

Metformin Lowered Mortality in Heart Failure

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MUNICH — Metformin-treated diabetic patients with heart failure had strikingly lower morbidity and mortality than did those on oral sulfonylureas, in a long-term observational study.

“Our data suggest metformin is probably safe—and potentially effective—in congestive heart failure patients compared to treatment with sulfonylureas

alone,” Dr. Chim C. Lang reported at the annual congress of the European Society of Cardiology.

The safety issue is key. Heart failure has long been considered a relative contraindication to metformin because of a supposedly increased risk of drug-related, potentially fatal, lactic acidosis. The concern has its origins in problems with phenformin, another insulin-sensitizing biguanide. But several lines of evidence suggest the concern over metformin has

little or no merit, said Dr. Lang of Ninewells Hospital and Medical School, Dundee, Scotland.

How best to manage diabetes in patients with heart failure is a pressing issue, particularly in light of recent problems with the use of thiazolidinediones in this setting. Metformin could be a cheaper and safer alternative in this extremely common clinical situation. The incidence of heart failure in type 2 diabetic patients is 30.9 cases per 1,000 person-years, Dr. Lang noted.

He reported on all 774 type 2 diabetic patients who developed new-onset chronic heart failure in Tayside, Scotland, during 1994-2003. Ninety were managed with metformin monotherapy, 381 with sulfonylurea monotherapy, and 303 with both.

At 10 years of follow-up, 60% of patients in the metformin group were dead, compared with 77% who received sulfonylureas alone and 66% with combination therapy.

Patients managed with sulfonylureas alone tended to be older, to be sicker, and to have worse renal function, and were less likely to be on β -blockers and aspirin, so those differences were adjusted for in a Cox regression analysis. The result: an adjusted 28% relative risk reduction in mortality with metformin alone.

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The mortality curves diverged within the first year of follow-up. At 1 year, 90% of patients in the metformin group remained alive. They had an adjusted 55% relative risk reduction in 1-year mortality

compared with the sulfonylurea-only group, while patients on both forms of therapy had a 34% relative risk reduction.

The combined risk of death or all-cause hospitalization was reduced by 26% in the metformin group compared with those on sulfonylureas alone. However, there was no significant difference between the sulfonylurea-only and combination therapy groups in the combined end point.

In an interview, Dr. Lang noted that he is conducting an ongoing, double-blind, placebo-controlled, randomized trial assessing whether 4 months of metformin improves exercise capacity, flow-mediated dilatation, and muscle enzyme activity in insulin-resistant patients with heart failure. It's a highly practical question, as poor exercise tolerance is one of the most debilitating aspects of heart failure.

The notion that metformin is safe in the setting of heart failure received a boost from a recent systematic review by investigators at the University of Alberta, Edmonton. They concluded, “Of the current antidiabetic agents, metformin is the only one not associated with any measurable harm in people with diabetes and heart failure and is associated with reduced mortality” (BMJ 2007;335:497).

In addition, the most recent Cochrane review concluded there were no cases of fatal or nonfatal lactic acidosis in 274 studies involving nearly 60,000 patient-years of metformin use (Cochrane Database Syst. Rev. Jan. 25, 2006 [epub doi:10.1002/14651858.CD002967.pub2]).

The observational Tayside study was funded by the British Heart Foundation. Dr. Lang's ongoing randomized trial is sponsored by the University of Dundee. ■

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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