Management of Hypertension: A Clinical Update

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BACKGROUND

I reviewed the 2003 Guidelines from the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure in the September, 2008 issue of JLGH.[1] An update of the Guidelines is anticipated sometime in 2009, but even before then, it is important to bring to your attention a recently published groundbreaking clinical trial that will almost certainly have a substantial impact on the management of hypertension.

QUESTIONS

Two central messages of my previous article were: 1) diuretics may not warrant their current lofty perch on top of the hypertension drug pyramid, and 2) combination therapy is often necessary and is frequently underutilized. The critically important ACCOMPLISH trial (Avoiding Cardiac Events through Combination Therapy in Patients Living with Systolic Hypertension), was published in the New England Journal of Medicine on December 4, 2008.[2] What does this trial tell us about the principles on which our current therapy is based?

UPDATE

It is reassuring that the trial underscores both of the aforementioned principles. The ACCOMPLISH trial looked at high-risk patients with hypertension. A majority had previously received multiple drugs and had a high incidence of cardiovascular risk factors – diabetes, left ventricular hypertrophy, stroke, ischemic heart and peripheral vascular disease. They were treated with a combination of benazepril/amlodipine (*Lotrel*®) or benazepril/hctz (*Lotensin*®/*Hctz*). The primary endpoint was the standard MACE (major adverse cardiovascular events – cardiovascular death, myocardial infarction, stroke, acute coronary syndrome, revascularization). Importantly, the study was stopped early, after the primary endpoint was reached in 9.6% of the patients in the amlodipine/benazepril arm vs. 11.8% in the benazepril/Hctz arm. This gave an absolute risk reduction of 2.2% and a relative risk reduction of 19.6% ($p < .0001$) in favor of the amlodipine/benazepril combination.

The outcomes in this trial can be rationally explained. The calcium-channel blocker amlodipine (Norvasc®) has been shown to increase vascular endothelial nitric oxide, which may be synergistic with ACE inhibitors such as benazepril (Lotensin®). Both ACE inhibitors and angiotension receptor blockers (ARBs) have anti-inflammatory properties, believed to act through lowering the effects of Angiotension II on vascular endothelium. Diuretics, on the other hand, have been shown in the VAL-Marc trial[3] to neutralize the anti-inflammatory effects of angiotensin blockers.

ACCOMPLISH can be criticized (as have many other trials) for using the diuretic HCTZ, which has been shown to be inferior to chlorthalidone in providing 24hr blood pressure control.[4] As pointed out in my previous article,[1] the evidence based medicine choice for a diuretic is chlorthalidone, although we uncommonly utilize it because of it's lack of available combination products, and difficulty spelling its name as opposed to HCTZ (though true, this is clearly inexcusable).

My personal experience is that amlodipine and other dihydroperidine calcium channel blockers are potent blood pressure medications across all populations. Their dose-limiting side effect of peripheral edema, which is due to arteriolar dilatation without concomitant venodilatation, can be counteracted by inducing venodilation with an accompanying balanced vasodilator such as an ace inhibitor or ARB. This effect is conveniently accomplished with a combination product that contains both a calcium blocker and an ace inhibitor or ARB (Table 1). As a nephrologist I also favor one of these RAAS (renin-angiotensin-aldosterone system) blockers as a cornerstone for hypertension management, since most of my patients have existing cardiovascular disease or are likely to develop it if they have chronic kidney disease.

TABLE 1

Generic Name	Trade Name	Usual Dosage	Usual Frequency
Amlodipine/benazepril	Lotrel	2.5/10, 5/20, 5/40, 10/20, 10/40	daily
Enalapril/felodipine	Lexxel	5/2.5, 5/5	daily or bid
Amlodipine/valsartan	Exforge	5/160, 5/320, 10/160, 10/320	daily
Amlodipine/olmesartan	Azor	5/20, 5/40, 10/20, 10/40	daily

SPECIAL NOTE

Finally, I would like to applaud the pharmaceutical company Novartis for completing this study. About half way through the trial the company lost the patent right (somewhat unexpectedly) for most strengths of Lotrel®. From a strictly financial standpoint they could easily have justified stopping the trial. To the contrary, they continued on and have provided us with important data. Too often we hear the negatives about the pharmaceutical industry, but without them many of our current trials in hypertension would never have been ACCOMPLISHed.

REFERENCES

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Dr. Martin has disclosed that he is on the Speaker's bureau for Novartis Pharmaceuticals.

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