Has the Use of Angiotensin Converting Enzyme Inhibitors and Calcium Channel Blockers Improved the Outcome for Hypertensive Patients?

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As you know, there have not, as yet, been any long-term clinical trials to answer the question regarding benefits of antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitors or calcium channel blockers (CCB). There are several studies presently underway. There are some data, however, in subsets of patients that demonstrate benefit with the ACE inhibitors and some controversial data regarding the CCB.

Table 1 lists the clinical trials that have shown a benefit for reducing cardiovascular disease in treated hypertensives. A statistically significant reduction in morbidity and mortality from stroke, coronary artery disease, congestive heart failure (CHF), and total cardiovascular disease has been demonstrated. All of these trials were diuretic- or β-blocker-based, and four compared a diuretic and a β-blocker.

RESULTS OF ACE INHIBITOR THERAPY IN PATIENT SUBSETS

The use of ACE inhibitors has clearly improved the outlook for patients with CHF due to systolic dysfunction and for patients with type I diabetic nephropathy. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, patients with CHF, symptomatic or asymptomatic, with ejection fractions < 35% who received an ACE inhibitor (enalapril) in addition to a diuretic and digitalis experienced a statistically significant reduction (P < .0036) in mortality, compared to the placebo group that also received the usual treatment for CHF, including digitalis, diuretics, and low-sodium diet, etc. In addition, there was a reduction in hospitalization for CHF in the ACE inhibitor group, as well as a reduction in myocardial infarctions (MI).

A minority of patients in these trials were hypertensive—2,653 compared to 4,100 who were normotensive. In the subset of hypertensive subjects, there was also a significant reduction in CHF, but other endpoint reductions that were statistically significant in the normotensive group failed to reach statistical significance in the hypertensive group; MI, angina, and total mortality were not reduced significantly in the hypertensive subjects. There were some reductions, and it is quite possible that a study that included more hypertensive patients would have yielded significant results. When cardiac endpoints were combined the ACE inhibitor-treated group showed a significant decrease (P < .003) compared to placebo (Figure 1).

The Survival and Ventricular Enlargement (SAVE) trial studied patients who had suffered a myocardial infarction and had ejection fractions < 40% in the postinfarction period. Some had symptomatic heart failure, some did not. Captopril was the ACE inhibitor that was used in this placebo-controlled trial. Significant risk reductions for death from cardiovascular causes, for recurrent MI, and for death from CHF were noted in the ACE inhibitor group.

Whether or not systolic dysfunction occurred after a myocardial infarction or whether it occurred for other reasons, the use of an ACE inhibitor (in addition to a diuretic or digitalis in most instances) has been shown to prolong life, prevent recurrent CHF, and in some cases prevent MI.

A metaanalysis of 16 randomized trials demon-
TABLE 1. CLINICAL TRIALS IN HYPERTENSION: INITIAL DRUG

<table>
<thead>
<tr>
<th>INITIAL DRUG</th>
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<tbody>
<tr>
<td>Diuretic</td>
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<td>Australian</td>
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<tr>
<td>VA-NHLBI</td>
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<td>VA</td>
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<td>MRFIT</td>
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<td>SHEP</td>
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<tr>
<td>β-Blocker</td>
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<td>Coope and Warrender (comparison)</td>
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<td>HAPPHY</td>
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<tr>
<td>MRC-Elderly</td>
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<tr>
<td>Others</td>
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<td>None</td>
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VA, US Department of Veterans Affairs; NHLBI, National Heart, Lung, and Blood Institute; MRFIT, Multiple Risk Factor Intervention Trial; SHEP, Systolic Hypertension in the Elderly Program; USPHS, US Public Health Service; EWPHE, European Working Party on Hypertension in the Elderly; HDFP, Hypertension Detection and Follow-Up Programs; STOP-Hypertension, Swedish Trial in Old Patients with Hypertension; HAPPHY, Heart Attack Primary Prevention in Hypertension; MRC, Medical Research Council; IPPPSH, International Prospective Primary Prevention Study in Hypertension.

Stratified that the benefits in terms of reduction in total mortality were dependent upon the pretreatment ejection fraction (EF). In patients with EF < 25% there was a significant reduction in total mortality of about 31%, but this trend did not apply to subjects with EF > 25%. There was no significant reduction in sudden death or mortality from MI.

I believe that the ACE inhibitors are beneficial for hypertensive and normotensive patients with CHF due to systolic dysfunction.

ACE INHIBITORS AND THE KIDNEY

In 1987 Parving et al reported that in 11 insulin-dependent (type I) diabetics who already had some evidence of nephropathy antihypertensive treatment reduced the slope of the decline in glomerular filtration rate (GFR). Before treatment, the GFR was declining at a rate of almost 1 mL/min/month, whereas after antihypertensive treatment was initiated, blood pressure was reduced and the GFR decline retarded to as little as 0.1 mL/min/month, and proteinuria also diminished. Although this study included only 11 patients, they were insulin-dependent diabetics with advancing renal failure due to diabetic nephropathy. The medications used in these studies were metoprolol, hydralazine, methyldopa, a diuretic, and guanethidine.

The question is whether or not any of the newer antihypertensive drugs, such as the ACE inhibitors or CCB have a specific effect in protecting the kidney in patients with diabetes mellitus, or is the benefit achieved solely the result of blood pressure (BP) lowering?

In a multicenter, randomized trial of patients with type I diabetes mellitus and nephropathy (or retinopathy), the ACE inhibitor captopril was compared to placebo in a double-blind fashion. Approximately 75% were hypertensive and for these subjects, BP control was achieved by adding diuretics and β-blockers to their regimens when necessary. The addition of ACE inhibitors and CCB was forbidden. At the end of the trial, the captopril group had a slightly lower diastolic BP, mainly because of the normotensives in the captopril group. There was a significant reduction in the number of subjects who progressed to end-stage renal disease or death and a 50% reduction in the time it took for a doubling of the creatinine level in the captopril group. It is apparent from this study that ACE inhibition is of value in the management of type I diabetics who already have some evidence of nephropathy.

There are risks however, in using ACE inhibitors in azotemic patients. There is a risk of abrupt worsening of renal function with possible acute renal failure, and the danger of producing hyperkalemia. Patients must be carefully monitored.

It is probably prudent not to give an ACE inhibitor to patients who have serum creatinine levels of > 3 mg/dL. Although there are no data on long-term benefits with ACE inhibitors in most hypertensive subjects, there is evidence that these agents are useful in treating patients with type I diabetic nephropathy and patients with systolic dysfunction of the left ventricle.

CALCIUM CHANNEL BLOCKERS

Is there any evidence that calcium antagonists offer specific advantages in the therapy of hypertension?
ACE INHIBITORS, CCBs, AND HYPERTENSION

During their acute MI and who received diltiazem did better than the placebo group. When the non-CHF and the CHF groups were combined, there was no statistically significant reduction in post-MI events.

Yusuf et al. reviewed the effect of verapamil and diltiazem on mortality following MI. There were no statistically significant benefits from the use of these agents. In the same analysis reinfarction rates were reduced 20% to 22%, but this was not statistically significant. These studies used short-acting formulations of these agents. The results with dihydropyridines, at least the short-acting ones, after an MI are quite negative. A metaanalysis of these suggests that the use of nifedipine actually increased mortality.

But what about data in hypertensive subjects? There are no prospective studies, but the results of several case control studies are of concern. In one large study, low, medium, and high doses of a β-blocker were compared to low, medium, and high doses of short-acting CCB on the occurrence of MI in treated hypertensives. The higher the dose of the β-blocker, the more protection against MI; whereas as the dose of the CCB increased, there was an increase in the risk of MI (Figure 2). The increase in MI achieved statistical significance for a high dose of short-acting calcium antagonists, primarily nifedipine. Risk was also increased for subjects taking a CCB when compared to those taking a diuretic.

In another study, elderly hypertensive subjects who were taking various short-acting calcium antagonists (verapamil, diltiazem, and nifedipine) experienced an increase in the risk of CHF compared to those taking a β-blocker or an ACE inhibitor (Figure 3). There are other studies with short-acting CCB that suggest an increase in ischemic heart disease events and no significant benefit with regard to retarding the process of atherogenesis.

Recent reports suggesting that the calcium antago-

FIGURE 2. Doses of β-blockers and calcium channel blockers related to risk of myocardial infarction in subjects with and without clinical cardiovascular disease. RR, risk ratio; CI, confidence interval. Reproduced from Psaty BM et al. 13

Again, there are no long-term studies, so we must examine some subsets of patients and then, if possible, speculate on possible benefits.

Numerous studies have been done in an attempt to established whether or not the CCB are protective after a myocardial infarction. It has been well established that β-blockers reduce morbidity and mortality in patients with a previous MI, but the data on calcium channel blockers are equivocal or negative. In one study, diltiazem was given soon after an acute MI and continued for a period of 2 to 3 years. Overall, this treatment did not have a significant effect on recurrent cardiac events, specifically recurrent MI or heart failure, when compared to placebo, but there were subgroup differences. Patients who had some clinical evidence of pulmonary congestion during their acute infarction were actually worse off, in terms of recurrent cardiac events, when they were given diltiazem compared to the placebo group. However, those subjects who had no evidence of heart failure during their acute MI and who received diltiazem did better than the placebo group. When the non-CHF and the CHF groups were combined, there was no statistically significant reduction in post-MI events.

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nists increase gastrointestinal bleeding \(^{17}\) and the risk of cancer \(^{18}\) await confirmation.

**SUMMARY**

While there is as yet no evidence that the use of ACE inhibitors or CCB reduce morbidity and mortality in long-term studies of hypertensive subjects, there is evidence that ACE inhibitors are indicated (usually with a diuretic) in the treatment of patients with type I diabetic nephropathy or patients with impaired systolic function. While CCB may lower BP and decrease angina, and are generally well-tolerated, there is little evidence that morbidity and mortality are reduced, at least by the short-acting compounds. There is some evidence that ischemic heart disease events may actually be increased or CHF worsened.

The recommendations of the Fifth Joint National Committee (JNC V) that diuretics and \(\beta\)-blockers remain the preferred initial therapy appears to be reasonable based on the data with the newer medications. \(^{19}\)

**REFERENCES**