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## EDITORIAL COMMENT

# Optimal Blood Pressure Levels in Patients With Coronary Artery Disease*

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Hypertension is very prevalent and represents an important modifiable risk factor for coronary artery disease. Current guidelines recommend treatment of blood pressure (BP) to levels of <140/90 mm Hg, irrespective of the presence or absence of coronary artery disease (in those without coexisting diabetes or chronic kidney disease) (1). However, few clinical trials have specifically evaluated the relationship of treatment to different BP levels and cardiovascular events. Epidemiologic studies have suggested that BP <115/75 mg Hg is associated with the lowest rates of cardiovascular events in the general population (2). However, concerns have been raised that lowering BP too far in patients with coronary artery disease may compromise myocardial blood flow. Indeed, a number of observational studies have suggested that a J-curve exists with higher cardiovascular event rates in patients with lower on-treatment BP, especially diastolic BP <80 mm Hg. In the INVEST (International Verapamil-Trandolapril Study), a trial in 22,000 patients with hypertension and coronary artery disease, lower diastolic BP was associated with a significant increased risk of myocardial infarction (3). In the subgroup of patients with coronary artery disease in the prospective randomized hypertension optimal treatment, a J-curve relationship between treated diastolic BP (<80 mm Hg) and myocardial infarction also was observed (4). As such, the optimal BP levels in patients with coronary artery disease have been far from clear.

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The CAMELOT (Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis) trial assessed the effect of antihypertensive therapy in 1,991 patients with coronary artery disease present on angiography and BP in the "normal" range as defined by the investigators as a diastolic BP <100 mm Hg (5). The therapeutic intervention groups were randomized to placebo, 10 mg amlodipine, or 20 mg enalapril daily on a background of standard care therapies. The primary outcomes consisted of a composite measure of clinical events, including cardiovascular death, myocardial infarction, cardiac arrest, percutaneous coronary intervention or coronary artery bypass grafting surgery, hospitalization with angina or congestive heart failure, stroke or transient ischemic attack, and new peripheral vascular disease. The study, published in 2004, reported that amlodipine, but not enalapril, decreased the composite of cardiovascular events significantly compared with placebo (hazard ratio 0.69; $p = 0.003$) (5). An intravascular ultrasound (IVUS) substudy was performed in 274 patients and showed progression of coronary atherosclerosis in the placebo-treated patients ($p = 0.001$). However, no progression of atherosclerosis was observed with either enalapril or amlodipine. With both active treatment groups combined, there appeared to be no significant progression of atherosclerosis with reduction in systolic BP of approximately 10 mm Hg and evidence of regression with reductions >10 mm Hg. This decrease in cardiovascular events and regression of coronary atherosclerosis occurred in the presence of strong adherence to the secondary prevention guidelines in place at the time the study was conducted. The mean low-density lipoprotein (LDL) in study subjects was 100 mg/dl, and 95% of patients received aspirin, 83% were on a statin, and 76% were taking a beta-blocker (5). These findings suggest that achieving a systolic BP substantially below 140 mm Hg in patients with pre-existing coronary artery disease is associated with lower risk of clinical events, without any evidence of a J-curve.

The paper by Sipahi et al. (6) in this issue of the *Journal* further extend the findings from the CAMELOT trial. For this post hoc analysis, the 274 patients in the IVUS study were divided into 3 groups depending on their baseline BP: normal defined as <120/80 mm Hg, pre-hypertensive defined as BP 120 to 139/80 mm Hg to 89 mm Hg, and hypertensive defined as BP >140/90 mm Hg. There were no significant baseline differences in these groups in the amount of atheroma present on the IVUS studies as defined as the percentage atheroma volume (%AV). The major finding was that the hypertensive group showed significant progression of atherosclerotic vascular disease (mean increase %AV of 12 $mm^3$) compared with the normotensive group who had a reduction (regression) in %AV of 4.6 $mm^3$. The pre-hypertensive group had no significant change in %AV. The atheroma progression rate was also significantly lower in the group that had transition from pre-hypertensive to normal BP compared with the group who remained pre-hypertensive over the course of the study.

This trend to regression in the normotensive group has not been reported in any other IVUS-based trial except a study using a short-term infusion of a high-density lipoprotein mimetic (apolipoprotein A-1 Milano phospholipids complex) (7) and a study lowering LDL to a mean of 61 mg/dl with 40 mg rosuvastatin over a 24-month period (8). This degree of effect on atheroma volume was not seen in the REVERSAL (Reversal of Atherosclerosis With Ag-

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gressive Lipid-Lowering) trial, which produced an aggressive level of LDL reduction to 79 mg/dl with 80 mg atorvastatin, although this trial was 18 months in duration (9). The significant changes in atherosclerosis were not affected by adjusting for the treatment arm, further suggesting that the effect is due to BP and not the method of getting there.

The authors should be commended for conducting such a detailed, well-reported, and thought-provoking study. This analysis provides important mechanistic insights regarding the relationship between systolic BP and progression of coronary atherosclerosis. The study suggests that there is a continuous relationship between systolic BP and the progression rate of coronary atherosclerosis, with benefits extending to levels of BP below 115/75 mm Hg. These results also suggest that to favorably effect the progression of atherosclerosis, decreasing the BP from a pre-hypertensive level to a normotensive level may be as important as administering intensive lipid-lowering treatment.

There are several issues that must be considered before generalizing these findings. Because this was a post hoc analysis, the patient groups studied differed in a number of other important characteristics besides BP. The hypertensive group of patients were older, were more likely female, and had more assignment to the placebo arm. A prospective intention-to-treat trial with different BP targets would be a preferred design to evaluate the relationship between atherosclerosis progression and target BP, maintaining other treatment parameters equal. The number of subjects studied is relatively limited, and this is a select cohort of patients willing to consent to multiple IVUS evaluations. Patients with diastolic BP >100 mm Hg were excluded. There has also been some debate about the methodology used in IVUS studies of atheroma volume. There can be differences in the pullback length between 2 anatomic points from the baseline IVUS study to the exam at 2 years, for example, the distance between the left anterior descending (LAD)/diagonal bifurcation and the left main/LAD bifurcation may vary up to 15%. Also, the length of artery that is interrogated may differ between patients. To address these issues, the core laboratory measured the total atheroma volume per segment and then divided by the length to get an average area of atheroma per patient. This value is then multiplied by the average length of artery imaged for all the patients. This number is not necessarily the same as the actual atheroma volume for the patient's segment of artery that was imaged. It would also be helpful if these IVUS results were reproduced by an independent core laboratory reanalyzing the original data tapes.

This IVUS-based study is important, because it provides correlation between clinical findings and an anatomic justification for the results. If regression of coronary artery disease is the desired outcome, then treatment to systolic BP levels well below current guideline recommendations is better. If true, there are millions of patients with coronary artery disease that would benefit from further reductions in their systolic BP. However, it is critical to note that the degree to which regression documented by IVUS will translate into a reduction in clinical events in patients with coronary artery disease is unknown. Defining the optimal blood pressure level in patients with established coronary artery disease will require randomized clinical trials sufficiently powered to detect differences in cardiovascular event rates. Assessment of the benefits (and risks) of various blood pressure levels within the so-called normal range and different BP-lowering strategies should be further evaluated in such prospective trials. The important implication of this study is that there is a critical need to reassess the guidelines for managing BP in patients with coronary artery disease. Perhaps what has traditionally been considered "normal" BP is not necessarily optimal nor healthy in patients with coronary artery disease.

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