

Editorial

The Last Nail in Hydrochlorothiazide's Coffin?

Firas J. Al Badarin, MD,^{*†} Carl J. Lavie, MD, FACC,^{‡§} James H. O'Keefe, MD, FACC^{*†}

^{*}Saint Luke's Hospital Mid America Heart Institute, Kansas City, MO

[†]University of Missouri-Kansas City, Kansas City, MO

[‡]John Ochsner Heart and Vascular Institute, Ochsner Clinic Foundation, New Orleans, LA

[§]The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA

The 7th report of the Joint National Committee (JNC 7) on the detection, prevention, and treatment of hypertension (HTN) recommends a thiazide diuretic, used singly or in combination with other antihypertensive medications, as initial therapy for patients with HTN.¹ Although physicians tend to view the thiazides as a homogenous class of diuretics, significant differences exist among these drugs, especially with respect to their efficacy of blood pressure lowering and, more important, the outcomes data supporting their ability to improve the long-term prognosis for HTN. Although hydrochlorothiazide continues to be US physicians' overwhelmingly favored thiazide for treating HTN, a closer look at the data suggests that its preferred status is not warranted.

A recent meta-analysis adds fuel to the fire of this debate.² The authors show that hydrochlorothiazide,

at doses of 12.5 to 25 mg daily, is inferior to other classes of antihypertensive medications, and they conclude that it should not be the thiazide diuretic of first choice for treatment of HTN. How do these new data fit with what we already know and what inferences can be made from the totality of the available evidence?

Our group has recently published a formal review of published literature evaluating the impact of thiazide diuretics on cardiovascular (CV) prognosis in patients with HTN.³ While studies of head-to-head comparison between thiazide diuretics are lacking, we found that hydrochlorothiazide (25 mg daily) was consistently inferior to other comparators (except atenolol—another antihypertensive agent with poor outcomes data)⁴ in preventing CV events.^{5–9} Conversely, data with chlorthalidone (12.5 to 25 mg daily)^{10–12} and indapamide (0.625 to 2.5 mg daily)^{13–15} were considerably more robust and showed unequivocal reductions in adverse CV events (Figure). These findings argue against a class effect with thiazide-type diuretics and suggest instead that diuretics with better track records (such as chlorthalidone and indapamide) should be preferentially used when a thiazide is indicated. Put differently, hydrochlorothiazide should not be a first-line thiazide because it has a relatively weak antihypertensive effect and no appreciable evidence supporting its role in improving CV prognosis and outcomes of patients with HTN. Whether or not using hydrochlorothiazide at higher doses (50 mg daily) would be more beneficial is unclear because such high daily doses have been associated with higher risk of hypokalemia and sudden cardiac death.

The reasons for this obvious disconnect between the poor performance of hydrochlorothiazide in improving the long-term outcomes of patients with HTN and its highly favored status among physicians are not entirely clear. Hydrochlorothiazide is mostly used out of habit and/or the ease of its widely recognized

Address correspondence to

James H. O'Keefe, MD, FACC

Saint Luke's Hospital Mid America Heart Institute

4330 Wornall Road, Suite 2000

Kansas City, MO 64111

Tel: (816) 751-8480

Fax: (816) 756-3645

Email: jhokeefe@cc-pc.com

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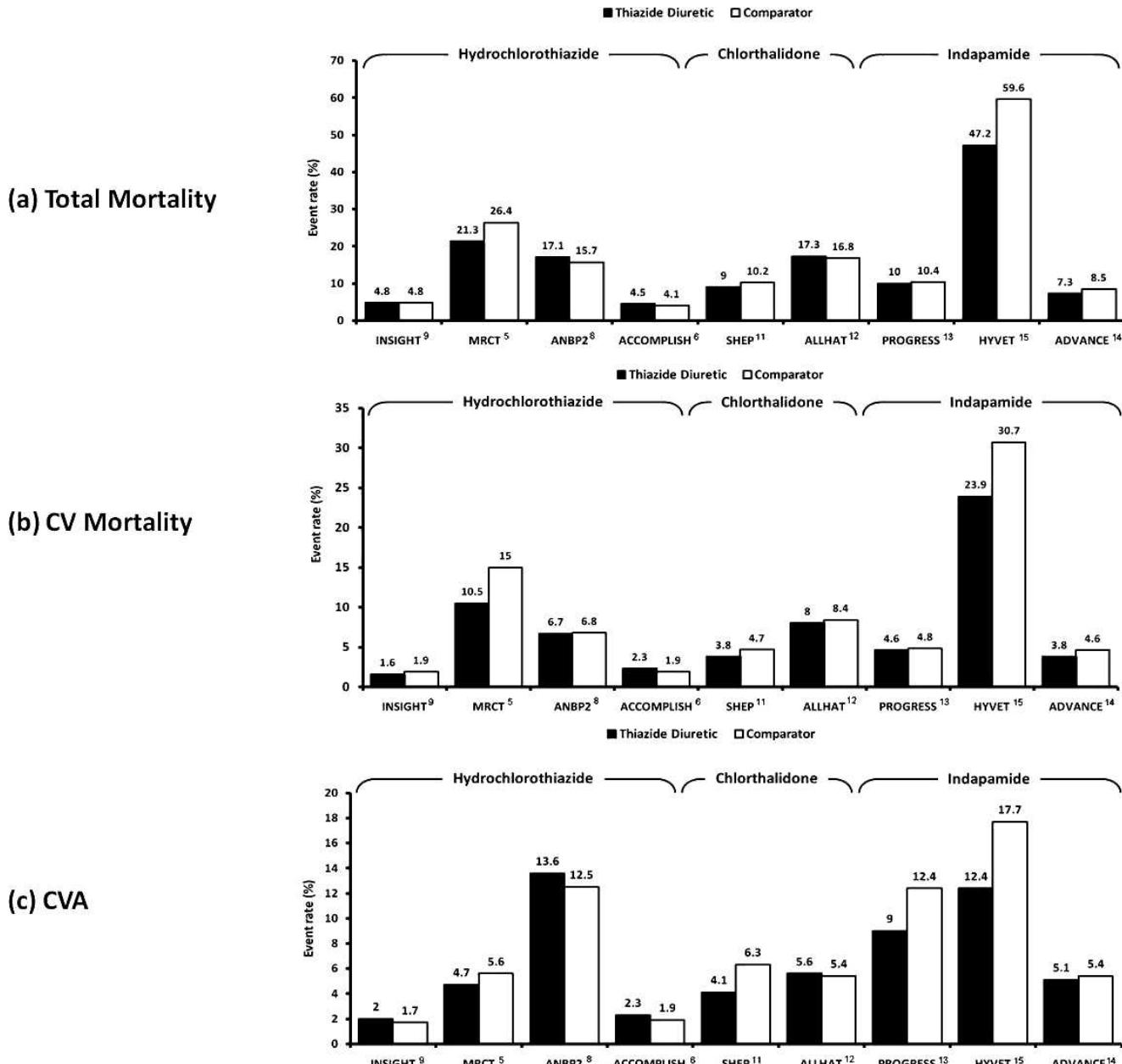


Figure. Data summary from landmark outcomes studies on the impact of thiazide diuretics (hydrochlorothiazide, chlorthalidone and indapamide) on major cardiovascular endpoints: (a) total mortality, (b) CV mortality, (c) CVA. CV: cardiovascular, CVA: cerebrovascular accidents (INSIGHT: hydrochlorothiazide/amiloride vs. atenolol; MRCT: hydrochlorothiazide vs. atenolol; ANBP2: hydrochlorothiazide vs. enalapril; ACCOMPLISH: hydrochlorothiazide + benazepril vs. amlodipine + benazepril; SHEP: chlorthalidone vs. placebo; ALLHAT: chlorthalidone vs. amlodipine vs. lisinopril; PROGRESS: perindopril \pm indapamide vs. placebo; HYVET: indapamide \pm perindopril vs. placebo; ADVANCE: indapamide + perindopril vs. placebo).

abbreviations (HCT or HCTZ).^{16,17} Moreover, hydrochlorothiazide is available in a host of fixed-dose combinations with a variety of other blood-pressure lowering medications, likely another key reason for its widespread use. Using indapamide or chlorthalidone combined with other antihypertensive agents with more compelling outcomes data (such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) will not only

improve blood pressure (BP) control, but is also likely to impact CV prognosis favorably. Moreover, this combination is likely to mitigate the risk of hypokalemia, a potential complication typically seen at higher doses of more potent thiazides. The use of antihypertensive combinations becomes particularly important when we realize that two-thirds of patients with HTN require at least 2 medications to achieve BP targets.¹⁸

As a final practical matter, all of these thiazide diuretics are available for \$4 per month; therefore, cost should not be a significant barrier to using either chlorthalidone or indapamide instead of hydrochlorothiazide, even for those without insurance coverage for prescription medications.

With scientific evidence consistently indicating that hydrochlorothiazide is suboptimal for reducing the risk of adverse CV events and optimizing BP control, its use as the thiazide of choice for patients with HTN becomes exceedingly hard to justify. On the other hand, the available evidence strongly supports the use of chlorthalidone¹⁹ or indapamide when a thiazide diuretic is indicated for HTN.

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003 May 21;289(19):2560-2572; Epub 2003 May 14. Erratum in: *JAMA*. 2003 Jul 9;290(2):197.
2. Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. *J Am Coll Cardiol*. 2011 Feb 1;57(5):590-600.
3. Al Badarin FJ, Abuannadi MA, Lavie CJ, O'Keefe JH. Evidence-based diuretic therapy for improving cardiovascular prognosis in systemic hypertension. *Am J Cardiol*. 2011 Apr 15;107(8):1178-1184.
4. Ram CV. Beta-blockers in hypertension. *Am J Cardiol*. 2010 Dec 15;106(12):1819-1825; Epub 2010 Nov 2.
5. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ*. 1992 Feb 15;304(6824):405-412.
6. Jamerson K, Weber MA, Bakris GL, et al; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008 Dec 4; 359(23):2417-2428.
7. Leren P, Helgeland A. Coronary heart disease and treatment of hypertension. Some Oslo Study data. *Am J Med*. 1986 Feb 14;80(2A):3-6.
8. Wing LM, Reid CM, Ryan P, et al; Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting—enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003 Feb 13;348(7):583-592.
9. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet*. 2000 Jul 29; 356(9227):366-372; Erratum in: *Lancet*. 2000 Aug 5; 356(9228):514.
10. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. *JAMA*. 1979 Dec 7; 242(23):2562-2571.
11. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991 Jun 26; 265(24):3255-3264.
12. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002 Dec 18;288(23):2981-2997; Errata in: *JAMA*. 2003 Jan 8; 289(2):178. *JAMA*. 2004 May 12;291(18):2196.
13. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001 Sep 29;358(9287):1033-1041; Errata in: *Lancet*. 2001 Nov 3; 358(9292):1556. *Lancet*. 2002 Jun 15;359(9323):2120.
14. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007 Sep 8;370(9590):829-840.
15. Beckett NS, Peters R, Fletcher AE, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008 May 1;358(18):1887-1898; Epub 2008 Mar 31.
16. Elliott WJ, Grimm RH Jr. Using diuretics in practice—one opinion. *J Clin Hypertens (Greenwich)*. 2008 Nov;10(11):856-862.
17. Mitka M. Experts argue not all diuretics the same. *JAMA*. 2007 Jul 4; 298(1):31.
18. Cushman WC, Ford CE, Cutler JA, et al; ALLHAT Collaborative Research Group. Success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Clin Hypertens (Greenwich)*. 2002 Nov-Dec;4(6):393-404.
19. Kostis JB, Cabrera J, Cheng JQ, et al. Association between chlorthalidone treatment of systolic hypertension and long-term survival. *JAMA*. 2011 Dec 21;306(23):2588-2593.