studied (400 nM), blood loss from a tail clip was not increased compared with saline controls.

By comparison, at 5% ferric chloride, a dose of heparin (200 U/kg) that causes bleeding in all animals in this thrombosis/bleeding model has no effect on arterial thrombosis, said Dr. Baglin. At 1000 U/kg, heparin reduces occlusion but universally causes fatal bleeding.

He concluded that an antibody that appears to prevent thrombosis without causing bleeding has been identified. A therapeutic derivative of this IgA may potentially permit unlimited dose escalation of antithrombotic therapy without increasing bleeding, given the dissociation of the antithrombotic effect from the bleeding effect.

Use of Dalteparin Beyond 6 Months in Cancer Patients With VTE Is Feasible

Written by **Maria Vinall**

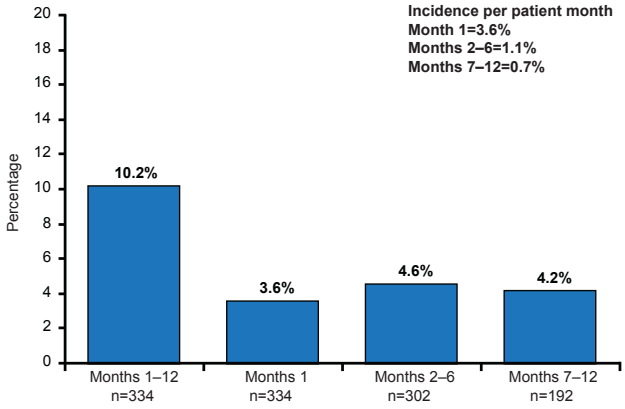
Although the guidelines for treating venous thromboembolism (VTE) in cancer patients recommend anticoagulation with low-molecular-weight heparin for at least 3 to 6 months, or for the duration of the malignancy, uncertainty exists concerning whether to extend anticoagulation longer to prevent recurrence of VTE. In a study presented by The Lord Ajay K. Kakkar, MD, University College London, London, United Kingdom, dalteparin sodium administered beyond 6 months was not associated with an increase in bleeding relative to the initial period of therapy.

The objective of the Evaluation of Dalteparin for Long-Term (One Year) Treatment of Blood Clots in Subjects With Cancer study [DALTECAN; NCT00942968] was to assess the consequences of extending anticoagulation with dalteparin beyond 6 months in cancer-associated VTE. This was a Phase 4 multicenter, single-arm, open-label study that enrolled men and women aged ≥18 years with histologically confirmed cancer and a new VTE (objectively confirmed deep vein thrombosis [DVT], proximal vein thrombosis, pulmonary embolism, or both). All patients received treatment with dalteparin 200 IU/kg daily subcutaneously for 1 month, followed by 150 IU/kg daily for up to 11 months. The study was conducted at 50 sites in the United States, Europe, and Canada.

The primary study endpoint was major bleeding events for Months 7 to 12 relative to Months 2 to 6 of dalteparin therapy. Secondary endpoints included rate of recurrent VTE, time to symptomatic recurrent VTE, rate of minor bleeding events, time to first major or any bleeding event, and safety and tolerability of extended treatment with dalteparin. Bleeding and recurrent VTE were centrally adjudicated.

Patients had a mean age of 64 years and about half were men. Most (78%) were Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1. Of the 334 patients who received drug treatment, 109 (32.2%) completed the 12-month study. Of the 229 patients who discontinued the study, 76 were due to death and 60 were due to an adverse event. The remaining discontinuations were due to withdrawal of consent (n=42) or "other" reasons (n=51). Most (92%) patients had solid tumors and the majority was stage III or IV. Therapy adherence was 96% across the entire cohort, with a median treatment duration of 211 days. The overall frequency of major bleeding was 10.2%, observed at a rate of 1.3% per patient-month.

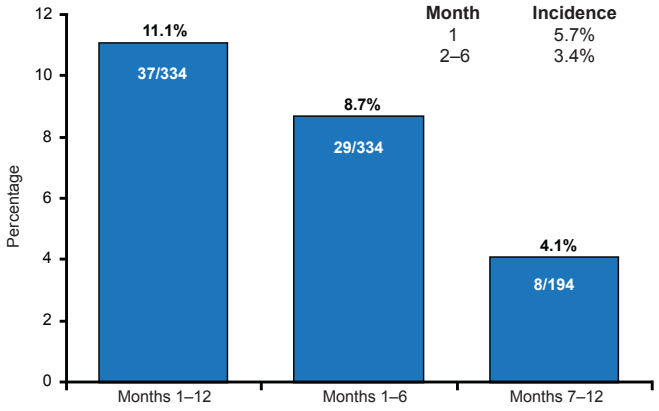
Figure 1. The Incidence of Major Bleeding Events



The highest major bleeding rate was in the first month of dalteparin therapy at 3.6%, with the frequency declining to 1.1% during Months 2 to 6, and 0.7% over Months 7 to 12, with no statistically significant difference in rates between Months 2 to 6 and 7 to 12 (p=0.39). The incidence of all bleeding events was 13.2% in Month 1, 4.5% in Months 2 to 6, and 2.7% in Months 7 to 12, with a total 1 to 12 month incidence rate of 33.5%.

The incidence of new or recurrent VTE was 11.1% (37 patients), a rate of 1.4% per patient-month. The rate was highest for Month 1 at 5.7%, falling thereafter to 0.8% per month for Months 2 to 6 (incidence 3.4%) and 0.7% per month for Months 7 to 12 (incidence 4.1%). The investigators were unable to identify any predictive factors for the occurrence of VTE.

Figure 2. Incidence of New or Recurrent VTE



Extending dalteparin was not associated with an increase in major bleeding and adherence to therapy was high, leading the investigators to conclude that it is feasible to extend dalteparin therapy beyond 6 months in patients with cancer.

Investigational Small Molecule Rapidly Reverses Effects of New Oral Anticoagulants, Heparins

Written by **Wayne Kuznar**

An investigational synthetic antidote for the new oral anticoagulants (NOACs) and heparins demonstrated full reversal of anticoagulation in preclinical studies. The properties and mechanisms of action of the agent, PER977, and preclinical data were discussed by Bryan Laulicht, PhD, Perosphere Inc., Mt. Kisco, New York, USA.

Although new generation Factor Xa and IIa inhibitors offer significant advantages over heparins and warfarin in terms of their route of administration, drug interactions, and predictability of bioactivity, the NOACs lack a specific reversal agent. Thus, concern over the need for rapid reversal should a patient start to bleed or require an emergency procedure when taking an oral factor Xa or IIa inhibitor is heightened.

Dr. Laulicht described PER977, a synthetic small molecule designed as an anticoagulant antidote. PER977 showed no procoagulant effects in human blood on thromboelastography (TEG) *ex vivo*.

In silico modeling data predicted the sites of noncovalent hydrogen bonding between PER977 and new oral anticoagulants and heparins. Data from *in vitro* dynamic light scattering correlate the *in silico*-predicted noncovalent binding specificity of PER977 directly to the approved new generation oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban (approved in Japan only), and heparins.

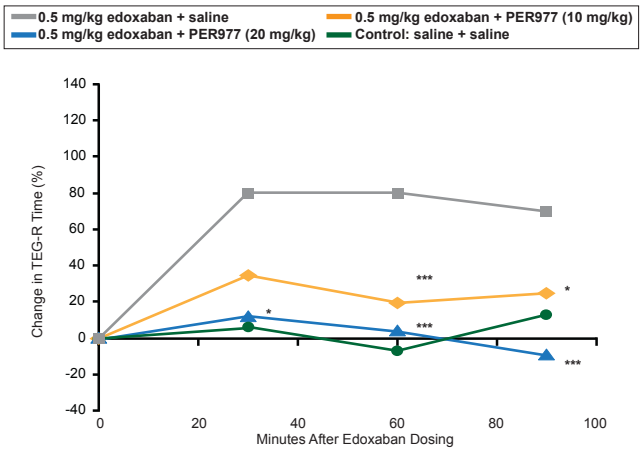
PER977 bonds to 6 sites on heparins, preventing them from binding to antithrombin III. Dynamic light scattering of mixtures of PER977 and enoxaparin provides evidence for the formation of molecular complexes formed at a mass ratio of 1:1, increasing in size at 10:1 ratios, indicating a strong physical, noncovalent association between PER977 and enoxaparin that accounts for the enoxaparin reversal activity of PER977

TEG reaction time (TEG-R) measurements demonstrate a statistically significant decrease ($p<0.01$) back to normal TEG-R levels in enoxaparin-anticoagulated rats within 30 minutes of intravenous administration of PER977 at 30 mg/kg, compared with rats receiving enoxaparin followed by a saline sham.

Preclinical *in vivo* anticoagulant (rat-tail transection bleeding) assays demonstrated improved reversal of enoxaparin with 30 mg/kg of PER977 compared with protamine sulfate ($p<0.05$).

PER977 binds to two sites on edoxaban, preventing it from inhibiting Factor Xa. Within 30 minutes of administration, 10 and 20 mg/kg of PER977 reversed edoxaban anticoagulation in rats measured by TEG in a dose-dependent manner (Figure 1), with full reversal at 20 mg/kg, compared with rats receiving edoxaban followed by a saline sham ($p<0.05$ with 10 mg/kg; $p<0.001$ with 20 mg/kg vs control). Blood loss mass in rats treated with 12.5 mg/kg of oral edoxaban was reduced significantly with administration of PER977 31.25 mg/kg ($p<0.01$).

Figure 1. PER 977 Reverses Edoxaban Anticoagulation in Measured by TEG



*p<0.05; ***p<0.001 With respect to control.

NOTE TO GGI: Interval bars deleted; include "Adapted" in the Permissions line

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