Most Eligible, Appropriate Patients Get an ICD

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TORONTO — The rate at which eligible, appropriate patients with a low left ventricular ejection fraction miss out on getting an implantable cardioverter defibrillator might be lower than most people think.

After ineligible patients and those who refused the device were accounted for, the "true miss" rate, or rate of patients with ejection fractions of 35% or less who failed to get an ICD was 7% in a random sample of 228 patients who underwent echocardiography scanning during 2005-2007 at Jefferson Medical College, Philadelphia.

However, the ICD implant rate in large, observational studies has usually been reported as about 25%-40% in patients with ejection fractions of 35% or less, Dr. Shaw Natan said while presenting a poster at the 14th World Congress on Heart Disease.

At Jefferson, the implant rate in the 228 patients who were the focus of this study was 42%, suggesting a miss rate of 68%. But assessing each patient individually showed that in most cases there was a good reason for the omission," said Dr. Natan, a cardiologist formerly at Jefferson and now at St. Elizabeth's Medical Center in Boston, in an interview.

The 228 patients in the sample had an average age of 66 (range 29-96), and 68% were men. Their average LVEF was 21%.

Among the 132 patients in the sample who did not get an ICD, 89 (39% of the total) were ineligible: 34 had an inadequate trial of medical treatment or revascularization, 19 died, 17 had a life expectancy of less than 1 year or dementia, 10 were lost to follow-up, and 9 had other reasons.

Of the remaining 43 patients who were eligible for an ICD, 27 declined the device when it was offered. This left 16 patients (7% of the total number of patients evaluated) who were true misses for an ICD: They had no contraindications and were willing to receive treatment. ■

Table 8
Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Patients[1] Undergoing Abdominal or Colorectal Surgery

	Dosing Regimen			
	Lovenox 40 mg q.d. SC n = 1228 %		Heparin 5000 U q8h SC n = 1234 %	
Adverse Event	Severe	Total	Severe	Total
Hemorrhage	<1	7	<1	6
Anemia	<1	3	<1	3
Ecchymosis	0	3	0	3

[1] Excluding unrelated adverse events.

Table 9
Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Patients[1] Undergoing Hip or Knee Replacement Surgery

	Dosing Regimen									
	Lovenox 40 mg q.d. SC				Lovenox 30 mg q12h SC		Heparin 15,000 U/24h SC		Placebo q12h SC	
	Peri-operative Period n = 288[2] %		Extended Prophylaxis Period n = 131[3] %		n = 1080 %		n = 766 %		n = 115 %	
Adverse Event	Severe	Total	Severe	Total	Severe	Total	Severe	Total	Severe	Total
Fever	0	8	0	0	<1	5	<1	4	0	3
Hemorrhage	<1	13	0	5	<1	4	1	4	0	3
Nausea					<1	3	<1	2	0	2
Anemia	0	16	0	<2	<1	2	2	5	<1	7
Edema					<1	2	<1	2	0	2
Peripheral edema	0	6	0	0	<1	3	<1	4	0	3

[1] Excluding unrelated adverse events.

[2] Data represents Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox peri-operatively in an unblinded fashion in one clinical trial.

[3] Data represents Lovenox 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

Table 10
Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Medical Patients[1] With Severely Restricted Mobility During Acute Illness

	Dosing Regimen	
	Lovenox 40 mg q.d. SC n = 360 %	Placebo q.d. SC n = 362 %
Adverse Event		
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

[1] Excluding unrelated and unlikely adverse events.

Table 11
Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Patients[1] Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

	Dosing Regimen					
	Lovenox 1.5 mg/kg q.d. SC n = 298 %		Lovenox 1 mg/kg q12h SC n = 559 %		Heparin aPTT Adjusted I.V. Therapy n = 544 %	
Adverse Event	Severe	Total	Severe	Total	Severe	Total
Injection Site Hemorrhage	0	5	0	3	<1	<1
Injection Site Pain	0	2	0	2	0	0
Hematuria	0	2	0	<1	<1	2

[1] Excluding unrelated adverse events.

Adverse Events in Lovenox-Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction:
Non-hemorrhagic clinical events reported to be related to Lovenox therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC Lovenox than in patients treated with IV heparin.

Serious adverse events with Lovenox or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox group are provided below (irrespective of relationship to drug therapy) [see Table 12].

Table 12
Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox-Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction

	Dosing Regimen	
	Lovenox 1 mg/kg q12h SC n = 1578 n (%)	Heparin aPTT Adjusted IV Therapy n = 1529 n (%)
Adverse Event		
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

Adverse Reactions in Lovenox-Treated Patients With acute ST-segment Elevation Myocardial Infarction:
In a clinical trial in patients with acute ST-segment elevation myocardial infarction, the only additional possibly related adverse reaction that occurred at a rate of at least 0.5% in the Lovenox group was thrombocytopenia (1.5%)

6.2 Postmarketing Experience
There have been reports of epidural or spinal hematoma formation with concurrent use of Lovenox and spinal/epidural anesthesia or spinal puncture. The majority of patients had a postoperative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis.

Local reactions at the injection site (*e.g.* nodules, inflammation, oozing), systemic allergic reactions (*e.g.* pruritus, urticaria, anaphylactic/anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, skin necrosis (occurring at either the injection site or distant from the injection site), thrombocytosis, and thrombocytopenia with thrombosis [see *Warnings and Precautions (5.5)*] have been reported. Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward the development of hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparing drugs, administration of potassium, hematoma in body tissues). Very rare cases of hyperlipidemia have also been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate reliably their frequency or to establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS
Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring [see *Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category B
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes the potential of Lovenox to increase the risk of developmental abnormalities above background risk.

Fetal Risk Summary
Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox contains 15 mg benzyl alcohol per 1 mL as a preservative [see *Warnings and Precautions (5.8)*].

Clinical Considerations
It is not known if either dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see *Warnings and Precautions (5.7) and Use in Specific Populations (8.6)*]. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired