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, amiodipine 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
started on a hypertensives. For others, who are ports that choice for African-American
seems to be little added risk for car-
metary urate or calcium excretion. Type
of thiazide-related reductions in uri-
may occur. These effects are the result
serum potassium. Gout remains an oc-
lyte measurement and monitoring of
drug requires baseline serum electro-
of these two drug combinations can be
way, most hypertensives placed on one
of these two drug combinations can be
well controlled. Using a thiazide-type
drug requires baseline serum electro-
measured and monitoring of
serum potassium. Gout remains an oc-
casional adverse reaction as a conse-
quence of diuretic-induced hyperuricemia,
and infrequently, hypercalcemia may
occur. These effects are the result of
thiazide-related reductions in urina-
rate or calcium excretion. Type 2 diabetes may develop during the
course of thiazide-type diuretic treat-
ment, yet in elderly patients, there
seems to be little added risk for car-
diovascular events compared with pre-
existing diabetes. For those patients
who develop hypokalemia on low-
dose thiazide-type diuretics, a diagno-
sis 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 adrenalecto-
my. No study has clearly shown that
surgical treatment for primary aldosteron-
is superior to effective medical
management.

Loop-Active Agents
As indicated by the Figure, furosemide
and its analogs (bumetanide or
torsemide) interrupt resorption of so-
dium, 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 treat-
ment of hypertension, must be given
twice daily. Renal insufficiency re-
lected by reduced creatinine clearance
limits the effectiveness of thiazide-
type diuretics. In contrast, furosemide
is highly effective despite renal im-
pairment, although high doses are of-
ten needed when serum creatinine in-
creases. The loop-active diuretics may
cause hypokalemia, which can be
 countered by potassium supplemen-
tation 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 cal-
cium 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 once
quite popular, especially in combina-
tion with a thiazide diuretic, spirono-
lactone 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 treat-
ment 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 re-
action for men treated with spironola-
tone because of the antiandrogen effect
of this drug. Premenopausal women
treated with spironolactone may de-
velop menstrual irregularities, so that
spironolactone is most likely to have
sustained acceptance only by post-
menopausal women. Eplerenone has
recently been developed as a selective
mineralocorticoid antagonist whose
adverse effect profile is far more ac-
ceptable 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 (Coamilizide) 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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