BY HEIDI SPLETE

Boston — A statewide program to get patients with severe heart attacks to hospitals faster significantly reduced disparities in reperfusion treatment times for women and elderly patients, based on a study of more than 900 patients in North Carolina. Disparities exist in the use and timing of reperfusion therapy for STEMI.

The investigators compared 518 patients treated prior to the RACE initiative and 409 patients treated after the initiative. The patients ranged in age from 51 to 73 years, and the baseline characteristics were similar in patients seen before and after RACE implementation. Overall, median door-to-ECG times of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of treatment-related adverse events occurred in 1.0% of valsartan-treated patients and 0.8% of captopril-treated patients. Include assessment of renal function when evaluating patients with heart failure or post-myocardial infarction. In placebo-controlled clinical trials, valsartan treatment was discontinued for elevations in creatinine or potassium (total 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, severe renal artery stenosis, or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances is advised, particularly in patients at risk for hyperkalemia such as those with renal impairment. Caution is advised with concomitant use of valsartan with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium. 5.8 Renal Artery Stenosis 

Aliskiren

In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

5.9 Cyclosporine

When aliskiren was given with cyclosporine, the blood concentrations of aliskiren were significantly increased. Concomitant use of aliskiren with cyclosporine is not recommended [see Drug Interactions (7)].

6. ADVERSE REACTIONS

6.1 Clinical Studies Experience

The following serious adverse reactions are discussed in greater detail in other sections of the label:

• Risk of fetal/neonatal morbidity and mortality [see Warnings and Precautions (5.1)]

• Head and neck angioedema [see Warnings and Precautions (5.2)]

• Hypotension [see Warnings and Precautions (5.3)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Valturna

Valturna has been evaluated for safety in more than 1,225 patients, including over 316 patients for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event (including over 316 patients for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event (including uncontrolled hypertension) occurred in 4% of patients treated with Valturna versus 2.7% of patients given placebo. Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with Valturna and at a higher incidence than placebo included:

• Hypotension (2.8% vs. 1.4%) and postural hypotension (2.6% vs. 2.2%)

• Diarrhea (1.4% vs. 0.9%), upper respiratory tract infection (1.4% vs. 1.1%), urinary tract infection (1.4% vs. 0.6%), influenza (1.1% vs. 0.2%), and upper respiratory tract infection (1.2% vs. 0.3%). Hyponatremia has been observed as a serum electrolyte abnormality in Valturna clinical trials [see Warnings and Precautions (5.7)].
before and after RACE dropped from 30 minutes to 8 minutes in men, and from 15 minutes to 8 minutes in women.

The median door-to-door time for men dropped from 85 to 55 minutes, and times for women dropped from 124 to 65 minutes. Median door-to-needle times decreased from 33 to 29 minutes in men, and from 42 to 30 minutes in women. For the median intervention, women’s times were significantly longer than men’s. Post intervention times for both genders were nearly identical, Dr. Glickman noted. The median door-to-ECG times for patients younger than 70 years dropped from 10 to 7 minutes before and after the RACE initiative, and the times for patients aged 70 years and older dropped from 18 to 9 minutes.

Overall, median door-to-EKG times before and after RACE dropped from 10 minutes to 8 minutes in men, and from 15 minutes to 8 minutes in women.

Mediana door-in door-out times for patients younger than 70 years dropped from 81 to 48 minutes, and times for patients 70 years and older dropped from 117 to 76 minutes. Median door-to-needle times for patients younger than 70 years dropped from 32 to 28 minutes, and from 48 to 36 minutes for patients aged 70 years and older.

The results were limited by a lack of regional comparators during the study period, but the findings showed a reduction in baseline care disparities between men and women, Dr. Glickman said. Disparities persist in the elderly, despite improvements after the RACE initiative, Dr. Glickman noted, which suggests the need for additional study and intervention focused on older patients.

The research was supported by the American Heart Association, the Robert Wood Johnson Foundation, and Blue Cross Blue Shield of North Carolina.

A video interview with Dr. Glickman is at www.youtube.com/cardiologynews.

For details on the RACE initiative, visit www.nccacc.org/race.html.

Adverse reactions reported for valsartan for indications other than hypertension may be found in the prescribing information for Diovan.

### 6.2 Clinical Laboratory Test Abnormalities

**HbC count, hemoglobin and hematocrit**

Small mean decreases from baseline were seen in RBC count, hemoglobin and hematocrit in both monotherapies and combination therapy. These changes were small, but changes in hemoglobin were slightly more pronounced with the combination therapy (-0.28 g/dL) than with monotherapy regimens (-0.04 g/dL in aliskiren or -0.13 g/dL in valsartan) or placebo (-0.07 g/dL).

**Blood urea nitrogen (BUN)/Creatinine**

Elevations in BUN (<40 mg/dL) and creatinine (>2.0 mg/dL) in any treatment group were less than 1.0%. For creatinine, 0.5% (3/599) of patients on combination treatment had a creatinine level >1.5 mg/dL at the end of the study and a 30% increase from baseline compared to none in either monotherapy or placebo.

**Serum Electrolytes:** See Warnings and Precautions (5.7)

### 7 Drug Interactions

No drug interaction studies have been conducted with Valutama and other drugs, although studies with the individual aliskiren and valsartan components are described below.

**Aliskiren**

**Effects of Other Drugs on Aliskiren**

Based on in vitro studies, aliskiren is metabolized by CYP 3A4.

Irbetan: Coadministration of irbesartan reduced aliskiren Cmax up to 50% after multiple dosing.

P-glycoprotein Effects: Pgp (MDR1/MDR1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter. Coadministration of aliskiren with Pgp substrates or inhibitors to moderate inhibitors such as atenolol, digoxin, and amiodipine did not result in clinically relevant interactions.

Alovastatin: Coadministration of atorvastatin resulted in about a 50% increase in aliskiren levels and AUC after multiple dosing.

Ketoconazole: Coadministration of 200 mg twice-daily ketoconazole, a potent Pgp inhibitor, with aliskiren resulted in approximate 85% increase in plasma levels of aliskiren. A 400-mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.

Cyclosporine: Coadministration of 200 mg and 600 mg cyclosporine, a highly potent Pgp inhibitor, with 75 mg aliskiren resulted in an approximately 2.5-fold increase in Cmax and 5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with cyclosporine is not recommended.

**Drugs with no clinically significant effects:** Coadministration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amiodipine did not result in clinically significant increases in aliskiren exposure.

**Effects of Aliskiren on Other Drugs**

Aliskiren does not inhibit the CYP1A2 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.

**Furosemide:** When aliskiren was coadministered with furosemide, the AUC and Cmax of furosemide were reduced by about 30% and 50%, respectively.

**Ramipril:** Patients receiving furosemide could find its effect diminished after starting aliskiren.

**Diet:** Coadministration of aliskiren with high protein diets, a diet rich in fructose and a diet high in omega-3 fatty acids did not result in significant increases in aliskiren exposure.

**Body as a Whole:** allergic reaction, asthma

**Musculoskeletal:** muscle cramps

**Neurologic and Psychiatric:** paresthesia

**Respiratory:** sinusitis, pharyngitis

**Urinary:** impotence

Other reported events seen less frequently in clinical trials were: angioedema.

Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,293 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo.

Two cases of angioedema with respiratory symptoms were reported with aliskiren in the clinical trials. Two other cases of pericardial edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.096%

In addition, 28 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation. In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroup at 150 mg similar to those seen at 300 mg for men or younger patients (all rates about 2%). Other GI symptoms included abdominal pain, dyspepsia, and gas, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, losartan), the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% vs. 0.2%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One patient had a predisposing cause for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and cerebral imaging results were reported. Aliskiren was discontinued and there was no rechallenge in either case.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dryness, fatigue, upper respiratory tract infection, back pain and cough.

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Valsartan

Valsartan has been evaluated for safety in more than 4,000 hypertensive patients in clinical trials, including over 400 treated for over 6 months, and more than 160 for over 1 year.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129 patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or losartan were 20%, 19%, and 89% respectively (p<0.001).

Other adverse reactions, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan are:

- **Body as a Whole:** allergic reaction, asthama
- **Musculoskeletal:** muscle cramps
- **Neurologic and Psychiatric:** paresthesia
- **Respiratory:** sinusitis, pharyngitis
- **Urinary:** impotence

Other reported events seen less frequently in clinical trials were: angioedema.