

Heart Valves in Pregnancy Require Trade-Offs

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SNOWMASS, COLO. — There is no ideal solution when it comes to managing anticoagulation in the pregnant patient with a mechanical heart valve, Dr. Carole A. Warnes stressed at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

“This is not the same as getting your patient through noncardiac surgery. It’s very

different. The blood is stickier than at any other time you’ll have to manage a mechanical valve,” cautioned Dr. Warnes, professor of medicine at the Mayo Clinic, Rochester, Minn.

Other normal physiologic changes in pregnancy that increase the risk of thromboembolic events in patients with mitral or aortic valve prostheses include a nearly 50% increase in circulating blood volume, accompanied by a 30% rise in cardiac output and a 10-20 beat-per-minute increase in resting heart rate. And uterine contractions can trigger sudden jumps in systolic and diastolic blood pressure.

What makes managing thromboembolic risk in these patients so challenging is the need to trade off maternal versus fetal risk.

Unfractionated heparin doesn’t cross the placenta. It is often considered safer for the fetus than warfarin in pregnancy. But unfractionated heparin is a poor anticoagulant in pregnancy. The response to the standard dosage varies widely because of the background increases in factor VIII and fibrinogen, so the risk of a thrombosed valve or other thromboembolic event with prolonged heparin is about 10%. The maternal hemorrhage risk is also increased.



Warfarin is far more effective than unfractionated heparin at preventing valve thrombosis in pregnancy. However, it crosses the placenta, and fetal exposure during gestational weeks 6-9 can result in warfarin embryopathy. The risk is about 6%, but might be dose dependent.

Whatever strategy is used, a daily baby aspirin in the second and third trimesters is safe and probably beneficial.

DR. WARNES

Warnes at the conference, which was cosponsored by the American College of Cardiology.

Some advocate low-molecular-weight heparin throughout pregnancy as the best approach, but Dr. Warnes is leery. The supporting data are limited. Moreover, she has seen thromboembolic complications occur even when LMWH dosing was guided by monitoring of factor Xa levels rather than relying on fixed-dose therapy.

The most popular management strategy in the United States entails a switch from warfarin to unfractionated heparin as soon as pregnancy is diagnosed, with a switch back to warfarin at 13 weeks’ gestation, after the risk of embryopathy is over. This is followed by another switch

back to heparin at about 35 weeks in anticipation of delivery, because the fetus can’t safely pass through the birth canal while anticoagulated. The heparin is stopped for as short a time as possible around delivery. Heparin is resumed 6-12 hours post partum, because that’s still a high-risk period for valve thrombosis.

If this strategy is used, it’s important to give heparin at an adequate intensity. This means maintaining the activated partial thromboplastin time at greater than twice control. If factor Xa monitoring is used, aim for 0.35-0.7 U/mL of anti-factor Xa, Dr. Warnes urged.

The highest-risk situation in pregnancy in terms of thromboembolism involves a tilting disc prosthesis in the mitral position. This is a situation in which continued use of warfarin throughout pregnancy is a reasonable strategy until the switch to intravenous heparin at week 35, even though the Physicians Desk Reference lists warfarin as contraindicated in pregnancy, she said.

Warfarin throughout pregnancy is a particularly attractive strategy in a high-risk woman who was well controlled on the anticoagulant at 5 mg/day or less prior to pregnancy, which might lessen the risk of warfarin embryopathy.

Whatever anticoagulation strategy is used in pregnancy, a daily baby aspirin during the second and third trimesters is safe and probably beneficial. It should be used routinely, said Dr. Warnes. ■

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia (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 ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). †Denominator 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: Headache (24% and 17%); Paresthesia (2% and 1%).

Central & Peripheral Nervous System Disorders: Headache (24% and 17%); Paresthesia (2% and 1%).

Gastrointestinal Disorders: Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 2%); Abdominal Pain (2% and 1%); Flatulence (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 Disorder[†] (14% and 2%); Anorgasmia[‡] (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: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=247 Lexapro; N=195 placebo). †Denominator 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 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=737) and Placebo (N=636)); Libido Decreased (3% and 1%); Anorgasmia (6% 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 World Health Organization (WHO) terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1429 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 1/1000 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/10,000 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, lightness 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, anxiety, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruising, 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 for Lexapro and N=905 for placebo. 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, pupil 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, hyposensitivity, hypocalcemia, 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, procloniaemia, 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.

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Careful β -Blocker Use a Possibility in Pregnancy

SNOWMASS, COLO. — Don’t hesitate to continue β -blocker therapy throughout pregnancy when the situation calls for it, Dr. Carole A. Warnes urged at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

“In practice I have been using β -blockers in pregnancy for 30 years. I’ve never had a significant problem with a baby after the mother has had a β -blocker,” said Dr. Warnes, professor of medicine at the Mayo Clinic, Rochester, Minn.

“Do we worry about the growth of the fetus? Yes, and it needs to be monitored. At the time of delivery the baby may be bradycardic or may have hypoglycemia, but we can deal with that very easily. So for the woman who needs a β -blocker—for example, a patient with hypertrophic cardiomyopathy, or perhaps hypertension with a dilated aorta—we can use them and use them safely. And if it’s better for the mother to continue, then we do so,” she asserted at the conference, which was cosponsored by the American College of Cardiology.

There are four key principles to keep in mind when prescribing cardiovascular drugs in pregnancy: Stick to those with a long safety record, use the lowest effective dose and for the shortest duration, avoid multidrug regimens, and steer clear of agents labeled category D or X by the Food and Drug Administration, Dr. Warnes advised.

In addition to many of the β -blockers, other cardiovascular drugs that Dr. Warnes listed as being relatively safe during pregnancy include calcium channel blockers, digoxin, procainamide, methyldopa, hydralazine, and furosemide.

Agents that are not safe for pregnancy include statins, ACE inhibitors, angiotensin receptor blockers, phenytoin, and folic acid antagonists, including some antibiotics, she noted. ■

Focus on Prevention In Acute Pericarditis

SNOWMASS, COLO. — Avoiding corticosteroids in treating acute pericarditis is the best way to prevent development of chronic relapsing pericarditis, Dr. Rick A. Nishimura said at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

“[Chronic relapsing pericarditis] is a terrible disease. It’s incredibly debilitating and incredibly difficult to treat. The best treatment is to not ever give steroids in the first place for your typical viral pericarditis,” said Dr. Nishimura, professor of medicine at Mayo Medical School, Rochester, Minn.

Chronic relapsing pericarditis most often follows treatment of an episode of acute pericarditis using a several-week burst of prednisone followed by a quick taper. Patients experience multiple recurrences of pericardial pain and an elevated erythrocyte sedimentation rate (ESR) whenever the prednisone dosage drops below, say, 15 mg/day.

Acute pericarditis is an inflammation of the pericardium, typically from an upper respiratory tract infection or other viral

infection. A burst of prednisone is a popular therapy because it’s the fastest way to get rid of the pericardial pain, but the safest and best therapy is high-dose aspirin or an NSAID for at least a month, followed by a slow taper, he said at the conference cosponsored by the American College of Cardiology.

Treatment options for chronic relapsing pericarditis are limited. The patient can receive high-dose aspirin while a very slow taper off prednisone is attempted. If that’s unsuccessful, there is some anecdotal support for off-label use of rituximab (Rituxan), the B-cell-depleting rheumatoid arthritis drug. “The alternative is complete pericardiectomy—that’s open-heart surgery for a patient who started out with a simple acute pericarditis.”

Acute pericarditis is diagnosed on the basis of pericardial pain, presence of a precordial friction rub, elevated ESR indicative of acute inflammation, and ECG findings of diffuse ST elevation and PR depression without pathologic Q waves. “You don’t need an ECG to diagnose pericarditis,” he noted. ■