JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 4, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.11.025

EDITORIAL COMMENT

Hydrochlorothiazide as the Diuretic of Choice for Hypertension

Time to Kick the Habit*

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Early cardiovascular (CV) outcome trials of patients with hypertension used high-dose thiazide diuretic agents, often 100 mg of hydrochlorothiazide or 50 to 100 mg of chlorthalidone (1-4). Although these studies showed consistently greater CV risk reduction versus placebo, the MRFIT (Multiple Risk Factor Intervention Trial) study, which used both hydrochlorothiazide (HCTZ) and chlorthalidone, noted a greater reduction in CV events in the chlorthalidone arm, such that all participants were eventually transitioned to this agent. Retrospective analysis subsequently confirmed that there were fewer CV events in those treated with chlorthalidone (5). A recent analysis of smaller studies demonstrated that chlorthalidone is more potent than HCTZ, resulting in a larger antihypertensive effect, but also in more hypokalemia (6).

Further differences between agents comes from ambulatory blood pressure monitoring (ABPM) data showing that chlorthalidone has preserved antihypertensive effects beyond 24 h, whereas HCTZ has antihypertensive effects for approximately 12 to 14 h (7,8). This is particularly important, as the highest rates of CV events are in the early morning hours, a time when blood pressure levels are at their highest and shorter-acting agents from the day prior are no longer effective (9).

Despite the overwhelming CV outcome data and established 24-h efficacy of chlorthalidone, prescription patterns are unchanged, with HCTZ remaining the drug of choice due to concerns regarding hypokalemia and greater likelihood of new-onset diabetes. This is despite long-term (>12-year) follow-up of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) cohort showing that new-onset diabetes and hypokalemia did not adversely affect outcomes of interest when treated appropriately (10).

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In this issue of the *Journal*, Pareek et al. (11) report the results of a randomized double-blind trial evaluating the efficacy of low-dose chlorthalidone (6.25 mg), HCTZ (12.5 mg), or a continuous-release HCTZ, known as HCTZ-CR (12.5 mg), over a 12-week period. The primary outcome was a change in 24-h ambulatory systolic and diastolic blood pressure between time zero and weeks 4 and 12. Patients were required to be younger than 65 years of age, have stage 1 hypertension (systolic pressure <160 mg Hg, diastolic pressure <100 mm Hg), and be free of additional comorbidities. Fifty-four patients were enrolled, with a mean office blood pressure of 149/93 mm Hg. At both 4 and 12 weeks, patients receiving chlorthalidone or HCTZ-CR experienced significant declines in blood pressure by ABPM, whereas those given the standard preparation HCTZ did not. At 12 weeks, patients treated with chlorthalidone or HCTZ-CR achieved blood pressure reductions of 11.1/7.8 mm Hg, and 10.3/8.2 mm Hg, respectively, versus 6.0/4.2 mm Hg in the HCTZ arm. Perhaps more notable were the differences in nocturnal pressures noted by ABPM between HCTZ and the other groups. The chlorthalidone and HCTZ-CR groups had mean nocturnal systolic pressure decreases of 10.2 and

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12.7 mm Hg, respectively; those receiving HCTZ had decreases in systolic blood pressure of 4.9 mm Hg. It is therefore the overnight and early morning blood pressure readings that illustrate the major advantage between these agents. Finally, although the criteria for adverse electrolyte or metabolic effects were not specifically defined, no episodes of hyponatremia were noted, and rates of hypokalemia and hyperuricemia were similar among treatment groups.

It could be argued that the superiority of chlorthalidone in CV outcome trials is not attributable to its potency but rather its duration of action given its extended effects on nocturnal blood pressure. As such, HCTZ-CR was able to achieve comparable antihypertensive effects in terms of blood pressure reduction and duration of effect. These long-acting preparations are crucial to blood pressure control during the early morning hours, when one is most vulnerable to CV events. That such low doses can achieve meaningful reductions in blood pressure is not surprising. A recent meta-analysis (12) notes that low-dose administration typically captures approximately 75% of the antihypertensive efficacy of full-dose therapy, while provoking only 25% of the adverse events. Although this trial may appear to reflect a lower rate of side effects, specifically the absence of hyponatremia, the trial duration was short, the study was underpowered to detect this outcome, and those at highest risk, that is, people older than 65 years of age, were excluded.

The larger question is, are these data generalizable to a broader population? Although the pharmacology and blood pressure-lowering effects are indisputable, the study design has limitations. First, only one-third of those screened were enrolled, suggesting that just a fraction of the patients seen on a daily basis would fit the focused study criteria, namely the exclusion of those with any additional comorbidities or an age in excess of 65 years. Additionally, because the study was conducted in a Southeast Asian country, it remains unclear whether the results can be extrapolated to those on Western diets or of other ethnicities. Finally, given the small number of patients per arm, the standard deviation around a given reduction in pressure was extremely wide, suggesting that the true effect in a broader population may be markedly different.

In conclusion, the clear message is that a low dose of a long-acting diuretic therapy can have a meaningful impact on the management of hypertension and on CV outcomes.

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KEY WORDS antihypertensive agents, blood pressure, outcomes