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Heartbeat

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Tailored Treatment for Hypertension



The treatment of hypertension is the reason for most office visits for adults (non-pregnant) to physicians in the United States and for use of prescription drugs.¹ This translates into

greater than 60 million people with hypertension and this number is likely to increase with the aging of our population and the increasing incidence of obesity.

Hypertension, which has a direct causal relation to coronary artery disease (CAD)—**the principal disease state leading to the number one cause of death**—is a very important topic. Since May is National High Blood Pressure (HBP) Month, this *Heartbeat* will present a plan for tailored treatment of hypertension and review the recent guideline recommendations for the elderly emphasizing the difficult job ahead of us.

Definitions

The following definitions were suggested in 2003 by the seventh report of the Joint National Committee (JNC 7) based upon the average of two or more properly measured readings at each of **two or more visits after an initial screen**²:

- **Normal (optimal) BP:** systolic <120 mmHg and diastolic <80 mmHg.
- **Pre-hypertension (high normal):** systolic 120-139 mmHg or diastolic 80-89 mmHg.
- **HBP Stage 1:** systolic 140-159 mmHg or diastolic 90-99 mmHg.
- **HBP Stage 2:** systolic ≥160 or diastolic ≥100 mmHg

Isolated systolic hypertension is considered to be present when the blood pressure is ≥140/<90 mmHg and isolated diastolic hypertension is considered to be present when the blood pressure is <140/≥90 mmHg.

These definitions apply to adults on no antihypertensive medications and who are not acutely ill. If there is a disparity in category between the systolic and diastolic pressures, the higher value determines the severity of the hypertension. Similar but not identical definitions were suggested in the European Societies of Hypertension and Cardiology guidelines for the management of arterial hypertension that were published in 2007.³

Individualized Strategy

Instead of the “one size fits all” strategy as suggested by the treatment guidelines we’d like to focus on the clinical predictors of response to various drugs and the underlying pathophysiology as suggested by Laragh back when I was a cardiology fellow (*Am J Med* 1973; 55:261).

Despite the availability of several antihypertensive drug classes and numerous individual agents, hypertension remains poorly controlled in many patients. Improving control rates will require tailoring of therapy to individual patient factors. In a recent issue of the *American Journal of Hypertension*, three studies address the heterogeneity of response to various antihypertensive drugs.^{4 5 6}

The following proposed individualized strategy reflects a growing consensus^{7 8} that would combine a patient based and pathophysiologic approach **incorporating patient-specific factors that might improve the odds of successful blood pressure control.**

- **Low plasma renin activity (PRA): more common in older patients and non-whites**—depicted as a spectrum with pure volume overload (which responds favorably to volume depleting agents [diuretics] and calcium channel blockers [CCBs]) at the one end and
- **High PRA: more common in younger white patients**—pure vasoconstriction (which responds better to angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and direct renin inhibitors) at the other end.

Use the patient's ethnicity to estimate where they are likely to lie on the spectrum of hypertensive pathophysiology.

Base initial treatment on the patient's probable location in the spectrum: CCB or diuretic for older patients and non-whites and ACE inhibitor or ARB for younger, white patients.

The second add-on if needed in older or non-whites would be the other volume depleting agent not used initially. For the younger or white population on an ACE or ARB we prefer adding a CCB first based on the **ACCOMPLISH** trial (discussed later).

If the two-drug combination doesn't work, add a third agent from the missing class (e.g. a diuretic if the patient is on an ACE and CCB). Resistant hypertension (HBP that requires 3 or more drugs) occurs in 30% of the hypertensive population.

If the three-drug combination doesn't work, measure the PRA level: If the level is normal add an alpha-blocker; if the level is high, add a beta-blocker; if the level is low, change the diuretic drug or dose. Also reconsider whether the hypertension is secondary to a renal-vascular or endocrine condition.

This is a rational, physiologic approach to tailoring therapy for individual patients, particularly those with difficult-to-control hypertension.

New Guidelines for the Elderly

A new consensus document from the **American College of Cardiology** and the **American Heart Association** provides updated information on the management of elderly patients with hypertension.⁹ By the age of 65, most people in this country are hypertensive. The vast majority are not treated. It is believed that part of the problem is that physicians feel there wasn't sufficient evidence in the elderly because many trials exclude elderly patients. "We felt that this was a misperception that justified clarification", said **Dr Carl Pepine** (University of Florida, Gainesville), cochair of the writing committee.

Recent modern studies have included large cohorts of elderly and the recently published Hypertension in the Very Elderly Trial (**HYVET**) cemented the benefit of treatment in older patients when investigators showed that antihypertensive treatment with a sustained-release formulation of the diuretic **indapamide (Lozol)**, with or without the addition of

perindopril, significantly reduced fatal stroke, all-cause mortality, and heart failure in patients 80 years of age and older.¹⁰

- For individuals aged 65 to 79 years old, the recommended treatment target is < 140/90 mm Hg.
- Start one drug at the lowest dose, gradually increasing the dose based on the blood-pressure response; if the antihypertensive response is insufficient, a second drug from a different class should be added; if a diuretic is not the first drug prescribed, it is usually indicated as the second drug.
- Caution is recommended because of the propensity of elderly patients to have orthostatic hypotension, dizziness, and possible falls. That said, data from the clinical trials show that while clinicians should be cautious starting, most patients need two or more antihypertensive drugs to achieve blood-pressure control.

Important Caveats

Combination treatment: In instances when the systolic goal is more than 20 mmHg or the diastolic goal is more than 10 mmHg, 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.

Based on the **ACCOMPLISH** trial the *combination of an ACE inhibitor and a CCB should be, at a minimum, part of every three drug combination* (a diuretic being the third). The Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (**ACCOMPLISH**) trial was a major morbidity and mortality trial showing that a single-tablet dual-mechanism therapy initiated in high-risk hypertensive patients significantly reduced the risk of morbidity and mortality by 20% compared with conventional therapy.¹¹ The

trial, which was stopped prematurely at 3 years, compared the effects of two forms of antihypertensive combination therapies on major fatal and nonfatal cardiovascular (CVD) events. Treatment with the ACE inhibitor **benazepril** plus the CCB **amlodipine (Lotrel)** was more effective than the ACE inhibitor plus diuretic. The results of this trial should change JNC 8 guidelines coming out later this year.

Even though the lower dose combinations of Lotrel are generic, it is an expensive generic and *using amlodipine and lisinopril as separate prescriptions is more cost effective* (\$20 for a 3 month supply of both). It is recommended to start the ACE inhibitor at full dose. If ACE inhibitors aren't tolerated an ARB is the recommended replacement.

Diuretics: A recent meta-analysis concludes: "The antihypertensive efficacy of hydrochlorothiazide (HCTZ) in its daily dose of 12.5 to 25 mg as measured in head-to-head studies by ambulatory BP measurement is consistently inferior to that of all other drug classes. Because outcome data at this dose are lacking, **HCTZ is an inappropriate first-line drug for the treatment of hypertension.**"¹² Studies do indicate that HCTZ is more useful as an "enhancer" or "sensitizer" in combination with other anti-hypertensive drug classes than as a monotherapeutic agent. However, even when combined with a renin-angiotensin system blocker, outcome data suggest that HCTZ is inferior to amlodipine, as was reported in **ACCOMPLISH**.

Indapamide (Lozol)—2.5 to 5mg/daily—or chlorthalidone (Hygroton)—25mg/daily—are the two long-acting thiazide diuretics of choice especially as initial stand-alone therapy. Both have proven outcomes benefits.

Correct Administration of Antihypertensive drugs: BP normalization is crucial to reduce the CV risk of hypertensive patients. However, while BP

reduction is a fairly easy target, BP normalization is much more difficult to achieve. One of the main reasons for the lack of efficacy of pharmacological treatment is that drugs are very often not administered at the correct dosage.¹³ This is particularly the case for ACE inhibitors, compounds characterized by a non-linear dose-response curve. A low dose of an ACE inhibitor has the same potency as a high dose but a shorter duration of action. If a low dosage is administered to a hypertensive patient, it causes BP fluctuations, which have been associated with negative CV outcomes.

Antihypertensive drug classes can be divided into two groups according to the characteristics of their dose-response curve. Current guidelines suggest the initiation of a low-dose antihypertensive treatment. However, this strategy can be applied only to drugs that present a linear dose-response curve, i.e. their BP-lowering effect is proportional to the dose used. With prescription of these drugs, which include long-acting diuretics (mentioned above), β -blockers, α_1 -adrenoceptor antagonists, and CCBs, the dosage can be tailored to the clinical characteristics of each patient.

In contrast, for drug classes characterized by a non-linear dose-response curve, dosages differ mainly in terms of duration of action, rather than in BP-lowering effect. Typical examples of such drugs are ACE inhibitors¹⁴ and possibly some angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]).¹⁵ To better explain this concept, the extent of BP reduction produced by an ACE inhibitor at a low dosage (e.g. enalapril 5mg/day) at peak is the same as that produced by a high dosage (e.g. 20mg). The difference between the two dosages concerns the duration of action, which is several hours with the 5mg/day dosage, but covers an entire day with the 20 mg/day dosage.

The utilization of ACE inhibitors at low dosage is a big clinical mistake, not only in terms of evidence based medicine (improved outcomes are at the higher doses) but also in terms of pharmacologic properties of these drugs. The lower doses are for heart failure to establish tolerability in patients taking concomitant diuretic treatment.

Take Home Points

- The recognition of hypertension as a major contributor to CV risk is increasing. Diagnosis and appropriate treatment of hypertension are still sub-optimal.
- Ethnicity, age and pathophysiology are important in determining an optimal treatment program.
- Patients are never too old to treat. The elderly benefit from anti-hypertensive treatment and a treatment guideline was just released.
- 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 sooner and subsequently improve CV outcomes.
- Knowing the pharmacology of the medications we use is important.
- Lifestyle changes (not covered) are an important part of therapy.

Happy Blood pressure lowering!

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