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Amanda Amy Diep

University of the Pacific, a.amy.diep@gmail.com

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Is more always better? Efficacy of HCTZ, low versus high dose therapy in dual combination treatment for hypertension.

By

Amanda Amy Diep

Capstone Project

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Introduction

The silent killer, hypertension (HTN), impacts about 1 in 3 U.S. adults, contributing to roughly 1,000 deaths per day in the U.S., and increases healthcare costs for HTN patients by three times compared to costs for patients without HTN.^{1,2} High blood pressure (BP) in the early 1900s was thought to be a consequence of age and not a risk factor that needed controlling. Now, it is well known that high BP is associated with greater incidence of mortality.³ It increases a person's risk for a number of life-threatening conditions, such as ischemic heart disease, stroke, heart failure, atherosclerosis, and renal insufficiency. Furthermore, only about 54% of U.S. patients with HTN have their BPs under control.⁴ As such, health authorities and clinicians continue to research a means by which patients can achieve better control of this disease. Improved control of this disease is evidenced by reductions in BP values, usually seen after lifestyle modifications and/or pharmacological therapies. Over the years, the Joint National Committee (JNC) has redefined control, but in its most recent guidelines, JNC 7 classified BP into four classes⁵:

BP Classification	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 HTN	140-159	or 90-99
Stage 2 HTN	≥160	or ≥100

Adapted from JNC 7 Express: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD: U.S. Dept. of Health and Human Services; 2003.

In addition, JNC categorized BP goals based on patient age and comorbidities. For patients aged 60 and older, who do not have co-existing diabetes or chronic kidney disease (CKD), the BP goal is <150/90 mmHg.⁶ As for patients aged 18-59 without co-existing major

comorbidities, and for patients aged 60 and older with diabetes and/or CKD, the BP goal is <140/90 mmHg.

In order to achieve these BP goals, the guidelines recommend four different drug classes as first-line treatment for HTN: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide-type diuretics.⁶ In many cases, patients will require a minimum of two antihypertensive drugs for BP control.⁵

Currently, 1 in 5 U.S. adults are not aware that they have HTN; thus, a minimum of 20% of patients have BPs that are not at goal.⁷ With such a large number of patients untreated and uncontrolled, efforts have been made to improve patient attainment of these BP goals. Single-pill fixed-dose combination drugs were made available for this purpose. This option reduces medical costs for patients, increases medication compliance, and provides greater therapeutic results. Looking at trends for fixed-dose combination antihypertensive therapy, a commonly used formulation is a thiazide diuretic combined with an ARB.⁸

Per the European Society of Hypertension-European Society of Cardiology guidelines, agents used in combination therapy are more effective when they have complementary mechanisms of action, such as those that occur between a thiazide and an ARB.⁹ While a thiazide works in the kidney to inhibit sodium reabsorption and increase sodium and water excretion, an ARB blocks angiotensin II receptor effects on cells. ARBs block the vasoconstriction and aldosterone-secretion effects of angiotensin II, consequently inhibiting reabsorption of sodium and water at the distal tubules of the kidneys.^{10,11} These two drug classes work in conjunction to ultimately lower BP. While the current guidelines suggest that

most patients with uncontrolled BP will require two antihypertensive drugs, the next questions to answer are how much of each drug is needed and what numerical drop in BP is required for an effective combination. The dose-dependent side effects of these drugs should also be considered. In particular, some providers find no benefit in treating patients with the lowest dose of hydrochlorothiazide (HCTZ), a common antihypertensive thiazide currently used in practice, and instead start treatment with a moderate dose of HCTZ. On the contrary, some providers find there is no difference in BP lowering effects when comparing low versus moderate HCTZ dosing. This anecdotal information poses the question of whether BP is lowered more effectively with 25 mg of HCTZ compared to 12.5 mg of HCTZ, when used in dual therapy with an ARB, over a minimum course of 8 weeks.

Discussion

A comprehensive literature review was done to evaluate the BP lowering effects of low versus high dose HCTZ in combination therapy, specifically, when HCTZ is combined with an ARB. Several clinical trials and pooled analyses were found that addressed this comparison.

In a phase III, randomized, double-blinded trial by Rump *et al.*⁹, the efficacy and tolerability of HCTZ 12.5 mg versus 25 mg in dual antihypertensive therapy was examined. This 16-week study had two phases during which all BP measurements were made using a standardized sphygmomanometer and taken at the trough of the medication therapeutic window. All patients were allowed to rest for at least 10 minutes prior to having their BP measurements taken. During phase I of the trial, week 0 to week 8, patients who failed to achieve adequate BP control on olmesartan (OM) monotherapy were entered into phase II of the trial and randomized into 1 of 4 groups: OM 40 mg, OM/HCTZ 20/12.5 mg, OM/HCTZ

40/12.5 mg, and OM/HCTZ 40/25 mg. After an additional 8 weeks of dual therapy, results revealed that the addition of HCTZ showed statistically significantly larger BP reductions versus monotherapy OM and that these reductions were dose-dependent. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) reductions were greater in the OM/HCTZ 40/25 mg versus 40/12.5 mg group. The OM/HCTZ 40/25 mmHg group showed the greatest number of patients achieving target BPs, followed by the OM/HCTZ 40/12.5 mmHg group. In both groups, the onset of efficacy was seen after 4 weeks of dual therapy, with a majority of the SBP and DBP reductions seen by 8 weeks of dual therapy. When evaluating safety and tolerability, the occurrence of treatment-emergent adverse events was comparable across all treatment groups. Specifically, however, metabolic and nutritional related adverse events were more commonly reported in the OM/HCTZ 40/25 mg group versus the 40/12.5 mg group. More importantly, in this large randomized study, patients with stage 2 HTN had the greatest SBP and DBP reductions with the OM/HCTZ 40/25 mg combination group. However, these BP reductions were only a few mmHg greater than those achieved by the group taking OM/HCTZ 40/12.5 mg. In addition, the sample size in the OM/HCTZ 40/25 mg group was nearly half the size of the OM/HCTZ 40/12.5 mg group, which potentially underestimates the overall rate of adverse events related to the higher dose group. Overall, this study suggested that the 25 mg HCTZ group had greater efficacy in BP reduction compared to the 12.5 mg HCTZ group when used in combination with an ARB. Nevertheless, its results were limited by the much smaller sample size of the higher dose HCTZ group compared to the lower dose HCTZ group.

Shortly after the Rump *et al.*⁹ trial results were published, Rosenbaum *et al.*¹² conducted a pooled analysis that included two phase III, randomized, double-blinded trials, one of which

was Rump's study. In the pooled analysis, data were taken from two similarly designed studies evaluating OM/HCTZ combination therapy at various doses versus OM monotherapy. Evidence from this analysis revealed that although all patients on combination therapy achieved greater BP reductions compared to OM monotherapy, the OM/HCTZ 20/25 mg and 40/25 mg groups achieved the greatest reductions in both SBP and DBP. Both of these reductions which were statistically significant. As for medication tolerability and safety, a lower incidence of treatment-emergent adverse events, all of which were considered drug unrelated, were associated with a lower dose of HCTZ. The authors of this pooled analysis concluded that doubling the dose of HCTZ in combination therapy allowed for greater antihypertensive effects, thus supporting the use of HCTZ 25 mg over 12.5 mg. The authors' conclusions are further strengthened as they are consistent with the current JNC treatment guidelines, which recommend add-on therapy (addition of a second drug) instead of increasing a monotherapy dose.

In 2016, a separate investigation by Rump *et al.*¹³ (a phase III randomized, parallel-group trial), revealed data that supported the addition of HCTZ to dual therapy OM and amlodipine. In this study, patients were on dual antihypertensive therapy for 8 weeks, during which those patients with inadequate BP control by week 8 were then randomized into 1 of 3 groups. Patients were either continued on the same dual therapy or had HCTZ 12.5 mg or 25 mg added to their regimen. Similarly, as performed in the trials discussed above, an average of 3 BP measurements were recorded in this study. Compared to the dual therapy OM and amlodipine group, the triple therapy group with HCTZ 25 mg was the only group that achieved statistically significant BP reductions. However, both low and high dose HCTZ groups achieved target BP goals and greatest seated BP reductions by week 16. Between the HCTZ groups, the reductions

in systolic and diastolic BPs were comparable. When BPs were measured by ambulatory-monitoring, a greater percentage of patients in the low dose HCTZ group reached their ambulatory BP goal compared to the high dose HCTZ group, despite both groups having similar reductions in BP. Unlike the prior studies, the Rump *et al.*¹³ 2016 study reported that the number of treatment-emergent adverse events were comparable among all groups, including between both triple therapy groups. Regardless, these study results favor the use of higher dose HCTZ in combination antihypertensive therapy. This study's strengths are its large sample size and randomization design, which more accurately reflect real-life practices. Its weakness, however, is its relatively short duration, which does not provide long term data on the antihypertensive effects of these medications.

In contrast to the above studies, a large, open-label, non-interventional, observation study by Bramlage *et al.*¹⁴ revealed no statistically significant differences in BP reduction between OM/HCTZ 40/12.5 mg and 40/25 mg doses. Both treatment groups had statistically significant BP reductions compared to baseline. Similar to findings observed in the Rump *et al.*⁹ 2010 study, a greater percentage of patients in the HCTZ 12.5 mg group achieved target BP by the end of the study observation period. However, the limitations of this observational study are that it lacks a control group, randomization, and information on medication compliance. Nevertheless, the study design reflects real-life situations, such as variations in daily medication dose times and in medication compliance. Moreover, the data revealed no significant differences in efficacy between low and high dose HCTZ antihypertensive combination therapy.

Lastly, a retrospective study by Neldam *et al.*¹⁵ found that in patients with both HTN and moderate to severe renal impairment, some patients observed better BP outcomes with low

dose HCTZ combination therapy. This particular study reviewed pooled data from seven independent randomized and double-blinded trials, comparing effects of monotherapy telmisartan with placebo versus combination therapy telmisartan with HCTZ 12.5 mg or 25 mg. Specifically, all baseline SBP groups, except those groups with SBPs from 140 to 159 mmHg or ≥ 170 mmHg, receiving the T80/H25 treatment showed smaller SBP reductions from baseline compared to those in the T80/H12.5 group. Similarly, patients in the T80/H25 group with baseline DBPs ≥ 105 mmHg, had smaller BP reductions when compared to the T80/H12.5 treatment group. Overall, the study results suggest that in some cases, low dose HCTZ has better efficacy compared to high dose HCTZ in dual antihypertensive therapy. The reasons for these findings are not apparent, however, they may have resulted from either the small T80/H12.5 group sample size or the post hoc analysis study design.

In summary, most of the evidence in the above studies suggests that HCTZ 25 mg used in combination therapy with an ARB has greater BP lowering effects than HCTZ 12.5 mg in combination with the same dose of the ARB. Nonetheless, patients in the HCTZ 12.5 mg group still exhibited great reductions in BP when compared to monotherapy (ARB alone) or placebo groups. In many instances, the differences in BP reduction between the groups receiving 12.5 mg and 25 mg only varied by a few mmHg. Though most of the studies showed superiority of combinations with 25 mg versus 12.5 mg of HCTZ, some of the studies showed a greater percentage of patients achieved target BP goals on 12.5 mg versus 25 mg of HCTZ. However, the reason for this discrepancy was not explained. Lastly, a majority of the studies found that both HCTZ doses were well tolerated, with comparable treatment-emergent adverse events.

Conclusion

The evidence in the currently available literature suggests that the combination of an ARB with HCTZ at a 25 mg dose compared to a 12.5 mg dose is more effective in lowering BPs from their baseline high values. However, since subjects on 12.5 mg HCTZ combination therapy reached their BP goals more frequently than the 25 mg dose group, the overall significance of the superiority of the 25 mg dose is lowered, especially since side effects may have been less frequent in the 12.5 mg HCTZ group. In view of these findings, patients may find the same benefit of taking 12.5 mg HCTZ as with 25 mg HCTZ in combination therapy with an ARB. Therefore, current evidence does not support changing today's practice of using one particular dose of HCTZ over the other when used in combination with an ARB for HTN treatment. Long-term studies exploring the antihypertensive effects of different doses of HCTZ would be helpful for determining the therapeutic value of each mmHg reduction in BP, and how each mmHg reduction in BP effects morbidity and mortality in patients with HTN. If a specific minimum mmHg reduction in BP is shown to confer maximal long-term therapeutic benefits, of which both low and high doses of HCTZ can achieve, then selecting a lower dose of HCTZ in combination antihypertensive therapy can be justified.

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