

18-Month Outcomes of REVERSE Favor CRT

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TORONTO — In patients with mild heart failure, cardiac resynchronization therapy improved composite clinical response scores at 18 months, was associated with left ventricular reverse remodeling, reduced the risk of heart failure hospitalization, and lowered the combined risk of morbidity and mortality, compared with optimal medical therapy.

The 18-month data from the European cohort of the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial supported secondary conclusions from the previously reported 12-month analysis, which, although it indicated that the trial missed its primary clinical composite end point, showed evidence of remodeling and clinical benefit with CRT in mild heart failure (HF).

“Ongoing CRT trials in New York Heart

Association class I and II patients may confirm these observations and expand the indication for CRT to this population of heart failure patients,” said Dr. William T. Abraham, who presented the data at the annual meeting of the Heart Failure Society of America.

The REVERSE trial was a multinational prospective effort involving 610 patients with mild or asymptomatic HF and ventricular dyssynchrony. All patients received a CRT device in addition to optimal med-

ical therapy; 191 were randomized to have the device turned on and 419 were randomized to have it turned off.

Eligible patients had left ventricular ejection fractions below 40%, had QRS durations of at least 120 milliseconds, and were already on optimal medical therapy.

The study's main results were published online in the *Journal of the American College of Cardiology* in September (doi:10.1016/j.jacc.2008.08.027). They showed that the trial failed to reach statis-



Rx only

Brief Summary of full prescribing information

WARNING: SPINAL / EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Monitor patients for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [see Warnings and Precautions (5.1) and Drug Interactions (7)].

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Deep Vein Thrombosis

Lovenox is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- in patients undergoing abdominal surgery who are at risk for thromboembolic complications [see *Clinical Studies* (14.1)].
- in patients undergoing hip replacement surgery, during and following hospitalization.
- in patients undergoing knee replacement surgery.
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

1.2 Treatment of Acute Deep Vein Thrombosis

Lovenox is indicated for:

- the **inpatient treatment** of acute deep vein thrombosis **with or without pulmonary embolism**, when administered in conjunction with warfarin sodium;
- the **outpatient treatment** of acute deep vein thrombosis **without pulmonary embolism** when administered in conjunction with warfarin sodium.

1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial Infarction

Lovenox is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

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

Lovenox has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute STEMI receiving thrombolysis and being managed medically or with Percutaneous Coronary Intervention (PCI).

4 CONTRAINDICATIONS

- Active major bleeding.
- Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium.
- Known hypersensitivity to enoxaparin sodium (e.g., pruritus, urticaria, anaphylactic/anaphylactoid reactions) [see *Adverse Reactions* (6.2)].
- Known hypersensitivity to heparin or pork products.
- Known hypersensitivity to benzyl alcohol (which is in only the multi-dose formulation of Lovenox).

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Hemorrhage

Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs [see *boxed Warning, Adverse Reactions* (6.2) and *Drug Interactions* (7)].

Lovenox should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.

Bleeding can occur at any site during therapy with Lovenox. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

5.2 Percutaneous Coronary Revascularization Procedures

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between Lovenox doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC Lovenox. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation [see *Dosage and Administration* (2.1)].

5.3 Use of Lovenox with Concomitant Medical Conditions

Lovenox should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction and hemorrhage.

5.4 History of Heparin-induced Thrombocytopenia

Lovenox should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

5.5 Thrombocytopenia

Thrombocytopenia can occur with the administration of Lovenox.

Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 1.3% in patients given Lovenox, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials.

Platelet counts less than 50,000/mm³ occurred at a rate of 0.1% in patients given Lovenox, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, Lovenox should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death [see *Warnings and Precautions* (5.4)].

5.6 Interchangeability with Other Heparins

Lovenox cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

5.7 Pregnant Women with Mechanical Prosthetic Heart Valves

The use of Lovenox for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed [see *Use in Specific Populations* (8.6)].

5.8 Benzyl Alcohol

Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed [see *Use in Specific Populations* (8.1)].

5.9 Laboratory Tests

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox in patients with significant renal impairment. If during Lovenox therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox [see *Clinical Pharmacology* (12.3)].

tical significance for its primary end point, the proportion of patients worsened at 12 months using a HF clinical composite score. Encouragingly, differences were seen in several secondary end points favoring CRT, including left ventricular end-systolic volume index (LVESVI) and left ventricular ejection fraction, suggesting that reverse left ventricular remodeling had in fact occurred. CRT patients also were less likely to require hospitalization for HF, compared with control patients.

At this meeting, Dr. Abraham presented the 18-month results from 262 patients in the European cohort, for whom follow-up is continuing to 24 months. These pa-

tients, he noted, differed significantly from the North American cohort in their baseline characteristics: They were younger, less likely to have ischemic cardiomyopathy, and less likely to have an implantable cardioverter defibrillator. The European patients had similar ejection fractions to the North American cohort, but had a bit more left ventricular enlargement and slightly longer QRS durations.

In this study population the primary end point significantly favored CRT therapy at 18 months, reported Dr. Abraham, director of the division of cardiovascular medicine at the Ohio State University, Columbus. The proportion of patients who had

worsened at 18 months was 29% in the control group vs. 15% in the CRT group, a highly significant difference.

LVESVI improvements seen at 12 months were sustained at 18 months. Also, left ventricular end-diastolic volume index and ejection fraction were both improved in CRT patients, compared with controls.

Furthermore, all-cause mortality did not differ between treatments, while a "remarkable" 58% reduction was seen in the risk of HF hospitalization in the CRT group at 18 months. The absolute rates of hospitalization at 18 months were 13.5% in the control arm and 5.5% in the CRT arm. The combined risk of first HF hospital-

ization and death was reduced 50% with CRT. Rates of non-HF hospitalization were identical in the CRT on and off groups.

These results "show that there is a favorable impact on remodeling that continues beyond 12 months and that there is a favorable impact on heart failure outcomes ... and no signal of an adverse effect on mortality," commented Dr. William G. Stevenson of Brigham and Women's Hospital in Boston.

REVERSE was sponsored by Medtronic Inc. Dr. Abraham reports research grants, speaker honoraria, and consulting fees from Medtronic, St. Jude Medical Inc., and Biotronik GmbH. ■

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Hemorrhage

The incidence of major hemorrhagic complications during Lovenox treatment has been low.

The following rates of major bleeding events have been reported during clinical trials with Lovenox Injection [see Tables 2 to 7].

Table 2
Major Bleeding Episodes Following Abdominal and Colorectal Surgery¹

Indications	Dosing Regimen	
	Lovenox 40 mg q.d. SC	Heparin 5000 U q8h SC
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)

¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

Table 3
Major Bleeding Episodes Following Hip or Knee Replacement Surgery¹

Indications	Dosing Regimen		
	Lovenox 40 mg q.d. SC	Lovenox 30 mg q12h SC	Heparin 15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis ²		n = 786 31 (4%)	n = 541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis Peri-operative Period ³	n = 288 4 (2%)		
Extended Prophylaxis Period ⁴	n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis ²		n = 294 3 (1%)	n = 225 3 (1%)

¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.

² Lovenox 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

³ Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

⁴ Lovenox 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox patients versus 1.8% of the placebo patients.

Table 4
Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness¹

Indications	Dosing Regimen		
	Lovenox ² 20 mg q.d. SC	Lovenox ² 40 mg q.d. SC	Placebo ²
Medical Patients During Acute Illness	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

² The rates represent major bleeding on study medication up to 24 hours after last dose.

Table 5
Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment¹

Indication	Dosing Regimen ²		
	Lovenox 1.5 mg/kg q.d. SC	Lovenox 1 mg/kg q12h SC	Heparin aPTT Adjusted IV Therapy
Treatment of DVT and PE	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

² All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovenox or standard heparin therapy and continuing for up to 90 days.

Table 6
Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen	
	Lovenox ¹ 1 mg/kg q12h SC	Heparin ¹ aPTT Adjusted IV Therapy
Unstable Angina and Non-Q-Wave MI ^{2,3}	n = 1578 17 (1%)	n = 1529 18 (1%)

¹ The rates represent major bleeding on study medication up to 12 hours after dose.

² Aspirin therapy was administered concurrently (100 to 325 mg per day).

³ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥ 3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Table 7
Major Bleeding Episodes in acute ST-segment Elevation Myocardial Infarction

Indication	Dosing Regimen	
	Lovenox ¹ Initial 30-mg IV bolus followed by 1 mg/kg q12h SC	Heparin ¹ aPTT Adjusted IV Therapy
acute ST-segment Elevation Myocardial Infarction	n = 10176 n (%)	n = 10151 n (%)
- Major bleeding (including ICH) ²	211 (2.1)	138 (1.4)
- Intracranial hemorrhages (ICH)	84 (0.8)	66 (0.7)

¹ The rates represent major bleeding (including ICH) up to 30 days

² Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by ≥ 5 g/dL. ICH were always considered major.

Thrombocytopenia:

[See Warnings and Precautions (5.5)]

Elevations of Serum Aminotransferases

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox should be interpreted with caution.

Local Reactions

Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of Lovenox.

Other

Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox group, are provided below [see Tables 8 to 11].