A
tention must be paid to the article by Roush et al ¹ in this
edition of Hypertension. The authors use robust statistics
to compare the antihypertensive potency and adverse effects of
hydrochlorothiazide versus indapamide in the 10 publications
that could be identified, wherein the 2 drugs were compared
head-to-head in trials lasting 24 weeks. Indapamide, used as
2.5 mg tablets in all but 1 trial, provided a 54% greater reduc-
tion in systolic blood pressure, that is, −5.1 mm Hg (confidence
interval, −8.7 to −1.6) than seen with hydrochlorothiazide in
doses from 12.5 to 50 mg/d. The relative doses were greater for
hydrochlorothiazide in 5 trials and equivalent in 3 trials.
The blood pressures were measured by office sphygmo-
manometry in all these trials but reference is given to studies
using 24-hour ambulatory measurements, which showed ≥24-
hour duration of diuretic and antihypertensive efficacy with
the immediate formulation of indapamide and ≥32-hour dura-
tion with the sustained formulation (which was used in only
one of the trials).² Roush et al³ refer to multiple additional
vasodilatory actions described in the literature in support of
the greater reduction of blood pressure and the longer duration
of action of indapamide, well beyond the 12- to 16-hour dura-
tion of action of hydrochlorothiazide.

Indapamide Versus Chlorthalidone
The first 2 authors of this article have been involved in stud-
ies documenting a longer and stronger antihypertensive effect
of chlorthalidone over hydrochlorothiazide, studies that were
published as far back as 2004³ and reiterated in the current
article with data from 3 head-to-head comparisons.¹
No such comparisons between chlorthalidone and inda-
pareide could be found. Both probably provide full 24-hour antihypertensive efficacy so the choice between them must be
based on known additional characteristics of the 2 drugs. There
are at ≥3 features which could influence the choice and all 3
favor indapamide over chlorthalidone. These are (1) Ease of
use: In the US, generic chlorthalidone is only available as a 25
mg tablet. To approximate the most frequently used 12.5 mg
dose of hydrochlorothiazide, the chlorthalidone tablet must be
cut in half. Generic indapamide, both in the immediate and
delayed action formulations, is available as 1.5, 2.5, and 5 mg
tables so no such manipulation is needed. (2) Cost: The cost
of many drugs is higher in United States than in other coun-
ctries, adding to the markedly higher spending on healthcare
in the United States than in countries with a national health-
care system. The cost of 30 tablets of generic chlorthalidone
in 4 local multiple-chain pharmacies varies from $21 to $31,
whereas the cost of 30 tablets of all strengths of generic inda-
pamide is $4.00. Most generic formulations of other classes
of antihypertensive drugs are also available for $4.00 for 30
tablets. (3) Hypokalemia: The fall in serum potassium with
12.5 mg doses of chlorthalidone is ≈0.1 mmol/L greater than
that seen with equivalent doses of hydrochlorothiazide.⁴ As
noted by Roush et al,¹ the fall in serum potassium with 2.5
mg/d doses of indapamide averages only 0.054 mmol/L more
than that seen with hydrochlorothiazide.
In addition, no significantly greater changes in serum
sodium, glucose, cholesterol, or uric acid were seen. The one
advantage of hydrochlorothiazide over both chlorthalidone
and indapamide is its extensive availability in formulations
with other classes of antihypertensive drugs in both 12.5 and
25 mg doses, most of which cost only $4.00 for 30 tablets.
Chlorthalidone is marketed only with the generally discred-
ted β-blocker atenolol and the recently approved angiotensin
receptor blocker azilsartan,⁵ but the cost of 30 tablets of this
still patented angiotensin receptor blocker is $170.99. The only
marketed combination of indapamide is with the angiotensin-
converting enzyme inhibitor perindopril but this combination
is not available in the 4 pharmacies contacted in Dallas.
Therefore, if a second drug is needed with indapamide, the
cost of almost any of the generic formulations of the other
classes of drugs should be only an additional $4.00.

Nocturnal Protection
The wisdom of using indapamide or chlorthalidone is sup-
ported further by Roush et al¹ who wrote: “While HCTZ has
less than a 24 hour duration of diuretic and antihypertensive
actions, indapamide even in the immediate release form has
at least a 24 hour duration of action for blood pressure reduc-
tion…. Duration of action is important in view of the fact
that targeting nighttime BP may reduce cardiovascular events
above and beyond the reduction in events relative to targeting
daytime BP”.
The authors conclude that these head-to-head compari-
sions demonstrate that, like chlorthalidone, indapamide has
a greater antihypertensive potency than hydrochlorothiazide
at commonly prescribed doses without evidence for greater
adverse metabolic effects.¹
The Addition of a Mineralocorticoid Receptor Antagonist

Although not addressed by Roush et al., one additional drug should be considered with whatever diuretic is chosen, namely a mineralocorticoid receptor antagonist (MRA). As most vigorously advocated by John Funder, an MRA will almost certainly provide additional cardiovascular protection to whatever type of antihypertensive drug used. In a recent review, he concludes that an MRA should be included in current antihypertensive therapy for all hypertensives with reasonable renal function and normal potassium levels.

The MRA spironolactone is available for $4.00 for 30 tablets but, inexcusably beyond financial avarice, the now generic and less bothersome MRA eplerenone remains costly in the United States, $114 for 30 tablets.

It may be even more difficult to convince practitioners to switch from hydrochlorothiazide to indapamide or chlorthalidone than to convince them to also add an MRA. If a choice is needed, the switch to indapamide seems most critical, at least until a generic formulation of indapamide combined with an MRA enters the therapeutic armamentarium, thereby most effectively controlling our most common and fastest growing cardiovascular risk factor.

Disclosures

None.

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