

Outcomes ‘Terrible’ After Stent Thrombosis

BY BRUCE JANCIN
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VIENNA — Urgent percutaneous coronary intervention for stent thrombosis is a situation that comes up more frequently and leads to considerably worse outcomes than generally is appreciated, Dr. Francesco Burzotta said at the annual congress of the European Society of Cardiology.

He presented the results of the Out-

come of PCI for Stent Thrombosis Multicentre Study (OPTIMIST), a prospective unfunded registry of all patients who underwent PCI for stent thrombosis at 11 Rome-area hospitals during 2005 and 2006.

OPTIMIST involved 110 patients who experienced 120 stent thromboses, making this the largest-ever single series of patients with angiographically defined stent thrombosis ever reported, according to Dr. Burzotta of Catholic University of the Sacred Heart, Rome.

Stent thrombosis accounted for 3.6% of all urgent PCIs performed for ST-elevation MI at participating hospitals during the study period, so it is not a rare event. And the frequency will increase as the number of stent procedures climbs worldwide, he observed.

Clinical outcomes were disappointing, despite state-of-the-art treatment, Dr. Burzotta said. Mortality was 12% at 30 days and 16% at 6 months. The combined rate of death, myocardial infarction, stroke, or a repeat interventional procedure was 29% at 6 months.

Of the 120 stent thromboses, 62 involved drug-eluting stents (DES); the rest involved bare-metal stents (BMS). The study was not designed to assess whether the thrombosis rate was higher with DES. However, OPTIMIST did show that the clinical circumstances in which thrombosis occurs tend to be different with DES, as compared with BMS.

Stent thrombosis within 15 days after discontinuing antiplatelet therapy was nearly eightfold more frequent with DES.

And thrombosis involving DES was more likely to occur late: 33 cases of stent thrombosis occurred more than 1 month post DES implantation, compared with 14 cases with BMS.

“However, once thrombosis has occurred and the patient has been directed to the cath lab, the outcome after stent thrombosis and PCI isn’t significantly affected by whether it’s a drug-eluting or bare-metal stent,” the cardiologist said.

Of the 110 patients, 27 underwent PCI with thrombectomy, with the choice of thrombectomy device being left to the operator. Thrombectomy was safe when performed in the high-risk setting of stent thrombosis, with no increased risk of adverse effects observed.

There was a nonsignificant trend toward higher rates of excellent TIMI-3 grade coronary blood flow in patients who underwent thrombectomy; this trend became highly significant when patients in cardiogenic shock at the time of presentation with stent thrombosis were excluded.

In a multivariate analysis, two factors were independently associated with increased 6-month mortality. Stent thrombosis occurring more than 1 year post implantation was associated with a 10-fold increased risk, while implantation of another stent during PCI for stent throm-

bosis conferred a 5.4-fold increased risk of mortality.

Dr. Burzotta said these findings have practical implications for interventional cardiologists: Consider keeping patients on antiplatelet therapy indefinitely after stent placement in order to reduce the risk of late thromboses, and focus on re-

opening the occluded artery without implanting an additional stent in an effort to prevent restenosis.

Thrombectomy during urgent PCI for stent thrombosis appears to have merit in patients without

cardiogenic shock, he added.

Dr. Freek W.A. Verheugt noted in an interview that one-quarter of patients who experience stent thrombosis never make it to the catheterization laboratory because they die immediately.

“The Italian study shows that stent thrombosis—whether with a bare-metal or drug-eluting stent—is a malignant disease. One out of four patients die immediately, and the other three-quarters face an in-hospital mortality of 12%. That’s terrible. We haven’t seen anything like that in many years,” he said.

“That’s like the in-hospital mortality in the placebo arm of the lytic trials 15 years ago,” continued Dr. Verheugt, professor and chairman of cardiology at University Medical Center, Nijmegen, the Netherlands. ■

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia² (2% and <1%); *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. ¹Primarily ejaculatory delay. ²Denominator used was for males only (N=225 Lexapro; N=188 placebo). ³Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Lexapro (N=429) and Placebo (N=427)):** **Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Fatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder² (14% and 2%); Anorgasmia² (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. ¹Primarily ejaculatory delay. ²Denominator used was for males only (N=182 Lexapro; N=195 placebo). ³Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125):** Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%). *Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383)); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=137) and Placebo (N=636)):** Libido Decreased (2% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but in at least 1/1,000 patients. **Cardiovascular - Frequent:** palpitation, hypertension. **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. **Central and Peripheral Nervous System Disorders - Frequent:** light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. **Gastrointestinal Disorders - Frequent:** heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General - Frequent:** allergy, pain in limb, fever, hot flushes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders - Infrequent:** bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders - Frequent:** increased weight. **Infrequent:** decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders - Frequent:** arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders - Frequent:** appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders/Female* - Frequent:** menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. N= 905 Respiratory System Disorders - Frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders - Frequent:** rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. **Special Senses - Frequent:** vision blurred, tinnitus. **Infrequent:** taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders - Frequent:** urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram -** Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

Pioglitazone May Lower Risk of MI, Stroke

BY MARY ANN MOON
Contributing Writer

Pioglitazone appears to lower the risk of death, myocardial infarction, and stroke in diabetes patients, just the opposite of the closely related drug rosiglitazone, according to separate meta-analyses on the two agents.

It is not yet clear why these two thiazolidinediones may have such disparate effects on cardiovascular outcomes, the investigators said.

In one meta-analysis, Dr. A. Michael Lincoff and his associates at the Cleveland Clinic used data provided by Takeda Pharma, manufacturer of Actos, to assess pioglitazone’s effect on the incidence of ischemic cardiovascular complications. They pooled data on 19 randomized, double-blinded, controlled clinical trials of the drug in 16,390 diabetes patients.

The investigators found that the composite outcome of death, myocardial infarction, or stroke was 18% lower in patients who took pioglitazone than in those who received placebo or other diabetes medications.

“The magnitude and direction of this protective effect ... was homogeneous across trials of different durations ranging from 4 months to 3.5 years, across studies

using a variety of control or concomitant diabetic therapies, and among trials of patients with and without established vascular disease,” Dr. Lincoff and his associates said (JAMA 2007;298:1180-8).

Like rosiglitazone, pioglitazone was found to raise the rate of congestive heart failure. However, it did not increase the incidence of heart failure mortality.

“These findings suggest that the net

The composite outcome of death, MI, or stroke was 18% lower in patients who took pioglitazone, compared with placebo or other diabetes medications.

clinical cardiovascular benefit with pioglitazone therapy is favorable, with an important reduction in irreversible ischemic events that is not attenuated by the risk of more frequent heart failure complications,” Dr. Lincoff and his associates said.

In contrast, Dr. Sonal Singh of Wake Forest University, Winston-Salem, N.C., and his associates found in their meta-analysis that rosiglitazone significantly raised the risk of both myocardial infarction and heart failure.

This led them to conclude that “regulatory agencies ought to reevaluate whether

rosiglitazone should be allowed to remain on the market.”

The researchers pooled the results of four randomized clinical trials of at least 1 year’s duration (14,291 patients) and three systematic reviews to assess rosiglitazone’s effect on MI, heart failure, and cardiovascular mortality.

The drug approximately doubled the risk of heart failure, and increased the risk of MI by 42%. However, it did not affect the risk of cardiovascular death.

“We estimate that there may be more than 3.5 million current users of rosiglitazone in the United States alone,” which may account for 4,000 excess MIs and 9,000 excess heart failure events among Americans each year, the researchers wrote (JAMA 2007;298:1189-95).

In August, the U.S. Food and Drug Administration announced that the labels of all thiazolidinediones will now carry a black box warning about the risk of heart failure.

“Health plans and physicians should not wait for regulatory actions. They should avoid using rosiglitazone in patients with diabetes who are at risk of cardiovascular events, especially since safer treatment alternatives are available,” Dr. Singh and his associates said. ■