mean interval of 15 months (range 10–36 months) and the progression of aortic valve calcium and coronary calcium determined. Patients were divided into two groups according to their LDL levels. Group 1 contained 57 patients with LDL ≤ 130 mg/dL, and Group 2 contained 47 patients with LDL > 130 mg/dL.

The mean progression of aortic valve calcium for Group 1 patients was 9% ± 22%, whereas for Group 2 patients it was 43% ± 44% ($P \leq .001$). There was no significant influence of the amount of aortic calcification in the initial scan on the rate of progression. There was a significant correlation between the progression of coronary and aortic valve calcification ($R = .42$, $P < .001$); the mean coronary calcium progression was 16.1% ± 22% in Group 1, compared with 39.7% ± 46% in Group 2 ($P < .001$). There was no influence of smoking, hypertension, diabetes, or patient age on the rate of progression, possibly because of the small size of the respective subgroups. Although the use of cholesterol-lowering medication by itself had no significant influence on the progression of aortic valve calcification, when patients treated with statins were divided according to their LDL levels a statistically significant difference of annualized aortic valve calcium progression was found.

*The data suggest that a limitation in the progression of aortic valve calcification, and hopefully in aortic stenosis, may be a secondary outcome of treatment of hyperlipidemia.*

The authors note a number of limitations to their study. First, it was a retrospective analysis of patients referred for coronary calcification scanning and therefore subject to selection bias, because patients with cardiovascular risk factors tend to be over-represented. Second, the sample size was small. Most importantly, they assessed only aortic valve calcification, with no measure of the functional status of the valve. Thus an increase in calcification may not have been associated with an increase in severity of stenosis. Despite the limitations, a commonality in response of coronary calcification and aortic valve calcification to LDL levels reinforces the concept of the common pathologic mechanism of these two disorders. The data do suggest that a limitation in the progression of aortic valve calcification, and hopefully in aortic stenosis, may be a secondary outcome of treatment of hyperlipidemia. Further studies are required that relate these findings to the more important question of progression of stenosis and clinical outcomes. ■

# Hypertension

## Risk Associated with "Normal" Blood Pressure

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### Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease

Vasan RS, Larson MG, Liep EP et al.
*N Engl J Med.* 2001:345:1291–1297.

It has been accepted dogma that increasing systolic and diastolic blood pressure remains a continuum of risk–the higher the measured pressure, the higher the risk of cardiovascular (CV) events. There is very little data documenting the absolute risk differential between patients in the nonhypertensive categories as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC- VI) and World Health Organization–International Society of Hypertension (WHO-ISH) criteria:

- Optimal blood pressure (OBP): systolic < 120 mm Hg, diastolic < 80 mm Hg
- Normal blood pressure (NBP): systolic between 120 and 129 mm Hg or diastolic between 80 and 84 mm Hg
- High normal blood pressure (HNBP): systolic pressure between 130 and 139 mm Hg or diastolic between 85 and 90 mm Hg

The authors of this study have used that segment of the Framingham Heart Study population with no evidence of heart disease (n = 6859) as the population studied.

*Blood pressure increases that occur within the "normal range" are associated with increase CV events.*

In terms of the characteristics of the study subjects, women were more likely to have optimal blood pressure than men. Subjects with HNBP were more likely to be older, heavier, and have higher levels of cholesterol than those with OBP. About one third of the study population were smokers and about 2% were diabetic.

**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**

1. Panza JA. High-normal blood pressure–more "high" than "normal." *N Engl J Med.* 2001;345:1337–1339.

# 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.*