Dose-Dependent Reductions

Resistant Hypertension *from page 1*

which is developing darusentan and funded the study.

All patients in the current study had systolic blood pressure higher than goal despite being on three or more drugs from different classes (with one of them a diuretic) at full or maximally tolerated doses. Goals for systolic BP were less than 130 mm Hg for patients with diabetes or chronic kidney disease and less than 140 mm Hg for all others.

Darusentan produced an absolute 8– to 10–mm Hg greater decrease in systolic BP than did placebo.

DR. WEBER

These were high-risk patients at baseline, Dr. Weber noted, as evidenced by heart disease in 25%-30%, diabetes in 39%-42%, chronic kidney disease in 21%-28%, and microalbuminuria in 21%-30% of the four treatment groups, and an average body mass index of 31-33 kg/m^2.

At baseline, 99%-100% were on diuretics (mainly thiazides but loop diuretics in 5%-17%), 95%-99% were on ACE inhibitors and/or angiotensin receptor blockers, 69%-79% were on calcium channel blockers, 61%-68% were on beta-blockers, and 18%-28% were on other drugs.

Given the aging population and increasing incidence of diabetes and kidney disease, "there's a clear unmet need" for better treatments for high-risk patients with treatment-resistant hypertension, said Dr. George Bakris, a co-investigator in the study. "You have now a kind of magic bullet" for patients with uncontrolled blood pressure despite optimal treatment with other drugs, said Dr. Bakris, director of the hypertension center and professor of medicine at the University of Chicago. He has been a consultant, speaker, or adviser for Gilead.

Patients initially were randomized to placebo or 50 mg/day darusentan, with some patients in the darusentan group titrated up to 100 or 300 mg/day.

In the primary outcome, systolic blood pressure at baseline fell from 151 mm Hg to 139 mm Hg on placebo, and on darusentan dropped from 150 to 135 mm Hg (50-mg group), from 152 to 134 mm Hg (100-mg group), or from 152 to 134 mm Hg (300-mg group), the intent-to-treat analysis found.

The proportions of patients that achieved systolic blood pressure goals were 27% on placebo, 53% on 50 mg or 100 mg per day of darusentan, and 48% on 300 mg/day of the drug.

Diastolic blood pressures fell by 5 mm Hg on placebo, by 10 mm Hg on 50 or 100 mg/day of darusentan, and by 11 mm Hg in the 300-mg group. The decreases on darusentan were significant when compared with placebo.

In measurements of mean ambulatory 24-hour blood pressures, systolic and diastolic blood pressures decreased 1 mm Hg on placebo, with 9– to 10–mm Hg declines in systolic pressures and 7– to 8–mm Hg declines in diastolic pressures on darusentan, which were significant differences.

The most common adverse events were edema in 10% on placebo and in 15%-24% on darusentan or fluid retention in 5% on placebo or 50 mg and 11% on 100 or 300 mg of the drug. There was no evidence of liver toxicity, which has been issue with another drug in the same class—bosantan—that is approved to treat primary pulmonary hypertension, Dr. Weber said. There was one sudden cardiac death in the placebo group, and two patients on darusentan who had a history of coronary artery disease developed MIs. One patient with a history of heart failure (against the enrollment protocol) developed a recurrence on darusentan. Two other patients with possible new heart failure most likely had fluid retention, he said. ■

BP Therapy Boosts Diabetic AF Patients

Diabetic patients with atrial fibrillation obtained greater absolute benefits from BP-lowering treatment than did those without in a study of more than 11,000 patients with type 2 diabetes.

The study findings suggest that an estimated 5 years of active blood pressure–lowering treatment would prevent one cardiovascular death among every 42 patients with atrial fibrillation (AF) at baseline, compared with one death among 120 patients without AF, said Dr. Xin Du of the University of Sydney, and associates (Eur. Heart J. 2009 March 12 [doi:10.1093/eurheartj/ehp055]).

AF was present at baseline in 847 (7.6%) of the 11,140 patients with type 2 diabetes who participated in the Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study, which was jointly funded by the National Health and Medical Research Council of Australia and Servier, France. The outcomes measured were all-cause mortality cardiovascular death, MI, stroke, and heart failure.

Over a mean follow-up of 4.3 years, 879 patients died. Of those deaths, 468 (53%) were due to cardiovascular causes and 15% of the total deaths occurred in patients with AF. Patients with AF at baseline had significantly higher rates of both all-cause and cardiovascular mortality, at 3.9% and 2.4%, respectively, than did those who did not have AF, whose all cause and cardiovascular mortality rates were 1.7% and 0.9%, respectively.

After adjustment for covariates, those hazard ratios were 1.61 and 1.77, respectively. Patients with AF also had higher risk of major cerebrovascular events, with a hazard ratio of 1.68 that was similar for ischemic and hemorrhagic subtypes, reported the authors, several of whom other than Dr. Du have received lecture fees or grant support from, or served on an advisory board for, Servier.

—Miriam E. Tucker

Fixed Doses Seen as Less Effective

Combo Pill *from page 1*

and valsartan-amlodipine. Off-label versions are being studied.

Choosing a fixed-dose combination may reduce "clinical inertia"—a clinician's failure to initiate or intensify therapy when indicated, said Dr. Angela L. Brown of Washington University, St. Louis.

She has been a consultant, adviser, or lecturer for Novartis, Boehringer Ingelheim, and Forest Laboratories, some of which market fixed-dose antihypertensive combinations.

Reducing the pill burden improves adherence, particularly in the case of older patients with more comorbidities.

DR. BROWN

Reducing a patient's "pill burden" with a fixed-dose combination improves adherence to therapy, she added. A meta-analysis found a 23% increase in compliance in patients taking fixed-dose combinations compared with patients taking the two medications separately (Am. J. Med. 2007;120:713-9). "This is particularly true for older patients who, because of increased comorbidity, tend to have a much higher pill burden," she said.

Other data have shown that noncompliant patients with hypertension have a 2% higher absolute risk of adverse cardiovascular outcomes.

Two fixed-dose combinations each produced excellent blood pressure control in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial in 11,506 patients at high risk for cardiovascular events, Dr. Brown said.

Blood pressure control rates improved from 37% at baseline to 72% on benazepril plus HCTZ and from 38% to 75% on benazepril plus amlodipine (N. Engl. J. Med. 2008; 359:2417-28). The benazepril-amlodipine combination significantly reduced adverse cardiovascular outcomes.

Fixed-dose combinations of antihypertensives may be more efficacious than combining single agents and could lower overall health care costs, Dr. Brown said.

Barry L. Carter, Pharm.D., disagreed. "Fixed-dose combination therapy should *not* be initial therapy for hypertension, said Dr. Carter, professor of pharmacy practice and of family medicine at the University of Iowa, Iowa City.

He said he has no conflicts of interest related to these topics.

Most fixed-dose combinations that include a diuretic use a too-low dosage of HCTZ at 12.5-25 mg/day, Dr. Carter said. Outcome-based studies that found antihypertensive benefit from HCTZ used a minimum of 25-50 mg/day, he noted. A dose of 12.5-25 mg/day is appropriate for the diuretic chlorthalidone, which he prefers for antihypertensive therapy.

The cost of fixed-dose, tier 3 drugs 'will be a more significant issue for many patients rather than pill burden.'

DR. CARTER

The key to successful treatment is rapid titration and optimization of the individual antihypertensives, not necessarily fixed-dose combinations, Dr. Carter said.

In a randomized trial of 179 patients with uncontrolled hypertension, having pharmacists make recommendations to physicians resulted in blood pressure control in 89% of patients (including 82% of those with diabetes) after 9 months compared with a 53% control rate in the group that did not get pharmacist advice, he and his associates reported (J. Clin. Hypertens. 2008;10:260-71).

"This trial by and large was not using any fixed-dose combinations," he said. The 89% control rate is better than control rates seen in studies of fixed-dose combinations, he added.

Dr. Carter published the treatment algorithm used to achieve the 89% control rate in February (J. Clin. Hypertens. 2009;11:94-9).

Many new fixed-dose combination antihypertensives are "tier 3" drugs that will cost patients $40-$60 per month in most health plans, compared with no copayment for generic single ingredients. "Cost will be a more significant issue for many patients rather than pill burden. … You have to engage your patients in a dialogue and determine what's most important to them," he said.

Fixed-dose combinations may contribute to clinical inertia, not lessen it, he added. In the practices that he and his associates have studied, "It's very common for a fixed-dose combination to be initiated and then not changed. If it *is* changed, it's often changed to an entirely different fixed-dose combination, basically starting all over again" in a pattern that leaves the blood pressure uncontrolled, he explained. ■