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Dual Therapy Recommendations in Hypertension: Progress with a Single-pill Combination

Alliston - In recent years, increased awareness of blood pressure (BP) control has resulted in better treatment with multiple drug strategies. However, it has become increasingly difficult for physicians to find the optimal anti-hypertensive treatment combination and to also encourage patient adherence. This is especially true in patients with comorbidities requiring additional medications. The 2011 Canadian Hypertension Education Program proposes a guideline to simplify the choice of combination strategies, but the difficulty of adherence with multi-pill treatment remains. The first single-pill combination (SPC) of an angiotensin receptor blocker and a calcium channel blocker has been approved in Canada. Both agents have proven effective in reducing BP. The SPC of both agents is regarded as a means to simplify treatment decision-making, increase adherence and maximize the likelihood of achieving target BP goals with fewer side effects in a cost-effective fashion.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

As discussed here at the CHC by Dr. George Dresser, Associate Professor of Medicine, University of Western Ontario, London, most patients require at least 2 drugs to achieve blood pressure (BP) control and very often 3. Deciding which drugs to choose and in which order can be difficult: Dr. Dresser calculated over 200,000 initial choices based on the Ontario drug plan alone. Too many choices can actually become a barrier to therapeutic decision-making as it creates confusion and can lead to "therapeutic inertia." Then there is "therapeutic turbulence." "Patients who experience frequent changes in drug therapy are less likely to persist with therapy, so changing drugs frequently is not good, either," Dr. Dresser told delegates.

Rationale for Combination Therapy

It has been shown that using 2 BP-lowering agents at low doses produces a greater reduction in BP than uptitrating a single drug. When used together, they can often eliminate side effects, such as peripheral edema observed with the calcium channel blocker (CCB) amlodipine and hypokalemia with the thiazide diuretics. For example, combining a renin-angiotensin system (RAS) inhibitor with amlodipine can attenuate the risk of peripheral edema.

One strategy to solve both therapeutic inertia and therapeutic turbulence is a single-pill combination (SPC) of a RAS inhibitor with a CCB. This SPC for the initial control of hypertension, especially when BP is significantly elevated over target levels or patients are high-risk, allows for a specific simplified drug choice and has proven effective.

For example, in the TEAMSTA diabetes study, the once-daily combination of the angiotensin receptor blocker (ARB) telmisartan 80 mg and the CCB amlodipine 10 mg reduced systolic BP by 29 mm Hg vs. 22.9 mm Hg for the CCB alone and more patients on the SPC achieved target BP goals than those on monotherapy (*J Hypertens* 2011;29(e-suppl A);7A.09).

If physicians are hesitant to start patients on full-dose SPC, a lower dose can first be administered. "Even if you start with a low dose of an SPC, you can easily uptitrate; you are not changing what the patient is getting, they simply need more of it, and I think this gets away from creating turbulence on the part of the patient," Dr. Dresser explained. Should a third drug be required, that choice can again be fairly straightforward. With initial treatment of the telmisartan/amlodipine SPC, choosing the long-acting diuretic chlorthalidone will afford BP protection for up to 72 hours with chronic dosing as third drug. Patients who are on either monotherapy, or no therapy, and who present with a systolic BP of ≥160 mm Hg will likely do better with an SPC than with sequential monotherapy. "If you combine chlorthalidone with this particular SPC, you will have a wonderful 3-drug cocktail that is very effective and patients' [BP]… will be well controlled," Dr. Dresser concluded.

Re-evaluating Diuretics with RAS Inhibitors

It has generally been accepted that RAS inhibitors, including ACE inhibitors and ARBs, must be administered with a diuretic to maximize effectiveness. According to Dr. Ellen Burgess, Professor of Nephrology and Endocrinology, University of Calgary, Alberta, this is not so. In fact, recent Canadian Hypertension Education Program (CHEP) guidelines suggest that in select high-risk patients, combining an ACE inhibitor with a long-acting dihydropyridine (CCB) is preferable to combining it with a thiazide or thiazide-like diuretic.

This recommendation was based on the ACCOMPLISH study in which 2 fixed-dose, ACE inhibitor-based combinations were compared in a total of 11,506 hypertensive patients at high risk for cardiovascular (CV) events (*J Am Coll Cardiol* 2010;56:77-85). BP control rates were similar at approximately 75% in the benazepril/amlopidine group and 72% in the benazepril/hydrochlorothiazide (HCTZ) group. "When we

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look at event rates, however, there was a healthy and significant 20% relative risk reduction between the 2 groups in favour of the ACE inhibitor/CCB combination (*P*=0.0002)," Dr. Burgess told CHC delegates.

This reduction was not only in "soft end points," such as hospitalization for angina and revascularization, but also in hard end points, including death from CV causes, nonfatal myocardial infarction (MI) and nonfatal stroke. "Not only does the ACCOMPLISH study show that this combination (i.e. a CCB and a RAS inhibitor) will reduce hospitalization, but we might [also] end up reducing hard events. What may be even more important is that we may also reduce plaque progression, not just in the coronaries but in every artery," Dr. Burgess emphasized. She noted that a large volume of earlier work demonstrated that as a class, the CCBs slowed atherosclerotic disease progression and even prevented atherosclerosis in animal models.

ALLHAT and STAR Key Points

Clinical investigator Dr. Phil McFarlane, St. Michael's Hospital, Toronto, Ontario, countered that not all thiazide diuretics are the same and that chlorthalidone, which many argue is not a thiazide diuretic, is more effective than HCTZ and, indeed, is equal to amlodipine in efficacy. In ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), for example, chlorthalidone provided the same degree of protection against CV events as amlodipine after a mean follow-up of 4.9 years (*JAMA* 2002;288:2981-97). On the other hand, more patients on chlorthalidone in ALLHAT developed diabetes than those on the CCB amlodipine or the ACE inhibitor lisinopril.

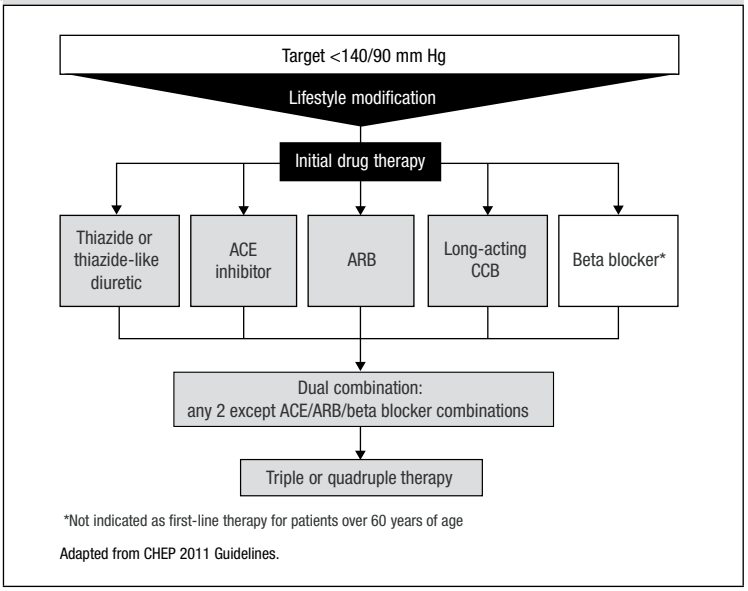
Further advocating combination therapy, in the STAR study (Study of Trandolapril/Verapamil SR and Insulin Resistance), the ACE inhibitor/CCB combination achieved equal BP control to that provided by an ARB/thiazide diuretic in metabolic syndrome patients with impaired glucose tolerance, and it was not associated with worsening of glucose values (*Diabetes Care* 2006;29:2592-7).

Pill Burden

As noted by Dr. Raj Padwal, Associate Professor of Internal Medicine, University of Alberta, Edmonton, obese patients remain a challenge in the treatment of hypertension. Increases in sympathetic nervous system activity fuelled by the release of leptin from adipose tissue drives the hypertensive process in the obese and makes it very difficult for them to sustain any initial gains from lifestyle interventions over time, he explained.

This means that most obese hypertensive patients will require multiple drug classes for BP control on top of an already considerable pill burden for frequent comorbidities. "A lot of the patients we see have refractory hypertension and they are already on ASA, a number of anti-diabetic agents and now, you are going to add multiple antihypertensive agents. [Consequently], adherence becomes a huge problem for them because of drug burden," Dr. Padwal stated. In this situation, SPC is one way to help decrease pill burden. "Adherence is directly related to cost as well, and since a lot of our patients really struggle to make ends meet, this new (telmisartan/amlodipine) SPC costs about one-third of the combined price of the component drugs," Dr. Padwal told delegates.

Figure 1. **Antihypertensive Therapy: General CHEP Recommendations**



Summary

CHEP guidelines suggest that 2 first-line agents can be considered as initial treatment of hypertension if BP is above target (systolic 20 mm Hg, diastolic 10 mm Hg). Based on earlier studies showing that CCBs slow atherosclerotic disease progression and the proven efficacy of ARBs, the newly approved telmisartan/amlodipine once-daily SPC provides a simple new option to treat hypertension, is cost-effective and encourages patient adherence. □

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