Commentary in Support of a Highly Effective Hypertension Treatment Algorithm

All of the evidence-based national guidelines for the treatment of hypertension present alternative first line drug treatment classes, rather than specific drugs (1-3). Many patients with hypertension have comorbidities representing compelling indications for specific drug classes (1). Further complicating the primary care landscape is the presence of treatment options based on race, region of origin, and age (2). In the absence of evidence from the clinical trials, these treatment algorithms generally add on alternative first line classes that were not selected in the first round. With so many acceptable drug sequence options, what is a busy clinician expected to do?

The tie breaker for a plethora of treatment options should be simplicity and successful implementation. In publicly reported United States Medicare population HEDIS 2012 comparisons of 261 health plans representing 2011 data, Kaiser Permanente (KP) geographical regions accounted for seven of the top ten performers (4). KP regions are achieving greater than 85% hypertension control for a patient population of approximately 1.5 million adults, and 88% for members with hypertension age 65 to 85 (4). Within the context of many chronic disease conditions, each demanding priority, a simple hypertension treatment protocol promotes performance (Figure).

In six steps, three hypertension drugs are maximized. Spironolactone is the preferred fourth drug within specified safety parameters for primary care providers. Within KP, uptitrations occur at 2 to 4 week intervals with no copayment walk-in blood pressure checks by Medical Assistants expanding the medical home and improving access.

Stepped Care Combination Therapy Promotes More Rapid Control and Improves Access

The Simplified Treatment Intervention to Control Hypertension Study (STITCH) was a cluster randomization trial demonstrating improved six month hypertension control with a fixed dose combination scheme compared to traditional stepwise monotherapy (5). Reviews have enumerated the benefits of combination therapy including balanced and complementary physiologic mechanisms (6). The vast majority of patients require more than a single agent to control hypertension. A combination of a thiazide diuretic and an angiotensin converting enzyme (ACE) inhibitor balance opposing potassium effects. Use of an ACE inhibitor mitigates the calcium channel blocker (CCB) edema effect by allowing a lower dose of the CCB, and possibly by reducing intracapillary hypertension induced by the CCB (7).

Importantly there is a medication delivery system rationale for more rapid control. Use of the KP hypertension treatment algorithm allows full dose treatment of two drugs with three direct or indirect patient encounters in six weeks. Important advantages of fixed dose combination therapy include 1) reduced patient copayments to promote medication adherence, and 2) improved access due to reduced patient contacts and appointments. Using a treatment intensification plan of $\frac{1}{3}$ tablet, to 1 tablet, to 2 tablets guarantees use of all previous pills prior to the next step. Therefore, there is no wasted medication, and no unused pills piling up and confusing the patient.
What About the ACCOMPLISH Trial?

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed significant reduction in a primary combination endpoint favoring stepped care titration of fixed dose combination of ACE inhibitor and CCB over a stepped care fixed dose combination of ACE inhibitor and hydrochlorothiazide (HCTZ) (8). However, ACCOMPLISH is not definitive because of suboptimal HCTZ dosing. Drug dosing should be based on hard CVD endpoint outcome trials rather than drug doses in common usage. In the INSIGHT trial, HCTZ 50 mg was used in a comparable dose to chlorthalidone 25 mg in ALLHAT, and outperformed the CCB comparator for both nonfatal myocardial infarction and hospitalized heart failure (9).

The 24 hour ambulatory blood pressure substudy of ACCOMPLISH surprisingly showed equivalent nocturnal blood pressure control comparing HCTZ 12.5 to 25 mg with amlodipine 5 to 10 mg in combination with identical milligram amounts of benazepril (10). If in fact, 24 hour blood pressure control is truly the same, the significant difference in the primary combination endpoint was due to a pleiotropic drug effect. What we don’t know is whether that effect is intrinsic to ACEI/CCB or to HCTZ underdosing. The KP hypertension treatment algorithm maximizes HCTZ to 50 mg when lisinopril/HCTZ is advanced to 20/25 mg x 2.

Improved hypertension control along with overall cardiovascular disease risk factor reduction has been associated with reduction of myocardial infarction and stroke in the KP population (11,12).

HCTZ/ACEI Combination Allows Inclusion of Patients with Chronic Kidney Disease and Diabetes

ACE inhibitors and angiotensin receptor blockers (ARBs) are recommended for patients with chronic kidney disease (CKD), particularly those with proteinuria (13). Unfortunately, chronic kidney disease is frequently under-diagnosed and under-treated (14,15), and these patients are not receiving appropriate therapy to reduce the slope of renal decline. Some societies and treatment algorithms recommend ACE inhibitors or ARBs first line for patients with diabetes (16). Diabetes is also under-recognized (17). Therefore, an HCTZ/ACE inhibitor combination allows preferential treatment for patients with CKD and diabetes, both with recognized and unrecognized disease. Accelerated blood pressure control with combination drug therapy may reduce CVD events for higher risk patients (18,19).

HCTZ/ACEI Combination Allows Inclusion of All Races and Age Groups

ALLHAT included a large prespecified group of African American patients and showed that sufficient dose thiazide-type diuretic outperformed the ACE inhibitor and CCB comparators (20). The International Society of Hypertension in Blacks (ISHIB) has recommended prescription of thiazide-type diuretic in doses showing benefit in successful CVD endpoint trials (21). Though systolic blood pressure reduction in black patients is greater with thiazide-type diuretics and CCBs compared to ACE inhibitor monotherapy, the combination of HCTZ with ACE inhibitor equals racial responsiveness (22).

Rationale for Spironolactone Dosing in the Kaiser Hypertension Treatment Algorithm
Spironolactone was selected as the preferred fourth drug in the KP hypertension treatment algorithm because of successful usage of this drug in the fourth position in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT), as well as the general experience of spironolactone for resistant hypertension (23,24). The KP treatment algorithm is directed towards primary care practitioners and doctors of pharmacy, and therefore the 12.5 to 25 mg dose range is more constrained than usage up to 100 mg which has been reported (25). The 12.5 to 25 mg range carries significant efficacy (26). Specified safety net parameters for primary care prescription guard against the combination of renin-angiotension system blockade with spironolactone unopposed by HCTZ due to potentially dangerous hyperkalemia (27), restrict usage to patients with baseline potassium less than 4.5 mEq/L to avoid excess risk in patients already challenged by potassium homeostasis, and seek to reserve spironolactone use for CKD 3 and higher for practitioners with greater experience.

**Research Gaps**

There is a lack of hard clinical endpoint trials comparing adequately dosed combination therapy with sequential monotherapies. Combination therapy may include fixed dose combination pills as well as individual monotherapy pills taken together.

**Take all Hypertensive Medications Together Once Daily in the Morning When You Brush Your Teeth**

Patients are more likely to adhere to simple once daily prescription regimens. When pills are split between morning and bedtime applications, unnecessary complexity is introduced and medication adherence is more likely to falter. While of interest, the MAPEC study does not provide sufficient direction on which classes of medications may be more beneficial at bedtime, and is further limited by the lack of hypertension control as determined by final clinic blood pressure determinations (28). Medication adherence is improved with once daily regimens (29), and patients are less likely to experience early medication discontinuation when taking pills in the morning compared to the evening (30). Antihypertensive medications within the KP treatment algorithm are advised to be taken altogether with a habitual activity in the morning.

**Conclusion: Simplicity Works**

The simplicity of the Kaiser Permanente hypertension treatment algorithm applies both to provider prescriptions and patient medication adherence. Simplicity means fewer steps, fewer pills, faster control, and fewer patient visits with improved primary care access. An HCTZ/ACEI combination promotes optimal treatment for patients with both recognized and unrecognized CKD and diabetes. Inclusion of HCTZ maximized to 50 mg represents excellent treatment for all races. Excess point of care decision alerts in the electronic health record that slow down busy workflows are avoided. A simple easy to remember hypertension treatment algorithm for primary care providers has led to control rates of 88% for several regional KP health plans. Simplicity equals performance, and is an importance component of treatment success.
References:


