

Bosentan Slows Progression in Class II PAH

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VIENNA — Patients with functional class II pulmonary arterial hypertension had significantly slower disease progression when treated with bosentan in a study with 185 patients, a finding that may shift the time to diagnose and start treatment of this disease.

The results support starting treatment of pulmonary arterial hypertension (PAH) “as soon as possible after the diagnosis is made because the majority of patients with PAH are in functional class II or III; the majority of PAH patients need treatment [with bosentan] according to these data,” Dr. Nazzareno Galiè said at the annual congress of the European Society of Cardiology. “In PAH it’s very important to prevent deterioration, and that’s what treatment with bosentan does. The results



EARLY showed that in a pure cohort of class II patients, early treatment may delay PAH progression.

DR. RUBIN

show that PAH is a progressive disease, even in class II, highlighting the need for early diagnosis and treatment.”

The Endothelin Antagonist Trial in Mildly Symptomatic PAH Patients (EARLY) study “is the only study to focus on class II patients,” and it included a strict definition of class II, said Dr. Galiè, professor of cardiology and head of the Pulmonary Hypertension Centre at the University of Bologna, Italy.

Based on these and other findings, applications have been filed with the Food and Drug Administration and similar agencies in other countries to expand bosentan treatment to patients with class II PAH. Bosentan (Tracleer) is already marketed for treating classes III and IV PAH by Actelion. The new study was sponsored by Actelion, and Dr. Galiè is a speaker for and consultant to Actelion.

“The EARLY study results, and the results from [five] other studies that included class II PAH patients, support the benefit of treating patients with less-severe PAH. The added strength of the data from EARLY is that they demonstrated in a pure cohort of class II patients that early treatment may delay progression of the disease,” commented Dr. Lewis J. Rubin, a coauthor of the study and professor of medicine and director of pulmonary and critical care medicine at the University of California, San Diego. Dr. Rubin is a consultant to Actelion.

The study enrolled patients aged 12 years and older, mean age 44, with PAH rated as functional class II by World Health Organization criteria. The disease could have been idiopathic (as it was in about 60% of patients), or caused by congenital heart disease (in about 17%), connective tissue disease (in about 18%), or HIV infection (in about 5%). The average

duration of PAH was about 3 years. Patients were randomized to treatment with either 62.5 mg bosentan b.i.d. for 4 weeks, followed by 125 mg b.i.d. for 5 months, or placebo.

After 6 months of treatment, the change from baseline in pulmonary vascular resistance, one of two primary end points, was increased by about 7% among 88 evaluable patients in the placebo group, and was decreased by about 16% in 80 patients in the bosentan group. The overall

effect of bosentan treatment was to lower pulmonary vascular resistance by 23%, compared with placebo, a statistically significant effect.

The second primary end point was change in exercise capacity, measured by distance walked in 6 minutes. By this measure, bosentan was linked to a significant, 19-meter boost in distance walked, compared with placebo, Dr. Galiè reported.

Bosentan treatment also led to significant improvements in time to clinical

worsening, and a reduction in the percentage of patients whose condition worsened. Symptomatic progression of PAH occurred in 10% of patients on placebo, compared with 1% of the patients treated with bosentan. “With bosentan, there is more preservation of functional class,” said Dr. Galiè. Bosentan also led to significant improvements in self-rated quality of life, and a significant reduction in serum levels of NT-probrain natriuretic peptide (NT-proBNP). The drug was well tolerat-

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LOVENOX® (enoxaparin sodium injection) in the Management of ST-segment Elevation Myocardial Infarction: An Overview of ExTRACT-TIMI 25

Results from a recent landmark trial demonstrated that enoxaparin was effective in the management of STEMI

Marc Cohen, MD

Introduction: Redefining Antithrombotic Therapy in ACS Patients Receiving Lytics

Among patients presenting with acute coronary syndrome (ACS) in the United States, 500,000 (roughly 30%) will experience ST-segment elevation myocardial infarction (STEMI). The remainder of patients will have unstable angina (UA) or NSTEMI.¹

Current guidelines advocate giving fibrinolytics along with an antiplatelet agent, such as oral aspirin, and an anticoagulant, such as unfractionated heparin (UFH) or low molecular weight heparin.¹ Recently, the superiority of LOVENOX® versus UFH in acute STEMI patients undergoing fibrinolysis was established by the landmark Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction 25 (ExTRACT-TIMI 25) study.²

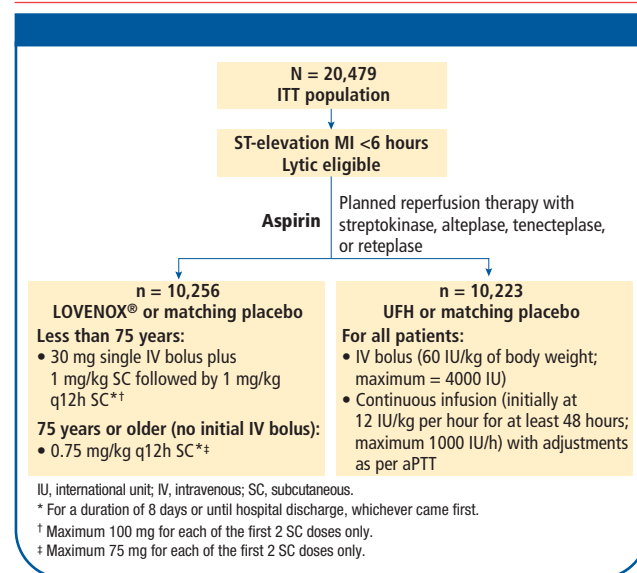
Acute STEMI: A New Indication for LOVENOX®

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).

LOVENOX® vs UFH in STEMI Patients Undergoing Fibrinolysis: ExTRACT-TIMI 25 Findings

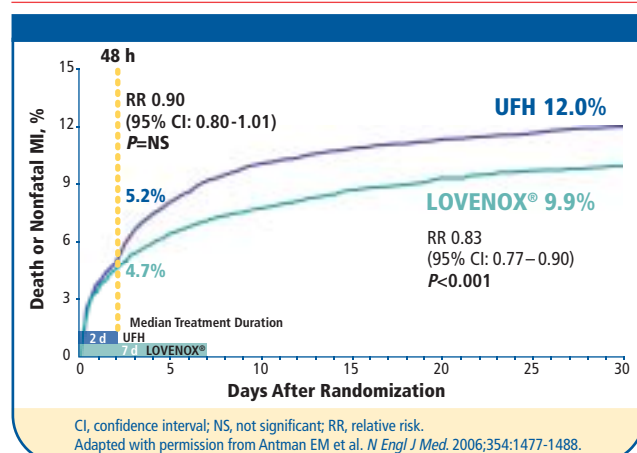
ExTRACT-TIMI 25 was a randomized, double-blind, double-dummy clinical outcomes trial that compared the use of a strategy of LOVENOX® or UFH during index hospitalization in 20,479 adults with STEMI who underwent fibrinolysis at 674 sites in 48 countries.² Figure 1 presents the study design.³ Findings were published in April 2006 in the *New England Journal of Medicine*.²

Figure 1. ExTRACT-TIMI 25 Study Design



Significantly better efficacy was reported for LOVENOX®. The study’s primary composite endpoint—death or nonfatal myocardial infarction (MI) at 30 days—occurred in 12% of the UFH group versus 9.9% of the LOVENOX® group ($P < 0.001$) (Figure 2).² Similarly, LOVENOX® was superior to UFH for the secondary composite endpoint of death, nonfatal MI, or urgent revascularization at 30 days. This endpoint occurred in 11.7% of the LOVENOX® group versus 14.5% of the UFH group ($P < 0.001$).²

Figure 2. ExTRACT-TIMI 25—Primary Endpoint Results



ed, with an adverse event profile similar to the placebo group.

To boost the number of patients with PAH who start treatment early, Dr. Galie suggested screening for PAH in groups that are known to have a relatively high prevalence of PAH. This includes patients with connective tissue diseases, such as scleroderma, patients infected with HIV, and patients with congenital heart disease.

Three other reports at the meeting dealt with using bosentan to treat PAH; all three studies also were sponsored by Actelion.

One study enrolled 157 patients who had a specific, relatively common form of PAH, chronic thromboembolic pul-

monary hypertension (CTEPH), which was inoperable or recurrent. The results showed that treatment with bosentan was safe and led to improvements in pulmonary vascular resistance and other measures, Dr. Irene Lang, professor of vascular biology at the Medical University of Vienna, reported at the meeting.

The Bosentan Effects in Inoperable Forms of CTEPH (BENEFIT) study randomized patients to treatment with 62.5 mg bosentan b.i.d. for 4 weeks, followed by 125 mg b.i.d. for 12 weeks or placebo. Their average age was 63 years. Bosentan was linked with a significant, 24% reduction in peripheral vascular resistance in 66

evaluable patients, compared with 71 placebo patients. Treatment also significantly boosted cardiac index, and cut NT-proBNP levels and dyspnea scores. Bosentan treatment had no significant effect on 6-minute walk distance.

Another study assessed the acute hemodynamic effect of a single, 25-mg dose of sildenafil in 44 patients with PAH already on chronic bosentan treatment. The results showed that the single sildenafil dose was safe, and after 60 minutes led to a significant drop in pulmonary vascular resistance, total pulmonary resistance, pulmonary artery pressure, and cardiac output.

The third study examined the pharmacokinetics of a new formulation of bosentan designed for use in children. Results from 35 patients aged 2-11 years showed that the formulation led to reasonable serum levels and a good safety profile.

"New drugs such as bosentan have dramatically improved outcomes for patients with pulmonary arterial hypertension. It is gratifying to see extension of the research into patients with early disease and in children," commented Dr. Daniel Jones, professor of medicine and dean of the medical school at the University of Mississippi, Jackson, and president of the American Heart Association. ■

Safety endpoints included major bleeding, which occurred in 2.1% of the LOVENOX® group and 1.4% of the UFH group by Day 30 ($P < 0.001$).² There was no statistically significant difference in intracranial hemorrhage between LOVENOX® and UFH (0.8% vs. 0.7%, respectively; $P = 0.14$).

LOVENOX® Dose Adjustments for Specified Patient Populations

STEMI dosing schedule for LOVENOX®^{4*}

STEMI patient population	
<75 years of age	30 mg single IV bolus plus 1 mg/kg SC followed by 1 mg/kg q12h SC (maximum 100 mg for each of the first 2 SC doses only)

STEMI DOSING FOR SPECIAL POPULATIONS	Elderly	
	≥75 years of age	No initial IV bolus; 0.75 mg/kg q12h SC (maximum 75 mg for each of the first 2 SC doses only)
	Severe renal impairment (creatinine clearance [CrCl] <30 mL/min)	
	<75 years of age	30 mg single IV bolus plus 1 mg/kg SC followed by 1 mg/kg SC once daily
≥75 years of age	No initial IV bolus; 1 mg/kg SC once daily	

Thrombolytic therapy	
When LOVENOX® administered in conjunction with thrombolytic (fibrin-specific or non-fibrin-specific)	Give LOVENOX® between 15 minutes before and 30 minutes after start of fibrinolytic therapy
Patients managed with PCI	
If the last LOVENOX® SC administration was given:	
<8 hours before balloon inflation	No additional dosing needed
>8 hours before balloon inflation	Administer an IV bolus of 0.3 mg/kg of LOVENOX®

In ExTRACT-TIMI 25...

- The first SC dose of LOVENOX® was given within 15 minutes of administration of the IV bolus dose²
- The LOVENOX® treatment duration was 8 days or until hospital discharge, whichever came first. An optimal duration of treatment is not known, but is likely to be longer than 8 days^{2,4}
- The incidence of bleeding complications was higher in patients ≥65 years of age compared with younger patients (<65 years of age)⁴

IV dosage proven effective in acute STEMI patients

- 5 minutes after IV dosing of LOVENOX®, mean anti-Xa levels increase from 0 to 1.25 U/mL and then decrease to 0.63 U/mL at 8 hours⁵
- After an initial IV bolus of LOVENOX® followed by the first SC dose, adequate anti-Xa levels (-0.66 ± 0.23 IU/mL) are reached immediately and are maintained until the SC dose is absorbed⁶

* All patients should receive oral aspirin therapy as soon as they are identified as having STEMI and be maintained with 75 mg to 325 mg once daily unless contraindicated.

IMPORTANT SAFETY 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 nonsteroidal 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]).

LOVENOX® (enoxaparin sodium injection) cannot be used interchangeably with other low molecular weight heparins or unfractionated heparin, as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. As with other anticoagulants, use with extreme caution in patients with conditions that increase the risk of hemorrhage. Dosage adjustment is recommended in patients with severe renal impairment. Unless otherwise indicated, agents that may affect hemostasis should be discontinued prior to LOVENOX® therapy. Bleeding can occur at any site during LOVENOX® therapy. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site (see WARNINGS and PRECAUTIONS).

In the STEMI pivotal trial, the rates of major hemorrhages (defined as requiring 5 or more units of blood for transfusion, or 15% drop in hematocrit or clinically overt bleeding, including intracranial hemorrhage) at 30 days were 2.1% in the LOVENOX® group and 1.4% in the unfractionated heparin group. The rates of intracranial hemorrhage at 30 days were 0.8% in the LOVENOX® group and 0.7% in the unfractionated heparin group. The 30-day rate of the composite endpoint of death, myocardial infarction or ICH (a measure of net clinical benefit) was significantly lower in the LOVENOX® group (10.1%) as compared to the unfractionated heparin group (12.2%).

Thrombocytopenia can occur with LOVENOX®. In patients with a history of heparin-induced thrombocytopenia, LOVENOX® should be used with extreme caution. 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 have been observed in clinical practice. (See WARNINGS.)

The use of LOVENOX® has not been adequately studied for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves. (See WARNINGS.)

LOVENOX® is contraindicated in patients with hypersensitivity to enoxaparin sodium, heparin, or pork products, and in patients with active major bleeding.

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Please see brief prescribing information, including boxed warning, on the next page.