Diuretics for Hypertension
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A 67-year-old African-American woman was referred to a hypertension specialty clinic for refractory hypertension and intermittent hypokalemia. Evaluations for primary aldosteronism and renal artery stenosis were negative; plasma renin was low. She had been hypertensive for 15 years. Most recently, she had taken chlorthalidone 25 mg, amlodipine 5 mg, and metoprolol 50 mg twice daily. She was not diabetic and had never smoked. Her blood pressures were in the range of 160 to 170/95 to 100 mm Hg. Except for her being mildly overweight (body mass index, 28), the physical examination was unremarkable, with no sign of target organ damage. Voltage criteria for left ventricular enlargement were present on the ECG. She was considered to be adherent to medication. Spironolactone 50 mg/d was prescribed, and her dose of chlorthalidone was reduced to 12.5 mg/d. Over the next year, her blood pressure fell to the range of 135 to 145/85 mm Hg, and serum potassium was consistently normal.

Comment
This patient was taking three antihypertensive drugs, including a diuretic, which is considered by many as a necessary component for her management, yet remained uncontrolled, with an especially high risk of stroke. The addition of another diuretic was successful in bringing her pressure into an acceptable range and reversed the tendency toward hypokalemia that was caused by the thiazide-type diuretic. What is the lesson here? First, diuretic combinations from different subclasses play an important role in the management of hypertension. Second, salt-sensitive refractory hypertension in the African-American population, reflected clinically by low renin levels, can provide a clue to optimal management.1,2

Role of Diuretics in Management of Hypertension
Treatment of hypertension that uses a diuretic-based strategy has been effective in preventing stroke and cardiac disease in the earliest randomized clinical trials in the 1960s, with a consistently successful "track record" extending to contemporary trials, as emphasized in ALLHAT.3 A very high fraction of all hypertensives, but especially African-Americans, can be well controlled on simple two-drug regimens, combining a thiazide-type diuretic with either a β-blocker or an ACE inhibitor, each given once a day. Cost is minimal, control rates are high, and adherence to medication is probably optimum. There is a substantial argument that a thiazide-type diuretic should be the initial treatment for all hypertensives.4 A side issue related to that argument is that there is no detectable difference between chlorthalidone (used in ALLHAT and SHEP) and other thiazides.5 That said, diuretics are not a single drug class but rather can be divided into three distinct subclasses, and each of these has an important role to play in the management of most hypertensive patients. Although most diuretics have been in clinical use for many years, there has been drug development within this class. We will focus on the three diuretic classes used to treat hypertension: (1) thiazide-type, (2) loop-active agents, and (3) the potassium-sparing agents, which act as either mineralocorticoid antagonists or inhibitors of the epithelial sodium channel of the late distal renal tubule or collecting duct. Another subclass, the carbonic anhydrase inhibitors, is not used to treat hypertension. The Figure displays the sites at which the diuretic subclasses have their major effects on electrolyte and water resorption in the nephron after glomerular filtration has occurred.

Thiazide-Type Diuretics
As monotherapy and in combination with β-blockers, ACE inhibitors, or
Angiotensin receptor blockers, hydrochlorothiazide and its many variants lower blood pressure. There remains some controversy as to whether a thiazide-type diuretic should be the initial treatment for all hypertensives. The evidence from the SHEP study emphasizes the value of a low-dose thiazide-type drug as initial therapy for isolated systolic hypertension in older patients, and ALLHAT strongly supports that choice for African-American hypertensives. For others, who are started on a β-blocker, ACE inhibitor, or angiotensin receptor blocker and whose pressure remains above goal, there is a convincing argument that a diuretic should be the next step. Either way, most hypertensives placed on one of these two drug combinations can be well controlled. Using a thiazide-type drug requires baseline serum electrolyte measurement and monitoring of serum potassium. Gout remains an occasional adverse reaction as a consequence of diuretic-induced hyperuricemia, and infrequently, hypercalcemia may occur. These effects are the result of thiazide-related reductions in urinary urate or calcium excretion. Type 2 diabetes may develop during the course of thiazide-type diuretic treatment, yet in elderly patients, there seems to be little added risk for cardiovascular events compared with pre-existing diabetes. For those patients who develop hypokalemia on low-dose thiazide-type diuretics, a diagnosis of primary aldosteronism may be considered. Addition of potassium-sparing drugs, spironolactone, eplerenone, or amiloride, may achieve effective control of hypertension and correct hypokalemia without the need for extensive diagnostic assessment or consideration of adrenalectomy. No study has clearly shown that surgical treatment for primary aldosteronism is superior to effective medical management.

**Loop-Active Agents**

As indicated by the Figure, furosemide and its analogs (bumetanide or torsemide) interrupt resorption of sodium, calcium, and potassium in the distal renal tubule at the ascending limb of the loop of Henle at sites distinct from the thiazide-sensitive loci. These loop-active agents have a short duration of action and, for treatment of hypertension, must be given twice daily. Renal insufficiency reflected by reduced creatinine clearance limits the effectiveness of thiazide-type diuretics. In contrast, furosemide is highly effective despite renal impairment, although high doses are often needed when serum creatinine increases. The loop-active diuretics may cause hypokalemia, which can be countered by potassium supplementation or potassium-sparing diuretics. Close monitoring of serum potassium is necessary in these circumstances. Unlike the thiazide-type agents, the loop-active diuretics increase calcium excretion and can reduce serum calcium as a treatment for hypercalcemia.

**Potassium-Sparing Diuretics: Mineralocorticoid Antagonists and Sodium Channel Antagonists**

Spironolactone, an inhibitor of the mineralocorticoid receptor, has been used for many years. Although quite popular, especially in combination with a thiazide diuretic, spironolactone nearly fell out of view (except for its use as a medical treatment for primary aldosteronism) until it was resurrected for its value in the treatment of congestive heart failure. As indicated by the comments related to our case study, spironolactone can be highly effective in many patients with refractory hypertension in combination with a thiazide-type diuretic and can correct hypokalemia as well. However, gynecomastia is a limiting adverse reaction for men treated with spironolactone because of the antiandrogen effect of this drug. Premenopausal women treated with spironolactone may develop menstrual irregularities, so that spironolactone is most likely to have sustained acceptance only by postmenopausal women. Eplerenone has recently been developed as a selective mineralocorticoid antagonist whose adverse effect profile is far more acceptable to a broader range of patients compared with spironolactone. Eplerenone should be considered an alternative for those who have a good clinical response to spironolactone but who develop unacceptable adverse reactions.

Amiloride and triamterene are also customarily used drugs that inhibit the epithelial sodium transport channel (ENaC) of the collecting duct. The overall activity of this channel is con-
trolled by the action of aldosterone. The ENaC inhibitors reduce potassium excretion as a consequence of their inhibition of the ENaC in preventing sodium resorption. The ENaC inhibitors have, in general, a minimal effect on blood pressure as monotherapy and are most effective for their potassium-sparing effects. The combination of a thiazide-type diuretic and amiloride (Co-amilizide) as initial treatment has been directly compared in a large randomized outcome trial (INSIGHT) with the long-acting calcium channel blocker, nifedipine GITS. The results of this trial found no statistically significant difference between the two treatments. However, a nonsignificant trend favored the diuretic combination.9 It is likely that, in the United States, the combination of a thiazide-type diuretic and a potassium-sparing agent, such as amiloride (which is a very-well-tolerated, inexpensive, and generic drug), is underused.

Rarely, salt-sensitive hypertensives may have gain-of-function mutations of the ENaC, resulting in an autosomal recessive trait (Liddle’s syndrome), which conveys a curative role for amiloride in this setting. It has been suggested that heterozygotic patterns may account for salt-sensitive and amiloride-responsive hypertension in some larger population groups.10

Conclusions
Contrary to the rumors of only a few years ago, diuretics have not fallen into disuse but have a highly important and multifaceted role to play in the treatment of hypertension. Identifiable but large subgroups within the hypertensive population (isolated systolic hypertension of the elderly and African-American hypertensives) are those for whom diuretic treatment as initial management may achieve the most benefit. Combinations of the thiazide-type and potassium-sparing subclasses may be highly effective, providing nearly optimal therapy for some, and might be considered more often in the treatment of hypertension.

References
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