

Hypertension Pharmacotherapy: Practice Changing Updates in the Management of Hypertension

Theunis van Zyl, MD Candidate (2018) ¹

¹Schulich School of Medicine and Dentistry, Western University, London, ON

Background

Hypertension affects approximately 23% of Canadians, with prevalence estimated to continue increasing.^{1,2} A third of patients with hypertension are uncontrolled, having blood pressures (BP) above 140/90 due to either lack of treatment or undertreatment.² This is important as hypertension is a major burden on the healthcare system, consuming \$13.9 billion CAD dollars or 10.2% of Canada's healthcare budget.¹ Given these trends, proper treatment and control of hypertension is paramount.

In an effort to combat the disease, Hypertension Canada releases annual guidelines (CHEP) on the diagnosis, prevention, and treatment of hypertension, with the most recent update in 2017 recommending numerous changes to the management of hypertension.³

Thiazide Diuretics: Why Do We Use What We Use?

In hypertension pharmacotherapy, few drugs are more well-known than thiazide diuretics, with hydrochlorothiazide (HCTZ) being a staple for primary care providers. The 2017 Canada Hypertension guidelines update recommends multiple first-line treatments, including ACE-inhibitors (ACE-I), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide-like diuretics.³ It recommends that the preferred first-line treatment should be a thiazide-like diuretic.³ This is hardly news to most primary care providers.

The recommendation of thiazide-like diuretics as first choice is based on the ALLHAT trial. This double-blind, randomized control trial (RCT) of over 33,000 patients with hypertension compared treatment with chlorthalidone, a thiazide-like diuretic, to amlodipine, a CCB, or lisinopril, an ACE-I.⁴ The trial followed patients for 4-8 years and compared adverse cardiac events and mortality.⁴ ALLHAT found that thiazide-like diuretics resulted in a 25% lower risk of heart failure and better BP control compared to CCB and ACE-I.⁴ Given these results and the lower price of thiazides, ALLHAT and the CHEP guidelines concluded that thiazide-like diuretics should be the preferred first line treatment of hypertension.^{3,4}

Thiazides, Are They All The Same?

Most providers assume all thiazide diuretics are, if not identical, very substitutable. However, there are two types of thiazide diuretics: thiazide-type diuretics, such as HCTZ, which are shorter acting with 12-hour efficacy, and thiazide-like diuretics, such as chlorthalidone and indapamide, which are longer acting with 24-hour efficacy.⁵ While similar, they are far from identical. When examining physician prescribing habits, thiazide-type HCTZ is significantly favoured over longer acting, thiazide-like chlorthalidone, likely secondary to cost and familiarity.⁶ Twenty-two percent of all patients treated for hypertension in the United States receive HCTZ, while only 1% receive chlorthalidone.⁶

As mentioned earlier, however, thiazide diuretics are not all identical and differ in their length of action.⁽⁵⁾ The recommendation of thiazides as first-line treatment for hypertension was based on the ALLHAT trial, which specifically studied chlorthalidone and not HCTZ.⁽⁴⁾ When read closely, CHEP guidelines specifically recommend thiazide-like diuretics (chlorthalidone) as first line and not thiazide-type (HCTZ).⁽³⁾ If this is the case, then why are so many physicians overwhelmingly prescribing HCTZ? Is there even a clinically significant difference between the two thiazides?

HCTZ vs. Chlorthalidone

The HCTZ vs. chlorthalidone question was recently addressed in a meta-analysis of 21 RCTs by Engberink et al.⁷ While both decreased adverse cardiac events compared to placebo, only chlorthalidone was superior to other anti-hypertensives (HCTZ, CCB, ACE-I) in decreasing adverse cardiac events.⁷ Even with similar BP reductions between treatment groups, Chlorthalidone resulted in a 12% reduction in adverse cardiac events and a 21% reduction in heart failure compared to HCTZ.⁷ Chlorthalidone was found to have superior 24 hour BP control, likely due to its longer length of action, which was theorized to account for the lower rates of adverse cardiac events and heart failure.⁷ Both HCTZ and chlorthalidone had similar rates of side effects compared to each other and other anti-hypertensives.⁷

The CHEP guidelines specifically recommends thiazide-like diuretics (chlorthalidone) as first line and not thiazide-type (HCTZ).³ Based on literature, starting new hypertensive patients on HCTZ as a first line is an inferior treatment.⁷ As mentioned earlier, chlorthalidone has lower rates of adverse cardiac events, similar rates of side effects, and, while more expensive than HCTZ, it is still a relatively affordable medication.⁷ If a

Corresponding Author:
Theunis van Zyl
theunis9@hotmail.com

patient is currently well controlled on HCTZ, the CHEP guidelines recommends continuing with the treatment.³ However, next time you consider starting a patient on a thiazide diuretic for hypertension, remember to use chlorthalidone.

Combination Therapy

Another major addition in the 2017 update to the CHEP guidelines is the recommendation for single-pill combination (SPC) therapy as a first line treatment for hypertension.³ Combination therapy is the combination of two anti-hypertensives, such as an ACE-I and CCB, also available in a single pill formulation. Evidence suggests lower doses of two anti-hypertensives results in better BP control and fewer side effects than a larger dose of one anti-hypertensives.⁸

One recent meta-analysis examined 42 RCTs comparing doubling doses of monotherapy vs adding a second anti-hypertensive at initial doses (combo therapy) in management of hypertension.⁸ The study reported significantly larger decreases in BP and fewer side effects for combo therapy compared to higher doses of monotherapy.⁸ Compared to placebo, the respective reduction of systolic BP was 5 mmHg with monotherapy, 6 mmHg with double dose monotherapy, and 9 mmHg with combo therapy of two anti-hypertensives at initial monotherapy dose levels.⁸ This was true across all classes of anti-hypertensives.⁸

Combo therapy was also significantly more effective at preventing strokes and adverse cardiac events than double dose monotherapy when treating hypertension.⁸ Compared to placebo, the respective reduction in cardiac events and stroke was 25% and 35% with monotherapy, 29% and 40% with double dose monotherapy, and 40% and 54% with combo therapy. The evidence suggests that patients who fail monotherapy be trialed on combination therapy of two anti-hypertensives at initial doses, and not on increased doses of monotherapy given the preventative benefits and lower rate of side effects.

Initial Combo Therapy vs. Step-Up Therapy

While it is well known that combo therapy can improve control after stepping up from monotherapy, recent evidence has led the 2017 CHEP guidelines to recommend initial treatment with combo therapy.³ Two studies compared initial combo therapy to step-up therapy and found that patients initially treated with combo therapy were more likely to reach BP control at 6 months. Furthermore, these patients had a 34% relative risk reduction (RRR) in adverse cardiac events or death.^{9,10} In fact, patients treated with monotherapy who stepped up to combo therapy were found to have no difference in incidence of adverse cardiac events compare to treating solely with monotherapy.¹⁰

The study suggested that initial combo therapy is superior as BP reduction is achieved faster resulting in reduced rates of cardiac events.¹⁰ Also, initial combo therapy reduced healthcare resource use, with patients requiring fewer emergency room visits, hospitalizations, and outpatient visits per year.¹⁰ While these data are only observational, initial combo therapy is a reasonable choice supported by the CHEP 2017 guideline update.³

Single Pill Combo Or Two Separate Pills?

When considering starting a hypertensive patient on initial combo therapy, a provider may wonder if a SPC is necessary given their often prohibitive cost? Why not give two anti-hypertensives at once?

With hypertension being asymptomatic, treatment adherence is poor at 67%, and decreases with increasing number of pills and doses.^{11,12} The effect of SPC therapy on adherence in hypertension was evaluated in two meta-analyses by Sherrill et al and Gupta et al.^{13,14} SPC was compared to dual pill therapy for hypertension and was found to increase adherence by 8 to 29%, as well as increase persistence with therapy by 29%.^{13,14} Better adherence should improve health and SPCs were associated with \$2000 lower healthcare costs annually compared to dual pill therapy when treating hypertension.¹³

Keeping in mind that treating hypertension with initial combo therapy is superior to both monotherapy and stepping-up therapy (from mono to combo therapy),¹⁰ consider the added benefits in adherence when using a single pill treatment.¹³ If a patient can afford it, physicians should prescribe SPC therapy as initial, first-line treatment for hypertension.

Which Single Pill Combo To Choose?

With multiple SPC options, including ACE-I/CCBs and ACE-I/diuretics, it may not be clear with which medication to start. However, ACCOMPLISH, a large multi-center RCT of over 11,500 patients was conducted to partially answer this question.¹⁵ It compared treatment of hypertension with an ACE-I/CCB to ACE-I/diuretic, looking specifically at benazepril/amlodipine vs. benazepril/HCTZ.¹⁵ In the study, the ACE-I/CCB combo had a 17% RRR and 1.7% absolute risk reduction (ARR) in adverse cardiac events, and a 21% RRR and 1.3% ARR in death from cardiac causes compared to an ACE-I/diuretic.¹⁵

Based on this data, a good choice for initial combo therapy in hypertension would be an ACE-I/CCB combo. The 2017 CHEP guideline update also recommends starting with an ACE-I/CCB when choosing a combo therapy.³

Summary

In summary, there are two major updates to take away from the 2017 CHEP guidelines with regards to pharmacotherapy for hypertension. First, chlorthalidone should be the first line treatment when considering diuretics, not HCTZ. Chlorthalidone has demonstrated superior BP control and lower rates of adverse cardiac events compared to HCTZ. If patients still have difficulty controlling their BP after treatment with a thiazide-like diuretic, it is recommended to change their medication to an ACE-I/CCB combo rather than simply increasing their chlorthalidone dose. Combo therapy is significantly more effective at reducing BP and preventing strokes and adverse cardiac events than increasing the dose of a single anti-hypertensive medication.

Finally, initial ACE-I/CCB single pill combo therapy is now also considered a first-line treatment, as it results in better rates of compliance and BP control and lower rates of adverse cardiac events compared to initial monotherapy stepped up to combo therapy. Initial ACE-I/CCB combo therapy is an ex-

cellent choice in patients unlikely to get adequate BP reduction with a single medication.

References

- Weaver CG, Clement FM, Campbell NRC, James MT, Klarenbach SW, Hemmelgarn BR, et al. Healthcare costs attributable to hypertension: Canadian population-based cohort study. *Hypertension* [Internet]. 2015;66(3):502–8. Available from: <http://hyper.ahajournals.org/content/66/3/502.short>
- Padwal RS, Bienek A, McAlister FA, Campbell NRC. Epidemiology of hypertension in Canada: an update. *Can J Cardiol* [Internet]. Canadian Cardiovascular Society; 2016;32(5):687–94. Available from: [http://www.onlinecjc.ca/article/S0828-282X\(15\)01306-9/abstract](http://www.onlinecjc.ca/article/S0828-282X(15)01306-9/abstract)
- Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. *Can J Cardiol* [Internet]. 2017;33(5):557–76. Available from: [http://www.onlinecjc.ca/article/S0828-282X\(17\)30110-1/fulltext](http://www.onlinecjc.ca/article/S0828-282X(17)30110-1/fulltext)
- The 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). *J Am Med Assoc* [Internet]. 2002;288(23):2981–97. Available from: <https://jamanetwork.com/journals/jama/fullarticle/195626>
- Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension* [Internet]. 2004;43(1):4–9. Available from: <http://hyper.ahajournals.org/content/43/1/4>
- Shah SJ, Stafford RS. Current trends of hypertension treatment in the United States. *Am J Hypertens* [Internet]. 2017;30(10):1008–14. Available from: <https://academic.oup.com/ajh/article/30/10/1008/3844728>
- Engberink RHGO, Frenkel WJ, Bogaard B van den, Brewster LM, Vogt L, van den Born B-JH. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: systematic review and meta-analysis [Internet]. *Hypertension*. 2015. 622-628 p. Available from: <http://hyper.ahajournals.org/content/early/2015/03/02/HYPERTENSIO-NAHA.114.05122.short>
- Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med* [Internet]. Elsevier Inc.; 2009;122(3):290–300. Available from: [http://www.amjmed.com/article/S0002-9343\(08\)00992-3/abstract](http://www.amjmed.com/article/S0002-9343(08)00992-3/abstract)
- Corrao G, Nicotra F, Parodi A, Zambon A, Heiman F, Merlino L, et al. Cardiovascular protection by initial and subsequent combination of antihypertensive drugs in daily life practice. *Hypertension* [Internet]. 2011;58(4):566–72. Available from: <http://hyper.ahajournals.org/user/logout?current=node/250932>
- Gradman AH, Parisé H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: A matched cohort study. *Hypertension* [Internet]. 2013;61(2):309–18. Available from: <http://hyper.ahajournals.org/content/61/2/309.short>
- Claxton AJ, Cramer J, Pierce C. A systematic review of the association between dose regimens and medication compliances. *Clin Ther* [Internet]. 2001;23(8):1296–310. Available from: [http://www.clinicaltherapeutics.com/article/S0149-2918\(01\)80109-0/abstract](http://www.clinicaltherapeutics.com/article/S0149-2918(01)80109-0/abstract)
- Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int J Clin Pract* [Internet]. 2008;62(1):76–87. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1742-1241.2007.01630.x>
- Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. *J Clin Hypertens* [Internet]. 2011;13(12):898–909. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1751-7176.2011.00550.x>
- Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* [Internet]. 2010;55(2):399–407. Available from: <http://hyper.ahajournals.org/content/55/2/399.short>
- Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* [Internet]. 2008;359(23):2417–28. Available from: <http://www.nejm.org/doi/full/10.1056/nejmoa0806182>