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 medical 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-

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 patients, 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 hospitalization 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. ■

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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 Surgery[1]

	Dosing Regimen	
	Lovenox	Heparin
Indications	40 mg q.d. SC	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 Surgery[1]

	Dosing Regimen		
	Lovenox	Lovenox	Heparin
Indications	40 mg q.d. SC	30 mg q12h SC	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 Illness[1]

	Dosing Regimen		
	Lovenox[2]	Lovenox[2]	Placebo[2]
Indications	20 mg q.d. SC	40 mg q.d. SC	
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 Treatment[1]

	Dosing Regimen[2]		
	Lovenox	Lovenox	Heparin
Indication	1.5 mg/kg q.d. SC	1 mg/kg q12h SC	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

	Dosing Regimen	
	Lovenox[1]	Heparin[1]
Indication	1 mg/kg q12h SC	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

	Dosing Regimen	
	Lovenox[1]	Heparin[1]
Indication	Initial 30-mg IV bolus followed by 1 mg/kg q12h SC	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].