Primary PCI in STEMI: Stick to Culprit Lesions

BY BRUCE JANCIN

Snowmass, Colo. — Primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction and multivessel disease is best limited to the culprit vessel in hemodynamically stable patients, according to the first large population-based study on this issue to include long-term outcomes.

Staged PCI of other lesions causing residual ischemia can safely be done later during the same hospitalization or anytime in the next couple months, Dr. Spencer B. King III reported at a confer-

<table>
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<th>Mortality Following Culprit- vs. Multivessel PCI in STEMI</th>
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<tbody>
<tr>
<td>Culprit-Vessel Revascularization at Time of Primary PCI</td>
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<tr>
<td>In-hospital</td>
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<tr>
<td>12 months</td>
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<td>24 months</td>
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<td>42 months</td>
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Notes: Based on New York State PCI Registry data from 2003 to June 30, 2006. Differences are statistically significant.

Source: Dr. King

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

RBC 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 (+0.2 g/dL) than with monotherapy regimens (+0.4 g/dL in aliskiren or +0.1 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 1.0x. 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.

7 Drug Interactions

No drug interaction studies have been conducted with Valturna and other drugs. However, 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 CYP3A4. Any one of the potential drug interactions will likely depend on the degree of inhibition of this transporter. Coadministration of aliskiren with Pgp substrates or weak to moderate inhibitors such as atenolol, digoxin, and amiodarone did not result in clinically relevant interactions.

Atorvastatin: Coadministration of atorvastatin resulted in about a 50% increase in Cmax and AUC of atorvastatin. Aliskiren does not interact significantly with Pgp and CYP450 enzymes and is not significantly affected by atorvastatin.

Ketoconazole: Coadministration of 200 mg twice-daily ketoconazole, a potent Pgp inhibitor, with aliskiren resulted in about 80% 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 250 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.

Dietary and lifestyle changes (including weight loss, smoking cessation, and increased physical activity) can be used to manage prediabetes and type 2 diabetes. In addition, lifestyle changes can help to reduce the risk of developing diabetes. Therefore, lifestyle changes should be emphasized to all patients.

Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 controlled clinical trials with valsartan are:

Other adverse reactions, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan, were 20%, 19%, and 69% respectively (p<0.001). 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 incidence of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 68% respectively (p<0.001). Other adverse reactions, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan are:

Back pain: allergic reaction, asthma
Musculoskeletal: muscle cramps
Neurologic and Psychiatric: paresthesia
Respiratory: sinusitis, pharyngitis
Urogenital: impotence

Other reported events seen less frequently in clinical trials were:

Aliskiren

Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,250 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 use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 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 arms, 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 ≥ 75) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups 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 gastrointestinal reflux, 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, lisinopril) arms, 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. 0.3%), 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 predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and imaging results were not 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, dizziness, fatigue, upper respiratory tract infection, back pain and cough.

No clinically meaningful changes in vital signs or in EEG (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 169 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 group 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 lisinopril were 20%, 19%, and 68% respectively (p<0.001).

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

Back pain: allergic reaction, asthma
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Other reported events seen less frequently in clinical trials were:

Angioedema.
Prior studies examining the topic of culprit-versus multivessel PCI in STEMI patients have generally been small, showing conflicting results in their findings. As a result, practices vary widely, with some cardiologists restricting themselves to opening only the culprit vessel, while others opt to treat additional lesions at the time of primary PCI, and still others wait a day, several weeks, or months before addressing lesions shown on the basis of stress testing or fractional flow reserve to be a likely source of residual ischemia.

“There are a host of different opinions out there on how to deal with this,” observed Dr. King, the conference program director and president of St. Joseph’s Heart and Vascular Institute, Atlanta.

To help bring clarity to the situation, he and his investigators compared mortality through 42 months of follow-up in STEMI patients with multivessel disease who underwent primary PCI in New York State, where reporting of PCI outcomes is mandatory, from January 2003 through June 2006 (JACC Cardiovasc. Interv. 2010;3:22-31).

In that study, mortality rates were significantly lower in 458 hemodynamically stable patients whose revascularization was limited to the culprit vessel than in an equal number of propensity-matched patients who underwent multivessel revascularization at the time of primary PCI (see table on opposite page).

On the other hand, mortality rates in hospital and at 12, 24, and 42 months of follow-up were similar in 259 patients who underwent culprit-PCI only and in 259 propensity-matched patients who had staged multivessel revascularization during the index hospitalization.

In fact, the staged multivessel PCI group showed a consistent trend for fewer deaths at all time points. Similarly, among 538 patients who underwent stem-PCI only and were alive at 60 days, mortality rates at 12, 24, and 42 months of follow-up were not statistically different compared with the rates in an equal number of propensity-matched patients who had staged multivessel revascularization within 60 days on a non-emergency basis. Once again, there was a consistent albeit statistically non-significant trend for lower mortality in the staged multivessel revascularization group.

A staged interventional approach to STEMI patients with multivessel disease makes solid sense to Dr. David O. Williams. “When I was at Rhode Island Hospital, the mean time it took from when the patient hit the door of the cath lab, often fully dressed, to the balloon going up, was 18 minutes,” recalled Dr. Williams, who is now director of the cardiovascular laboratory and interventional cardiology at Brigham and Women’s Hospital, Boston.

“It’s very tough to learn much about the patient who’s undergoing primary PCI—and their ability to take dual antiplatelet therapy—given the haste with which we do these cases. We’re on the clock. When you talk about multiple stents, multiple lesions, I think it might be good to have the opportunity to get to know a little bit more about the background of the patient, including any other illnesses that might relate to the decision,” he said.

Disclosures: Dr. King disclosed serving as a consultant to BG Medicine, Celonova Biosciences, Cordis, Medtronic, and NorthPoint Domain. Dr. Williams is a consultant to Abbott Vascular, Cordis, and Volcano.

CYP 450 Interactions: In vitro metabolism studies have indicated that CYP450 mediated drug interactions between valsartan and coadministered drugs are unlikely because of low extent of metabolism [see Pharmacokinetics – Valsartan (12.3) in the full prescribing information].

Transporters: The results from an in vitro study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter (OATP1B1, OATP1B3, and MRP2). Inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporters (P-gp) may increase the systemic exposure to valsartan.

As with other drugs that block angiotensin II or its effects, concomitant use of potent gastric secretory drugs (e.g., proton pump inhibitors) or potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients increases in serum creatinine.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category D [see Warnings and Precautions (5.1)]. Valturna contains both aliskiren (a direct renin inhibitor) and valsartan (an angiotensin II receptor blocker). When administered during the second or third trimester of pregnancy, drugs that act directly on the renin-angiotensin-aldosterone system can cause fetal and neonatal morbidity and death.

Valturna can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Angiotensin II receptor antagonists, as valsartan, and angiotensin-converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin-aldosterone system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with a 2-4 fold increased risk of postnatal renal dysfunction and neonatal death. If angiotensin II receptor antagonists are discontinued, it may be preferable to use aliskiren.

8.1.1 Nursing Mothers
Aliskiren
Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan
Limited data are available related to overdosage in humans. The most likely effect of overdose with valsartan would be hypotension and tachycardia. bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock can also be seen.

Valturna
Limited data are available related to overdosage in humans. If symptomatic hypotension occurs, provide supportive treatment.

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Valsartan is not removed from the plasma by hemodialysis.

Valsartan was not grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient)

16 STORAGE
Stable at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in original container. [See USP Controlled Room Temperature.] Protect from moisture. Dispense in tight container (USP).

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