Targeting Better Blood Pressure Control—Combination Therapy

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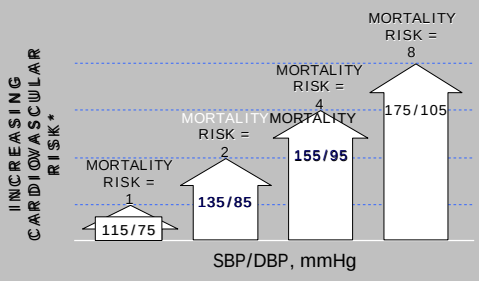
High blood pressure remains an important and very serious public health problem contributing to cardiovascular mortality. Despite an ever growing choice of treatment options, control rates in patients with hypertension remain low. This Heartbeat will review the cardiovascular (CV) mortality risk of hypertension, address the issue of relatively poor control rates and discuss more aggressive combination therapy as a means to achieve blood pressure (BP) goals.

Risk of Hypertension

The effect of BP on CV mortality was clearly shown by a meta-analysis of one million individuals in 61 prospective observational studies of BP and mortality.[1]

- Information was obtained on adults with no previous vascular disease recorded at baseline; during 12.7 million person-years at risk, there were approximately 56,000 vascular deaths.
- At ages 40–69 years, each difference of 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) was associated with more than a two-fold difference in the stroke death rate, and with two-fold differences in the death rates from ischemic heart disease and from other vascular causes.
- This meta-analysis demonstrated that BP is strongly and directly related to vascular (and overall) mortality, with no evidence of a threshold down to at least 115/75 mmHg (Figure 1.). This is why normal blood pressure is < 120/80 mm Hg and SBP 120-139mm Hg and DBP of 80-89 mm Hg are considered pre-hypertensive (**not benign**) and require health-promoting lifestyle modifications to prevent CVD.

Figure 1. CV Mortality Risk Doubles With Each 20/10 mmHg Increase in BP



*Individuals aged 40–69 years (N=1 million).

By contrast, just as mortality increases with higher BP levels, therapeutic reduction of BP is associated with a corresponding (linear) reduction in mortality. This was shown in a meta-analysis that included 136,124 patients in 27 randomized controlled trials. The analysis found that all antihypertensive drug classes appeared to demonstrate similar long-term efficacy and safety, and that reductions in CV mortality could be explained by achieved differences in SBP.[2] **Lowering BP to goal levels of 120/80 mg Hg will decrease heart attacks, heart failure, stroke, kidney disease and save lives.**

The JNC 7 Report

CVD is by far the largest single component of total mortality in the U.S. (38%) [3] —and this mortality can be reduced by therapeutically lowering BP. According to Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), a lot of hypertension is not recognized—approximately 30%. Patients who are diagnosed with hypertension tend to be under-treated (> 40%), and their hypertension poorly controlled (< 2/3), despite physician awareness that hypertension significantly increases mortality. Currently, only about one third of patients

receiving antihypertensive medication achieve the BP goal of <140/90. This low rate of control prompted JNC to renew the call for aggressive diagnosis and aggressive therapy for hypertension in the current recommendations of their JNC 7 Report.[4]

The JNC 7 Report is very clear on another point: effective BP control can and must be achieved in most patients with hypertension, but will generally require two or more antihypertensive drugs—often 3 or 4 medications.

- The committee recommends that the clinician promptly and aggressively initiate combination therapy when BP remains above the goal.
- In instances when the systolic goal is more than 20 mmHg or the diastolic goal is 10 mmHg above the goal, the likelihood of achieving BP goals sooner with fewer side effects is increased when pharmacologic treatment is started using two drugs, either in fixed-dose combinations or as separate prescriptions.

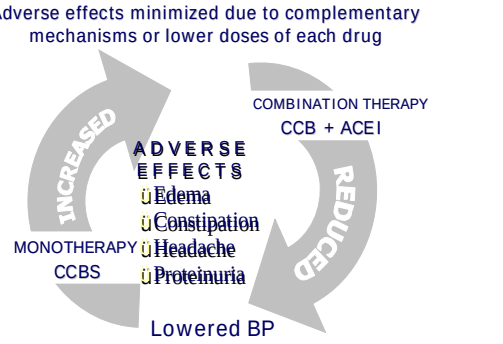
Combination Therapy

The rationale for combining two different classes of agents is that the combination may provide complementary, additive, or synergistic effects through different mechanisms. At the same time, lower doses of each drug may be used than would have been necessary to achieve a therapeutic effect with monotherapy. The use of two agents at smaller doses versus monotherapy at a higher dose allows the clinician to avoid the clinical consequences of increasing dose-dependent adverse drug reactions related to dose increases—potentially enhancing tolerability and improving compliance.

Some antihypertensives have complementary properties suggesting potential benefits when the agents are administered together. For example, the combination of a dihydropyridine calcium channel blocker (CCB) and an angiotensin converting enzyme inhibitor (ACEI) offers potential benefits for a wide range of hypertensive patients. CCBs and ACEIs reduce vasoconstriction through different mechanisms:

- The CCB component provides potent arterial vasodilation. There may be particular benefits for CCBs in African Americans, elderly patients, and patients with isolated systolic hypertension or low-renin hypertension.
- The ACEI component blocks the renin-angiotensin-aldosterone system (RAAS) and offers potent arterial and venous vasodilation. Importantly, ACEIs provide benefits particularly in the larger population of younger and white patients, and among Latino patients. Considering the action of CCBs in these smaller populations and the action of ACEI in these larger populations, a fixed-dose combination of a CCB/ACEI offers great clinical utility.
- The lower doses used in fixed-dose combination therapy minimize the potential for dose-dependent adverse effects. In addition, the adverse effects specific to one of the components can be limited by the physiological actions of the other component. Lotrel (Novartis) is a perfect example as the co-administration of an ACEI (benazepril HCL-20mg) with a CCB (amlodipine besalate-5mg) improves the peripheral edema that is characteristic of CCBs (dilatation of the afferent arteriole without dilatation of the efferent arteriole), primarily due to ACEI-activated venodilation (efferent arteriole). Through this same mechanism, the proteinuria precipitated by the amlodipine is reversed by the benazepril.

Figure 2. Counterbalancing Benefits of Fixed-dose Combination Therapy vs Monotherapy



- There is also evidence that the constipation and headache sometimes seen with CCBs are reduced, due to lower doses of CCB provided in the fixed-dose combination therapy.

Another example of a combination benefit in addition to complementary, additive, or synergistic effects exerted by the components of combination antihypertensive therapy—via different mechanisms or at different sites is that one of the drugs may check the counter-regulatory system activity triggered by the other component. An example is the natriuretic effect of thiazide diuretics which tend to secondarily activate the renin angiotensin aldosterone system (RAAS) which can result in elevated BP. The addition of a RAAS-blocker such as an ACEI or an angiotensin receptor blocker (ARB) reduces the RAAS activity, thereby re-establishing BP control.

Start Combination Treatment Early

A few years ago, the common wisdom for treating hypertension was to start with one agent and titrate up and then add medications as needed. There is emerging evidence that starting combination therapy early may be best for the patient. Studies are emphasizing the need to start combination therapy early in the treatment process as a way of improving response rates. Blood pressure needs to be normalized as quickly as possible. We don't have the luxury of taking months or years because high BP is a huge CV risk. Combination therapy will help get you to your goal target faster.

Two new studies of antihypertensive treatment in African Americans with hypertension and/or diabetes suggest that by combining fixed doses of drugs that block the renin angiotensin system with a diuretic or calcium channel blocker in a single tablet, blood-pressure goals can be achieved without sacrificing end-organ protection. The belief that drugs that block the RAAS don't work as well in African Americans compared to whites has meant that when ACEIs are indicated in heart failure, diabetes, and diabetic nephropathy they don't get used the way that they should. If you have the perception that blacks shouldn't get this therapy, you're in part contributing to the unfortunately disproportionate rates of dialysis and end-stage renal disease in this group. The really important message here is that you can get target organ protection and not give up any efficacy. Using drugs that block the RAAS, although not novel, has tremendous clinical impact.

Hypertension and T2DM both significantly increase the risk of micro- and macro-vascular complications and, when they coexist, put patients at particularly high risk. For every level of BP, African Americans have a higher risk of adverse outcomes than the general population, so when hypertension and diabetes (T2DM) or metabolic syndrome (MetS) occur in these patients, they constitute one of the highest-risk groups we have for CV and renal complications. Combination therapy is usually required to get these patients to a lower target goal of <130/80 mm Hg.

In the **Lotrel and Enalapril in African Americans with Diabetes** (LEAAD) trial, the combination of the ACE inhibitor **benazepril** and the calcium channel blocker **amlodipine** (Lotrel) achieved BP goals in more patients with diabetes and hypertension than those treated with enalapril with or without an add-on diuretic.[5] About three quarters of each group required a diuretic, which is not surprising since it usually takes three-plus drugs to control BP in patients with T2DM. The side effect profile was equal.

The **African American Diovan (valsartan) Amlodipine (Norvasc) Clinical Efficacy** (AADVANCE) trial tested a combination of the angiotensin receptor blocker (ARB) **valsartan** and **hydrochlorothiazide** (Diovan HCT, Novartis) against **amlodipine** (Norvasc, Pfizer) and showed the strategies to be equivalent (not inferior) in lowering blood pressure in African Americans with mild to moderate hypertension.[6]

In another study, dubbed **INCLUSIVE**, presented at the American Society of Hypertension 20th Annual Scientific Sessions last month, more than 70% of a broad population of hypertensives who had already failed to achieve BP goals on monotherapy, reached treatment targets over several months on a fixed dose combination ARB/diuretic (**irbesartan** and **hydrochlorothizide**-Avalide [Bristol-Myers Squibb/Sanofi-Synthelab]. A variety of challenging subgroups of patients—including the elderly, African Americans, Hispanics and those with T2DM or metabolic syndrome (MetS) reached BP goals (77% for SBP and 83% for DBP). This is one of the first large trials to use SBP as a primary endpoint. SBP is now known to be more predictive than DBP for CV events in middle-aged and older patients.

Take Home Points

- The recognition of hypertension as a major contributor to CV risk is increasing.
- All blood pressures above 120/80 mm Hg are abnormal.
- Diagnosis and appropriate treatment of hypertension are still sub-optimal.
- Studies show that a fixed-dose regimen of a complementary combination of drugs is much more effective than any monotherapy could be in a group of difficult to treat patients.
- The data support what JNC-7 and other groups have said, that using combination therapy in patients with stage-2 systolic hypertension should be considered even first line, and certainly much earlier in the management of all hypertension. It just decreases the number of pills and improves the success rate.
- More physicians are now realizing that using combination therapy, more aggressively and earlier on in the management of hypertension, will get many more patients to goal and subsequently improve CV outcomes.
- Ethnicity is important in determining risk but should not be used as the only basis for treatment decisions.
- Blocking the RAAS with an ACEI or ARB should be part of every anti-hypertensive program, (especially in certain comorbid conditions—T2DM, MetS, heart failure, CVD and anyone with azotemia or microalbuminuria) and we still favor ACEI over ARBs as first choice for its superior outcomes benefit and better cost profile.

JNC 7 BP Classification

BP Level (mm Hg)		Category
Systolic	Diastolic	
< 120	and < 80	Normal
120-139	or 80-89	Pre-hypertension (Abnormal)
140-159	or 90-99	Stage 1 Hypertension
≥ 160	or ≥ 100	Stage 2 Hypertension

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