Did all thiazides take undue credit of good work of chlorthalidone?

Diuretics have been used as antihypertensive agents since the advent of mercurial diuretics. However, resurrection of thiazides in treatment of hypertension began after the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial[10] which brought back diuretics to the forefront in Joint National Committee 7 (JNC 7) recommendations for hypertension.[11] ALLHAT showed that chlorthalidone as an antihypertensive drug was associated with fewer incidents of heart failure (HF) than amlopidine and fewer strokes than lisinopril. The secondary outcomes for amlopidine versus chlorthalidone were similar except for a higher 6-year rate of HF with amlopidine (10.2% vs. 7.7%; relative risk [RR], 1.38; 95% confidence interval [CI], 1.25–1.52). Comparing lisinopril versus chlorthalidone, lisinopril had higher 6-year rates of combined cardiovascular (CV) disease (33.3% vs. 30.9%; RR, 1.10; 95% CI, 1.05–1.16), stroke (6.3% vs. 5.6%; RR, 1.15; 95% CI, 1.02–1.30), and HF (8.7% vs. 7.7%; RR, 1.19; 95% CI, 1.07–1.31).[11] Diuretics were back with a bang! Barring the alpha-blocker doxazosin which had failed in the ALLHAT trial, diuretics were here to claim their justified place as antihypertensive drugs at par with the more fancied angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers and hitherto revered beta blockers.

Prologue to this was a dwindling interest in diuretics due to robust and scientific data that had started emerging for newer generation antihypertensive agents, suchs the data from the Heart Outcomes Prevention Evaluation (HOPE) trial supporting ramipril.[13] The potent calcium channel blocker amlopidine, without reflex tachycardia, was the new heartthrob among calcium channel blockers.[14] Prescriptions for good old diuretics were dwindling the world all over. However, diuretics were never evaluated before the ALLHAT era, unlike the newer molecules whose efficacy and safety were proven in well-designed randomized controlled trials such as HOPE. Diuretics needed a similar head on comparison data for their revival.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Hypertension in the Very Elderly Trial (HYVET) were like the long needed breather for diuretics though in a different perspective. ASCOT showed that the combination of ACE inhibitors with calcium channel blockers did better than a combination of a diuretic with atenolol. The study was stopped prematurely after 5.5 years’ median follow-up and accumulated a total 106,153 patient-years of data and evidence. Although not statistically significant, compared with the atenolol-based regimen, fewer individuals on the amlopidine-based regimen had a primary endpoint (unadjusted hazard ratio [HR] 0.90, \( P = 0.1052 \)) fatal and nonfatal stroke (HR 0.77, \( P = 0.0003 \)), total CV events and procedures (HR 0.84, \( P < 0.0001 \)), and all-cause mortality (HR 0.89, \( P = 0.025 \)). The incidence of developing diabetes was less in the amlopidine-based regimen (HR 0.70, \( P < 0.0001 \)).[15] Many ascribed the difference to a lower reduction in the latter combination but the “pro-diuretic” lobby realized that benefits of diuretics may be nullified by adding a beta blocker! It also made us ponder why what worked for chlorthalidone in ALLHAT did not work for bendroflumethiazide in ASCOT. Was there any difference among different molecules in the “diuretic class”? Was it probably the strength of the individual molecule rather than a class effect? The HYVET trial, however, continued to reinforce the strength and the merits of diuretics though the molecule evaluated here was indapamide. Pharmacologists ascribed the benefits in these two molecules to “pleiotropic effects” such as nitric oxide donor property and other similar effects.

Meanwhile, meta-analysis by Carlberg B et al.[6] about beta blockers had shown that atenolol as an antihypertensive agent was as good as placebo in terms of reduction of CV events. This pushed the beta blockers out of the league. The subsequent National Institute for Health and Care Excellence and British Hypertension Society guidelines excluded beta blockers as preferred choice of antihypertensive agents in patients without compelling indications such as ischemic heart disease or HF. These studies relegated the once favorite beta blockers to the fourth choice as antihypertensive drugs. Proponents of beta blockers, however, contented that it was a step brotherly approach to all beta blockers for the “sins” of one molecule viz., atenolol.

Something on the same lines meanwhile was developing for the diuretics. Going back and analyzing data for old generation diuretics from trials such as multiple risk factor intervention trial (MRFIT) and the Systolic Hypertension in the Elderly Program and Systolic Hypertension in Europe (SYST-EUR) studies, the results were yielding hitherto unknown information. Most of the good data existed with chlorthalidone and indapamide while all other thiazides were not that appealing. MRFIT stands out as one of the studies that compared chlorthalidone and hydrochlorothiazide (HCTZ).[7] Not only chlorthalidone did better in terms of event reduction as compared to hydrochlorothiazide but also the patients who switched from hydrochlorothiazide to chlorthalidone did better. Six years into the MRFIT trial, it was observed that in the nine clinics that predominately used HCTZ, mortality was 44% higher compared with the usual care group. The opposite was true in the six clinics that predominately used chlorthalidone. The MRFIT Data Safety Monitoring Board changed the protocol near the end of the trial to use chlorthalidone only. In the initial clinics that used HCTZ, the trend was reversed after the protocol was changed to chlorthalidone, and they then had a 28% lower risk (\( P = 0.04 \) for comparison of coronary heart disease mortality at the 2 time periods). It was concluded that one month of treatment with chlorthalidone added an additional day to the life span of the patient. Post-JNC 7 recommendations, it was hydrochlorothiazide that had taken most of the prescription boom that happened in the pharmaceutical industry, even though most of the data existed for chlorthalidone! It was time for resurrection for chlorthalidone to regain it’s well-deserved

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place. Most of the journals and guidelines favor allowing chlorthalidone, the place which has been so far been, perhaps wrongfully, accorded to hydrochlorothiazide.

A noteworthy outcome of these collective analyses and trials has been the attempt to reclassify thiazides as “thiazide-like” diuretics that include chlorthalidone and indapamide and the rest of the diuretics of this group as thiazides. The era of “thiazide-like diuretics” is here to stay as the pharmaceutical sales trends in the West show. Chlorthalidone may be the old wine in new bottle, but it does have the “kick”! Cynics might however say wait until a new trial or guideline emerges that changes the preferred “star drug.”

Kamal H. Sharma
Department of Cardiology, U.N. Mehta ICRC, B.J. Medical College, Ahmedabad, Gujarat, India
E-mail: kamalcardiodoc@gmail.com

References

1. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. 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;288:2981-97.
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. JAMA 2003;289:2560-72.
3. Sleight P. The HOPE study (Heart Outcomes Prevention Evaluation). J Renin Angiotensin Aldosterone Syst 2000;1:18-20.
4. Oparil S. Long-term morbidity and mortality trials with amloidipine. J Cardiovasc Pharmacol 1999;33 Suppl 2:S1-6.
5. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amloidipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. Lancet 2005;366:895-906.
6. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: Is it a wise choice? The Lancet 2004;364:1684-9.
7. Tziomalos K, Athyros VG, Mikhailidis DP, Karagiannis A. Hydrochlorothiazide vs. chlorthalidone as the optimal diuretic for the management of hypertension. Curr Pharm Des 2013;19:3766-72.

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How to cite this article: Sharma KH. Did all thiazides take undue credit of good work of chlorthalidone?. Indian J Pharmacol 2016;48:479-80.