

Congenital Heart Disease Prognosis Still a Mystery

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TORONTO — Experts continue to look for the best way to assess the risk for sudden death in adults with congenital heart disease.

Adults with congenital heart disease face a threat from sudden cardiac death that is far higher than that of the general population, with a mortality risk of 0.9 events per 1,000 patients per year in pa-

tients who are younger than age 20 years. But as of now, there is no good way to distinguish patients with the highest risk from those congenital heart disease patients who have a substantially lower risk.

“No single hemodynamic or electrophysiologic risk factor appears to be sufficiently predictive,” Dr. Louise Harris said at the 14th World Congress on Heart Disease. Overall, she said, about a quarter of the deaths that occur in adults with con-

genital heart disease are sudden cardiac deaths.

Researchers may eventually develop a scoring system that takes into account several risk factors, she said. Recent findings have established that patients with congenital heart disease may have abnormalities in several organ systems, and risk assessment needs to take all these variables into account. Renal function, for example, is impaired in a significant percentage of patients with congenital heart disease, and

was linked with an increased risk for death (Circulation 2008;117:2320-8).

“Sudden cardiac death is not one physiologic entity, but a manifestation of a number of disorders,” said Dr. Harris, who is a cardiologist in the congenital cardiac center for adults at Toronto General Hospital.

The risk for sudden cardiac death is highest in patients who survived any of four types of congenital heart diseases: tetralogy of Fallot, transposition of the great arteries, coarctation, and aortic stenosis. Among these patient groups, the most studied have been patients treated for tetralogy of Fallot.

Most sudden cardiac deaths in congenital heart disease survivors involve an electrophysiologic disorder, such as an arrhythmia. These can be ventricular tachycardia, ventricular fibrillation, an atrial arrhythmia, or asystole. But sudden death can also occur secondary to a

vascular catastrophe, including pulmonary embolism or an aneurysm rupture. Hemodynamic abnormalities causing both mechanical and structural issues, such as acute heart failure, also cause sudden death.

In patients who survived tetralogy of Fallot, a QRS duration of more than 180 msec is a reliable predictor of ventricular tachycardia and sudden death. Patients with a QRS duration this long have had a greater-than-twofold increased risk of sudden death, compared with patients who had a shorter QRS interval, Dr. Harris said at the congress, which was sponsored by the International Academy of Cardiology.

Indicators of hemodynamic abnormalities—such as increased right ventricular dimension, decreased right ventricular function, or a left ventricular ejection fraction of less than 40%—boost the risk for sudden death when they are coincident with prolonged QRS in patients who had tetralogy of Fallot.

In addition, inducible sustained monomorphic or polymorphic ventricular tachycardia during an electrophysiology study predicted sudden death with a sensitivity of 77% and specificity of 79%. Other noninvasive electrophysiologic measures—such as a signal-average ECG, T-wave alternans, and ambulatory ECG monitoring—have been less reliable for predicting risk.

A significant limitation on risk stratification of congenital heart disease patients is that this strategy presumes that identifying a high-risk patient is to be followed by an intervention that improves the patient's outcome. So far, limited data exist to prove that effective interventions are available to help these patients, Dr. Harris said. ■

thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches [see *Boxed Warning*]. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data

- *Human Data* - There are no adequate and well-controlled studies in pregnant women.

A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves has been conducted [see *Warnings and Precautions* (5.7)].

- *Animal Data* - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m²/day and 410 mg/m²/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox is administered to nursing women.

8.4 Pediatric Use

Safety and effectiveness of Lovenox in pediatric patients have not been established.

8.5 Geriatric Use

Prevention of DVT in hip, knee and abdominal surgery; Treatment of DVT. Prevention of ischemic complications of unstable angina and non-Q-Wave myocardial infarction

Over 2800 patients, 65 years and older, have received Lovenox in pivotal clinical trials. The efficacy of Lovenox in the geriatric (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between geriatric and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox were employed. The incidence of bleeding complications was higher in geriatric patients as compared to younger patients when Lovenox was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Lovenox should be used with care in geriatric patients who may show delayed elimination of enoxaparin. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered [see *Warnings and Precautions* (5.9) and *Clinical Pharmacology* (12.3)].

Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)

In the clinical study for treatment of acute STEMI, there was no evidence of difference in efficacy between patients ≥75 years of age (n = 1241) and patients less than 75 years of age (n=9015). Patients ≥75 years of age did not receive a 30-mg IV bolus prior to the normal dosage regimen and had their SC dose adjusted to 0.75 mg/kg every 12 hours [see *Dosage and Administration* (2.3)]. The incidence of bleeding complications was higher in patients ≥65 years of age as compared to younger patients (<65 years).

8.6 Patients with Mechanical Prosthetic Heart Valves

The use of Lovenox has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism [see *Warnings and Precautions* (5.7)].

8.7 Renal Impairment

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)]. In patients with renal failure, treatment with enoxaparin has been associated with the development of hyperkalemia [see *Adverse Reactions* (6.2)].

8.8 Hepatic Impairment

The impact of hepatic impairment on enoxaparin's exposure and antithrombotic effect has not been investigated. Caution should be exercised when administering enoxaparin to patients with hepatic impairment.

8.9 Low-Weight Patients

An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg). All such patients should be observed carefully for signs and symptoms of bleeding [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Accidental overdosage following administration of Lovenox may lead to hemorrhagic complications. Injected Lovenox may be largely neutralized by the slow IV injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of Lovenox may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

If at least 12 hours have elapsed since the last enoxaparin sodium injection, protamine administration may not be required; however, even with higher doses of protamine, the aPTT may remain more prolonged than following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

17 PATIENT COUNSELING INFORMATION

Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they are treated with Lovenox, and that they should report any unusual bleeding or bruising to their physician [see *Warnings and Precautions* (5.1, 5.5)].

Patients should inform physicians and dentists that they are taking Lovenox and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken [see *Warnings and Precautions* (5.3)].

Patients should inform their physicians and dentists of all medications they are taking, including those obtained without a prescription [see *Drug Interactions* (7)].

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