Diastolic Blood Pressure Control in Coronary Artery Disease: How Low Is Too Low?

Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006;144:884–93.

Study Overview

Objective. To determine if low blood pressure (BP) is associated with excess morbidity and mortality in patients with coronary artery disease (CAD) and hypertension.

Design. Secondary analysis of data from a randomized controlled trial, the International Verapamil-Trandolapril Study (INVEST) [1].

Setting and participants. 22,576 clinically stable patients with hypertension and CAD from 14 countries were enrolled. Patients were excluded if they had a myocardial infarction (MI) within 3 months of enrollment or class III or IV congestive heart failure. Patients were randomly assigned to sustained-release verapamil or atenolol to achieve BP < 140/90 mm Hg (< 130/85 mm Hg for patients with diabetes or renal impairment).

Main outcome measures. The primary outcome was the first occurrence of all-cause mortality, nonfatal MI, or nonfatal stroke. Secondary endpoints were the components of the primary endpoint, all MI, and all stroke. The relationship between average-on-treatment BP and the endpoints was modeled using unadjusted quadratic proportional hazards models and models that adjusted for differences in baseline covariates.

Main results. A J-shaped relationship existed between diastolic BP and risk for the primary outcome. Compared with diastolic BP ranging from > 80 to ≤ 90 mm Hg, diastolic BP ranging from > 60 to ≤ 70 mm Hg was associated with a nearly twofold increased risk for the primary outcome, and the risk was almost tripled with diastolic BP ≤ 60 mm Hg. Adjustment for covariates greatly attenuated the relationship between low diastolic BP and increased risk for the primary outcome but did not eliminate it. The J-shaped relationship between systolic BP and the primary outcome was much less pronounced than that for diastolic BP and the primary outcome. The risks for all-cause death and MI but not stroke were also increased at low diastolic BPs. There was a significant interaction between diastolic BP and prior coronary artery revascularization; the risk for the primary outcome at low diastolic BPs was greater for patients who had not undergone prior revascularization. In adjusted analyses, risk for the primary outcome was lowest at a systolic BP of 129.5 mm Hg and diastolic BP of 73.8 mm Hg. The relationships between BP and outcomes were similar in the verapamil and atenolol treatment groups.

Conclusion. The risk for all-cause mortality and MI in CAD patients on antihypertensive therapy increases progressively with lower diastolic BP. Excessive reduction in diastolic BP should be avoided in patients with CAD and hypertension.

Commentary

Messerli et al's secondary analysis of the large INVEST trial [1] shows that CAD patients with low diastolic BP (< 70 mm Hg) during antihypertensive treatment had higher cardiovascular morbidity and all-cause mortality than those with diastolic BPs in the 80 to 90 mm Hg range. However, the authors pointed out that their results do not demonstrate causation because patients were not randomized to different treatment BPs. One or a combination of the following mechanisms could be responsible for the observed relationship: (1) low diastolic BP could cause MI or death by provoking inadequate tissue perfusion, especially myocardial ischemia; (2) low diastolic BP could merely be a marker of high risk—increased pulse pressure and the associated advanced atherosclerosis and arterial noncompliance are more common among hypertensive patients with low diastolic BP; and/or (3) low diastolic BP could be caused by underlying illness. The fact that patients with low diastolic BP who had not undergone revascularization appeared to be at greater risk for the primary outcome compared with revascularized patients argues for the first explanation, but the other 2 mechanisms could easily contribute to the observed relationships. Because patients were selected for their diagnosed hypertension, those with low diastolic BP during treatment probably had low baseline diastolic BP and high pulse pressure, suggesting that low diastolic BP is merely a reflection of patients' baseline cardiovascular risk. Adjusting for covariates substantially reduced the relationship

between low diastolic BP and worse outcomes, and had the adjustment for covariants been perfect, the relationship may have disappeared altogether. The third mechanism could be especially relevant if patients developed systolic dysfunction during the study and would not be accounted for by including the presence/absence of heart failure at baseline as a covariate.

Applying these findings to clinical practice is challenging. The clinical question remains: For a patient with CAD and a systolic BP that is not at goal, is there a diastolic BP below which the benefits of intensifying antihypertensive therapy would be outweighed by the risk of inducing diastolic hypotension? This question is especially relevant to patients with CAD and wide pulse pressures. This question could be addressed by analyzing data from placebo-controlled trials of antihypertensive drugs in persons with known CAD stratified by baseline diastolic BP where the BPs differed by treatment group (unlike Messerli et al's study). This analysis has not yet been performed, but the results from several trials of antihypertensive drugs in patients with high CAD risk and near-normal BP provide some reassurance that the diastolic BPs achieved in these studies was not harmful and that the treatment effects of aggressive BP lowering are beneficial or neutral in stable CAD patients [2–6].

Applications for Clinical Practice

Diastolic BPs below approximately 70 mm Hg portend a worse prognosis in patients with treated hypertension and stable CAD. At present, it is unclear how this information should be used to guide treatment of patients with uncontrolled systolic hypertension and CAD.

—Review by Stephen D. Persell, MD, MPH

References

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