NEW FEATURE

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Priority Updates from the Research Literature from the Family Physicians Inquiries Network

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IN THIS ARTICLE

PURLs methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

HYPERTENSION WITH METABOLIC SYNDROME

Think thiazides are old hat? ALLHAT says think again

Outcomes support chlorthalidone despite its metabolic profile

Practice changer

Use thiazide-type diuretics for hypertension in patients with metabolic syndrome to reduce stroke and heart failure.

Strength of recommendation

B: Single well done randomized controlled trial

Wright JT Jr, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2008; 168:207–217.[1]

ILLUSTRATIVE CASE

Your new patient is a 57-year-old African American man. His blood pressure is 150/95 mm Hg, fasting glucose 115 mg/dL, body mass index 32, and triglycerides 155 mg/dL; he is on no prior medications. During the course of his care you diagnose hypertension with metabolic syndrome and decide to recommend an antihypertensive. Thiazide-type diuretics are your standard initial therapy, but this patient has metabolic syndrome, and you know that certain antihypertensive agents have a more favorable metabolic profile than thiazide diuretics. Furthermore, metabolic differences among races have been touted as reason to use other agents in black patients. Should you recommend a thiazide diuretic, or another agent?

Until now, we've had no simple approach to treating hypertension in patients with metabolic syndrome—and half or more of our hypertensive patients over the age of 55 have this disorder.

Now, however, we can base decisions on clinical outcomes data from a subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[1] This new subgroup analysis supports use of thiazide-type diuretics in these patients—particularly in black patients—despite the more favorable metabolic profile of calcium channel blockers, alpha-blockers, and angiotensin-converting enzyme (ACE) inhibitors.

Cost is no longer as big a factor as it once was, now that ACE inhibitors and alpha-blockers, as well as thiazide diuretics, are available generically.

Does a better metabolic profile improve outcomes?

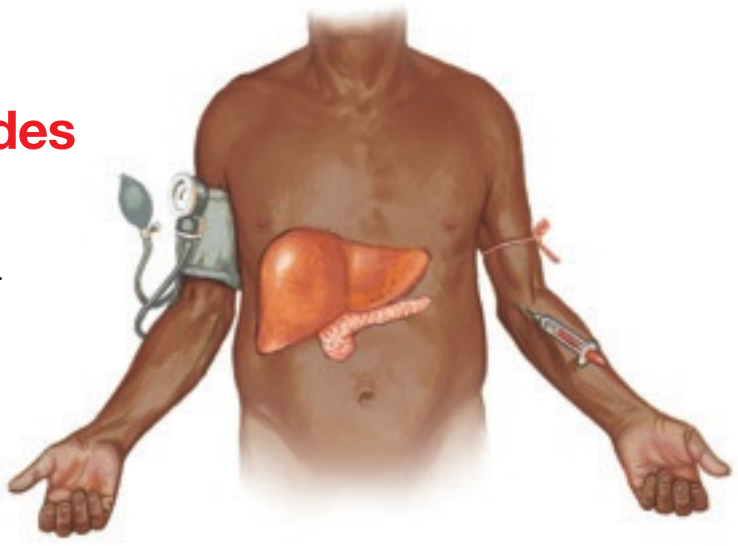
We have had reason to be concerned about the metabolic adverse effects of thiazide-type diuretics in the past. Studies published before this ALLHAT subgroup analysis showed that hydrochlorothiazide for essential hypertension had adverse effects on potassium, glucose, and lipid metabolism. Some speculated that these changes aggravate the metabolic changes

FIGURE

Outcomes favor thiazides

We know many physicians who have adopted thiazide-type diuretics as the first-line treatment for hypertension in metabolic syndrome, but until now, data have been inadequate to support this decision.

A subgroup analysis from the ALLHAT[1] concludes: "The ALLHAT findings fail to support the preference for calcium channel blockers, alpha-blockers, or angiotensin-converting enzyme inhibitors compared with thiazide-type diuretics in patients with the metabolic syndrome, despite their more favorable metabolic profiles. This was particularly true for black participants."



Hypertension
Blood pressure target for patients enrolled in the ALLHAT was <140/90 mm Hg

Metabolic syndrome, in the subgroup analysis, was defined as hypertension plus 2 of the following risk factors for coronary heart disease:

1. Obesity
Body mass index at least 30

2. Lipid disorder
Fasting triglyceride level >150 mg/dL and high-density lipoprotein cholesterol level <40 mg/dL in men, or <50 mg/dL in women

3. Glycemic disorder
Fasting glucose level >100 mg/dL, or nonfasting glucose level >200 mg/dL, or history of diabetes

in early diabetes[2-4] and may contribute to increased coronary heart disease risk.[5,6]

ACE inhibitors and ARBs

The metabolic benefits of ACE inhibitors and angiotensin-receptor blockers (ARBs) are widely known. In comparative studies prior to this ALLHAT subgroup analysis, ACE inhibitors were thought to be preferable to thiazide diuretics and beta-blockers for patients with obesity[7] or the metabolic syndrome.[8] These agents also protect against diabetic nephropathy.[9] Other studies attribute additional vascular benefits to ACE inhibitors,[10] beyond that of lowering blood pressure.

A 2005 meta-analysis by Abuissa et al[11] showed that ACE inhibitors and ARBs were associated with significant reductions in the incidence of newly diagnosed diabetes, which, in turn, might lead to reduced heart disease. That report concluded that use of ACE inhibitors or ARBs should be considered in patients with prediabetic conditions such as metabolic syndrome, hypertension, impaired fasting glucose, family history of diabetes, obesity, congestive heart failure, or coronary heart disease.

Calcium-channel blockers and alpha-blockers

Calcium-channel blockers and alpha-blockers also do not appear to have the adverse metabolic effects of thiazides, and have also been advocated over beta-blockers and thiazides for hypertensive patients with metabolic syndrome.[12-15]

Racial differences

In a consensus statement developed before the findings from the ALLHAT subgroup analysis were available, it was noted that racial differences in metabolic syndrome may make the selection of antihypertensive agents particularly important in African American patients.[16]

ALLHAT and JNC7 recommendations

The 2002 ALLHAT demonstrated that chlorthalidone (a thiazide-type diuretic) is superior to lisinopril, amlodipine, and

FAST TRACK

ACE inhibitors, ARBs, calcium-channel blockers, and alpha-blockers have better metabolic profiles than thiazides

How is conflicting information playing out in practice?

It is unclear to us how this conflicting information has played out in current practice. We know that many physicians already choose thiazides as their first-line agent for hypertensive patients with metabolic syndrome. And we suspect that many choose other agents.

We analyzed the National Ambulatory Medical Care Survey data (http://www.cdc.gov/nchs/about/major/ahcd/ahcd1.htm) from 2004 and 2005 and found that only 3% to 5% of outpatients with diabetes and hypertension were taking thiazides at all (unpublished data). Metabolic syndrome is not a variable in this dataset, so we could not determine the use of thiazides in hypertension and metabolic syndrome.

Our informal polling of colleagues suggested that large numbers of hypertensive patients with metabolic syndrome are not currently receiving the more beneficial thiazides.

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Some physicians already use thiazides for hypertension with metabolic syndrome

doxazosin in preventing 1 or more major forms of cardiovascular disease. No difference was observed, however, for fatal coronary heart disease, nonfatal myocardial infarction, or all-cause mortality.[17] These findings persisted in subgroup analyses stratified by race, diabetic status, and level of renal function, but ALLHAT did not identify patients with metabolic syndrome a priori.

The ALLHAT influenced the 2003 Joint National Commission VII (JNC7) Report, which recommends thiazide diuretics for first-line treatment of hypertension in the absence of compelling indications to begin an alternative antihypertensive agent.[18]

Special consideration, but no recommendation. The JNC7 Report mentions the metabolic syndrome as a special consideration, but does not explicitly recommend a first-line therapy other than thiazides.

Anecdotally, we know many physicians who have adopted thiazide-type diuretics as the first-line treatment for hypertension in metabolic syndrome, but until now, data have been inadequate to support this decision.

STUDY SUMMARY

Chlorthalidone outcomes were equivalent or better

Wright and colleagues analyzed a subgroup[1] of the ALLHAT cohort, which consisted of 42,418 participants, aged ≥55, with hypertension and at least 1 other cardiovascular risk factor (**FIGURE**). Patients were randomly assigned to therapy with chlorthalidone, amlodipine, lisinopril, or doxazosin. After randomization, if patients failed to reach the target blood pressure (<140/90 mm Hg) with their assigned therapy, they were started on atenolol, clonidine, or reserpine. If they required a third agent, they received hydralazine. The doxazosin arm was stopped early due to increased stroke and heart failure risk.

The ALLHAT was well done and designed for adequate power to evaluate clinical outcomes in racial subgroups, as well as the general population.

Outcomes were compared by race in hypertensive patients with and without metabolic syndrome.

A total of 23,077 (54%) patients met all criteria; 12,818 were black, 7327 (57%) of whom had metabolic syndrome.

Not surprisingly in a study of this size, the expected metabolic effects of all 4 antihypertensive agents were detected. Patients taking chlorthalidone had higher glucose levels (1–4 mg/dL) and higher levels of cholesterol, although these higher glucose and cholesterol levels were not statistically significant for all comparisons over time and between different drugs.

Outcomes in the chlorthalidone group were equivalent or superior to the 3 other therapies, generally. This pattern held true regardless of race (**TABLE**):

Heart failure rates were significantly higher in patients with metabolic syndrome across all treatments compared with chlorthalidone.

Combined cardiovascular disease rates were higher with lisinopril and doxazosin compared with chlorthalidone.

Stroke rates were higher among black participants only in the lisinopril group.

TABLE

Number needed to treat to prevent blood pressure-related adverse outcomes in patients with hypertension and metabolic syndrome

NUMBER NEEDED TO TREAT (NNT) = number of patients that would need to take chlorthalidone to prevent 1 outcome, compared with the alternate drug (4.9 years of chlorthalidone instead of lisinopril or amlodipine or 3.2 years of chlorthalidone instead of doxazosin). Smaller numbers indicate a bigger effect.

OUTCOME	CHLORTHALIDONE VS AMLODIPINE		CHLORTHALIDONE VS LISINOPRIL		CHLORTHALIDONE VS DOXAZOSIN	
	Black	Non-black	Black	Non-black	Black	Non-black
Combined cardiovascular disease	22	NS	18	53	14	34
Stroke	NS	-111	59	NS	37	NS
Heart failure	29	48	28	143	28	25
All-cause mortality	NS	NS	NS	NS	NS	NS

NS = not significant.

Source: The authors calculated the NNTs from the event rates reported.[1]

WHAT'S NEW

Most effective, least expensive

First-line use of thiazide diuretics for hypertension gained major support from the findings of the first ALLHAT report, published in 2002. A year later, JNC7 supported the practice. Yet questions have persisted about whether the choice of initial antihypertensive agent in patients with metabolic syndrome warrants special consideration.

The difference for one patient is small, but when you consider the high prevalence of hypertension, the cumulative benefit at a population level is significant. This subgroup analysis confirms that there is no harm, and potentially a small benefit, in using chlorthalidone as a first-line agent for treating hypertension in patients with metabolic syndrome, regardless of race—despite the measurable and presumably adverse effects of diuretic agents on metabolic measurements.

How large is the benefit of first-line thiazides, overall?

Although, statistically, the relative risks (RR) are not large, the sheer number of patients means that there is significant benefit to the selection of thiazides as first-line treatment in most patients.

CAVEATS

Is stroke a concern? Was follow-up sufficient?

In this study, the only finding of harm in the diuretic group was an increased risk for stroke compared with amlodipine among non-black patients with metabolic syndrome. While this finding does raise some uncertainty, we still think that, on balance, thiazides are the most beneficial, even in this subgroup, as there was a larger benefit in preventing heart failure.

Another theoretical possibility is that follow-up was too short to demonstrate harm from the metabolic effects of thiazides. However, the metabolic effects of thiazides are very small and we believe that the evidence of benefit shown during this study period easily outweighs any such theoretical harms.

We also assume that hydrochlorothiazide, a commonly prescribed thiazide, has the same benefits as chlorthalidone, the medication studied.

Most ALLHAT participants with metabolic syndrome already had diabetes: 67.6% of black participants and 51.8% of non-black participants. Another subgroup analysis of the ALLHAT studied patients with metabolic syndrome without diabetes, and found similar results.[19] Of note, lisinopril reduced the onset of diabetes over 5 years (number needed

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FAST TRACK

There is no harm and potentially a small benefit despite presumably adverse effects of diuretics on metabolic measurements

to treat [NNT] = 22.2), at the cost of increased heart failure (RR = 1.31; 95% confidence interval [CI], 1.04-1.64) and combined cardiovascular disease (RR = 1.19; 95% CI, 1.07-1.32). This potentially confounds the claim that thiazides are effective in preventing diabetes, since so many people had it to begin with.

The criteria for metabolic syndrome did not include waist circumference, which is the National Cholesterol Education Program definition. The World Health Organization definition, however, does allow substitution of BMI. Purists would have you believe waist circumference is necessary. In practice, we have come to use BMI as an adequate surrogate. Some say it has, in fact, replaced waist circumference.

CHALLENGES TO IMPLEMENTATION

Inertia

Few interventions are as simple as this. Thiazide diuretics are well tolerated, need to be taken only once daily, and are inexpensive. Because generics are available, little to no pharmaceutical marketing is done to promote their use. The major barriers to implementing this practice may be overcoming clinical inertia, and the message of pharmaceutical marketing on behalf of the more expensive alternatives. ■

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The major barrier to increasing the use of thiazides for these patients will probably be clinical inertia

Acknowledgement

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