Compared with normotensive men with a history of cardiovascular disease, those with prehypertension as defined by Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VII had an 18% greater risk of cardiovascular death after adjustment for age, smoking, alcohol intake, diabetes, physical activity, body mass index, and geographic region. Prehypertensive women had a 21% increase in risk.

Men and women with stage 1 hypertension had risk increases of 24% and 62%. Cardiovascular mortality was increased by 71% in men with stage 2 hypertension and by 72% in stage 2 women. ■

Biofeedback Cuts BP in Type 2 Diabetes

BY MIRIAM E. TUCKER
Senior Writer

COPENHAGEN — Self-treatment with a biofeedback device that guides breathing can significantly lower blood pressure among patients with type 2 diabetes, Dr. Moshe H. Schein reported at the annual meeting of the European Association for the Study of Diabetes.

The device, called RESPeRATE, is made by InterCure Ltd., Lod, Israel. It was approved for use by the Food and Drug Administration in 2002 for use in stress reduction and as adjunctive treatment for hypertension, together with other pharmacologic and nonpharmacologic interventions. It works by using melodic tones to guide the patient through progressively slower inhalation and exhalation.

Previous data have shown that the device-guided technique results in significant blood pressure reductions among hypertensive patients who use it at home on a daily basis (J. Hum. Hypertens. 2001;15:271-8).

In the new study, a total of 60 patients with type 2 diabetes who had blood pressures greater than 130/80 mm Hg were randomized to use of the device for 15 minutes a day along with usual treatment, or to usual treatment alone for 8 weeks. The group was 60% male, with a mean age of 64 years and a mean body mass index of 30 kg/m^2.

At baseline, mean blood pressure was 149/82 mm Hg in the treatment group and 146/81 mm Hg in the control group, even though the majority of patients—78% of the treatment group and 89% of the controls—were taking blood pressure medication, said Dr. Schein, director of the Family Medicine Unit, Hadassah University Hospital, Jerusalem.

Systolic blood pressure dropped by 9.5 mm Hg in the group using the device, compared with an increase of 2.1 mm Hg among the controls, a significant difference between the two groups.


INTERCURE LTD.

The RESPeRATE device uses melodic tones to slow the patient's breathing.

The change in pulse pressure also was significantly different at 2 months; it dropped by 5.9 mm Hg from a mean of 67 mm Hg at baseline in the guided-breathing group, and increased by 3.6 mm Hg from a mean of 66 mm Hg in the controls.

Diastolic blood pressure dropped slightly in both groups, by 3.5 mm Hg in the guided-breathing patients and by 1.5 mm Hg among the controls. That difference was not significant.

There was a dose-response relationship between use of the device and systolic blood pressure reduction: The longer the patient spent in the slow breathing exercise, the greater the drop. (Although patients had been instructed to perform the device-guided breathing exercise daily, they actually did it for a mean of 5.6 sessions per week. However, the duration of each session lasted 15.9 minutes, slightly longer than the instructed 15 minutes, and patients spent a mean of 40.4 minutes per week in slow breathing.)

Blood pressure control—defined as 130/80 mm Hg or below—was achieved by 8 of 30 (27%) in the device group, compared with just 2 of the 30 (7%) of the controls, Dr. Schein reported. ■

Other:
Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, 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 Injection group, are provided below.

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

	Dosing Regimen			
	Lovenox Inj. 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.

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

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

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

	Dosing Regimen	
	Lovenox Inj. 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.

Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction:
Non-hemorrhagic clinical events reported to be related to Lovenox Injection 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 Injection than in patients treated with i.v. heparin.
Serious adverse events with Lovenox Injection 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 Injection group, are provided below (irrespective of relationship to drug therapy).

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

	Dosing Regimen	
	Lovenox Inj. 1 mg/kg q12h SC n = 1578	Heparin aPTT Adjusted i.v. Therapy n = 1529
Adverse Event	n (%)	n (%)
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 Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

	Dosing Regimen					
	Lovenox Inj. 1.5 mg/kg q.d. SC n = 298		Lovenox Inj. 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.

Ongoing Safety Surveillance:
Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative 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. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
Other Ongoing Safety Surveillance Reports:
Local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, thrombocytosis, and thrombocytopenia with thrombosis (see **WARNINGS, Thrombocytopenia**). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

OVERDOSAGE
Symptoms/Treatment:
Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. Injected Lovenox Injection may be largely neutralized by the slow i.v. injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox Injection, 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 Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.
After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found 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, USP, products.
A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

DOSAGE AND ADMINISTRATION
All patients should be evaluated for a bleeding disorder before administration of Lovenox Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring Lovenox Injection activity, routine monitoring of coagulation parameters is not required (see **PRECAUTIONS, Laboratory Tests**).
Note: Lovenox Injection is available in two concentrations:
1. 100 mg/mL Concentration: 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes, 300 mg / 3.0 mL multiple-dose vials.
2. 150 mg/mL Concentration: 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.
Adult Dosage:
Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.
Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.
Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovenox Injection has been well tolerated in the controlled clinical trial.
Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovenox Injection is **1 mg/kg** administered SC **every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox Injection. 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. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox Injection has been well tolerated in clinical trials.
Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC **or 1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox Injection). Lovenox Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovenox Injection administration has been well tolerated in controlled clinical trials.
Renal Impairment:
Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.
The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in the following table (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations** and **PRECAUTIONS, Renal Impairment**).

Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30mL/minute)

Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily

Administration:
Lovenox Injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.
The use of a tuberculin syringe or equivalent is recommended when using Lovenox multiple-dose vials to assure withdrawal of the appropriate volume of drug.
Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.
Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.
Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

• Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

• Inject using standard technique, pushing the plunger to the bottom of the syringe.

• Remove the syringe from the injection site keeping your finger on the plunger rod.

• Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

• Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature].
Keep out of the reach of children.

[1] Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *Br J Obstet Gynec* 2001; 108 (11): 1134-40.

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LOVENOX®
(enoxaparin sodium injection)