Table 1
Cardiovascular Event Rates in Men and Women from the Framingham Heart Study with Optimal, Normal, or High Normal Blood Pressure after 11.1 Years of Follow-Up

Blood Pressure	CV Events in Women	CV Events in Men
OBP	1.9%	5.8%
NBP	2.8%	7.6%
HNBP	4.4%	10.1%

Event rates for first cardiovascular events after age-adjustment during the 11.1 years of follow-up are shown in Table 1. A stepwise increase of cardiovascular risk is seen in both men and women, with men having higher risks in each of the blood pressure categories. An increase in blood pressure class (OBP→NBP→HNBP) during the follow-up period among those studied led to higher CV event rates in both men and women. In the cohort of younger subjects (35–64 years of age) with HNBP, the 10-year cumulative incidence of CV events was 4% among women and 8% among men. In the older cohort (65–90 years of age) the incidence rate was 18% in women and 25% in men. For the older patient population, particularly among the men, this rate would place them in a high-risk category, defined as >20% overall absolute risk of any cardiovascular event within 10 years. Therefore, patients older than 65 years of age with HNBP would constitute a group that should be treated with an antihypertensive agent.

Patients older than 65 years of age with high-normal blood pressure constitute a group that should be treated with an antihypertensive agent.

In an editorial accompanying the Vasan article, Panza describes the factors that may explain the increased risk of CV events in these non-normotensive patients, particularly a clustering of risk factors including cholesterol and insulin insensitivity.[1] In addition, the association between blood pressure and atherosclerosis may be related to the development of endothelial dysfunction. In patients with hypertension, there is reduced activity of nitric oxide, a molecule with antiplatelet and vasodilating effects, with simultaneous increased activity of endothelin-1, an endothelium-derived agent which has potent vasoconstrictive and pro-atherosclerotic effects. The clinical relevance of these findings is confirmed in hypertensive patients who have a diminished forearm vasodilatory response to acetylcholine, an index of microvascular function. ■

References

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Heart Failure

Angiotensin Receptor Antagonist Therapy Fails to Reduce Heart Failure Mortality

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Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity and mortality in patients with heart failure but do not completely suppress angiotensin II formation.[1,2] Previous studies have shown that physiologically active levels of angiotensin II persisted despite long-term therapy with an ACE inhibitor in heart-failure patients.[2] Angiotensin receptor antagonists represent an alternative pharmacological approach to blocking the renin–angiotensin system. Because formation of angiotensin II can take place through alternative pathways as well as through the converting-enzyme route, AT_1 receptor blockers would block angiotensin II that is generated through this alternative pathway, which would not be altered by the administration of an ACE inhibitor. It is also possible that shunting of angiotensin II from the AT_1 to the AT_2 receptor, which has antigrowth properties, might represent another potential benefit of the receptor blockers.[3] Angiotensin receptor antagonists do not, however, block the breakdown of bradykinin. In some experiments, the favorable effects of the ACE

Physiologically active levels of angiotensin II persisted despite long-term therapy with an ACE inhibitor.

inhibitors on cardiac remodeling can be blocked with bradykinin receptor antagonists.

Trials of angiotensin receptor antagonists in patients with chronic heart failure have been limited. The Evaluation of Losartan in the Elderly Study II (ELITE II) randomized 3152 ACE inhibitor–naive patients (aged 65 years or more) with New York Heart Association (NYHA) class II–IV heart failure and ejection fractions of 40% or less to losartan titrated to 50 mg once daily or captopril titrated to 50 mg 3 times daily, for 48 weeks.[4] This trial showed a mortality rate of 15.9% with captopril versus 17.7% with losartan, which was not statistically significantly different (relative risk 1.13; 95% confidence interval [CI] 0.95-1.25, P = .16). An alternative approach to testing this class of agents is to evaluate the addition of an angiotensin receptor antagonist to standard heart-failure therapy.

A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure

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In the journal article for this review, Dr. Jay Cohn and colleagues report the results of the Valsartan Heart Failure Trial (Val-HeFT). This study aimed to assess the long-term effects of the addition of the angiotensin receptor blocker valsartan to standard therapy for heart failure. The study included 5010 patients from 300 centers in the United States and Europe. Most patients were in NYHA class II (61.7%) or III (36.2%) at baseline. At baseline, 93% of patients were on ACE inhibitors and 36% of patients were on β-blockers. Patients were randomized to placebo or to valsartan. Valsartan was initiated at a dose of 40 mg twice daily, then was titrated up to a target dose of 160 mg twice daily. Valsartan was well tolerated with an average dose of 254 mg/day. The primary outcomes were mortality and the combined endpoint of mortality and morbidity, defined as the incidence of cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least 4 hours.

After about 2 years of follow-up, analysis of the data showed no effect of valsartan on the outcome of all-cause mortality, 19.7% with valsartan versus 19.4% with placebo (odds ratio 1.02; 95% CI 0.88-1.18, P = .80). There was a reduction in the combined endpoint of death, hospitalization, resuscitated sudden death, and need for intravenous inotrope or vasodilator. This was decreased from 32.1% to 28.8%, a 13% reduction (P = .009). Modest improvements in patients' NYHA functional class, ejection fraction, and signs and symptoms of heart failure were shown. Most of the morbidity benefit with valsartan was confined to the 7% of patients who were not on ACE inhibitors at baseline.

Background therapy with ACE inhibitors and β-blockers influenced the response to valsartan. The patients were divided into four subgroups on the basis of the use or nonuse of ACE-inhibitor and β-blocker therapy at baseline. Significant interactions were seen for mortality and the morbidity/mortality endpoint. In the 1610 patients receiving ACE inhibitors and β-blockers at baseline, treatment with valsartan was associated with a 42% increased risk of mortality (P = .009). The combined endpoint was significantly reduced in the 226 patients who were treated with neither an ACE inhibitor nor a β-blocker (P = .012).

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The finding that valsartan reduced the need for hospitalization among patients with heart failure is limited by the finding that patients already receiving treatment with an ACE inhibitor and a β-blocker had higher mortality rates with valsartan. Standard therapy for heart failure due to systolic dysfunction remains an ACE inhibitor, β-blocker, and aldosterone antagonist.[5] For patients who cannot tolerate an ACE inhibitor, this study demonstrates a beneficial effect of adding valsartan to the medical regimen. For patients who cannot tolerate a β-blocker, adding an angiotensin receptor antagonist to an ACE inhibitor may be considered, but the benefits are modest.

Other heart failure trials in progress will hopefully clarify whether angiotensin-receptor blockers have a role in the treatment of heart failure. ■

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