CHAPTER

149

Combination Drug Therapy in Hypertension

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Hypertension affects 1 billion people worldwide and remains the most common readily identifiable and reversible risk factor for myocardial infarction, stroke, heart failure, atrial fibrillation, aortic dissection and peripheral arterial disease. With increasing longevity and epidemic of obesity will add fuel to this fire and it is projected that one third of the world population will be consumed by hypertension by 2025. High blood pressure accounts for two thirds of all the strokes and half of ischemic heart disease case worldwide[1], making it the leading cause of death worldwide.

Despite being easy to diagnose and plethora of guidelines available; achievement of blood pressure targets remain dismal across all societies and countries. Even in developed countries like the United States blood pressure remains elevated—140/90 mm Hg or higher—in more than half of affected persons[2]. Physicians under treatment, pill burden, prescription drug costs, medication side effects, and insufficient time for patient education contribute to medication nonadherence and failure to achieve blood pressure targets[3]. It is this elevated blood pressure which contributes to 14% of deaths and 6% of DALYs lost globally[4].

Monotherapy achieves optimal guideline recommended blood pressure targets only in 20%–30% of patients with most hypertensive patients requiring a combination of two or more BP-lowering drugs[5]. Although Joint National Committee (JNC) 7 reserved combination drug therapy for mainly stage 2 hypertension (BP ≥ 160/110 mm Hg), European guidelines on hypertension[6] and the more recent JNC 8 recognize low dose combination therapy as an excellent way to initiate drug therapy even for those with mild hypertension[7]. In this article, we review approach to the management of HTN in light of recent advances in combination therapy (Table 1).

Rationale for combination therapy

1. Hypertension results from the complex interplay of environmental and genetic factors leading to the activation or suppression of one or more of a host of physiological systems involved in blood pressure regulation[8].It is these host physiological responses which determine drug response; most patients diagnosed with hypertension do not manifest a single disease causing mechanism[9]. Treatment therefore remains empirical, often requiring three or more pharmacologic agents with complementary mechanisms of action.
2. Monotherapy will act on a single physiological systems involved in blood pressure regulation and can lead to counter regulatory mechanism in other system which results in uncontrolled BP. eg. Calcium channel blockers (CCB) and diuretics cause vasodilatation and natriuresis respectively can activate the renin angiotensin aldosterone system (RAAS). This counter regulatory mechanism can be limited by combining CCB/ diuretics with RAAS Blockade caused by ACE Inhibitors or angiotensin receptor blockers (ARB's).
3. Persistently elevated blood pressure escalates cardiovascular risk; every 20 mmHg increase in systolic blood pressure, there is an approximate doubling of cardiovascular (CV) risk[10] by use of combination therapy there is better achievement of target BP goals thereby reduction in CV risk.
4. Monotherapy especially with beta blockers results in variability in visit to visit BP recordings which is a strong predictor of both stroke and myocardial infarction[11]; this effect is reduced with combination drug therapy.
5. In hypertensive patients with high cardiovascular risk early control of blood pressure is essential to reduce CV risk, as documented in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, patients who achieved BP target at 6 months had fewer subsequent CV events. Furthermore, an earlier BP response within 1 month was predictive of better outcomes[16]. Both the said goals are achieved with combination therapy. Moreover, in a recent matched cohort study in patients with HTN, initial combination therapy was associated with a 34% risk reduction in CV events compared with monotherapy, and a more rapid achievement of BP target was the main contributor to this risk reduction[17].
6. Fixed Dose Combination (FDC) therapy in a single pill reduces pill burden and improves compliance. In a meta-analysis of nine studies comparing the administration of FDC's with their separate components, the adherence rate was improved by 26% in patients receiving FDC's.[12]
7. Combination therapy reduces dose of individual agent thereby reducing side effects; besides two drugs may even reduce each other's side effects.

Table 1: Comparison between different Hypertension Management Strategies[44]

	Low-dose monotherapy	High-dose monotherapy	Free combination therapy	Single-pill combination therapy
Efficacy	-	+	++	++
Time to reach BP target	-	+	++	++
BP variability	-	-	+	+
Simplicity	+	+	-	+
Flexibility	+	+	+	+
Compliance	+	+	-	+
Tolerabihty	+	-	+	++

Abbreviations: HTN, hypertension; BP, blood pressure

E.g. pedal edema associated with dihydropyridine CCBs is partially relieved by co-administration of RAAS blockers[13,14] and RAAS blockers may reduce the incidence of hypokalemia induced by thiazides[15].

COMBINATION THERAPY VS. UPTITRATION OF SINGLE AGENT

Monotherapy achieves Target BP Goals in a small proportion of patients (about 20%–30%), here increasing dose of single agent may not necessary result in incremental BP reduction; as seen with RAAS inhibitors doubling the dose has minimal incremental effect on blood pressure. In contrast, with CCBs, additional antihypertensive efficacy can be gained when dose of amlodipine is doubled at the cost of increased pedal edema. Additional blood pressure fall from combining drugs from two different classes is approximately 5 times greater than doubling the dose of a single drug[18].

COMBINATION THERAPY VS SUBSTITUTION OF SINGLE AGENT

When a single agent is ineffective or produces severe adverse effects such as angioedema in RAAS inhibitors substitution is indicated. It may also be effective in blacks were RAAS inhibitors are unlikely to be effective even here combination therapy is superior. E.g. patients not responding to RAAS inhibitors addition of diuretics will activate RAAS and improve response of RAAS inhibitors as well as diuretics[19].

Anti-Hypertensive options currently available are diuretics, beta-adrenoceptor antagonists, CCBs, angiotensin converting enzyme inhibitors (ACEIs), ARBs, direct renin inhibitors (DRIs), alpha-blockers, and centrally acting agents(clonidine, alpha-methyldopa). Therefore, many combinations are possible.

PREREQUISITES OF COMBINING ANTIHYPERTENSIVE AGENTS:

1. The agents to combine should have an additive BP-lowering effect by acting on complementary mechanisms involved in the pathogenesis of HTN and blocking the counter-regulatory pathways triggered by one another[20]. For example, diuretics and CCBs will activate RAAS; therefore, the addition of a RAAS inhibitor to any of these agents will lead to potentiation of their BP-lowering effect[21,22].
2. Each agent of the combination therapy should neutralize the adverse effects of the other, thus improving the overall tolerability. A CCB-induced peripheral edema secondary to arteriolar vasodilation can be attenuated by the postcapillary venodilation exerted by the RAAS inhibitor.[23] Similarly, thiazide diuretic-induced hypokalemia can be counterbalanced by addition of a RAAS inhibitor or a potassium-sparing diuretic such as amiloride, triamterene or spironolactone.[21]

NOT ALL COMBINATIONS ARE BENEFICIAL!

1. Combining a beta-blocker with a centrally acting agent (clonidine, alpha-methyldopa) can lead to bradycardia and heart block, and their abrupt withdrawal can result in a hypertensive crisis.[24]
2. Dual RAAS Blockade as demonstrated in the ONTARGET[25] and ALTITUDE[26] trial is harmful. In the ONTARGET Study, combination of an ACEI and an ARB lead to increased incidence of adverse effects with no improvement in outcomes, similarly the ALTITUDE trial in Type 2 Diabetes, the addition of the DRI to an ARB resulted in increased incidence of hypotension, renal impairment, and hyperkalemia, which might have accounted for the significantly higher incidence of cardiac arrest in the combination therapy group.
3. Combination of beta-blockers with a nondihydropyridine CCB (such as verapamil) can lead to potentiation of the negative inotropic and chronotropic effect of these drugs[27].

International guidelines classify various combinations as preferred, acceptable, or not acceptable on the basis of large, outcome-driven clinical trials on safety and on the efficacy of the combination (Table 2).[28]

Table 2: Classification of Combination Therapy

Preferred Combination	Acceptable Combination	Not Acceptable Combination
ACEI or ARB/ DHP CCB	Beta-blocker/ diuretic	Dual RAAS inhibition
ACEI or ARB / DIURETIC	DHP CCB/ diuretic	RAAS inhibitor/ beta-blocker
	DHP CCB/beta-blocker	Non-DHP CCB/ beta-blocker
	Thiazide diuretic/ potassium-sparing diuretic	Centrally acting agent/ beta-blocker
	DHP CCB/non-DHP CCB	
	DRI/DHP CCB	
	DRI/diuretic	
	RAAS inhibitor/ non-DHP CCB	

Abbreviations: HTN, hypertension; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP, dihydropyridine; CCB, calcium channel blocker; RAAS, Renin angiotensin aldosterone system; DRI, direct renin inhibitor.

PREFERRED COMBINATIONS

Renin–angiotensin–aldosterone system inhibitors and calcium channel blockers (ACEI or ARB/ DHP CCB)

The ACCOMPLISH trial showed that fixed combination of an ACE-Inhibitor (benazepril) with a CCB (amlodipine) was more beneficial with regard to morbidity and mortality reduction than the fixed combination of the same ACE-Inhibitor with hydrochlorthiazide.[29] Generally, similar endpoint reductions have been demonstrated with ACE-Inhibitors and ARBs, although there is a suggestion that ACE-Inhibitors may be slightly more cardio protective and that ARBs may confer some advantages in stroke prevention.[30]

The addition of a RAAS blocker has been shown to mitigate this adverse effect. A recent meta-analysis has shown that ACE-Inhibitors are somewhat more efficacious than ARBs in decreasing peripheral edema associated with CCB therapy[23].

In the ACCOMPLISH trial, [31] hypertensive patients were randomized to a combination of the ACE-Inhibitor, benazepril, with either hydrochlorothiazide, or the CCB, amlodipine. After 3 years follow up, blood pressure levels were reduced similarly in the two arms of the trial, but cardiovascular events were significantly reduced by 20% in benazepril/amlodipine arm compared with the benazepril/hydrochlorothiazide arm. This included significant reduction in Myocardial infarction and non-significantly (16%) reduction in stroke. The beneficial effects were seen in both diabetic and non-diabetic patients

Thus combining ACE Inhibitor/ ARB with a CCB apart from achieving BP reduction provides CV risk reduction. Beside cost-effective analysis from the NICE Guidelines also demonstrates that CCBs and ACE-Is or ARBs are more cost-effective treatment choices than beta-blockers or thiazide diuretics.[32]

Renin–angiotensin–aldosterone system inhibitors and diuretics

As discussed earlier combination of RAAS blockade with diuretic enhances efficacy of both drugs and reduces adverse effect of both. Furthermore, the addition of a RAAS inhibitor will reduce the incidence of thiazide-induced hypokalemia as well as new-onset diabetes[33].

In elderly hypertensive patients the addition thiazide-like diuretic, indapamide, ACE-Inhibitor, perindopril, reduced the incidence of stroke and heart failure as documented in the HYVET trial.[34]The ADVANCE trial a randomized, double-blind, placebo-controlled trial that aimed to assess the effects of an single pill combination of an ACEI (perindopril) and indapamide in a large population of patients with type 2 diabetes achieved a 9% relative risk reduction in major macrovascular and microvascular events. The relative risk for death from CV causes was reduced by 18% and that for death from any cause by 14%.[35]

Among the diuretics chlorthalidone has been shown to be more effective than HCTZ in maintaining 24 hour BP control, including better nighttime BP control[36] and may be preferred diuretic for combination with RAAS inhibitors.

Beta blockers with diuretics

Diuretics enhance the antihypertensive efficacy of beta-blockers in low renin hypertension e.g. African-American patients. The combination results in reduction in morbidity and mortality. But both the drug classes increase the risk of glucose intolerance, new-onset diabetes, fatigue, and sexual dysfunction.[32]

Calcium channel blockers and diuretics

Addition of hydrochlorthiazide to Amlodipine resulted in reduction in morbidity and mortality similar to valsartan with hydrochlorthiazide combination in the VALUE study at a cost of higher risk of new onset diabetes and hyperkaliemia when compared with the valsartan with hydrochlorthiazide combination.[37]

Dual calcium channel blockade

The combination of a dihydropyridine CCB with either verapamil or diltiazem has been documented by a meta-analysis to have an additive effect on blood pressure lowering without significantly increasing adverse events. Dual CCB blockade may be useful in patients with documented angioedema on RAAS inhibitors or in patients with advanced renal failure at risk for hyperkaliemia. However, no outcome data are available with dual CCB therapy and long-term safety remains undocumented.

Table 3: Before selecting a Combination therapy for a given patient recommended drug classes for specific compelling indications must be borne in mind

	Recommended Drugs*						
Compelling Indication*	**Diuretic**	**BB**	**ACEI**	**ARB**	**CCB**	**ALDOANT**	**Clinical Trial Basis‡**
Heart failure	•	•	•	•	•	•	ACC/AHA Heart Failure Guideline,[40] MERIT-HF[41] COPERNICUS,[42] CIBIS,[43] SOLVD.[44] AIRE,[45] TRACE.[46] ValHEFT,[47] RALES[48]
Postrnyocardial infarction		•	•			•	ACC/AHA Post-MI Guideline,[49] BHAT,[50] SAVE,[51] Capricorn,[52] EPHESUS[53]
High coronary disease Risk	•	•	•		•		ALLHAT,[33] HOPE,[34] ANBP2,[36] LIFE.[32] CONVINCE[33]
Diabetes	•	•	•	•	•		NKF-ADA Guideline,[21,22] UKPDS,[54] ALLHAT[33]
Chronic kidney disease			•	•			NKF Guideline,[22] Captopril Trial,[55] RENAAL[56] IDNT,[57] REIN[58] AASK[59]
Recurrent stroke prevention	•		•				PROGRESS[35]

Calcium channel blocker with beta blocker

The addition of a dihydropyridine CCB to a beta-blocker will result in a complementary and additive BP-lowering effect.[39] but combining a non dihydropyridine CCB (verapamil or diltiazem) with a beta blocker is not acceptable in lieu of bradycardia and heart block.

Dual RAAS Blockade

As demonstrated in the ONTARGET[25] and ALTITUDE[26] trial is harmful. In the ONTARGET Study, combination of an ACEI and an ARB lead to increased incidence of adverse effects with no improvement in outcomes, similarly the ALTITUDE trial in Type 2 Diabetes, the addition of the DRI to an ARB resulted in cardiovascular mortality, attributable to hyperkalemia.

Renin–angiotensin–aldosterone system blockers and beta-blockers

The said combination is preferred in patients with myocardial infarction and heart failure but it is not preferred combination for management of hypertension, as combination produces little additional blood pressure reduction compared with either monotherapy.

Triple drug combination

About 24% to 32% of patients with HTN will require more than two drugs to achieve their BP target[29, 40]. A rational combination in this setting would be an RAAS inhibitor, a CCB, and a diuretic[6].

A prospective, randomized, double-blind trial aimed to assess the efficacy and safety of an SPC containing VAL/AML/HCTZ compared with a dual-combination SPC of the same components (VAL/AML, V AL/HCTZ, and AML/HCTZ) in 2271 patients with stage 2 HTN. At the end of this 12-week study, significantly more patients achieved BP target in the triple-therapy group (about 70% of patients) compared with in the dual-combination groups (around 50%of patients). In addition, the triple-combination therapy was well-tolerated, with reportedly less peripheral edema.

In the TRINITY (triple therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in hypertensive patients study) trial, the efficacy and tolerability of a triple SPC containing OM/AML/HCTZ was compared with the components' dual combinations (OM/AML, OM/HCTZ, and AML/HCTZ) in patients with moderate to severe HTN. At 12 weeks, the triple-combination therapy resulted in significantly more BP reduction when compared with dual therapy, with no significant difference in adverse events.[42]

RESISTANT HYPERTENSION

In Resistant hypertension in addition to maximum doses or maximum tolerated doses of three antihypertensive drugs including a RAAS blocker, a CCB, and a thiazide diuretic, quadruple therapy is frequently required. Spironolactone added to triple therapy is associated with substantial further reductions in blood pressure of on average, 22/9.5 mm Hg.[43]Spironolactone is therefore recommended as a component of combination therapy in patients with resistant hypertension.

CONCLUSIONS

A large number of patients remain uncontrolled with monotherapy, combination of antihypertensive agents with complementary mechanisms of action helps to achieve BP targets in such patients. The JNC 8 recommends low dose combination therapy as an excellent way to initiate drug therapy even for those with mild hypertension[7]. At times not just two but triple or even quadruple therapy may be required as in cases with resistant hypertension. While choosing a combination therapy for a given patient the underlying compelling

indications for selecting specific drug class based on comorbidity such as heart failure, myocardial infarction, renal disease or stroke should be borne in mind (Table 3). Combination therapy should always be combined with LIFE STYLE MODIFICATION which is the key element in management of hypertension.

Fixed Dose Combination (FDC) therapy in a single pill, reduces pill burden and improves compliance. In a meta-analysis of nine studies comparing the administration of FDC's with their separate components, the adherence rate was improved by 26% in patients receiving FDCs[12]Whenever convenience and cost outweigh other considerations fixed-dose combinations rather than individual drugs should be used.

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