-fashioned, may promote an early diuresis. The **dose of furosemide** required in **resistant CHF** may be **very high** (500 to **1500 mg daily**). Alternatively, the principle of **sequential nephron blockade** may be used with a lower dose of **furosemide**, and consideration should be given to **intermittent dopamine**.

### *Sequential nephron blockade.*

*Sequential nephron blockade* is the principle whereby addition of a diuretic acting at a different site, such as a thiazide to a loop diuretic, is logical (see Fig. 4-3). However, beware of overdiuresis as previously warned.<sup>[88]</sup>

### **ACE inhibitors.**

ACE inhibitors are now **standard** agents for **all stages of heart failure**. In CHF, the action of diuretics may be inhibited by poor renal perfusion and **vasoconstrictive** formation of **renin**, with a low GFR lessening sodium excretion. Hence **ACE inhibitors** are **logical additions** to diuretics. They have an indirect diuretic effect ultimately by **inhibiting aldosterone** release. They also help to **maintain** cell **potassium** and **magnesium**.

### *Do long-term diuretics for heart failure have dangers?*

Prolonged high-dose diuretic therapy may be harmful by (1) further activation of the renin-angiotensin and sympathetic nervous systems, and (2) hyponatremia (less often hypokalemia and hypomagnesemia) can result direct diuretic-driven negative effects on nephron function and prolonged solute-driven water loss.<sup>[78]</sup> The potential harm of chronic non-potassium-sparing diuretics in heart failure is highlighted in a secondary analysis of 7788 patients from the DIG trial, matched by propensity scoring.<sup>[94]</sup> These authors and others<sup>[5].<sup>[16]</sup></sup> challenge the *routine* use of diuretics in asymptomatic or minimally symptomatic patients without fluid retention.

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## Summary

1. **In hypertension.** The benefit-risk ratio of diuretic therapy has been particularly well-documented in three groups of patients: older adult patients, black patients, and obese patients. Low doses are required to lessen metabolic side effects such as new diabetes. Patients with renal impairment require a loop diuretic (or metolazone). For many hypertensives, a low-dose thiazide diuretic, with a potassium-retaining component (amiloride, triamterene, spironolactone-epplerenone or ACE inhibition-ARB) is appropriate. Most combination diuretic tablets contain too much HCTZ. Thiazide diuretics combine well with ACE inhibitors or ARBs, in which case another potassium-sparing component is not advisable.
2. **Thiazide-like diuretics.** Chlorthalidone and indapamide differ from the standard thiazides, and hence are now called *thiazide-like*. Some recent data suggest that chlorthalidone is superior to HCTZ, being longer acting and better at reducing nocturnal BP. Both chlorthalidone and indapamide slow-release are preferentially recommended for hypertension by the British NICE group as having positive outcome studies in hypertension, which the standard thiazides do not have.
3. **Amiloride, triamterene, and spironolactone.** Amiloride, triamterene, and spironolactone are “old-fashioned drugs” making a comeback, the first two for hypertension associated with renal epithelial sodium channel defects, and spironolactone for resistant hypertension and heart failure.
4. **CHF with fluid retention.** The benefit-risk ratio of diuretics is high and their use remains standard. Yet not all patients require vigorous diuresis; rather, each patient needs careful clinical evaluation with a specific cardiologic diagnosis so that surgically correctable defects are appropriately handled. First choice of therapy for mild fluid retention is a thiazide logically combined with an ACE inhibitor or ARB. With increasing severities of failure, larger doses of thiazide are used before switching to or combining with a loop diuretic such as furosemide.
5. **Non-congested heart failure.** Diuretics may be harmful by renin-aldosterone stimulation but countered by spironolactone-epplerenone.
6. **Sequential nephron block.** Sequential nephron block is an important principle calling for the progressive addition of diuretics acting at different nephron sites as the severity of heart failure increases: thiazides, loop diuretics, and then aldosterone antagonists. With concurrent use of ACE inhibitors or ARBs, hyperkalemia is best limited by low doses of spironolactone—epplerenone.
7. **Hypokalemia.** Hypokalemia remains one of the frequent complications of diuretic therapy. In hypertension this is avoided by the use of a low-dose thiazide with a potassium-retaining component: amiloride, triamterene, spironolactone, or epplerenone. In heart failure, we stress that automatic addition of oral potassium supplements is far from ideal practice. Rather, the combination of a loop diuretic plus low-dose thiazide plus potassium-retaining agent is reasonable. Concurrent ACE inhibitor or ARB therapy also counters hypokalemia by an antialdosterone effect. For mild to moderate heart failure with fluid retention, some combination of diuretics, plus ACE inhibitors and ideally with  $\beta$ -blockade, is standard therapy.
8. **Hyponatremia.** Hyponatremia is a potentially serious complication of chronic heart failure, often associated with increased plasma vasopressin and prolonged use of loop diuretics. Thiazides can cause hyponatremia in older hypertensives. *Aquaretics* are a new class of diuretic that promote solute-free water clearance to correct hyponatremia by inhibiting aquaporin, the vasopressin-sensitive water transport channel found in the apices of the renal collecting duct cells. Specific examples are conivaptan, tolvaptan, and lixivaptan, a grouping often called the *vaptans*. However, an outcome study with tolvaptan was disappointing (see Chapter 6, p. 189).

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