Drug Tx for Prehypertension Deemed Feasible

Researchers warn more data are needed before drugs oust lifestyle modification as a first-line treatment.

BY BRUCE JANCIN
Denver Bureau

ATLANTA — A first baby step toward drug therapy for prehypertension was taken with the presentation of the Trial of Preventing Hypertension results at the annual meeting of the American College of Cardiology.

TROPHY, a 4-year, 772-patient trial, showed that 2 years of treatment with the angiotensin II receptor blocker candesartan delayed the otherwise nearly inexorable transition from prehypertension to stage 1 hypertension.

But both the TROPHY investigators and other observers were quick to emphasize that key questions remain to be answered by future studies before a policy shift from lifestyle modification to medication as first-line therapy can be seriously considered.

Indeed, Dr. Stevo Julius, chair of the TROPHY executive committee, said the investigators were unwilling to make any major treatment recommendations based on this one study. Their sole strong new recommendation based on TROPHY, he added, is that prehypertensive patients deserve closer follow-up than what is now the norm. That's because nearly two-thirds of those on placebo converted to stage 1 hypertension in 4 years.

"Since there was a very high rate of transition, we are rather confident in recommending that once you have diagnosed prehypertension, these patients should be followed more frequently than they are followed now in order to then detect the development of stage 1 hypertension—and we think that follow-up at 3-month intervals is reasonable," said Dr. Julius, professor emeritus of medicine and physiology at the University of Michigan, Ann Arbor.

TROPHY participants had to have baseline prehypertension as defined by repeated automated blood pressure readings of either 130-139 mm Hg systolic and 89 mm Hg or lower diastolic, or a systolic pressure of 139 mm Hg or lower plus a diastolic value of 85-89 mm Hg. Their mean age was 48 years. While that's far younger than the patients in other hypertension trials, Dr. Julius expressed regret they weren't even younger, since that might have enabled TROPHY to show whether a brief drug intervention, given early enough, could permanently arrest the hypertensive process.

TROPHY participants were randomized to 2 years of double-blind candesartan (Atacand) at 16 mg once daily or placebo, followed by 2 years in which all participants received placebo.

The primary end point was development of clinical hypertension. At the 2-year mark, it had developed in 14% of the candesartan group and 40% of the patients on placebo, for a 66% relative risk reduction. Blood pressure began to climb soon after drug therapy stopped, and at 4 years, stage 1 hypertension was present in 53% of the candesartan arm and 63% of the placebo arm, for a still significant 16% relative reduction. Drug side effects were mild and similar to those seen with placebo.

It has been estimated that up to 70 million Americans have prehypertension as defined by blood pressures of 120-139 mm Hg systolic or 80-89 mm Hg diastolic. So why consider redefining this group as having a condition warranting drug therapy? Because prehypertension (previously called transient hypertension, borderline hypertension, and high-normal blood pressure) is an established precursor of clinical hypertension and is associated with increased cardiovascular morbidity and mortality.

Furthermore, hypertension is a self-accelerating condition, and animal studies have suggested a relatively brief period of drug therapy during the prehypertensive phase might favorably alter the natural history by reversing the arteriolar hypertrophy and endothelial dysfunction that define prehypertension—thereby not just delaying but preventing clinical hypertension. And last, because guideline-recommended lifestyle modifications have failed badly.

"It is important to acknowledge that although nonpharmacologic therapy has been recommended first as a population strategy, it hasn't worked," Dr. Julius said. "Body weight is increasing in the population; diabetes is increasing. The time has come to look at this problem in a different way with some large-scale research."

He said the best-ever performance of lifestyle modification, seen in the Trials of Hypertension Prevention, showed an absolute 8% reduction in new-onset hypertension over 2 years (Arch. Intern. Med. 1997;157:657-67), versus 27% with candesartan in TROPHY.

During the discussion, Dr. William J. Elliott expressed concern that the slope of the curve of new-onset hypertension in the candesartan arm during years 2-4 appeared to be the same as in years 0-2 in the placebo arm. This suggests, disappointingly, that drug therapy didn't halt the hypertensive express train and prehypertensive individuals might need to take drugs for their entire lives to benefit.

He added that lowering the traditional threshold for drug therapy from 140/90 mm Hg to encompass some portion of the 70 million Americans with prehypertension could be a health care budget buster.

"I quake in my boots to think that the economy is strong enough to pay for that and all the other things [President Bush] has proposed," said Dr. Elliott, professor of preventive medicine, internal medicine, and pharmacology at Rush Medical College, Chicago. TROPHY was funded by AstraZeneca, from which Dr. Julius receives grant support. ■

ARBs Are Preferred Agents for Stalling Nephropathy in Hypertensive Diabetics

BY BRUCE JANCIN
Denver Bureau

SNOWMASS, COLO. — What's the preferred first-line antihypertensive agent in type 2 diabetic patients with hypertension and macroalbuminuria?

Most nondiabetologists will probably be surprised to learn it's an angiotensin II receptor blocker (ARB), according to American Diabetes Association's treatment guidelines. "I suspect most cardiologists would guess it would be an ACE inhibitor," said Dr. John S. Schroeder at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

For hypertensive type 2 diabetic patients with microalbuminuria—defined by a 24-hour urinary albumin excretion rate of 30-299 mg—the guidelines list both ACE inhibitors and ARBs as the preferred initial treatment choices, based on level A data showing they delay progression to macroalbuminuria (Diabetes Care 2003;26:S33-50).

But ARBs were singled out as the first-line antihypertensive drug class in patients with macroalbuminuria. The guidelines urge that an ARB "should be strongly considered" in such patients on the basis of compelling level A evidence that this drug class reduces the rate of progression to diabetic nephropathy.

The supporting data come from several clinical trials, including the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, and the Irbesartan Diabetic Nephropathy Trial (IDNT).

For Dr. Schroeder, the most impressive evidence is from the Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA II) trial in which 590 microalbuminuric type 2 diabetic patients with hypertension were randomized to 150 or 300 mg/day of irbesartan or placebo in addition to other antihypertensive agents as needed to achieve good blood pressure control. The 5.2% rate of progression to nephropathy at 2 years in patients on 300 mg/day of irbesartan represented a 70% reduction in the relative risk of the primary study end point, compared with placebo (N. Engl. J. Med. 2001;345:870-8).

'I think you should really consider ARBs in all patients who have diabetes and hypertension.'

DR. SCHROEDER

Most diabetics who are hypertensive "already have some degree of nephropathy and microalbuminuria, and therefore I think you should really consider ARBs in all patients who have diabetes and hypertension," said Dr. Schroeder, professor of cardiovascular medicine at Stanford (Calif.) University.

The notion that combined ARB and ACE inhibitor therapy might have additive cardioprotective effects superior to those of either agent alone is being tested in the randomized, double-blind Ongoing Telmisartan Alone or in Combination with Ramipril Global Endpoint Trial (ONTARGET) involving roughly 25,000 patients. Dr. Schroeder is on the speakers' bureau for Boehringer Ingelheim Pharmaceuticals Inc., which markets telmisartan (Micardis) and sponsors ONTARGET. ■

Personality Traits May Predict Blood Pressure

DENVER — Age and low hostility are independent predictors of poor blood pressure in women over a 10-year period, suggesting a link between certain personality traits and disease development, Jocelyne Leclerc reported in a poster presented at the annual meeting of the American Psychosomatic Society.

Ms. Leclerc and her colleagues at the University of British Columbia, Vancouver, compared the results of ambulatory blood pressure monitoring and personality questionnaires of 112 healthy adults at baseline and after 10 years. The study group included 54 men and 63 women; the average age was 40 years at baseline. Average blood pressure monitoring was done on predetermined days when the patients did not expect significant stressful events. Overall, blood pressure and personality traits were stable over the 10 years. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly correlated with depression at baseline. Baseline hostility predicted increased DBP 10 years later; baseline SBP predicted hostility later.

Gender and family history may moderate the impact of personality on blood pressure, they said (Pers. Individ. Diff. 2006;40:1313-21). Increased age and low hostility significantly predicted SBP in women, while high levels of self-deception were the only significant predictors of SBP and DBP over time in men. The observation of low hostility in women predicting high BP suggests a need to consider "possibly differential adaptiveness of the same personality features of women and men." In those with a family history of high blood pressure, age and high levels of self-deception were significant SBP predictors , and self-deception was the lone significant DBP predictor. In those without a family history of high blood pressure, only age was a significant SBP predictor. No variables were significant DBP predictors.

—Heidi Splete