

# Glucose Levels Tied to Liver Transplant Outcomes

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ORLANDO — Intraoperative glucose levels were often “undesirably high” among orthotopic liver transplant recipients in a 5-year, retrospective study at Tufts Medical Center in Boston.

These glucose levels, and their fluctuations, directly affected the probability of mortality and the length of stay in the surgical ICU, the researchers found.

In addition, “these effects were pronounced in diabetics,” Dr. Roman Schumann said. The analysis included 86 liver transplant recipients, 20 of whom had a history of diabetes mellitus.

Although control of glucose levels during cardiac surgery is well studied (Anesth. Analg. 2008;107:51-8; Ann. Intern. Med. 2007;146:233-43), data are limited regarding links between glycemic control and outcomes in patients undergoing orthotopic liver transplantation.

For that reason, Dr. Schumann and his colleagues looked at mean and peak glucose levels and variability of glucose levels, as well as insulin administration, in the years prior to adoption of an intraoperative glucose control protocol at Tufts.

They found a mean intraoperative glucose level of 187 mg/dL among nondiabetic recipients and 213 mg/dL among the diabetic patients; the difference was statistically significant. Mean peak glucose levels, however, did not differ significant-

ly: 262 mg/dL among nondiabetic patients and 281 mg/dL for diabetic patients.

“Mean glucoses were fairly high for all patients, and peak glucoses were very high, I would say,” Dr. Schumann noted at the annual meeting of the American Society of Anesthesiologists.

“It turned out that peak glucose and variability were important for length of stay in the ICU,” Dr. Schumann said. Mean glucose levels, in contrast, were not significantly associated with a longer length

## ADVERTISEMENT

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THE-PRINCE (Thromboembolism Prevention in Cardiac or Respiratory Disease With Enoxaparin) was a multicenter, controlled, randomized, open-label trial that assessed the efficacy and safety of unfractionated heparin (UFH) and LOVENOX® (enoxaparin sodium injection) in patients with CHF or severe respiratory disease.<sup>14</sup> LOVENOX® was shown to be at least as effective as UFH in the prevention of thromboembolic events in patients with heart failure or severe respiratory disease. The overall VTE rate for LOVENOX® was 8.4% vs 10.4% for UFH.

### LOVENOX® Was Effective in Reducing the Incidence of DVT/PE in Patients Undergoing Abdominal or Pelvic Surgery for Cancer

In ENOXACAN (Enoxaparin and Cancer), patients undergoing abdominal or pelvic surgery for cancer were randomized to either LOVENOX® 40 mg subcutaneously (SC) once daily or UFH 5000 IU 3 times daily given 2 hours before surgery and continued for 10 ± 2 days.<sup>15</sup> There was no significant difference in thromboembolic events comparing LOVENOX® 40 mg SC once daily with UFH 5000 IU SC 3 times daily (14.7% vs 18.2%, respectively).<sup>15</sup>

Overall, there was no difference in the incidence of major hemorrhagic events between LOVENOX® 40 mg SC once daily and UFH 5000 IU SC 3 times daily (4.1% vs 2.9%, respectively).<sup>15</sup>

LOVENOX® was demonstrated to be as safe and effective as UFH given 3 times daily for prophylaxis of DVT/PE in patients undergoing abdominal or pelvic surgery for cancer.<sup>15</sup>

#### Incidence of DVT/PE in patients undergoing cancer surgery<sup>15</sup>

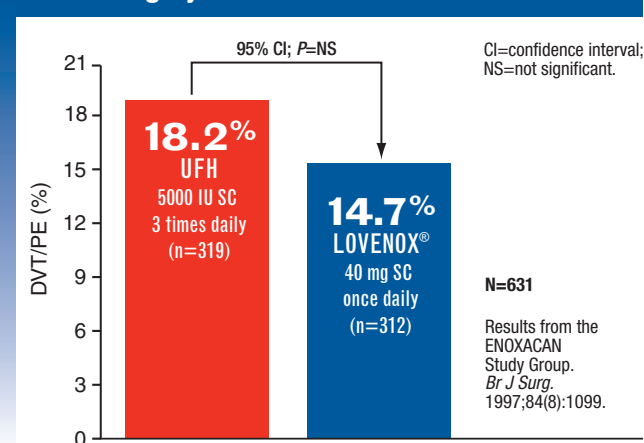


Figure 3. Incidence of DVT/PE in patients undergoing cancer surgery.

### In Patients Undergoing Hip- or Knee-Replacement Surgery, LOVENOX® Reduced the Incidence of DVT/PE Compared to Warfarin

In a large, randomized, multicenter, open-label, parallel-group clinical trial with over 3000 patients undergoing total hip arthroplasty, LOVENOX® significantly reduced DVT risk versus warfarin during hospitalization (0.3% vs 1.1%, respectively).<sup>16</sup>

The incidence of major bleeding episodes was comparable between LOVENOX® and warfarin-treated patients (0.6% vs 0.3%, respectively).<sup>16</sup>

#### Incidence of DVT in patients undergoing hip-replacement surgery<sup>16</sup>

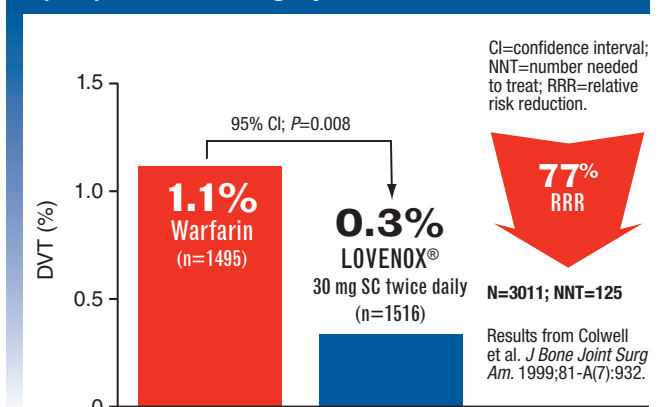


Figure 4. Incidence of DVT in patients undergoing hip-replacement surgery.

In patients undergoing total knee arthroplasty, a randomized, multicenter, open-label, parallel-group study demonstrated that LOVENOX® was able to significantly reduce the incidence of DVT/PE compared to warfarin (25.4% vs 45.5%, respectively).<sup>17</sup>

There was no significant difference in the number of major bleeding episodes between both treatment groups.<sup>17</sup>

#### Incidence of DVT/PE in patients undergoing knee-replacement surgery<sup>17</sup>

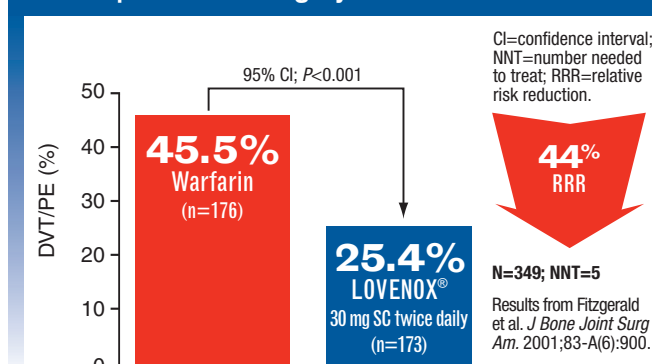


Figure 5. Incidence of DVT/PE in patients undergoing knee-replacement surgery.

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of ICU stay. None of these factors was significantly associated with length of hospital stay.

Dr. Schumann was an anesthesiologist at Tufts at the time of the study. He currently works at Beth Israel Deaconess Medical Center, also in Boston.

Mean fluctuations in intraoperative glucose did not differ significantly between groups: 138 mg/dL among nondiabetic patients vs. 142 mg/dL among diabetic patients.

Not surprisingly, a lower percentage of nondiabetic patients, 38%, received intraoperative insulin, compared with 65% of diabetic patients. Length of hospital stay,

time to extubation, and probability of hospital mortality did not differ significantly between those who received insulin and those who did not.

The study included 61 men and 25 women with a mean age of 52 years. Average body mass index was 28 kg/m<sup>2</sup>. Demographic variables were similar, except diabetic recipients were older and required more time to extubation. All patients had chronic liver failure and received livers from brain-dead donors. Combined liver-kidney transplant recipients were excluded.

Glycemic control was managed at the discretion of the anesthesia team. Glucose determinations were performed hourly at

a satellite laboratory in the operating room.

Dr. Schumann and his associates used a surrogate measure for probability of hospital mortality, the Simplified Acute Physiology Score (SAPS) II. They found that increasing patient age and Model for End-Stage Liver Disease (MELD) score were each significantly associated with increased probability of mortality. "All glucose values, as they increased, adversely affected SAPS score," he said.

Three patients died, Dr. Schumann said in response to a meeting attendee's question. "Only three died over 5 years?" the attendee asked. "Yes, this was a small number of patients," Dr. Schumann replied.

The retrospective design was a limitation, Dr. Schumann said during a question-and-answer session. Another limitation was that the researchers considered only intraoperative glucose levels. "There are a lot of factors besides glucose that can affect these factors, so it's a bit bold to say glucose is involved to the extent we think it may be," he said.

The study results support use of protocol-driven glycemic control during orthotopic liver transplantation, Dr. Schumann said. Precise target values remain unknown, however. Future prospective studies may be able to determine the ideal target levels, he added. ■

Despite evidence-based clinical practice guidelines for the prophylaxis of DVT and PE, recommendations are underutilized and many patients are not receiving proper anticoagulation. This is not only detrimental to patient care but also increases the burden on the health care system.

*Authored by Frank Michota, MD; Cleveland Clinic; sanofi-aventis consultant.*

## 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 (UFH), 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 (HCT) or blood pressure should lead to a search for a bleeding site. (See WARNINGS and PRECAUTIONS)

- In the ST-segment elevation myocardial infarction (STEMI) pivotal trial, the rates of major hemorrhages (defined as requiring 5 or more units of blood for transfusion, or 15% drop in HCT or clinically overt bleeding, including intracranial hemorrhage [ICH]) at 30 days were 2.1% in the LOVENOX® group and 1.4% in the UFH group. The rates of ICH at 30 days were 0.8% in the LOVENOX® group and 0.7% in the UFH group. The 30-day rate of the composite endpoint of death, myocardial infarction (MI), or ICH (a measure of net clinical benefit) was significantly lower in the LOVENOX® group (10.1%) as compared to the UFH group (12.2%)
- Thrombocytopenia can occur with LOVENOX®. In patients with a history of heparin-induced thrombocytopenia (HIT), LOVENOX® should be used with extreme caution. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm<sup>3</sup>, LOVENOX® should be discontinued. Cases of HIT have been observed in clinical practice. (See WARNINGS and PRECAUTIONS)
- The use of LOVENOX® has not been adequately studied for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves. (See WARNINGS and PRECAUTIONS)
- 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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