# 'J Curve' Persists Despite Intensive Lipid Control

BY SHERRY BOSCHERT

SAN FRANCISCO — Bringing blood pressure levels too far down increased the risk for cardiovascular events in a post hoc analysis of data on 10,001 patients with coronary artery disease in a trial of aggressive lipid-lowering therapy.

There has been some controversy around the idea of a "J curve" relationship between blood pressure and the risk for cardiovascular events, in which a higher rate of events is seen with very low and very high blood pressure levels. Every previous study, except one that looked for this phenomenon, found evidence of a J curve, but it's been unclear whether the J curve exists when other cardiovascular risk factors such as LDL cholesterol levels are managed aggressively, Dr. Franz H. Messerli said in a press conference at the annual meeting of the American Society of Hypertension.

Data for the current analysis came from the double-blind Treating to New Targets trial that randomized patients aged 35-75 years with LDL cholesterol levels below 130 mg/dL to daily cholesterol-lowering therapy with 10 or 80 mg of atorvastatin. That study found significantly reduced cardiovascular risk when LDL levels were reduced to 100 mg/dL.

The post hoc analysis revealed a J curve for blood pressure. Patients with blood pressures below or above 130-140 mm Hg systolic or 70-80 mm Hg diastolic were at higher risk for the primary end point, a composite of death from coronary disease, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

The nadirs for safe low blood pressures were 141 mm Hg systolic and 80 mm Hg diastolic, Dr. Messerli, director of the hypertension program at St. Luke's Roosevelt Hospital, New York, said in a poster presentation. The study's lead investigator was Dr. Sripal Bangalore of Harvard Medical School, Boston.

"The good news is that it is a relatively shallow curve," with mild increases in risk just below those blood pressure nadirs, Dr. Messerli said. But once blood pressure drops to 110 mm Hg systolic or 60 mm Hg diastolic or lower, risk for the primary cardiovascular end point tripled.

Similar J-curve relationships were found for secondary end points analyzed individually—all-cause mortality, cardiovascular mortality, nonfatal MI, or stroke.

Systolic blood pressure was a stronger predictor of all-cause mortality or cardiovascular mortality. Diastolic blood pressure was a stronger predictor of nonfatal MI. Systolic and diastolic pressures equally predicted the risk for stroke.

**'With coronary artery disease and diastolic blood pressure, you have to be a bit careful' in how low to go.**

DR. MESSERLI

All patients in the study had coronary artery disease. Lower systolic pressures were better tolerated by patients aged 65 or younger, those who had undergone revascularization procedures, and those with no prior coronary artery bypass graft. The relationship between blood pressure and cardiovascular risk was not affected by gender, diabetes, heart failure, or prior MI.

Hypertensive specialists consider very low blood pressures a "relatively minor" concern, Dr. Messerli said, because most patients fail to reach blood pressure targets. However, "most of us would agree that at least with coronary artery disease and diastolic blood pressure, you have to be a bit careful" in how low to go.

Dr. William B. White of the University of Connecticut, Farmington, who moderated the press conference, said that as a hypertension specialist at a cardiology center, he sees patients who have blood pressures around 102/60 mm Hg on routine visits. "That's the message here—that this does happen in real-life practice," he said.

If patients with these low pressures report dizziness or fatigue, he may adjust therapy to let blood pressures rise 10-12 mm Hg. "They'll probably be just as protected but have more energy and less risk of underperfusing their coronary circulation," he said.

Dr. Messerli offered three possible explanations for the J curve. When blood pressure is too low, the coronaries are underperfused, increasing the risk of an MI. Secondly, a lower diastolic blood pressure means that pulse pressure is high, which indicates endothelial dysfunction and stiff arteries, which can lead to morbidity and mortality. Third, patients with low blood pressure may have concomitant pathology that produces higher mortality.

The study was funded by Pfizer Inc., which markets atorvastatin. Dr. Messerli has been a consultant, adviser, or speaker for companies that make antihypertensives and lipid-lowering drugs, but has no relationship with Pfizer. ■

# Getting Pressure to Goal Reduces LV Hypertrophy, Regardless of Regimen

BY SHERRY BOSCHERT

SAN FRANCISCO — For left ventricular mass to be reduced in patients with hypertension, getting the blood pressure to goal is what matters, not which antihypertensives you use, according to a phase III study.

The findings challenge conventional wisdom that credits renin angiotensin-aldosterone system inhibitors with being the most effective antihypertensives for left ventricular hypertrophy (LVH) regression, followed by calcium channel blockers, then beta-blockers, then diuretics.

"It turns out that's not the case," Dr. Alan B. Miller said at the annual meeting of the American Society of Hypertension. "It probably doesn't matter what drug you use. If you get to the blood pressure goal, good things happen—in this case, left ventricular regression, and I suspect clinical outcomes will follow," said Dr. Miller, professor of cardiology at the University of Florida, Jacksonville.

The multicenter, double-blind study included 287 patients with class 1 or class 2 hypertension and documented left ventricular hypertrophy who were being treated with 20 mg/day of the ACE inhibitor lisinopril. Patients were randomized to adjunctive therapy with up to 80 mg/day of the nonselective beta-blocker/alpha-1 blocker carvedilol CR (Coreg), up to 100 mg/day of the beta-blocker atenolol, or up to 40 mg/day of lisinopril without beta-blockade. Some patients also required concomitant hydrochlorothiazide or hydrochlorothiazide plus amlodipine to control hypertension.

During 12 months of treatment, 73% of the carvedilol/lisinopril group, 67% of the atenolol/lisinopril group, and 79% of the high-dose lisinopril group reached recommended blood pressure goals (less than 130/80 mm Hg for the 25% of patients who had diabetes, or less than 140/90 mm Hg for other patients).

Follow-up echocardiography or cardiac MRI showed left ventricular mass regressed by a mean 6.3 $g/m^2$ in the carvedilol/lisinopril group, 6.7 $g/m^2$ in the atenolol/lisinopril group, and 7.9 $g/m^2$ in the high-dose lisinopril group, the Coreg and Left Ventricular Mass Regression (CLEVER) study found.

**'If you get to the blood pressure goal, good things happen—in this case, left ventricular regression.'**

DR. MILLER

The CLEVER results support the idea that "if you lower blood pressure enough, you'll regress left ventricular hypertrophy regardless of what you use," said session moderator Dr. Marvin Moser of Yale University, New Haven, Conn.

Rates of side effects were low, as might be expected with these established medications, Dr. Miller said. Cough was somewhat more common (17%) in the high-dose lisinopril group than in the atenolol (5%) or carvedilol (9%) groups. Fatigue was more common with atenolol (17%) than in the other two groups (7% each). Headaches were reported by 12%-15% of patients.

Dr. Miller has been a consultant and speaker for GlaxoSmithKline, which markets Coreg and funded the study, and has been a speaker for AstraZeneca and received research funds from Merck. Dr. Moser reported having no conflicts of interest. ■

# *Depressed Patients Less Likely to Adhere to Hypertension Therapy*

MONTREAL — Hypertensive patients who have depression are less likely to stick to their therapy regimen than are those without, or in remission from, depression, according to a study of 161 patients.

"This suggests that any change in depressive symptomatology over time can affect medication adherence and may be clinically important," Sara Gallagher said at the annual meeting of the Society of Behavioral Medicine.

Her study was embedded in a randomized, controlled trial that tested the effect of a motivational interviewing on medication adherence. It involved hypertensive African Americans (mean age 54; 87% women) who were followed in primary care practice.

Depressive symptomatology was assessed at baseline and at 6 and 12 months with the Center for Epidemiologic Studies–Depression Scale. Forty-four percent were classified as nondepressed, and 19% were considered depressed. Thirty-seven percent were classified as remittent, having progressed from depressed to nondepressed over the course of the study, said Ms. Gallagher of New York (N.Y.) University.

Medication adherence was assessed at baseline and at 12 months with the self-reported Morisky scale. At baseline, 64% reported nonadherence. This dropped to 48% by study's end.

A multivariate analysis showed that depressive symptoms were associated with medication nonadherence, Ms. Gallagher said. Among the depressed patients, 34% reported adherence at 12 months, compared with 66% in the nondepressed group and 47% in the remittent group.

The finding that a remittence of symptoms can result in improved adherence suggests a benefit to addressing patient depression in this context, Ms. Gallagher said.

**—Kate Johnson**

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